D.170.67366
E-105/83/2023

Annexure III

Our Ref: 202221034803/Pre-Grant

Date: 24th March, 2023

To,

200318055

The Controller of Patents
The Patent Office
Mumbai

Subject/ Reference: Reply to Pre-grant opposition under Section 25(1) against Patent Application No. 202221034803, dated 17/06/2022

Maharaja Krishnakumarsinhji Bhavnagar University, Gaurishankar Lake Road, Bhavnagar, 364 002 ...Applicant

Versus

Mr. T. Iyer, 124, Anaikkuraipatty, Madurai, Tamil Nadu ...Opponent

Sir,

We write to you with respect to the captioned matter, i.e., reply to Pre-grant opposition under Section 25(1) against Patent Application No. 202221034803, dated 17/06/2022. Kindly find enclosed herewith, a copy of the reply statement with supporting documents (exhibits).

We request you to take the said document on record. We further request the Learned Controller to grant us an opportunity of being heard in the matter.

भारत सरकार, पेटेन्ट कार्यालय, मुंबई
15 JUN 2022
GOVT. OF INDIA, PATENT OFFICE, MUMBAI

Yours faithfully,

(Signature of the Applicant)

Enclosed: As stated

Copy to: Mr. T. Iyer, 124, Anaikkuraipatty, Madurai, Tamil Nadu

Reply Statement and Evidence under Section 25(1) of the Patents (Amendment) Act, 2005 and Rule 58 of The Patents (Amendment) Rules, 2006

In

Maharaja Krishnakumarsinhji Bhavnagar University, Bhavnagar

... Applicant

Versus

Mr. T. Iyer ... Opponent

INDIAN PATENT NUMBER 353491 BASED ON APPLICATION NO. 202221034803

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3	Form No. 28 and Supporting Evidence to prove state government university	Exhibit P2
4	Bishwanath Prasad Radhey Shyam v Hindustan Metal Industries (AIR1982SC1444)	Exhibit P3
5	IN202221034803 – Form 2 Complete Specification	Exhibit P4
6	Birgul Ozden Kasimogullari et al., Fused Heterocycles: Synthesis of Some New Imidazo (1,2-a)-pyridine derivatives, Molecules, 2004, Vol. 9, 894-901 (as cited D1 in pre-grant opposition)	Exhibit P5

7	Manual Of Patent Practice And Procedure The Patent Office, India	Exhibit P6
8	Sandeep Jain et al., Novel Arylidene derivatives of quinoline based thiazolidinones: Synthesis, in vitro, in vivo, and in silico study as antimalarials, Experimental Parasitology, 185, 2018, 107e114 (as cited D2 in pre-grant opposition)	Exhibit P7
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12	Intellectual Property Appellate Board in Fresenius Kabi Oncology Limited Case No. 162 of 201	Exhibit P11

Yours faithfully,

Signature of Applicant

Date: 24th March, 2023

BEFORE THE CONTROLLER OF PATENTS, MUMBAI

IN THE MATTER OF

A representation under Section 25(1) of the Patent Act, 1970 as amended by the Patents (Amendment) Act, 2005("the Act") and Rules 55-A to 59 of the Patent Rules 2003 ("the Rules") by **Mr. T. Iyer**

...Opponent

And

IN THE MATTER OF

Indian Patent Application No. 202221034803

Dtd. June 17, 2022 of

MAHARAJA KRISHNAKUMARSINHJI BHAVNAGAR UNIVERSITY,

Gaurishankar Lake Road, Bhavnagar, 364002, Gujarat, India

... Patent Applicant

And

IN THE MATTER OF

Reply Statement and Evidence under section 25(1) of the Patents Act, 1970 as amended by the Patents (Amendment) Act, 2005 ("the Act") and Rule 58 of the Patent Rules. 2003 as amended by the Patents (Amendment) Rules, 2006 ("the Rules") by

MAHARAJA KRISHNAKUMARSINHJI BHAVNAGAR UNIVERSITY

...Patent Applicant

REPLY STATEMENT OF THE PATENTEE UNDER RULE 58

1. The present Patent Applicant is Maharaja Krishnakumarsinhji Bhavnagar University having their office at Gaurishankar Lake Road, Bhavnagar, 364002, Gujarat, India.

A. ABOUT THE INVENTORS

2. (i) The present inventor is Dr. Desai Nisheeth Chhotalal having residence at Plor No. 1852-C-2-H, Atabhai Road, Bhavnagar. Prof. Desai was the former Head, the Department of Chemistry, M K Bhavnagar University, Bhavnagar and he has 40 years of research experience in the field of Medicinal Chemistry, and successfully guided 47 students for their Ph.D. degree and published more than 150 research papers in internationally reputed Journal of Medicinal Chemistry Journals of high impact factors. His cumulative impact factor is more than 200. He is also the Editor In Chief, of Analytical Chemistry Letters published by Taylor and Francis. Over and above he is editorial board member of several Journal like Anti-infective Agents, Bentham Publishers, Mini Review in Medicinal Chemistry, Bentham Publishers and BMC Chemistry, Springer Nature.

   (ii) Dr. Jadeja Dharmpalsinh J obtained his Ph.D. degree in the year 2022 in the subject of Medicinal Chemistry on the topic of "Studies on synthesis, characterization and antimicrobial screening of some novel heterocyclic compounds". During his Ph.D. program, he synthesized 220 compounds based on heterocyclic chemistry and he has a strong background of synthesizing in heterocyclic compounds. He has published six research papers in internationally reputed Journals like Drug Development, Willy, SAR and QSAR in Environmental Research, Taylor, and Francis, and . Synthetic Communications, Taylor and Francis, etc.

   (iii) Dr Dhanji P Rajani is an eminent Microbiologist and Director of Microcare Lab & Tuberculosis Research Center, Surat-395003. His area of research interest

is Medical Microbiology, Diagnosis of tuberculosis, Non-tuberculosis Mycobacteria, antibiotic resistant, new synthetic drugs and Hospital Infection, and screening of antimalarial compounds. He published 83 research papers in reputed Journals and procure five patents in the field of heterocyclic compounds. Successfully completed two research projects.

B. PRELIMINARY OBJECTION

2. The present pre-grant opposition is a frivolous opposition as it does not raise any new challenge on the validity of the patent application that may not have been addressed during the prosecution of the present application.

C. ABOUT THE PATENT

3. The instant patent application was filed as an ordinary patent application in India, Patent Application No. 202221034803, dated 17th June 2022. The First Examination Report (FER) was issued on 29th August, 2020 and the response thereto was filed on 22nd November, 2022. The instant patent application is presently at the prosecution stage.

4. The factual matrix of IN354591 is as follows:

BIBLIOGRAPHIC INFORMATION	
PARTICULARS	**DATE/ RELEVANT INFORMATION**
INDIAN APPLICATION NUMBER	202221034803
APPLICANT NAME	Desai Niseeth Chhotalal Jadeja Dharampalsinh Jaydipsinh Khasiya Ashvinkumar Gopalbhai Mehta Harsh Kiritbhai Rajani Dhanji Popatbhai

DATE OF FILING	30th April 2019
TITLE OF INVENTION	"THIAZOLIDIN-3-YL-IMIDAZO-PYRIDINE-3-CARBOXAMIDE AS ANTIMALARIAL AGENTS"
PROSECUTION DETAILS	
DATE OF FILING	17h June 2022
FER DATE	29th August 2022
RESPONSE TO FER FILED ON	22nd November 2022
PUBLICATION DATE (U/S 11A)	22th July 2022
PRE GRANT OPPOSITION	PRE-GRANT OPPOSITION FILED
GRANT DATE	09th January 2023
PUBLICATION U/S 43(2)	12th January 2023

GROUNDS OF OPPOSITION TAKEN BY THE OPPONENT

5. The Opponent has primarily relied upon the below mentioned grounds in the written statement for the purpose of the present opposition:

    a. Novelty or anticipation by prior publication (Section 25(1)(b))

    b. Lacks inventive step (Section 25(1)(e))

    c. Not an invention (Section 25(2)(f))

    d. Clarity and insufficiency (Section 25(2)(g))

6. **DOCUMENTS RELIED ON BY THE OPPONENT**

SR. NO.	DOCUMENT NAME	DESCRIPTION
1	**Exhibit (1)**	Form 2 Complete Specification of the instant patent application 202221034803
2	**Exhibit (2)**	Govt. of Gujarat, The Maharaja KrishnakumarSinhji Bhavnagar University Act, 1978 (Gujarat Act of 1978)
3	**Exhibit (3)**	Birgul Ozden Kasimogullari et al., Fused Heterocycles: Synthesis of Some New Imidazo(1,2-a)-pyridine derivatives, Molecules, 2004, Vol. 9, 894-901 (D1))
4	**Exhibit (4)**	Sandeep Jain et al., Novel Arylidene derivatives of quinoline based thiazolidinones: Synthesis, in vitro, in vivo, and in silico study as antimalarials, Experimental Parasitology, 185, 2018, 107e114

The present patent applicant wishes to bring on record the following facts vide this reply:

7. One of the co-inventor of the instant patent, IN202221034803 has provided this reply statement. The inventor is the best person to describe his invention and the novelty in his invention. Reliance in this regard is placed on the decision of the Supreme Court of India in ***Bishwanath Prasad Radhey Shyam v Hindustan Metal Industries (AIR1982 SC1444)*** **(Exhibit P10)** which at Para. 46 reads as follows:

"46. The learned trial Judge then noted that Purshottam, who was stated to be the inventor, and, as such, was the best person to describe the invention, did not appear in the witness-box, though, as admitted by Sotam Singh (D.W. 3), Purshottam had attended on some dates of hearing. Sotam Singh tried to explain

Purshottam's disappearance from the Court without appearing in the witness-box, by saying that he had gone away due to illness. The learned Judge found this explanation unsatisfactory and rejected it-and in our opinion rightly-with the remark that recording of evidence lasted for several days and it was not difficult to secure Purshottam's attendance. Apart from being the best informed person about the matter in issue, Purshottam was not a stranger. He was a partner of the patentee firm and a brother of Sotam Singh (D.W. 3). ***He was the best informed person who might have answered the charge of lack of novelty leveled by the opponent side, by explaining what was the novelty of the alleged invention and how and after, what research, if any, he made this alleged 'discovery'.***" (emphasis added)

PARAWISE REPLY TO THE WRITTEN STATEMENT:

8. The content of Paragraph 2 of the written statement needs no reply. The opponent claims to be a pharmacist and researcher in the field of medicinal chemistry. However, there is no evidence on record to supplement and substantiate this claim of the opponent.

9. Paragraph 2 of the written statement states as follows:

> **Preliminary observations:**
> The Applicant has filed the Expedited request (RQ no. E20222027375, 27/07/2022) claiming that the applicant is *an institute established by a Central, Provincial or State Act, which is owned or controlled by the Government* and also, the Applicant has submitted a document *(Govt. of Gujarat, Gujarat Act No. 26 of 1978, as modified up to 31st December, 2017)* as support for the such claim. Such request has been considered by the Indian Patent Office and the Examination was carried out in the expedited mode and the FER was issued on 29/08/2022. It is clear from the document (as support) is effective up to 2017 whereas the date of application is 17/06/2022. It means that the document filed at the time of RQ (dated 27/07/2022) is not valid. Hence, the RQ (E20222027375, 27/07/2022) cannot be taken on record. Therefore whatever the submission and the amendment has been carried out at the time of FER Response (from the Applicant's end) may be disregarded. In view of the above, I being an opponent consider the as filed claims which have been published on 22/07/2022 by the Indian Patent Office and the objection/ground as herein below is in view of as filed claims only.

a) The patent applicant would like to draw attention of the Learned Controller to Form 28, attached herewith as Exhibit P2, which is filed with the instant patent application on 22nd June 2022.

b) The applicant would further like to draw the attention of the Learned Controller that Maharaja KrishnakumarSinhji Bhavnagar University is a state-established government university. The name of this University was changed from **"Bhavnagar University"** to **"Maharaja Krishnakumarsinhji Bhavnagar University"** by the Government of Gujarat. These are facts known to the public and also supported by evidence.

c) Page 3 of Exhibit P2 is a testament to the fact that Bhavnagar University was established by the Government of Gujarat. The aforementioned Exhibit is the Gazette published by the Government of Gujarat for the establishment of Bhavnagar University under the Bhavnagar University Act, 1978. The said Gazette was published on 17th April 1978. Pages 4 and 5 of Exhibit P2 shows the copy of latest amendment was brought in 2017.

d) Page 6 of Exhibit P2 is a letter of the University Grant Commission (UGC), Government of India, which is copy of notification published to announce that the change of name of the university from "**Bhavnagar University**" to "**Maharaja Krishnakumarsinhji Bhavnagar University**" (hereinafter referred to as MKBU in short).

e) The name MKBU is displayed on the website of UGC as a recognized Indian University by the University Grants Commission. The same is substantiated by the website URL https://www.ugc.ac.in.

f) Further, the applicant would like to quote herewith the Rule 24(c)(f) of the Patents Act 1970, which states:

(f) That the applicant is an institution established by a Central, Provincial or State Act, which is owned or controlled by the Government.

Therefore, the applicant Maharaja Krishnakumarsinhji Bhavnagar University is eligible to file an expedited examination request with the Indian Patent Office. Therefore, this preliminary observation should be waived by the patent office in the interest of justice.

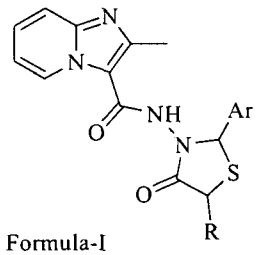
10. Paragraph 3 of the written statement merely states the grounds on which the opposition has been filed. All grounds of opposition raised therein are denied in totality.

GROUND: NOVELTY

11. Paragraph 3 of the written statement merely states that a ground of opposition under Section 25(1)(b) has been filed. This ground of opposition, too, is denied in totality. A copy of the filed specification, i.e., IN202221034803, including the claims is enclosed herewith as Exhibit P4.

EXPLANATION OF THE INSTANT PATENT (IN 202221034803)

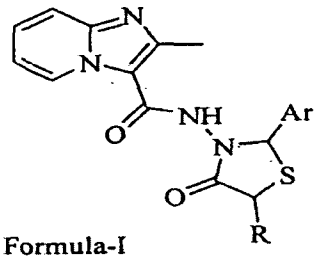
12. The instant patent (IN 202221034803) discloses a series of hybrid molecules of 2-methyl-N-(4-oxo-2-arylthiazolidin-3-yl)imidazo[1,2-a]pyridine-3-carboxamides containing imidazo-pyridine embedded with 4-thiazolidinones and amide linker present on the 3rd position of imidazo-pyridine heterocyclic motifs (Formula-I). The synthetic procedure was performed via one pot reaction and process for preparation and formulas (IV), (III), and (II) are condensed together, optimizing the in-process isolation of intermediate compounds thereof. The synthesized hybrids were evaluated for antimalarial activity against P. falciparum by utilizing quinine as a standard drug. A tri-substituted derivative (2,3,4-$(OCH_3)_3$) was found to be higher potency than the standard drug.



Formula-I

13. <u>Claims 1 to 5 of the document (Granted Patent – IN 202221034803):</u>

Claim 1: An anti-malarial compound Thiazolidin-3-yl-imidazo-pyridine-3-carboxamide of formula I, or its metabolites thereof,



Formula-I

wherein R is -H or $-CH_3$, $-CH_2$-COOH.

Aryl/heteroaryl ring is substituted by mono or di-substituents with nitro, halogen, N,N-dimethyl, cinnamyl, methyl and methoxy groups or derivatives, metabolites thereof.

Claim 2. The compound of Thiazolidin-3-yl-imidazo-pyridine-3-carboxamide of formula I as claimed in claim-1, wherein the compound is,

a. N-(2-(3-chlorophenyl)-4-oxothiazolidin-3-yl)-2-methylimidazo[1,2-a]pyridine-3-carboxamide;

b. N-(2-(3-fluorophenyl)-4-oxothiazolidin-3-yl)-2-methylimidazo[1,2-a]pyridine-3-carboxamide;

c. N-(2-(2-hydroxyphenyl)-4-oxothiazolidin-3-yl)-2-methylimidazo[1,2-a]pyridine-3-carboxamide;

d. N-(2-(4-hydroxyphenyl)-4-oxothiazolidin-3-yl)-2-methylimidazo[1,2-a]pyridine-3-carboxamide;

e. N-(2-(4-hydroxy-3-methoxyphenyl)-4-oxothiazolidin-3-yl)-2-methylimidazo[1,2-a]pyridine-3-carboxamide;

f. 2-Methyl-N-(4-oxo-2-(o-tolyl)thiazolidin-3-yl)imidazo[1,2-a]pyridine-3-. carboxamide;

g. 2-Methyl-N-(4-oxo-2-(3,4,5-trimethoxyphenyl)thiazolidin-3-yl)imidazo[1,2-a]pyridine-3-carboxamide;

h. N-(2-(2-methoxyphenyl)-4-oxothiazolidin-3-yl)-2-methylimidazo[1,2-a]pyridine-3-carboxamide;

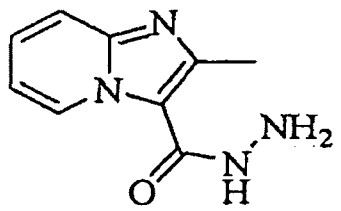
i. N-(2-(4-methoxyphenyl)-4-oxothiazolidin-3-yl)-2-methylimidazo[1,2-a]pyridine-3-carboxamide;

j. 2-Methyl-N-(2-(3-nitrophenyl)-4-oxothiazolidin-3-yl)imidazo[1,2-a]pyridine-3-carboxamide;

k. 2-Methyl-N-(2-(4-nitrophenyl)-4-oxothiazolidin-3-yl)imidazo[1,2-a]pyridine-3-carboxamide; and

l. 2-Methyl-N-(4-oxo-2-styrylthiazolidin-3-yl)imidazo[1,2-a]pyridine-3-carboxamide.

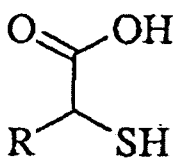
Claim 3. The one-pot synthesis of Thiazolidin-3-yl-imidazo-pyridine-3-carboxamide of formula I as claimed in claim-l optimizing the in-process isolation of intermediate compounds of formulae IV, III and II in presence of a catalyst



(Formula -IV)

Ar-CHO

Formula III;



Formula II.

Claim 4. The one-pot synthesis of compound of formula 1 as claimed in claim 3 wherein the catalyst is ammonium persulphate (APS).

14. The document cited by the opponent D1 - Fused heterocycles: synthesis of some new imidazo[1,2-a]- pyridine derivatives, Birgul Ozden Kasimogullari 1, Zafer Cesur – (**ExhibitP5**). The research article relates to some new thiazolidines and spirothiazolidines derived from hydrazones of 2-methylimidazo[1,2-a]pyridine-3-carboxylic acid hydrazide, a bioisosteric derivative of isoniazid, were synthesized and characterized by analytical, IR, 1H- and 13C-NMR and mass spectral data. Some of the newly synthesized compounds were screened for their

antimycobacterial activities. None of the tested compounds showed significant in vitro antituberculous activity at 6.25 μg/mL (MIC rifampin 0.031 μg/mL).

15. The points raised for novelty ground are completely unsubstantiated with regard to evidence. To anticipate any prior art, an invention must comprise entirely within a single document.

16. The applicant states and submits that as per the IP India Manual,

> *"In order to demonstrate lack of novelty the anticipatory disclosure must be entirely comprised within a single document. If more than one document is cited, each must stand on its own. The cumulative effect of the disclosures cannot be taken into consideration nor can the lack of novelty be established by forming a mosaic of elements taken from several documents." 3.3.4, Page No. 22.*

Attached herewith and marked as Exhibit P6 is the Manual Of Patent Practice And Procedure The Patent Office, India.

17. The applicant also brings on record, "**Enlarged" Concept Of Novelty: Initial Study Concerning Novelty And The Prior Art Effect Of Certain Applications Under Draft Article 8(2) Of The Splt**" published by International Bureau as **Exhibit P8**. The draft of the International Bureau recites as:

> "As regards court decisions concerning novelty determination in France, the courts apply novelty in a strict sense. An item of the prior art can destroy novelty only where it is one single piece that is, it is found entirely in the patent (TGI Toulouse, October 31, 1996, PIBD 1997 III, p.92). In principle, in order to form part of the prior art, an item of prior art shall contain all the elements of the claimed invention, with definite character, with the elements which constitute the same form, the same arrangement, and the same function in view of the same

technical result; the item of prior art destroys novelty only where the essential characteristics are represented (Cour de cassation, March 12, 1996, PIBD 1996 611 III p.273; CA Paris February 28, 1991, PIBD 1991 506 III p.497). Consequently, it is not sufficient for the characterization of lack of novelty that the patent recaptures a major part of the item of prior art (TGI Paris March 19, 2002). **On the contrary, an invention is considered novel because of the only fact that, for example, it claims a function different from that of the item of the prior art, even if its structure, its form, and its arrangement are identical** (Cour d'appel de Paris, February 9, 2001, PIBD 2001 725 III p.389)." 37, Page No. 10.

18. The opponent has relied on document D1 (Exhibit P6) and document D2 (Exhibit P7) to raise an objection to the novelty of the present application. In order to allege a lack of novelty, a prior document objecting to the novelty of a patent application is required. Therefore, the applicant requests the Learned Controller to dismiss and deny the objection on the ground of lack of novelty raised by the opponent herein.

GROUND: LACK OF INVENTIVE STEP

19. Paragraph 4 of the written statement states the ground of opposition under Section 25(1)(e). This ground of opposition is denied in totality. The ground in the pre-grant opposition states:

"*The above finding as stated in the novelty ground can be applied for assessment of inventive step in the present context. D1 suggests imidazo-pyridine ring and D2 suggests quinoline base 4-thiazolidinone for antimalarial activity. Then it is obvious for a skilled person to combine the teaching of D1 & D2 in order to reach the compound as claimed in claim 1 of the impugned application. No unexpected*

effect/surprising feature is observed in the impugned application as filed."

20. The applicant herein requests the Ld. Controller to kindly refer to Paras 16 and 19 of the said reply related to the document D1 (Exhibit P5) and document D2 (Exhibit P7).

21. The inventors of the present patent applications are involved actively in research in the field of medicinal chemistry for a long time. Any person skilled in the art of research must appreciate that it is not an easy task to synthesize a novel and innovative compound, that too, merely based on the knowledge of the formation of amide bonds between Imidazo-pyridine motif and 4-thiazolidinone derivative.

22. It is submitted that the document D2 (Exhibit P7) does not teach or disclose the formation of the amide bond with the 4-thiazolidinones derivatives.

23. Synthesized compounds of cited document D1 (Exhibit P5) were screened against an **antitubercular strain,** while compounds of Exhibit P5 were screened against an **antimalarial strain**. Compounds of Exhibit P7 contain quinoline and 4-thiazolidinone moieties **having antimalarial activity**. This goes on to indicate that both compounds reported in both documents have different medicinal effect. The instant application claims antimalarial properties of the Thiazolidin-3-yl-imidazo-pyridine-3-carboxamide of formula I.

24. The patent applicant herewith also provides supporting documents, in the form of two Published PCT applications. The applicant also presents herewith, two patent application references: WO2012024620 of applicant Amira Pharmaceuticals, Inc. (Exhibit P9) and WO2015077503 of applicant Pharmakea Inc. (Exhibit P10). These two PCT patent applications also claim a variety of different novel and

innovative heterocyclic compounds in the medicinal field. Further, these two PCT applications have also been conferred patents from patent offices of different countries. This clearly shows that an objection on the ground of lack of inventive step merely based on just structure similarities cannot be accepted, since it is difficult to synthesize and purify each and every chemical compound.

25. In light of the above argument, the applicant herewith requests the Learned Controller to reject the argument of the opponent on the ground of lack of inventive step in the instant application.

GROUND: NOT AN INVENTION

26. Page 7 of the written statement deals with the ground of opposition under Section 25(1)(f). Ground of opposition is denied in totality. The ground of not an invention in the pre-grant opposition states as:

> *"Impugned application talked about the antimalarial activity of the compound (Table 2, 1a-1l) in view of 'potency'. The 'potency' is different from the "therapeutic efficacy" as the compound patent as India is concerned. The requirement for Section 3(d) is that there must be a study & data thereof which could establish the claimed compound (Formula I) will produce an enhanced or superior efficacy (therapeutic) on molecular basis than what could be achieved with imidazo-pyridine or quinoline based 4-thiazolidinones individually. The impugned application is absolutely failed to disclose such study/data. Hence, section 3(d) attracts the instant claims".*

27. Section 3(d) of the Patents Act, 1970 states:

> *"(d) the mere discovery of a new form of a known substance which does not result in the enhancement of the known efficacy of that substance or the mere discovery of any new property or new use for a known*

substance or of the mere use of a known process, machine or apparatus unless such known process results in a new product or employs at least one new reactant."

28. The patent applicant also annexes supporting document **Exhibit P11.** The order of the IPAB. IPAB is crystal clear through its order passed in ***Fresenius Kabi Oncology Limited Vs Glaxo Group Limited, Order No. 162 of 2013*** (Para no. 56, **Exhibit P11**) that to raise a challenge or on the objection under Section 3(d), one has to specifically allege and identify at least following three questions:

a) What is the specific "known" substance?
b) How and why the claimed molecule(s) or substance(s) is a derivative or is otherwise a new form of known substance?
c) What is the basis to asset that the alleged "known" substance and the claimed molecule or substance has the same "known" efficacy?

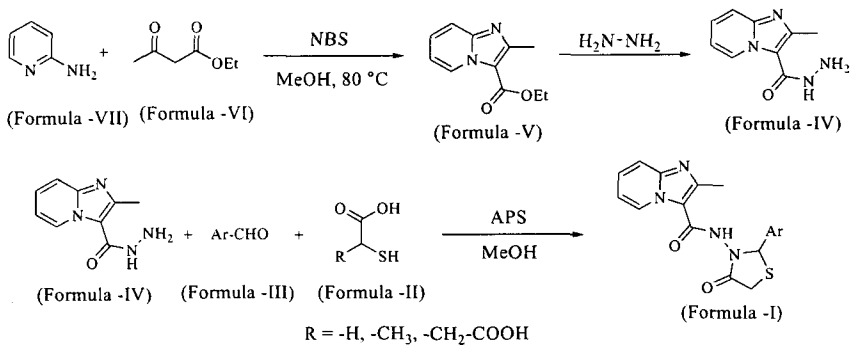
29. The opponent has categorically failed to provide any evidence which possibly indicates that the Formula I of the instant application is known. Therefore, the applicant herein requests the Learned Controller to reject the opponent's argument on the ground "Not an invention as under Section 3(d)".

GROUND: INSUFFICIENCY & CLARITY

30. Page 7 of the written statement states the ground of opposition raised under section 25(1)(g). This ground of opposition is denied in totality. The ground of insufficiency and lack of clarity in the pre-grant opposition states,

"How to synthesize the compound Thiazolidin-3-yl-Imidazo-pyridine-3-carboxamide of formula I is not clear from the claim as there is no process steps."

31. The applicant has claimed a new and innovative chemical compound, Formula I in the instant application. The complete specification (Exhibit P4) of the instant Application No. 202221034803 clearly provides complete details pertaining to the synthesis of Formula I. The applicant requests the Learned Controller to kindly refer to Example 1 to 15 provided in detail on Page Nos. 16 to 19 of Exhibit P4. Further, the applicant would like to bring to the notice of the Learned Controller, Scheme 1 given in the complete specification.



(Formula -VII) (Formula -VI) (Formula -V) (Formula -IV)

(Formula -IV) (Formula -III) (Formula -II) (Formula -I)

32. Therefore, the applicant herein requests the Learned Controller to reject the opponent's arguments of insufficiency and lack of clarity. All foregoing arguments of the opponent are denied *in toto*.

33. Paragraph on page 2 of the written statement summarizes the grounds of opposition under the sections 25(1)(b), 25(1)(e), 25(2)(f), and 25(2)(g) on which the opposition has been filed. Grounds of opposition are denied in totality.

34. All of the foregoing arguments of the opponent are denied *in toto*. The contents of paragraphs 1 to 35 of the present reply statement are submitted by the Patent applicant in response to the arguments of the Opponent.

VERIFICATION

We, the undersigned applicants, **MAHARAJA KRISHNAKUMARSINHJI BHAVNAGAR UNIVERSITY**, do hereby solemnly affirm that the contents of paragraphs (1) to (35) are true to the best of our knowledge and records.

Signature by the Applicant

Date: 24th March, 2023

PRAYER

In view of the above statements and exhibits filed in support of patent application 202221034803, the Patent applicant prays to the Learned Controller the following reliefs:

a) the pre-grant opposition be dismissed;

b) costs of the opposition be awarded to the patent applicant; and

c) any other relief/s as the Controller may deem appropriate.

Dated: 24th March, 2023

For Maharaja Krishnakumarsinhji Bhavnagar University, Bhavnagar

Signature of the Applicant

BEFORE THE CONTROLLER OF PATENTS

Maharaja Krishnakumarsinhji Bhavnagar University, Gaurishankar Lake Road, Bhavnagar, 364 002 ... Applicant

Versus

Mr. T. Iyer, 124, Anaikkuraipatty, Madurai, Tamil Nadu ... Opponent

NOTARY
V. SAMUTHIRA VIJAYAN
CHENNAI CITY
G.O.MS.No.59 (Law) dt.28.02.2019
Expiry on : 27.02.2024
GOVT. OF TAMIL NADU

AFFIDAVIT IN SUPPORT OF INTERLOCUTORY APPLICATION

I, Mr. T. Iyer, son of Mr. Balakrishnan Iyer, aged about 51 years, working for gain at ML Laboratory, Madurai, Tamil Nadu – 625536, India, do hereby solemnly affirm and sincerely state as follows:-

1. I am the Appellant herein and I am well acquainted with the facts and circumstances of the case.

2. I am referring to and relying upon the following documents in support of appeal and in order to substantiate the contentions raised in the appeal:-

A	The Impugned INTERLOCUTORY APPLICATION dated 10/06/2023
B	TWO NOTICES ISSUED DATED BY TWO DIFFERENT HEARING OFFICER SIMULTANEOUSLY WITHOUT CANCELLING THE EARLIER ONE AND WITHOUT ANY REASON WHATSOEVER FOR CHANGE OF HEARING OFFICER

1. I humbly submit that the documents set out above will prove Appellant's contentions, statements and submissions made in its appeal.

2. I submit that the Appellant is filing the available documents in support of the appeal. I reserve my right to file additional documents, as advised, by way of appropriate miscellaneous petition before this Hon'ble Board.

3. In the light of the above, it is humbly prayed that this Hon'ble Tribunal may be pleased to take on record the documents mentioned above in this proceeding and proceed with the merits of

NOTARY
V. SAMUTHIRA VIJAYAN
CHENNAI CITY
G.O.MS.No.59 (Law) dt.28.02.2019
Expires on : 27.02.2024
GOVT. OF TAMILNADU

x

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the case and allow the Interlocutory Application and thereby render justice.

AND I make the solemn declaration and say that what is stated in paragraphs 1 to 4 above are true to the best of my knowledge and belief based on the records maintained by me and my concern and upon legal advice, and para 5 is my humble submission to the Hon'ble Board.

Solemnly affirmed at CHENNAI
on 10th day of June 2023
and the deponent signed his name
in my presence.

x

Before Me

Appellant

Notary Public, CHENNAI

NOTARY
V. SAMUTHIRA VIJAYAN
CHENNAI CITY
G.O.MS.No.59 (Law) dt.28.02.2019
Expires on : 27.02.2024
GOVT. OF TAMIL NADU

10/06/2023

V.SAMUTHIRA VIJAYAN, M.Com., B.L.,
Advocate, Notary Public & Commissioner of OATHS
No.164, Nisha Plaza, First Floor, Karuneegar Street,
Adambakkam, Chennai-600 088.
Ph.: 94444 36893, Email: samuthiravijayan@gmail.com

Annexure II

बौद्धिक सम्पदा भारत
एकस्व / अभिकल्प / व्यापार चिन्ह / भौगोलिक संकेत
INTELLECTUAL PROPERTY INDIA
PATENTS / DESIGNS / TRADEMARKS / GEOGRAPHICAL INDICATIONS

सत्यमेव जयते
भारत सरकार
पेटेंट कार्यालय – बौद्धिक सम्पदा भवन
एस.एल. रोड, नजदीक अन्टॉप हिल डाकघर, अन्टॉप हिल, मुंबई – ४०००३७
Government of India
Patent Office - Boudhik Sampada Bhawan
S.M. Road, Near Antop Hill Post office, Antop Hill, Mumbai - 400037

दूरभाष Tel: 022-24130466

Email: mumbai-patent@nic.in
Website: www.ipindia.nic.in

No. 202221034803/3856 Date: 24/03/2023

To:

Prof. Nisheeth Chhotalal Desai.
Department Of Chemistry,
Maharaja Krishnakumarsinhji Bhavnagar University,
Bhavnagar-364001, Gujarat.

Sub: A representation by way of opposition u/s 25(1) of the Act in respect of application for patent No. 202221034803

Sir / Madam,

A notice is hereby given under rule 55(3) of the Patents Rules, 2003 (as amended), that Mr. T. Iyar, 124, Anaikkaraipatty, Madurai, Tamil Nadu - 625536 has filed a representation by way of opposition u/s 25(1) of the Patents Act, 1970 (as amended) on 09th January, 2023 against the application for patent No. 202221034803.

The grounds of opposition, as raised by the opponent have been mentioned in the representation filed under section 25(1) of the Act, which is already uploaded in the electronic file wrapper of the instant application and available on the official website of the Patent Office: (*https://ipindiaservices.gov.in/PublicSearch/PublicationSearch/ApplicationStatus*).

In view of the above, the applicant shall, if he so desires, file his statement and evidence, if any, in support of his application within three months from the date of this notice with a copy to the opponent as per rule 55(4) of the Patents Rules, 2003 (as amended).

Yours faithfully,

(Dr. Amarandra Samal)
Deputy Controller of Patents & Designs

Copy to: Mr. T. Iyar, 124, Anaikkaraipatty, Madurai, Tamil Nadu - 625536

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 Annexure I

Gmail T Iyer <tiyer68@gmail.com>

Notice of Opposition for Patent Application No. 202221034803

Soumen Ghosh <soumen.ghosh@nic.in> Mon, Jan 30, 2023 at 2:20 PM
To: dnisheeth@rediffmail.com
Cc: tiyer68@gmail.com

Dear Sir, Date - 30/01/2023
A pre-grant opposition u/s 25(1) against the Patent Application No. 202221034803 has been filed by the opponent. Therefore, Notice of Opposition under Rule 55(3) is being communicated to you. The details of representation is available in the website as uploaded documents for said application no. .
Regards,

Soumen Ghosh,
Dy. Controller of Patents & Designs,
Patent Office,
Kolkata.

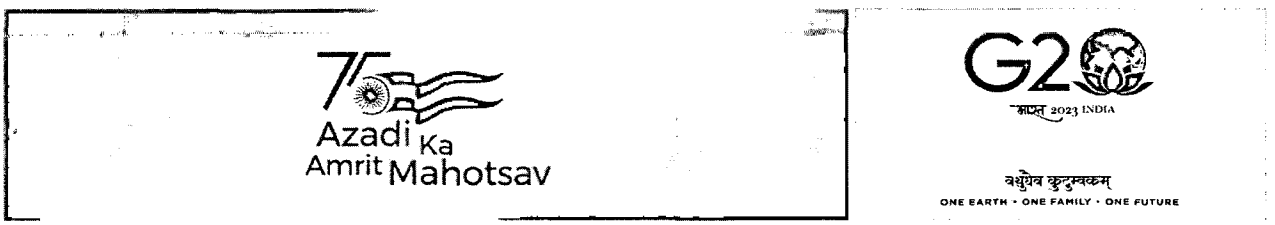
From: "KAUSIK BAG" <kausik.ipo@gov.in>
To: "Soumen Ghosh" <soumen.ghosh@nic.in>
Sent: Wednesday, January 25, 2023 2:35:08 PM
Subject: Pregrant opposition against expedited application no. 202221034803

Respected Sir,

This is for your kind information that one pregrant opposition u/s 25(1) of the Act has been filled on 12/01/2023 by MR. T. IYAR (hereby reffered as Opponent) against Expedited application no. 202221034803 dated 17/06/2022. The pregrant document is hereby attached herewith for your kind consideration. Kindly do the needful in this regard.
Applicant: MAHARAJA KRISHNAKUMARSINHJI BHAVNAGAR UNIVERSITY (dnisheeth@rediffmail.com)
Opponent: MR. T. IYAR (tiyer68@gmail.com)

with regards,

Kausik Bag, Ph.D
Examiner of Patents & Designs
IPO, Kolkata (Chemical Section)



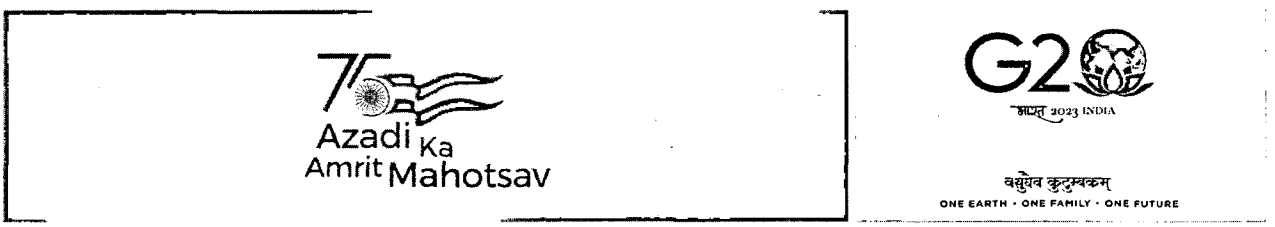


Exhibit P1

Brief Bio-Data of Professor N C Desai, Former Prof. & Head, Department of Chemistry, Maharaja Krishnakumarsinhji Bhavnagar University, Bhavnagar - 364 002, India

(A) Academic Qualifications: M Sc. (1979), Ph.D. (1982)

Contact details: dnisheeth@rediffmail.com, dnisheeth@gmail.com
Experience: 40 Years in Teaching including Professor of 14 years (10 years as Professor and 4.5 years as Senior Professor), administrations and Research

- Designation: Ex. Senior Professor & Head, Department of Chemistry, since 13th June, 2008 to 3rd August, 2019, and currently I was working as Senior Professor, Present salary as per the 7th pay commission:

(b) Areas of Research Specialization:

- Basic and Applied research in
  (i) Organic and Medicinal Chemistry, synthesis, characterization and biological activities of some smart heterocyclic compounds (anti-HIV, anticancer, antimalarial and antimicrobial agents). Several heterocyclic compounds based different molecular diversities were developed by my research group.
  (ii) Green Chemistry

- Research and Publications:
  152 Research Papers where in 105 (hundred and five) in Journals of International repute and 47 (Forty seven) in journals of National repute, One Book review and Four Book Chapters.
- Ph. D. Guidance: 47 (Forty Seven) students have successfully pursued and obtained Ph. D. and currently seven students (03) are pursuing their doctoralresearch work for Ph. D. Degree.
- Three students have successfully completed Post-Doctoral guidance.

(C) Distinguished Career Award:

- Received prestigious Career Award for Young Scientist from University Grants Commission, New Delhi, for a period of 3 years (1995-1998) which carried Rs. 2 lakh for further research on HIV and cancer chemotherapy.
- Received a special grant of Rs. 7 lakhs by University Grants Commission, New Delhi under "UGC-BSR" scheme.
- Received Life Time Achievement Award from Indian Society of Chemists and Biologists, Lucknow in year 2019 for outstanding contribution to science.
- Selected as a Bentham Ambassador of India, Bentham Science Publishers, USA for the year 2018-2019.

Exhibit P1

(D) Special Recognition:

- Got the recognition among top 2% scientists/researchers across the globe from Stanford University, USA. PLoS Biol 18(10): e3000918. https://doi.org/10.1371/journal. pbio. Since last three years i.e. 2020, 2021, 2022 and 2023.
- Successfully completed major research projects from funding agencies like UGC, CSIR, DST, BRNS, and MoES.

- **Outstanding achievements:**

(E) Citation Index, Patenting and Research Consultancy:

Cumulative Impact factor	Citation	i10-index	h-index
242	3639	99	34

- Number of Patents: Three Indian patents to the credit of Medicinal Chemistry research.
- Worked as international reviewer for reviewing projects - Research Fund Secretariat of the Food and Health Bureau, Hong Kong
- Industrial consultancy with Alembic Limited, Vadodara

(F) Contribution to editorial work in leading Journals

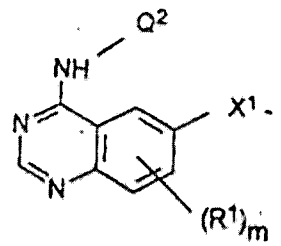
(a) Associate Editor, Chemistry and Biology Interphase, published by Indian Society for Chemist and Biologist, Lucknow.
(b) Member of Editorial Board: Mini Review in Medicinal Chemistry, Bentham Publishers
(c) Member of Editorial Board: Ant-infective Agents, Bentham Publishers
(d) Member of Editorial Board: BMC Chemistry, Springer Nature

****

- Y: The Petitioner has chosen –NH- from 9 primary classes of disclosed linking groups.
- R^5: The Petitioner has chosen halogen from 18 classes of disclosed endgroups, and has chosen chlorine from the multiple halogen options.
- n: The Petitioner has chosen "1" for the n value from the three options, and also chooses the particular position for that single substituent.
- R^3: Where R^3 is defined as ZR^4, the Petitioner has chosen from 3 possible linkers between Z and R^4. Then the Petitioner has chosen to optionally substitute that moiety, and to choose not only one substituent from the myriad of possibilities, but also the precise position of that substituent.
- R^1: The Petitioner has chosen a furan ring from a list of possible R1 substituents that is literally a page long (see page 11), and then chooses to optionally substitute the furan ring. In referring to an alkyl amine substituent on that ring (i.e. such as NHs CHs -) the Petitioner has even gone beyond the disclosed possibilities in terms of the substitution for such a heteroaromatic group for R^1.

Exhibit 2: WO 97/30034

20. According to the respondent the Petitioner has particularly selected some of the possible substituent groups of the Markush structure without any reasoning. The Petitioner has started with the genus of Exhibit 2, as shown in Paragraph 8(a)(vii) as Formula (I)



and has selected from at least the following numbers of substituents (which selected choices in combination reflect well over a billion (109) possibilities) in order to construct the compound.

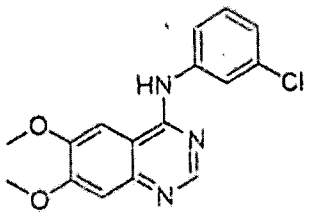
21. According to the respondent a person of ordinary skill in the art would not combine the teachings of Exhibit 1 and Exhibit 2 in order to arrive at the compound of Formula of the present invention. Ex.2 does not provide any motivation to the person skilled in the art to combine the teachings of Exhibit 1 and Exhibit 2 to reach the compound claimed in the Patent. The compound claimed in the Patent is entirely different from the compounds defined by Formula (I) of Exhibit 2 due to the specific substitution pattern. As such, it is respectfully submitted that, save for the basic 'quinazoline core structure', there is no

structural similarity existing between the compounds of Exhibit 2 and the compound claimed in claim 1 of Indian Patent No.221017. The Petitioner has also completely failed to establish a structural similarity between the compound claimed in claim 1 of Indian Patent No.221017 and the compounds disclosed in Exhibit 1.

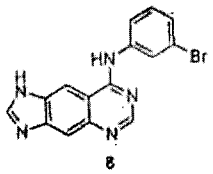
22. Without prejudice, even if a person skilled in the art would combine the generic structure or the hypothetical structure deduced by the Petitioner from either of Exhibits 1 and 2, the combination still does not result in the compound of the present invention. The Petitioner has completely failed to provide teaching to link the "**methylsulphonyl**-aminomethyl-amino" group with the furan ring.

23. According to the respondent that it is not correct to state that there is a close structural similarity between the compound claimed in the Patent and the compounds disclosed in either of Exhibit 1 or Exhibit 2. There was no motivation to choose any such compounds disclosed in either of Exhibit 1 or Exibit 2. There was no motivation to choose any such compounds disclosed in either of Exhibit 1 or Exhibit 2 even as a starting point for finding a dual EGF-R and c-erbB-2 inhibitor. The respondent submitted it is not correct to state that choosing any such compounds disclosed in either of Exhibit 1 or Exhibit 2 and 'arriving at' the compound claimed in the Patent is 'nothing more than mere trial and error and experimentation' given the significant structural differences involved and the specific substitution pattern of the compound claimed in the Patent. Although the Petitioner had indicated that the compound claimed in the Patent and the prior art compounds are all protein tyrosine kinase inhibitors, such a general statement does not show that the compound claimed in the Patent is obvious and lacking in inventive step.

24. According to the respondent the Sinha Affidavit and its analysis of the binding mode for a kinase inhibitor was not correct. The presentation of the binding mode of Lapatinib as suggested by the applicants witness is incorrect based on X-ray crystal structure analysis as discussed in the Heerding Affidavit. In the Heerding Affidavit, it is indicated that Lapatinib (the compound of formula



27. According to the respondent Exhibit B evaluates the enzyme inhibition of EGFR by compounds bearing tricyclic heteraromatic cores, including 1H-imidazo[4,5-g] quinazolines. Exhibit B only describes enzyme inhibition of EGF-R and makes no mention of inhibition c-erbB-2 or of overall kinase selectivity of the compounds discussed therein. These compounds were compared to their previously published bicyclic quinazoline EGF-R inhibitors (in Exhibit A). As with Exhibit A, no description of pharmacokinetic data or other drug-like properties are described in Exhibit B. The most potent compound in terms of enzyme inhibition of EGF-R highlighted by the authors is shown below (compound 8).



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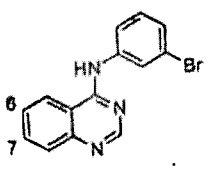
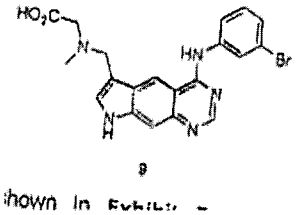
The salient structure-activity relationship aspects from the previously described bicyclic quinazoline series have been summarized in Exhibit B. In particular, "small electron-donating substituents at the 6- and 7-positions were desirable for high potency." However, Lapatinib has a substituted furan at the 6-position and a furan group cannot be considered as an electron donating substituent on an aromatic ring and the substituted furan is clearly not small. In fact, the Exhibit B clearly says that increasing the bulk at the 6- and/or-7 position "has been shown to be disadvantageous in the quinazoline series."



kinase and prefer a specific conformation of a characteristic Asp-Phe-Gly motif such that the Asp and Phe are both oriented towards the ATP binding site (so-called DFG-In).



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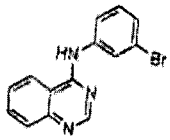

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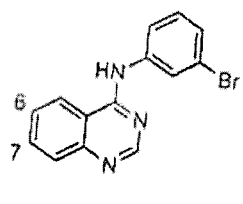
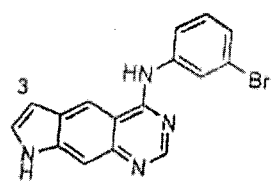
shown in Exhibit .

However, as shown in Exhibit D, the substitution pattern around the bicyclic quinazoline core of lapatinib unexpectedly results in a binding mode in EGF-R that is described as a Type II kinase inhibitor. This class of kinase inhibitors is characterized by their ability to bind to the inactive form of the kinase. They are also generally more kinase selective and believed to be less susceptible to drug resistance due to kinase domain mutations. In the case of lapatinib, the binding to EGF-R is described as a DFG-in, alpha C-helix out conformation. This unexpected binding mode contributes to the extremely high kinase selectivity observed for lapatinb when profiled against 287 distinct human protein kinases or approximately 55% of the human protein kinome (as discussed in Karaman et al., *Nature* Biotechnology, 2008, 26, 127, enclosed herewith as **Exhibit E**). Once again, this is an unexpected difference distinguishing lapatinib from the bicyclic and tricyclic EGF-R kinase inhibitors described in Exhibits A,B and C. For all these reasons the respondent defended the patent

30. The Application was filed along with two prior arts Exs 1 and 2 and the affidavit of Dr. Surajit Sinha. The Counter statement was filed along with Exhibit- D Bikker at al J.Med.Chem 2009 52,1493; EX E Karaman et.al Nature Biotechnology 2008 ,26, 127 and Ex F; Yun et. Al Cancer Cell 2007 11(3) 217. and the affidavit of Dr. Heerding. To this a reply statement was filed along with a second affidavit of Dr. Sinha and the Exhibits A to I.

28. According to the respondent the main thrust of Ex. C is the activities of tricyclic heteroaromatic EGF-R tyrosine kinase inhibitors (8h-pyrrolo[3,2-g] quinazolines and 1h-pyrazolo[4,3-g]quinazolines). These compounds are compared to the bicyclic quinazoline series of EGF-R and there is no mention of inhibition of c-erbB-2 or of overall kinase selectivity of the compounds discussed therein. As with Exhibits A and B, no description of pharmacokinetic data or other drug-like properties are described in Exhibit C. It states that the "poor aqueous solubility of these compounds is a major drawback to their further development." According to the respondent the fact that lapatinib has been successfully developed into an effective marketed medicine clearly distinguishes it from the bicyclic quinazolines described in these manuscripts. The importance of small electron-donating substituents at position -6 and position -7 for the potency of the bicyclic quinazoline series is also reiterated in the Introductory paragraph of Exhibit C. The authors then go on to show in the case of the tricyclic 8H-pyrrolo[3,2-g] quinazolines that bulky substituents are in fact tolerated at C-3. This finding sharply contrasts with the previous statement about small electron-donating groups, leading one to believe that the tricyclic 8H-pyrrolo[3,2-g] quinazolines represent a separate chemical series from the bicyclic quinazoline analogs with distinct structure activity relationship requirements.



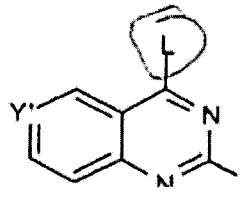


29. According to the respondent Exhibit C describes a binding mode for two of the analogs. The description fits what is known as a Type I kinase inhibitor (*as discussed in Bikker et al., J.Med.Chem., 2009,52, 1493* enclosed herewith as **Exhibit D**). These inhibitors are only capable of binding to the active for of the

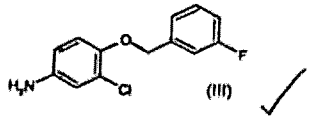
"Salts of the compound of formula (1) may comprise acid addition salts derived from a nitrogen in the compound. The therapeutic activity resides in the moiety derived from the compound of the invention as defined herein and the identity of the other component is of less importance, although for therapeutic and prophylactic purposes It is, preferably, pharmaceutically acceptable to the patient. Examples of pharmaceutically acceptable acid addition salts include those derived from mineral acids, such as hydrochloric, hydrobromic, phosphoric, metaphosphoric, nitric and sulphuric acid and organic acids, such as tartaric, acetic, trifluoroacetic, citric, malic, lactic, fumaric, benzoic, glycolic, gluconic, succinic and methanesulphonic and arylsulphonic, for example p-toluenesulphonic, acids."

"According to a further aspect of the present invention there is provided a process for the preparation of a compound of formula (I) as defined above which comprises the steps:

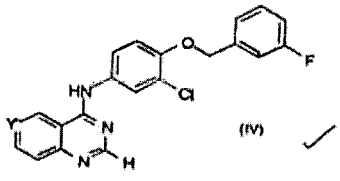
(a) the reaction of a compound of formula (11)



wherein Y' is CL'; and L and L' are suitable leaving groups, with a compound of formula (III)



to prepare a compound of formula (IV)



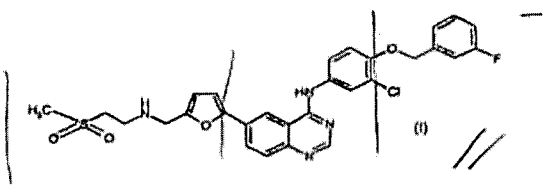
and subsequently (b) reaction with appropriate reagent(s) to substitute the ({[2-(methanesulphonyl)ethyl]amino}methy)-2-furyl group by replacement of the leaving group L'."

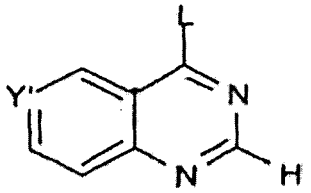
"Alternatively, the Compound of formula (11) as defined above is reacted with the appropriate reagents to substitute the ({[2-methanesulphonyl) ethyl]amino}methyl) -2-furyl group by replacement of the leaving group L' and then the product thereby obtained (of formula (V) below) is reacted with the compound of formula (III) as defined above.

In a variant of this alternative the compound of formula (V)

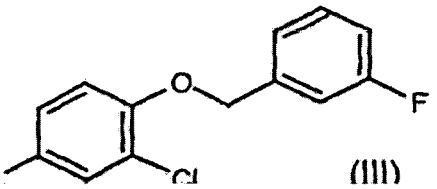
31. The learned Counsel Mr. S. Majumdar for the appellant and Mr. Praveen Anand for the respondent made elaborate submissions and also filed written arguments.

32. We extract some parts of the complete specifications. This was the version that was shown to us. *Later we were informed by the applicant that the PCT application was much longer and the specifications mentioned that"this invention relates to quinoline, quinazoline, pyridopyridine and pyridopyrimidine derivatives which exhibit protein kinase inhibitors". We will deal with this issue later.*

> "The present invention envisages, in particular, the treatment of human malignancies, for example breast, non-small cell lung, ovary, stomach, and pancreatic tumours, especially those driven by EGF-R or erbB,-2 using the compounds of the present invention. For example, compounds which are highly active against the c-erbB-2 protein tyrosine kinase often in preference to the EGF receptor kinase allow treatment of c-erbB-2 driven tumours. However, compounds which are highly active against both c-erbB-2 and EGF-R receptor kinases allow treatment of a broader range of tumour."
>
> "More particularly, the present invention envisages that disorders mediated by protein tyrosine kinase activity may be treated effectively by inhibition of the appropriate protein tyrosine kinase activity in a relatively selective manner, thereby minimising potential side effects.
>
> "Accordingly, the present invention provides the compound N-{3-Chloro-4-[(3-fluorobenzyl) oxy]phenyl} -6- [5- ({ [2-(methanesulphonyl) ethyl]amino}methyl) -2-furyl]-4-quinazolinamine (hereinafter the compound of formula (I)); or a salt or solvate thereof, particularly pharmaceutically acceptable salts or solvates thereof.
>
> 
>
>
> Solvates of the compound of formula (I) are also included within the scope of the present invention."
>
> "WO 95/19774 discloses heterocyclic tyrosine kinase inhibitors which lack the present ({[2-(methanesulphonyl) ethyl] amino}methyl) -2- furyl substituent. Intermediate document WO 98/02434 discloses compounds of a general formula encompassing the compound of formula (I), but it does not teach the present combination of substituents."
>
> "The compound of formula (I) is of particular interest in the context of c-erbB-2 activity."
>
> "The compound of formula (1) may exist in tautomeric forms other than that shown in the formula and these are also included within the scope of the present invention."

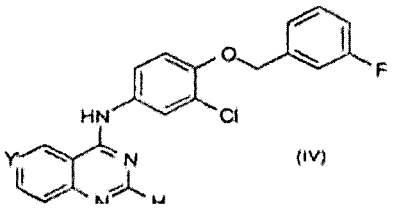


wherein V is CL'; and L and L' are suitable leaving groups, with a compound of formula (III)



(III)

to prepare a compound of formula (IV)

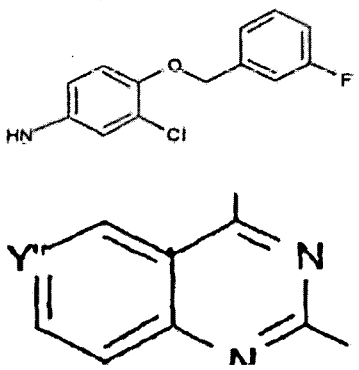


(IV)

and subsequently (b) reaction with appropriate reagent(s) to substitute the ({[2-(methanesulphonyl)ethyl]amino}methyl)-2-furyl group by replacement of the leaving group L'.

4. A process for the preparation of a compound of formula (I) as claimed in aim 1 which comprises the steps:

a) reacting a compound of formula (IV) as claimed in claim 3 with appropriate reagent(s) to prepare a compound of formula (VIII)



wherein Y" is CT; and T is an appropriately functionalised group; and

(b) subsequently converting the group T into the ({[2-(methanesulphonyl) ethyl]amino}methyl)-2-furyl group by means of appropriate reagent(s).

Ex F WO 1996/09294 28th Mar 1996

EX G Copy of publication PNAS Vol 95 12022-12027 Sept 1998

Ex H Fry D .W. Experimental cell research 284(2003)131-139

Ex I Journal Medical Chemistry Toxicology 1992. 5,211-219.

Ex J Journal Cancer Research 52 4379-4384 15th Aug 1992

33. Miscellaneous Petition No.49/2013 is for amending the address of the respondent. It is allowed. Miscellaneous Petition Nos.4, 9 & 10/2013 relate to reception of additional evidence and the rebuttal evidence. We have allowed the miscellaneous petitions and received the evidence subject to relevances. The evidentiary value of the documents will be dealt with herein below.

S.8 Objection :

34. We will deal at some length how Section 8 should be pleaded and proved, both in this application and in the ORA/22/2012/PT/KOL to revoke the patent granted for Lapatinib ditosylate. The applicant had merely stated that Section 8 requirements were not complied with. The language of the Section was alone reproduced without giving details.

35. In the counter statement at paragraphs 106 to 110 the respondent had pleaded that they had furnished all the documents that were to be filed, according to Section 8 (a) & (b) of the Patents Act, 1970 and in the Annexure to the counter statement they had also given a Tabular Column of the details so furnished in Form 3 of the Patents Rules, 2003.

36. In reply to the counter statement at paragraph 37, the applicant had stated as follows:

> "With reference to paragraphs 106 to 110 of the counter statement it is stated that the contents therein are incorrect and wholly denied."

Nothing more had been stated in the reply to the counter statement. There are no pleadings to show why and how the averments made in the counter statement regarding compliance with Section 8 are incorrect. Therefore it is on the basis of these pleadings that the matter came up for hearing.

37. In M.P.4 of 2013, the applicant filed additional documents as Exhibits EA1 to EA13. The affidavit sworn by one Ramanathan Sankaran does not say how

purpose and in effect, obliterate it from the statute book, should be eschewed. If more than one construction is possible, that which preserves its workability and efficacy is to be preferred to the one which render it otiose or sterile"

43. The Ayyangar Report makes it clear that the purpose for introducing this provision was to ensure that it would be an advantage for our Patent Office to know the objections raised by the patent offices outside India regarding the patentablity of the invention and the amendment if any made or to be made. It also says that it would be of great use for the proper examination to know if the invention was anticipated. In the Hindustan Lever case we had held that it was in order to secure disclosure of the relevant information regarding the foreign applications that the Ayyangar Report recommended that failure to disclose would be a ground for challenge.

44. In Chemtura Corporation vs Union of India the Delhi High Court said, "*It is not possible to accept the submission, made by referring to the Halsbury's Laws of England that since the omission to furnish particulars is not serious enough to affect the grant of the patent; it did not impinge on its validity. Section 64 (1) (j) and (m) indicate to the contrary. Further under Section 43 (1) (b) a patent can be granted only when the application has been found not to be contrary to any provision of the Act. It cannot be said that the omission to comply with the requirement of Section 8 (2) was not serious enough to affect the decision of the Controller to grant the patent to the Plaintiff. The information, if provided, would have enlightened the Controller of the objections raised by the US patent office and the extent to which the Plaintiff had to limit its claims to the torus shape of the compression spring, which was a key feature of the subject device.*"

45. The object of this provision is to ensure disclosure. We will adopt that construction which is to advance the object. This section has been introduced to make sure that the person who is given an exclusive monopoly is candid and fair in his conduct and discloses all the official actions regarding patent filing outside India in respect of the same or substantially the same inventions. So we cannot adopt a construction which relieves the patentee of this duty.

given. Nothing more is stated. In the petition filed for receiving additional documents, the affidavit filed by the applicant merely lists the documents were downloaded. We do not think that is sufficient. We understand that the S.8 ground is being raised regularly only after the Delhi High Court's Chemtura judgment and the IPAB orders mentioned above. The Examiners have not given this provision the attention that it deserves. But these proceedings have to be conducted correctly, consistently and fairly. Patentees must comply with S.8 (1) provision however inconvenient it is.

52. In the present case we are rejecting the S.8 objection only because the applicant has not made out the grounds of attack by stating the facts. A bald statement will not suffice by merely reproducing the language of the section. The facts have to be pleaded and the applicant must state how the particular undisclosed application was for the same or substantially the same invention. It is also not enough to just file the documents along with an affidavit. The least that the deponent shall state is how it is the same or substantially the same. In this case the respondent had stated in the counter statement that the two documents filed were in compliance of the provision. In the reply the applicant had merely denied it, without saying why it was not in full compliance. That is not enough. We have indicated the principles behind a S.8 objection, how it should be raised, defended and decided. For the above reasons, we hold that violation of Section 8 has not been proved by the applicant and this ground is rejected.

Section 3(d) :

53. As regards Section 3 (d) objection, the case of the applicant is that the Claimed compound is a derivative of prior art compounds, and that there is no data in the alleged specification to show that the claimed compound differs significantly having regard to the efficacy of the known compound of prior art especially those Exhibit-1 and Exhibit-2. It was submitted that the respondent had admitted the prior arts in Exhibit 1 and Exhibit 2, but has failed to provide comparative data nor had they shown any enhancement in efficacy and the therapeutic effect. The respondent submitted that this is a new chemical entity

consider if it is necessary to be filed. Not every document which is downloaded is worthy of being "uploaded" in to the litigation.

50. When we look at the Ayyangar Committee Report it indicates that the object behind introducing S.8 is that the applicant should disclose all foreign applications so that the examiner here may know if it contains obviousness objections or any amendments and so on. The application outside India must be for the same invention or for substantially the same invention. The Ayyangar Committee Report also speaks of anticipation coming to light if the disclosure is made. So the Ayyangar Committee Report is clearly talking of the same invention or almost the same invention. The subject matter of the invention must be the same or almost the same. If there is a divisional, then according to the Indian law there is a plurality of inventions, which means there are more than one invention. The applicant may argue that the divisional application is not"the same or substantially the same invention". There are no guidelines for the office to construe these words. In view of what is stated in the Ayyangar Committee Report, we are of the opinion if in any of the foreign offices the patentee had made a division or was required to make a division, in respect of the same or substantially the same invention or had amended or was required to amend in respect of the same invention or substantially the same invention, such information regarding division or amendment would also be information required to be furnished under Section 8. It is therefore necessary that the person seeking revocation demonstrates that the foreign application the details of which were not furnished, was for the same or the substantially the same application. It is true that the IPAB is not bound by the rules of the CPC, and it is enough if the procedure is guided by the principles of natural justice. If the opponent does not know what the case against him is, then there is a clear violation of natural justice which implies procedural fairness. The strict technical requirements may not be insisted upon e.g. witnesses do not appear before us. But an issue will still have to be pleaded and proved.

51. In this case in the Revocation application, the applicant has merely stated that S.8 has not been complied with and foreign filing particulars have not been

and the applicant will have to show and prove that Section 3 (d) bars the grant and that it is the mere discovery of a new form of a known substance. The applicant has contented himself with saying that the prior arts in Exhibit-1 and Exhibit-2 is known compound and the invention is a mere discovery of a known form.

54. The respondent submitted that there are no pleadings in this regard and that the claimed compound is a New Chemical Entity. According to the respondent the Annexure –A to the FER comparative data on selectivity and kinase inhibitory values during the patent prosecution was provided, and the patent specification provides a long range of values in Table 1&2 in relation to the kinase inhibitory values of Lapatinib. .According to the respondent the claimed compound is not a derivative of a known substance,

55. In the Novartis case decided by the Supreme Court, it was held that the Section 3 (d) sets up a secondary tier of qualifying standards for chemical substance/Pharmaceutical in order to leave the door open for true and genuine invention. The Supreme Court held that Section 3 (d) places the invention threshold further higher. The Explanation to Section 3 (d) says that for the purpose of this clause "salts esters, ethers..... And other derivatives of known substance shall be considered to be the same substance." In the earlier Novartis case decided by the Madras High Court, it was held " Therefore when the Explanation to the amended section says that any derivatives must differ significantly in properties with regard to efficacy, it only means that the derivatives should contain such properties which are significantly different with regard to efficacy to the substance from which the derivative is made. Therefore in sum and substance what the amended section with the Explanation prescribes is the test to decide whether the discovery is an invention or not is that the Patent applicant should show the discovery has resulted in the enhancement of the known efficacy of that substance and if the discovery is nothing other than the derivative of a known substance, then, it must be shown that the properties in the derivatives differ significantly with regard to efficacy"

inhibitory activities much. It was submitted that out of 6 anti-cancer drugs Erlotinib, Varlitnib Gefitinib, Dasatinib have the same primary pharmacophore as Lapatinib. It was further submitted that out of these ERlotinib and Gefitinib are prior art and both these have polar bulky groups at 6 and 7 positions which enables solubility and other druggable properties. For the alteration of said structure, bulky groups could be used in positions 6 and 7 but not in position 3'. Then Ex C clearly shows that position -6 and -7 have a role in solubility. The third ring can be fused with bicyclic quinazoline system without loss of binding affinity. According to the applicant, Ex. C shows that pyridopyrimidine show similar Structure Activity Relationship to quinazoline, so those teachings may be extrapolated to Quinazoline, since both quinazoline and pyridopyrimidine have similar activities. The applicant relied upon the expert affidavits of Dr. Surjith Sinha. The most effective substitution of the 3- substituted Pyroloquinazoline ring series included Alkylamino quinazoline series of compounds of 4 to 9 of the said documents. Therefore according to the expert, based on the Structure Activity Relationship (SAR) study, the skilled worker looking for further compounds against EGFR activity is likely to modify R-Group attached to the Quinazoline ring at position 6. From the SAR study, it will be known that this must be analogous in character. It was submitted that the primary Pharmocophore was known from Exhibit-A and Exhibit-C. EXs A, B, & C teach the importance of 4- Anilinoquinazoline. The applicant also referred to the slides shown by the respondents in connection with ORA/22/2011/PT/KOL relating this Anti Cancer molecular structures of which the five have the same primary Pharmocophore as that of Lapatinib and all have activities against EGFR out of which Erlotinib and Gefitinib are prior art. But they have polar drug group and for alteration of the said structure, the bulk groups would be used in position 6- and 7- as cited in Exhibit-E. The skilled worker would look for Compounds with substitution in these positions keeping in mind the importance of Furan.

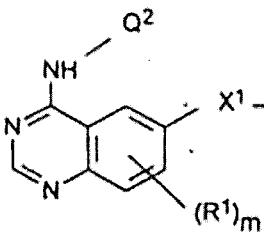
60. Mr. Sinha's affidavit shows that the most effective substitution of the 3-substituted Pyrolominoline Ring series included Alkylamine series of compounds 4 to 9 of Exhibit-C. The extract in Exhibit-C also teaches the structure activity

independently saturated, unsaturated or aromatic and contain only carbon and hydrogen; halo includes fluoro.

62. If all the above substitutions are incorporated then a structure may be arrived at which is the structure of the invention excluding the methane sulphonyl 6 substitution. Then the applicant says that since Ex 1 says at page 12 that R1 may preferably be selected as furan and if furan is substituted then one would arrive at the structural formula which would be identical to the Invention except for the further substitution on the 5-position of the furan. The applicant admits that the Exhibit 1 does not teach a fused phenyl ring nor the sulphonyl group on the alkyl amine substituent.

So we go to

Exhibit 2 – WO 97/30034.



wherein X' is a direct link or a group of the formula CO, $C(R^2)_2$ $CH(OR^2)$, $C(R^2)_2$-$C(R^2)_2$ $C(R^2)$, C=C, CH(CN), O, S, SO, SO 0, S, SO_2, $N(R^2)$, $CON(R^2)$, $SO_2N(R^2)$, $N(R^2)CO$, $N(R^2)SO2$, $OC(R^2)$, $SC(R^2)2$, $N(R^2)C(R^2)2$, $C(R^2)2O$,$C(R^2)2S$ or $C(R^2)2N(R^2)$, and each R2 is independently hydrogen or (1-4C)alkyl;

wherein Q' is phenyl, naphthyl or a 5- or 6-membered heteroaryl moiety containing up to 3 heteroatoms selected from oxygen, nitrogen and sulphur, which heterocyclic moiety is a single ring or is fused to a benzo ring, and Q' optionally bears up to 3 substituents selected from halogeno, hydroxy, ammo, trifluoromethoxy, trifluoromethyl, cyano, nitro, carboxy, carbamoyl, (l-4C) alkoxycarbonyl, (l-4C)alkyl, (l-4C)alkoxy, (2-4C)alkenyloxy, (2-4C) alkynyloxy, (l-3C)aikylenedioxy, (l-4C)alkylamino, di-[(l-4C)alkyl]amino, pyrrolidin-1-yl, piperidino, 1-yl, piperidino, morpholino, piperazin-1-yl, 4-(l-4C)alkylpiperazin-l-yl, (2-4C)alkanoylamino, N-(1-4C)alkyicarbamoyl, N,N-di-[(l-

pharmacophore is known to be a dual inhibitor, the substituents do not contribute to the inventiveness of the patent. According to him, Exhibit-A to C have been mentioned in Sinha-I to show the general knowledge in the field of quinazoline derivatives and with these background teachings chosen the specific substitutents from Exhibits 1 and 2 is not wild or beyond the purview of skilled worker. So in view of Ex 1 and 2 in the back ground of the other exhibits, the invention is obvious.

69. The respondent countered the obviousness argument. Mr.Praveen Anand submitted that Lapatinib is a new chemical entity it has chemical structure that can be split into three parts for convenience.

> A) The Quinazoline Pharmocophore
>
> B) At the 4-position , (A) is substituted with a 3' chloro-aniline and the phenyl ring of the aniline is substituted by a 3-fluoro-benzyloxy group at the 4'position
>
> C) At the 6-position (A) is substituted with a 2-furyl ring system having a further substitution on the 5-position of the furan with methyl-sulfonyl-ehtyl-amino-methyl.

70. *The combination of distinct structural characteristics has not been taught* by any prior document. The prior documents have provided a number of choices and except by hindsight, this Lapatanib Compound could not have been arrived at nor predicted. According to the respondent, the specific substitution on the Aniline ring system gives specific advantages. According to him, Dr. Dirk Heerding's affidavit shows that each different element contributes to optimal cellular activity. The complete specification discloses Biological data Lapatinib and it has been tested for Protein kinase inhibitor activities in substrate phosphorylation assays and cell proliferation assays. According to the respondent, the applicant's own pleadings and affidavit speaks of the Complexity of Oncology, the Selectivity of Protein Tyrosine Kinase Mechanism ,described the importance of position of Atoms and substituents on Pharmocophore. He referred to the observations of the Delhi High Court in **ROCHE Vs. CIPLA** which observed that,

clearly not small. In fact the authors .....go on to say that increasing the bulk at the 6- and/or 7-position 'has been shown to be disadvantageous in the quinazoline series"

75. Regarding Ex C Heerding says that it only describes enzyme inhibition of EGFR and makes no mention of c-erbB 2 or overall kinase inhibiting activity and while discussing the bicyclic quinazolines it says the poor aqueous solubility of these compounds is major drawback for further development. He therefore concludes that the success of lapatinib would clearly distinguish it from these compounds mentioned in Ex.C. He has also explained why furan cannot mimic ATP. .

76. The respondent has filed the affidavit of Mr. Kaizad Hazari to prove the secondary considerations. He has spoken of the great commercial success of Lapatinib which is the active ingredient in the marketed product TYKERB® and TYVERB®

77. The respondent has also filed a second affidavit of Dr. A. Heerding to meet Sinha II. With regard to figure 2 in Sinha II, Heerding says that instead of looking at enzyme activity, one should consider the structurally distinct compound which are compound specific activity data disclosed in Exhibit-E contain a 'benzyloxy group' substitution at the 4-position in the anilio ring. He has stated the persons skilled in the art would know that to achieve potency against an isolated enzyme target is but one aspect to consider within the ambit of small molecule drug discovery. According to him, there is nothing in disclosure of Exhibit-F which would motivate a person skilled in the art to arrive at the specific group substitution claimed in the Patent without the benefit of hindsight knowledge. According to him, the Exhibit-F does not teach a furan ring substituted at the 6-position of the quinazoline ring and being further substituted at the 5-position by a methylsulphonylethylaminomethyl group. As regards, the example 120 which according to the applicants expert is a compound that a person skilled in the art would use as a starting point for the further development. This expert says that Exhibit 120 contains a methoxy group at the 3—position of

86. We will now consider the issue of obviousness. We have already explained how the applicant had built his case of the teachings from Exs 1 & 2. There are other documents which were referred to by the applicant's experts.

Ex A concludes that the SAR in the 4-(phenylamino) quinazoline class of EGFR tyrosine kinase inhibitors indicate a requirement for small lipophilic electron withdrawing groups at the 3-position on the aniline and for electron-donating groups at the 6 and 7 positions of the quinazoline and a possible more specific requirement for high electron density in the vicinity of the 8-position of the quinazoline ring. It says that 4-(phenylamino) quinazoline is the primary pharmacophore for this class of EGFR inhibitors. In the two series explored in this it was found that the benzylamino compounds were less effective than the corresponding (3-bromophenyl) amino derivatives.

Ex B shows that it explores the effects of incorporating the electron donating amino substituents into a fused 5- or 6- membered ring which is part of the aromatic system. It deals with the synthesis. It mentions whether protected amino functions without increasing steric bulk would increase the potency; this is because this has been shown to be disadvantageous in the quinazoline series. It also says that the results obtained were consistent with SAR studies previously developed for the 4-[(3-bromophenyl)amino]quinazolines which suggested that small electron donating substituents at the 6- and 7- positions were desirable for high potency as exemplified by the 6,7-dimethoxy derivative7.

Ex C. refers to Ex A and B and says that the poor aqueous solubitlty of the compounds 2a and 3a is a major drawback to their further development. The known quinazolines were converted to thiones, then methylated to form thioethers, these were alkylated and the resulting products were reacted with 3-bromoaniline to give the desired aniline derivatives. This was found to be a significantly superior to the previously reported route to these compounds via the 4-chloroquinazolines which give lower yields due to poorer solubility. This exhibit discusses a possible binding model for these inhibitors on the EGFR enzyme. It noted that both previous SAR for the general class of 4-(phenylamino)quinazolines and molecular modelling studies suggested significant bulk tolerance at the 6 and 7 position. It studies N-substituted pyrazolo and pyrrolo compound listed in Table 2 to probe the extent of bulk tolerance and found that the 3-substituted pyrrolo series was over all the most effective. But it also records that "no clear trend was present.". Only one binding mode was found that satisfied all the SAR data" and which had no major unfavourable steric interactions. The results showed that N-1 and C-3 substituted pyrroloquinazolines in particular retain high potency against the enzyme. It identified a possible binding mode for this class of tricyclic inhibitors, where the *pyrrolo* or *pyrazolo* ring occupies the *entrance of the ATP binding pocket of the of the enzyme with the nitrogen* located at the bottom of the cleft and the C-3 position pointing towards a pocket corresponding to the ribose binding site of ATP. A similar approach had been reportedly made to the dianilinopthalimide EGFR inhibitor CGP 52411 , but it was different from the one which was published for a series of related 4-(phenylamino)pyrrolopyrimidines and that the extensive SAR data presented in Ex C excluded that binding mode.

Ex D is prior to ex A and this speaks of 4-(3-chloroanilino)quinazoline as a novel and potent lead in the search for tyrosine kinase inhibitor. It was found to act as an ATP analogue but there were differences too. **This is part of the bibliography of the above three Exhibits and yet the subsequent prior arts had chosen bromine.**

13. Hence, these appeals.

14. Mr. Asthana, learned Counsel for the appellant, has canvassed these points:

(i) The method and means claimed by the respondent in Patent No. 46368-51 did not involve any inventive step or novelty.

(ii) The Appellate. Bench of the High Court was in error in holding that the supporting of an article in a lathe by the pressure of the point of a pointed tailstock constituted the novelty of the invention, inasmuch as it overlooked the fact that the scope of the patented invention in the "claims" in the complete specification does not contain an assertion of novelty of the pointed tailstock, but rather it specifically says that the pressure spindle may be pointed or blunt".

(iii) The Division Bench of the High Court having held that a tailstock was used for holding the article to be worked upon and that if a pointed tailstock was used always for a very long time prior to the patent for holding an article in metal spinning by pressure, contradicted itself in concluding that holding an article by the pressure of a pointed tailstock was neither used nor known. The High Court thus made out a new case for the paintiff, which had not been alleged either in the specifications in the subject of the patent or in the pleading.

(iv) The alleged inventor, Purshottam Dass, though he attended the Court on some dates of hearing, did not dare to appear in the witness-box, nor was he called as a witness in the case by the plaintiff to explain in what way, if at all, the method and means patented by the plaintiff was a novelty or involved an inventive step. The failure to examine Purshottam Dass who was a partner of the plaintiff-firm, would give rise to an inference adverse to the plaintiff.

15. As against this, Mr. Mehta, appearing for the respondent, submits that whether the process got patented by the respondent involves a method of new manufacture or improvement, is one purely of fact, and should not, as a matter of practice, be disturbed by this Court. Even in cases of doubt-proceeds the argument-the Court should uphold the parent. It is submitted that a patent is granted by the Controller after due inquiry and publication and, unless the contrary is proved, should be presumed to have been duly granted. In the instant case, it is urged, that presumption is stronger because the trial Judge as well as the Appellate Bench of the High Court have concurrently held that the process patented had utility.

16. Before dealing with these contentions let us have a general idea of the object, the relevant provisions and the scheme of the Act.

17. The object of Patent Law is to encourage scientific research, new technology and industrial progress. Grant of exclusive privilege to own, use or sell the method or the product patented for a limited period, stimulates new inventions of commercial utility. The price of the grant of the monopoly is the disclosure of the invention at the Patent Office, which after the expiry of the fixed period of the monopoly, passes into the public domain.

18. The fundamental principle of Patent Law is that a patent is granted only for an invention which must be new and useful. That is to say, it must have novelty and utility. It is essential for the validity of a patent that it must be the inventor's own discovery as opposed to mere verification of what was, already known before the date of the patent.

19. " 'Invention' means any manner of new manufacture and includes an improvement and an allied invention". [Section 2(8) of 1911 Act]. It is to be noted that unlike the Patents Act 1970, the Act of 1911 does not specify the requirement of being useful in the definition of 'invention'. But Courts have always taken the view that a patentable invention, apart from being a new manufacture, must also be useful. The foundation for this judicial interpretation is to be found in the fact that Section 26(1)(f) of the 1911 Act recognises lack of utility as one of the grounds on which a patent can be revoked.

20. 'Manufacture' according to the definition of the term in Section 2(11) of the Act, includes not only "any art, process or manner of providing, preparing or making an article" but also "any article prepared or produced by the manufacture".

21. It is important to bear in mind that in order to be patentable an improvement on something known before or a combination of different matters already known, should be something more than a mere workshop improvement; and must independently satisfy the test of invention or an 'inventive step'. To be patentable the improvement or the combination must produce a new result, or a new article or a better or cheaper article than before. The combination of old known integers may be so combined that by their working inter relation they produce a new process or improved result. Mere collocation of more than one integers or things, not involving the exercise of any inventive faculty, does not qualify for the grant of a patent. 'It is not enough', said Lord Davey in Rickmann v. Thierry (1896) 14 Pat. Ca. 105 'that the purpose is new or that there is novelty in the application, so that the article produced is in that sense new, but there must be novelty in the mode of application. By that, I understand that in adopting the old contrivance to the new purpose, there must be difficulties to be overcome, requiring what is called invention, or there must be some ingenuity in the mode of making the adoption'. As Cotton L.J. put in Blackey v. Latham (1888) 6 Pat. Ca. 184, to be new in the patent sense, the novelty must show invention". In other words, in order to be patentable, the new subject matter must involve 'invention' over what is old. Determination of this question, which in reality is a crucial test, has been one of the most difficult aspects of Patent Law, and has led to considerable conflict of judicial opinion.

22. This aspect of the law relating to patentable inventions, as prevailing in Britain, has been neatly summed up in Encyclopaedia Britannica, Vol. 17, page 453. Since in India, also, the law on the subject is substantially the same, it will be profitable to extract the same hereunder:

23. "A patent can be granted only for 'manner of new manufacture' and although an invention may be 'new' and relate to a 'manner of manufacture' it is not necessarily a 'manner of new manufacture'-it may be only a normal development of an existing manufacture. It is a necessary qualification of a craftsman that he should have the knowledge and ability to vary his methods to meet the task before him-a tailor must cut his cloth to suit the fashion of the day-and any monopoly that would interfere with the craftsman's use of his skill and knowledge would be intolerable.

24. "A patentable invention, therefore, must involve something which is outside the probable capacity of a craftsman-which is expressed by saying it must have 'subject matter' or involve an 'inventive step'. Novelty and subject matter are obviously closely allied.... Although these issues must be pleaded separately, both are invariably raised by a defendant, and in fact 'subject matter' is the crucial test, for which they may well be novelty not involving an 'inventive step', it is hard to conceive how there can be an 'inventive step' without novelty.

25. Whether an alleged invention involves novelty and an 'inventive step', is a mixed question of law and fact, depending largely on the circumstances

37. The trial Judge then found that mere addition of a bracket did not amount to a novelty. He further observed that Circumstance VI was of a neutral character because it could not be definitely held that the work had been suspended due to a defect in the contrivance which was then in use. It might well be due to labour trouble as the witnesses examined by the appellant had deposed. From Circumstances I, II, III and IV, inspection of the machines (Ex. CC and Ex. XVI), produced by the appellant and the other material on record, the trial Court found both issue, set out above, against the patentee-firm.

38. We have ourselves examined the evidence on record with the aid of the learned Counsel for the parties, and have ourselves compared the machines (Ex. CC and Ex. XVI) which were produced before us. We do not want to rehash the evidence. Suffice it to say, we do not find that any piece of evidence has been misread, overlooked or omitted from consideration. The view taken by the trial Court was quite reasonable and entitled to due weight. In our opinion, it did not suffer from any infirmity or serious flaw which would have warranted interference by the Appellate Bench.

39. Be that as it may, from the discussion that follows, the conclusion is inescapable that the invention got patented by M/s. Hindustan Metal Industries, respondent herein, was neither a manner of new manufacture, nor a distinctive Improvement on the old contrivance involving any novelty or inventive step having regard to what was already known and practised in the country for a long time before 1951.

40. Let us now have a look at the invention described in the 'specifications' and the 'claims' in the patent in question. In the provisional specification, the title or subject of the patent is described as follows:

> Method of end means for mounting metallic utensils or the like on lathe for turning them before polishing.

The title of the patent mentioned in the complete specification is as under:

41. "Means for holding utensils for turning purposes". Then follows a description of the old method of manufacture, and it is stated:

> This invention relates to means for mounting metallic utensils for the purpose of turning the same before polishing and deals particularly, though not exclusively, with utensils of the type which cannot be conveniently and directly gripped by the jaws of the chucks and where the utensil tends to slip off the chuck and a certain amount of risk is involved in applying the tool in the turning operation.

Thereafter, the new method of manufacture is described with reference to three figures or sketches. The crucial part of this specification runs as below:

> According to a preferred feature of this invention the pressure end of the pressure spindle is rotatably mounted and for this purpose it comprises an independent piece engaged by a hollowed end in a spindle, said hollowed end being preferably fitted with ball bearings to enable the said independent piece to revolve with friction when it is in contactual relationship with the utensil. This independent piece may have a forward pointed end *or said forward end may be a blunt end*, the pointed end or the blunt end as the case may be, *being firmly held against the utensil. The blunt end may, e.g. be of 1 cm. in diameter.*
>
> (Emphasis added)

Then, at the foot of the complete specification, 9 Claims are set out, which read as under:

> 1. Means for mounting and holding metal utensils more particularly of the shallow type for the purpose of turning before polishing comprising a shaft or spindle carrying at its one end and adapter having a face corresponding to the shape of the article or utensil to be held, the utensil being maintained in held position by an independent pressure on the utensil when seated on the adapter.
>
> 2. Means for the purpose herein setforth end as claimed in Claim I in which the pressure spindle is adapted to pass through a guide block and has a regulating handle at the outer end the inner end of the spindle pressing against the utensil, means being provided to set and lock the pressure spindle in any desired position.
>
> 3. Means as claimed in Claims 1 and 2 in which the pressure end of the pressure spindle is rotatably mounted and for this purpose it comprises an independent piece engaged by a hollowed end in a spindle, said hollowed and end being preferably fitted with ball bearings to enable the said independent piece to revolve with friction when it is in contractual relationship with the utensil.
>
> 4. Means as claimed in previous claims in which the pressing or inner end of the pressure spindle is pointed or blunt.
>
> 5. Means as claimed in Claim 1 in which the pressure spindle passes through a bracket or the like end said bracket may comprise the arm of an angle shaped bracket whose other arm may be fixed to a stand or the like.
>
> 6. Means as claimed in Claims 1, 2 & 3 in which the pressing end of the spindle may be a fixed end or a revolving end.
>
> 7. Means as claimed in Claim 1 in which the adapter is shaped to seat the utensil.
>
> 8. Means as claimed in Claim 1 in which the adapter is made of wood or any other material.
>
> 9. Means for holding the utensil for the purpose herein setforth and substantially as described and illustrated and utensils so turned.

42. As pointed out in Arnold v. Bradbury (1871) 6 Ch. A. 706 the proper way to construe a specification is not to read the claims first and then see what the full description of the invention is, but first to read the description of the invention, in order that the mind may be prepared for what it is, that the invention is to be claimed, for the patentee cannot claim more than he desires to patent. In Parkinson v. Simon (1894) 11 R.P.C. 483 Lord Esher M.R. enunciated that as far as possible the claims must be so construed as to give an effective meaning to each of them, but the specification and the claims must be looked at and construed together.

43. The learned trial Judge precisely followed this method of construction. He first construed and considered the description of the invention in the provisional and complete specification, and then dealt with each of the claims, individually. Thereafter, he considered the claims and specification as a whole, in the light of the evidence on record.

44. With regard to Claim No. 1, the learned Judge commented:

> The pressure spindle in a lathe is a well known contrivance. Pressure spindle or a tailstock was in use in this industry much before 1951. So neither the means for mounting and holding metallic utensil nor the independent pressure spindle can be said to be an invention.

45. In Claims 3, 4, 6 and 7, also, he found no novelty or inventive step having regard to the fact that these were well-known and were in use long before 1951. Regarding Claim No. 5, he found that the use of the bracket was new; but the end bracket can hardly be said to be an invention.

46. The learned trial Judge then noted that Purshottam, who was stated to be the inventor, and, as such, was the best person to describe the invention, did not appear in the witness-box, though, as admitted by Sotam Singh (D.W. 3), Purshottam had attended on some dates of hearing. Sotam Singh tried to explain Purshottam's disappearance from the Court without appearing in the witness-box, by saying that he had gone away due to illness. The learned Judge found this explanation unsatisfactory and rejected it-and in our opinion rightly-with the remark that recording of evidence lasted for several days and it was not difficult to secure Purshottam's attendance. Apart from being the best Informed person about the matter in issue, Purshottam was not a stranger. He was a partner of the patentee firm and a brother of Sotam Singh (D.W. 3). He was the best informed person who might have answered the charge of lack of novelty leveled by the opponent side, by explaining what was the novelty of the alleged invention and how and after, what research, if any, he made this alleged 'discovery'. Being a partner of the respondent-firm and personally knowing all the circumstances of the case, it was his duty as well as of the respondent-firm, to examine him as a witness so that the story of the particular invention being a new manufacture or improvement involving novelty, could, in all its aspects, be subjected to cross-examination. By keeping Purshottam away from the witness-box, the respondent-firm, therefore, took the heavy risk of the trial Court accepting the charge of lack of novelty made by the appellant herein.

47. The trial Judge further noted that the witnesses examined by the patentee-firm had given a garbled, account as to the patented invention. The witnesses were speaking with discordant voices as to the alleged inventive step involved in the patent. Mata Parashad (D.W. 2) stated the invention lies in fixing the Charhi on the pointer on the same iron base. In variance with it, Sotam Singh (D.W. 3) said that his patent covers three factors-the side supporting iron plate, the pointer with the nut, and the adapter. In this connection, we may add that Lakshmi Dass (D.W. 1) another witness examined by the patentee-firm, had admitted that machines like Ex. XVI (which was the machine produced by Bhagwati Prasad and was alleged by the patentee to be an imitation of the patented one), were in use even before 1951-52.

48. After a critical appraisal of the evidence produced by the parties the learned trial Judge found that manufacturers in the industry have been using adapters of various sizes and shapes to suit the article handled; that tailstock or pointer was also in use; that it was a common practice to fix the headstock and tailstock permanently to a single framework. In regard to the use of the bracket or angle in Ex. CC, the learned Judge held that although it was new, it was not a new idea, and concluded: "There is hardly any difference between fixing the headstock end tailstock to a common base (as the case in the machine Ex. XVI produced by Bhagwati Prasad) or fixing the tailstock in a bracket which is connected with the framework on which the headstock is fixed. Whether we consider Ex. CC as a whole or look at the invention in its separate parts, we do not find any novelty in the alleged invention.

49. In our opinion, the findings of the learned trial Judge to the effect that the patent is not a manner of new manufacture or improvement, nor does it involve any inventive step having regard to what was known or used prior to the date of patent, should not have been lightly disturbed by the Appellate Bench. These were, as already observed, largely findings of fact, based on appreciation of the evidence of witnesses and the trial Court had the initial advantage of observing their demeanour in the witness-box. Moreover, the approach adopted by the trial Court was quite in conformity with the basic principles on the subject, noticed in an earlier part of this judgment. The patented machine is merely an application of an old invention, known for decades before 1951, for the traditional purpose of scraping and turning utensils, with a slight change in the mode of application, which is no more than a 'Workshop improvement', a normal development of an existing manner of manufacture not involving something novel which would be outside the probable capacity of a craftsman. The alleged discovery does not lie outside the Track of what was known before. It would have been obvious to any skilled worker in the field, in the state of knowledge existing at the date of patent, of what was publicly known or practised before about this process, that the claim in question viz., mere addition of a lever and bracket did not make the invention the subject of the claim concerned. There has been no substantial exercise of the inventive power or innovative faculty. There is no evidence that the patented machine is the result of any research, independent thought, ingenuity and skill. Indeed, Sotam Singh frankly admitted that he did not know whether Purshottam had made any research or any experiments to produce this combination. Nor does this combination of old integers involve any novelty. Thus judged objectively, by the tests suggested by authorities, the patent in question lacked novelty and invention.

50. We will close the discussion of trial Court's Judgment by referring to a decision of the House of Lords in Harwood v. Great Northern Dy. Co. (1864) 11 H.L.C. 654 as, in principle, that case is analogous to the one before us. In that case, a person took out a patent, which he thus described: "My invention consists in forming a recess or groove in one or both sides of each fish (plate), so as to reduce the quantity of metal at that part, and to be adapted to receive the square heads of the bolts, which are thus prevented from turning round when the nuts are screwed on." His claim was "for constructing fishes for connecting the rails of railways, with a groove adapted for receiving the ends of the bolts employed for securing such fishes; and the application of such fishes for connecting the ends of railways in manner hereinbefore described. The constructing of fish joints for connecting the rails of railways with grooved fishes fitted to the sides of the rails, and secured to them by bolts or nuts, or rivets, and having projecting wings firmly secured to and resting upon the sleeper's or bearers, so as to support the rails by their sides and upper flanges." It was proved that before the date of his patent, fish-joints had been used to connect and strengthen the rails of railways. In some cases, the fishes were flat pieces of iron, with round holes for bolts, the heads of the bolts being held in their places by separate means. In others the extreme ends of the holes were made square and the bolt-heads square, to put into them, and, in some, square recesses were made in the flat pieces of iron for the same purpose; but, till the time of the patent, fishes for connecting the railways had never been made with a groove in their lateral surfaces so as to receive the square heads of the bolts, and render the fish lighter for equal strength, or stronger for an equal weight of metal.

51. On these facts, it was held that what was claimed as an invention was not a good ground to sustain a patent. Blackburn L.J., succinctly summed up the rule of the decision, thus:

> In order to bring the subject-matter of a patent within this exception, there must be invention so applied as to produce a practical result. And we quite agree with the Court of Exchequer Chamber that a mere application of an old contrivance in the old way to an analogous subject, without any novelty or invention in the mode of applying such old contrivance to the new purpose, is not a valid subject-matter of a patent.

52. The above enunciation squarely applies to the facts of the present case. We will now consider the judgment of the Appellate Bench, which, it may be recalled, has found that the novelty and invention of the patent lay in "the method of holding an article by the pressure of a point of a pointed tailstock (which) was neither used or known.

53. This finding, if we may say so with respect, is inconsistent with the Appellate Bench's own findings Nos. (5) and (6), the consolidated substance of which is to the affect, that lathe consisting of a headstock and a tailstock and its uses for centering the article, holding along work by a pointed tailstock by pivoting it and holding an article in metal spinning by the pressure of a pad attached to the tailstock, have been well known for a long time. Finding No. (7) of the Appellate Bench goes beyond the scope of the specifications and claims made by the patentee, himself, in the subject of the patent. From a perusal of the specification and the 'claims', extracted earlier, it is evident that there is no assertion therein, of novelty for the pointed tailstock; rather it is stated that "the pressure spindle may be pointed or blunt." Furthermore, this_ finding of the Appellate Bench stands in contradiction to what Sotam Singh (D.W. 3) patentee himself has admitted in the witness-box. In cross-examination, Sotam Singh (D.W. 3) said: "I am not using any other pointer than that of Ex. CC. I never used pointer of any other type. I have not used any rotating pointer either at Banaras or at Mirzapur.... If any body uses a wooden adapter in a chuck and does scraping work on a Katore in such a wooden chuck without a pointer, there would be no infringement of my patent.... I conducted no experiments before obtaining the patent. I do not know what kind of experiments Purshottam carried out. I have got no apparatus for scraping utensils except like Ex. CC." Sotam Singh further admitted that machines like Ex. XVI (the one which was produced by the appellant and is said to infringe the patent of the respondent-firm) are sold in the market and one can purchase a pointer like Ex. XI in a lathe.

54. In the face of the admissions of the representative of the patentee, it was not possible for the Court to work out Finding No. (7) on its own, without allowing itself to get into the unenviable position of appearing more Royalist than the King. We have ourselves examined and compared the machines (Ex. CC and Ex. XVI). We find that the tailstock in each of these machines has blunt end of slightly above 1 cm. in diameter. It may be re-emphasised that according to Sotam Singh, himself, his patented machine has no other end of tailstock excepting of the (bunt) type in Ex. CC.

55. For all the reasons aforesaid, we have no hesitation in holding that the learned Judges of the Appellate Bench were in error in reversing the findings of the trial Court on Issues 1 and 1-A. The learned trial Judge was right in holding that the patented machine was neither a manner of new manufacture or novel improvement, nor did it involve any inventive step, having regard to what was publicly known or used at the date of the patent. The grant of the patent in question was therefore, invalid and was liable to be revoked on the grounds mentioned in Clauses (d) and (e) of Section 26(1) of the Act.

56. Before parting with this judgment, we will like to dispose of another argument of Mr. Mehta. The argument is that since the Courts below have concurrently held that the invention had utility, the patent should be sustained. We are unable to accept this contention. As pointed out already, the crucial test of the validity of a patent is whether it involves novelty and an 'inventive step' ? That test goes against the patentee.

57. In the result, the appeals are allowed, the judgment of the Appellate Bench is set aside and that of the trial Court restored. In the peculiar circumstances of the case, the parties are left to bear their own costs throughout.

EXHIBIT P4

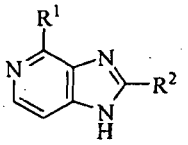
FIELD OF THE INVENTION

The present invention relates to development of new heterocyclic hybrids consisting of Thiazolidin-3-yl-Imidazo-pyridine-3-carboxamide as per Formula-I. More specifically, the present invention relates to strategically designed Thiazolidin-3-yl-Imidazo-pyridine-3-carboxamide of Formula-I as antimalarial agent. Formulas (IV), (III), and (II) are condensed together, optimizing the in-process isolation of intermediate compounds. Further the present invention also relates to novel process for preparing the Thiazolidin-3-yl-Imidazo-pyridine-3-carboxamides thereof. Furthermore, the present invention relates to the chemical composition of heterocyclic hybrids of Formula-I, demonstrating molecular docking to evaluate higher inhibitory potency against *Plasmodium falciparum* thereof.

BACKGROUND OF THE INVENTION

Despite efforts to eradicate the malarial disease in the tropical century, infection remains a major global problem. According to the World Health Organization's most recent global malaria report 2021, there are an estimated 241 million malaria infections and 627,000 malaria deaths in 2020, that equates to 14 million more cases in 2020 than in 2019, and 69000 more deaths. *Plasmodium falciparum and Plasmodium vivax* are the two species spread through the bites of infected female Anopheles mosquitos, with the former being lethal. Malaria is particularly prevalent in Africa, where children under five account for 90% of all deaths. Malaria has a significant financial and socioeconomic impact in countries where it is endemic due to the illness's chronic and severe symptoms. Approximately 25% of the endemic nation's wages are spent on treating malaria, hence reducing the impact of this infection. The financial load on the African continent is projected to be $12 billion per year. In 2020, India had 1.7% of malaria infections and 1.2% of malaria deaths.

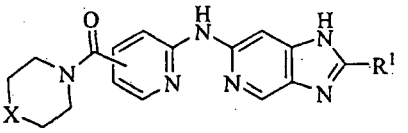
a]pyrazin-2(1*H*)-yl)-1*H*-imidazo[4,5-*c*]pyridines (Formula-2) (André Horatscheck et al., *J. Med. Chem.* 2020, *63* (21), 13013–13030). These reactions were carried out through multi-step reactions and characterized through various spectroscopic techniques. All synthesized compounds were screened for antimalarial activity.



Formula-2

R^1 and R^2 = Different substituents

Claire Le Manach et al., synthesized substituted 1*H*-imidazo[4,5-*c*]pyridin-6yl)amino)pyridin 4-yl)(piperidin-1-yl)methanones (Formula-3) (Claire Le Manach et al. *J. Med. Chem.* 2018, *61*(20), 9371-9385). The reaction was carried out via multi-step and characterized through various analytical tools. The *in-vitro* screening of antimalarial activity was carried out against *P. falciparum*.



Formula-3

R^1 = Various derivatives

X = NR, CR'R", O, SO_2

Tao Wu et al., have synthesized some novel *N*,2-bis(4-fluorophenyl)-5,6,7,8-tetrahydroimidazo[1,2-a] pyrazin-3-amines (Formula-4) (Tao Wu et al. *J. Med. Chem.* 2011, *54*, 5116-5130) via multi-step reactions and characterized through various analytical techniques. All the synthesized substituents were evaluated for their *in-vivo* antimalarial activity.

Still there is a need to offer a compound showing higher potency as antimalarial agents. The inventors have approached to strategically design heterocyclic hybrids Thiazolidin-3-yl-Imidazo-pyridine-3-carboxamide to develop as antimalarial agents. The said compounds are based on the fusion of two different pharmacophores i.e. imidazo-pyridine and 4-thiazolidinones which is promising to demonstrate the improved molecular docking to offer a better inhibitory potency against malaria specifically the *P. falciparum* thereof

OBJECTIVES OF THE INVENTION

The main objective of the present invention is to design and synthesize novel nitrogen and sulfur-containing heterocyclic hybrids, Thiazolidin-3-yl-Imidazo-pyridine-3-carboxamide of formula I.

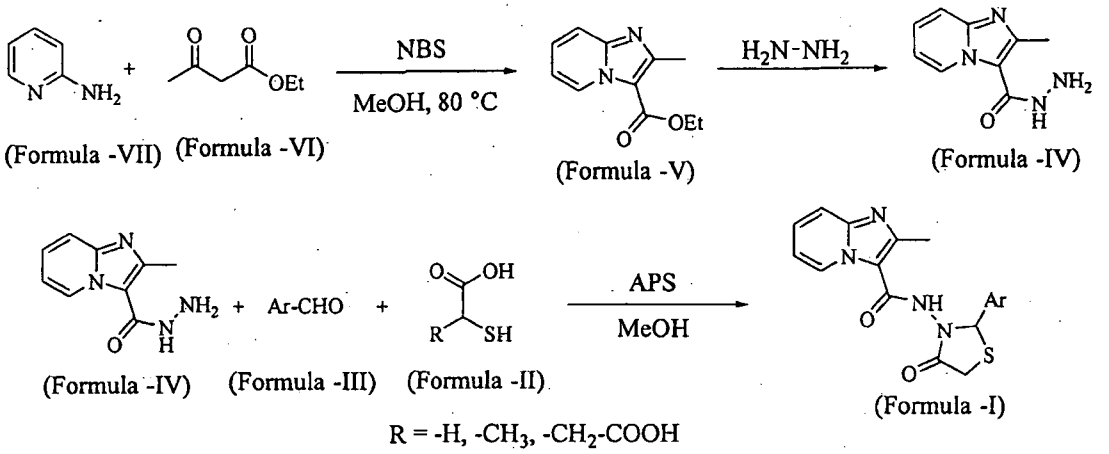
Another objective of the invention is to disclose a novel process for preparing nitrogen and sulfur-containing heterocyclic hybrids, Thiazolidin-3-yl-Imidazo-pyridine-3-carboxamide of formula I optimizing the in-process isolation of intermediate compounds.

Yet another objective of the invention is to treat malaria using a method of treatment involving novel nitrogen and sulfur-containing heterocyclic hybrids, Thiazolidin-3-yl-Imidazo-pyridine-3-carboxamide of formula I.

Yet another objective of the invention is treating *P. falciparum* using a method of treatment involving novel nitrogen and sulfur-containing heterocyclic hybrids, Thiazolidin-3-yl-Imidazo-pyridine-3-carboxamide of formula I.

BRIEF DESCRIPTION OF THE DRAWINGS

Fig. 1 Graphical Biological Results of Thiazolidin-3-yl-Imidazo-pyridine-3-carboxamide (Give the graphical results at the end of specification)



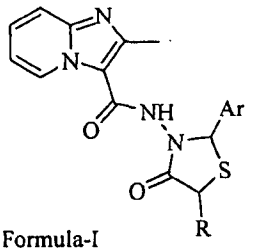
Scheme-1

In another embodiment, the invention relates to the use a novel imidazo-pyridine bearing 4-thiazolidinone moiety, to target multiple pathways associated with antimalarial diseases.

DETAILED DESCRIPTION OF THE INVENTION

This invention provides the design and development of novel antimalarial compounds demonstrating different structural configuration and optimizing their activity as well compared to the currently available drugs in the market i.e. chloroquine, hydroxychloroquine, quinine sulphate, primaquine, and mefloquine. These drugs are based on quinoline-containing heterocyclic compounds. Currently, malarial parasites have developed resistance to these drugs. In addition, the inventors have strategically designed and developed compound of formula (I), which contains a completely novel approach in designing of structure of a synthetic hybrid of two distinct pharmacophores through an amide linker, which will play a key role in the attachment of two heterocyclic moieties. Furthermore, we have developed a one-pot synthesis in the present invention optimizing the in-process isolation of intermediate compounds wherein which formulas (IV), (III), and (II) are condensed together, reducing the expense of intermediate isolation and also eliminating the yield loss during the process. The

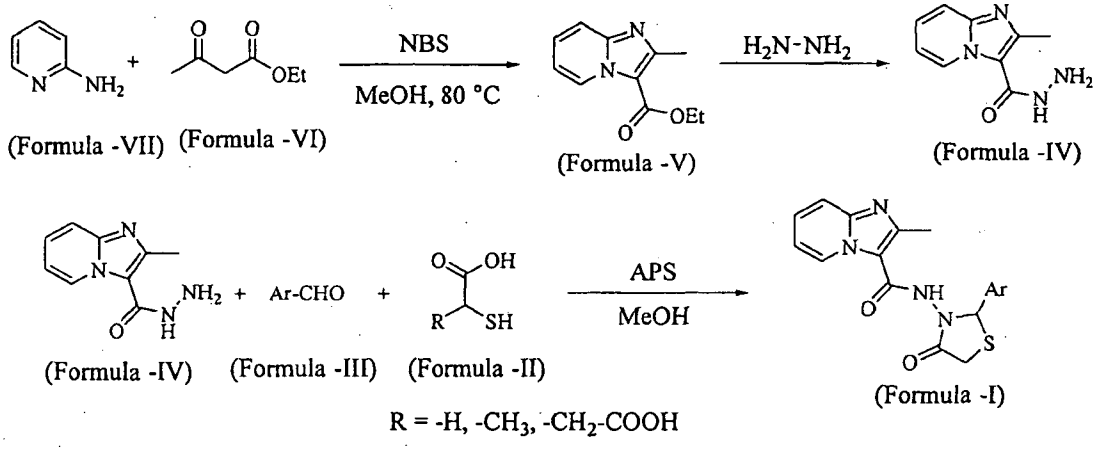
EXHIBIT P4



Formula-I

The -Ar in compound of formula 1 is aryl / heteroaryl ring which is specifically consisting of a substituted mono or di-substituents aryl / heteroaryl. Further the said aryl/heteroaryl is consisting of nitroaryl, halogen, *N,N*-dimethyl, cinnamyl, methyl and methoxy.

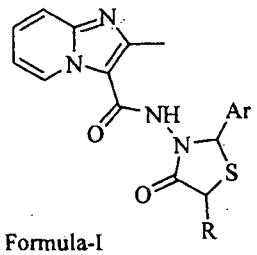
Further the present invention also relates to novel process for preparing the Thiazolidin-3-yl-Imidazo-pyridine-3-carboxamides thereof as per the process depicted in Scheme 1.



General Formula-I was obtained by the reaction of Formula-IV, substituted aromatic aldehydes (Formula-III), thioglycolic acid (Formula-II) and catalytic amount of ammonium persulphate (APS) in methanol, wherein Ar is defined as per Formula (I):

Furthermore, the present invention relates to the chemical composition of heterocyclic hybrids of Formula-I, demonstrating molecular docking to evaluate higher inhibitory potency against *P. falciparum* thereof.

EXHIBIT P4

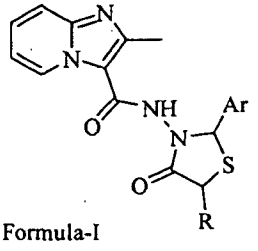


Formula-I

wherein,

Ar is defined as various derivatives of aromatic compounds as mentioned in the Table-1, metabolites thereof. Formula-I. or pharmaceutically acceptable salts, derivatives, metabolites thereof.

The specific compound of Formula-1 synthesized in accordance with the present invention is further elaborated here.



Formula-I

Table-1

Compounds	-Ar	-R
1 a	-3-Cl-C_6H_4	-H
1 b	-3-F-C_6H_4	-H
1 c	-2-OH-C_6H_4	-H
1 d	-4-OH-C_6H_4	-H
1 e	-3-OCH_3-4-OH-C_6H_3	-H
1 f	-2-CH_3-C_6H_4	-H
1 g	-2,3,4-$(OCH_3)_3$-C_6H_2	-H
1 h	-2-OCH_3-C_6H_4	-H
1 i	-3-OCH_3-C_6H_4	-H

includes such aromatic radicals as phenyl, biphenyl, and benzyl, as well as fused aryl radicals such as naphthyl, anthryl, phenanthrenyl, fluorenyl, and indenyl and so forth.

The term "aryl" refers to an aromatic group for example, which is a 6 to 10 membered monocyclic or bicyclic ring system, which may be unsubstituted or substituted. Representative aryl groups may be phenyl, naphthyl etc. When said ring is substituted, the substituents are selected from halogen (e.g., F, Cl, Br, I), hydroxy, alkoxy, nitro.

The term "alkylaryl" or "arylalkyl" refers to alkyl-substituted aryl groups such as butylphenyl, propylphenyl, ethylphenyl, methylphenyl, 3,5-dimethylphenyl, *tert*-butylphenyl and so forth. The term "Haloaryl" refers to aryl radicals in which one or more substitutable positions has been substituted with a halo radical, examples include 4-fluorophenyl, 4- chlorophenyl, 4-bromophenyl and so forth.

The term "halogen" or "Halide" refers to fluorine, chlorine, bromine and iodine. Also included in the family of compounds of Formula-I and the pharmaceutically acceptable salts thereof. The phrase "pharmaceutically acceptable salts" connotes salts commonly used to form alkali metal salts and to form addition salts of free acids or free bases. The nature of the salt is not critical, provided that it is pharmaceutically acceptable. Suitable pharmaceutically acceptable acid addition salts of compounds of Formula-I may be prepared from an "acid" wherein the acid is selected from inorganic acid or from an organic acid. Examples of such "inorganic acids" are hydrochloric, hydrobromic, hydroiodic, nitric, carbonic, sulfuric, and phosphoric acid.

The following specific examples will be used to best describe our invention. These examples are provided to show the many specific and preferred embodiments and approaches in further detail. However, it should be noted that numerous alterations and modifications can be accomplished while remaining within the scope of the present invention. The Formula-I is

temperature to furnish crystals of desired product. The completion of reaction was checked by TLC [n-hexane/ethyl acetate (V/V=3:2)]. Yield: 74%; Solid; M.P. 166-168°C.

Example-3: 2-Methyl-*N*-(4-oxo-2-arylthiazolidin-3-yl)imidazo[1,2-*a*]pyridine-3-carboxamide was prepared according to the literature method (Ebrahimi, *J. . Sulphur Chem.* 2016, 37:587-592), (Formula IV).

A mixture of formula IV (1 mmol), aromatic aldehydes (1 mmol), thioglycolic acid and APS (10 mol%) in methanol (10 mL) was refluxed for 60 min. The product formed was filtered off and washed with water and recrystallized from ethanol. The completion of the reaction was checked by TLC [n-hexane/ethyl acetate (V/V=1:4)].

Example-4: *N*-(2-(3-chlorophenyl)-4-oxothiazolidin-3-yl)-2-methylimidazo[1,2-*a*]pyridine-3-carboxamide **[1 a]**

A mixture of formula IV (1 mmol), 3-chlorobenzaldehyde (1 mmol), thioglycolic acid and APS (10 mol%) in methanol (10 mL) was refluxed for 60 min. Then do the further process as disclosed in example-3. Yield 66%; solid; M.P. 200-203 °C.

Example-5: *N*-(2-(3-fluorophenyl)-4-oxothiazolidin-3-yl)-2-methylimidazo[1,2-*a*]pyridine-3-carboxamide **[1 b]**

A mixture of formula IV (1 mmol), 3-fluorobenzaldehyde (1 mmol), thioglycolic acid and APS (10 mol%) in methanol (10 mL) was refluxed for 60 min. Then do the further process as disclosed in example-3. Yield 46%; solid; M.P. 172-176 °C.

Example-6: *N*-(2-(2-hydroxyphenyl)-4-oxothiazolidin-3-yl)-2-methylimidazo[1,2-*a*]pyridine-3-carboxamide **[1 c]**

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Example-11: *N*-(2-(2-methoxyphenyl)-4-oxothiazolidin-3-yl)-2-methylimidazo[1,2-*a*]pyridine-3-carboxamide **[1 h]**

A mixture of formula IV (1 mmol), 2-methoxybenzaldehyde (1 mmol), thioglycolic acid and APS (10 mol%) in methanol (10 mL) was refluxed for 60 min. Then do the further process as disclosed in example-3. *Yield 37%; solid; M.P. 207-210 °C.*

Example-12: *N*-(2-(3-methoxyphenyl)-4-oxothiazolidin-3-yl)-2-methylimidazo[1,2-*a*]pyridine-3-carboxamide **[1 i]**

A mixture of formula IV (1 mmol), 3-methoxybenzaldehyde (1 mmol), thioglycolic acid and APS (10 mol%) in methanol (10 mL) was refluxed for 60 min. Then do the further process as disclosed in example-3. Yield 61%; solid; M.P. 194-197 °C.

Example-13: 2-methyl-*N*-(2-(3-nitrophenyl)-4-oxothiazolidin-3-yl)imidazo[1,2-*a*]pyridine-3-carboxamide **[1 j]**

A mixture of formula IV (1 mmol), 3-nitrobenzaldehyde (1 mmol), thioglycolic acid and APS (10 mol%) in methanol (10 mL) was refluxed for 60 min. Then do the further process as disclosed in example-3. Yield 89%; solid; M.P. 223-226 °C.

Example-14: 2-methyl-*N*-(2-(4-nitrophenyl)-4-oxothiazolidin-3-yl)imidazo[1,2-*a*]pyridine-3-carboxamide **[1 k]**

A mixture of formula IV (1 mmol), 4-nitrobenzaldehyde (1 mmol), thioglycolic acid and APS (10 mol%) in methanol (10 mL) was refluxed for 60 min. Then do the further process as disclosed in example-3. Yield 84%; solid; M.P. 220-224 °C.

Example-15: 2-methyl-*N*-(4-oxo-2-styrylthiazolidin-3-yl)imidazo[1,2-*a*]pyridine-3-carboxamide **[1 l]**

EXHIBIT P4

Structure activity relationship (SAR) and Biological screening of compound of Formulae I as per present invention:

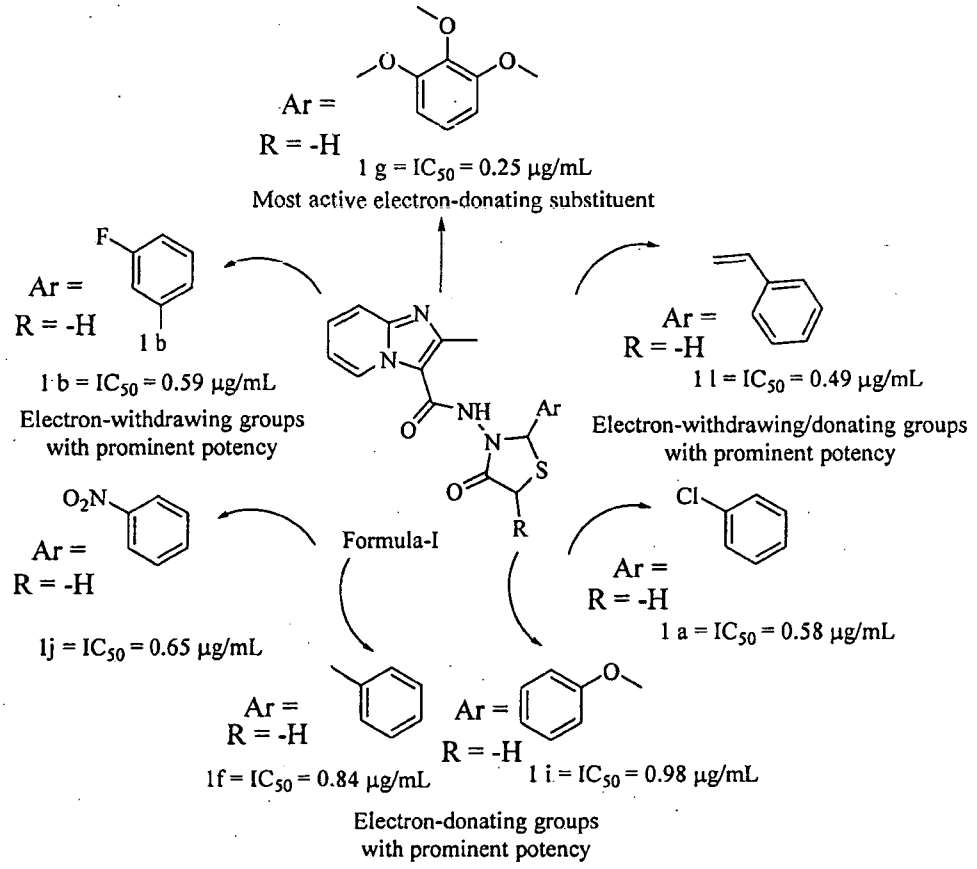

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Fig. 3: Schematic representation of innovation in the of structure-activity relationship based on Formula (I)

In this invention, we synthesized imidazo-pyridine hybrids bearing 4-thiazolidinone motif. To evaluate the structure activity relationship (SAR) of the synthesized hybrids, several electron-withdrawing and electron-donating functional groups were incorporated into the hybrid entity. The difference in antimalarial activity was mediated by the substitution pattern and electronic nature of the synthesized hybrids. Results of the antimalarial evaluation suggested that compound **1 g** was found to be the most active (MEAN IC_{50} = 0.25 µg/mL) against

EXHIBIT P4

3-yl-Imidazo-pyridine-3-carboxamide of formula I that are synthesized using novel approach of one-pot synthesis optimizing the in-process isolation of intermediate compounds. The synthesized compounds are having commercial potential to offer potency to treat malaria specifically *P. falciparum*.

For, M K Bhavnagar University, Bhavnagar,

Date: 9th June, 2022

Prof. Nisheeth C. Desai

EXHIBIT P4

f. 2-Methyl-*N*-(4-oxo-2-(*o*-tolyl)thiazolidin-3-yl)imidazo[1,2-*a*]pyridine-3-carboxamide

g. 2-Methyl-*N*-(4-oxo-2-(3,4,5-trimethoxyphenyl)thiazolidin-3-yl)imidazo[1,2-*a*]pyridine-3-carboxamide

h. *N*-(2-(2-methoxyphenyl)-4-oxothiazolidin-3-yl)-2-methylimidazo[1,2-*a*]pyridine-3-carboxamide

i. *N*-(2-(4-methoxyphenyl)-4-oxothiazolidin-3-yl)-2-methylimidazo[1,2-*a*]pyridine-3-carboxamide

j. 2-Methyl-*N*-(2-(3-nitrophenyl)-4-oxothiazolidin-3-yl)imidazo[1,2-*a*]pyridine-3-carboxamide

k. 2-Methyl-*N*-(2-(4-nitrophenyl)-4-oxothiazolidin-3-yl)imidazo[1,2-*a*]pyridine-3-carboxamide

l. 2-Methyl-*N*-(4-oxo-2-styrylthiazolidin-3-yl)imidazo[1,2-*a*]pyridine-3-carboxamide

3. The one-pot synthesis of Thiazolidin-3-yl-Imidazo-pyridine-3-carboxamide of formula I as claimed in claim-1 optimizing the in-process isolation of intermediate compounds of formulae IV, III and II in presence of a catalyst,

4. The one-pot synthesis of compound of formula 1 as claimed in claim 3 wherein the catalyst is ammonium persulphate (APS).

5. The Thiazolidin-3-yl-Imidazo-pyridine-3-carboxamide of formula I, or its pharmaceutically acceptable salt as claimed in claim 1 for the treatment of Malaria.

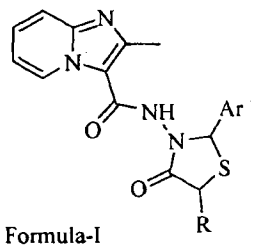
6. The Thiazolidin-3-yl-Imidazo-pyridine-3-carboxamide of formula I, or its pharmaceutically acceptable salt as claimed in claim 6 for the treatment of *Plasmodium falciparum.*

EXHIBIT P4

Thiazolidin-3-yl-Imidazo-pyridine-3-carboxamide as antimalarial agents

Abstract

In the present invention we have developed a series of hybrid molecules of 2-methyl-*N*-(4-oxo-2-arylthiazolidin-3-yl)imidazo[1,2-*a*]pyridine-3-carboxamides containing imidazo-pyridine embedded with 4-thiazolidinones and amide linker present on the 3rd position of imidazo-pyridine heterocyclic motifs (Formula-I). The synthetic procedure was performed via one pot reaction and process for preparation and formulas (IV), (III), and (II) are condensed together, optimizing the in-process isolation of intermediate compounds thereof. The synthesized hybrids were evaluated for antimalarial activity against *P. falciparum* by utilizing quinine as a standard drug. A tri-substituted derivative (2,3,4-$(OCH_3)_3$) was found to be higher potency than the standard drug.



Formula-I

For, MK Bhavnagar University, Bhavnagar,

Date: 9th June, 2022

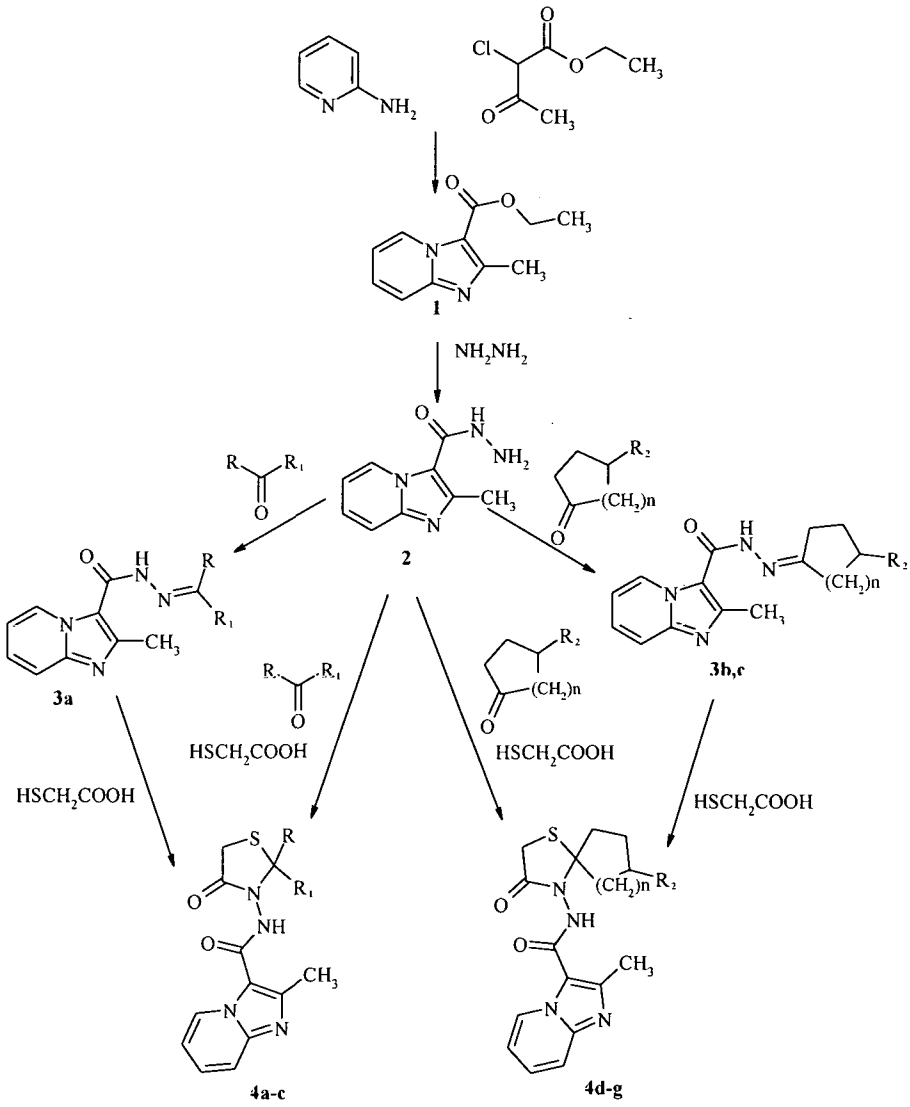
Prof. Nisheeth C. Desai

synthesized some new ketone-hydrazones **3a-c**, thiazolidines **4a-c** and spiro compounds **4d-g** incorporating an imidazo[1,2-*a*]pyridine moiety. These compounds were characterized by their elemental and spectral analyses (IR, ^{1}H-NMR, ^{13}C-NMR and mass spectra).

Results and Discussion

The synthetic pathway followed in the preparation of the compounds is outlined in Scheme 1. The starting materials, ethyl 2-methylimidazo[1,2-*a*]pyridine-3-carboxylate (**1**) and 2-methylimidazo[1,2-*a*]pyridine-3-carboxylic acid hydrazide (**2**), were obtained by previously described methods [3,4].

Scheme 1



The IR spectra of the starting materials **3** showed C=O bands in the 1654-1679 cm^{-1} region. A new strong band at 1690-1710 cm^{-1} in the spectra of **4** provided firm support for ring closure. The most significant evidence for the reaction was the presence of two doublets (dd, 2H, J=16 Hz) at about 3.61 and 3.68 in the ^{1}H-NMR spectrum of **4b** [6]. In the spectra of **4a,c-g**, the same protons were observed as singlets (2H) at about 3.40-3.72 ppm due to the lack of chirality. ^{13}C-NMR and DEPT (135) spectra of the prototypes (**4b,d** and, **e**) were also studied and are detailed. Signals at about 71.44-76.59 ppm, which are not seen in DEPT spectra, were assigned to the quarternary (spiro) carbon atoms. According to the data obtained from DEPT and HETCOR experiments the signals at about 28.80-29.72 ppm were assigned to the CH_2 group located in the thiazolidine moiety [7]. The mass spectra of all the compounds were relatively simple and showed (except for **4g**) the peaks due to molecular ions.

Antituberculous Activity

Primary screening was conducted at 6.25 μg/mL against *M. tuberculosis* H_{37}Rv. The *M. tuberculosis* H_{37}Rv was grown in a medium containing a radiolabeled substrate. Labeled CO_2 produced was detected and quantitated with a BACTEC 460 automatic radiometric system. Compounds giving inhibitions < 90 % (MIC > 6.25 μg/mL, MIC rifampin 0.031 μg/mL) were not evaluated further [5]. None of the compounds showed antituberculous activity at the tested concentration.

Acknowledgements

We thank Dr. Joseph A. Maddry from the Tuberculosis Antimicrobial Acquisition and Coordination Facility (TAACF), National Institute of Allergy and Infectious Diseases Southern Research Institute, Birmingham, AL (USA) for the *in vitro* evaluation of antituberculous activity. This work was supported by Istanbul University Research Fund Project No. T-452/071197.

Experimental

General

Melting points determined with a Buchi 530 melting point apparatus in open capillaries and are uncorrected. IR (KBr disks) and ^{1}H- and ^{13}C-NMR spectra (DMSO-d_6) were recorded on Perkin Elmer Model 1600 and Bruker AC 200 and DPX 400 instruments, respectively. Microanalyses were carried out on a Carlo Erba 1106 elemental analyzer. All starting materials were purchased E. Merck (Darmstadt, Germany).

Ethyl 2-methylimidazo[1,2-a]pyridine-3-carboxylate (**1**) [3].

2-Aminopyridine (0.01 mol) was heated under reflux with ethyl 2-chloroacetoacetate (0.1 mol) in 96 % C_2H_5OH (25 mL) for 6h and then cooled. Excess C_2H_5OH was evaporated *in vacuo*. The residual red oil was partitioned between ether-water. After drying, the ether extracts were evaporated and the residual oil was allowed to crystallize. M.p. 69 °C, yield 45.05%.

2-Methylimidazo[1,2-a]pyridine-3-carboxylic acid hydrazide (**2**) [4].

Ethyl 2-methylimidazo[1,2-*a*]pyridine-3-carboxylate (0.01 mol) was heated under reflux with H_2NNH_2 (0.1 mol) in 96% C_2H_5OH (15 mL) for 5h and then cooled. The crystals formed were washed with H_2O, dried and recrystallized from C_2H_5OH (96 %). M.p.180 °C, yield 27.16 %.

General procedure for preparation of 2-methylimidazo[1,2-a]pyridine-3-carboxylic acid (alkylidene / cycloalkylidene) hydrazides **3a-c**.

2-Methylimidazo[1,2-*a*]pyridine-3-carboxylic acid hydrazide (**2,** 0.01 mol), the appropriate ketone (0.011 mol), a drop of conc. H_2SO_4 and 96 % C_2H_5OH (20 mL) were heated under reflux for 6h. The crude products which precipitated on cooling were filtered and recrystallized from an C_2H_5OH-H_2O mixture.

2-Methylimidazo[1,2-a]pyridine-3-carboxylic acid sec-butylidenehydrazide (**3a**)**:** IR: 1654 (C=O) cm^{-1}; ^{1}H-NMR: δ (ppm) = 1.04 (3H, t, CH_2CH_3), 1.98 (3H, s, CH_3), 2.28 (2H, q, CH_2CH_3), 2.53 (3H, s, 2-CH_3), 7.01 (1H, t, 6-H), 7.38 (1H, t, 7-H), 7.58 (1H, d, 8-H), 8.88 (1H, d, 5-H), 10.03 (1H, s, CONH); EIMS (%) = 244 ($M^{+\cdot}$, 38), 159 (100).

2-Methylimidazo[1,2-a]pyridine-3-carboxylic acid cyclopentylidenhydrazide (**3b**)**:** IR: 1670 (C=O) cm^{-1}; ^{1}H-NMR: δ (ppm) = 1.68-1.83 (4H, m, cyclopentylidene-3H,4H), 2.34-2.49 (4H, m, cyclopentylidene-2H,5H), 2.54 (3H, s, 2-CH_3), 7.00 (1H, t, 6-H), 7.40 (1H, t, 7-H), 7.58 (1H, d, 8-H), 8.89 (1H, d, 5-H), 9.91 (1H, s, CONH); EIMS (%) = 256 ($M^{+\cdot}$, 100).

2-Methylimidazo[1,2-a]pyridine-3-carboxylic acid cyclohexylidenhydrazide (**3c**)**:** IR: 1679 (C=O) cm^{-1}; ^{1}H-NMR: δ (ppm) = 1.4-1.78 (6H, m, cyclohexylidene 3H,4H,5H), 2.21-2.31 (2H, m, cyclohexylidene-2H,6H, axial), 2.33-2.60 (2H, m, cyclohexylidene-2H,6H, equatorial), 2.52 (3H, s, 2-CH_3), 7.01 (1H, t, 6-H), 7.37 (1H, t, 7-H), 7.56 (1H, d, 8-H), 8.86 (1H, d, 5-H), 10.28 (1H, s, CONH); EIMS (%) = 270 ($M^{+\cdot}$, 72), 78 (100).

General procedures for preparation of 2-methylimidazo[1,2-a]pyridine-3-carboxylic acid amides **4 a-g**.

Method A

A mixture of **3a-c** (0.01 mol) and $HSCH_2COOH$ (0.15 mol) was heated under reflux for 6h in dry benzene (30 mL) using a Dean-Stark trap for removal of water of condensation. Excess benzene was evaporated *in vacuo*. The residue was triturated with saturated $NaHCO_3$ until CO_2 evaluation ceased and then allowed to stand overnight. The solid thus obtained was filtered, washed with H_2O and recrystallized from an C_2H_5OH-H_2O mixture.

Method B

The appropriate ketone (0.011 mol) was added to a solution of **2** (0.01 mol) in dry benzene (30 mL) and the mixture was heated under reflux for 1.5h using a Dean-Stark trap. After cooling $HSCH_2COOH$ (0.15 mol) was added dropwise to the solution and the resulting mixture was refluxed for 6h. The compounds were purified using the procedure described under Method A.

2-Methylimidazo[1,2-a]pyridine-3-carboxylic acid (2,2-dimethyl-4-oxo-1,3-thiazolidin-3-yl)amide (**4a**): IR: 1662 (CONH), 1690 (thiazolidine C=O) cm^{-1}; ^{1}H-NMR: δ (ppm) = 1.36 (6H, s, $-C(CH_3)_2$), 2.44 (3H, s, 2-CH_3), 3.52 (2H, s, CH_2S), 6.88 (1H, t, 6-H), 7.25 (1H, t, 7-H), 7.42 (1H, d, 8-H), 8.65 (1H, d, 5-H), 9.81 (1H, s, CONH); EIMS (%) = 304 ($M^{+\cdot}$, 3), 156 (100).

2-Methylimidazo[1,2-a]pyridine-3-carboxylic acid (2-ethyl-2-methyl-4-oxo-1,3-thiazolidin-3-yl)amide (**4b**): IR: 1662 (CONH), 1690 (thiazolidine C=O) cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ (ppm) = 1.04 (3H, t, CH_2CH_3), 1.66 (3H, s, C-CH_3), 1.76-1.84,1.92-1.99 (1H, 1H, 2m, CH_2CH_3), 2.60 (3H, s, 2-CH_3), 3.61, 3.68 (1H, 1H, dd, J=16 Hz, CH_2S), 6.93 (1H, t, 6-H), 7.34 (1H, t, 7-H), 7.46 (1H, d, 8-H), 9.22 (1H, d, 5-H), 7.93 (1H, s, CONH); ^{13}C-NMR δ(ppm) = 168.67/161.73 (thiazolidine CO and CONH), 148.19/146.57 (imidazopyridine C_2 and C_{8a}), 128.19 (imidazopyridine C_5), 127.80 (imidazopyridine C_7), 117.14 (imidazopyridine C_8), 114.33 (imidazopyridine C_3), 71.44 (thiazolidine C_2), 34.72 ($\underline{C}H_2CH_3$), 29.72 (thiazolidine C_3), 28.32 (CH_3), 16,73 (2-CH_3), 9.53 ($CH_2\underline{C}H_3$); EIMS (%) = 318 ($M^{+\cdot}$,100).

2-Methylimidazo[1,2-a]pyridine-3-carboxylic acid (2,2-diethyl-4-oxo-1,3-thiazolidin-3-yl)amide (**4c**): IR: 1662 (CONH), 1690 (thiazolidine C=O) cm^{-1}; ^{1}H-NMR: δ (ppm) = 0.8 (6H, t, CH_2CH_3), 1.50-1.65 (4H, m, CH_2CH_3), 2.40 (3H, s, 2-CH_3), 3.40 (2H, s, CH_2S), 6.64 (1H, t, 6-H), 7.22 (1H, t, 7-H), 7.40 (1H, d, 8-H), 8.66 (1H, d, 5-H), 9.72 (1H, s, CONH); EIMS (%) = 332 ($M^{+\cdot}$, 4.5), 46 (100).

2-Methylimidazo[1,2-a]pyridine-3-carboxylic acid (3-oxo-1-thia-4-azaspiro[4.4]non-4-yl)amide (**4d**): IR: 1662 (CONH), 1691 (spiro[4.4]nonane C=O) cm^{-1}; ^{1}H-NMR: δ (ppm) = 1.67-1.97 (4H, m, spiro-7H,8H), 2.15-2.21 (2H, m, spiro-6H,9H axial), 2.23-2.40 (2H, m, spiro-6H,9H equatorial), 2.64 (3H, s, 2-CH_3), 3.72 (2H, s, CH_2S), 7.05 (1H, t, 6-H), 7.46 (1H, t, 7-H), 7.62 (1H, d, 8-H), 8.90 (1H, d, 5-H), 9.98 (1H, s, CONH); ^{13}C-NMR δ (ppm) = 168.67/161.73 (spiro[4.4]nonane C_3 and CONH), 148.05/146.62 (imidazopyridine C_2 and C_{8a}) , 128.25 (imidazopyridine C_5), 127.85 (imidazopyridine C_7), 117.12 (imidazopyridine C_8), 114.74 (imidazopyridine C_3), 114.34 (imidazopyridine C_6), 76.79 (C_5), 39.22 (spiro[4.4]nonane C_6 and C_9), 29.72 (spiro[4.4]nonane C_2), 23.62 (spiro[4.4]nonane C_7 and C_8), 16.75 (2-CH_3); EIMS (%)= 330 (M^+, 66.45), 90 (100).

2-Methylimidazo[1,2-a]pyridine-3-carboxylic acid (3-oxo-1-thia-4-azaspiro[4.5]dec-4-yl)amide (**4e**): IR: 1673 (CONH), 1709 (spiro[4.5]decane C=O) cm^{-1}; ^{1}H-NMR: δ (ppm) = 1.05-2.54 (10H, m, spiro-6H,7H,8H,9H,10H), 2.67 (3H, s, 2-CH_3), 3.64 (2H, s, CH_2S), 7.07 (1H, t, 6-H), 7.44 (1H, t, 7-H), 7.62 (1H, d, 8-H), 8.90 (1H, d, 5-H), 9.93 (1H, s, CONH); ^{13}C-NMR δ (ppm) = 168.67/161.73 (spiro[4.5]decane C_3 and CONH), 148.00/146.00 (imidazopyridine C_2 and C_{8a}), 128.29 (imidazo-pyridine C_5), 127.84 (imidazopyridine C_7), 117.11 (imidazopyridine C_8), 114.80 (imidazopyridine C_3), 114.37 (imidazopyridine C_6), 73.04 (spiro[4.5]decane C_5), 28.80 (spiro[4.5]decane C_2), 24.90 (spiro[4.5]decane C_8), 23.76 (spiro[4.5]decane C_6 and C_9), 23.62 (spiro[4.5]decane C_6 and C_{10}), 16.78 (2-CH_3); EIMS (%) = 344 (M^+, 92.4), 160 (100).

2-Methylimidazo[1,2-a]pyridine-3-carboxylic acid (8-methyl-3-oxo-1-thia-4-azaspiro[4.5]dec-4-yl) amide (**4f**): IR: 1662 (CONH), 1693 (spiro[4.5]decane C=O) cm^{-1}; ^{1}H-NMR: δ (ppm) = 0.67 (3H, s, CH_3), 1.28-1.63 (9H, m, spiro-6H,7H,8H,9H,10H), 2.43 (3H, s, 2-CH_3), 3.43 (2H, s, CH_2S), 6.85 (1H, t, 6-H), 7.22 (1H, t, 7-H), 7.40 (1H, d, 8-H), 8.67 (1H, d, 5-H), 9.79 (1H, s, CONH); EIMS (%) = 358 (M^+, 4), 46 (100).

2-Methylimidazo[1,2-a]pyridine-3-carboxylic acid (8-ethyl-3-oxo-1-thia-4-azaspiro[4.5]dec-4-yl) amide (**4g**): IR: 1672 (CONH), 1710 (spiro[4.5]decane C=O) cm^{-1}; ^{1}H-NMR: δ (ppm) = 0.84 (3H, s, CH_2CH_3), 1.05-1.98 (11H, m, spiro-6H,7H,8H,9H,10H, CH_2CH_3), 2.64 (3H, s, 2-CH_3), 3.64 (2H, s, CH_2S), 6.99 (1H, t, 6-H), 7.37 (1H, t, 7-H), 7.67 (1H, d, 8-H), 8.86 (1H, d, 5-H), 9.99 (1H, s, CONH); EIMS (%) = 46 (100).

In vitro evaluation of antituberculous activity [5]

A primary screen was conducted at 6.25 μg/mL against *M. tuberculosis* $H37R_V$ in BACTEC 12B medium using a BACTEC 460 radiometric system. Compounds **3a-c, 4b,d-e**, chosen as prototypes, did not show *in vitro* antituberculous activity at 6.25 μg/mL (MIC rifampin 0.031 μg/mL).

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Samples Availability: Available from the authors.

EXHIBIT P6

INTELLECTUAL PROPERTY INDIA
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GEOGRAPHICAL INDICATIONS

MANUAL

OF

PATENT PRACTICE AND PROCEDURE

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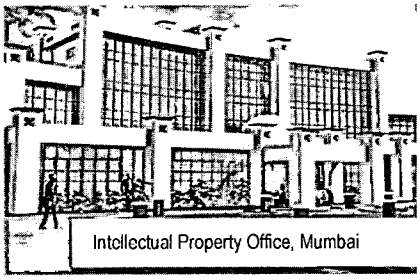
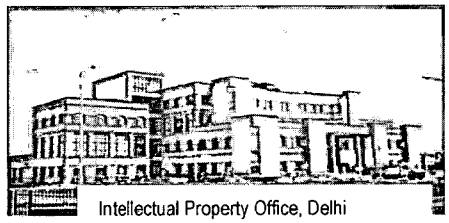

Intellectual Property Office, Mumbai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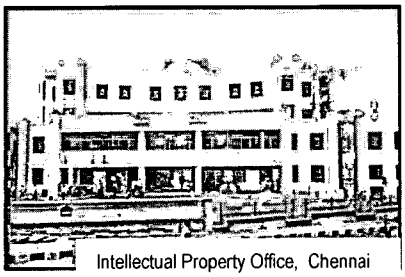
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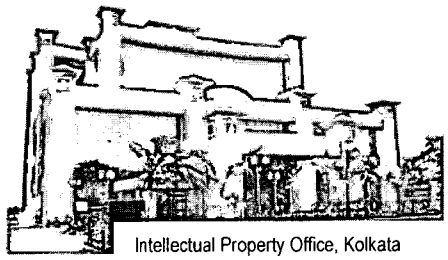
Intellectual Property Office, Kolkata

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Boudhik Sampada Bhawan
S.M. Road, Antop Hill
Mumbai – 400 037.

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Third Edition – 2008

Manual of Patent Practice & Procedure

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PREFACE

This Manual is intended to provide detailed information to the public and users of Patent System on the practices and procedures followed by Patent Office for processing of patent applications. The Manual incorporates provisions of the Patents Act, 1970 as amended by the Patents (Amendment) Act, 2005 and the Patents Rules, 2003 as amended by the Patents (Amendment) Rules, 2006.

The format of the Manual is to reproduce successive sections and relevant rules of the Patents Act and Patents Rules followed by explanation and past decisions of the Patent Office, wherever available. References to decisions of the courts of India and other countries have been included to provide guidance and help the users.

The Manual does not constitute rule making and hence do not have the force and effect of law. Statements made in the Manual are not in themselves an authority for any action by an officer of the Patent Office. While the Manual may be regarded as a guide, it does not impose any particular line of such action and may not be quoted to that end.

The Manual will be updated periodically in order to reflect important judgments, decisions and changes in practice and to correct errors, if any. Due care has been taken to avoid mistakes. However, if any shortcomings are noticed by the users, suggestions to improve the Manual will be appreciated.

(V. RAVI)
Controller General of Patents, Designs &Trade Marks

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CHAPTER I

Introduction

The Patent System in India

1.1 A patent is granted as an exclusive right by the Government for an invention, for a limited period of time in consideration of disclosure of the invention by an applicant. A patentee enjoys exclusive right to prevent the third party from unauthorized act of making, using, offering for sale, selling or importing the patented product or process within the country during the term of the patent. A patented invention becomes free for public use after expiry of the term of the patent or when the patent ceases to have effect, by non-payment of any renewal fee.

1.2 History of Indian Patent System

1.2.1 The first legislation in India relating to patents was the Act VI of 1856. The objective of this legislation was to encourage inventions of new and useful manufactures and to induce inventors to disclose secret of their inventions. The Act was subsequently repealed by Act IX of 1857 since it had been enacted without the approval of the sovereign. Fresh legislation for granting 'exclusive privileges' was introduced in 1859 as Act XV of 1859. This legislation contained certain modifications of the earlier legislation, namely, grant of exclusive privileges to useful inventions only and extension of priority period from 6 months to 12 months. This Act excluded importers from the definition of inventor. This Act was based on the United Kingdom Act of 1852 with certain departures including allowing assignees to make application in India and also taking prior public use or publication in India or United Kingdom for the purpose of ascertaining novelty.

1.2.2 In 1872, the Act of 1859 was revisited to provide protection relating to designs. It was renamed as "The Patterns and Designs Protection Act" under Act XIII of 1872. The Act of 1872 was amended in 1883 (XVI of 1883) to introduce a provision to protect novelty of the invention, which prior to making application for their protection were disclosed in the Exhibition of India (?). A grace period of 6 months was provided for filing such applications after the date of the opening of such Exhibition.

1.2.3 This Act remained in force for about 30 years without any change but in the year 1883, certain modifications in the patent law were made in United Kingdom (UK) and it was considered that those modifications should also be incorporated in the Indian law. In 1888, new legislation was introduced to consolidate and amend the law relating to invention and designs in conformity with the amendments made in the U.K. law. The modifications introduced in the Indian law, by Act V of 1888, over the UK legislation, *inter alia*, includes:

- Shifting of authority to administer the Act from the Home department to Secretary to Government of India;

- Extension of the jurisdiction of the Act to other courts apart from High Courts of Madras, Calcutta and Bombay;
- Reduction in the fee;
- Provision for detailed disclosure of the invention, including best mode of working the invention in full clear, concise and exact terms so as to enable any person skilled in the art or science to make use of the invention;
- Provision of powers to call for a model of the invention;
- Change of time for filing petition in respect of patent granted in United Kingdom from 12 months from the 'letters patent' to 12 months from the 'date of sealing';
- Extension of term of exclusive privileges to ------
- Provision for granting compulsory licence where invention is not made accessible to public, on reasonable terms;
- Appointment of Agents to encourage filing by foreign inventor;
- Introduction of provision for protection of new or original design;
- Provision for counting the grace period for filing application for invention displayed in the Exhibition from the date of admission of the invention into the Exhibition instead of the date of the opening of the Exhibition.

1.2.4 In 1911, the Indian Patents and Designs Act, 1911, (Act II of 1911) was brought in replacing all the previous Acts. This Act brought patent administration under the management of Controller of Patents for the first time. This Act was amended in 1920 to provide for entering into reciprocal arrangements with UK and other countries for securing priority. In 1930, further amendments were made to incorporate, *inter-alia,* provisions relating to grant of secret patents, patent of addition, use of invention by Government, powers of the Controller to rectify register of patent and increase of term of the patent from 14 years to 16 years. In 1945, another amendment was made to provide for filing of provisional specification and submission of complete specification within nine months.

1.2.5 After Independence, it was felt that the Indian Patents & Designs Act, 1911 was not fulfilling its objective. It was found desirable to enact comprehensive patent law owing to substantial changes in political and economic conditions in the country. Accordingly, the Government of India constituted a committee under the Chairmanship of Justice (Dr.) Bakshi Tek Chand, a retired Judge of Lahore High Court, in 1949, to review the patent law in India in order to ensure that the patent system is conducive to the national interest. The terms of reference included—

a) to survey and report on the working of the patent system in India;
b) to examine the existing patent legislation in India and to make recommendations for improving it, particularly with reference to the provisions concerned with the prevention of abuse of patent rights;
c) to consider whether any special restrictions should be imposed on patent regarding food and medicine;
d) to suggest steps for ensuring effective publicity to the patent system and to patent literature, particularly as regards patents obtained by Indian inventors;
e) to consider the necessity and feasibility of setting up a National Patents Trust;

f) to consider the desirability or otherwise of regulating the profession of patent agents
g) to examine the working of the Patent Office and the services rendered by it to the public and make suitable recommendations for improvement; and
h) to report generally on any improvement that the Committee thinks fit to recommend for enabling the Indian Patent System to be more conducive to national interest by encouraging invention and the commercial development and use of inventions.

1.2.6 The Committee submitted its interim report on 4th August, 1949 with recommendations for prevention of misuse or abuse of patent right in India and for amendments to sections 22, 23 & 23A of the Patents & Designs Act, 1911 on the lines of the United Kingdom Acts of 1919 and 1949. The main recommendations of the Committee were as follows:-

(a) Any interested person may apply for a compulsory licence or revocation of the patent on any of the following grounds, namely—

  (i) patented invention, being capable of being commercially worked in India, is not being commercially worked therein to the fullest possible extent;
  (ii) demand for the patented article in India is not being met to an adequate extent or on reasonable terms;
  (iii) commercial working of the invention in India is being prevented or hindered by the importation of the patented articles; and
  (iv) the refusal of the patentee to grant a licence or licences on reasonable terms, whereby the commercial or industrial activities in India are prevented or hindered;

(b) for obtaining relief against abuse of patent rights, an application can be made to the Controller of Patents and Designs any time after the sealing of the patent and the order of the Controller to be appealable before the appellate authority which should be an ad-hoc Special Tribunal nominated by the Central Government consisting of –

  (i) a sitting or retired judge of a High Court (as the President),
  (ii) a barrister or advocate of not less than ten years standing, preferably conversant with patent law and procedure, and
  (iii) a technical expert in the particular subject with which the patent in question is concerned.

The functions of the Special Tribunal should be judicatory and not advisory, and its decisions should be final and it should have the power to award costs.

1.2.7 The committee also observed that the Patents Act should contain clear indication to ensure that food and medicine and surgical and curative devices are made available to the public at the cheapest price commensurate with giving reasonable compensation to the patentee.

1.2.8 Based on the above recommendation of the Committee, the 1911 Act was amended in 1950 (Act XXXII of 1950) in relation to working of inventions and compulsory licence/revocation. Following grounds were provided for making applications for compulsory licence:

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1.4 Administrative Structure of the Patent Office

1.4.1 Patent system in India is administered under the superintendence of the Controller General of Patents, Designs, Trademarks and Geographical Indications (CGPDTM), appointed under sub-section (1) of Section 3 of the Trade Marks Act, 1999. The Office of the Controller General of Patents, Designs and Trade Marks functions under the Department of Industrial Policy and Promotion, Ministry of Commerce and Industry. The Office of the CGPDTM is located at Mumbai. There are four Patent Offices in India. The Head Office is at Kolkata and other Patent Offices are located at Delhi, Mumbai and Chennai. The Controller General of Patents, Designs and Trade Marks delegates his powers to Senior Joint Controller of Patents & Designs, Joint Controllers of Patents & Designs, Deputy Controllers of Patents & Designs and Assistant Controllers of Patents & Designs regarding various procedures for patent grant. Examination of patent applications is done by Examiners of Patents & Designs.

CHAPTER - II

PREAMBLE AND DEFINITIONS

2.1 The Patents Act, 1970 (39 of 1970)

An Act to amend and consolidate the law relating to patents.
Be it enacted by Parliament in the Twenty-First Year of the Republic of India as follows:--

2.1.1 The Patents Act was enacted by the Government of India in the year 1970 in pursuance of its powers under Entry 49 of the List I of Schedule VII of the Constitution of India. List I contains the list of the items in the Union List and Entry 49 reads, "Patents, inventions and designs; copyright; trade-marks and merchandise marks." The Act was notified on 19th September 1970 as Act 39 of 1970.

2.1.2 The word 'amend' is used to indicate the fact that patent law was in existence before the enactment of the Patents Act, 1970. The history of patent legislations in India is given in Chapter-I. Enactment of a new legislation while repealing the previous legislations does not de-legitimise the patents granted and other action taken under the previous law [see section 162(3) and (5)].

2.1.3 In the statement of objects and reasons of the Patent Bill, 1970, it is stated, "a need for a comprehensive law so as to ensure more effectively that patent rights are not worked to the detriment of the consumer or to the prejudice of trade or the industrial development of the country was felt as early as 1948". This gives fair indication to the intention of the Act. The patents law is also kept in line with the "development of technological capability in India, coupled with the need for integrating the Intellectual Property system with international practices and intellectual property regimes," as stated in the statement of objects and reasons of the Patents (Second Amendment) Bill, 1999. "The object of the patent law is to encourage scientific research, new technology and industrial progress. Grant of exclusive privilege to own, use or sell the method or the product patented for the limited period, stimulates new inventions of commercial utility. The price of the grant of the monopoly is the disclosure of the invention at the Patent Office, which after the expiry of the fixed period of the monopoly passes into public domain." [Bishwanath Prasad Radhey Shyam vs. H.M. Industries A.I.R. 1982 S.C. 1444 at paragraph 17].

2.2 Section 1 : *Short title, extent and commencement.*—

(1) This Act may be called the Patents Act, 1970.
(2) It extends to the whole of India.
(3) It shall come into force on such date as the Central Government may, by notification in the Official Gazette, appoint
Provided that different dates may be appointed for different provisions of this Act, and any reference in any such provision to

the commencement of this Act shall be construed as a reference to the coming into force of that provision.

2.2.1 The applicability of the Patents Act extends to the whole of India. A patent granted as per the Act can only be enforced in the territorial limits of India, subject to the provisions of section 49 of the Act. Patents granted as per this Act only are valid in India.

2.2.2 Proviso to sub section 3 enables the Government to bring into force different provisions of the Act at different times. For instance, provisions relating to Appellate Board *vide* sections 116-117H were brought into force from 2nd April, 2007 although other provisions had been brought into force earlier. The Patent Office is required to act under the provisions of a particular section only from the date those provisions are brought into force.

2.3 Definitions

Section *2.* ***Definitions and interpretation.—***

(1) In this Act, unless the context otherwise requires—

(a) "Appellate Board" means the Appellate Board referred to in section 116;

2.3.1 The reference is to the Intellectual Property Appellate Board (IPAB), Chennai. Provisions relating to the IPAB were brought into force with effect from 2nd April, 2007.

(ab) "assignee" includes an assignee of the assignee and the legal representative of a deceased assignee and references to the assignee of any person include references to the assignee of the legal representative or assignee of that person;

(aba) "Budapest Treaty" means the Budapest Treaty on the International Recognition of the Deposit of Micro-organisms for the purposes of Patent Procedure done at Budapest on 28th day of April, 1977, as amended and modified from time to time;

2.3.2. India became a member of this Treaty on 17th Dec., 2001-----

|(ac) "capable of industrial application", in relation to an invention, means that the invention is capable of being made or used in an industry;

2.3.3 The term 'industrial application' was introduced in the Patents Act through the amendment in 2002. As per the definition of 'invention' prior to the amendment, an invention had to be new and useful for grant of patent. As per Section 64(1)(g), lack of utility is a ground for revoking a patent. In Lakhapati Rai & Ors. Vs. Srikissen Dass & Ors. (1917), it was held that 'utility' does not mean improvement. It means practicability. The test of utility is whether the invention will work and whether it will do what is claimed for it.

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(b) "Controller" means the Controller General of Patents, Designs and Trade Marks referred to in section 73;

(c) "convention application" means an application for a patent made by virtue of section 135;

d) "convention country" means a country or a country which is member of a group of countries or a union of countries or an Intergovernmental organization preferred to as a convention country in section 133;

(e) "district court" has the meaning assigned to that expression by the Code of Civil Procedure, 1908 (5 of 1908);

(f) "exclusive licence" means a licence from a patentee which confers on the licensee, or on the licensee and persons authorised by him, to the exclusion of all other persons (including the patentee), any right in respect of the patented invention, and exclusive licensee shall be construed accordingly;

(g) omitted w.e.f.1-1-2005

2.3.4 The omitted clause (g) read, "'food' means any article of nourishment for human consumption and also includes any substance intended for the use of infants, invalids or convalescents as an article of food or drink;"

(h) "Government undertaking" means any industrial undertaking carried on—

(i) by a department of the Government, or

(ii) by a corporation established by a Central, Provincial or State Act, which is owned or controlled by the Government, or

(iii) by a Government company as defined in section 617 of the Companies Act, 1956 (1 of 1956), [4][or]

(iv) by an institution wholly or substantially financed by the Government;

(i) "High Court", in relation to a State or Union territory, means the High Court having territorial jurisdiction in that State or Union territory, as the case may be;

(ia) "international application" means an application for patent made in accordance with the Patent Cooperation Treaty;

2.3.5 India became a member of the Patent Cooperation Treaty on 7th December, 1998.

(j) "invention" means a new product or process involving an inventive step and capable of industrial application;

2.3.6 Considering the question what is an 'invention'. It was held in Raj Parkash vs, Mangat Ram Choudhary as under:

"Invention is to find out or discover something not found or discovered by anyone before and it is not necessary that the invention should be anything complicated and the essential thing is that the inventor was the first one to adopt it and the principle therefore is that every simple invention that is

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2.3.8 In Writ Petition (Civil) 12598 Of 1985 in the matter of Shri Kirshna Gyanoday Sugar Ltd. & Anr. Vs. State Of Bihar, the Supreme Court referred to R.C.Cooper's Case in the following words:

In its normal connotation "property" means "highest right a man can have to anything, being that right which depend on another's courtesy: It includes ownership, estates and interests in corporeal things, and also rights such as trade-marks, copyrights, patents and even rights in personam capable of transfer or transmission, such as debts; and signifies a beneficial right to or a thing considered as having a money value." (Date Of Judgment: 18th February, 2003.)

2.3.9 Unlike other property rights, a patent right may be revoked, amended or abandoned.

(n) "patent agent" means a person for the time being registered under this Act as a patent agent;

(o) "patented article" and "patented process" means respectively an article or process in respect of which a patent is in force;

(oa) "Patent Cooperation Treaty" means the Patent Cooperation Treaty done at Washington on the 19th day of June, 1970 as amended and modified from time to time;

(p) "patentee" means the person for the time being entered on the register as the grantee or proprietor of the patent;

(q) "patent of addition" means a patent granted in accordance with section 54;

(r) "patent office" means the patent office referred to in section 74;

2.3.10 The head office of the Patent Office is located at Kolkata and the branch offices at Chennai, Delhi and Mumbai.

(s) "person" includes the Government;

(t) "person interested" includes a person engaged in, or in promoting, research in the same field as that to which the invention relates;

(ta) "pharmaceutical substance" means any new entity involving one or more inventive steps;

(u) "prescribed" means,—

(A) in relation to proceedings before a High Court, prescribed by rules made by the High Court;

(B) in relation to proceedings before the Appellate Board, prescribed by rules made by the Appellate Board; and

~~(C)~~(C) in other cases, prescribed by rules made under this Act;

(v) "prescribed manner" includes the payment of the prescribed fee;

(w) "priority date" has the meaning assigned to it by section 11;

(x) "register" means the register of patents referred to in section 67;

~~3.3.7~~3.3.8 Matter becomes part of the state of the art on the date it first becomes available to the public, wherever in the world this may be, and whatever manner or language the disclosure takes place. There is no limit on the age of the disclosure.

~~3.3.8~~3.3.9 Different claims may have different priority dates of documents, such as patent specifications, textbooks or technical journals which have been published in the conventional sense of that term, for example, by being on sale or available in libraries.

~~3.3.9~~3.3.10 Any document is regarded as having been published, and thus forming part of the state of the art, if it can be inspected as of right by the public, whether on payment of a fee or not; this includes, for example, the contents of the "open" part of the file of a patent application once the application has been published.

3.3.11 Prior publication does not however depend on the degree of dissemination. The communication to a single member of the public without inhibiting fetter is enough to amount to making available to the public (*Bristol-Myers Co's Application*, [1969] RPC 146). There is no need even to show that a member of the public has actually seen the document. *For example*, in Monsanto *Brignac's) Application*, [1971] RPC 153, it was held that a company had published a document by supplying it to its salesmen, since it had been given to them with no restriction on disclosure; indeed it had been put into their hands with the intention that they should make the information available to the public.

3.3.12 The invention lacks novelty if information about anything falling within its scope has already been disclosed. Thus, for example, if a claim specifies alternatives or defines the invention by reference to a range of values (e.g. of composition, temperature etc), then the invention is not new if one of these alternatives, or if a single example falling within this range, is already known. Thus a specific example is sufficient to destroy the novelty of a claim to the same thing defined generically. For example, disclosure of a metal coil spring anticipates a claim to resilient means. On the other hand, a generic disclosure does not impugn the novelty of a more specific claim, so that an earlier reference to a metal coil spring cannot be used to attack the novelty of a claim specifying such a spring made of copper. In some cases however the disclosure of a comparatively small and restricted field of possible alternatives might properly be held to be a disclosure of each and every member; for example, "fluid" may be taken to disclose both liquid and gas, if the context warrants it, and a reference to an electric motor may be regarded as disclosing the use of both series- and shunt-wound types.

3.4 Illustrative Cases

Example 1:

The subject matter disclosed prior to the filing of patent application will destroy the novelty of the invention. To constitute a prior disclosure of a

of a contract to supply 3900 KVA & 5400 KVA traction transformers. The photocopies of work order did not define any constructional features of the traction transformer. Only by stating that they are the first in the field of manufacturing, the applicant company cannot be stopped from obtaining a patent unless the opponents establish that they were manufacturing an identical product before the date of filing.

Example 5 :

In the case of Monsanto company verses Coramandal Indag Products (P) Ltd. (1986) (1 SCC 642: AIR 1986 712: 1986 PTC 195 SC) it was held that invention was publicly known since its formula was published in the report of the International Rice Research Institute in the year 1968 and its common name Butachlor was published in the same report in the year 1969.

Example 6 :

In T 0814/04, a process for the production of trypsin in a filamentous fungus of an Aspergillus species was claimed. In a cited document it was disclosed that 'trypsin like protease' was isolated from a strain of Fusarium oxysporum a culture which had been deposited at the DSM under the accession number DSM 2672. The protease was characterized by its amino acid sequence consisting of 224 amino acids which was represented in the sequence listing by the sequence listed as SEQ, ID NO:2. The same protease was acknowledged to be a trypsin and this trypsin was found to be equally homologous to trysins from Strptomyces griseus, S.erythraeus and to bovine trypsin. Further, it was stated that the gene encoding the trypsinogen corresponding to that trypsin from Fusarium oxysporum with a signal peptide was expressed by the process as claimed in the present invention i.e. by the same fungal expression vector p777 was used to prepare an expression vector that is co-transformed into the particular strain IFO 4177 of Aspergillus oryzae together with plasmid pToC90 or with plasmid pToC186. Both plasmids carrying the amdS gene from Aspergillus nidulans. The subject matter as claimed was held as not novel.

Example 7 :

In *Kirin-Amgen Inc. v Roche Diagnostics GmbH* [2002] RPC 1, it was held that "the law of patents is ultimately concerned with practicality", and so a prior art experiment which, when performed, reliably produced a particular result "more than 99 percent of the occasions on which it is conducted" would be regarded for the purposes of disclosure as "inevitably" leading to the result in question. It follows that a claim which defines an invention by reference to parameters, for example, of a process or a product, is anticipated by a disclosure , which when put into practice would necessarily fall within the scope of the claim, even if the disclosure does not refer to these particular parameters.

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Example 8 :

In T 303/86 (CPC Int) [1993] EPOR 241, the Technical Board of Appeal of the EPO considered anticipation arising from two cook-book recipes of a process for making flavour concentrates from vegetable or animal substances by extraction with fat solvents under pressure in the presence of water. The claim specified certain parameters for the ratio between the vapour pressure of the water in the meat or vegetables and the vapour pressure of the free water. It was observed that "It is sufficient to destroy the novelty of the claimed process that this process and the known process are identical with respect to the starting material and reaction conditions since processes identical in these features must inevitably yield identical products." Furthermore, it did not matter that the cook had not realised that he was not only frying a chicken, but also making a "flavour concentrate" in the surplus oil. It was enough, as the Board said, that "some flavour of the fried chicken is extracted into the oil during the frying process even if this is not the desired result of that process."

Example 9 :

In *Merrell Dow Pharmaceuticals Inc v H N Norton & Co Ltd* [1996] RPC 76, the court held that the section did not confine the state of the art about products to knowledge of their chemical composition. It is the invention which must be new and which must therefore not be part of the state of the art. It is therefore part of the state of the art if the information which has been disclosed enables the public to know the product under a description sufficient to work the invention. Thus, in Merrell Dow, which centred on a claim to an acid metabolite formed in the liver after administration of terfenadine (itself the subject of an earlier patent), the acid metabolite was held to be anticipated not by prior use but because it was the inevitable result of carrying out the directions in the earlier terfenadine patent.

Example 10 :

In *Norton Healthcare Ltd v Beecham Group Plc* (BL C/62/95) Jacob J held that a prior suggestion of a combination of sodium or potassium clavulanate with amoxycillin or ampicillin trihydrate (four possible combinations only) was a disclosure of each of the combinations.

Example 11 :

In *Union Carbide Corp. v BP Chemicals Ltd* [1998] RPC 1 Jacob J held that "the information given by a direction not to do X because it will have adverse consequences is not equivalent to a direction to do X because it has beneficial consequences or does not have the supposed adverse consequences" and so novelty will not be impugned by an earlier disclosure which in effect gives clear directions not to do that which is claimed in a later application. It was observed that " An invention can lie in finding out that which, in the art thought ought not be done, ought to be

Decision of the Controller (1942) Re. Patent Application No. 27709.)

Example 17:

A "mosaic" of separate steps each known in manufacturer, will not suffice to constitute such anticipation as to warrant the refusal of a grant of a patent, though they may have a bearing upon the question of quantum of ingenuity which arises when a court is called upon to consider whether there is "subject matter" for a patent in the invention. (Decision of the Deputy Controller (1946) Re. Patent Application No. 32384.)

Example 18:

In patent law, in order to render a document a prior publication, it must be shown that it contains all that is material to instruct the public how to put the invention in practice. (Pope Alliance Corp. v. Spanish River Pulp & Paper Mills Ltd., A.I.R. 1929 P.C. 38).

Example 19:

To be effective prior knowledge of an invention prior publication should contain such information as would enable one conversant with the art to which the invention relates to perceive the very discovery and to carry it into practical use. (Decision of the Controller upheld by the Central Government (1944) Re. Patent Application No. 29089).

Example 20:

The disclosure of a document to two or more selected individuals in Government service does not appear to be sufficient to constitute public knowledge of the said document. (Decision of the Controller (1945) Re. Patent Application No. 29180).

3.5 Enabling Prior Art

~~3.5.1~~3.5.1 For establishing anticipation by the prior art, the prior invention should be sufficiently disclosed so that a person skilled in the art is able to work the invention without undue burden of experimentation.

3.5.2 Determination of enablement of a prior disclosure for the purpose of anticipation stands on the same footing as the test of enablement of the patent itself for the purpose of sufficiency. However, depending on the facts of the case the application of the test would differ. In the case of sufficiency the skilled person is attempting to perform a claimed invention setting the goal in mind, whereas in the case of prior art the subject-matter may have been disclosed in the invention but not identified it as such [*SmithKline Beecham Plc's (Paratoxetine Methanesulfonate) Patent* [2006] RPC 10]. The ordinary skilled person must be able to perform the invention, which satisfies the requirement of disclosure.

3.5.3 Thus the requirement of sufficiency of the disclosure and enablement with

regard to prior art is different. In particular, the role of the person skilled in the art is different. In the case of sufficiency, the skilled person is taken to be trying to understand what the author meant. His common general knowledge forms the background in construing the disclosure, with the patent being construed on similar principles. Once this is performed, to determine whether or not the disclosure would infringe, the person skilled in the art has no further part to play. On the other hand, for enablement, the person skilled in the art is assumed to be willing to make trial and error experiments to get it to work, and the question is not what the skilled person would think the disclosure meant, but rather whether he would be able to work the disclosed invention.

3.6 PRIOR PUBLIC USE

3.6.1 Prior public use of the invention in India before the date of filing of application destroys the novelty of the invention. However, there is an exception to this general rule. The Act provides that if an invention has been publicly worked in India within one year before the priority date by the patentee or applicant for the patent or by any third person from whom he derives the title or by the person who has obtained a consent to work the invention and such working of invention was only for the purpose of reasonable trial and it was necessary to effect such trial or working in public in view of the nature of the invention then such working of invention does not anticipate the invention **(Section 32).**

3.6.2 Public user does not mean a user by the public but a user in a public manner (Lallubhai Chakubhai v. Chimanlal Chunilal & Co. 37 Bom L.R. 665).

Example 1:

In Lallubhai Chakubhai v. Chimanlal Chunilal & Co. A.I.R., 1936 Bom. 99, it was held that public user does not mean a user by the public but a user in a public manner. It was further held that the use of an invention for purposes of trade, whether by the inventor himself or by others, may constitute public user of the invention. It was also held that public sale of articles is strong evidence that the user is commercial and not experimental. But to constitute evidence of public user, the sale must be open and in the ordinary way of business.

Example 2:

In patent application No. 23077, Controller held that an invention should be deemed to be publicly used if in the course of regular business (as distinguished from experimental user), the invention has been used without observing any secrecy about it, in any place to which persons without confidential relationship are allowed access.

Example 3:

In Lallubhai Chakubhai v. Shamaldas Sankalchand A.I.R., 1934. Bom. 407, it

was held that if an article manufactured under a secret process is of such a character that any body by examining it can find out the secret of that manufacture, then the sale of that article in public would amount to public user of the process. It was also held that secret use of an invention by the inventor himself for experimental purposes of the manufacture of an invention for the inventor by a manufacturer, who is under injunction to keep the invention secret will not make the patent invalid.

Example 4:

In Monsanto Co. V. Coromandel Indag Products (P) Ltd. 1986 A.I.R. 712, it was held that "to satisfy the requirement of being publicly known as used in clauses (e) and (f) of section 64(1), it is not necessary that it should widely used to the knowledge of the consumer public. It is sufficient if it is known to the persons who are engaged in the pursuit of knowledge of the patented product or process either as men of science or men of commerce or consumers."

Example 5:

In patent application No.23077, it was held by the Controller that an invention should be deemed to be made publicly known if a document containing an adequate description of it, whether issued as a general publication or not, has in the course of ordinary business and without imposing any secrecy, reached an appreciable section of the public interested in the art to which the invention relates.

Example 6:

In the patent application No.29180, it was held by the Controller that disclosure of a document to two or more selected individuals in Government service does not appear to be sufficient to constitute "public knowledge" of the said document.

Example 7: EXHIBIT P6

In *Lux Traffic Controls Ltd v Pile Signals Ltd and Faronwise Ltd*, [1993] RPC 107 Aldous J recognized that what was made available to the public often differed according to whether the public had an article in their possession to handle, measure and test or whether they could merely look at it. Depending on the circumstances a skilled person might be able to determine how an article was constructed and operated or nothing material might be disclosed.

If an article or a material is unconditionally supplied to a member of the public, possibly as the result of just a single sale (T482/89 OJEPO 11/92), this is regarded as also making available any information which could be obtained by dismantling or analysing the article or material, even to destruction (G1/92 OJEPO 5/93).

EXHIBIT P6

Novelty is destroyed by prior use of a product if analysis of the product using available techniques shows the skilled person that it falls within the scope of the claims (T952/92 OJEPO 11/1995).

Example 8:

In the case of *Ram Narain Kher* v. *Ambassador Industries, (*AIR 1976 Del 87*.), it was held that* At the time the patent is granted to a party it is essential that the party claiming patent should specify what particular features of his device distinguish it from those which had gone before and show the nature of the improvement which is said to constitute the invention. A person claiming a patent has not only to allege the improvement in art in the form but also that the improvement effected anew and very useful addition to the existing state of knowledge. The novelty of the invention has to be succinctly stated in the claim. It is no doubt true that the claim made is addressed to the skilled persons in the art or trade and not to a common man yet there can be no escape from the fact that the novelty of the claim or the advantage derived by the invention has to be succinctly stated in the claim and must not be left to an inference raised on a general review of the specification. It is equally true that even when the invention 'was not itself new', 'the particular use of it for the purpose described in combination with the other elements of the system, and producing the advantageous results', would be a sufficient element of novelty to support the patent. It may be only a small step but that may be a step forward and that is all that is necessary so far as the subject-matter is concerned.

Example 9:

In Staridipack Private Limited v. *Oswal Trading Co. Ltd (*1999 (19) PTC 479 (Del)) the invention was related to thickness of the layers of pouch. The issue was about "the thickness of plastic film/layer depends upon the tolerance of the contents in the pouch". It was held that the invention is merely an arrangement and rearrangement of the items and cannot be termed as a novel concept and does not have any novelty. Such arrangement and rearrangement of mixture of the materials cannot become an invention, for it is only an improvement by adding microns as per the strength of the layers. Thus, *prima facie* the invention claimed by the plaintiff in respect of the thickness of the layers of the aforesaid pouch cannot be called an invention as envisaged within the definition clause of the Patents Act. Besides, the documentary evidence placed on record *prima facie* indicates that the claim made by the plaintiff is already known in the trade and the patent was pre-published.

Example 10:

In *Milliken Denmark AS v Walk Off Mats Ltd and anr* [1996] FSR 292 Jacob J held that the hiring of mats to customers who were free to inspect them amounted to anticipatory prior use even though the mats relied on perforations not visible to the naked eye for their function. While there was no reason to suppose that any customer should have conducted tests which would have revealed the perforations, a skilled person called on to investigate the mats would none the less have discovered them. The knowledge of the

EXHIBIT P6

specification filed in pursuance of an application for a patent made in India and dated before or claiming the priority date earlier than that date.

3.7.1 In order to prove prior claiming of the invention, following conditions should be complied with:--

(i) that the application(x) where the invention has been claimed prior to the application(y) claiming alleged invention, has been filed in India

(ii) the application(x) must have been filed earlier to the date of filing or priority date of application(y) in question

(iii) the application(x) should have been published on or after the date of application(y) in question.

3.7.2 In the matter of application for patent no. 123140, Centron Industrial Alliance Private Limited v Harbans Lal Malhotra and Sons Private limited, [DPD, Vol.1, p 133], application filed on 15th September 1969 in respect of " Improvements in or relating to blades of razors and like instruments." Claimed in Claim1:A method of manufacturing. superior quality blades of razors and like instruments as herein defined, which includes coating the blades **with** polytetrafluoroethylene, characterised in that the said method consists of atomic or molecular deposition in vacuum of a thin film of particles of a corrosion resistant material on the cutting edge or edges of the blades of the said instruments before coating the said blades with said polytetrafluoroethylene.

Prior filed application 120345 filed on 14th March 1969 cited for prior claiming claimed in claim 1: A method of manufacturing. superior quality blades of razors and like instruments as herein defined, which consists atomic or molecular deposition in vacuum of a thin film of particles of a corrosion resistant material on the cutting edge or edges of the blades of the said instruments and thereafter coating the said blade with polytetrafluoroethylene.

Controller found the application completely anticipated by prior claiming

Prior art filed application 120651 of 31st March 1969 was found anticipating by prior claiming in part. 120651 claimed Rhodium as deposited material on the cutting edges of the blade instead of a general expression "corrosion resistant material" of impugned claim. The only difference of '651 was the use of Rhodium as a thin film of particle deposited. The Controller observed that the characteristic property of Rhodium is identical with the identical property of corrosion resistant material. This lead to the conclusion that the claim at issue was anticipated by cited document in part by prior claiming.

In the similar manner 120652 (31st March 1969) used platinum and was held as anticipating in part by prior claiming.

EXHIBIT P6

118127 (16th October 1968) used razor blades made of carbon steel or haedened stainless steel having a coating of chromium. This was also, held as anticipating in part by prior claiming.

3.8 Novelty in case of selection inventions:

3.8.1 A prior disclosure in general terms embracing a number of alternatives may amount to no more than a mere suggestion that any of the members, including any specifically exemplified, might be used, and may therefore be regarded as not anticipating a claim to a specific one of the members. An invention so claimed is generally referred to as a "selection" invention and should meet the criteria as-

1. the selection must be based on some substantial advantage gained or some substantial disadvantage avoided,
2. substantially all the selected members must possess the advantage in question, and

~~(3)~~3. the selection must be in respect of a quality of special character which can fairly be said to be peculiar to the selected group. However, this is not necessarily nullified if it transpires that some other members of the class from which the selection is made have this quality, but the claim may be invalid if it is found that the quality is common to many other members in addition to those selected (IG Farbenindustrie AG's Patent, 47 RPC 289 P.322).

document is necessary. In the case of obviousness many documents can be considered.

3.10.4 In Gillette Industries Ltd., v. Yeshwant Bros. A.I.R., 1938. Bom. 347., it was held that mere simplicity is not necessarily an objection to the subject matter of an invention, though matters of ordinary skilled designing or mere workshop improvements are not inventions.

3.10.5 When the invention is just an automatic or obvious extension of Prior Art, the invention lacks in inventive step.

3.10.6 To judge the inventive step, the question to be answered is-
" Would a person with ordinary skills in the art have thought of the alleged invention?" If the answer is No, then the invention is non- obvious. The question, "Is there an inventive step?" arises only if there is novelty in the invention.

3.10.7 The question is therefore, does the invention make available to the person skilled in the art something that he would not reach by normal exercise of his skill? If so, the inventor has made a contribution to the art which provides the consideration justifying the grant of a patent. This is not to say that it must be technically complex; simplicity does not count against an invention . But there is no invention in appreciating commercial features alone , for example in realizing that there is a market for a new product, however surprising this may be.

3.10.8 Just as an invention will lack novelty if the claim to it would re-monopolize something already disclosed, likewise it will be regarded as obvious if a claim to it would inhibit the rights of a skilled workman to carry out routine modifications of what is already in the public domain

3.10.9 For anticipation it is seen that it would be wrong to enable the patentee to prevent a man from doing what he has lawfully done before the patent was granted. In a similar way, the consideration behind obviousness is that it would be wrong to prevent a man from doing something which is merely an obvious extension of what he has been doing or of what was known in the art before the priority date of the patent granted [1985] RPC 59, p. 77)

3.10.10 The term "obvious" means that which does not go beyond the normal progress of technology but merely follows plainly or logically from the prior art, i.e. something which does not involve the exercise of any skill or ability beyond that to be expected of the Person Skilled in the Art.

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3.10.11 For this purpose a Person Skilled in the Art should be presumed to be an ordinary practitioner aware of what was general common knowledge in the relevant art at the relevant date. In some cases the Person Skilled in the Art may be thought of as a group or team of persons rather than as a single person.

3.10.12 Some examples to illustrate the points mentioned above are given below:

i. The invention must be considered as a whole for consideration of inventive step. It is thus not sufficient to draw the conclusion that a claimed invention is obvious merely because individual parts of the claim taken separately are known or might be found to be obvious.

j. If a claim relates to a composition comprising known ingredients, it is likely to be obvious, unless the mixture/combination leads to some new effect, say, for example , synergistic effect.

k. If an invention lies merely in verifying the previous predictions, without substantially adding anything for advancement in the art, the inventive step is lacking.

l. In general, where an invention comprises a collection of known or obvious parts, it must be shown before raising the objection for obviousness that it was obvious to combine these parts.

m. Where an invention can be thought of as the result of a selection from a number of alternatives, to demonstrate that the invention is not obvious, it is usually only necessary to show that it solves a technical problem in a surprising or unexpected way.

3.12 <u>Ex-Post Facto Analysis in relation to Inventive Step</u> :

3.12.1 The examiner (or any other person) who is considering the question of whether or not an invention is obvious must beware of ex-post facto analysis. It can be very easy to be misled by a line of reasoning involving taking the solution and working backwards to the problem by a succession of easy steps. In considering a prior publication the examiner must avoid looking at the document under the influence of the application he is examining, and should attempt to place himself in the shoes of the skilled person faced with the problem at hand.

In [1985] RPC 59, the *Windsurfing International Inc. v Tabur Marine (Great Britain) Ltd,* Court of Appeal held that the question of obviousness "has to be answered, not by looking with the benefit of hindsight at what is known now and what was known at the priority date and asking whether the former flows naturally and obviously from the latter, but by hypothesizing what would have been obvious at the priority date to a person skilled in the art to which the patent in suit relates".

3.13 Inventive Step in relation to combination invention

i) In assessing the inventive step involved in an invention based on a combination of features, consideration must be given to whether or not the state of the art was such as to suggest to a skilled person precisely the combination of features claimed. Thus the question is not whether the skilled person, with access to the entire prior art, could have made the combination according to the invention, but whether he actually would have done so in expectation of an improvement

ii) The fact that an individual feature or a number of features were known from prior art does not conclusively show the obviousness of a combination (T 37/85, T 666/93, T 1018/96); but whether the state of the art would lead a skilled person to this particular overall combination of possibly already known features. In such a case, it would be impossible for a combination consisting exclusively of known individual features to involve an inventive step (T 388/89, T 717/90, T 869/96).

iii) A mere aggregation of features must be distinguished from a combination invention. The existence of a combination invention requires that the relationship between the features or groups of features be one of functional reciprocity or that they show a combinative effect beyond the sum of their individual effects.

iv) In T 406/98 the board found that as a rule, particularly when large numbers of citations were involved, it was necessary to ask why the skilled person would consider documents in that specific combination, and whether, not knowing the invention, he had reason to do so. In this case, a complete solution to the problem required deliberate selection from a large number of citations.

v) A combination invention is to be judged whether these features or sets of features are functionally interdependent, i.e. mutually influence each other to achieve a technical success over and above the sum of their respective individual effects as assumed in the case of a combination of features

vi) It was held that there was no inventive step in combining the claim's two features, both known per se, since they related to the solving of two entirely separate partial problems and the solutions could be assessed separately against the prior art [T 597/93, T 687/94]

3.14 Determination of Inventive Step :

A) Issues involved in assessment of Inventive Step

The following aspects need to be looked into while determining inventive step in the alleged invention :

a) What was the problem which the patented development addressed?
b) How long had that problem existed?
c) How significant was the problem seen to be?
d) How widely known was the problem and how many were likely to seeking a solution?
e) What prior art would have been likely to be known to all or most of those who would have been expected to be involved in finding a solution?
f) What other solutions were put forward in the period leading up to the publication of the patentee's development?
g) To what extent were there factors which would have held back the exploitation of the solution even if it was technically obvious?
h) How well had the patentee's development been received?
i) To what extent could it be shown that the whole or much of the commercial

success was due to the technical merits of the development? (Haverman vs Jackal (1999) FSR 685 at 699-701)

B) Steps in Determination of Inventive Step:

a. Determining scope and content of the prior art to which the invention pertains

b. Assessing the technical result (or effect) and economic value achieved by the claimed invention

c. Assessing differences between the relevant prior art and the claimed invention

d. Defining the technical problem to be solved as the object of the invention to achieve the result

e. Final determination of non-obviousness, which is made by deciding whether a person of ordinary skill could bridge the differences between the relevant prior art and the claims at issue.

C) **Assessing Inventive Step:**

When assessing an inventive step, combining the teachings of different documents within the prior art [mosaics] is permissible, if it is obvious to do so at the time of filing or priority date of patent application, to the skilled person in the art.

The applicant may, for example, have presented his invention as a combination of features A, B, C, and D which he admits as known in combination, with a further feature E which it would undoubtedly be inventive to add to the acknowledged combination.

It may be however that a prior document discloses the combination of features A and E, and that the addition of the remaining features B, C, D is then the most natural way of completing the disclosure in the prior document and therefore obvious.

3.15 Person Skilled in the Art

i) The person skilled in the art should be presumed to be an ordinary practitioner aware of what was common general knowledge in the art at the relevant date (average skilled person).

ii) He should also be presumed to have had access to everything in the state of the art, in particular the documents cited in the search report, and to have had at his disposal the normal means and capacity for routine work and experimentation

iii) Such person should not possess any inventive capability. It was the presence of such capability in the inventor, which set him apart from the notional skilled person. His attitude is considered to be conservative. He would never go

against an established prejudice, nor try to enter unpredictable areas nor take incalculable risks.

iv) The skilled person can be expected to look for suggestions in neighbouring fields if the same or similar problems arise in such fields. The skilled person can be expected to look for suggestions in a general technical field if he is aware of such fields. The notional skilled person would perform a transfer of technology from a neighbouring field to his specific field of interest, if this transfer involved routine experimental work comprising only routine trials

Example 1

In *Tetra Molectric Ltd v Japan Imports Ltd* ([1976] RPC 547) the Court of Appeal held that a claim to a smoker's lighter using piezoelectric ignition was obvious. Since the possibility of using piezoelectricity in a lighter would have occurred to the industry, a skilled lighter manufacturer, himself not an expert in piezoelectricity, could reasonably be expected to seek advice from those who were. If such experts had been consulted, they would have advised that the suggestion was definitely worth trying, and they could have solved such problems as arose. The hypothetical skilled man in this case was therefore a team which included persons skilled in piezoelectricity, and not simply persons engaged in the lighter industry.

v) The skilled man should not be expected to try all combinations unless he has a problem in mind and particular combinations might assist him in solving it; he is not to be expected to take steps or try processes which he would not regard as worthwhile as a possible means of achieving or assisting in practice the objective which he has in view (see the judgment of the Court of Appeal in *Hallen Co v Brabantia (UK) Ltd* [1991] RPC 195.

vi) In advanced technical fields the competent "skilled person" could be taken to be a group of people as "skilled person" from the relevant technical branches such as a research or production team.

vii) The person skilled in the art is normally not assumed to be aware of patent or technical literature in a remote technical field. In appropriate circumstances, however, the knowledge of a team consisting of persons having different areas of expertise can be taken into account (T 141/87, T 99/89). Solutions of general technical problems in non-specific (general) fields are considered to be part of the general technical knowledge

This would be the case in particular if an expert in one particular field was appropriate for solving one part of the problem, while for another part one would need to look to another expert in a different area (T 986/96).

Thus, in real life the semiconductor expert would consult a plasma specialist if his problem concerned providing a technical improvement to an ion-generating plasma apparatus (T 424/90) or the average skilled person in electronics, particularly if he did not have an adequate knowledge of programming languages himself, might be expected to consult a computer programmer if a publication contained sufficient indications that further details

of the facts described therein were to be found in a program listing attached as an annex thereto (164/92) or in advanced laser technology, the "skilled person" may be as a production team of three experts in physics, electronics and chemistry respectively (T 222/86)

viii) The average skilled person would not engage in creative thinking (T 500/91). Yet he or she could be expected to react in a way common to all skilled persons at any time, namely that an assumption or hypothesis about a possible obstacle to the successful realisation of a project

Example:1

In T 412/93 the patent related to the production of erythropoietin. The parties agreed that in this particular case the skilled person should be treated as a team of three, composed of one PhD researcher with several years' experience in the aspect of gene technology or biochemistry under consideration, assisted by two laboratory technicians fully acquainted with the known techniques relevant to that aspect. The composition of the team might vary depending on the knowledge and skills required by the particular aspect dealt with.

Example: 2

In T 455/91 (OJ 1995, 684) the board set out considerations on the skilled person's likely attitude to possible changes, modifications or adjustments in known products (eg a plasmid) or procedures (eg an experimental protocol). Its aim was to answer, objectively and avoiding any ex post facto analysis, the question whether it would be obvious to the skilled person to make given changes in a structure or procedure. The skilled person in this field was well aware that even a small structural change in a product (eg a vector, protein, or DNA sequence) or procedure (eg a purification process) could produce dramatic functional changes. He would therefore adopt a conservative attitude. For example, he would neither go against an established prejudice, nor venture into "sacrosanct" or unpredictable areas, nor take incalculable risks. (T 441/93).

Example:3

In application number 94/CAL/2002 (Applicant : Sanjiv Agarwal, Fairfest Media Private Limited), the Controller held, "... the contention of the agent of the applicant that the examiner or the controller is not supposed to be a person skilled in the art is not well founded. On the contrary we find that the Act imposes it on them that they should put themselves at the place of person skilled in the art not only to determine the inventiveness but also to determine the novelty and sufficiency of disclosure of the alleged invention."

3.16 Lack of Inventive Step : Examples

a. When invention lies only in providing equivalents (mechanical, electrical or chemical) to the known art:

~~b.~~*For example*- Use of hydraulic motor instead of electric motor in a pump

~~e.~~b. When the Prior Art is incomplete and the invention lies in "Filling the gap", which would naturally or readily occur to the skilled person

~~d.~~*For example-* The invention is a building structure made from Aluminium. The prior art discloses such a structure of light weight material but does not mention Aluminium

~~e.~~c. Invention consists of a new use of well-known material employing the known properties of that material

~~f.~~*For example*_– Washing composition containing detergent which is a known compound having property of lowering the surface tension of water; the property being known as the essential one for detergents

~~g.~~d. When an invention consists of a new use of well-known material employing the known properties of that material, inventive step is lacking

For example: A washing composition containing detergent which is a known compound having property of lowering the surface tension of water; the property being known as the essential one for detergents

~~k.~~e. Substitution of a recently developed material in a known device whose properties make it suitable for that use as earlier

~~l.~~*For example*_- An electric cable comprises a polyethylene sheath bonded to a metallic shield by an adhesive. The invention lies in the use of a particular newly developed adhesive known to have the property of being suitable for metal bonding

~~m.~~f. Selecting a particular range of parameters from a limited range of possibilities, which is obvious The invention can be arrived at as a mere a simple extrapolation in a straightforward way from the known art

~~n.~~g. Use of a known technique in a closely analogous situation

~~o.~~*For example*-Application of a pulse control technique to an electric motor driving an auxiliary mechanisms of an industrial truck such as a fork –lift truck , where the use of this technique is already known for the electric propulsion motor of the truck.

~~p.~~h. Juxtaposition of known devices or processes not producing any non– obvious working inter-relationship

3.17 Indicators of Inventive Step

a. **Distance :**It is to be decided as to how much is the distance between the subject-matter of the invention and the prior-art. If such distance is large , establishing the inventive step is easier.

b. **Surprising Effect:** The inventive step may be present if there is a surprising or unexpected effect. However , if the measures which lead to this effect ,are near at hand by themselves, a surprising effect is not sufficient for granting a patent.

c. **Long Felt Need:** If the claim solves a "long felt need", there is a presumption that a claim is not obvious as other inventors might have also tried to solve it but could not provide the solution to fulfil the need.

e. **Failure of Others:** If other inventors have tried to solve a problem and were not successful, the claim will likely involve an inventive.

g. **Complexity of Work:** If the work undertaken by the inventor in order to produce the invention was particularly complex, and not readily carried out, that is an indication that it was not a matter of routine. In such cases the invention can be non-obvious.

i. **Commercial Success:** Commercial success is indicative (but not conclusive) of an inventive step.

k. Cheaper and more economical Product and simplicity of the proposed technological solution.

l. Prior art motivation.

3.18 Long Standing Problem: The fact that no-one has followed a particular path before does not of course dispose of an objection of obviousness; otherwise any invention which was new would automatically be inventive. However, the reasons why this has not been done before may well be important.

(i) If the inventor has solved a long-standing problem by using in a conventional way the materials or techniques which have only recently become available then this is not inventive.

(ii) It is also not inventive to respond to a change in economic circumstances; for example if a product has not been made from a particular material or by a particular process for reason of cost, and the material or process becomes cheaper or the market value of the product increases, it is not inventive to take advantage of this.

(iii) If a newly- arisen problem is solved by the use of available resources in an obvious way, then there is no inventive step (unless the inventor has been the first to identify the problem).

(iv) But if the inventor has solved a long-recognised problem by means which others could have used but did not, then there may be an inventive step (*Minnesota Mining & Manufacturing Co v Rennicks Ltd* [1992] RPC 331).

Example:

In *Chiron Corpn v Organon Teknika Ltd* [1994] FSR 202 a claim to a polypeptide comprising an antigenic determinant of the hepatitis C virus was found to be non-obvious because despite the attempts of numerous research groups over a 10 year period to identify the agent responsible for Non-A, Non-B Hepatitis (latterly named Hepatitis C), the patentees succeeded in a unique fashion by adopting a known technique which would not have been obvious to try in the circumstances.

o.**3.19 Fulfilling Need:** Evidence that an invention fulfils a long-felt want and has been commercially successful may be taken into account in assessing obviousness (*Hickman v Andrews*, [1983] RPC 147 and *PLG Research Ltd v Ardon International Ltd*, [1993] FSR 197), Optical Coating Laboratory Inc. v Pilkington P.E. Ltd. [1995] RPC 145, P.166.

It is important to have an evidence of a long-felt want or unsuccessful attempts to solve a particular problem, any evidence as to novelty, years of delay in developing the prior art and an advantage stemming from the invention. Sometimes commercial success of the invention may be attributable to factors achieved independently of the invention, such as the quality or price of the product, or to superior marketing.

Example:

In *Tetra Molectric Ltd v Japan Imports Ltd*, [1976] RPC 547 on the other hand, it was held that the commercial success of a cigarette lighter was due in large part to hammer mechanisms developed since the date of the invention; although claim 1 covered lighters which had enjoyed commercial success, it also covered lighters which could never do so, and no features which might ensure success were recited.

p.**3.20 Advantages of invention:** Where a variation from published matter proposed by the applicant has no advantages, or is even disadvantageous, although it can be argued that the resulting inferior procedure is not obvious in the sense that no skilled man would regard it as obvious to do something inferior, the application should nevertheless, if the variation is one whose possibility a skilled man would appreciate, be refused on the ground that there is no inventive step. [T119/82, OJEPO 5/84]. The position is of course different if the applicant has discovered that a variation thought to be disadvantageous is in fact not so, or if from a large number of variants which would have been regarded as no more than feasible alternatives with no advantages, the applicant has selected a variant with an unexpected advantage.

q.**3.21 Obvious to try:** Where a skilled worker in a particular field could be expected to know of a use of material to achieve a certain result in that field, an invention which is concerned with the use of that material to achieve the same result in a part of that field, which had not been previously disclosed, is obvious if a person versed in the art would assess the likelihood of success sufficient to warrant a trial.

Example:

The invention was concerned with the use of particular flocculating agents in asbestos cement manufacturing. It was held that, filtration processes being common to many industries, two cited documents, although addressed primarily to the mining and paper industries respectively, were likely to be read by those concerned with the asbestos cement industry, and that such readers would have realised that here was a newly-introduced flocculating agent which it was well worth trying out in their filtration process *[Johns-Manville Corporations Patent,* [1967] RPC 479 P 494]

An effect which was revealed by following the obvious course of action did not make the action non-obvious. It was wrong to ask whether you would have predicted the effect *[Bristol-Myers Squibb Co v Baker Norton Pharmaceuticals Inc* [1999] RPC 253]

However, mere possible inclusion of something within a research program on the basis you will find out more and something might turn up is not enough to show obviousness. If it were otherwise there would be few inventions that were patentable. The 'obvious to try' test really only works where it is more-or-less self-evident that what is being tested ought to work" **For example**, the cited prior art pointed to the possibility that using a Zn/Al alloy as a coating for a cast iron pipe to be buried in soil might be beneficial by showing results for this alloy coating for buried steel plates. It was not however possible for the skilled person to predict success, so the invention was not obvious. [In *Saint-Gobain PAM SA v Fusion Provida Ltd and Electrosteel Castings Ltd* [2005] EWCA Civ 177, [2005] IP & T 880]

Contribution to the art disclosed by the patent specification is also crucial in considering whether something is obvious to try. The court held that the contribution to the art made by the specification had to be assessed in order to decide whether it was sufficient to show that something was an obvious candidate for testing without any expectation of success, or whether it was necessary to show that the skilled person must have had an expectation of success sufficient to induce him to use it in practice[*Angiotech Pharmaceuticals Inc's* [2006] RPC 28]

If the specification gave no indication of the likelihood of success, side-effects or efficacy, the invention was likely to be held obvious. For example, the patent specification disclosed that taxol could be incorporated on a stent (a tubular device which acts as scaffolding to hold a diseased artery open), but gave no suggestion that this would be safe or prevent restenosis (closure of the lumen of the artery caused by proliferation of smooth muscle cells). Therefore, a claim to a taxol-coated stent was held to be invalid as it was concluded to be obvious to a skilled person that taxol should be incorporated onto a stent with a view to seeing if it prevents restenosis and is safe ([2007] RPC 20).

r.3.22 Selection: Although there is no inventive step if it is clear from the prior art that taking that step is likely to lead to success, there may be invention if that is only one of many courses possible, and there is no reason to infer from the prior art that this one is more likely than the others to be profitable.

Example 1:

In *Bayer AG (Baatz's) European Application* [1982] RPC 321, carbonless copying paper was characterised by microcapsules made of a particular polymer, which was already known for forming coatings on textiles, leather, wool and metal. Even if these were thought to be neighbouring fields, there was no reason to expect that improved results would be obtained by the use of this material (as the results of comparative experiments showed they were), and thus it was not obvious to select it from the enormous number possible.

Example 2:

In *Olin Mathieson Chemical Corporation v Biorex Laboratories Ltd*, [1970] RPC 157 at page 192, it was held not to be obvious that a useful drug would be obtained by substituting -CF_3 for -Cl in a known drug, given the large amount of prior material, leading in a number of different directions, which was before the skilled person at the date of the invention.

A "selection" invention should meet the criteria namely the selection must be based on some substantial advantage gained or some substantial disadvantage avoided substantially. All the selected members must possess the advantage in question and selection must be in respect of a quality of special character which can fairly be said to be peculiar to the selected group. This is not necessarily nullified if it transpires that some other members of the class from which the selection is made have this quality, but the claim may be invalid if it is found that the quality is common to many other members in addition to those selected [47 RPC 289 ,P 322-3]

The advantage relied upon to justify a selection invention should be clearly disclosed if it would not otherwise be apparent to a person skilled in the art. For example, in *Glaxo Group Ltd's Patent* [2004] RPC 43, the Patents Court held that unexpected bonus effects not described in the specification could not form the basis of a valid claim to a selection invention. If there is no statement of advantage in the specification at the time of filing it may not normally be added later , although such a statement (which will of course be open to public inspection) may be filed and may be taken into account.

Although the size of the class from which a member or members have been chosen is not relevant to the question of novelty of a selection invention, it may be relevant to the question of obviousness (*Du Pont de Nemours &c (Witsiepe's) Application*, [1982] FSR 303, P 310). In the *Du Pont* case, the relevance of a document describing a composition with a general formula to a claim to a particular composition falling within that formula was considered.

The technical significance of the parameters by which the product or process is selected should be considered. Where unusual parameters are used in a claim it may be difficult to prove whether or not the prior art would have inevitably exhibited those parameters, but in *Raychem Corp.'s Patents* [1998] RPC 31 it was held that "although it may not be obvious, in the common use of that word, to limit a claim by reference to some particular meaningless and arbitrary parameter, that had nothing to do with patentability. Patents are not given for skill in inventing technically meaningless parameters." If a product or process with obviously desirable characteristics happens to fall within the limits of such claims then they cover what is obvious and will thus be invalid.

Example 3:

In *Union Carbide Corporation (Hostettler's) Application*, [1972] RPC 601, P 609, it was observed that if in fact the step taken was an obvious step, it remains an obvious step however astonishing the result of taking it may be. An added benefit, however great, will not found a valid patent if the claimed innovation is obvious for another purpose

Example 4 :

In *Hallen Co v Brabantia (UK) Ltd* [1991] RPC 195), it was held to be obvious to coat a corkscrew of self-pulling type with PTFE to facilitate its penetration into a cork; the claimed invention was not saved by the non-obvious additional advantage of facilitating extraction of the cork from the bottle (although it might have been saved as a selection patent if the specification had contained clear assertions that the corkscrew in question turned the use of PTFE to special advantage over other corkscrews in the extraction stage, thus overcoming a problem of all previous self-pullers).

In general, an otherwise obvious combination is not saved from a finding of obviousness by some unexpected advantage caused by an unpredictable co-operation between the elements of the combination (see *Glaxo Group Ltd's Patent* [2004] RPC 43).

~~5.~~**3.23 Overcoming Technical Prejudice:** An invention may be regarded as non-obvious if it goes against the generally accepted views and practices in the art. In *Appliances Ltd v Hoover Ltd* [2001] RPC 26, it was held that the common general knowledge held by the skilled person may have both positive and negative aspects, and it is necessary to take account of both; in other words to take account of what the skilled person would consider doing and what the skilled person would be prejudiced against doing, as a result of that knowledge. If the common general knowledge was such that the skilled person did not perceive a problem with the prior art, it becomes "considerably more difficult" to establish the obviousness of taking a particular step which would bring that prior art within the scope of the claims in question.

In the case in question it was held that the common general knowledge of the skilled person at the relevant time, along with a lack of a perceived problem, would mean that the skilled person would never have considered using anything other than bag technology in a vacuum cleaner. Further examples are if persons skilled in the art would regard certain materials or techniques as unsuitable for a particular purpose, then if the inventor has found that this prejudice is not well-founded, then he has made an inventive contribution to the art. Likewise the omission of a step hitherto thought to be necessary may constitute an inventive step.

Example:

Thus a rooted objection to the regular use of b2-antagonists in the treatment of asthma, which was the subject of an ongoing dispute amongst specialist physicians, was not ascribed to the skilled person. Another situation is where scientific opinion is out of accord with what is done in the market, as occurred in *Ancare New Zealand Ltd's Patent* [2003] RPC 8 for a sheep drench comprising two known agents, one active against round worms and one active against tapeworms. Here, the patentee argued that an inventive step lay in including the tapeworm agent because there was scientific hostility against treating tapeworms in sheep. However, it was common practice for New Zealand farmers to treat their lambs for tapeworm at the priority date.

The Privy Council, upholding judgments of the New Zealand High Court and Court of Appeal to revoke the patent for obviousness and not involving any inventive step over what was known or used before the priority date of the claim in New Zealand, held that "the fact that scientific opinion might have thought that something was perfectly useless did not mean that practising it, or having the idea of making a preparation to do it, was an inventive step. Otherwise, anyone who adopted an obvious method for doing something which was widely practised but which the best scientific opinion thought was pointless could obtain a patent".

There is also no invention in merely tolerating the disadvantages which have deterred others. For example , if an inexpensive plastics material is thought unsuitable for making tools because it is not durable, there is no invention in using it to make a cheap screwdriver intended only for light work and accepting that it will have only a short life.

Some of these points may be illustrated by a hypothetical example: Suppose that it has been stated for years in textbooks that a particular class of chemical reaction carried out under elevated pressure, gives poor yields, and an inventor now claims the synthesis of a particular compound by such a process. If all he has done is to take advantage of the high price commanded by the product, or the cheapness of the starting materials, and has decided to accept the disadvantage of low yield, then that is not inventive; it is an obvious response to prevailing economic circumstances. On the other hand, if the inventor has discovered that good yields can be obtained by the use of still higher pressures, a fact not suggested in the prior art, then that would be inventive. But if higher yields would be

expected at difficult-to-obtain pressures, and the inventor has merely taken advantage of new techniques making such pressures more available, then that is not inventive. Finally, if the inventor has discovered that the standard accepted views on the low yields, while being normally true for this reaction, are not in fact true for this particular compound, then there is inventive step in the choice of this process.

3.24. Case Studies --Assessment of Inventive Step :

Example 1:

In case of *Rickett & Colman of India Ltd.* V *Godrej Hi Care Ltd.*,(2001 PTC 637 (PO)).Application of M/s. Rickitt & Colman of India Ltd.

The patent "A Mosquito/Insect Repellant Device" - Challenged by opponents on various grounds of section 25 of the Act including lack of inventive step.

The issue in this case was , "whether the applicant's devices involve any inventive step and the opponents has lead any evidence as to patentability".

It was held that the alleged device is obvious and clearly does not involve any inventive step. Further the opponents have not adduced any evidence regarding grounds of patentability. So, it is construed that opponents have dropped the aforesaid grounds. As the opposition has been successful on the ground of section 25(l)(e), the ground 25(l)(a), i.e. wrongfully obtained need not be discussed. Hereby the grant of patent is refused.

Example 2:

In case of application *No. IN/PCT/2002/00020/DEL, U/S 25(1)* , it was concluded that invention as claimed in finally revised claims 1 to 49 in the Patent application no. IN/PCT/2002/00020/Del does not involve any "inventive step" having regard to the prior art citations JP-8059512 published on 05/03/1996 and US Patent 5,885,617 published on 23/03/1999. Therefore it cannot be considered as an invention under section 2(l)(j) of the Patents Act. As it is a mere admixture and therefore not patentable under section 3(e) of the Patents Act.

It was held that "the selection of particular range of ingredients from the ranges already known prior art in this case cannot amount to establish the inventive step and The variations in the amounts of the known ingredients appear merely workshop improvements achieved by a person skilled in the art without performing any substantial experiments and can not be said a technical advancement of an existing knowledge which is required by the definition of the "inventive step" as mentioned in section 2fl(ja)J of the Patents Act, 2005." and for the ground u/s 3(e) that

"The existence of already known characteristics of composition with known ingredients cannot be termed as synergy among the ingredients of claimed composition"

Example 3:

In case of Patent No. 173953 (223/BOM/1991) the invention was related to "process for making a soap composition containing glycerol". Opposition was lodged on the ground of prior publication, prior public knowledge, obviousness, not an invention within the meaning of the Act and does not sufficiently define the invention

It was held that the ingredients recited in the principal claim have a very specific and narrow range of proportions, which are not taught by cited documents. Cited document do not teach how to obtain the right balance of salt & glycerol in order to avoid a soap which is too hard or too soft. Also, in cited documents there is no mention of balancing the quantities of glycerol or salt against the quantities of total fatty matter. So opponents failed to establish the grounds.

Example 4:

In case of Patent No. 183455 (203/BOM/1997) the invention relates to a process for preparation of injectable Nimesulide composition. Opposition was lodged on the ground of obviousness among other grounds such as prior publication, prior public knowledge In view of the cited Srilanakan Patent, the alleged invention stands anticipated as cited document disclosed the invention or disclose information in such a way as to make it part of the state of the art.

The claim lacks in novelty if information about anything falling within its scope has already been disclosed in the prior art. Thus, for example if a claim specifies alternative, or defines the invention by reference of range of values, then the invention is not new if one of these alternatives, or if a single example falling within this range, is already known. Thus a specific example is sufficient to destroy the novelty of a claim when the same is defined generically.

The grant of patent was refused on the above grounds

Example 5:

In case of Ajay Industrial Corporation v. Shiro Kamas of Iberaki City (AIR 1983 Del 496.) The specification and claims have all to be read together and reasonably and benevolently construed. In the absence of any technical or expert evidence either indicating that these statements are wrong or that the article produced incorporates no new devices to get over these defects, it cannot be held that the patent embodies no new discovery or invention. Appellant has not discharged the onus that lay on it to establish that the respondent's patent could not have been registered and, therefore, needs to be revoked.

Example 6:

In case of *Monsanto Company* v. *Coramandal Indag Products (P) Ltd.,* (1986) (1 SCC 642: AIR 1986 712: 1986 PTC 195 SC) Herbicide CP 53619 (Butachlor) was publicly known before Patent Number 125381 was granted. Its formula and use had already been made known to the public by the report of the International Rice Research Institute for the year 1968. No one claimed any patent or any other exclusive right in Butachlor. To satisfy the requirement of being publicly known as used in clauses (e) and (f) of section 64(1), it is not necessary that it should be widely used to the knowledge of the consumer public. It is sufficient if it is known to the persons who are engaged in the pursuit of the knowledge of the patented product or process either as men of science or men of commerce or consumers. The section of the public, who as men or science or men of commerce, were interested in knowing about Herbicides which would destroy weeds but not rice, must have been aware of the discovery of Butachlor. There was no secret about the active agent Butachlor as claimed by the plaintiffs since there was no patent for Butachlor, as admitted by the plaintiffs. Emulsification was the well-known and common process by which any Herbicide could be used. Neither Butachlor nor the process of Emulsification was capable of being claimed by the plaintiffs as their exclusive property. The solvent and the emulsifier were not secrets and they were admittedly not secrets and they were ordinary market products. From the beginning to the end, there was no secret and there was no invention by the plaintiffs. The ingredients the active ingredients the solvent and the emulsifier, were known the process was known, the product was known and the use was known. The plaintiffs were merely camouflaging a substance whose discovery was known throughout the world and trying to enfold it in their specification relating to Patent Number 125381. The patent is liable to be revoked.

Example 7:

In Franz Zaver Huemer v. New Yesh Engineers, (1996 PTC (16) 164 Del.) the court observed that the plaintiff is not an inventor of the patent device as the device is already being used in machines for several years in several countries especially in India vide para 9 to 16 of the affidavit, the defendant has set out several details the machines already being manufactured for over one and a half decade leading to an inference that there was nothing new in the plaintiff's device. Arrangement or rearrangement of the already known device does not amount to an invention. As sufficient ground exist for revocation of the plaintiff's patent, the defendant has a very good defence to the plaintiff's suit.

Example 8 :

In Surendra Lai Mahendra v. Jain Glazers [1981 PTC 112 Del] it was held that the plaintiff's patent is nothing more than an indigenous combination of certain integers which form part of Morance machine designed to be less expensive and cheaper apparatus. No doubt it may be termed as simplification of the apparatus to some extent but it is difficult *ex facie* to say that it involves an exercise of inventive step or inventive faculty. No doubt he has produced a

workable machine but it incorporates almost all the integers and components of Morance machine. So it cannot be said that he has added a scintilla of invention to produce the same. On his own showing the plaintiff had to handle a couple of Morance machines which were not found to be workable in India and therefore, his services had to be secured by the parties concerned as a skilled technician to put the same in working order. It is thus no wonder that having tried his hand on Morane machines, he was able to devise an apparatus of his own by virtually copying the same process and making some alterations and adjustments here and there so as to obviate the necessity of sophisticated and costly integers used by Morance

Example 9 :

What constitutes an inventive step may depend on the nature of the invention. The matter was considered in *Biogen Inc v Medeva plc* [1997] RPC 1 (at page 34) as follows:

"Whenever anything inventive is done for the first time it is the result of the addition of a new idea to the existing stock of knowledge. Sometimes, it is the idea of using established techniques to do something which no one had previously thought of doing. In that case the inventive idea will be doing the new thing. Sometimes it is finding a way of doing something which people had wanted to do but could not think how. The inventive idea would be the way of achieving the goal. In yet other cases, many people may have a general idea of how they might achieve a goal but not know how to solve a particular problem which stands in their way. If someone devises a way of solving the problem, his inventive step will be that solution, but not the goal itself or the general method of achieving it."

Example 10 :

The invention related to an isolated nucleic acid molecule having the nucleotide sequence of either SEQ ID No 1 OR SEQ ID No 3 as shown in the sequence listing was obvious in view of 3 cited documents (T 0255/05). It was stated that the combined review of the cited documents motivates the person skilled in the art to identify further nucleic acid molecules encoding such receptor proteins but also suggests various methodologies to achieve this goal, such as homology screening, positional cloning, PCR or, as applied in the present application, computational and bioinformatic methodologies.

When the appellant has pointed out that the claim 1 is a narrower claim, the board expressed the opinion that even if the scope of claim 1 might be narrow, the claimed nucleic acid molecules would not appear to be anything but an arbitrary selection, among all other possible choices, of a fragment of the human genome encoding the Mas-related G protein-coupled receptor of one of the cited documents, the specific fragment lacking any unexpected properties or effects on which an inventive step could be based.

No arguments have been put forward by the appellant in this respect, except for the allegedly novel expression pattern of the nucleic acid molecules described in the application. However the Board notes that a possible expression of the described molecules in erythroleukemia cells and testis,

which has been computationally predicted on the basis of a virtual Northern blot and a PCR-based screening panel, does not constitute a property or an effect on which an inventive step for the claimed nucleic acid molecules could be based.

Therefore it was concluded that having regard to the teachings of the cited documents the subject matter of the claims was obvious to a person skilled in the art.

Example 11 :

It was held that the description shall be used to interpret the claims when assessing the inventive step (T 0516/06)

The alleged invention was related to Adenovirus vectors containing heterologous transcription regulatory elements wherein it is claimed that in the context of adenovirus vector, a first heterologous TRE is "different" from a second heterologous TRE when the polynucleotide sequence identity between the two heterologous TREs is less than about 95%, preferably less than about 90%, preferably less than about 85%, preferably about less than about 75%.
The Board therefore has understood that the unexpected property of "genetic stability" of the vectors is due to the presence of two different TREs with as much sequence identity as eg. 94% because of which such vectors would undergo significantly less homologous recombination than that occurring between two strictly identical TREs. Further the Board has felt the difficulty as otherwise in accordance with the case law T 16/87 [OJ EPO 1992, 212] wherein it is stated that the description shall be used to interpret the claims when assessing the inventive step.

In the instant case it is unambiguous from the description that TREs with a very high level of identity fall within the definition of "different heterologous TREs" and it was not denied that these TREs could undergo homologous recombination. Thus, not all constructs comprised within the claim possess the property – genomic stability – that would possibly justify acknowledging inventive step.

In other words, the advantageous effect argued to impart inventive step is not obtained over the scope of the claim. On claiming by the appellant that the vectors of the prior art were unstable the Board has opined that it could only serve to back up a conclusion of inventive step as regard the proposed solution if the claimed subject matter entirely consisted of vectors, which had lost this undesirable property.

For these reasons, it was concluded that the subject matter of the invention lacks inventive step.

Example 12 :

The invention is related to an enzyme capable of degrading cellulose or hemicellulose (T 1336/04) An established case law was relied upon wherein it is stated that if the inventive step of a claimed invention is based on a given

unexpected technical effect, this effect must be achievable over the whole area claimed i. e. for all products claimed. The Board felt in the instant case the alleged technical effect has only been demonstrated for a single product, namely the EGV of H. insolens and this effect does not serve the basis for a acknowledging inventive step to the subject matter of claim 1 as a whole. Thus it was opined that the alleged invention lacks an inventive step.

Example 13 :

A method for controlling fungi on plants by the aid of a hydrophobic extracted neem oil has been claimed which was refused for lacking in an inventive step due to availability of a prior scientific publication on the "Effect of volatiles of some plant extracts and their oils on Conidia of Erysiphe polygoni DC."(T 0416/01)

The report of the publication states with respect to the effect of volatiles of garlic extract and oil, neem oil and ginger (Zingiber officinale Rosc.) rhizome extract on conidia of powdery mildew (Erysiphe polygoni DC) of pea (pleum sativum L.).It was also stated that the extracts and oil from neem, ginger and garlic exhibit antifungal activity. The prior publication discloses that the neem oil is extracted by Soxhlet process. However the said document does not disclose which solvent should be used.

Accordingly, the skilled person would use his / her general knowledge of the isolation of natural products from plants. This commonly takes place by means of solvent extraction and solvent elution. These are well known practices used in all laboratories of natural products and merely imply arranging the solvents to be used according to their solvent strength. Basically whatever the technique chosen it is normally started with a non-polar hydrophobic solvent as first option and then it is continued in increasing degree of polarity up to hydrophilic solvents including water.

Since no other parameters have been discussed in the alleged invention the extraction therefore includes Soxhlet extraction is also included. Therefore it was decided that the alleged invention lacks inventive step and consequently the patent was revoked.

Example 14 :

In the crucial decision T 641/00 (OJ 2003, 352) the patent in suit related to a method in a digital mobile telephone system of the GSM type in which a subscriber identity module (SIM card) was allocated at least two identities which were selectively activated by the user in order to distribute the costs between private and service calls. The board held that an invention consisting of a mixture of technical and non-technical features and having technical character as a whole was to be assessed with respect to the requirement of inventive step by only taking account of those features which contributed to that technical character. Features making no such contribution could not support the presence of inventive step.

Example 15:

In *Mutoh Industry Ltd's Application* ([1984] RPC 35) the hearing officer held that a drawing board employing magnetic bearings was obvious, since it was reasonable for the drawing-board man concerned with the problem of reducing friction to consult a bearings expert. The Patents Court however allowed an appeal, finding that users of the known device were not struggling to overcome a problem which inhibited their activities, nor were manufacturers failing to put the known device on the market because it was not sufficiently friction-free; there was therefore no reason for the manufacturer or user to look for outside assistance.

Example 16:

In *ABT Hardware Ltd's Application* (BL O/36/87), the hearing officer held the invention to be obvious. It was concerned with the use in a letter plate of a known type of magnet comprising an elastomer loaded with ferrite powder to hold a flap in sealing engagement with a frame over an opening in the frame. There were specific problems associated with prior magnetic letter plates which could arguably have led the applicants to seek specialist advice, and the general availability and widespread use of the magnets in question might also reasonably be expected to have led the applicants naturally to consider their adoption in letter plates, with or without consultation of specialists.

3.25 Industrial Applicability: -

3.25.1 The third Criteria of patentability is that the invention should be capable of industrial application. It is defined in Section 2 (1) (ac) of the Patents Act

Section 2 (1) (ac)

"Capable of Industrial application", in relation to an invention, means that the invention is capable of being made or used in an industry.

i) If the subject matter is devoid of industrial application it does not satisfy the definition of "invention" for the purpose of the Act.

ii) "Industry" should be understood in its broad sense as including any useful and practical, as distinct from intellectual or aesthetic activity. It does not necessarily imply the use of a machine or the manufacture of a product and covers such thing as a process for dispersing fog or a process of converting energy from one form to another.

iii) Vague and speculative indication of possible objectives that might or might not be achievable by carrying out further research with the tool as described is not sufficient for fulfilment of the requirement of industrial applicability. The purpose of granting a patent is not to reserve an unexplored field of research for an applicant.

~~iii)~~iv) Methods of testing are generally regarded as capable of industrial application if the test is applicable to the improvement or control of a product, apparatus or process which itself is capable of industrial application. It is therefore advisable to indicate the purpose of the test if this is not otherwise apparent

~~iv)~~v) Processes or articles alleged to operate in a manner which is clearly contrary to well-established physical laws, such as perpetual motion machines, are regarded as not having industrial application, as was held in *Paez's Application* (BL O/176/83) and *Webb's Application* (BL O/84/88)

~~v)~~vi) An invention for a method of treatment of the human or animal body by surgery or therapy or of diagnosis practised on the human or animal body shall not be taken to be capable of industrial application.

~~vi)~~vii) Parts /pieces of the human or animal body to be used in transplants are objected as not being capable of industrial application

3.25.2 Case studies : Industrial applicability

Example 1:

It was held that the requirement that the invention can be made or used "in any kind of industry" so as to be "capable of industrial application" carries the connotation of trade or manufacture in its widest sense and whether or not for profit and , further, that no industry exists in that sense to make or use that which is useless for any known purpose [In *Chiron Corp v Murex Diagnostics Ltd and other* [1996] RPC 535 (page 607)]

Example 2:

Views of the High Court of Australia in *NRDC's Application*, [1961] RPC 134, give a good guide to the meaning to be attributed to industrial application. There must be a product, but this need not be an article or substance, but must be something in which a new and useful effect, be it creation or alteration, may be observed. It may, for example, be a building, a tract or stratum of land, an electrical oscillation, but it must be useful in practical affairs. A method of eradicating weeds was held to give rise to a product (an improved crop) because this was an artificially created state of affairs; moreover it was one whose significance was economic.

Example 3:

In *Melia's Application* (BL O/153/92), where an application relating to a scheme for exchanging all or part of a prison sentence for corporal punishment was held to lack industrial applicability and also to be a method for doing business .

Example 4:

In *John Lahiri Khan's Application* (BL O/356/06) a method for effecting introductions with a view to making friends was held not to be industrially

applicable, even though it could be carried out by a commercial enterprise. It was also found to be excluded as a method of doing business.

Example 5:

In *Eastman Kodak Co. v American Photo Booths Inc.* (BLO/457/02), which concerned a patent for a photo-booth camera, it was held that the folded optical path as described and claimed could not give rise to the claimed narrowing of the depth of field. As a result, the hearing officer held that the invention could not work as described and claimed, and so lacked both industrial applicability and sufficiency of disclosure. Objecting to insufficiency may be particularly appropriate if the claims do not refer to the intended function or purpose of the invention, for example if a "flying gyroscope" is claimed merely as an article having a particular specified construction.

Example 6 :

In one of the decided cases wherein the invention is related to Novel PTP20, PCP-2, BDP1, CLK and SIRP proteins and related products and methods it was observed that the alleged invention discloses the description of proteins, structural features [amino acid sequences] and their enzymatic activities. BDP1 polypeptide is taken as example for further understanding the case herein. The amino acid sequence for BDP1 polypeptide was given as SEQ ID NO 3 in the description and the said polypeptide is found to be associated with tyrosine phosphatase activity. A method and means for making it by DNA techniques is also described. A possible role in cellular housekeeping and in certain types of cancers has been hypothesized.

Although BDP1 polypeptide could be " made & used " as a further tool, in addition to the many already available in the art, for exploring the complex cellular signal transduction pathways and their implications in the regulation of cellular processes and possibly disease states, the whole burden is left to the reader to guess or find a way to exploit it in industry by carrying out work in search for some practical application geared to financial gain, without any confidence that any practical application exists.

Since no industrial applicability could be derived from the description the Board in their judgment opined that a vague and speculative indication of possible objectives that might or might not be achievable by carrying out further research with the tool as described is not sufficient for fulfilment of the requirement of industrial applicability. The purpose of granting a patent is not to reserve an unexplored field of research for an applicant.

CHAPTER IV

INVENTIONS NOT PATENTABLE

Section 3 : What are not inventions:-

The following are not inventions within the meaning of this Act, -

(a) an invention which is frivolous or which claims anything obviously contrary to well established natural laws;

(b) an invention the primary or intended use or commercial exploitation of which could be contrary public order or morality or which causes serious prejudice to human, animal or plant life or health or to the environment;

(c) the mere discovery of a scientific principle or the formulation of an abstract theory or discovery of any living thing or non-living substances occurring in nature;

(d) the mere discovery of a new form of a substance which does not result in the enhancement of a known efficacy of that substance or the mere discovery of a new property or new use of a known process, machine or apparatus unless such known process results in a new product or employs at least one new reactant.

Explanation: For the purpose of this clause, salts, easters, ethers, polymorphs, metabolites, pure form, particle size, isomers mixtures of isomers, complexes, combinations and other derivatives of known substance shall be considered to be the same substance, unless they differ significantly in properties with regard to efficacy

(e) a substance obtained by a mere admixture resulting only in the aggregation of the properties of the components thereof or a process for producing such substance;

(f) the mere arrangement or re-arrangement or duplication of known devices each functioning independently of one another in a known way;

(g) Omitted.

(h) a method of agriculture or horticulture;

(i) any process for the medicinal, surgical, curative, prophylactic [diagnostic therapeutic] or other treatment of human beings or any process for a similar treatment of animals to render them free of disease or to increase their economic value or that of their products.

(j) plants and animals in whole or any part thereof other than micro-organisms but including seeds, varieties and species and essentially biological processes for production or propagation of plants and animals;

(k) a mathematical or business method or a computer program per se or algorithms;

(l) a literary, dramatic, musical or artistic work or any other aesthetic creation whatsoever including cinematographic works and television productions;

(m) a mere scheme or rule or method of performing mental act or method of playing game;

(n) a presentation of information;

(o) topography of integrated circuits;

(p) an invention which in effect, is traditional knowledge or which is an aggregation or duplication of known properties or traditionally known component or components.

4.1 The section "Inventions - non-patentable" describes certain products and processes, which are not to be regarded as patentable inventions as per the Act. These statutory exclusions are illustrated in the following paragraphs.

3(a) "An invention which is frivolous or which claims anything obviously contrary to well

4.2 Some examples of frivolous and claims contrary to natural laws are:~~For example:~~

a. A machine purporting to produce perpetual motion will not be patentable because it is impossible to prepare such machine
b. A machine alleged to be giving output without any input is not patentable as it is contrary to natural law.
c. "A method of showing time on the basis of metric system" wherein dial of time piece having three hands for indicating, hour, minutes and seconds was divided into 10 parts for hours, each hour into 100 minutes and each minute into 100 seconds. The invention was held frivolous and not considered a patentable invention. (Indian patent application no. 101/Bom/72)
d. Merely making in one piece, articles previously made in two or more pieces is frivolous. Mere usefulness is not sufficient [Indian Vacuum Brake' Company Ltd vs Laurd (AIR 1962, Cal 152)].
~~c.~~e. A machine alleged to give 100% performance is also not patentable
~~d.Any well-established natural law like Newton's law of gravitation is not a patentable subject matter~~

3(b) "An invention the primary or intended use or commercial exploitation of which could be contrary public order or morality or which causes serious prejudice to human, animal or plant life or health or to the environment."

4.3 Some examples are:

(i) The invention, the use of which is contrary to the law which is in force, or use of which is prohibited is not patentable.

For example:

a. Any device, apparatus or machine or method for committing theft/burglary
b. Any machine or method for counterfeiting of currency notes
c. Any device or method for gambling,
d. An invention the use of which can cause injury to human beings, plants and animals.

(ii) Inventions, the established or intended use or commercial exploitation of which is found to be injurious to public, animal or plant life or health are not patentable
For example: Method of adulteration of food.

(iii) The invention, the present or intended use of which is likely to violate the well accepted and settled social, cultural , legal norms of morality is not allowable e.g method of cloning

(iv) If the invention is such that the primary or proposed use of which would disturb the public order is not patentable e.g. A device for house-breaking, ~~weapons for mass destruction,~~

(v) terminator gene technology

3(c) "The mere discovery of a scientific principle or the formulation of an abstract theory or discovery of any living thing or non-living substances occurring in nature"

4.4.1 There is a difference between discovery and invention. A discovery adds to the amount of human knowledge by disclosing something already existent, which has not been seen before, whereas an invention adds to the human knowledge by creating a new product or processes involving a technical advance as compared to the existing knowledge.

4.4.2 A claim for discovery of scientific principle is not patentable, but such a principle when used with process of manufacture resulting into a substance or an article may be patentable.

4.4.3 A scientific theory is a statement about the natural world. These theories themselves are not patentable, no matter how radical or revolutionary an insight they may provide, since they do not result in a product or process. However, if the theories lead to practical application in the process of manufacture of article or substance, they may well be patentable. A claim for formulation of abstract theory is not patentable. For example, the fact that a known material or article is found to have a hitherto unknown property is a discovery and not an invention. But if the discovery leads to the conclusion that the material

can be used for making a particular article or in a particular process, then the article or process could be patentable.

4.4.4 Finding out that a particular known material is able to withstand mechanical shock is a discovery and therefore not patentable, but a claim to a railway sleeper made of the material would not fall foul of this exclusion, and would be allowable if it passed the tests for novelty and inventive step.

Similarly, finding of a new substance or micro-organism occurring freely in nature is a discovery and not an invention e.g. in *Kirin-Amgen v Hoechst Marion Roussel* [2005] RPC 9].~~A DNA sequence of a gene was not an invention as standing alone, though it was a "discovery as such"; but if it were necessary to isolate and extract it then a process developed for this purpose could be patentable.~~

~~4.4.7A mathematical method is one which is carried out on numbers and provides a result in numerical form (the mathematical method or algorithm therefore being merely an abstract concept prescribing how to operate on the numbers) and not patentable. However, its application may well be patentable, for example, in *Vicom/Computer-related invention* [1987] 1 OJEPO 14, (T208/84) the invention concerned a mathematical method for manipulating data representing an image, leading to an enhanced digital image.~~

~~4.4.8~~4.4.5 ~~Claims to a method of digitally filtering~~ data ~~performed on a conventional general purpose computer were rejected, since those claims were held to define an abstract concept not distinguished from a mathematical method. However, claims to a method of image processing which used the mathematical method to operate on numbers representing an image can be allowed. The reasoning was that the image processing performed was a technical (i.e. non-excluded) process which related to technical quality of the image and that a claim directed to a technical process in which the method used does not seek protection for the mathematical method as such. Therefore the allowable claims as such went beyond a mathematical method.~~

~~4.4.9~~4.4.6 A claim as relating to a method of analyzing samples which were subject to chromatographic and spectrometric analysis techniques such that a multi-variant statistical analysis technique was employed to make it easier to identify time locations where the characteristics of samples were different. The contribution was identified as being "A method for comparing two samples by an analytical technique which uses chromatography and then spectrometry, followed by a particular sequence of data analysis techniques, to give results which enable the retention time at which the samples differ to be identified." [*Waters Investments Limited's Application* (BL O/146/07)].It was held that the contribution lay in technical field of sample analysis using chromatography and spectrometric techniques and hence the invention was patentable

Example: Any well-established natural law like Newton's law of gravitation is not a patentable subject matter

3(d) *The mere discovery of a new form of a known substance which does not result in the enhancement of the known efficacy of that substance or the mere discovery of any new property or new use for a known substance or of the mere use of a known process, machine or apparatus unless such known process results in a new product or employs at least one new reactant.*

Explanation:- For the purposes of this clause, salts, esters, ethers, polymorphs, metabolites, pure form, particle size, isomers, mixtures of isomers, complexes, combinations and other derivatives of known substance shall be considered to be the same substance, unless they differ significantly in properties with regard to efficacy.

4.5.1 Mere discovery of a new form of a known substance which does not result in the enhancement of the known efficacy of that substance is not patentable. According to the proviso to this sub-section, a known substance in its new form such as amorphous to crystalline or crystalline to amorphous or hygroscopic to dried, one isomer to other isomer, metabolite, complex, combination of plurality of forms, salts, hydrates, polymorphs, esters, ethers, or in new particle size, shall be considered same as of known substances unless such new forms significantly differ in the properties with regard to efficacy. Accordingly such forms could be considered patentable provided they significantly enhances known efficacy of that substance at the time of filing the application.

4.5.2 In order to be patentable any salts, esters, ethers, polymorphs, metabolites, pure form, particle size, isomers, mixtures of isomers, complexes, combinations and other derivatives of known substance ,they must differ significantly in the properties with regard to efficacy. The requirement here is two fold, namely the new form must result in enhancement of known efficacy of known substance and secondly, in order to be distinct from the known substance, the new form must differ in the properties with regard to efficacy

4.5.3 The comparison with regard to properties or enhancement of efficacy must be made between the known substance and the new form of known substance. In case the new form is further converted into another new form, the comparison must be made between the already existed form and another new form but not between the base compound and another new form.

4.5.4 The comparison with regard to properties or enhancement of efficacy must be made at the time of date of filing of the application or priority date in the application is claiming the priority of any earlier application but not at the stage of subsequent development.

4.5.5 The efficacy need not be quantified in terms of numerical value to determine whether the product is efficacious because it is not possible to have a standard numerical value for efficacy for all products including pharmaceutical products.

4.5.6 In regard to 'efficacy' in pharmaceutical products, the Madras High Court observed, "going by the meaning for the word "efficacy" and "therapeutic" ... ..., what the patent applicant is expected to show is, how effective the new discovery made would be in healing a disease/ having a good effect on the body? In other words, the patent applicant is definitely aware as to what is the "therapeutic effect" of the drug for which he had already got a patent and what is the difference between the therapeutic effect of the patented drug and the drug in respect of which patent is asked for."
"Due to the advanced technology in all fields of science, it is possible to show by giving necessary comparative details based on such science that the discovery of a new form of a known substance had resulted in the

enhancement of the known efficacy of the original substance and the derivatives so derived will not be the same substance, since the properties of the derivatives differ significantly with regard to efficacy." (Novartis AG Vs. Union of India W.P. 24760/06)

4.5.7 Some of the examples of new forms are given below without limiting the scope of the application of the provisions of the Act.

(i) **Isomers:-** Isomers are different compounds that have the same molecular formula which may be broadly divided into two kinds, namely,

- structural isomers or positional isomers and,
- stereo isomers.

Structural isomers or positional isomers may be structurally similar or dissimilar compounds. The simplest examples are butane and isobutane and ethanol and dimethyl ether. In the former case the compounds are having structural and functional similarity. However, In the second set of compounds, although they have the same molecular formula but are structurally and functionally different. Such isomers even having close similarity may be considered to be novel over the prior art. Isomers having the same empirical formula but having structural differences may be considered novel and may not normally offend "obviousness" as they are structurally different.

Example:

Cyclohexylstyrene is not considered prima facie obvious over prior art isohexyl styrene.

(ii) Stereo Isomers: - Stereo isomers are prima facie obvious.

Once a compound having a chiral center is known, its enantiomers are obvious because a person skilled in the art knows that a compound having a chiral center exists in two optically active forms. Hence, a product patent may not be granted for the enantiomer form. However, when a new compound is claimed having chiral center(s) for the first time, such a new compound may be patentable.

In a case where an (S)-enantiomer of a compound, capable of exhibiting better efficacy over the (R)-enantiomer, for instance producing enhanced anti-diabetic effects is claimed, wherein the said claim is not allowable when the same chemical compound possessing anti-diabetic property is known from the prior art.

(iii) Homologues: - Homologues normally display add-on property. They are

structurally similar and provide the example of Structure – Function linearity and may lack inventive step. However the cases are to be decided on case to case basis.
e.g. Polymerization process using a sterically hindered amine was held non-obvious over a similar prior art process because the prior art disclosed a large number of unhindered amines.

Further, prior art structures do not have to be true homologs or isomers to render structurally similar compounds prima facie obvious.
e.g. Claims and Prior art were for heterocyclic carbamoyloxmino compounds having pesticidal activity. The only structural difference was that the ring structures of the claimed compounds had two carbon atoms between two sulphur atoms whereas the prior art ring structures had either one or three carbon atoms between two sulphur atoms. The court held that although the prior art compounds were not true homologs or isomers of the claimed compounds, the similarity between the chemical structures and properties is sufficiently close that one of ordinary skill in the art would have been motivated to make the claimed compounds in searching for new pesticides.

(iv) Polymorphs: - Some compounds are present in polymorphic forms, i.e., they crystallize in diverse forms. Such forms can be deemed within the prior art and therefore not patentable. However, process patent may be allowed for the new polymorph, if the polymorph is prepared by novel process involving inventive step.Some therapeutically active ingredients, present in polymorphic forms, may have different properties that are more or less significant in terms of their therapeutic use. Such forms can be deemed within the prior art, and therefore, non-patentable if they were inevitably obtained following the process of the basic patent on the active ingredient or if they were covered by a previous product patent.

(v) Metabolites:- Metabolites are the compounds that are formed inside a living body during metabolic reaction. The types of metabolites are-

(i) Active metabolites formed from inactive precursors (e.g DOPA & Cyclophosphamide)

(ii) Active metabolites formed from precursors that show mechanism of action that is different from that of parent compound (e.g Buspirone & 1-pyrimidyl piperzine Fenflouromine & norfenfleuromine)

(iii) Active metabolites which contribute to the duration of action of the parent compound (e.g. Hexamethylmelamine & Clobazam)

(iv) Active metabolites that show antagonistic effect on the activity of the parent compound (e.g Trezodone & m-chlorophenyl pierzine, Aspirin & salicylate)

A metabolite is not patentable since giving the drug to a patient naturally and inevitably results in formation of that metabolite.

(vi) Prodrugs :- Prodrugs are inactive compounds that can produce an active ingredient when metabolized in the body. Hence prodrugs and metabolites are interlinked. When metabolyzed in the body, inactive compounds(pro-drug) can produce a therapeutically active ingredient,. It must be determined whether the patent on the compound covers the prodrug and the extent to which claims relating to certain compounds should also be allowed to include their prodrugs. The inventive aspects of a prodrug may be decided based **on the merits of the case.**

However, if there is a marked improvement in performance over the primary drug, prodrugs may be patentable.

(vii) Hydrates and other Substances:-

Hydrates, acid addition salts and other derivatives, which are routinely prepared, prima facie lack an inventive step. However, where there is a problem like stability, absorption etc., and there is a long standing problem in preparing the derivatives, patentability of such process may be considered.

(viii) Purification Compounds:

Mere purification of known material is not patentable as they are considered the purified compound. However the purification process or the purified compound which never existed before due to inherent long standing problem can be considered patentable.

4.5.8 **Mere discovery of new property of a known substance: -**

A mere discovery of a new property of known substance is not considered patentable. For instance, the paracetamol has antipyretic property. Further discovery new property of paracetamol as analgesic can not be patented. Similarly ethyl alcohol is used as solvent but further discovery of it new property as anti knocking thereby making it usable as fuel can not be considered patentable

4.5.9 **Mere discovery of any new use of known substance:-**

A mere discovery of new property of known substance is not considered patentable. For instance new use of Aspirin for treatment of the cardio-vascular disease, which was earlier used for analgesic purpose, is not patentable. However, a new and alternative process for preparing Aspirin is patentable. Similarly the New use of methyl alcohol as antifreeze in automobiles- The Use of methanol as a solvent is known in the prior art. A New use has been claimed in this claim as antifreeze which is not allowable Further, a new use of Chloroquine for Sarcoidosis (a fungal disease) and for Infectious mononucleosis (a viral disease) and for Diabetic neuritis(inflammation of nerves) is not patentable.

4.5.10 The Mere use of a known process, machine or apparatus unless such known process results in a new product or employs at least one new reactant:- Mere use of a known process is not patentable unless such known process results in a new product or employs at least one new reactant. Similarly mere use of known apparatus or machine for another purpose is also not considered patentable

Examples 1:

"Metric time showing device" (101/Bom/72) was held not patentable. The device comprises a normal clock or watch having usual hands for indicating hours, minutes and seconds; wherein dial or like visual numerical indicators are divided into 10 large divisions for hours, hours divisions are divided into 100 divisions indicating minutes and each minute is divided into 100 parts representing seconds. It was held to be a mere use of known device and hence, not patentable.

Examples 2:

A food-packing machine used for packing the desired amount of talcum powder. Since this claim does not characterize any changes in the said food-packing machine, it is presumed that the same machine has been used for the purpose of packing talcum powder. Therefore, it is understood from the claim that the same packing machine, which is in vogue, is used for packing the material other than food. Hence this is also not allowable

4.5.11 Biotechnological inventions

In the field of biotechnology, the claimed invention may relate to a wide variety of subject matter like living entity of natural origin, such as animal, plant, human beings including parts thereof; living entity of artificial origin, such as micro-organism, vaccines, transgenic animals and plants etc., biological materials such as DNA, Plasmids, genes, vector, tissues, cells, replicons etc., process relating to living entities, process relating to biological material, methods of treatment of human or animal body, biological process or essentially biological process etc .

The following points are to be noted in this context .

1. The living entities of natural origin such as animals, plants, in whole or any parts thereof, plant varieties, seeds other than micro-organism are not patentable.
2. Any process of manufacture or production relating to such living entities is also not patentable.

5 Any method of treatment such as medicinal, surgical, curative, prophylactic, diagnostic and therapeutic of human beings or animals or other treatments of similar nature are not patentable.

6 Any living entity of artificial origin such as transgenic animals and plants and any part thereof are not patentable.

7 The entities of artificial origin such as micro-organism, vaccines are considered patentable.

8 The biological materials such as organs, tissues, cells, viruses etc. and process of preparing thereof are not patentable under Section 3 (c). The biological material such as recombinant DNA, Plasmids and processes of manufacturing thereof are patentable provided they are produced by substantive human intervention and functional aspects of said DNA or plasmid shall be defined.

9 Natural Gene / protein sequences are not patentable

10 Genetically modified Gene / DNA sequences may be patentable provided their functions are duly disclosed

11 The processes relating to micro-organisms or producing chemical substances using such micro-organisms may be patentable.

12 Essentially biological processes for the production of plants and animals such as method of crossing or breeding etc. are not patentable.

13 Any biological material and method of making the same which is capable of causing serious prejudice to human, animal or plant lives or health or to the environment including the use of those would be contrary to public order and morality are not patentable such as terminator gene technology.

14 The processes for cloning human beings or animals, processes for modifying the germ line, genetic identity of human beings or animals, uses of human or animal embryos for any purpose are not patentable as they are against public order and morality.

15 In case of use of biological material in the invention disclosed in the patent application the source or geographical origin of such material is required to be mentioned in the specification.

16 In case of use of new biological materials in the invention, disclosed in the patent application, it is necessary to deposit such materials in any of the International Depositary Authorities (IDA) recognized under the BUDAPEST Treaty on or before filing of the application, in order to supplement the description for sufficiency of disclosure of the invention and reference of such deposit is to be made in the patent specification.

17 Any invention which in effect is traditional knowledge or which is an aggregation or duplication of known properties of traditionally known components is not patentable.

4.5.12 In ~~an~~ patent application no. 782/Cal/1981, dated 13.07.1981, an invention related ~~ing~~ to pharmaceutical composition exhibiting anti-phlogistic, antipyretic and analgesic activity and high geastroenteric tolerance in unit doses ~~es~~ form which contains imidazol salicylate as the active ingredient ~~imidazol salicylate~~ in the amount of 100-600 mg and an inert carriers was

claimed which was later amended to a process for the preparation of novel composition containing imidazole salicylate having formula I ~~shown in the accompanying drawings~~, as the active principle ~~of antipholgistic, antipyretic and analgesic products,~~. The invention was characterized in that a product is previously obtained by reacting, mole by mole, acetylsalicylic acid with imidazole in an inert organic solvent and that, using the solid product obtained in the reaction after purification by recrystalization ~~lation~~, homogenous composition were ~~are~~ produced with pharmaceutically acceptable vehicles suitable for oral, parental or topic administration.

It was held by the Controller that the active compound such as imidazole salicylate is known in the art and applicant could not develop any special property or even improve upon the property of the compound to be mixed up with the usual carrier to form the composition. Further-more, the description contained ~~s~~ no indication of using any special type of solvent for its purification by re-crystallization and, therefore, the invention was ~~is~~ not patentable under section 3(d) of the Act.

Further, the pharmaceutical vehicle having the primary intended function of acting as vehicle or carrier or diluent performed ~~s~~ the very function when incorporated in the composition. There was ~~is~~ no explicit disclosure ~~or~~ or experimental data to indicate that the presence of the carrier in any way influenced ~~s~~ the antiphlogistic, antipyretic and analgesic activity of the active ingredients. Therefore, the invention was held ~~is~~ not allowable under Section 3(e) of the Act as well as and ~~same is a~~ merely an admixture. ~~of non components~~ (decisions on patent and designs vol. (4) published by patent office technical society page 21)

4.5.13 In the application for patent no. 134883, dated 08.03.1972, a method of control of post-embryonic development stages of coleoptera and Diptera inhabiting in the soil was claimed. The invention was ~~,~~ characterized by applying to said soil a toxic amount of a compound selected from the group consisting of o,o-diethyl S-(tert butylthio) methyl phosphorodithuoate and o.o-diethyl S-[(1,,1-dimethypropyl)thio]methyl phosphorodithicate.

~~was claimed~~It ~~which~~ was amended to a method for preparing a long effective pasticical preparation useful in the control of the postembryonic stages of coleoptera and ~~D~~diptera inhabiting the soil having ~~an~~ long residual ~~of~~ paesticidal activity and un-objectionable odour which comprise~~d~~s treating (i) sorptive or non -sorptive granular particles of a material like di-atomite or silica~~s~~ with 5% to 25% of o,o-diethyl 3-(tert-butylthio) methyl phospho-rodithicate and when preferred (a) applying a super coating of an inert material like clay or talc on the treated granular non-sorptive material or (b) applying a deactivator to the surface of the sorptive material before treating with the said phosphorodithicate, using one or more conventional solvents.

It was held by the Controller that materials and solvent specified in the claim were ~~are~~ conventional and customary application ~~ors~~ well known in the pesticidal art. Further, the method for preparation of ~~the~~ formulation was ~~are~~ conventional ~~methods~~ and gave ~~iven~~ a pestisicidally active compound, which every person skilled in the pesticidal art would ~~ill have to~~ make as a

formulation by applying active compound by conventionasl metjhod to the conventional applicators for using the ppesticidal active compound. Accordingly, a method of making a formulation by applying a conventional method a pesticidal compound to a conventional applicator is only steps in the use of compound or substance for treting the patient. Therefore invention falls within section 3(d) as the mere non substance or non compound.

4.5.14

In case of M/s. Astra Aktiebolag [Patent Application No. 1354/del/1998], the controller in his decision dated 12th June 2007, held that the patent application is not patentable under section 3(d) of the Patent Act 1970, as "present pharmaceutical formulation is a selection from the prior art formulation due to the specific selection of HPMC of cloud point above 45.6° C having similar medicinal use and with the same therapeutic efficacy... the benefit claimed by the applicant in the present application is not accruable to the user in terms of therapeutic quality of the product but to the manufacturer only in terms of consistency in the production of formulation...".

4.5.15 In patent application No. 1577/DEL/1996 was refused *inter alia* under the provisions of section 3(d) of the Patents Act, 1970. The controller in his decision dated 12th June 2007 held that "the present invention provides a new form of known substance either in anhydrous or hydrated form III of Atorvastatine having same therapeutic activity and in the same field. It only claims some improvement in physical property, which does not make any change in therapeutic efficacy of the compound as compared to the prior art compound. Therefore this new form does not qualify the requirement under section 3(d)."

3(e) A substance obtained by a mere admixture resulting only in the aggregation of the properties of the components thereof or a process for producing such substance;

4.6.1 Invention not patentable under section 3 (d) &(e) (to be also incorporated in (e) :- In a patent application no. 782/Cal/1981, dated 13.07.1981, an invention related to pharmaceutical composition exhibiting anti-phlogistic, antipyretic and analgesic activity and high gastroenteric tolerance in unit doses form which contains imidazol salicylate as the active ingredient in the amount of 100-600 mg and an inert carrier was claimed which was later amended to a process for the preparation of novel composition containing imidazole salicylate having formula I, as the active principle . The invention was characterized in that a product is previously obtained by reacting, mole by mole, acetylsalicylic acid with imidazole in an inert organic solvent and that, using the solid product obtained in the reaction after purification by recrystalization , homogenous composition were produced with pharmaceutically acceptable vehicles suitable for oral, parental or topic administration.

It was held by the Controller that the active compound such as imidazole salicylate is known in the art and applicant could not develop any special property or even improve upon the property of the compound to be mixed up with the usual carrier to form the composition. Furthermore, the description

contained no indication of using any special type of solvent for its purification by re-crystallization and, therefore, the invention was not patentable under section 3(d) of the Act.

~~4.6.1~~4.6.2 A mixture of sugar and some colorants in water to produce a soft drink is a mere admixture resulting into aggregation of the properties. Similarly a mixture of different types of medicament or medicine to cure multiple diseases is also a mere admixture of substances and is not a patentable invention.

~~4.6.2~~4.6.3 However, an admixture resulting into synergistic properties of a mixture is not considered as mere admixture e.g. soap, detergent, lubricants and polymer composition etc. Hence they are patentable.

~~4.6.3~~4.6.4 A process for producing a substance by admixing, which is resulting into the aggregation of the properties of the components thereof, is also not patentable invention.

~~4.6.4~~4.6.5 In assessing the inventive step involved in an invention based on a combination of features, consideration must be given to whether or not the state of the art was such as to suggest to a skilled person precisely the combination of features claimed. The fact that an individual feature or a number of features were known does not conclusively show the obviousness of a combination.

~~4.6.5~~4.6.6 A mere aggregation of features must be distinguished from a combination invention. The existence of a combination invention requires that the relationship between the features or groups of features be one of functional reciprocity or that they show a combinative effect beyond the sum of their individual effects. The features should be functionally linked together which was the actual characteristic of a combination invention.

~~4.6.6~~4.6.7 An anti-perspirant composition for application to human skin (63/Bom/75) was held not patentable.

~~4.6.7~~4.6.8 A composition comprises of non-cellulosic moisture absorbing polymer capable of absorbing moisture at least equivalent to its weight and a carrier. The composition was held as mere admixture, for the reason that it has got total sum of the properties of two components, namely, the properties of absorbent polymer to absorb moisture or to absorb perspiration on being applied to human skin, which has not been in any way influenced by the presence of said carrier to act as carrier or diluents.

~~4.6.8~~4.6.9 A composition of two drugs, i.e. Paracetamol and Ibuprofen for curing fever and pain or process of preparation thereof is not patentable for the reason that the composition is a mere admixture of two drug components resulting into aggregation of properties thereof; since Paracetamol is well known for treatment of fever and Ibuprofen for treatment of pain.

~~4.6.9~~4.6.10 However, if the mixture of drugs exhibits some unexpected results or synergistic properties in their action , then such composition is considered as patentable subject matter.

~~4.6.10~~4.6.11 In general all the substances which are produced by mere admixing, or a process of producing such substances should satisfy the requirements of synergistic effect in order to be patentable. The synergistic effect should be clearly brought out in the description and examples by way of comparison at the time of filing of the application and should be stressed in the principal claim.

~~4.6.11~~4.6.12 In the matter of an application for Patent No. 63/Bom/75 Decisions on patents and designs, vol.1, published by The Patent Office Technical Society p.17, Hindustan Lever Limited, Applied for Patent for an invention relating to an antiperspirant composition. It was held by the Controller that an admixture having only the aggregation of the individual properties of the components thereof is not an invention within the meaning of the Act and is thus not patentable, A process for producing such an admixture is also not patentable. In case the presence of one or more components of the composition influence the properties of the other components of the composition with the result that the ultimate properties of the composition would be different from the aggregation of the individual properties of the components thereof, such an admixture would be patentable under the Patents Act, 1970.[Page 26, point 10]

3(f) ***The mere arrangement or re-arrangement or duplication of known devices each functioning independently of one another in a known way.***

~~4.7.1~~4.7.1. It was observed in BISWANATH PRASAD RADHEY SHYAM V. HINDUSTAN METAL INDUSTRIES [1978] INSC 255 (13 December 1978) that it is important to bear in mind that in order to be patentable an improvement on something known before or a combination of different matters already known, should be something more than a mere workshop improvement; and must independently satisfy the test of invention or an 'inventive step'. To be patentable the improvement or the combination must produce a new result, or a new article or a better or cheaper article than before. The combination of old known integers may be so combined that by their working inter relation they produce a new process or improved result. Mere collocation of more than one integers or things, not involving the exercise of any inventive faculty, does not qualify for the grant of a patent.

~~4.7.2~~4.7.2 It was observed in Lallubhai Chakubhai v. Chimanlal and Co. (AIR 1936 Bom 99) : A new and useful application of an old principle may be good subject- matter. An improvement on something known may also afford subject-matter; so also a different combination of matters already known. A patentable combination is one in which the component elements are so combined as to produce a new result or arrive at an old result in a better or more expeditious or more economical manner. If the result produced by the combination is either a new article or a better or cheaper article than before, the combination may afford subject-matter of a patent.

4.7.3 In application for patent no. 228/Del/77 for an invention relating to a compact device for measuring the settlement characteristic of buildings and the like civil engineering structure comprising a set of base plates to be fixed at desired parts of the buildings having mounted thereon, a water level, a tilt meter and means to measure crack-width developing in structure over a desired interval were claimed. It was held by the Controller that the compact

device comprising a water level, tilt meter and crack-width meter measuring means, all three well known in the art prior to this application and working independently of one another in a known manner with no modifications in their functioning.

4.7.4 A mere juxtaposition of known devices in which each device functions independently is not patentable. It is accepted as sound law that mere placing side-by-side old integers so that each performs its own function independently of the others is not a patentable combination (British Celanese Ltd. vs Courtaulds Ltd (52) RFC 171), e.g. a floor mill provided with sieving means.However, where the old integers when placed together have some working interrelation, producing a new or improved results, then there is a patentable subject matter in the working interrelation brought about by the collection of the integers.

4.7.5 A mere juxtaposition of features, already known before the priority date, which have been chosen arbitrarily from amongst a number of a different combinations, which could be chosen, is not a patentable invention.

4.7.6 Further, when two or more features of an apparatus or device are known, and they are juxtaposed without any inter dependence on their functioning of the apparatus or device, they should be held to have been already known (Rampratap vs. Bhabha Atomic Research Center, 1976 IPLR 28 P. 35)]. e.g., an umbrella with fan(388/Bom/73), Bucket fitted with torch, Clock and transistor in a single cabinet. These are not patentable subject matter , since they are nothing but mere arrangement and rearrangement of items without having any working interrelationship between them and functioning independently of each other.

4.7.7 Another example is of a play-cum-educational device (1532/Cal/76). The device comprises of a chart, a set of tokens for players and one or more dice. It was held not patentable under the provisions of this section since the chart, token and dice, all are working independently of each other and there is no interrelation between them.

4.7.8 In case of the *Franz Zaver Huemer* v. *New Yesh Engineers,* (1996 PTC (16) 164 Del.) it is held that the plaintiff can not claim the to be an inventor of the patent device as the device is already being used in machines for several years in several countries especially in India vide para 9 to 16 of the affidavit, the defendant has set out several details of the machines already being manufactured for over one and a half decade leading to an inference that there was nothing new in the plaintiff's device. Arrangement or rearrangement of the already known device does not amount to an invention. As sufficient ground exists for revocation of the plaintiff's patent, the defendant has a very good defence to the plaintiff's suit.

4.7.9 In case of *1985 (5) PTC 71 (Del)*, the application for grant of patent was in respect of apparatus for producing metallic bellows. During the opposition proceedings it was held that both hydraulic machine and roll forming machine are undoubtedly the separate machines functioning independently of other there being no novel feature stated by the applicant. Hence, the ground that there is no invention is accepted as the applicant is seeking the patent right on known types of hydraulic forming and roll forming machines which is not allowable.

4.7.10 In the matter of an application made by Figurette and Cosmetics Private Limited (Applicant) for application No. 388/Bom/73. dated 28 Nov'73 filed for an invention entitled "Improvements in or relating to umbrellas or Parasols and the like fitted with cooling devices" and the complete specification relates

to umbrellas or parasols which provides ventilation and circulation of air in addition to providing protection to rain or sum, and the claims were mainly objected to "section 3(f) of The Patent Act, 1970.The principal claim read as "An umbrella, parasol and the like, comprising an electric motor having a fan propeller fitted on its shaft and housed at the top of the umbrella, parasol, arranged to blow air downwardly and an electric current supply means for the said electric motor". The applicant argued that the interrelation between the two known devices is that the electric motor is mounted at the upper end of the central rod of the umbrella and that the electric motor cannot start functioning unless the umbrella is opened. The Controller held that it can be seen from the drawings accompanying the complete specification, the housing in which the electric motor is located is above the cloth covering the umbrella and thus would function irrespective of the fact whether the umbrella is in opened or closed condition. Moreover, simply mounting the electric motor at the central rod of the umbrella merely amounts to an inter-relation as regards to the placing of known devices and does not amount to an interrelation as regards to the functioning of the known devices... ... ... accordingly, I am of the opinion that both the known devices in the applicants invention namely the umbrella and the electric motor function independently of each other in their usual known way and as such there is no interrelation in their functioning and the invention falls within the purview of section 3(f) of Patent Act and thus not Patentable. (Para 11 Page 79, 80, 81).

~~4.7.12~~4.7.11 A new combination may be the subject matter of a patent although every part of the combination, *per se*, is old for here the new article is not the parts themselves but the assembling and working of the parts, together. (Lallubhai Chakkubhai vs. Shamaldas Sankalchand Shah, A.I.R 1934 Bom. 407).

~~4.7.13~~4.7.12 The merit of a new combination very much depends upon the result produced. Where a slight alteration turns that which was practically useless intowhat is useful and important, it is fit subject matter for a patent ((Lallubhai Chakkubhai vs. Shamaldas Sankalchand Shah, A.I.R 1934 Bom. 407).

3(h) A *method of agriculture or horticulture.*

4.8.1 A method of producing a new form of a known plant, even if it involved a modification of the conditions under which natural phenomena would pursue their inevitable course, is not patentable. (N.V. Philips Gloeiammpenfabrieken's Application 71 RFC 192).

4.8.2 A method of producing improved soil from the soil with nematodes by treating the soil with a preparation containing specified phosphorathioates was held not patentable (Virginia Carolina Chemical Corporation application 1958 RFC 38).

4.8.3 A method of producing mushroom plant (64/Cal/79) and a method for cultivation of an algae (445/Del/93] were held not patentable respectively..

3(i) Any *process for the medicinal, surgical, curative, prophylactic, diagnostic therapeutic or other treatment of human beings or any process for a similar treatment of animals to render them free of disease or to increase their economic value or that of their products.*

4.9.1 A method of treatment of malignant tumour cells and method of removal of dental plaque and carries are not patentable, since they are held as treatment of human beings. Also, treatment of sheep for increasing wool yield (1958 RPC 85) was held as not patentable.

4.9.2 An invention of a method of treatment of the human or animal body by surgery or therapy or of diagnosis practised on the human or animal body shall not be taken to be capable of industrial application.

4.9.3 The art of curing illness cannot be said to be patentable.

4.9.4 The term "therapy'' includes prevention as well as treatment or cure of disease. Therefore, the process relating to therapy is also not patentable as held in *Unilever Limited (Davis') Application,* [1983] RPC 219

4.9.5 Although some medical dictionaries pointed towards a narrow interpretation of the term, other works of reference, including non-specialist dictionaries, indicated a more general meaning; this was preferred in this case, following the principle that words in statutes dealing with matters relating to the general public are presumed to be used in their popular, rather than their narrowly legal or technical, sense. However, for a treatment to constitute therapy, there must be a direct link between the treatment and disease state being cured, prevented or alleviated, (BL O/248/04).

4.9.6 It appears that any medical treatment of a disease, ailment, injury or disability, i.e. anything that is wrong with a patient and for which he would consult a doctor, as well as prophylactic treatments such as vaccination and inoculation, is to be regarded as therapy. The same considerations apply for animals as for human patients, so that for example prophylaxis and immunotherapy in animals are regarded as therapy[T 24/91]

4.9.7 In *Ciba-Geigy AG's Application* (BL O/30/85), a method of controlling parasitic helminths (worms which may develop in the animal body, for example, in the intestinal tract of animals such as sheep) by the use of a particular (novel and inventive) anthelmintic composition was held non patentable as such an infestation was a disease requiring medical treatment of the animal and that such treatment, whether curative or preventative, constituted therapy practised on the animal body.

4.9.8 Prophylactic treatment, aimed at maintaining health by preventing ill effects that would otherwise arise, amounts to a method for treatment by therapy Both prophylactic and curative methods of treating disease are covered by the word therapy, since both are directed to the maintenance or restoration of health The same consideration applies for animals as well as for human beings. For example prophylatic immuno-therapy in animals are regarded as therapy.

4.9.9 An application of substance to human body purely for cosmetic purposes is not a treatment or therapy. On the other hand, the application to the skin of an ointment designed to be effective to remove keratoges from the skin would be the instance of medical treatment. Here, "Treatment" in relevant senses means that the purpose of application of a process or substance to the body must be to arrest or cure of a disease or diseased condition or correcting some malfunction or amelioration of some incapacity or disability (Joos Vs. Commissioner of Patent (1973) RPC 59).

4.9.10 Application of substances to the body for purely cosmetic purposes is not therapy. In allowing claims to a process for improving the strength and elasticity of human hair and finger nails, the High Court of Australia observed that, while a process for the treatment of the human body as a means of curing or preventing a disease or other disorder was not patentable,

"Those who apply chemical preparations to the skin to prevent sunburn in climates which enjoy sunshine and moderate air temperatures can scarcely be regarded either as, in a relevant sense, treating their bodies or as undergoing treatment. On the other hand, the application to the skin of an ointment designed and effective to remove keratoges from the skin would be an instance of medical treatment. To be treatment in the relevant sense, it seems to me that the purpose of the application to the body whether of a substance or a process must be the arrest or cure of a disease or diseased condition or the correction of some malfunction or the amelioration of some incapacity or disability" (*Joos v Commissioner of Patents*, [1973] RPC 59).

4.9.11 It was held in Lee Pharmaceuticals application [(1978) RPC 51] that, since, one of the reasons of grinding pits and fissures in teeth was to prevent the onset of dental decay, the purpose of the treatment was therapeutic rather than cosmetic.

4.9.12 Patent, may however be obtained for surgical, therapeutic or diagnostic instrument or apparatus. Also the manufacture of prostheses or artificial limbs and taking measurements therefor on the human body are patentable.

4.9.13 The claims to a method of removing dental plaque and / or caries were refused in Oral Health Products Inc (Habtead's Application, (1977) RPC 612), as the claim was to a method of cleaning teeth, which embraced both curative and cosmetic effects.

4.9.14 This decision has been followed in another case, where a claim was refused to a method of cleaning teeth which removed both plaque and stains. It was argued that, when applied to perfectly healthy teeth, the method was purely cosmetic. But the hearing officer observed that practically all *medical* treatments which are preventive in nature (such as vaccination) must, at times, be applied to people who would have remained healthy anyway, but they remained medical treatments

4.9.15 In *Oral Health Products Inc (Halstead's) Application,* [1977] RPC 612, claims to a method of removing dental plaque and/or caries were refused, as was a claim to a method of cleaning teeth which embraced both curative and cosmetic effects. This decision has been followed under the 1977 Act in *ICI Ltd's Application No 7827383* (BL O/73/82), where a claim was refused to a method of cleaning teeth which removed both plaque and stains; it was argued that when applied to perfectly healthy teeth the method was purely cosmetic, but the hearing officer observed that practically all medical treatments which are preventative in nature (such as vaccination) must at times be applied to people who would have remained healthy anyway, but they remained medical treatments

4.9.16 In T 290/86 the Board held that the use of a lanthanum-containing composition for cleaning plaque and/or stains from human teeth...will always inevitably have a therapeutic effect (at least in the prophylactic sense) as well as a cosmetic effect. Thus the invention as here claimed is not directed solely to a cosmetic effect, but is also necessarily defining a treatment of the human body by therapy and hence excluded from patentability.

4.9.17 Methods of treatment of the human or animal body by surgery are excluded. 'Surgery' is defined as the treatment of disease or injury by operation or manipulation. It is not limited to cutting the body but includes manipulation such as the setting of broken bones or relocating dislocated joints (sometimes

called "closed surgery"), and also dental surgery. In general, any operation on the body, which required the skill and knowledge of a surgeon, would be regarded as surgery and includes non-curative treatments such as cosmetic treatment, the termination of pregnancy, castration, sterilization, artificial insemination, embryo transplants, treatments for experimental and research purposes and the removal of organs, skin or bone marrow from a living donor are, if carried out by surgery, regarded as surgical treatments. Once it has been decided that a method constitutes surgery, therapy or diagnosis practised on the human or animal body, it is necessarily non-patentable. For example, methods of abortion, induction of labour, control of oestrus or menstrual regulation are always therapy, irrespective of the reason for the treatment.

4.9.18 In Unilever Limited (Davis1) Application, [1983] RPC 219, it was observed that any method of surgical treatment, whether curative, prophylactic or cosmetic, is not patentable. This view was upheld in an another case also, while refusing to allow claims to a method of implanting an embryo transplant from a donor mammal into the uterus of a recipient mammal, since the method would necessarily have to be carried out by a surgeon or veterinary surgeon.

4.9.19 Methods of diagnosis practiced on the human or animal body are excluded. Methods of diagnosis performed on tissues or fluids, which have been permanently removed from the body are, therefore, not excluded from patentability.

4.9.20 Diagnosis is the identification of the nature of a medical illness, usually by investigating its history and symptoms and by applying tests. Determination of the general physical state of an individual (e.g. a fitness test) is not considered to be diagnostic if it is not intended to identify or uncover a pathology. Section relates to methods of diagnosis practised on the human or animal body; diagnosis in itself is a method of performing a mental act and is excluded from patentability. Typically, the process of diagnosis involves a number of steps leading towards identification of a condition. For a claim to fall under this prohibition, it must include both the deductive step of making the diagnosis and preceding steps constructive for making that diagnosis involving specific interactions of a technical nature with the human or animal body. The exclusion is therefore a narrow one, and also requires all the method steps of a technical nature to be practised on the body. In determining whether or not a method is a diagnostic, the Board held that it is irrelevant whether it is necessary for a medical or veterinary practitioner to be involved. Furthermore, a method is "practised on the human or animal body" if it involves any interaction which necessitates the presence of the patient, so will include both invasive and non-invasive methods. Methods of diagnosis performed on tissues or fluids which have been permanently removed from the body are not excluded. "Body" should be taken to mean living body, and a method practised on a dead body, for example in order to determine the cause of death, would not be exclude.

4.9.21 Methods of therapy carried out on materials temporarily removed from the body, for example, when blood is circulated through an apparatus while remaining in living communication with the body, are not patentable *(cf Calmic Engineering Co Ltd's Application, [1973] RPC 684).*

4.9.22 *In Ciba-Geigy AG's Application* , the objection was raised to certain claims for a method of controlling parasitic helminthes (worms which may develop in the animal body, for example, in the intestinal tract of animals such as sheep) by the use of a particular (novel and inventive) antihelmintic composition, The applicants contended that the composition when administered to an animal would prevent the reproduction of the helminthes and kill them should they infest the animal, but without affecting the animal's body, and that its use was therefore not "therapy". However, the applicants' specification made it clear that an infestation of helminthes worms can result in restricted growth, damage to the animals and even death, if not properly treated. Moreover, the application made no mention of controlling helminthes by the use of the composition in any environment other than the animal body. The hearing officer considered that such an infestation was therefore a disease requiring medical treatment of the animal and that such treatment, whether curative or preventative, constituted therapy practiced on the animal body and consequently held that the claims in question were not allowable.

4.9.23 In G 1/04 (OJ 2006, 334) the Enlarged Board of Appeal held that whilst the legislator had chosen the legal fiction of lack of industrial applicability, the exclusion from patentability of the above-mentioned methods under Art. 52(4) EPC seemed actually to be based on socio-ethical and public health considerations. Medical and veterinary practitioners should be free to take the action they considered suited to diagnosing illnesses by means of investigative methods. Consequently, the policy behind the legal fiction referred to above appeared to be aimed at ensuring that those who carry out diagnostic methods as part of the medical treatment of humans or veterinary treatment of animals were not inhibited by patents (see T 116/85).

4.9.24 In case of M/s. A G A Medical Corporation, USA [Patent Application No.1283/DEL/2004], the controller held that "The purpose of the invention is to provide a method for determining the nominal or stretched diameter of an internal opening or defect with in a patient and particularly determining the stretched diameter of a septal defect within the heart of a patient is inseparably connected with the method of treatment" and therefore it is not patentable under section 3(i) of the Patent Act 1970.

4.9.25 In an application no **1377/DEL/1999** the claimed invention was related to a method for in vitro production of isolated langerhans islets endocrine cells free from fibroblasts so as to be suitable for transplantation. The process discloses the steps of culturing and proliferating the cells and back and forth aspiration to separate fibroblast from the cells, which will be capable of differentiating into insulin producing cells.The applicant argued that (1)the process is novel and has utility as fibroblast free langerhans islets are useful in the enhanced production of insulin. to control diabetes,(2)Kolkata High Court has already allowed patenting of a substance containing living organisms and(3)Indian Patent law does not bar the grant patent for such invention. However the Controller refused the application under section 15 on the grounds that the invention claimed is not patentable under section 3(i) as a method of treatment of human being, since langerhans islets are freshly taken from the body of patient in order to treat them to remove fibroblast so as to increase secretion of insulin. The end product of the process is nothing but a cluster of cells or piece of tissues of human body. The principles laid down in Kolkata High Court are not applicable as the end product of the process of present invention is not

commercial entity and cannot be passed on from one person to another upon the transaction of purchase or sale.

3(j) Plants and animals in whole or any part thereof other than micro-organisms but including seeds, varieties and species and essentially biological processes for production or propagation of plants and animals

4.10.1 As per this sub-section, while plants and animals, or any part of the plant or animal is not patentable, an exception is made in the case of micro-organisms. However, any discovered micro-organism from the nature is not patentable.

4.10.2 In Dimminaco – A.G vs. Controller of Patents & Designs and others (AID No.1 of 2001)the issue involved was the patenting of the process for preparation of infectious bursitis vaccine, which is invented for protecting poultry against infectious bursitis. The Controller held that the process of separation of the vaccine which has living entity cannot be considered a manufacture and hence not patentable under section 2(1)(j)of the Patents Act. He also held that since the vaccine contains living organism it cannot be patented. The court held that the matter involved is of a *new* process of preparation of vaccine under specific scientific conditions and the said vaccine is *useful* for protecting poultry against contagious bursitis infection and there is no statuary bar to accept a manner of manufacture as a patentable even if the end products contain living organism.

4.10.3 Plant varieties are provided protection in India under the provisions of the Protection of Plant Varieties and Farmers' Rights Act, 2002.

3(k) A mathematical or business method or a computer program per se or algorithms are not patentable.

Use the existing guidelines in Annexure II

4.11.1 A mathematical method is one which is carried out on numbers and provides a result in numerical form (the mathematical method or algorithm therefore being merely an abstract concept prescribing how to operate on the numbers) and not patentable. However, its application may well be patentable, for example, in *Vicom/Computer-related invention* [1987] 1 OJEPO 14 (T208/84) the invention concerned a mathematical method for manipulating data representing an image, leading to an enhanced digital image. Claims to a method of digitally filtering data performed on a conventional general purpose computer were rejected, since those claims were held to define an abstract concept not distinguished from a mathematical method. However, claims to a method of image processing which used the mathematical method to operate on numbers representing an image can be allowed. The reasoning was that the image processing performed was a technical (i.e. non-excluded) process which related to technical quality of the image and that a claim directed to a technical process in which the method used does not seek protection for the mathematical method as such.

Therefore the allowable claims as such went beyond a mathematical method.

4.11.2 The patent application No.558/DELNP/2005 related to method of operating the credential management processor. This was refused as it was found to be attracting the provisions of section 3(k) as the alleged method was relating to 'receiving ', 'de-referencing' and 'storing' ~~was~~ being purely a computer implemented software application. As well as the enhancement of security as claimed in method claims was already disclosed in the cited document and is obvious to a person skilled in the art.

3(l) A literary, dramatic, musical or artistic work or any other aesthetic creation whatsoever including cinematographic works and television productions;

4.12.1 Writings, music, works of fine arts, paintings, sculptures, computer programs, electronic databases, books, pamphlets, lectures, addresses, sermons, dramatic-musical works, choreographic works, cinematographic works, drawing, architecture, engraving, lithography, photographic works, applied art, illustrations, maps, plans, sketches, three-dimensional works relating to geography, topography, translations, adaptations, arrangements of music, multimedia productions, etc. are not patentable. Such works fall within the domain of the Copyright Act, 1957.

3(m) ***Schemes, rules and methods for performing mental acts, playing games***

4.13.1 Method of performing mental act or method of playing game or a mere scheme or rule are as such excluded from patentability, because they are considered as outcome of mere mental process.

a. Method of learning a language.
b. Method of playing chess.
c. Method of teaching.
d. Method of learning
e. Method of operating a machine or equipment as per the set of instructions

3(n) A presentation of information

4.14.1 Any manner, means or method of expressing information whether visual, audible or tangible by words, codes, signals, symbols, diagrams or any other mode of representation is not patentable. For example, a speech instruction means in the form of printed text where horizontal underlining indicated stress and vertical separating lines divided the works into rhythmic groups is held not patentable

4.14.2 In the matter of ~~2.~~ Application number 94/CAL/2002, the controller held that "~~Section 15, Applicant~~ The patent system is therefore meant for protecting only one kind of creativity, i.e., technological creativity. ", Since the claimed invention related to business method and method of presenting information.

~~**Placement of content in the manual as decided on 22.01.2008/ as explanation/ as example**~~

~~**1.** [May be attached to the interpretation of Section 3]~~

3(o) ***Topography of integrated circuits;***

~~For example :~~ 4.15.1 Since protection of Layout Designs of Integrated Circuits is governed separately under the Semiconductor Integrated Circuit Lay-out Designs Act, 2000.

~~T~~three-Dimensional configuration of the electronic circuits used in microchips and semiconductor chips is ~~held~~ not patentable.

3(p) ***An invention which in effect, is traditional knowledge or which is an aggregation or duplication of known properties of traditionally known component or components;***

4.16.1 Traditional Knowledge, being knowledge already existing, is ~~already in public domain, and hence,~~ **not patentable,** for example: ~~Wound healing property of turmeric.~~The anti-septic property of turmeric for wound healing. The pesticidal, insecticidal properties of neem

~~However, any value-addition using Traditional Knowledge leading to a new process or product, possessing novelty, inventive step and industrial applicability, can be **patentable.**~~

~~PATENTABILITY OF VARIOUS FORMS OF CHEMICAL SUBSTANCES:~~

~~a) Isomers~~

~~Isomers are different compounds that have the same molecular formula which may be broadly divided into two kinds, namely,~~

~~-structural isomers or positional isomers and.~~
~~-stereo isomers.~~

~~Structural Isomers or positional isomers may be structurally similar or dissimilar compounds. The simplest examples are butane and isobutane and ethanol and dimethyl ether. In the former case the compounds are having structural and functional similarity. However, In the second set of compounds, although they have the same molecular formula but are structurally and functionally different.. Such isomers even having close similarity may be considered to be novel over the prior art.~~

~~Isomers having the same empirical formula but having structural differences may be considered novel and may not normally offend "obviousness" as they are structurally different.~~

~~Example: Cyclohexylstyrene is not considered prima facie obvious over prior art isohexyl styrene.~~

~~b) Stereo Isomers are prima facie obvious.~~

~~Once a compound having a chiral center is known, its enantiomers are obvious because a person skilled in the art knows that a compound having a chiral center exists in two optically active forms. Hence, a product patent may not be granted for the enantiomer form. However, when a new compound is claimed having chiral center(s) for the first time, a product patent may be granted.~~

~~In a case where an (S) enantiomer of a compound, capable of exhibiting better efficacy over the (R) enantiomer, say for exampleproducing enhancedanti-diabetic effects is claimed, wherein the said claim is not allowable when the same chemical compound possessing anti-diabetic property is known from the prior art.~~

~~c) Homologues~~

~~Homologues normally display add-on property. They are structurally similar and provide the example of Structure – Function linearity and may lack inventive step. However the cases are to be decided on case to case basis.~~

~~e.g. Polymerization process using a sterically hindered amine was held non-obvious over a similar prior art process because the prior art disclosed a large number of unhindered amines.~~

~~Another interesting example is that prior art structures do not have to be true homologs or isomers to render structurally similar compounds prima facie obvious.~~

~~e.g. Claims and Prior art were for heterocyclic carbamoyloxmino compounds having pesticidal activity. The only structural difference was that the ring structures of the claimed compounds had two carbon atoms between two sulphur atoms whereas the prior art ring structures had either one or three carbon atoms between two sulphur atoms. The court held that although the prior art compounds were not true homologs or isomers of the claimed compounds, the similarity between the chemical structures and properties is sufficiently close that one of ordinary skill in the art would have been motivated to make the claimed compounds in searching for new pesticides.~~

~~d) Polymorphs~~

~~Some compounds are present in polymorphic forms, i.e., they crystallize in diverse forms. Such forms can be deemed within the prior art and therefore not patentable. However, process patent may be allowed for the new polymorph, if the polymorph is prepared by a novel process involving inventive step.~~

~~Some therapeutically active ingredients, present in polymorphic forms, may have different properties that are more or less significant in terms of their therapeutic use. Such forms can be deemed within the prior art,~~**~~and therefore, non-~~**

patentable if they were inevitably obtained following the process of the basic patent on the active ingredient or if they were covered by a previous product patent.

e) Metabolites:

Metabolites are the compounds that are formed inside a living body during metabolic reaction. The types of metabolites are-

i) Active metabolites formed from inactive precursors (e.g DOPA & Cyclophosphamide)

(ii) Active metabolites formed from precursors that show mechanism of action that is different from that of parent compound (e.g Buspirone & 1-pyrimidyl piperzine Fenflouromine & norfenfleuromine)

(iii) Active metabolites which contribute to the duration of action of the parent compound (e.g. Hexamethylmelamine & Clobazam)

(iv) Active metabolites that show antagonistic effect on the activity of the parent compound (e.g Trezodone & m-chlorophenyl pierzine, Aspirin & salicylate)

A metabolite is **not patentable** since giving the drug to a patient naturally and inevitably results in formation of that metabolite.

f) Prodrugs :

Prodrugs are inactive compounds that can produce an active ingredient when metabolized in the body. Hence prodrugs and metabolites are interlinked. When metabolyzed in the body, inactive compounds(pro-drug) can produce a therapeutically active ingredient,. It must be determined whether the patent on the compound covers the prodrug and the extent to which claims relating to certain compounds should also be allowed to include their prodrugs. The inventive aspects of a prodrug may be decided based **on the merits of the case.**

However , if there is a marked improvement in performance over the primary drug, prodrugs may be patentable.

g) Hydrates And Other Substances

Hydrates, acid addition salts and other derivatives, which are routinely prepared, prima facie lack an inventive step. However, where there is a problem like stability, absorption etc., and there is a long standing problem in preparing the derivatives, patentability of such process may be considered.

h) Purification Compounds:

Mere purification of known material does not result in the patentable subject matter due to lack of novelty and inventive step.

i) Pharmaceutical Compostions

t.The pharmaceutical compositions, other than mere admixtures resulting in the aggregation of properties of the ingredients, having synergistic effect may normally be patentable.

u.The known pharmaceutical compositions in different new dosages and different forms such as capsules, tablets, syrups, suspensions etc, are not patentable under sections 2(1)(j) , 3(d) and 3(e). of the Act

v.New use of known substance or its new use in a pharmaceutical composition is not patentable.

For example –

a) The New use of methyl alcohol as antifreeze in automobiles-
The Use of methanol as a solvent is known in the prior art. A New use has been claimed in this claim as antifreeze which is not allowable under section 3(d) of the Act

b) A new use of Chloroquine for Sarcoidosis(a fungal disease) and for Infectious mononucleosis(a viral disease) and for Diabetic neuritis(inflammation of nerves) is claimed . Since the claim pertains to a new use of Chloroquine, which is an antimalarial drug known in the prior art, it is not allowable under section 3(d) of the Patents Act

c) A food packing machine used for packing the desired amount of talcum powder. Since this claim does not characterize any changes in the said food-packing machine, it is presumed that the same machine has been used for the purpose of packing talcum powder. Therefore, it is understood from the claim that the same packing machine, which is in vogue, is used for packing the material other than food. Hence this is also not allowable under section 3(d) of the Patents Act

d) Any method of using pharmaceutical composition is not patentable

oAny invention which in effect is traditional knowledge or which is an aggregation or duplication of known properties of traditionally known components is not patentable.

oAny method of agriculture or horticulture is not patentable.

INVENTIONS RELATING TO ATOMIC ENERGY

Section 4: "No Patent shall be granted in respect of an invention relating to atomic energy falling within subsection (1) of section 20 of the Atomic Energy Act, 1962 (33 of 1962)"

~~(i)~~4.17.1 No patent shall be granted for the invention which in the opinion of Central Govt. is useful for or related to the production, control, use or disposal of atomic energy or prospecting mining extraction, production, physical and chemical treatment fabrication, enrichment, canning or use of any prescribed substance or radioactive substance or the insuring of safety in atomic energy operation (in pursuance of S. 20(1) of Atomic Energy Act, 1962).

~~(ii)~~4.17.2 According to S. 20(1) of Atomic Energy Act, atomic energy means energy released from atomic nuclei as a result of any process including the fission and fusion processes.

4.17.3 Under this Act "prescribed substances" means any substances including any mineral which the Central Govt. may, by notification, prescribe, being a substance which in its opinion is or may be used for the production or use of atomic energy or research into matters connected therewith and includes uranium, plutonium, thorium, beryllium, deuterium or any of these respective derivative or compounds or any other materials containing any of the aforesaid substances.

4.17.4 Under the atomic energy Act, the term "radioactive substances" or "radioactive material" is defined as any substance or material, which spontaneously emits, radiation in excess of the levels prescribed by notification by the central govt.

4.17.5 As per the " Revised Notification on Prescribed Substances, Prescribed equipment and Technology " in the Gazette of India (extraordinary, Part II, Section 3, sub-section (ii), dated 20th January, 2006, the Department of Atomic Energy, in supersession of earlier notifications, has specified in the following as the Prescribed Substances, Prescribed equipment and Technology.

NOTIFICATION
DEPARTMENT OF ATOMIC ENERGY
(Mumbai, the 18th January 2006)

S.O. 61(E).- In pursuance of clauses (f) and (g) of sub-section (1) of Section 2 and Section 3 of the Atomic Energy Act, 1962 (No.33 of 1962) and in supersession of the notifications of the Government of India in the Department of Atomic Energy vide numbers S.O.211 (E) dated the 15th March, 1995 and S.O.212(E) dated the 15th March, 1995, the Central Government hereby notifies the substances, equipment and technology specified in the Schedule appended hereto as Prescribed Substances, Prescribed Equipment and Technology.

Category – 0: Nuclear materials, nuclear-related other materials, equipment and technology.

OA Prescribed substances

Note: Any radioactive material in Category OA shall additionally attract the provisions of the Atomic Energy (Radiation Protection) Rules, 2004 made under the Atomic Energy Act, 1962 and the provisions of Section-16 of the Atomic Energy Act,1962.

OA1 Source Material

OA101 Uranium containing the mixture of isotopes occurring in nature

OA102 Uranium depleted in the isotope 235.

OA103 Thorium

OA104 Any of the foregoing in the form of metal, alloy, chemical compound, or concentrate or any substance.

OA105 Any other material containing one or more of the foregoing.

Prescribed quantitative limits: as given below and in any period of 12 months:

a. Uranium (containing the mixture of isotopes in nature) exceeding 100 kilograms.
b. Depleted uranium (uranium depleted in the isotope 235 below that occurring in nature) exceeding 1000 kilograms.
c. Thorium exceeding 1000 kilograms.

OA2 Special Fissionable Material

OA201 Plutonium-239

OA202 Uranium-233

OA203 Uranium enriched in the isotopes 235 or 233

OA204 Neptunium.

OA205 Any material containing one or more of the foregoing

OA206 Such other fissionable material determined by the Central Government from time to time, but the term "special fissionable material " which does not include source material.

Note: Any quantity of special fissionable material is prescribed substance.

OA3 Other Materials.

'Other Materials' means non-nuclear materials for reactors, nuclear related dual-use materials indicate below and such materials as determined by the Central Government from time to time.

OA301 Deuterium, heavy water (deuterium oxide) and any other deuterium compound, in which the ratio of deuterium to hydrogen atoms exceeds 1:5000, in quantities exceeding 5 kilograms of deuterium in one consignment or 25 kilograms of deuterium in any period of 12 months.

OA302 Nuclear grade graphite / carbon, having a purity level better than 5 parts per million (ppm) boron equivalent and with a density greater than 1.5 gram/cc in quantities exceeding 30 metric tons in any period of 12 months.

OA303 Zirconium with hafnium content of less than 1 part to 500 parts of zirconium by weight (i.e. less than 2000 ppm) in the form of metal, its alloys, compounds, manufactures thereof, waste or scrap of any of the foregoing.

OA304 Beryllium, its compound, alloys and its minerals/concentrates including Beryl but excluding:

a. beryllium windows used for x-ray machines and gamma rays detectors and

b. beryl in the form of emeralds or aquamarines.

OA305 Lithium enriched in the Lithium-6 (6Li) isotope to greater than its natural isotope abundance (i.e. more than 7.5%) and the products or devices containing enriched lithium such as elemental lithium, alloys, compounds, mixtures containing lithium, manufactures thereof, waste or scrap of any of the foregoing.

OA306 Niobium and Tantalum, their metals, alloys and minerals including columbite and tantalite.

OA307 Titanium alloys having both of the following characteristics:

a. 'Capable of' an ultimate tensile strength of 900 Mpa or more at 293 K (20°); and

b. In the form of tubes or cylindrical solid forms (including forgings) with an outside diameter of more than 75 mm.

Technical note: The phrase 'capable of' encompasses titanium alloys before or after heat treatment.

OA308 Tritium, tritium compounds or mixtures containing tritium in which the ratio of tritium to hydrogen atoms exceeds 1 part in 1000, except when utilized in such quantities and for such purposes as for organic labeled compounds, Gas Filled Sources and as Tritiated Water for radiotracer studies.

OA309 Hafnium:

Hafnium metal, alloys containing more than 60% hafnium by weight, hafnium compounds containing more than 60% hafnium by weight, manufacturers thereof, and waste or scrap of any of the foregoing.

OA310 Radium-226:

Radium-226 (226Ra), radium-226 alloys, radium-226 compounds, mixtures containing radium-226, manufactures thereof, and products or devices containing any of the foregoing, except medical applicators and a product or device containing less than 0.37 GBq (10mCi) of Ra-226 in any form.

OA311 Boron

Boron enriched in the Boron-10(10B) isotope to greater than its natural isotopic abundance as follows:

Elemental boron, compounds, mixtures containing boron, manufactures thereof, waste or scrap of any of the foregoing.

OA312 Helium-3

Helium-3 (^{3}He), mixtures containing helium-3, and products or devices containing any of the foregoing.

Note: A product or device containing less than 1 gm of Helium-3 is excluded.

OA313 Alpha-emitting radionuclides:

Alpha-emitting radionuclides having an alpha half-life of 10 days or greater but less than 200 years, in the following forms:

a. Elemental;

b. Compounds having a total alpha activity of 37 GBq per kg or greater;

c. Mixtures having a total alpha activity of 37GBq per kg or greater;

d. Products or devices containing any of the foregoing.

Alpha emitters controlled by this item include:

Actinium-225	Actinium-227	Americium-242m
Californium-248	Calfornium-250	Californium-252
Californium-253	Calfornium-254	Carium-240
Curium-241	Curium-242	Curium-243
Curium-244	Einsteinium-252	Einsteinium-253
Einsteinium-254	Einsteinium-255	Fermium-257
Gadolinium-148	Mendelevioum-258	Neptunium-235
Plutonium-236	Plutonium-237	Plutonium-238
Plutonium-241	Polonium-209	Polonium-210
Polonium-208	Radium-223	Thorium-228
Thorium-227	Uranium-230	Uranium-232

OA314 *Titanium ores and concentrates (Ilmenite, Rutile and Leucoxene)

OA315 *Zirconium, its alloys and compounds and minerals/concentrates including zircon

*Note: These items (OA314 and OA315) shall remain prescribed substances only till such time the Policy on Exploitation of Beach Sand Minerals notified vide Resolution number 8/1(1)/97-PSU/1422 dated the 6th October, 1998 is adopted/revised/modified by the Ministry of Mines or till the 1st January 2007, whichever occurs earlier and shall cease to be so thereafter.

OB Prescribed Equipment

OB001 Nuclear Reactors; associated equipment, components and systems specially designed, prepared, or adapted or used or intended to be used in such reactors as follows:

a. Complete nuclear reactors
b. Nuclear reactor vessels
c. Nuclear reactor fuel charging and discharging machines
d. Nuclear reactor control rods and equipment
e. Nuclear reactor pressure tubes
f. Zirconium tubes and assembles of tubes in which hafnium to zirconium ratio is 1:500 or less
g. Primary coolant pumps
h. Nuclear reactor internals
i. Heat exchangers (steam generators) for use in the primary coolant circuit of a nuclear reactor
j. Neutron detection and measuring instruments for determining neutron flux levels within the core of a nuclear reactor

OB002 Plants for processing, production, concentration, conversion or recovery of Prescribed Substances (such as uranium, plutonium, thorium, deuterium, heavy water, tritium, lithium); associated equipment, components and

system, specially designed, prepared or adapted or used or intended to be used in such plants including but not limited to:

a. Plants for production or concentration of deuterium, heavy water
1. Water-Hydrogen Sulphide Exchange Towers
2. Blowers and Compressors for hydrogen-sulphide gas circulation
3. Ammonia-Hydrogen Exchange Towers greater than or equal to 35m in height with diameters of 1.5m to 2.5m
4. Tower Internals and Stage Pumps
5. Ammonia Crackers with operating pressures greater than or equal to 3 MPa
6. Infrared Absorption Analyzers capable of 'on-line' hydrogen/deuterium ratio analysis
7. Catalytic Burners for conversion of enriched deuterium gas into heavy water
8. Complete heavy water upgrade systems or columns therefore
b. Plants for the conversion of uranium
c. Plants for the conversion of plutonium
d. Tritium facilities or plants, and equipments therefore
e. Lithium isotope separation facilities of plants, and equipment therefore.

OB003 Plants for reprocessing of irradiated nuclear fuel and equipment, components and systems specially designed, prepared or adapted or used or intended to be used in such plants, including but not limited to:

a. Irradiated fuel element chopping machines designed for remote operation
b. Dissolvers capable of withstanding hot and highly corrosive for dissolution of irradiated nuclear fuel and which can be removed loaded and maintained.
c. Solvent extractors and solvent extraction equipment resistant to the corrosive effect of nitric acid.
d. Chemical holding or storage vessels resistant to the corrosive effect of nitric acid.
e. Industrial equipment including assemblies and components as follows:

1. High density (lead glass or other) radiation shielding windows
2. Radiation hardened TV cameras, or lenses therefore
3. 'Robots' or 'end effectors' specially designed for handling high explosives; and control units therefore
4. Remote manipulators that can be used to provide remote actions in radiochemical separation operations or hot cells

OB004 Plants for treatment, handling, storage and transportation of radioactive wastes from nuclear reactors or from plants for processing Source Materials or Special Fissionable Material or from nuclear reprocessing plants; irradiated nuclear fuel; Special Fissionable Materials, and equipment specially designed, prepared, adapted, or intended to be used therefor.

CHAPTER ~~III~~ V

APPLICATION FOR PATENTS

~~3.1~~PERSONS ENTITLED TO APPLY FOR A PATENT IN INDIA

Relevant sections and Rules:

Section 6.

Persons entitled to apply for patents;

(1) Subject to the provisions contained in section 134, an application for a patent for an invention may be made by any of the following persons, that is to say,—

(a) by any person claiming to be the true and first inventor of the invention;

(b) by any person being the assignee of the person claiming to be the true and first inventor in respect of the right to make such an application;

~~(b)~~(c) by the legal representative of any deceased person who immediately before his death was entitled to make such an application.

(2) An application under sub-section (1) may be made by any of the persons referred to therein either alone or jointly with any other person.

Section 2(1) (y) *"true and first inventor" does not include either the first importer of an invention into India, or a person to whom an invention is first communicated from outside India.*

Section 2(1) (s) *: "person" includes the Government;*

Section 2(1) (ab) *: "assignee" includes an assignee of the assignee and the legal representative of a deceased assignee and references to the assignee of any person include references to the assignee of the legal representative or assignee of that person; (see also Section 68)*

Section 2(1) (k) *: "legal representative" means a person who in law represents the estate of a deceased person;*

5.1.1 EXPLANATION

i) An application for a patent for an *invention* may be made by any of the following **persons** either **alone** or **jointly with another**

- True and first Inventor
- True & First Inventor's assignee
- Legal representative of deceased true and first Inventor or his/her assignee.

ii) The term "person" as defined in the Patents Act includes Government. [Section 2(1)(s)]

iii) The term "person" also defined in the General Clauses Act 1897 include any company or association or body of individual, whether incorporated or not ~~unalthough in such cases but not a firm, partnership or body which is unincorporate, individual~~In the case of a limited partnership, the application may be in the names of all personally responsible partners (see also 7.05)

~~iii)~~iv) **True and first Inventor** does not include either the first importer of an invention into India or a person to whom an invention is first communicated from outside India **(S. 2(1)(y)).** The applicant is required to disclose the name, address and nationality of the true and first inventor.

~~iv)~~v) Assignee can be a **natural person** or other than natural person like registered company, research organization, educational institute or **Government** *(S.2 (1)(s)).*

~~v)~~vi) **Assignee** includes assignee of the assignee also **(S. 2(1)(ab)).**

~~vi)~~vii) **'Proof of right'** to apply such as assignment deed should be submitted by the assignee. **Proof of Right** is required even when the applicant in convention country/ PCT international application is the same as that in India.

Legal representative means a person who in law represents the estate of a deceased person **(S.2 (1)(k)).** In such a case, the~~y~~ person should file death certificate alongwith other appropriate legal instruments ~~etc.~~ as proof of right. ~~The applicant shall be a national of India or any other country which is not notified by Government of India as countries not providing for reciprocity.~~

viii)

ix) **Convention country** means any country, which is a signatory or party, or group of countries or union of countries or intergovernmental organizations which are signatories or parties to an international, regional or bi-lateral treaty, convention or arrangement, of which India is also a party. A convention country/countries for the purpose of the Act (S 133), is one which accords the same rights in respect of the grant of patents and protection of patent rights to citizens of India, as it accords to its own nationals. **(S.133 & S.134).**

5.1.2 It was held that a firm can apply for a patent as assignee; Shinning Industries v. Shri Krishna Industries, AIR 1975 All 231.

5.1.3 *In case of the Dyer Meakin Breweries Ltd.* V *Scotch Whisky Association, (*AIR 1980 Del 125.*), it was held that* Section 68 of the Act provides that the Assignment Deed, when registered, shall have effect from the date of its execution. It is, therefore, apparent that as soon as the entry of registration of his deed was made by the Patent Office on 21st June 1979 the plaintiff became the assignee of the patent in question with effect from the date of execution of the deed *i.e.* 22nd May 1979. Section 68 of the Act provides that the assignment of

a patent shall not be valid unless the same were in writing and the agreement between the parties concerned is reduced to the form of a document embodying all the terms and conditions governing their rights and obligations and the application for registration of such deed is filed with the Controller within six months of the execution of the document. Section 68 of the Act has thus been compiled with.

5.1.4 In the matter of an application for patent no. 551/Del/78, 1DPD, 39, the Controller held that the expression "without prejudice to provisions contained in Section 6" should be interpreted only as to mean without detriment to the applicant's right to file an ordinary application".

~~3.2~~5.2.1 Where to Apply? (Rule. 4 and 5)

Relevant Sections and Rules

Rule 4:

Appropriate office;

(1) The appropriate office of the patent office shall—

(i) for all the proceedings under the Act, be the head office of the patent office or the branch office, as. the case may be, within whose territorial limits—

(a) the applicant or first mentioned applicant in case of joint applicants for a patent, normally resides or has his domicile or has a place of business or the place from where the invention actually originated; or

(b) the applicant for a patent or party in a proceeding if he has no place of business or domicile in India, the address for service in India given by such applicant or party is situated; and

(2) The appropriate office once decided in respect of any proceedings under the Act shall not ordinarily be changed.

Rule 5:

Address for service; Every person, concerned in any proceedings to which the Act or these rules relate and every patentee, shall furnish to the Controller an address for service in India and that address may be treated for all purposes connected with such proceedings or patent as the address of the person concerned in the proceedings or of the patentee. Unless such an address is given , the Controller shall be under no obligation either to proceed or deal with any proceeding, or patent or to send any notice that may be required to be given under the Act or these rules and the Controller may take suo motu decision in the matter.

EXPLANATION

5.2.2 Filing of application: Appropriate office

i) Application for the patent has to be filed in the respective patent office as mentioned below where the territorial jurisdiction is decided based on whether any of the following occurrence falls within the territory

a) Place of residence, domicile or business of the applicant (first mentioned applicant in the case of joint applicants)

b) Place from where the invention actually originated.

c) Address for service in India given by the applicant when he has no place of business or domicile in India. (Rule 5).

N.B: <u>An appropriate office once decided will not be changed ordinarily</u>

ii) A foreign applicant shall give an address for service in India and the jurisdiction will be accordingly decided. An Indian applicant also can give his Patent Agent's address as address for serving documents if he/she wishes to do so.

Patent Office	**Territorial Jurisdiction**
Mumbai	The States of Gujarat, Maharashtra, Madhya Pradesh, Goa, Chhattisgarh, the Union Territories of Daman & Diu and Dadra & Nagar Haveli.
Delhi	The States of Haryana, Himachal Pradesh, Jammu and Kashmir, Punjab, Rajasthan, Uttar Pradesh, Uttaranchal, National Capital Territory of Delhi and the Union Territory of Chandigarh.
Chennai	The States of Andhra Pradesh, Karnataka, Kerala, Tamil Nadu and the Union Territories of Pondecherry and Lakshdweep.
Kolkata	Rest of India.

5.2.3 FILING OF APPLICATION FOR PATENT

Relevant sections and Rules

Section 7 : Form of application;

(1) Every application for a patent shall be for one invention only and shall be made in the prescribed form and filed in the patent office.

(1A) Every international application under the Patent Cooperation Treaty for a patent, as may be filed designating India shall be deemed to be an application under this Act, if a corresponding application has also been filed before the Controller in India.

(1B) The filing date of an application referred to in sub-section (1A) and its complete specification processed by the patent office as designated office or elected office shall be the international filing date accorded under the Patent Cooperation Treaty.

(2) Where the application is made by virtue of an assignment of the right to apply for a patent for the invention, there shall be furnished with the application, or within such period as may be prescribed after the filing of the application, proof of the right to make the application.

(3) Every application under this section shall state that the applicant is in possession of the invention and shall name the person claiming to be the true and first inventor; and where the person so claiming is not the applicant or one of the applicants, the application shall contain a declaration that the applicant believes the person so named to be the true and first inventor.

(4) Every such application (not being a convention application or an application filed under the Patent Cooperation Treaty designating India) shall be accompanied by a provisional or a complete specification.

Rule 6

Leaving and serving documents;

(1) Any application, notice or other document authorised or required to be filed, left, made or given at the patent office, or to the Controller or to any other person under the Act or these rules, may be tendered by hand or sent by a letter addressed to the Controller at the appropriate office or to that person through post or registered post or speed post or courier service or by electronic transmission duly authenticated. If it is sent by post or registered post or speed post or courier service or by electronic transmission duly authenticated, it shall be deemed to have been filed, left, made or given at the time when the mail containing the same would have been delivered in the ordinary course of post or registered post or

speed post or courier service, or by electronic transmission duly authenticated, as the case may be. In proving such sending, it shall be sufficient to show that the mail was properly addressed and transmitted:

(2) Any written communication addressed to a patentee at his address as it appears on the register of patents or at his address for service given under rule 5, or to any applicant or opponent in any proceedings under the Act or these rules, at the address appearing on the application or notice of opposition, or given for service, shall be deemed to be properly addressed.

(3) All notices and all written communications addressed to a patentee, or to any applicant or opponent in any proceedings under the Act or these rules, and all documents forwarded to the patentee or to the said applicant or opponent, shall, except when they are sent by special messenger, be sent by registered post or speed post or courier service or by electronic transmission duly authenticated.

(4) The date of a notice or a written communication addressed to a patentee or to any applicant or opponent in any proceedings under the Act and these rules shall be the date of dispatch of the said notice or written communication, by registered post or speed post or courier or fax or electronic transmission duly authenticated, as the case may be, unless otherwise specified under the Act or these rules.

(5) In case of delay in receipt of a document or a communication sent by the patent office to a party to any proceedings under the Act or these rules, the delay in transmitting or resubmitting a document to the patent office or doing any act by the party may be condoned by the Controller if a petition for such condonation of delay is made by the party to the Controller immediately after the receipt of the document or a communication along with a statement regarding the circumstances of the fact and evidence in support of the statement:

Provided that the delay condoned by the Controller shall not exceed the period between the date on which the party was supposed to have received the document or communication by ordinary course of mail or electronic transmission and the actual date of receipt of the same.

5.2.4 Whether "Any other person under the Act" under the ambit of rule 6 include the "Patent Agent" apart from the Controller and the Patent Office when read with Section 2(1)(s). The Controller held that the expression "any other person under the Act or Rules" in rule 6 would mean that whenever there is a bi-party or multi-party proceedings viz. an opposition under section 25, 61, or 92 of the Act, the parties to the proceedings are required to serve certain documents such as statements and evidence on each other, under intimation to the Controller and also on the Controller. In the course of any of the said proceedings if any document has been sent by one party to the other party and to the Controller by post sufficiently in advance, then if there is a postal delay as a result of which the other party or the Controller receives the said documents late, the delay involved will be condoned by the Controller under Rule 6 and the documents will be taken on record and deemed to have been received on the due date..... Accordingly, I cannot accept .....with regard to the expression "any other person under the Act or the Rules" as including Patent agent to whom his client has send the documents.

Rule 7: Fees;

(1) The fees payable under section 142 in respect of the grant of patents and applications there for, and in respect of other matters for which fees are required to be payable under the Act shall be as specified in the First Schedule.

(2) (a) The fees, payable under the Act may either be paid in cash or through electronic means or may be sent by bank draft or cheque payable to the Controller of Patents and drawn on a scheduled bank at the place where the appropriate office is situated. If the draft or cheque is sent by post, the fees shall be deemed to have been paid on the date on which the draft or cheque would have reached the Controller in the ordinary course of mail.

(b) Cheques or drafts not including the correct amount of commission and cheques on which the full value specified therein cannot be collected in cash shall be accepted only at the discretion of the Controller.

(c) Where a fee is payable in respect of a document, the entire fee shall accompany the document.

(3) In case an application processed by a natural person is fully or partly transferred to a person other than a natural person, the difference, if any, in the scale of fee(s) between the fee(s) charged from a natural person and the fee(s) chargeable from the person other than the natural person in the same matter shall be paid by the new applicant with the request for transfer.

(4) Fees once paid in respect of any proceeding shall not ordinarily be refunded irrespective of whether the proceeding has taken place or not.

(5) (i) Subject to the approval of the Controller, any person may deposit money in advance and request the Controller to realise any fee payable by him from the said deposit and in such case the date of the receipt of the request to realise the fee or the date on which the request to realise the fee is deemed to have been received, whichever is earlier, shall be taken as the date of payment of the fee:

Provided that the requisite amount of money is available at the credit of the person making such request.

(ii) Subject to the approval of the Controller, any person may discontinue the deposit of money in advance and in such case the balance, if any, shall be refunded.

Rule 8:
Forms

(1) The Forms set forth in the Second Schedule with such variations as the circumstances of each case may require shall be used for the purposes mentioned therein.

(2) Where no Form is so specified for any purpose, the applicant may adopt any Form specified in the Second Schedule with such modifications and variations as may be required.

Rule 9:

Size, etc., of documents.;

(1) All documents and copies of documents, except affidavits and drawings, sent to or left at the patent office or otherwise furnished to the Controller shall be written or typewritten or printed either in Hindi or in English language (unless otherwise directed or allowed by the Controller) in large and legible characters with deep indelible ink with lines widely spaced upon one side only of strong white paper of a size A4 of approximately 29.7 centimetres by 21 centimetres with a margin of at least 4 centimetres on the top and left hand part and 3cm on the bottom and right hand part thereof. Any signature which is not legible or which is written in a script other than Hindi or English shall be accompanied by a transcription of the name either in Hindi or in English in block letters:

Provided that any document including drawing, if any, may also be filed in electronic form along with a copy of it on white paper:

Provided further that in case the application for patent discloses sequence listing of nucleotides and/or amino acids, the same shall be filed in electronic form.

(2) Additional copies of all documents shall be filed at the appropriate office, if required by the Controller.

(3) Names and addresses of applicants and other persons shall be given in full together with their nationality and such other particulars, if any, as are necessary for identification.

Rule 10:

Period within which proof of the right under section 7(2) to make the application shall be furnished.—

Where, in an application for a patent made by virtue of an assignment of the right to apply for the patent for the invention, if the proof of the right to make the application is not furnished with the application, the applicant shall within a period of six months after filing of such application furnish such proof.

Explanation.— For the purposes of this rule, the six months period in case of an application corresponding to an international application in which India is designated shall be reckoned from the actual date on which the corresponding application is filed in India.

Rule 11:

Order of recording applications.

The applications filed in a year shall constitute a series identified by the year of such filing. In case of an application filed corresponding to an international application in which India is designated, such application shall constitute a series distinct from the rest of the applications identified by the year of filing of corresponding applications in India

Rule 12:

Information and Undertaking regarding foreign applications;

(1) The statement and undertaking required to be filed by an applicant for a patent under sub-section (1) of section 8 shall be made in Form 3.

(1A). The period within which the applicant shall file the statement and undertaking under sub-section (1) of section 8 shall be ^six months] from the date of filing the application.

Explanation.—For the purpose of this rule, the period of six months in case of an application corresponding to an international application in which India is designated shall be reckoned from the actual date on which the corresponding application is filed in India.

(2) The time within which the applicant for a patent shall keep the Controller informed of the details in respect of other applications filed in any country in the undertaking to be given by him under clause (b) of sub-section (1) of section 8 shall be six months from the date of such filing.

(3) When so required by the Controller under sub-section (2) of section 8, the applicant shall furnish information relating to objections, if any, in respect of novelty and patentability of the invention and any other particulars as the Controller may require which may include claims of application allowed within six months from the date of such communication by the Controller.

Section 9.

Provisional and Complete specifications;

(1) Where an application for a patent (not being a convention application or an application filed under the Patent Cooperation Treaty designating India) is accompanied by a provisional specification, a complete specification shall

be filed within twelve months from the date of filing of the application, and if the complete specification is not so filed, The application shall be deemed to be abandoned.

(2) Where two or more applications in the name of the same applicant are accompanied by provisional specifications in respect of inventions which are cognate or of which one is a modification of another and the Controller is of opinion that the whole of such inventions are such as to constitute a single invention and may properly be included in one patent, he may allow one complete specification to be filed in respect of all such provisional specifications.

Provided that the period of time specified under sub-section (1) shall be reckoned from the date of filing of the earliest provisional specification.

(3) Where an application for a patent (not being a convention application or an application filed under the Patent Cooperation Treaty designating India) is accompanied by a specification purporting to be a complete specification, the Controller may, if the applicant so requests at any time within twelve months from the date of filing of the application, direct that such specification shall be treated, for the purposes of this Act, as a provisional specification and proceed with the application accordingly.

(4) Where a complete specification has been filed in pursuance of an application for a patent accompanied by a provisional specification or by a specification treated by virtue of a direction under sub-section (3) as a provisional specification, the Controller may, if the applicant so requests at any time before [2][grant of patent], cancel the provisional specification and post-date the application to the date of filing of the complete specification.

Section 10.

Contents of specifications;

(1) Every specification, whether provisional of complete, shall describe the invention and shall begin with a title sufficiently indicating the subject-matter to which the invention relates.

(2) Subject to any rules that may be made in this behalf under this Act, drawings may, and shall, if the Controller so requires, be supplied for the purposes of any specification, whether complete or provisional; and any drawings so supplied shall, unless the Controller otherwise directs be deemed to form part of the specification, and references in this Act to a specification shall be construed accordingly.

(3) If, in any particular case, the Controller considers that an application should be further supplemented by a model or sample of anything illustrating the invention or alleged to constitute an invention, such model or sample as he may require shall be furnished before the application is found in order for grant of a patent, but such model or sample shall not be deemed to form part of the specification.

(4) Every complete specification shall—

(a) *fully and particularly describe the invention and its operation or use and the method by which it is to be performed;*

(b) *disclose the best method of performing the invention which is known to the applicant and for which he is entitled to claim protection; and*

(c) *end with a claim or claims defining the scope of the invention for which protection is claimed;*

(d) *be accompanied by an abstract to provide technical information on the invention:*

Provided that;

(i) *the Controller may amend the abstract for providing better information to third parties; and (ii) if the applicant mentions a biological material in the specification which may not be described in such a way as to satisfy clauses (a) and (b), and if such material is not available to the public, the application shall be completed by depositing the material to an international depository authority under the Budapest Treaty and by fulfilling the following conditions, namely:—*

(A) *the deposit of the material shall be made not later than the date of filing the patent application in India and a reference thereof shall be made in the specification within the prescribed period;*

(B) *all the available characteristics of the material required for it to be correctly identified or indicated are included in the specification including the name, address of the depository institution and the date and number of the deposit of the material at the institution;*

(C) *access to the material is available in the depository institution only after the date of the application of patent in India or if a priority is claimed after the date of the priority;*

(D) *disclose the source and geographical origin of the biological material in the specification, when used in an invention.*

(4-A) *In case of an international application designating India, the title, description, drawings, abstract and claims filed with the application shall be taken as the complete specification for the purposes of this Act.*

(5) *The claim or claims of a complete specification shall relate to a single invention, or to a group of inventions linked so as to form a single inventive concept, shall be clear and succinct and shall be fairly based on the matter disclosed in the specification.*

(6) *A declaration as to the inventorship of the invention shall, in such cases as may be prescribed, be furnished in the prescribed form with the complete specification or within such period as may be prescribed after the filing of that specification,*

(7) Subject to the foregoing provisions of this section, a complete specification filed after a provisional specification may include claims in respect of developments of, or additions to, the invention which was described in the provisional specification, being developments or additions in respect of which the applicant would be entitled under the provisions of section 6 to make a separate application for a patent.

Rule 13:

Specifications;

(1) Every specification, whether provisional or complete, shall be made in Form 2.

(2) A specification in respect of a divisional application under section 16 shall contain specific reference to the number of the original application from which the divisional application is made.

(3) A specification in respect of a patent of addition under section 54 shall contain a specific reference to the number of the main patent, or the application for the main patent, as the case may be, and a definite statement that the invention comprises an improvement in, or a modification of, the invention claimed in the specification of the main patent granted or applied for.

(4) Where the invention requires explanation through drawings, such drawings shall be prepared in accordance with the provisions of rule 15 and shall be supplied with, and referred to in detail, in the specification:

Provided that in the case of a complete specification, if the applicant desires to adopt the drawings filed with his provisional specification as the drawings or part of the drawings for the complete specification, it shall be sufficient to refer to them in the complete specification as those left with the provisional specification.

(5) Irrelevant or other matter, not necessary, in the opinion of the Controller, for elucidation of the invention, shall be excluded from the title, description, claims and drawings.

(6) Except in the case of an application (other than a convention application or an application filed under the Patent Cooperation Treaty designating India) which is accompanied by a complete specification, a declaration as to the inventorship of the invention, shall be filed in Form 5 with the complete specification or at any time before the expiration of one month from the date of filing of the complete specification, as the Controller may allow on an application made in Form 4.

Explanation,—For the purposes of this rule, the date of filing of the complete specification with respect to an application corresponding to an international application in which India is designated shall be reckoned from the actual date on which the corresponding application is filed in India.

(7) (a) The abstract as specified under clause (d) of sub-section (4) of section 10, accompanying the specification shall commence with the title of the

invention. The title of the invention shall disclose the specific features of the invention normally in not more than fifteen words.

(b) The abstract shall contain a concise summary of the matter contained in the specification. The summary shall indicate clearly the technical field to which the invention belongs, technical problem to which the invention relates and the solution to the problem through the invention and principal use or uses of the invention. Where necessary, the abstract shall contain the chemical formula, which characterises the invention.

(c) The abstract may not contain more than one hundred and fifty words.

(d) If the specification contains any drawing, the applicant shall indicate on the abstract the figure, or exceptionally, the figures of the drawings which may accompany the abstract when published. Each main feature mentioned in the abstract and illustrated by a drawing shall be followed by the reference sign used in that drawing.

(e) The abstract shall be so drafted that it constitutes an efficient instrument for the purposes of searching in the particular technical field, in particular by making it possible to assess whether there is a need to consult the specification itself.

(8) The period within which reference to the deposit shall be made in the specification under sub-clause (A) of clause (ii) of sub-section (4) of section 10 shall be three months from the date of filing of the application.

Section 16:

Power of Controller to make orders respecting division of application;

(1) A person who has made an application for a patent under this Act may, at any time [before the grant of the patent], if he so desires, or with a view to remedy the objection raised by the Controller on the ground that the claims of the complete specification relate to more than one invention, file a further application in respect of an invention disclosed in the provisional or complete specification already filed in respect of the first mentioned application.

(2) The further application under sub-section (1) shall be accompanied by a complete specification, but such complete specification shall not include any matter not in substance disclosed in the complete specification filed in pursuance of the first mentioned application.

(3) The Controller may require such amendment of the complete specification filed in pursuance of either the original or the further application as may be necessary to ensure that neither of the said complete specifications includes a claim for any matter claimed in the other.

Explanation.—For the purposes of this Act, the further application and the complete specification accompanying it shall be deemed to have been filed on the date on which the first mentioned application had been filed, and the further application shall be proceeded with as a substantive application and be

examined when the request for examination is filed within the prescribed period

Section 54 :

Patents of addition.—*(1) Subject to the provisions contained in this section, where an application is made for a patent in respect of any improvement in or modification of an invention described or disclosed in the complete specification filed therefor (in this Act referred to as the "main invention") and the applicant also applies or has applied for a patent for that invention or is the patentee in respect thereof, the Controller may, if the applicant so requests, grant the patent for the improvement or modification as a patent of addition.*

(2) Subject to the provisions contained in this section, where an invention, being an improvement in or modification of another invention, is the subject of an independent patent and the patentee in respect of that patent is also the patentee in respect of the patent for the main invention, the Controller may, if the patentee so requests, by order, revoke the patent for the improvement or modification and grant to the patentee a patent of addition in respect thereof, bearing the same date as the date of the patent so revoked.

(3) A patent shall not be granted as a patent of addition unless the date of filing of the application was the same as or later than the date of filing of the application in respect of the main invention.

(4) A patent of addition shall not be granted before grant of the patent for the main invention.

Section 135.
Convention Applications;

(1) Without prejudice to the provisions contained in section 6, where a person has made an application for a patent in respect of an invention in a convention country (hereinafter referred to as the "basic application"), and that person or the legal representative or assignee of that person makes an application under this Act for a patent within twelve months after the date on which the basic application was made, the priority date of a claim of the complete specification, being a claim based on matter disclosed in the basic application, is the date of making of the basic application.

Explanation—Where applications have been made for similar protection in respect of an invention in two or more convention countries, the period of twelve months referred to in this sub-section shall be reckoned from the date on which the earlier or earliest of the said applications was made.

(2) Where applications for protection have been made in one or more convention countries in respect of two or more inventions which are cognate or of which one is a modification of another, a single convention application may, subject to the provisions contained in section 10, be made in respect of those inventions at any time within twelve months from the date of the earliest of the said applications for protection:

Provided that the fee payable on the making of any such application shall be the same as if separate applications have been made in respect of each of

the said inventions, and the requirements of clause (b) of sub-section (1) of section 136 shall, in the case of any such application, apply separately to the applications for protection in respect of each of the said inventions.

(3) In case of an application filed under the Patent Cooperation Treaty designating India and claiming priority from a previously filed application in India, the provisions of sub-sections (1) and (2) shall apply as if the previously filed application were the basic application:

Provided that a request for examination under section 11B shall be made only for one of the applications filed in India.

5.2.5 In the matter of Daniel AC Officine Meccaniche SPA V. Contoller of Patents and Designs (AID No. 19 of 1998), the High Court of Calcutta held that section 135 requires the basic application to be an "application of patent in respect of invention in a convention country. On a literal interpretation, the phrase plainly means that the basic application is made in order to qualify the applicant for a priority claim under section 135. In other words, an application made to a country, which may subsequently be declared, as a convention country will not do. Further the court also held that the provisions of sections 2(d) and 133 are not expressed in a language, which can be construed as operating retrospective. The applicants right flows from the provision of section 135 read with section 133(1) of the Patent Act. The notification was not given retrospective effect and the privileges of reciprocity were therefore extended to the 72 countries including Italy for the first time in 1995. The appellant's basic application was made in 1994 when Italy was not a convention country. Therefore, the application under section 135 could not be proceeded with.

5.2.6 In the matter of a petition made under rule 6 of The Patent Rules filed by International Chemical Company Limited (Applicant) for application No. 912/Cal/81 the Controller held that " when the provisions of any statute are definite and clear cut , the question of applying principles of natural justice does not arise. Under Section 135 of the Act a Convention application has to be made within 12 months from the date of the basic application. So it is the duty of the applicants to take care of all eventualities and see that their Convention applications are filed within the period stipulated in Section 135 of the Act.' In fact' Section 135 provides ample time to the applicants to guard against almost any eventuality. Hence the principle of natural justice cannot be applied and the period of 12 months provided in Section 135 cannot be extended.

5.2.7 Priority date not allowed after withdrawal of basic application for an application made under section 135: - An application no, 986/Cal/79 was filed on 21.09.1979 as conventional application based on U.K. application no. 37624/1979. However, the basic U.K. application was withdrawn before filing of the Indian application. The applicant argued that the priority of the withdrawn application should be allowed on the basis of said U.K. application as the same has the filing date and number and was mentioned in the statement of undertaking. The Controller of Patents however held that existence of application in the convention country at least on the date of filing the application in India is sine-quo-non for the claim of priority. Since the application in

the convention country has been withdrawn prior to the date of filing of application India the requirement of under section 135 have not been met and in fact in the eye of law there was no application in the convention country in consequence of withdrawal. Therefore, the priority date on the basis of withdrawn application could not be allowed.

Rule 15:

Drawings.

(1) Drawings, when furnished under section 10 by the applicants otherwise than on requisition made by the Controller, shall accompany the specifications to which they relate.

(2) No drawings or sketch, which would require a special illustration of the specification, shall appear in the specification itself.

(3) At least one copy of the drawing shall be prepared neatly and clearly on a durable paper sheet.

(4) Drawings shall be on standard A4 size sheets with a clear margin of at least 4 cm on the top and left hand and 3cm at the bottom and right hand of every sheet.

(5) Drawings shall be on a scale sufficiently large to show the inventions clearly and dimensions shall not be marked on the drawings.

(6) Drawings shall be sequentially or systematically numbered and shall bear—

(i) in the left hand top corner, the name of the applicant;

(ii) in the right hand top corner, the number of the sheets of drawings, and the consecutive number of each sheet; and

(iii) in the right hand bottom corner, the signature of the applicant or his agent.

(7) No descriptive matter shall appear on the drawings except in the flow diagrams.

Rule 16.

***Models.**—(1) Models or samples shall be furnished under section 10 only when required by the Controller.*

5.2.8. In the matter of an application for patent no. 551/Del/78, IDPD,
The Controller held that the expression "without prejudice to provisions contained in Section 6" should be interpreted only as to mean without detriment to theapplicant's right to file an ordinary application"

APPLICATION FOR PATENT

5.2.9 TYPES OF PATENT APPLICATIONS

The following types of applications for patent can be filed:

1. **Ordinary Application**

2. **Convention Application**
3. **PCT International Application**
4. **PCT National phase Application**
5. **Application for Patent of Addition**
6. **Divisional Application**

1. Ordinary Application (S.7)

An application for patent made in the Patent office without claiming any priority of application made in a convention country or without any reference to any other application under process in the office is called an ordinary application. Such an application can be filed by an inventor himself (as an applicant) or by a person to whom the invention is assigned by the inventor (an assignee is the applicant), without claiming any priority of application made in a convention country or without referring to any other application being processed in the Patent Office. The applicant can be either of Indian or foreign origin.

2. Convention Application (S.135)

When an applicant files the application for a patent, claiming a priority date based on the same or substantially similar application filed in one or more of the convention countries, it is called a convention application. In order to get convention status, an applicant should file the application in the Indian patent office within twelve months from the date of first filing of a similar application in the convention country. The priority document **(S.138 (1))** and its verified English translation (if required) **(S.138 (2))** also should be submitted by the applicant. A convention application shall be accompanied by a complete specification.

When two or more applications for patents constituting one invention have been made in one or more convention countries, one application may be made within twelve months from the date on which the earlier or earliest of those applications was made. **Multiple fees has to be remitted for claiming multiple priorities (S.137),** so that other applications filed earlier in the convention countries, will be deemed to have been published in India. An applicant of convention application shall furnish when required by the Controller, the copies of specification or documents **(priority documents)** certified by the official chief of the patent office of the convention country.

3. PCT International application

PCT is an International filing system for patents in which the applicant gets an international filing date in all the designated countries, conferring the late entry (up to 31 months) to the national offices without affecting the priority date. This is a simple and economical procedure for the applicants seeking protection for their inventions in many countries. Indian Patent office is a Receiving office for International Applications by nationals or residents of India. **((see Rules 17-23 in Chapter V))**

An international application shall be filed with the appropriate office under Rule(4) in triplicate either in English or in Hindi language

4. PCT-National Phase Application (S.7 (1)(A))

An international application **(S.2 (1)(ia))**, made according to the Patent Cooperation Treaty **[(S.2 (1)(oa)]**, designating India can enter national phase within 31 months from the priority date of international application or date of filing of international application whichever is earlier. This application filed before the Controller in the Indian patent office claiming the priority and international filing date is called PCT National Phase application. Applicant can enter national phase with a request made on a plain paper but Form 1 is preferred by the Indian Patent office during National Phase Entry. The title, description, drawings, abstract and claims filed with the application shall be taken as the complete specification for the purposes of filing in India (S.10 (4A)). The filing date of the application shall be the international filing date accorded under the Patent Cooperation Treaty **[S 7(1)(B)]**.

Although it is obligatory on the part of IB (WIPO) to send pamphlets to the designated offices for convenience and faster processing, the applicant shall submit the necessary documents in duplicate upon entry into national phase. The Patent Office may ask for any other documents, which are necessary in addition to what was submitted along with the application. Certified copies of the priority documents are to be filed within 3 months from the date of communication from the Patent Office. **(see more details in Chapter V)**

5. Application for Patent of Addition (S.54)

When an applicant feels that he has come across an invention which is a slight modification of the invention for which he has already applied for / has patent the applicant can go for patent of addition since the invention does not involve a substantial inventive step. It is also possible to convert an independent patent to a patent of addition at a later date if the subject matter was an improvement in or modification to a main invention for which he holds a patent. There is no need to pay separate renewal fee for the patent of addition during the term of the main patent. A Patent of Addition expires along with the main patent unless it is made independent according to the provisions in Section 54

However a Patent of Addition will not be granted unless the date filing of Application was the same or later than the date of filing of the complete specification in respect of the main invention

It should be noted that a patent of addition will not be granted before granting of the patent for the main invention. **(see Chapter IX *also)***

5.2.10 SPECIFICATION AND DRAWINGS

The prime requirement of the patent law is to protect the invention disclosed in the specification. The specification is a techno-legal document containing scientific information constituting patent rights. The specification, thus, forms a crucial part of the patent documents. It is mandatory on the part of the inventor to disclose clearly and completely various features constituting the invention. Under the patent law, the disclosure is in the form of provisional and complete specification as the case may be. Various features of these specifications are discussed in this section .

5.2.11 Provisional Specification (Section 9)

When the applicant finds that his invention has reached a presentable form but not the final shape, he may prepare a disclosure of the invention in the form of a written description and submit it to patent office as a **Provisional Specification** which describes the invention.

A provisional specification helps to establish the priority of the applicant over any other person who is likely to file an application for patent in respect of the same invention being developed concurrently. The applicant also gets twelve months time to fully develop the invention and ascertain its market potential without the fear of losing the priority right over the invention.

Immediately on receiving the provisional specification the patent office accords a filing date for the application and provides a period up to twelve months for filing the complete specification, during which the applicant can fully develop his invention by himself or with the help of others who are interested in the economic value of the patent. No extension of time is permissible for filing complete specification.

5.2.12 Filing Provisional Specification:

The provisional or complete specification is required to be submitted in Form 2 along with the application form 1 and other documents. The first page of the Form 2 should contain-

(a) Title of the invention,
(b) Name, address and nationality of each of the applicants for the patent
(c) Preamble to the description

A provisional specification is not a rough draft or a skeleton of the Complete specification. The Complete Specification, which follows a Provisional Specification, does not replace the latter. Both are permanent and separate documents.

(a) A Provisional Specification should essentially contain the title and description of the invention and shall start with a preamble **'The following specification describes the invention.'** Claims should not be included in the provisional specification, since it is not the purpose

of Provisional Specification to claim legal right, but, to obtain priority of invention.

(b) The description should start from the second page starting with the field of invention and containing the background of the invention, object of the invention, statement of the principle underlying the invention and general statement of the actual invention. It is advisable to include in the Provisional Specification as much information as the applicant has at the time of filing, but in any case the description should be adequate to identify the invention from the prior art.

(c) It should be noted that, the provisional specification cannot be filed if the application is a divisional or convention application or an application filed under the Patent Cooperation Treaty designating India. In such cases, only a complete specification is required to be filed **[Sec 9(1)]**.

(d) When an application for a patent is accompanied by a provisional specification, the complete specification (in Form 2) must be filed within twelve months from the date of filing of provisional specification, failing which the said application will be automatically abandoned.

(e) Nevertheless, the applicant may file a request for postdating of the application. Such a request should be filed before expiry of 12 months period from the date of filing of provisional specification. If the same applicant has filed more than one applications, accompanied by provisional specifications, which are cognate (related) or a modification of one another, the applicant can make a request on plain paper for filing a single complete specification in respect of all such provisional specifications. The complete specification should be filed within the period of twelve months taken from the date when the earliest of these provisional specifications was filed **(S.9(2))**.

(f) Where an application for a patent purporting to be a complete specification has been filed, then the applicant can convert it into a provisional specification by making a request (no form or fees required) to the Controller and must file the complete specification within twelve months from the date of filing of application **(S.9 (3))**.

(g) In case, the complete specification was filed in pursuance of an application with a provisional specification or a complete specification has been treated as provisional specification under Section 9(3), then application with such a provisional specification can be post dated to the date of filing of the complete specification and then the provisional specification will be treated as cancelled **(S.9 (4))**.

5.2.13 Complete Specification

The Complete specification is a techno-legal document which fully and particularly describes the invention and discloses the best method of performing it.

5.2.14 Main Features of Complete Specification

i) The Complete Specification must be framed with utmost good faith and must not contain any false representation or description of the invention or any material part of it, which would otherwise mislead the public. The Complete Specification must not be framed in ambiguous languages but must be as clear and concise as the nature of the subject would admit.

ii) The Complete Specification must be intelligible to an ordinary workman possessing the ordinary skill and knowledge of that branch or the useful art to which the invention relates. It is not required to describe the invention and the manner in which it is to be performed so fully as to instruct persons wholly ignorant of the subject matter.

iii) If the Complete Specification describes anything, which is not new, it must be clearly distinguished from the novel features of the invention

iv) An amendment by way of modifications and variations of the description if any, must fall within the scope of the description

v) If the inventor does not disclose all the relevant information or mislead the public or gives a false description of the invention, the patent would be liable to be revoked.

vi) The detailed description should be supplemented by drawings in all cases in which the inventions are capable of being illustrated.

vii) It is not enough if a mere list of the various parts that make up the apparatus or device is given. The mode of construction of the apparatus and the function of its different parts should be described.

5.2.15 Filing of Complete Specification:

i) An Application for Patent is to be filed in Form 1, in duplicate along with requisite fees as given in the First Schedule and should be accompanied by the complete specification in Form 2 and other essential documents in duplicate (Rule 13 & Rule 15)

ii) The first page of the Form 2 contains -

a) Title of the invention,
b) Name, address and nationality of each of the applicants for the patent
c) Preamble to the description

iii) The description should start from the second page of Form 2 followed by statement of claims for which protection is sought and end with the date and signature of the Applicant or his authorized agent.

iv) An abstract should be attached separately to the complete specification. Drawings, if any, referred in the specification shall be submitted along with the specification.

v) Documents to be attached along with complete specification:

a) Statement and Undertaking regarding foreign filing details in respect of the same invention (Form 3) (S. 8(1) & R. 12)

b) Declaration as to Inventorship (Form 5) : In case of a convention application, PCT National Phase application and when complete specification is filed after provisional [S.10(6) & Rule 13(6)]. It should be filed within one month from the date of filing.

c) Priority Document should be submitted within three months from the date when required by the Controller (S.138(1)). If the document is not in English, then a translated copy should be furnished (S.138(2)).

d) Power of Attorney (Form 26) (if the application is made through a patent agent) (Rule 135(1))

f) Proof of Right (if the application is made by the assignee (S.7 (2) & R 10) (Proof right to apply can be produced either in the body of the application (Declaration by the Inventor(s) /Applicant(s) in the convention country in **Form 1**) or by way of separate assignment deed. If the application is made by the legal representative *'death certificate or probate or certificate of inheritance'* of the deceased should be filed as proof of right. ***Proof of right shall be submitted within six months from the date of application.***

g) If the applicant wishes, he can request for early publication **on Form 9** along with the prescribed fee.

h) A request for examination on **Form 18** along with the prescribed fees should be submitted so that the application is taken up for examination.

5.2.16 International Application [Section 10 (4-A)] :

In case of an international application designating India, the title, description, drawings, abstract and claims filed with the international application shall be taken as the complete specification filed in India for the purposes of this Act

5.2.17 Information and undertaking regarding foreign applications
Statutory provisions: Sec. 8 (1) and (2)Rule12(1)a,(2),

It is the duty of the applicant to inform to the patent office filing particulars of same or similar application for patent filed outside India at the time of filing patent application in India. Further the applicant should keep the office informed of subsequent filing as per the provisions of the act.

Where an applicant for a patent under this Act is prosecuting either alone or jointly with any other person an application for a patent in any country outside India in respect of the same or substantially the same invention, or where to his knowledge such an application is being prosecuted by some person through whom he claims or by some person deriving title from him, **he shall file the following statement and undertaking in Form 3, along with his application or within six months from the date of filing of the application [(S 8(1),R 12(1A)].**

Statement setting out detailed particulars of such application including the name of the country, application number, date of application, status of such application etc.

The period of 6 months in case of an application corresponding to an international application in which India is designated is reckoned from the actual date on which the corresponding application is filed in India.

Example:

- International filing date – 20.5.1999
- Date of filing in India – 20.5.2001
- Six months period u/r 12 (1A) is reckoned from 20.5.2001 and not from 20.5.1999.

An undertaking that, up to the date of the grant of patent in India, the applicant would keep the Controller informed in writing, from time to time, the detailed particulars as required under clause (a) in respect of every other application relating to the same or substantially the same invention, if any, filed in any country outside India, subsequently to the filing of the statement referred to in the aforesaid clause, **within six months of such filing (R12(2),S 8(1)).**

The date of entry in the national phase shall be mentioned in form 3 against "Date of application" column in case of PCT national phase applications.

The period of six months in case of an application corresponding to an international application is reckoned from the actual date on which the corresponding application is filed in that country and not from the International filing date.

If there is no foreign filing, the applicant can give NIL statement.

As per the amended Act the time period for filing form 3 is six months, which can be extended further by the Controller for a period of 1 month. **[S.8(1), R.(12), R. (138)]**

At any time after an application for patent is filed in India and till the grant of patent or refusal to grant of patent is made thereon, the Controller may also require the applicant to furnish details as may be prescribed relating to the processing of the application in a country outside India, and in that event the applicant shall furnish information available to him to the Controller **within six months** from the date of receipt of the communication requiring such furnishing of information **[Section 8(2)]**. Such particulars include information relating to objections, if any, in respect of novelty and patentability of the invention and any other particulars as the controller may require which may include claims of application allowed

5.2.18 CONTENTS OF COMPLETE SPECIFICATION

Complete Specification is to be filed in the Patent Office along with Application Form 1. Title and preamble of Invention along with name , address, and nationality of the applicant is to be given on the first page of Form 2. Description should start on the next page . Complete Specification should have the following components

a) Field of Invention.
b) Use of Invention : A brief statement of the advantages of the invention
c) Prior Art
d) Problem to be solved.
e) Object of Invention(may be more than one)
f) General statement of invention
g) Detailed Description of Invention[with reference. to drawings , if any)
h) Best method /example of working of the invention
i) Statement of claims.
j) Signature with date
k) Drawings
l) Abstract

1) Preamble:

The following **preamble** should be given on the first page of **Form 2** along with other details like title of the invention, name, address and nationality of the applicant(s):

" The following specification particularly describes the invention and the manner in which it is to performed"

2) Title

The title should give a fair indication of the art or industry to which the invention relates. It should be brief, free from fancy expressions, free from ambiguity and as precise and definite as possible but it need not go into the details of the invention itself and should be normally within 15 words. It should verbally agree with the title stated in application.

The followings are not allowable in the title : -

a) The inventor's name b) The word 'Patent' c) Words in other languages d) The abbreviation "etc" e) Fancy words, e.g., "Washwell Soap", "Universal Rest Easy Patent Chair".

The following titles do not appear to be objectionable: -
Improved folding chair, Railway rail chair, Improvements in pneumatic tyres, Motorcar differential gear, Filaments for electric lamps etc.

3) Field of the invention

The description should preferably begin with a short general statement of the invention so as to show its scope, and to indicate briefly the subject matter to which the invention relates, e.g. *"This invention relates to* ……". It should be defined in general terms and also described with particularity, for example, by giving specific examples.

4) Prior Art

This part should indicate the status of the technology in the field of invention with reference to experiments going on in the field, patents and pending patent applications in the specific art. When the invention relates to an improvement on an existing apparatus or process, a short statement of the closest prior art may also be given. However, the description should fully and particularly describe the invention, by clearly distinguishing it from such a closest prior art, if available.

5) Object of the Invention

The purpose of this part is to clearly bring out the necessity of the invention. It shall say clearly the technical problems associated with the existing technology and the solution for that, bringing out the obvious differences between the claimed invention and the prior art.

The solution sought by the invention should be clearly brought out as object (s) of inventions with statements like *"It has already been proposed* ……"

followed by the objects which the inventions has in view e.g. *"The principal object of this invention is ……", "Another object of this invention is ……", "A further object of this invention is ……"etc.*

6) Statement of Invention

The description should include a statement of invention before giving the details of the invention and the method of performing it. The statement should clearly set forth the distinguishing novel features of the invention for which protection is desired.

This part is intended to declare different aspects of the invention in verbatim with the independent claims and to complement the omnibus claim in situations of infringement proceedings.

It usually starts like, *"Accordingly the invention provides an apparatus consisting of ---------- which is characterized in that ----------"*. Other aspects and processes, if any, can also be stated e.g. *"There is also provided a method of preparing ---------" etc.*

7) Detailed Description of Invention
(with Reference to drawings, if any)

i) **Description of an invention is required to be furnished in sufficient detail** so as to give a complete picture of the invention and follows the Statement of invention. The nature of improvements or modifications effected with respect to the prior art should be clearly and sufficiently described. The details of invention described here should be sufficient for a person skilled in the art to perform the invention by developing necessary technical know-how by himself. It can include examples / drawings or both for clearly describing and ascertaining the nature of invention. Sufficient number of examples must be included in the description especially in the case of chemical inventions

ii) **Reference to the drawings** should be specific and preferably in the following form:-

> **"This invention is illustrated in the accompanying drawings, through out which like reference letters indicate corresponding parts in the various figures".**

8) **The specification in respect of a Patent of Addition** should contain at the beginning of the description, a definite statement indicating an improvement in or modification of, the original invention, and the serial number of the application for patent in respect of the original invention should be quoted. The specifications should also contain a short statement of the invention as disclosed in the earlier specification.

9) Mention of Biological Material In Specification :

a) If the invention is using biological material, such a material shall be deposited for the completion of the application when such material is not available to the public and can not be described adequately as per the provisions of the act. The deposition shall be made with the International Depository Authority under the Budapest Treaty, on or before the date of filing/priority. The International Depository Authority in India is Microbial Type Culture Collection and Gene Bank (MTCC) – Chandigarh http://ipindia.nic.in/ipr/patent/d_inst_456.pdf.

Note: For further information on Microbial Type Culture Collection and Gene Bank (MTCC) please visit – http://wdcm.nig.ac.jp/CCINFO/CCINFO.xml?773]; http://www.imtech.res.in/mtcc.]

b) Reference of such material shall be made in the specification within three months from the date of filing giving all the available characteristics of the material required for it to be correctly identified or indicated including the name, address of the depository institution and the date and number of the deposit of the material at the institution

(c) . Further, the source and geographical origin of the biological material specified in the specification also should be disclosed therein

(d) Sequence listing may also be numbered in the specification if necessary in the case of Biotechnology Inventions.

(e) Sequence listing should be given in electronic form

(f) Access to the material is available in the depository institution only after the date of the application of patent in India or after the date of the priority, if a priority is claimed

10) Best Method of Working :

The Act specifically requires as per section s10(4)(a) and s 10(4) (b) that the Complete Specification must describe the best method of performing the invention known to the patentee as per all his knowledge relating thereto, including that, which he may have acquired during the period of provisional protection prior to the date of filing the Complete Specification

11) Terms in other languages, if any, used in the description should be accompanied by their English equivalents. The use of vague slang words and colloquialisms is objectionable and should be avoided

12) Advantages of the invention should be mentioned to bring out clearly the areas of application and preferable use of the invention. The applicant can substantiate

industrial applicability of the invention in this part and call for protection against duplication of invention in the related fields by specifying scope and ambit of the invention.

13) If, in any particular case, the Controller considers that an application should be further supplemented by a model or sample of anything such model or sample as he may require shall be furnished before the grant of a patent, but such model or sample shall not be deemed to form part of the specification.

14) Claims

Claims constitutes a techno-legal part of the complete specification. The description should end with a claim(s) when a complete specification is filed. In case of provisional specification, there is no need to file claims. Important features and construction of claims is discussed in detail in the next section

15) DRAWINGS

The Complete Specification should be followed by drawings that are referred to in the specification. Drawing should be filed on a standard A4 size sheet in duplicate. Drawing should be preferably drawn in black Indian indelible ink or durable paper with margin of 2.5 cm on each side, in upright position with respect to top & bottom position of the sheet. At left-hand top corner of the sheet the name of the applicant should be mentioned. Total number of sheets and consequential sheet number should be mentioned at the right hand top corner of each sheet. At the right-hand bottom, the signature of the applicant/agent should be given along with the name of signatory there under.

A reference letter/numerals as used in the description should also be used in denoting the corresponding component/part in the figure (s). No descriptive matter should appear on drawings, except under certain cases, such as, flow chart, chemical & other reaction etc. The same letters or numerals should be used in different figures for the same parts. In complicated drawings or when there is no room to write the reference letters in their proper places, the letters should be shown outside the figures and connected by fine lines with the parts to which they refer.

16) Abstract [Sec.10]

i) An abstract should provide brief technical information on the invention. It should start with the "Title of the invention" and should give concise summary of the invention ,preferably within 150 words, An abstract should be given on a separate page after claim(s).

ii) It has to be prepared in such a way that one can understand the technical field to which the invention belongs, technical problem

and solution to the problem through the invention and principal uses of the invention.

iii) If necessary, the most relevant figure of the drawings should also be included along with features of the invention (depicted with reference numbers in brackets) in the abstract, particularly, in case of engineering inventions. Where necessary, the abstract shall contain the chemical formula, which characterises the invention.

iv) The abstract is supposed to serve as an efficient instrument for the purposes of searching in the particular technical field and to assess whether there is a need to consult the specification itself. However, it cannot be used for the purpose of interpreting the scope of protection in legal proceedings.

v) The Controller may amend the abstract for providing better information to third parties

~~(v)~~.
~~(iv)~~

5.2.19 Submission of Documents in the Patents Office

(i) All documents and copies of document to be furnished in the patent office shall be written or typewritten or printed either in Hindi or in English language in large and legible characters with deep indelible ink with lines widely spaced upon one side only of strong white paper of a size A4 with a margin of at least 4 centimetres on the top and left hand part and 3cm on the bottom and right hand part thereof. Any signature which is not legible or which is written in a script other than Hindi or English shall be accompanied by a transcription of the name either in Hindi or in English in block letters (Rule 8)

ii) In case the application for patent discloses sequence listing of nucleotides and/or amino acids, the same shall be filed in electronic form.

iii) Leaving and serving documents [Rule 6] ;

a) Any application, notice or other document required to be furnished at the patent office may be tendered by hand or sent by a letter addressed to the Controller at the appropriate office through post or registered post or speed post or courier service or by electronic transmission duly authenticated. , it shall be deemed to have been filed, left, made or given at the time when the mail containing the same would have been delivered in the ordinary course

b) Any written communication addressed to a patentee at his address on the register of patents or at his address for service or to any applicant or opponent in any proceedings under the Act or these rules, at the address appearing on the application or notice of opposition, or given for service, shall be sent by registered post or speed post or courier service or by electronic transmission duly authenticated except when they are sent by special messenger.

c) The dale of such notice or written communication shall be the date of dispatch

d) The delay in transmitting or resubmitting a document to the patent office or doing any act by the party may be condoned by the Controller if a petition for such condonation of delay is made by the party to the Controller immediately after the receipt of the document or a communication along with a statement regarding the circumstances of the fact and evidence in support of the statement

e) Such period of delay condoned by the Controller shall not exceed the period between the date on which the party was supposed to have received the document or communication by ordinary course of mail or electronic transmission and the actual date of receipt of the same.

f) Usually immediately on receiving the application, patent office accords an application number to it such that the applications filed in a year constitute a series identified by the year of such filing. PCT National Phase applications constitute a different series **(Rule 11).**

5.3 CLAIMS IN COMPLETE SPECIFICATION

5.3.1 General Principles and Object of Claims:

Claims are considered to be the most important part of the patent document. In a complete specification the description is followed by the Statement of Claims. Since the claims constitute the legal part for claiming the protection of the patent rights, it is imperative that the claims should be drafted carefully to cover all the aspects of the protection being sought. while observing the following points:

(a) Each claim should be in a single sentence and should be clearly and worded

(b) Claim(s) should be succinct and should not involve unnecessary repetition

e(c) A claim (s) should not be verbose.

e(d) A claim is the statement of technical facts expressed in legal terms defining the scope of the invention sought to be protected.

e(e) **No monopoly is obtained for any matter described in the complete specification unless it is claimed in the claims. What is not claimed in the 'claims' stands disclaimed,** and falls open to the public use, even if the matter is disclosed in the description.

e(f) Claims define the boundaries of legal protection sought by the patentee and form a protective fence around the invention which is defined by the words and phrases in the claims.

e(g) The object of claims is **to define clearly the scope of the invention with conciseness, precision and accuracy the monopoly claimed**, so that others may know the exact boundaries of the area of protection in which they should not trespass.

e(h) Their primary object of claims is **to limit and not to extend the monopoly** unduly and, simultaneously, also let others know when they are infringing on the rights of the patentee.

e(i) Each claim is evaluated on its own merit and, therefore, if one of the claims is objected, it does not mean that the rest of the claims are invalid. It is therefore important to make claims on all of the invention to ensure that the applicant gets the widest possible protection.

5.3.2 Scope of Claims

e(a) As the value of a patent depends largely upon the scope of the claims, special care is necessary to ensure that the claims are drafted to include neither more not less than what the applicant desires to protect by his patent.

e(b) Claims must not be too extensive so as to embrace more than what the applicant has in fact invented. A claim, which is too wide, encroaches upon the subject matter, which may be in public domain or belong to others.

e(c) However a claim must not be too narrow also because such a claim would not be sufficiently effective in preventing infringement of the patent. An infringer would go scot-free, if the claim were too narrow and , hence, the full benefit of invention may not accrue to the inventor.

e(d) Having many claims, where each one has a different scope, allows the applicant to have legal title to several aspects of the invention. In a good drafting, it begins with broad claims and develops towards claims that are narrower in scope. In general, a narrow claim specifies more details than a broader claim.

e(e) Passages which confuse the scope of the invention or claims that are unspecific (e.g. those claiming "Any novel matter...") should not be filed

e(f) A claim shall be for the protection of either a product or process or apparatus or all of them, as the case may be, and shall be in one sentence according to the standard practice .

5.3.4 Features and Characteristics of Claims:

ea. The description of invention in the complete specification is to be followed by a "statement of claims" preceded by the prescribed preamble, **"I or we claim"** as the case may be.

eb. **Claims should start from the fresh page after full description** of the invention with the claims serially numbered.

ec. **There is no restriction to the number of claims** to be incorporated in the specification. But the applicant has to pay additional fee, if there are more than ten claims. (See the First Schedule)

od. **A claim (s) of a complete specification shall relate to a single invention, or to a group of inventions** linked so as to form a single inventive concept and, shall be clear and succinct and fairly based on the matter disclosed in the specification **(S.10 (5)).**

e(b) **A claim must be clear, complete and supported by description**. A claim must be clear in the sense that it should not cause the reader to speculate about the claim. For example, if the words like "thin", "strong", "a major part", "such as", "when required" or "any" are used, then it forces the reader to make a subjective judgment and not an objective observation, unless such expression follows any definite values.

e(c) **A claim must be specific and not vague, ambiguous, speculative or hypothetical in nature.** Each claim should be complete so that it covers the inventive feature and enough elements around it to put the invention in the proper context.

e(d) **Claims must be supported by the description (fairly based on the description).** This means that all the characteristics of the invention, that form the part of the claims must be fully explained in the description.

e(e) In addition, any term, which is used in the claims, must be either found in the description or clearly inferred from the description.

e(f) Trade marks are an indication of the origin rather than the composition or content of goods, and should not be used in patent applications where a generic term can be used instead. Trade marks are only permitted in claims where it can be shown that their use is unavoidable and does not introduce ambiguity . Where marks that are registered are mentioned, they should be acknowledged as such. If a trade mark is not registered, its owner should be indicated

5.3.4 Structure of Claims

i) A claim usually consists of three parts :

- **Introductory phrase,**
- **Body of the claim, and**
- **Link that joins the two segments.**

- The introductory phrase identifies the category of the invention and sometimes the purpose (For example, a machine for waxing paper, a composition for fertilizing soil).

- The body of the claim is the specific legal description of the exact invention, which is sought to be protected.

- The linking consists of words and phrases such as :
  - Which comprises
  - Including
  - Consisting of
  - Consisting essentially of
- **If the invention is an improvement to a product** existing in the market, the claims should set the boundary very clearly by characterizing the invention with respect to the prior art. In those cases, the claim will have two parts separated by the word ***'characterized by'*** **or** ***'wherein'***. **The part coming before** ***'characterized by'*** **is the prior art while that comes after will be the features of the invention.** It is equally applicable in the case of a process which is modification of the existing process.

For Example:

In the following example, "A data input device" is the introductory phrase, "comprising" is the linking word, and the rest of the claim is the body.

"A data input device comprising; an input surface adapted to be locally exposed to a pressure or pressure force, a sensor means disposed below the input surface for detecting the position of the pressure or pressure force on the input surface and for outputting an output signal representing said position and; an evaluating means for evaluating the output signal of the sensor means"

ii) Structure of Claims should be on the following lines:

a) Independent Claim :

This is the first claim which is also called the 'Principal Claim' should clearly define the essential novel features of the most preferred embodiment of the process, apparatus, device or the product that constitutes the invention and should be properly characterized with respect to the 'prior art', defining all the technical features essential to the invention or inventive concept. This should include the core integers as well as sufficient details of interrelationship, operation or utility to establish that the invention achieves the intended objectives and

b) Dependent Claim(s)

Dependent claims should be clubbed with the independent claims (or within themselves) to include all the features of the independent claim and characterized by additional non-essential features and even the minute aspects and optional features.

c) Further independent claims are only justified where the inventive concept covers more than one category, e.g. apparatus, process, product, complementary versions within one category constituting unity of invention, e.g. plug and socket, transmitter and receiver, which work only together.

Therefore, wherever possible, claims should not contain:--

a. Multiple unrelated inventions that would clearly give rise to a plurality objection
b. Multiple independent claims in any one category, even if only one inventive concept is present
c. Claims which are in principle unsearchable by reason of the number of alternatives embraced, or the choice of characterising parameters or desiderata
d. Dependent claims that are not fully limited by the terms of the preceding independent claim, e.g. dependent claims which omit, modify or substitute a feature of an independent claim

~~e~~

d) Omnibus Claim :

A claim known as 'omnibus claim' worded, for example, as *"An apparatus substantially as herein above described in the specification with reference to the accompanying drawings"* can be added as the last claim to get an integral protection of what is described in the specification and drawings. It is allowed only if the statement of invention is incorporated in the specification.

5.3.5 In Ram Narain Kher vs. M/s. Ambassador Industries New Delhi and another [AIR 1976 Delhi 87], it was observed:- When an invention is not itself new, the particular use of it for the purpose described in combination with the other elements of the system producing the advantageous results would be a sufficient element of novelty to support the Patent and in a claim for Patent pertaining to air cooler the claimant must specify what particular features of his device distinguish it from those which had gone before and show the nature of the improvement which is said to constitute the invention and the claim that there would be 25 per cent additional advantage of added cooled air by fixing the fan at the top of the cooler than in the customary way hitherto known in the front of the cooler must be succinctly stated in the claim before the Patent authority and must not be left to an inference raised on a general review of the specification.

Example of Claims :

~~e~~(a)"An apparatus for catching mice comprising, a base member for placement on a flat surface, a spring member..."

ɵ(b)"A chemical composition for cleaning windows which comprises 10-15% ammonia,...",

ɵ(c)The following example pertains to claims to a combination of plurality of legs in an umbrella tent frame :

1. An umbrella tent frame having plurality of legs, -each leg comprising a lower portion, an upper portion, and a pivot connector interconnecting the lower and upper portions; a clevis assembly comprising an upper clevis members, a lower clevis member, and stop means supported by the lower clevis member and projecting toward the upper clevis member and constructed and arranged to engage the upper clevis member to limit movement of the lower clevis member toward the upper clevis member; a plurality of radial pivot members each fixed to a different one of the upper leg portions; and a plurality of brace members each having one end pivoted to one of the radial pivot members and the other end pivoted to the lower clevis member; wherein the leg portion have transverse cross sections in the form of a rectangle with longer sides and shorter sides, the longer sides of the cross sections of the lower leg sections extending toward the interior of the tent frame when the frame is erected.

2. Umbrella as defined in claim 1, wherein the shorter sides of the cross sections of the upper leg portions extend toward the interior of the tent frame when the frame is erected, whereby the upper leg portions could bend more freely toward the upper clevis member as the tent frame is erected.

3. Umbrella as defined in claim 2, wherein the pivot connectors interconnecting the lower and upper leg portions are each in the form of an integral polymeric piece of generally U-shaped transverse cross section and the side walls thereof include portions spaced more closely together to accommodate the lower leg portion and portion spaced more widely to accommodate the upper portion.

4. An umbrella tent of claim 3 wherein said upper clevis member comprises a downwardly opening socket adapted to receive a post member extending from the lower clevis member.

5. An umbrella tent of claim 2 wherein said upper clevis member comprises a downwardly opening socket adapted to receive a post member extending from the lower clevis member.

6. An umbrella tent frame of claim 1 wherein said lower leg portions further comprise means to engage a floor portion of a tent when the tent frame is erected.

7. An umbrella tent of claim 6 wherein said upper clevis member comprises a downwardly opening socket adapted to receive a post member extending from the lower clevis member.

8. An umbrella tent frame of claim 1 wherein said clevis members are molded from polymeric material.

9. An umbrella tent of claim 8 wherein said upper clevis member comprises a downwardly opening socket adapted to receive a post member extending from the lower clevis member.

10. An umbrella tent frame comprising a plurality of legs each including a lower portion and an upper leg portion, the leg portions having transverse cross sections in the form of a rectangle having longer sides and shorter sides, the lower and upper leg portions being pivotally interconnected with the longer sides of their cross sections at right angles to each other. **(Independent claim)**

11. An umbrella tent frame of claim 10 further comprising a clevis assembly comprising an upper clevis member and a lower clevis member, and wherein the upper leg portion is connected to the upper clevis member, and wherein the shorter sides of the cross sections of the upper leg portions extend toward the interior of the tent frame when the frame is erected, whereby the upper leg portions can bend more freely toward the upper clevis member as the tent frame is erected.

12. An umbrella tent frame of claim 11 further comprising pivot members interconnecting the lower and upper leg portions and wherein the pivot connectors interconnecting the lower and upper leg portions are each in the from of an integral polymeric piece of generally U-shaped transverse cross section and the side walls thereof include portions space more closely together to accommodate the lower leg portion and a portions spaced more widely to accommodate the upper leg portion.

13. An umbrella tent frame of claim 11 wherein said clevis members are molded from polymeric material.

14. An umbrella tent of claim 11 wherein said upper clevis member comprises a downwardly opening socket adapted to receive a post member extending from the lower clevis member.

15. An umbrella tent frame of claim 10 wherein said lower leg portions further comprise means to engage a floor portion of a tent when the tent frame is erected

5.3.6 Claim Specimens:

The following examples, as sample claims, which have been granted by the Patent Office, are given for the purpose of providing help to the applicant in drawing up the Claims. They must, however, be regarded as samples of varying quality, selected more or less at random and no guarantee is given that they would be effective in a court of law.

i) Indian Specification No. 39285.

Title – "Wrapper for a package and method of preparing the same".

"We claim :-

1. A wrapper for a package, having a tear-tape united to its outer surface, the area of the wrapper to which the tear-type is united encircling the package and being bounded along at least one edge by perforations.
2. A wrapper as claimed in Claim I in which a narrow area of the tear tape, spaced from each edge of the tear-tape, is united to a narrow area of the wrapper defined on each side by a line of perforations which are covered by the outer portions of the tear-tape, the perforations facilitating tearing of the wrapper to remove the portion bounded to the tear-tape."

ii) Indian Patent Specification No.38069.

Title – "Improvements in or relating to gramophone records.

"We claim :-

1. A gramophone record in which the surface of the record containing the record grooves comprises 12 to 15 per cent of amorphous carbon, thermoplastic material and a filler consisting of non-fibrous natural mineral material.
2. A gramophone record according to Claim I, wherein the percentage of filler employed in the record is from 1 to 70 per cent.
3. A record according to Claim 1 or 2, wherein the percentage of thermoplastic material is 20 to 60 per cent.

iii) [Indian Patent Specification No. 34515.

Title- "Improvements in or relating to tin Openers".

"We claim,

1. A tool for opening metal containers, the tool comprising a spindle spit throughout its length, means for rotating the spindle, means on spindle for guiding the tool during an opening operation, which means also serves to facilitate the removal of the waste metal coiled around the spindle, and further means on the spindle for preventing the distortion of the spindle during and opening operation.

2. A tool according to Claim I, wherein the means for guiding the tool and facilitating the removal of the waste metal and the means for preventing the distortion of the spindle comprise two separate plates slidably and removable mounted on the spindle".

5.3.7 How to Assess Clarity of Claims ?

The following examples will be useful in judging clarity of claims.

i) Example: 1

A structure comprising a semiconductor substrate made of silicon, said structure further characterized by comprising a near-amorphous film comprising ZrO2.

Here the claim does not have a precise or well-recognized meaning for a skilled person. The term 'near-amorphous' used in the claim is vague and unclear and leaves the reader in doubt as to the meaning of the technical feature to which it refers, thereby rendering the definition of the subject-matter of said claim unclear.

ii) Example:2

A Diesel engine comprising an engine block and a cylinder head made of an Aluminum-Titanium alloy having a melting point between 1000 K and 1100 K.

The syntax of the claim is open to different interpretation: Either the engine block as well as the cylinder head are made of the alloy, or only the cylinder head is made of the alloy.

iii) Example:3

A digital photo-camera comprising a VLSI processing unit and a CCD image sensor, characterized in that it is adapted to operate at temperatures down to 200 K.

The camera is defined in terms of the object to be achieved (operation at very low temperatures) rather than in terms of the technical features (e.g. selected semiconductor materials, thermal insulation, etc.) that achieve the desired object.

The claim attempts to define the subject matter in terms of the result to be achieved. In this instance, however such formulation is not allowable because it appears possible to define the subject-matter in more concrete terms, i.e. in terms of how the effect is to be achieved.

iv) Example:4

In case of *Anup Engineering Ltd.*v *Bharat Heavy Electricals Ltd.* (1985 PTC 71). In the instant case, in regard to the ground of 'unfair description' the opponents have stated that important data like the dimension of the bellows produced and hydraulic pressure within the hydraulic forming machine have not been disclosed in the specification. Having regard to the fact that the invention claimed in statement of claims relates not to bellows but to apparatus for manufacturing bellows, these materials are not essential features of the invention. In regard to other defects like omission of reference numerals in the drawings accompanying complete specification and support of some claimed feature in the description; these defects are not of such nature as to make the alleged invention not clear or render the statement of claims ambiguous. These defects could have been corrected by effecting minor amendments in the description. The complete

specification does not sufficiently and clearly describe the invention. The opponents, accordingly, have established this ground.

5.3.8 Markush -Type Claims

A Markush claim refers to a chemical structure by means of symbols indicating substituent groups. In such a claim, one or more parts of the claimed compound comprise multiple functionally equivalent chemical entities

Example:

"The process for the manufacture of dyes which comprise coupling with a halogen substituted pyrazolone, a di-azotized unsulphonated material selected from the group consisting of aniline, homologues of aniline and halogen substitution products of aniline."

Markush type claims allow important innovations to be patented. For example, when a new organic compound, that has a novel structure never obtained before, is invented and can have many possible substituents that could be used, one can effectively group these possible substituents in a Markush type of claims. So one can claim the basic structure along with substituents like halogens, alcohols, hydrocarbons, etc. However, such group of compounds are allowable when supported by a single and definitive process.

With chemical structures, it is often possible to use many substituents in a given structure. The result is that you have a few to hundreds of possible formulations; and each possible substitution location could be a different substituent. There are often changes in the substituent groups that do not change the original use of the compound and, thus, can be thought of as part of the original invention.

5.3.9 Certain Statements not be regarded as claims:

i) The statements of the following form given are not to be regarded as claims, in as much as, they do not define the invention:-

   a) I claim to be the inventor of this appliance,
   b) I claim a patent and that no one else shall use my invention without leave.
   c) I claim that the machine described above is quite new and has never been seen or used before.
   d) I claim some reward.

ii) Also, the claims should not be made, as in the examples given below, for illustrating the efficiency or advantages of the invention:-

   a) I claim that this device is better and cheaper and more effectual than anything known.
   b) I claim that my process or machine will do such and such things

c) I claim the following advantages.
d) I claim an improved sewing machine
e) I claim a mechanism for converting heat into electrical energy without any loss of efficiency.
f) I claim a new method of making silk waterproof.

iii) Where products are claimed, the invention will not be properly defined if merely the properties of the products are referred to, as in the following example:-

"I claim a lubricating oil which is of specific gravity.... and boiling point "

iv) The claims, such as "I claim an improved sewing machine as described or as illustrated "or " I claim the invention described in the specification", which merely refer back to the description are not sufficiently definitive unless the description contains an explicit statement of distinguishing features which are characteristics of the invention.

5.3.10 UNITY OF INVENTION: S 10(5)

A single inventive concept may be recognized between independent claims of different categories as in the following examples:

(a) a claim for a product and claim for a process specially adapted for manufacture of the product;

(b) a claim for a process and claim for an apparatus or means specifically designed for carrying out the process;

(c) a claim for a product, claim for a process specially adapted for manufacture of the product and claim for an apparatus or means specifically designed for carrying out the process.

However , the above criteria can not be generalized and there may be occasions where all such claims may not be allowed in a single application based on the circumstances of the case.

Example:1

" A mould for casting an article, a method of making that mould, a process of casting the article by using the said mould and the article will constitute a single inventive concept".

(a) Unity between product and process claims requires that the process inherently results in the product when the novel product is obtained by the claimed process.

~~e~~(b) Unity between process and apparatus or means requires that the apparatus or means have been specifically designed for carrying the process, or at least a step of the process, but without excluding any other possible use.

~~e~~(c) Single inventive concept is permitted if the invention cannot readily be covered by a single generic claim.

Example:2

-- A locking system containing plug and socket wherein separate independent claims for a plug and socket is allowable

-- Likewise a broadcasting system comprising transmitter and receiver

Example:3

If one has invented a new kind of spray bottle, the invention can be claimed in the same application for :

~~+~~(a) The spray bottle itself (a product)

~~+~~(b) Method of making the spray bottle (a process)

~~+~~(c) Apparatus used for making the said spray bottle

Example:4

When a genetically modified Gene Sequence/ Amino Acid Sequence is novel, involves an inventive step and has industrial application, the following can be claimed.

~~+~~(a) Gene sequence / Amino Acid sequence

~~+~~(b) A method of expressing above sequence

~~+~~(c) An antibody against that protein / sequence

~~+~~(d) A kit made from the antibody / sequence

All of these claims are linked by the inventive concept if the genetically modified sequence is new, inventive and has industrial application

Example:5

A drug or pharmaceutical product, if it is novel, inventive and has industrial application, can be claimed for the following:

(a) a drug or pharmaceutical product,

(b) modified drug or pharmaceutical of a known compound, if proved to be more efficacious than the known compound

(c) a process of making the product as defined in (a) or (b).

(d) formulation containing the drug (a) or (b)

Example:6

In case of a herbal, chemical or pharmaceutical or a medicinal composition the following can be claimed:

(a) a product by itself, if it is novel

(b) a process of extraction and/or process of mixing the ingredients either pre-prepared or extracted.

(c) Apparatus, if novel, either for the process of extraction and/or for the process of preparation.

Example:7

In case of non-drug or non-pharmaceutical chemical, the following can be claimed:

(a) product, if it is novel

(b) process of making the chemical

(c) apparatus for the preparation of a chemical, if it is novel

However, application of a chemical e.g. when a catalyst is claimed as product, the process wherein the above catalyst is used for performing a chemical process, shall be taken as plurality of invention.

Example:8

A Biopolymer produced from a genetically modified bacterium can be claimed for the following (Accession Number of the bacterium & Name of the International Depository Authority should be mentioned in the complete specification) :

(a) Biopolymer, if it is novel

(b) Genetically modified bacteria for producing the above said Biopolymer, if it is novel

(c) Process of manufacturing genetically modified bacteria

(d) Process for manufacturing the said biopolymer

For further reading on the concept of unity of invention the "PCT Applicants Guidelines –International phase"may be referred at following URL

http://www.wipo.int/pct/guide/en/gdvol1/pdf/gdvol1.pdf

5.4.1 SUFFICIENCY OF DISCLOSURE

i) The Complete Specification describing the invention is a techno-legal document. It should disclose the invention completely to meet the requirement of the Patents Act and should also enable a person possessing average skill in the art to work the invention without assistance of the patentee . This is possible when the complete specification describes the invention fully and particularly and

describes its operation and/or method by which it is to be performed. It is also essential that the best method for performing the invention, which is known to the applicant is disclosed in the Complete Specification . [S. (10)(4)].

ii) If the applicant mentions biological material in the invention and it is not possible to describe the same in the complete specification, requirement of sufficiency of disclosure can be completed by depositing such material in an International Depository Authority under the Budapest Treaty. The same shall be deposited not later than the date of filing, however, the reference number to the deposit shall be made in the specification within 3 months from the date of filing the application. The complete specification shall contain the details of such deposition and the source and geographical origin of the biological material.

iii) It is thus clear that the complete specification, , should disclose the invention completely so that a person skilled in the art can perform the invention.
The technical advance, synergistic effect and efficacy of the claimed invention must be substantiated properly in the body of specification as well as by way of suitable examples.

Example:1

In Bishwanath *Prasad Radhey Shyam* v. *Hindustan Metal Industries, (*AIR 1982 SC 1444.*),it was held that* "Right way to construe a specification is not to read the claims' first and then see what the full description of the invention is, but first to read the description of the invention in order that the mind may be prepared for what it is, that the invention is to be claimed, for the patentee cannot claim more than he desires to patent."

Example:2

The ordinary skilled person must be able to perform the invention which satisfies the requirement of disclosure. The test for enablement of a prior disclosure for the purpose of anticipation is the same as the test of enablement of the patent itself for the purpose of sufficiency [held in *SmithKline Beecham Plc's (Paratoxetine Methanesulfonate) Patent* [2006] RPC 10].

There may however be differences in the application of this test to the facts; for example, because in the case of sufficiency the skilled person is attempting to perform a claimed invention and has that goal in mind, whereas in the case of prior art the subject-matter may have disclosed the invention but not identified it as such and it is to be judged from the point of view of the person skilled in the art .

5.4.2 Clarity of Disclosure :

i) Description of invention is addressed to a person skilled in the art who is doing his best to understand it and do not cast doubts on the scope of the invention. For example, in Press Metal Corporation Limited V. Noshir Sorabji Pochkhanawalla (1982 PTC 259 (Bom)), it was held that –

"It is the duty of a patentee to state clearly and distinctly the nature and limits of what he claims. If the language used by the patentee is obscure and ambiguous, no patent can be granted, and it is immaterial whether the obscurity in the language is due to design or carelessness or want of skill. It is undoubtedly true that the language used in describing an invention would depend upon the class of person versed in the art and who intend to act upon the specifications. In the present case, the invention is described in an obscure and ambiguous language, and on this ground, the patent is liable to be refused"

ii) Since disclosure of the invention is the consideration in return for which the applicant is granted a monopoly the highest degree of good faith is called for, and the disclosure should be clear, precise, honest and open. A designedly ambiguous description or one that is wanting in distinctness, either by negligence or unskillfulness , will invalidate a patent (*British Ore Concentration Syndicate Ltd v Minerals Separation Ltd*, 27 RPC 47; *Cincinnati Grinders (Inc) v BSA Tools Ltd* 48 RPC 33).

iii) A specification should not contain superfluous or irrelevant matter (*Francis' Application*, 27 RPC 87).

iv) Complicated mathematical calculations and analyses are undesirable unless they are necessary to a full understanding of the invention. The curtailment of an inordinately long specification may be requested (*LD Corporation's Applications*, 66 RPC 4), but this should be done only in the most extreme cases.

v) The description should not contain passages which confuse the scope of the invention. Therefore, phrases such as " the invention should be taken to include any modifications, whether novel or not..." are unacceptable.

vi) Where particular description or drawings do not exemplify the invention claimed, for example, where they are included by way of explaining the invention or for comparison or where they relate to prior art, the description should make this clear.

5.4.3 Technical or Specialized Terms

i) The description should be as clear and straightforward as possible, with the avoidance of unnecessary technical jargon. Since it is addressed to persons skilled in the art , it will be desirable that for its use by him the technical terms which are well known in that art should be used.

ii) Little known or specially formulated technical terms may be used provided they are adequately defined and that there is no generally recognised equivalent.

iii) Foreign terms may be used where there is no English equivalent.

iv) Terms already having an established meaning should not be used differently, if this is likely to cause confusion. But in some circumstances it may be appropriate for a term to be borrowed from an analogous art.

v) If a specification contains a reference to a proprietary article or specific product, the composition of which is not well known, the description should state the composition of the article or the way in which it is prepared. If the applicant maintains that the information is well known in the art, or if the specification so states, and the examiner is unable to verify this, evidence in support of the contention may be required.

vi) The use of proper names or similar words to refer to materials or articles is undesirable in so far as such words merely denote origin, or where they may relate to a range of different products. The product should be sufficiently identified, without reliance on the word, to enable the invention to be carried out by the skilled person. Such words which have generally accepted meanings as standard descriptive terms may however be used without further explanation; examples are Bowden cable, Belleville washer, zip fastener.

vii) A trade mark should not be used in a specification since it is an indication of origin rather than of composition or content and on that account cannot properly be used to describe an article. If a registered trade mark is used it should generally be accompanied by wording showing that it is a trade mark, since its use as a descriptive term without acknowledgement may be prejudicial to the rights of its owner .

5.4.4 COMPLETENESS OF DISCLOSURE

i) At least one embodiment of the invention or at least one method of performing the invention must be described. However ,where the claims cover a broad field several examples or alternative embodiments or variations extending over the area to be protected by the claims may be necessary.

ii) The disclosure must be sufficient to enable whole width of the claimed invention to be performed. It was held that the disclosure of a single embodiment will not always satisfy the requirement regardless of the width of the claim [*Biogen Inc v Medeva plc* [1997] RPC 1].

iii) It was held in *Kirin-Amgen Inc v Hoechst Marion Roussel* [2005] RPC 9 that whether the specification is sufficient or not was highly sensitive to the nature of the invention. To determine this question, the first step was to identify the invention and decide what it claimed to enable the skilled man to do. It was then possible to ask whether the specification enabled him to do it.

iv) In *Minnesota Mining & Manufacturing Co's (Suspension Aerosol Formulation) Patent* [1999] RPC 135 it was held that a specification is

also insufficient if it provides no teaching relating to the criteria according to which the skilled man is taken to be using the invention.

v) What will suffice to satisfy the criterion that the disclosure must be sufficient across the whole width of the claimed invention will vary depending upon the nature of the claim. Thus, for example, when there is more than one product which is claimed, the question has to be asked whether the invention of one product is the invention of the other, unless they are different inventions and each must be sufficiently described. A similar conclusion had been reached by the Court of Appeal in the case and *Chiron Corp. and ors v Murex Diagnostics Ltd and ors* [1996] RPC 535 (pages 612 and 613).

5.4.5 General Guidelines For Applicant for Filing

It is a common experience that through ignorance of patent law, inventors act indiscreetly and jeopardize the chance of obtaining patents for their inventions.

The most common of these indiscretions is to publish their inventions in newspapers or scientific and technical journals before applying for patents. Publication of an invention, even by the inventor himself, would (except under certain permissible circumstances) constitute a bar for the subsequent patenting of it. Similarly, the use of the invention in public or commercial exploitation of the invention in public or even in secrecy, prior to the date of filing the patent application, would be a fatal objection to the grant of a patent for such inventions thereafter. However, the secret working of the invention by way of reasonable trial or experiment, or disclosure of the invention to other person confidentially, may not result into loss of novelty.

After filing of patent applications, the applicant can use his invention commercially. However, provisional protection against infringement starts from the date of publication only. Express publication of the patent application is possible before the prescribed 18 months period under Sec. 11(A)(2) by filing a request for early publication in Form 9 along with the prescribed fees. The protection is provisional because an infringement suit can be filed only after the grant of a patent.

It is in the interest of an inventor/applicant to access the relevant prior published patent literature and other non-patent information on the subject-matter of his application already in the public domain before filing patent application so as to get the complete idea about prior art for his invention . This will provide great help in drafting the specification in a correct manner, to claim the full scope of the invention desired to be protected in an appropriate manner.

Another mistake, which is frequently made by inventors, is to wait until their inventions are fully developed for commercial working, before applying for patents. Delay in making application for a patent involves risks, namely, (i) that other inventors might forestall the first inventor in applying for the patent, and (ii) that there might be either an inadvertent publication of the invention by the inventor himself, or the publication thereof by others independently of him. It is, therefore, advisable to apply for a patent as soon

as the inventor's idea of the nature of the invention has taken a definite shape. In this connection inventors should note that it is permissible to file an application for a patent accompanied by a "Provisional Specification".

The inventors should not neglect to get clarification of their rights with reference to those of their employers, co-workers, contractors and assistants, if any, with whom they are brought into contact in the course of the development of their inventions. Negligence on this account may lead to loss of right and costly litigation.

5.4.6 INTERNATIONAL APPLICATIONS UNDER PCT

Relevant Sections and Rules:

Section 10(4)A:

In case of an international application designating India, the title, description, drawings, abstract and claims filed with the application shall be taken as the complete specification for the purposes of this Act.

Rule 17 : Definitions:

In this Chapter, unless the context otherwise requires:

(a) "Article" means an Article of the Treaty;
(b) "Treaty" or "PCT" means the Patent Cooperation Treaty.
(c) All other words and expressions used herein and not defined but defined in the PCT shall have the same meaning as assigned to them in that Treaty.

Rule 18: Appropriate office in relation to international applications:

(1) The receiving office, designated office and elected office for the purposes of international applications filed under the Treaty shall be the appropriate office in accordance with rule 4.

(2) The head office of the patent office shall be the appropriate office for dealing with the International Bureau of the World Intellectual Property Organisation, International Searching Authorities and International Preliminary Examining Authorities.

(3) An international application under the Treaty shall be filed at and processed by the appropriate office in accordance with the provisions of this Chapter, the Treaty and the regulations established under the PCT.

(4) Notwithstanding anything contained in sub-rule (2), on receipt of an international application, the appropriate office shall transmit one copy as record copy of such application to International Bureau of the World Intellectual Property Organisation and another copy as search copy to Competent International Searching Authority. The appropriate office shall simultaneously furnish complete details of such application to the head office of the patent offices.

Rule 19. International applications filed with appropriate office as receiving office:

(1) An international application shall be filed with the appropriate office in triplicate either in English or in Hindi language.

(2) The fees payable in respect of an international application filed with the appropriate office shall be, in addition to the fees as specified in the regulations under the Treaty, the fees as specified in the First Schedule.

(3) Where an international application filed with the appropriate office has not been filed as specified under sub-rule (1) and the applicant desires that the appropriate office should prepare the additional copies required, the fee for making such copies shall be paid by the applicant.

(4) On receipt of a request from the applicant and on payment of the prescribed fee by him, the appropriate office shall prepare a certified copy of the priority document and promptly transmit the same to the International Bureau of the World Intellectual Property Organisation for the purpose of an international application filed with the appropriate office with an intimation to the applicant and the head office.

Rule 20. International applications designating or designating and electing India:

(1) An application corresponding to an international application under the Patent Cooperation Treaty under section 7(1 A) may be made in Form 1.

(2) The Patent Office shall not commence processing of an application filed corresponding to international application designating India before the expiration of the time limit prescribed under sub-rule (4)(i).

(3) An applicant in respect of an international application designating India shall, before the time limit prescribed in sub-rule (4)(i),—

(a) pay the prescribed national fee and other fees to the patent office in the manner prescribed under these rules and under the regulations made under the Treaty;

(b) and where the international application was either not filed or has not been published in English, file with the patent office, a translation of the application in English, duly verified by the applicant or the person duly authorised by him that the contents thereof are correct and complete.

(4) (i) The time limit referred to in sub-rule (2) shall be thirty one months from the priority date as referred to in Article 2(xi);

(ii) Notwithstanding anything contained in clause (i), the Patent Office may, on the express request filed in Form 18 along with the fee specified in First Schedule, process or examine the application at any time before thirty one months.

(5) The translation of the international application referred to in sub-rule (3) shall include a translation in English of,—

(i) the description;

(ii) the claims as filed;

(iii) any text matter of the drawings;

(iv) the abstract; and

(v) in case the applicant has not elected India and if the claims have been amended under Article 19, then the amended claims together with any statement filed under the said Article;

(vi) in case the applicant has elected India and any amendments to the description, the claims and text matter of the drawings that are annexed to the international preliminary examination report.

(6) If the applicant fails to file a translation of the amended claims and annexure referred to in sub-rule (5), even after invitation from the appropriate office to do so, within a time limit as may be fixed by that office having regard to the time left for meeting the requirements, the amended claims and annexure shall be disregarded in the course of further processing the application by the appropriate office.

(7) The applicant in respect of an international application designating India shall when complying with sub-rule (3), preferably use Forms set out in the Second Schedule before the appropriate office as designated office.

Rule 21. Filing of priority document:

(1) Where the applicant in respect of an international application designating India has not complied with the requirements of paragraph (a) or paragraph (b) of rule 17.1 of the regulations under the Treaty, the applicant shall file with the patent office the priority document referred to in that rule before the expiration of the time limit referred to in sub-rule (4) of rule 20.

(2) Where priority document referred to in sub-rule (1) is not in the English language, an English translation thereof duly verified by the applicant or the person duly authorised by him shall be filed within the time limit specified in sub-rule (4) of rule 20.

(4) Where the applicant does not comply with the requirements of sub-rule (1) or sub-rule (2), the appropriate office snail invite the applicant to file the priority document or the translation thereof/ as the case may be, within three months from the date of such invitation, and if the applicant fails to do so, the claim of the applicant for the priority shall be disregarded for the purposes of the Act.

Rule 22: Effect of non-compliance with certain requirements:

An international application designating India shall be deemed to be withdrawn if the applicant does not comply with the requirements of rule 20.

Rule 23: The requirements under this Chapter to be supplemental of the regulations, etc., under the Treaty:

(1) The provisions of this Chapter shall be supplemental to the PCT and the regulation and the administrative instructions made there under.

(2) *In case of a conflict between any provisions of the rules contained in this Chapter and provisions of the Treaty and the regulations and the administrative instructions made there under, the provisions of the Treaty and the regulations and administrative instructions made there under shall apply in relation to international applications.*

5.4.7 Introduction: The Patent Cooperation Treaty is an agreement for international cooperation in the field of patents. It is the most significant advancement in international cooperation in this field since the adoption of the Paris Convention itself. It is, however, largely a treaty for rationalization and cooperation with regard to the filing, searching and examination of patent applications and the dissemination of the technical information contained therein. The PCT does not provide for the grant of "international patents". The task and responsibility for granting patents remains exclusively in the hands of the Patent Offices of, or acting for, the countries where protection is sought (the "regional Offices"). PCT is a special agreement under the Paris Convention open only to states, which are members of the Paris convention and is administered by International Bureau (IB) under World Intellectual Property Organization (WIPO), Geneva.

On 7th September 1998, India deposited its instrument of accession to the PCT and on 7th December 1998 thus became a member of the PCT, as the 98th Contracting State of PCT. The Patent Offices at Kolkata , Mumbai, Chennai and New Delhi are receiving the PCT applications.

5.4.8 Principal Objectives Of The PCT

The principal objective of the PCT is to simplify the patent system over the previously established means of applying for patent protection in several countries for inventions and to render it more effective and more economical in the interest of the users and the national patent offices, that have responsibility for administering PCT. Before introduction of the PCT system, virtually the only means by which protection of an invention could be obtained in several countries was to file a separate application in each country. Each of the application is dealt with in isolation, and thus, involves repetition of the work of the filing and examination in each country.

5.4.9 PCT facilitates the following in order to achieve the objectives:

1. establishes an international system which enables the filing of a single application with a single Patent Office ("Receiving Office"), or the "International Application", in one language, having effect in each of the countries which are party to the PCT which the applicant names ("designates") in his application;

2. provides the formal examination of the International Application by a single Patent Office: the Receiving Office;

3. subjects each International Application to an international search which results in a report, citing the relevant prior art (published patent documents and other publications, relating to previous inventions) which may have to be taken into account in deciding whether the invention may be patentable; that report is

made available first to the applicant and is later published; An exhaustive written opinion on patentability is also provided by ISA.

4. provides centralized international publication of International Applications along with the related international search reports including written opinion, declaration, priority document, translation, international examination report, as may be applicable to the particular application.

5. provides the option of an international preliminary examination of an international application, which enables national offices to decide whether or not to grant a patent to the applicant.

5.4.10 International Application

The procedure described under PCT involves two steps of processing the international application. The "International Phase" deals with conducting the search and allowing the applicant to amend the claims, if required. It also optionally deals with the international preliminary examination. Thereafter, the applicant has to enter the national phase (within the prescribed time limits). The grant of patent is the task of the designated / elected offices, that is, the national offices or regional offices.

Under the PCT system, by the time the International Application reaches the national / designated Office, it has already been searched by the International Searching Authority and possibly examined by an International Preliminary Examining Authority, thus providing the national Patent Offices with the important benefit of reducing their work loads since they have the benefit of these international phase centralized procedures and, thus, need not duplicate those efforts. Further, objectives of the PCT are to facilitate and accelerate access by industries and other interested sectors to technical information related to inventions and to assist developing countries on gaining access to technology.

5.4.11 Functions of the Receiving Offices

1. Receiving Offices receive the International Application from the applicant or from his authorized Agent.

2. Then the Receiving Office checks the International Application to determine whether it meets the prescribed requirements as to form and content of International Applications. This check is of a formal nature only and does not go into the substance of the invention. It therefore extends only to a certain number of rather elementary requirements specified in the Treaty as forming part of that check.

3. a) If the requirements of article 11 viz nationality / residence, language, format of the specification etc are fulfilled, then the international application number is allotted on the date of receipt of the application.

b) The receiving office shall accord as the international filing date; the date of receipt of the international application, provided the application is in order in accordance with Article 11 of PCT, at the time of receipt.

c) If the receiving office finds that the international application did not, at the time of receipt, fulfill the requirements listed in paragraph (a), it shall, as provided in the Regulations, invite the applicant to file the required correction(s).

d) If the applicant complies with the invitation, as provided in the regulations, the receiving office shall accord as the international filing date, the date on which the corrected copy is submitted.

4. Receiving Office checks certain formal and physical requirements (Article 14) as to form and content and whether the fees are not, or not fully, paid. In that case, the Receiving Office communicates with the applicant in order to give him an opportunity to correct any defect.

5. If after correction, if any, the international application meets the requirements of article 14, the Receiving office accords the International filing date.

6. If the language of filing of the International Application is the one acceptable by the Receiving Office but not acceptable by the International Searching Authority to carry out international search, the applicant is required to furnish, within one month from the filing date of the application, the translation into a language among the following:

- a language accepted by the International Searching Authority to carry out international search;
- a language of publication; and
- a language accepted by the Receiving Office (unless the International Application is filed in a language of publication).

In cases, where the applicant fails to furnish, within the applicable time limit, a translation for the purpose of international search, the Receiving Office invites the applicant to furnish the missing translation, in certain cases subject to the payment of a late furnishing fee. A separate invitation procedure is provided for the case where the request does not comply with language requirements. Where the applicant does not furnish the missing translation within the time limit fixed in the invitation, the International application will, subject to certain safeguards for the applicant, be considered withdrawn and the Receiving Office will so declare.

7. Not all the requirements of the International Application are required to be examined by the Receiving Office. For instance, the Receiving Office does not deal with substantive questions such as whether the disclosure of the invention in the application is sufficient and whether the requirement of unity of invention is complied with. It also does not check all the many detailed physical requirements of the International Application. Those requirements are only checked to the extent that compliance with such requirements is necessary for the purpose of reasonably inform international publication.

8. Typical examples of defects, which may be corrected without affecting the international filing date, are:

- Non – payment or partial payment of fees;
- Lack of signature of the request;
- Lack of a title of the invention;
- Lack of an abstract;
- Physical defects.

9. In all such cases, lack of correction leads to the application being considered withdrawn, except where a physical defect would not prevent reasonably uniform international publication and except for the payment of fees. With regard to the later, PCT rule 16 bis provides that the Receiving Office must invite the applicant to pay the missing fees together with a late payment fee. If the applicant still does not pay the fees within the time limit fixed in the invitation, the Receiving Office will declare that the International Application is being considered withdrawn. This solution protects the applicant against any loss of his application due to an erroneously delay or incomplete payment of fees.

10. The next step in the procedure before the Receiving Office is that it must transmit the *"record copy"* of the international Application to the International Bureau and the *"search copy"* to the International Searching Authority. The Receiving Office keeps a third copy, the *"home copy"*. The transmittals do not take place if, and as long as, national prescriptions concerning national security apply. The Receiving Office will then declare that national security provisions prevent the International Application from being treated as such.

11. The Receiving Office must mail the record copy promptly to the International Bureau and in any case not later than five days prior to the expiration of the 13th month from the priority date. In many cases, the International Application claims the priority of an earlier national application and is filed at the end of the 12-month priority period; the Receiving Office has only a few weeks for its processing tasks.

12. The search copy must be transmitted by the Receiving Office to the International Searching Authority at the time of the transmittal of the record copy of the International Bureau except, where the search fees has not been paid on time, in which case, the transmittal of search copy takes place after that fee has been paid.

13. If an applicant, who is a resident or national of a PCT Contracting State, erroneously files his International Application with a national office which acts as a Receiving Office under the Treaty but which is not competent under Rule 19.1 or 19.2, having regard to **the applicant's residence and nationality**, to receive that International Application, or if an applicant files his International Application with the competent Receiving Office in a language which is not acceptable by that Office under Rule 12.1 (a) but is in **a language** accepted under that Rule by the International Bureau as Receiving Office, the International Application will be considered to have been received by the national Office on behalf of the International Bureau as Receiving Office on the date ,on which it was received by the national office, and will be promptly transmitted to the International Bureau as Receiving Office (unless such transmittal is prevented by national security prescriptions). The transmittal may be subjected by the National Office to the

payment of a fee equal to the transmittal fee. All other fees, already paid to that Office, will be refunded by that Office to the applicant and the applicable fees will have to be paid to the International Bureau as Receiving Office.

5.4.12 The following conditions should be fulfilled for according an international filing date:

i) Prerequisite: A permission u/s 39 to file an application outside India should have been obtained or an application should have been filed at least six weeks earlier than the international (PCT) application and no secrecy direction should have been given u/s 35 before filing a PCT application.

(ii) The applicant should be resident or national of the Contracting State for which the Receiving Office acts, and has consequently the right to file with that Receiving Office (note, however, that the International Application is to be transmitted to the International Bureau as Receiving Office under Rule 19.4(a)(i), if that condition is not fulfilled);

iii) The International Application should be in English or Hindi (note, however, that the International Application is to be transmitted to the International Bureau as Receiving Office under Rule 19.4(a)(ii), if that condition is not fulfilled

(iv) The International Application should contain at least the following elements:

(a) an indication that it is intended to be an International Application,

(b) filing the request that constitutes the designation of all contracting states bound by the PCT for the grant of every kind of protection available and for the grant of both regional and national patents, (c) the name of the applicant in a form allowing the applicant's identity to be established, the inventor (normally) and the agent (if any)

d) a part which on the face of it appears to be a description,

(e) a part which on the face of it appears to be claim or claims.

(v) If one of these requirements is only complied with after correction, the international filing date will be the date on which the correction was received. In other words, in these cases a defect, which is corrected later, affects the international filing date. If all such defects are not properly corrected, the application will not be treated as an International Application.

(vi) For all the other cases, non-compliance with the formal requirements does not affect the international filing date. In other words, if the applicant corrects a defect in such cases, the international filing date remains unchanged. If the applicant does not correct, the defect properly, the International Application will, however, be considered withdrawn by the Receiving Office. Extension of the time limit fixed by the Receiving Office for the correction of defects under Article 14 may be requested.

5.4.13 Monitoring of time limits

Easy supervision and monitoring of only a few time limits and events is required by applicants, namely:

(i) Monitoring the time limits for payment of fees;
(ii) Checking the notification (Form PCT/IB/301) from the International Bureau for confirming the receipt of the record copy.

(iii) Deciding, after the receipt of the international search report, whether or not to file amended claims under Article 19, within the applicable time limit.
(iv) Monitoring the receipt, during the 19th month from the priority date, of the notice from the International Bureau (Form PCT /IB / 308) that the publication of the International Application has been effected.

(v) Deciding, after receipt of the international search report, whether or not to file a demand for international preliminary examination (which must be filed prior to the expiration of 22 months from the priority date.)

(vi)Entering the national phase before the expiration of 20/21 or 30/31 months from the priority date or international filing date, whichever is earlier, by paying the national fees and furnishing (if required) a translation of the International Application with duly verified for its correctness and completeness.

5.4.14 Filing of the International Application:

a) Request form (PCT / RO / 101)

1. International Application must be filed with any of the receiving offices i.e Patent office, Kolkata (RO/IN), New Delhi Mumbai, and Chennai or International Bureau (RO/IB) of WIPO. The request form and the documents attached therewith should be in triplicate. An application for the same invention has to be filed in India not less than six weeks before filing the International application or necessary permission under section 39 should be taken before filing the international application. The request for permission (U/S 39) for making patent application outside India including PCT international application should be made in form 25 with the prescribed fee as given in First Schedule (sub rule 1 of rule 71) and the Controller shall dispose the said request ordinarily within a period of 21 days from the date of filing of such request (sub rule 2 of rule 71).

2. The International Application must contain a request, a description, one or more claims, one or more drawings (where required) and an abstract; it must comply with the prescribed physical requirements; it must be in one of the prescribed languages; finally, the required fees must be paid. These requirements will be dealt with one by one.

3. The **Request** may be made on Form PCT / RO / 101, copies of which can be obtained free of charge from the Receiving Office or from the International Bureau of WIPO or can be downloaded from WIPO website. The request may also be presented as a computer printout as prescribed by Section 102(h) of the PCT Administrative Instructions or, alternatively, as a computer printout prepared using the PCT-EASY software, in which case it must be accompanied by a computer diskette containing a copy of the data as contained in the request in electronic form and copy of the abstract

4. The request must, first of all, contain a petition, that is, a request that the International Application be processed according to the PCT. It must further contain the title of the invention with necessary data concerning the applicant, the inventor and the agent representing the applicant. It must be signed by the applicant or his agent. Declaration of inventorship should be signed by the inventor(s) / the applicants in convention country as applicable and not by the agent. Where there are two or more applicants, each applicant must sign at his choice either the request or, if the request is signed by an agent, a separate power of attorney. The request should also contain details of priority (where applicable) and an indication of competent International Searching Authority.

5. The request may contain some optional indications, in particular, a priority claim according to the Paris Convention for the Protection of Industrial Property.

b) Priority

1. A certified copy is required for each priority of the application and the same is to be furnished within 16 months from the priority date; The copies for the designated offices are prepared by the International Bureau at no additional cost to the applicant –.

2. A request for transmittal of a copy of the priority document filed with the Receiving Office ,by the Receiving Office to the International Bureau, can be made in the Request Form and the applicable fee for a priority document paid to the Receiving Office.

c) Description

1. The description of the invention in the International Application must disclose the invention in a manner sufficiently clear and complete for the invention to be carried out by a person skilled in the art.

2. The description initially defines the field of invention. It then specifies pertinent technical field to which the invention relates. It indicates the so-called "background art", that is, the technical and, in particular, patent literature, pertaining to that technical field, constituting the "prior art" or "state of the art" or known technology for the newly filed application. It discloses the intention in a way, which allows the technical problem and it solution to be understood. It states the advantageous effects of the invention as compared with the known technology. It briefly describes the figures in the drawings. It sets forth the best mode contemplated by the applicant for

carrying out the invention and any other mode he wants to include. Finally, it indicates the way in which the invention is capable of exploitation in industry.

d) Sequence Listing:-

Section 806 of PCT allows a designated Office to require that a copy of a sequence listing part filed only on an electronic medium under new Section 801 be furnished, on paper for the purposes of the national phase.

1. For the applicants who do not wish to file the sequence listing part of their international applications under new Section 801, the current provisions will continue to apply, including the filing in written form only (under Rule 5.2) and the concurrent or subsequent furnishing, as provided under PCT Rule 13ter and Section 208, of the sequence listing parts in computer readable from but only for the purposes of International search and / or international preliminary examination. In such cases the current system for calculating the basis fee, on the basis for the total number of sheets of the international application including the sequence listing part, will continue to apply (see item 1(b) of the Schedule of Fees).

2. It is important to note that international application filed under new section 801 may only be filed with receiving Offices, which are prepared to accept them, and on such electronic media specified by the receiving Offices (for further details pl. See PCT Applicant's Guide).

e) Claims:

1. The claims must define the subject matter of the invention for which protection is sought. They must be clear and concise and fully supported by the description.

2. With respect to the structure and drafting of claims, the PCT requirements are largely similar to what is accepted in most Patent Offices.

f) Drawings:

The drawings are only required where they are necessary for the understanding of the invention. This will be the case for example for an engineering type of invention. It will not be the case when an invention cannot be drawn, as is the case for a chemical product. Here again, the requirements are similar to those of most Patent Offices.

g) Abstract:

1. The abstract is intended to serve the purpose of technical information. The treaty says clearly that it cannot be taken into account for any other purpose. This means in particular that it cannot be used for the purpose of interpreting the scope of the protection sought.

2. The abstract consists of a concise summary of the disclosure of the invention as contained in the description, claims and drawings in preferably within 50 to 150 words. It must be drafted in a way, which allows the clear

understanding of the technical problem, the gist of the solution of that problem through the invention, and the principal use of the invention.

h) Language of filing

1. The international Application must be filed in the language, or one of the languages, which the Receiving Office accepts for that purpose (Rule 12.1(a)). If the application is filed in any receiving office in India it has to be either in English or Hindi.

Neither the Treaty nor the Regulations enumerate the languages in which International Applications may be filed. Whether a given language can be used depends on the readiness of the Receiving Office to accept International Applications in that language. Each Receiving Office must, however, accept at least one language for the filing of International Applications, which is both a language accepted by at least one international Searching Authority, competent for the international searching of International Applications filed with that Receiving Office and one of the language of publication (that is, Chinese, English, French, German, Japanese, Spanish, Russian or Arabic). In other words, either the International Application in its original language or the translation will be sufficient for the processing by the Receiving Office, for international search and for international publication.

2. If the language of filing of the International Application is accepted by the Receiving Office and the International Searching Authority but is not a language of publication (at present, this is the case only where the International Application is filed in Dutch and certain Nordic languages), the International Application will be published in English, the translation into that language being prepared under the responsibility of the International Searching Authority which undertakes the searches (see Rule 48.3)

3. The request must always be filed in a language that is accepted by the Receiving Office and which is also one of the eight languages of publication.

5.4.15 International Search

1. International Search report is established by the International Searching Authority. For the purpose of Indian applicant following are Competent International Searching Authorities (ISAs).

1. Austrian Patent Office (AT)
2. Australian Patent Office (AU)
3. European Patent Office (EP)
4. China Intellectual Property Office (CN)
5. United States Patent & Trademark Office (US)
6. Swedish Patent Office (SE)

2. If the International Application did not claim any priority, the international search report is normally available within nine months from the international filing date. If priority is claimed, that report is available usually by the 16th month from the priority date. Even where priority is claimed, the

international search report is normally available in time before publication of the International Application. This allows time for the applicant to withdraw the application before publication, if desired.

5.4.16 PCT FEES (may vary from time to time)

Receiving Office (RO/IN) is The Patent Office, Kolkata, New Delhi Mumbai and Chennai

All PCT fees are subject to change periodically. For latest fees, please refer the latest PCT newsletter at URL **www.wipo.int.**

(i) Transmittal fee: as given in **the First Schedule** .
(ii) International Fee and, Search Fee is given in **Annexure II.**
(iii) Fee for preparing certified copy of priority document in respect of individual or legal entity is given in the First Schedule .

Failure to pay fees or underpayment of fees can be corrected under PCT rule 16 bis. An invitation to pay missing fees will be issued by the Receiving Office. Payment can be made within a month from International filing date or later with a late payment fee.

An Indian applicant, filing an International Application under Patent Cooperation Treaty, is required to remit the consolidated amount in US Dollar by Demand Draft, payable to the Controller of Patents at State Bank of India, New York Branch, for payment towards International Filing fee and search fee. The required fees, which must be paid to receiving Office, are the Transmittal Fee, the International Filing Fee and the Search Fee. These fees must be paid to the Receiving Office within the prescribed time.

The Transmittal Fee is for the benefit of the Receiving Office. It is intended to compensate that office for the work, which is required to be performed in connection with the International Application. The amount is fixed by the Receiving Office. It is to be paid within one month from the date of receipt of the International Application.

The international filing fee is for the benefit of the International Bureau. It is intended to cover the cost of the work; the International Bureau must perform under the PCT. The amounts are fixed in the Schedule of Fees, which forms part of the regulations. The international filing fee is to be paid within one month from the date of receipt of the International Application.

The Search Fee is for the benefit of the International Searching Authority. It is intended to compensate that Authority for the work it must perform in connection with the establishment of the international search report. It is also to be paid within one month from the date of receipt of the International Application. The amount is fixed by the International Searching Authority.

5.4.17 Withdrawal of Application

An International Application can be withdrawn before technical preparations for international publication have been completed (that is, not later than 15 days before the date of publication , which is 18 months from the priority date)

5.4.18 Amendments:

The claims can be corrected for conformity with the results of the international search report by amending them once (under Article 19) with effect in all designated States. Such amendments save costs for preparation of different sets of amendments and for local agents filing such amendments before designated Offices, and guarantee better provisional protection and patents in designated countries. Individual amendments before each Designated Office are also permitted in the national phase (under Article 28 or 41) and all parts of the application can be amended under Article 34(2)) during the international preliminary examination procedure under Chapter II.

5.4.19 International Preliminary Examination (Optional)

1. International Preliminary Examination is useful in the following ways:

i) It is optional for the applicant;

ii) provides, in addition to the international search report, an international preliminary Examination report containing a second opinion on the usual criteria of patentability before expenses are incurred for the national phase (for translation, fees and foreign agents);
iii) helps the applicant to adapt the International Application in accordance with the results of the International Search Report;

iv) allows, with effect for all elected Offices, the amending of all parts of International Application (description, claims and drawings) during international preliminary examination;

v) The international preliminary examination report gives for minimal cost, an opinion and the probability of obtaining a patent:

vi) If the report is negative and it is decided to abandon the application, the applicant has saved all the expenses otherwise incurred before the elected Offices for the payment of national fees, the preparation of translations and the appointment of local agents. However the opinions from ISA & IPEA are non-binding opinions for the member countries
2. The following are Competent International Preliminary Examining Authorities (IPEAs) for the purpose of Indian Applicant:]

- Austrian Patent Office (AT)
- Australian Patent Office (AU)
- European Patent Office (EP) (Only if ISA was AT, EP or SE)
- China Intellectual Property Office (CN)
- United States Patent & Trademark Office (US)

- Swedish Patent Office (SE)

The fees to be paid by the applicant when he opts for Preliminary examination to be carried out by IPEA is given in the PCT Newsletter which is available on the WIPO website, www.wipo.int

5.4.20 National Phase

1. The national phase follows the international phase. In the national phase before processing and examination in the designated or elected Offices, the applicant must perform certain acts thereby effecting "entry into the national phase". If the applicant does not enter the national phase, namely, if he does not perform these acts within the prescribed time limit, the International Application loses its effect in the designated or elected States concerned with the same consequences as the withdrawal of any national application in that State (Article 24).
2. For entry into the national phase before a designated office, it is necessary that the national fee is paid to it and, where the International Application has not been filed or published in the official language, or one of the official languages of that Office, a duly verified translation into an official language be filed. The time limit for entry into the national phase is 31 months in India.

3. The national fees to be paid are usually same as the fees required for the filing of a national or conventional application.

5.4.21 Advantages Of PCT Applications

1. Any patent application, drafted in accordance with the requirements of the PCT, allows maximum flexibility and benefit from the advantages of the PCT

(i) The same application documents can be used for filing national application;
(ii) No adaptation of the original application is then required in as much as the PCT format is valid for all designated offices (including the EPO, the Japanese Patent Office and the United States Patent and Trademark Office).

5.4.22 BASIC REQUIREMENTS TO ENTER NATIONAL PHASE IN INDIA

(i) Under the basic requirements to start the national phase in India, the applicant is required to file the national phase application within 31 months from the priority date or International application date, whichever earlier.
(ii) Application may be made in Form 1.
(iii) National fee in INR is to be paid as given in the First Schedule along with the application.
(iv) In case of more than one priority, multiple fees for every multiple priority is to be paid as per the First Schedule

(v) Where the international application has not been filed or published in one of the official languages (Hindi or English), a translation of the application, description, claims (if amended, both as originally filed and amended together with any statement under PCT Article 19 and Article 39(1)), drawings, if any, and abstract should be submitted along with the application.

(vi) Additional Special Requirements:

Under the said additional special requirements (PCT Rules 51 bis), no designated Office is to require before the expiration of the applicable time limit for entering the national phase, the performance of acts other than those referred to in Article 22, namely the payment of the national fee, furnishing of a translation and, in exceptional cases, the furnishing of a copy of the international application, and indication of the name and address of the inventor. All other requirements of the national law are referred as "special requirements" and they may be complied with once national processing has started. As per DO/IN or EO/IN the special requirements of the Office are as follows:

a) Name, nationality and address of the inventor if they have not been furnished in the "Request" part of the international application,

b) Instrument of assignment or transfer where the applicant is not the inventor.

c) Document evidencing a change of name of the applicant if the change has occurred after the international filing date and has not been reflected in a notification from the International Bureau (Form PCT / IB/ 306). Form 6 and/or Form 13 are also required.

d) Declaration of inventorship by the applicant,

e) Statement regarding filing of corresponding applications in other countries,

f) Power of attorney if an agent is appointed,

g) Address for service in India (but representation by an agent is not a must)

h) Verification of translation, and Copy of International application or its translation

CHAPTER VI

PUBLICATION AND EXAMINATION OF APPLICATIONS

6.1 Publication of applications

Relevant Sections and Rules :

Section 11:

(1) Save as otherwise provided, no application for patent shall ordinarily be open to the public for such period as may be prescribed.

(2) *The applicant may, in the prescribed manner, request the Controller to publish his application at any time before the expiry of the period prescribed under sub-section (1) and subject to the provisions of sub-section (3), the Controller shall publish such application as soon as possible.*

(3) *Every application for a patent shall, on the expiry of the period specified under sub-section (1), be published, except in cases where the application—*

(a) in which secrecy direction is- imposed under section 35; or
(b) has been abandoned under sub-section (1) of section 9; or
(c) has been withdrawn three months prior to the period specified under sub-section (1).

(4) *In case a secrecy direction has been given in respect of an application under section 35, then it shall be published after the expiry of the period prescribed under sub-section (1) or when the secrecy direction has ceased to operate, whichever is later.*

(5) *The publication of every application under this section shall include the particulars of the date of application, number of application, name and address of the applicant identifying the application and an abstract.*

(6) *Upon publication of an application for a patent under this section—*

(a) the depository institution shall make the biological material mentioned in the specification available to the public;
(b) the patent office may, on payment of such fee as may be prescribed, make the specification and drawings, if any, of such application available to the public.

(7) *On and from the date of publication of the application for patent and until the date of grant of a patent in respect of such application, the applicant shall have the like privileges and rights as if a patent for the invention had been granted on the date of publication of the application:*

Provided that the applicant shall not be entitled to institute any proceedings for infringement until the patent has been granted:

Provided further that the rights of a patentee in respect of applications made under sub-section (2) of section 5 before the 1st day of January, 2005 shall accrue from the date of grant of the patent:

Provided also that after a patent is granted in respect of applications made under sub-section (2) of section 5, the patent-holder shall only be entitled to

receive reasonable royalty from such enterprises which have made significant investment and were producing and marketing the concerned product prior to the 1st day of January, 2005 and which continue to manufacture the product covered by the patent on the date of grant of the patent and no infringement proceedings shall be instituted against such enterprises.

Section 143:

Restrictions upon publication of specification;

Subject to the provisions of Chapter VII, an application for a patent, and any specification filed in pursuance thereof, shall not, except with the consent of the applicant, be published by the Controller before the expiration of the period prescribed under sub-section (1) of section 11A or before the same is open to public inspection in pursuance of sub-section (3) of section 11A or section 43.

Rule 11:

Order of recording applications.

The applications filed in a year shall constitute a series identified by the year of such filing. In case of an application filed corresponding to an international application in which India is designated, such application shall constitute a series distinct from the rest of the applications identified by the year of filing of corresponding applications in India

Rule 24:

Publication of application

The period for which an application for patent shall not ordinarily be open to public under sub-section (1) of section 11A shall be eighteen months from the date of filing of application or the date of priority of the application, whichever is earlier.

Provided that the period within which the Controller shall publish the application in the Journal shall ordinarily be one month from the date of expiry of said period, or one month from the date of request for publication under rule 24A.

Rule 24:.

Request for publication;

A request for publication under sub-section (2) of section 11A shall be made in Form 9.

Rule 25:

Identification of published applications;

Publication of application under sub-sections (2) and (5) of section 11A shall be identified by the letter 'A' along with the number of application .

Rule 26:

Request for withdrawal;

A request for withdrawing the application under sub-section (4) of section 11B shall be made in writing.

Rule 27:
Inspection and supply of published documents;

After the date of publication of the application under section 11A, the application together with the complete specification and provisional specification, if any, the drawing, if any, and the abstract filed in respect of the application may be inspected al the appropriate office by making a written request to the Controller on payment of the fee in that behalf and copies thereof may be obtained on payment of fees specified in the First Schedule.

6.1.1 Numbering of Application:

Patent office accords an application number and filing date to the application immediately after filing by the applicant, such that the applications filed in a year constitute the series identified by the year of such filing. PCT National Phase applications constitute a different series (Rule 11).

6.1.2 Screening of Applications:

All the applications will be screened and have International Patent Classification to categorize the invention to the respective field of technology. Simultaneously, the applications are screened to find whether the invention is relevant for defence and atomic energy purpose so that the necessary procedure can be initiated.

6.1.3 Publication of Applications :

A) No application for patent shall ordinarily be open to public before the publication by Patent office under section 11A. At the end of 18 months period, the application will be published in the official journal except in the cases where,

i) Secrecy direction is imposed **u/s 35**

ii) The application has been abandoned **u/s 9(1)**

iii) It has been withdrawn three months prior to the publication period i.e. before the end of 15th month from the date of filing or priority, whichever is earlier **[S.11(A)].**

In case a secrecy direction has been given, the application will be published after expiry of the 18-month period or when the secrecy direction is lifted off, whichever is later (S. 11A(4)).

6.1.4 Early Publication:

If the applicant makes a request in Form 9 (before the expiry of 18 months from the date of priority if no priority claimed from the date of filing) with the prescribed fee (Rs.2,500/- for natural person(s) and Rs.10,000 for legal entity [other than natural person(s))], the application will be published within one month from the date of filing of such request.

6.1.5 Particulars of Publication:

i) Patent applications are published in the Patent Office Journal under section 11A(2) of the Patents (Amendment) Act 2005 and rule 24A of the Patents (Amendment) Rules, 2006.

b) The publication U/S 11A will be identified by the letter "A" along with the Number of Application

c) Publication of patent application includes information on the following parameters as may be applicable to a particular case

☐(a) Number of Application
☐(b) Date of filing of Application
☐(c) Title of Invention
☐(d) Publication date
☐(e) International Patent classification
☐(f) Name and Address of the Applicant
☐(g) Name of the Inventor(s)
☐(h) Priority details like Document Number, Date, Country, PCT application number and date, etc
☐(i) Patent of Addition to / Divisional Application to: along with filing date of the parent application /
☐(j) Abstract of the Invention including drawing (if any)

6.1.6 EFFECTS OF PUBLICATION:

1. After publication of the application for patent the depository institution will make the biological material (mentioned in the specification) available to the public

2. The Patent office will make the specification (complete as well as provisional, if any), and drawings filed in respect of the application available to the public on payment of the prescribed fee as given in the First Schedule.

3. The applicant shall have like privileges and rights, as if a patent for the invention had been granted from the date of publication of the application

until the date of grant. But he shall not be entitled to institute any proceedings for infringement until the patent has been granted.

4. The rights of patentee for applications filed u/s 5(2) before 1st day of January, 2005 will accrue from the date of grant of the patent.

6.2 EXAMINATION OF APPLICATIONS

Relevant sections and Rules :

Section 11B: Request for examination;

(1) No application for a patent shall be examined unless the applicant or any other interested person makes a request in the prescribed manner for such examination within the prescribed period.

(2) Omitted by Act 15 of 2005

(3) In case of an application in respect of a claim for a patent filed under sub-section (2) of section 5 before the 1st day of January, 2005 a request for its examination shall be made in the prescribed manner and within the prescribed period by the applicant or any other interested person.

(4) In case the applicant or any other interested person does not make a request for examination of the application for a patent within the period as specified under sub-section (1) or sub-section (3), the application shall be treated as withdrawn by the applicant:

Provided that—

(i) the applicant may, at any time after filing the application but before the grant of a patent, withdraw the application by making a request in the prescribed manner; and

(ii) in a case where secrecy direction has been issued under section 35, the request for examination may be made within the prescribed period from the date of revocation of the secrecy direction.

Section 12: Examination of application;

(1) When a request for examination has been made in respect of an application for a patent in the prescribed manner under sub-section (1) or sub-section (3) of section 11B, the application and specification and other documents related thereto shall be referred at the earliest by the Controller to an examiner for making a report to him in respect of the following matters, namely:—

(a) whether the application and the specification and other documents relating there to are in accordance with the requirements of this Act and of any rules made thereunder;

(b) whether there is any lawful ground of objection to the grant of the patent under this Act in pursuance of the application;

(c) the result of investigations made under section 13; and

(d) any other matter which may be prescribed.

(2) The examiner to whom the application and the specification and other documents relating thereto are referred under sub-section (1) shall ordinarily make the report to the Controller within such period as may be prescribed.

Rule 24 B: Examination of application.;

(1) (i) A request for examination under section 11 B shall be made in Form 18 within forty-eight months from the date of priority of the application or from the date of filing of the application, whichever is earlier;

(ii) The period within which the request for examination under sub-section 3 of section 11 B to be made shall be forty-eight months from the date of priority if applicable, or forty-eight months from the date of filing of the application;

(iii) The request for examination under sub-section (4) of section 11B shall be made within forty-eight months from the date of priority or from the date of filing of the application, or within six months from the date of revocation of the secrecy direction, whichever is later;

(iv) The request for examination of application as filed according to the 'Explanation' under sub-section (3) of section 16 shall be made within forty-eight months from the date of filing of the application or from the date of priority of the first mentioned application or within six months from the date of filing of the further application, whichever is later;

(ii) The period for making request for examination under section 11B, of the applications filed before the 1st day of January, 2005 shall be the period specified under the section 11B before the commencement of the Patents (Amendment) Act, 2005 or the period specified under these rules, whichever expires later.

(2) (i) The period within which the Controller shall refer the application and specification and other documents to the examiner in respect of the applications where the request for examination has been received shall ordinarily be one month from the date its publication or one month from the date of the request for examination whichever is later:

Provided that such reference shall be made in order in which the request is filed under sub-rule (1).

(ii) The period within which the examiner shall make the report under sub-section (2) of section 12, shall ordinarily be one month but not exceeding three months from the date of reference of the application to him by the Controller;

(iii) the period within which the Controller shall dispose off the report of the examiner shall ordinarily be one month from the date of the receipt of the such report by the Controller.

(3) A first examination report along with the application and specification shall be sent to the applicant or his authorised agent ordinarily within six months from the date or the request for examination or six months from date of publication whichever is later. In case other interested person files the request for examination, an intimation of such examination may be sent to such interested person.

(4) The time for putting an application in order for grant under section 21 shall be twelve months from the date on which the first statement of objection is issued to the applicant to comply with the requirements.

Section 13:

Search for anticipation by previous publication and by prior claim;

(1) The examiner to whom an application for a patent is referred under section 12 shall make investigation for the purpose of ascertaining whether the invention so far as claimed in any claim of the complete specification—

(a) has been anticipated by publication before the date of filing of the applicant's complete specification in any specification filed in pursuance of an application for a patent made in India and dated on or after the 1st day of January, 1912;

(b) is claimed in any claim of any other complete specification published on or after the date of filing of the applicant's complete specification, being a specification filed in pursuance of an application for a patent made in India and dated before or claiming the priority date earlier than that date.

(2) The examiner shall, in addition, make such investigation for the purpose of ascertaining whether the invention, so far as claimed in any claim of the complete specification, has been anticipated by publication in India or elsewhere in any document other than those mentioned in sub-section (1) before the date of filing of the applicant's complete specification.

(3) Where a complete specification is amended under the provisions of this Act before the grant of patent, the amended specification shall be examined and investigated in like manner as the original specification.

~~(2)~~(4) The examination and investigations required under section 12 and this section shall not be deemed in any way to warrant the validity of any patent, and

no liability shall be incurred by the Central Government or any officer thereof by reason of, or in connection with, any such examination or investigation or any report or other proceedings consequent thereon.

Rule 28:

Procedure in case of anticipation by prior publication;

(1) If the Controller is satisfied after investigation under section 13 that the invention so far as claimed in any claim of the complete specification has been published in any specification or other document referred to in clause (a) of sub-section (1) or subsection (2) of the said section, the Controller shall communicate the gist of specific objections and the basis thereof to the applicant and the applicant shall be afforded an opportunity to amend his specification.

(2) If the applicant contests any of the objections communicated to him by the Controller under sub-rule (1), or if he refiles his specification along with his observations as to whether or not the specification is to be amended, he shall be given an opportunity to be heard in the matter if he so requests:

Provided that such request shall be made on a date earlier than ten days of the final date of the period referred to under sub-section (1) of section 21:

Provided further that a request for hearing may be allowed to be filed within such shorter period as the Controller may deem fit in the circumstances of the case.

(3) If the applicant requests for a hearing under sub-rule (2) within a period of one month from the date of communication of the gist of objections, or, the Controller, considers it desirable to do so, whether or not the applicant has refiled his application, he shall forthwith fix a date and time for hearing having regard to the period remaining for putting the application in order or to the other circumstances of the case.

(4) The applicant shall be given ten days' notice of any such hearing or such shorter notice as appears to the Controller to be reasonable in the circumstances of the case and the applicant shall, as soon as possible, notify the Controller whether he will attend the hearing.

(5) After hearing the applicant, or without a hearing if the applicant has not attended or has notified that he does not desire to be heard, the Controller may specify or permit such amendment of the specification as he thinks fit to be made and may refuse to grant the patent] unless the amendment so specified or permitted is made within such period as may be fixed.

Rule 28A:

Procedure in relation to consideration of report of examiner under section 14;

In case the applicant contests any of the objections communicated to him, the procedure specified under rule 28 may apply.

Rule 29:

Procedure in case of anticipation by prior claiming.

(1) When it is found that the invention so far as claimed in any claim of the complete specification, is claimed in any claim of any other specification falling within clause (b) of sub-section (1) of section 13, the applicant shall be so informed and shall be afforded an opportunity to amend his specification.

(2) If the applicant's specification is otherwise in order for grant and an objection under clause (b) of sub-section (1) of section 13 is outstanding, the Controller may postpone the grant of patent and allow a period of two months for removing the objection.

Rule 30.:

Amendment of the complete specification in case of anticipation;

(1) If the applicant so requests at any time, or if the Controller is satisfied that the objection has not been removed within the period referred to in sub-rule (2) of rule 29, a date for hearing the applicant shall be fixed forthwith and the applicant shall be given at least ten days' notice of the date so fixed. The applicant shall, as soon as possible, notify the Controller whether he will attend the hearing.

(2) After hearing the applicant, or without a hearing if the applicant has not attended or has notified that he does not desire to be heard, the Controller may specify or permit such amendment of the specification as will be to his satisfaction to be made and may direct that reference to such other specification, as he shall mention shall be inserted in the applicant's specification unless the amendment is made or agreed to within such period as he may fix.

Section 14:

Consideration of the report of examiner by Controller.;

Where, in respect of an application for a patent, the report of the examiner received by the Controller is adverse to the applicant or requires any amendment of the application, the specification or other documents to ensure compliance with the provisions of this Act or of the rules made there under, the Controller, before proceeding to dispose of the application in accordance hereinafter appearing, shall communicate as expeditiously as possible the gist of the objections to the applicant and shall, if so required by the applicant within the prescribed period, give him an opportunity of being heard.

Section 144:

Reports of examiners to be confidential.—

The reports of examiners to the Controller under this Act shall not be open to public inspection or be published by the Controller; and such reports shall not be liable to production or inspection in any legal proceeding unless the court certifies that the production or inspection is desirable in the interests of justice, and ought to be allowed.

Section 15:
Power of Controller to refuse or require amended applications, etc., in certain case;

Where the Controller is satisfied that the application or any specification or any other document filed in pursuance thereof does not comply with the requirements of this Act or of any rules made there under, the Controller may refuse the application or may require the application, specification or the. Other documents, as the case may be, to be amended to his satisfaction before he proceeds with the application and refuses the application on failure to do so.

Section 16:
Power of Controller to make orders respecting division of application;

(1) A person who has made an application for a patent under this Act may, at any time before the grant of the patent, if he so desires, or with a view to remedy the objection raised by the Controller on the ground that the claims of the complete specification relate to more than one invention, file a further application in respect of an invention disclosed in the provisional or complete specification already filed in respect of the first mentioned application.

(2) The further application under sub-section (1) shall be accompanied by a complete specification, but such complete specification shall not include any matter not in substance disclosed in the complete specification filed in pursuance of the first mentioned application.

(3) The Controller may require such amendment of the complete specification filed in pursuance of either the original or the further application as may be necessary to ensure that neither of the said complete specifications includes a claim for any matter claimed in the other.

Explanation.—For the purposes of this Act, the further application and the complete specification accompanying it shall be deemed to have been filed on the date on which the first mentioned application had been filed, and the further application shall be proceeded with as a substantive application and be examined when the request for examination is filed within the prescribed period.

Section 17:
Power of Controller to make orders respecting dating of application;

(1) Subject to the provisions of section 9, at any time after the filing of an application and before the grant of the patent under this Act, the Controller may, at the request of the applicant made in the prescribed manner, direct that the application shall be post-dated to such date as may be specified in the request, and proceed with the application accordingly:

Provided that no application shall be post-dated under this sub-section to a date later than six months from the date on which it was actually made or would, but for the provisions of this sub-section, be deemed to have been made.

(2) Where an application or specification (including drawings) or any other document is required to be amended under section 15, the application or with the provisions specification or other document shall, if the Controller so directs, be deemed to have been made on the date on which the requirement is complied with or where the application or specification or other document is returned to the applicant on the date on which it is re-filed after complying with the requirement.

6.2.1. EXAMINATION OF PATENT APPLICATION

After publication of application, the next stage of processing of patent application is examination as to whether the patent can be granted for the invention as contained in complete specification . Examination stage is subject to filing request for examination u/s 11(B). This system of examination is called Deferred Examination System. The basic criteria for an invention to qualify for a patent grant is that it must have novelty, inventive step and capability of industrial application and also it should not fall under any of the categories of non-patentable inventions. This chapter explains how the criteria of patentability is examined and various relevant steps involved in the patent grant procedure starting from filing patent application laid down by the provisions of the Patents Act are checked during the examination of patent application.

6.2.2 Request for Examination

i) The application will be taken up for examination only on request made by the applicant or by any other interested person in Form -18. Such a request is required to be made within 48 months from the date of priority or from the date of filing, whichever is earlier, with the prescribed fees as given in the First Schedule.

"Person interested" (S.2(1)(t) includes a person engaged in, or in promoting research in the same field as that to which the invention relates. Any person including an organization that has a manufacturing or trading interest in the goods connected with the patented article or who has a financial interest in manufacturing such goods or who possesses patents related to the same subject, is considered a person interested.

ii) Request for examination can be made by the applicant or any other person interested. In case of other than applicants filing the request, it shall be supplemented with the evidence of interest.

(iii) In case of PCT-National Phase applications(PCT-NP), processing of the application starts only after expiry of 31 month -period from its priority date (Rule 20(2) and 20(4)). However an express request can be filed for early processing or examination, any time earlier than the prescribed time of 31 months, in Form 18 along with the prescribed fee as given in First Schedule, whereupon these applications may be taken up for examination before the said period

iv) All the applications will be screened to categorize the invention to the respective field of technology and to find whether the invention is relevant for defence purposes etc. so that the necessary procedures can be initiated in respect of those applications.

v) In respect of applications filed u/s 5(2), filed before the 1st day of January 2005, the request should be made within a period of 48 months from the date of priority (if applicable) or date of filing of the application.

vi) If no request for examination is made within the prescribed period the application will be treated as withdrawn by the applicant [S.11B (4)]

vii) In case of applications in which secrecy direction is imposed, the date of filing the request shall be with in 48 months from the date of filing the application or priority or six months from the date of revocation of such secrecy direction, whichever expires later.

viii) The request for examination in case of divisional application shall be filed within 48 months from the date of filing or priority of the parent application or within six months from the date of filing the divisional application, whichever expires later. Request for divisional application shall be filed only after filing request for the parent application to ensure the requirement of section 16(3).

6.2.3 Request for Withdrawal: The applicant can, however, withdraw his application at any time after filing the application but before the grant of a patent by making a request to that effect in writing with prescribed fee under entry No.23 of the First Schedule of the Patents Rules 2003. [S.11B (4) (i), R. 26].

6.2.4 Advantages of Deferred Examination System;

(a)By making an application for patent, an applicant/inventor obtains the date of patent and, hence priority also, without paying the fee for examination

(b)An applicant/inventor gets recognition as the owner of the invention because of '18 month publication', even if the application is not examined.

(c)Request for examination can be delayed up to 48 months so that the applicant can obtain financial support to exploit invention.

~~(d)~~A person who is interested in the commercial value of the invention can request for examination and get the license for patent later after consultation with the applicant.

~~(e)~~If the applicant wishes, he can withdraw the application before the end of 15th month of filing an application to prevent the publication, so that its novelty will not be lost (S.11B (4)(i), 11A(3)(c))

~~4.12~~6.2.5 Two stages of Examination of Patent Application at Patent Office

(i) Formal examination and
(ii) Substantive / Technical examination

6.2.6 Formal Examination:

The application for a patent, as filed, including all the relevant documents, payments etc are checked/scrutinized to ensure that the same are filed or submitted in conformity with the provisions of the Patents Act and Rules.[Sec12 (1)(a)]

a) Formal scrutiny/checking is carried out in respect of the following documents-

~~e~~1) All relevant forms, request, petitions, assignment deeds, translation etc.,
~~e~~2) Payment of fees and other details,
~~e~~3) Provisional and /or complete specification,
~~e~~4) Abstract,
~~e~~5) Drawings (if any),
~~e~~6) Presence of meaningful claim(s) or absence of claims in a complete specification,
~~e~~7) Proof of right,
~~e~~8) Form 5 (along with complete after provisional or for filing PCT-NP/Convention application)
~~e~~9) Power of Attorney or attested copy of General Power of Attorney (if any)
~~e~~10) Form 3 -information regarding foreign filing u/s 8(1).
~~e~~11) Whenever Form 6 is filed and assignment has taken place from individual to other than individual, difference in fee has to be called for (Rule 7(3)).

Screening

Screening is carried out for the following -

~~e~~a) Technical fields of invention
~~e~~b) Relevance to defence or atomic energy
~~e~~c) International and Indian Classification
~~e~~d) Correction/completing the abstract, if required.

After scrutiny of the documents, the lacunae, if any, in the application will be communicated to the applicant in FER.

6.2.7 Substantive /Technical Examination:

a) **Substantive examination mainly involves *exploring* the following *technical and legal matters* by the examiner-**

~~1.~~i. Whether the specification complies with the requirements of section 10 regarding contents of the specification

~~2.~~ii. Whether the subject matter is an invention within the meaning of section 2(1) (j), based on the criteria of novelty, inventive step and industrial applicability.

~~3.~~iii. Classification and conducting of search for anticipation by previous publication in any document in India and elsewhere and prior claiming in the patent applications filed in India.

~~4.~~iv. Whether the invention is one, which is not patentable under sections 3 & 4 of the Patents Act.

b) Steps involved in Substantive Examination

~~a~~i. Assessment of patentability of the subject matter
~~a~~ii. Assessment of sufficiency of disclosure
~~a~~iii. Check for unity of invention
~~a~~iv. Appraisal of Industrial applicability
~~a~~v. Classification of the invention
~~a~~vi. Novelty search
~~a~~vii. Determination of the inventive step
~~a~~viii. Judgment of validity of claims
~~a~~ix. Disclosure of geographical origin of the Biological material
~~a~~x. Permission from National Bio diversity Authority.

c) Examination of Industrial Applicability is based on the technical documentation in the patent application dossier (description, drawings, claims etc.), while the examination of novelty and inventive step requires documentary search for the assessment of prior art.

d) Before examination of novelty and inventive step, it is necessary to check whether the invention is fully defined

e) Novelty **is determined before inventive step** because the creative contribution of the inventor can be assessed only by knowing the novel element of the invention, which can justify it.

f) The examiner conducts novelty search to see whether the invention claimed in any claim of the complete specification has been anticipated by any of the following documents for the purpose of judging the novelty and inventive step of the invention.

~~a~~i. Indian patent specifications published before the date of filing of the application, but on or after 1st January, 1912 - [(S.13 (1)(a)] (Prior publication)

~~o~~ii. Indian patent specifications which are filed before the date of filing of the present case or claming a priority date earlier to the said date, but the publication of that document was effected on or after the filing date (S. 13(1) (b) – (Prior claiming)

~~o~~iii. Any publication in India or elsewhere in any document other than Indian Patent Specifications as mentioned *above* (S. 13(2) Prior publication including traditional knowledge in any form.

g) For establishing novelty of the invention, the requirement holds that all the features from the independent claim should be described in a single document. When even a single feature is missing from the cited document, the claim may be considered as novel. It is also necessary that all the features be described in the same combination in the single document.

h) According to international standards the novelty search results in the following documents, which form citation for the invention. Description for each type of the documents, Types – A, E, L, O, P, and T, X, Y is given below. The citations of the type X and Y are very important as they explicitly indicate lack of novelty and obviousness as per the search report prepared by the International Authority.

i) Special Categories of Cited Documents: -

Type	Description of Document
"A"	Document defining the general state of the art which is not considered to be of particular relevance
"E"	Earlier document but published on or after the international filing date
"L"	Document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O"	Document referring to an oral disclosure, use, exhibition or other means
"P"	Document published prior to the international filing date but later than the priority date claimed
"T"	Later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention.
"X"	Document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y"	Document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents; such combination being obvious to a person skilled in the art.
"&"	Document member of the same patent family

~~4.13~~6.2.8 Procedure for Substantive Examination

1) Applications will be taken up for examination according to the order in which the Request for Examination has been made.

2) Where the request for examination has been received, the Controller shall refer the application, specification and other document to the examiner in respect of the application, ordinarily within one month from the date of publication or request for examination, whichever is later [Rule 24 B (2)]

3) The *Controller* refers the application to an Examiner to make a report to him on

i) Whether the application, specification and other document are in accordance with the requirements of the Patents Act & Rules
ii) Whether there is any objection to grant of patent
iii) Results of search for anticipation made under Section 13

4) The Examiner shall make a report to the Controller on the above matters ordinarily within a period of 1 month but not exceeding three months from the date of such reference.

5) The Controller shall dispose the report of the examiner ordinarily within one month from the date of the receipt of such report.

6) This Report is called the First Examination Report *(FER).*

7) The time for putting the application in order for grant is 12 months from the date of FER.

6.2.9 Issuing First Examination Report And Procedures Thereafter:

i. A gist of objections made by the examiner will be communicated to the applicant in the First examination Report (FER). A FER along with the application and specification is sent to the Applicant or his Authorized Agent ordinarily within six months from the date of request for examination or six months from the date of publication, whichever is later?

ii. In case, any other interested person files the request for examination, an intimation of such examination of the application may be sent to such interested person.

iii. If any of the objections require amendment of the application, specification or drawings to ensure compliance with the provisions of the Act or the Rules, the same will be communicated to the applicant along with the FER.

iv. The applicant will be allowed to carry out the necessary amendments of the application, specification or drawings.

v. The amended documents (retyped sheets, if necessary) along with the superseded pages, if any, duly marked, cancelled and initialled by the applicant or his agent will be returned to the Controller. Copies of any pages that have been added or retyped and any drawing that has been added or substantially amended shall be submitted in duplicate.

vi. The amended documents together with the specification will be examined again in the same way as the original specification (S.13 (3)).

vii. The applicant will be given an opportunity of being heard, if he so requests, when the examination report is adverse to him and he contests any of objections or refiles his specification along with his observations regarding amendments of the same (S. 14 & R.24 (B), R28). The request for such hearing should made at least 10 days before the expiry date

~~viii)~~viii. There can be one or more correspondences after the issue of FER. However, the time for meeting the objections and putting the application in order for grant is 12 months from the date of issue of FER (S. 21(1), failing which the application will be abandoned.

ix. Examination procedure carried out under section 12 and 13 shall not be deemed in any way to warrant the validity of any patent, and no liability shall be incurred by the Central Government or any officer thereof because of any such examination or investigation or any report or other proceedings consequent thereon.

6.2.10 Example: In ***1999 (19) PTC 479*** Registration of patent does not entitle any presumption of validity in favour of patent in spite of investigation before its registration—Patent Act, 1970—Section 12,13 & 64.

Held: Section 13(4) of the Patents Act provides that the examination and investigations required under sections 12 & 13 shall not be deemed in any way to warrant the validity of any patent, and no liability shall be incurred by the Central Government or any officer thereof by reason of, or in connection with, any such examination or investigation or any report or other proceedings consequent thereon. Thus, grant of patent in any manner does not guarantee the validity of the patent. Reference may also be made to the provisions of Section 64 of the Patents Act which deals with revocation of patents. It provides that a patent whether granted before or after the commencement of the Act, may, on the petition of any person interested or of the Central Government or on a counter-claim in a suit for infringement of the patent, be revoked by the High Court on the ground that the subject of any claim of the complete specification is not an invention within the meaning of this Act or that the invention so far as claimed in any claim of the complete specification is not new having regard to what was publicly known or publicly used in India before the priority date of the claim or to what was published in India or elsewhere in any of thc documents referred to in Section 13 or that the invention so far as claimed in any claim of the complete specification is obvious or does not involve any inventive step, having regard to what was publicly known or publicly used in India or what was published in India or elsewhere before the priority date of the claim.

Despite all the safeguards and circumspection contemplated in various provisions of the Act against grant of patent in respect of a spurious, purloined or fake invention, the Legislature minced no words in clarifying its intendment that no presumption of validity would attach to a patent granted by the Controller under the Act, notwithstanding examination and investigation made under Sections 12 & 13 there of

6.2.11 Practice for Examination of Patent Application:

Examination of Patent Applications is carried out in the Patent Office as per criteria set up in the EAMINATION FORMAT as follows:

EXAMINATION FORMAT FOR PATENT APPLICATION

PATENT APPLICATION NO. (i) **NORMAL**
(ii) **PCT NATIONAL PHASE**

Kind of Application:

APPLICATION

1. Form of Application -Form 1
2. Name, Nationality and Address of Applicant
3. Title
4. Provisional / Date Complete / Date
5. Names, Nationality & address of –
   (a) Assignor -
      (i) Inventor
      (ii) Applicant in convention country
   (b) The deceased who had right to make application.
6. Endorsement by or assignment from inventor or Applicant in convention country or authority In favour of legal representative.
7. Death Certificate & proof of title Of the legal representative
8. Date & Signature
9. Duplicate
10. Miscellaneous
11. (1) Request for Examination
    No.....
    Date.....
    Filed by.....
    Fee.....
    (2) Pre-grant Opposition
    Name of person making representation
    Date of filing of representation

PCT NATIONAL PHASE

GENERAL

12. Date of Entry in to National Phase (Chapter I/II)
13. International PCT Application No. /Publication no.
14. Date of Earliest priority of filing
15. Entry in National Phase within prescribed time yes / no
16. Whether India Designated/Elected yes / no
17. International Search Report received yes / no
18. Preliminary Examination report received yes / no
19. Miscellaneous yes / no

CONVENTION APPLICATION

20. (1) No. Of Priority
    (2) Priority date/dates
    (3) Application made within 12 months
    From first application in a convention country

21. Certified copy/copies
22. Petition for extension of time
23. Name(s) of applicant(s) in convention country
24. No. of priorities claimed at the time
    of International filing
25. Fee paid for priority/priorities
26. Certified copy/copies filed at the time
    of entry into National Phase, Date of filing of certified copy/copies
27. Translated Priority document filed on_____
28. Certificate of authentication of translation
29. Priority Date/dates
30. Name of Country/Inter Governmental Organisation

AUTHORISATION

31. Name, address and nationality of applicant
32. Name and address of the registered Patent agent/agents
33. Title

34. Date and signature
35. Stamped
36. Miscellaneous

STATEMENT AND UNDERTAKING (Section 8, Rule 12)

37. Prescribed form
38. Name, address and nationality of applicant
39. Title
40. Date and signature
41. Miscellaneous
42. Application, if any, made in foreign countries,
    a. Prior filing - Petition under section 8(1).
    b. Post filing - Extension under rule 138.
    c. Extension under section 8(2).....F(4)

SPECIFICATION

Provisional Specification filed on_____

43. Prescribed form 2
44. Name, address and nationality of the applicants
45. Title
46. Preamble to the description
47. Reference to inventor
48. Reference to drawings
49. Reference to original patent
50. Date and signature
51. Duplicate
52. Miscellaneous

Complete Specification filed on_____

53. Prescribed, form 2
54. Name, address and nationality of applicant
55. Title
56. Preamble to description
57. Reference to drawings
58. Reference to original patent
59. Statement of claims (containing claims)
60. Date and signature
61. Duplicate
62. Miscellaneous
63. Abstract
64. Size of the document
    a. Language
    b. Electronic form
    c. Sequence in Electronic Form
    d. Numbering of pages

DECLARATION OF INVENTORSHIP

65. Prescribed form
66. Name of applicant
67. Name, address and nationality of inventors
68. Date and signature
69. Assent by the inventor

DRAWINGS

70. Not filed in time-post-dating
71. Reproducible
72. Name and signature
73. Number of sheets
74. Figures of drawings
75 Descriptive matter and measurement
76. Duplicate
77. Miscellaneous

GENERAL

78. Request for amending or correcting
    (a) Application
    (b) Specification
    (c) Drawings
79. Request for post-dating of an application

80. Specification and drawings generally unsatisfactory

PROVISIONAL / COMPLETE SPECIFICATION

81. **DESCRIPTION - Clear -**
- (a) Not in clear English
- (b) English equivalent necessary in respect of
- (c) Not clear in respect of where indicated in
- (d) Description in page inconsistent with
- (e) Distinguishing features as compared With prior art given is not clear
- (f) Drawings to be separated from specification

82. **DESCRIPTION - sufficient -**

- (a) Further description necessary
- (b) Revision necessary where indicated
- (c) Drawings required
- (d) Biological materials
  - (i) Deposit in authorised depository Institution
  - (ii) Date of Deposit
  - (iii) Date/number of deposit in the specification
  - (iv) Source/Geographical origin in the specification
- (e) Model or sample required

83. **DESCRIPTION - references -**

- (a) Reference to foreign patent applications/patents
  - (i) Should be replaced by Indian specification;
  - (ii) Or modified by substituting the serial number of the published British specification;
  - (iii) Or replaced or supplemented by equivalent or Supplemented by equivalent description.
- (b) Co-pending application No. Necessary
- (c) Co-pending application in page to be completed
- (d) Prior patent in page insufficient
- (e) Distinguishing features with reference to Prior specification nccessary
- (f) Grant deferred in view of unpublished Co-pending application

84. **DESCRIPTION - Clerical errors -**
- (a) In page to be corrected.

85. **DRAWINGS - clear -**
- (a) Figures not numbered.
- (b) Sectional lines not marked in figures.
- (c) Reference letter (numerals) not marked in figures.
- (d) Same reference letters used for different parts – (in figures)
- (e) Part denoted by reference letter in figure(s) Not same as that denoted by it in page.
- (f) Do / does not clearly illustrate Features described in pages.

86. DRAWINGS - sufficient -
(a) Arrangement described in page or / and
Claimed in claim should be illustrated.

87. **CLAIMS** - clear -
(a) Claims not clear in respect of the expression.
(b) Claims not clearly worded.

88. **CLAIMS - succinct -**
(a) Unnecessary repetition
(b) Verbose
(c) Large number
(d) Claim redundant.

89. **CLAIMS - definitive -**
(a) Claims do not sufficiently define the invention.
(b) Claim not sufficiently definitive in the absence
Of explicit statement of invention.

90. **CLAIMS - consistent -**
(a) Claims not consistent with description in page.
(b) Claims not supported by description.
(c) Claims not fairly based on the matter disclosed
In the specification.

91. **TITLE - appropriate -**
(a) Inconsistent with description and claims

92. **TITLE - precise -**
(a) Not precise.
(b) Not clear in respect of word(s).
(c) Vernacular word to be replaced.
(d) Does not sufficiently indicate the subject.
(e) Suitable amendments indicated.

93. **ABSTRACT**
(a) Title
(b) Concise summary
(c) Size
(d) Reference numerals of the Drawings
(e) Searchable

94. PATENTABILITY AND PRE-GRANT OPPOSITION

(A) Sufficiency of description
(i) Complete Specification does not sufficiently
And clearly describe the invention
(ii) Complete specification does not describe the method by
Which the invention is to be performed.
(iii) Non-disclosure or wrongful mentioning of source and
Geographical origin of biological material

(B) Subject matter
(a) (I) does not constitute an 'invention' under Section 2 (1) (j)
(ii) Inventive step / non obvious
(iii) Industrial application
(b) Claims fall within the scope of Section 3

(i) Invention frivolous / contrary to natural laws
(ii) Contrary to public order / morality
(iii) Prejudice to human / animal / plant life
Or health or environment
(iv) Mere discovery of a scientific principle or abstract
theory or discovery of any living thing or non-living
Substances occurring in nature
(v) Mere discovery of any new property / mere new use
For a known substance / mere use of a known
Process, machine or apparatus
Differing significantly in properties with regard to efficacy?
(vi) Substance obtained by a mere admixture resulting only in the
Aggregation of the properties or a process for producing such
Substance
(vii) the mere arrangement or re-arrangement or duplication
Of known devices each functioning independently
(viii) Method of agriculture / horticulture
(ix) Process for the medicinal / surgical / curative / prophylactic
Diagnostic / therapeutic / other treatment of human beings
Or any process for a similar treatment of animals
(x) Plants and animals in whole or any part thereof including
Seeds, varieties and species / essentially biological processes
For production or propagation of plants and animals
(xi) Computer programme per se other than its technical application to
Industry or a combination with hardware
(xii) Mathematical method / business method / algorithms
(xiii) Literary, dramatic, musical or artistic work or any other aesthetic
Creation including cinematographic works and television productions
(xiv) Mere scheme or rule or method of performing mental act /
Method of playing game
(xv) A presentation of information
(xvi) Topography of integrated circuits
(vie) traditional knowledge or an aggregation or duplication of known
Properties of traditionally known components

(c) Claims not allowable under section 4
(d) Is not proper for a patent of addition
(e) Statement of claim(s) not definitive in view of what
admittedly known, see page of the specification

C. Novelty:

(a) Invention anticipated by
(i)prior publication
(ii)prior claiming
(b) Claim (s) of conflict(s) with claim (s) of
(c) Invention claimed in claim (s) prime facie
lacking in novelty
(d) Specification not clearly worded
(e) Consideration deferred

D. Single Invention:

(a) Claims define a plurality of
distinct inventions.
(b) Each claims relates to an independent
invention
(c) Claim(s) relate (s) to an invention
distinct from the rest

(d) Consideration deferred

95. **IDENTITY - date -**

(a) Not allowable as an earlier application in respect of identical invention was filed in

96. **IDENTITY - Subject matter -**

(a) Does not constitute one invention or a group of invention so as to make a single invention. The application should be divided.

(b) Two or more applications for inventions cognate, additional fee required.

(c) The inventions disclosed in the specification filed with applications made in the convention countries are not so related as to constitute one invention or to a group of invention so as to form a single invention. The application should therefore be divided into separate applications.

(d) The inventions disclosed in the specifications filed with applications made in the convention countries are not so related as to constitute one invention or to a group of invention linked so as to form a single invention but are cognate or of which one is a modification of another accordingly, additional fees in respect of applications should be remitted immediately.

6.2.12 The Controller can take following actions as per Section 15

a) May refuse the application

When the application or specification or any other document filed does not meet the requirements of the Act or the Rules , the Controller can refuse the application for grant of patent by an order either suo-moto or after hearing the party to the application when a request for hearing is requested. The order of the controller is appealable before the Appellate board

b) May require the application to be amended before he proceeds further with the application

The Controller can stay the proceedings towards the grant of patent till requirements under the Act or Rules are met by the applicant to his satisfaction by way of amendments in the application or specification or any document, as the case may be. In case the applicant does not comply with the requirements within the time as prescribed under Sec.21, he may refuse the application.

~~4.14~~6.2.13 Divisional application (S. 16)

4.14.1 When an application made by applicant claims more than one invention, the applicant on his own or to meet the official objection may divide the application and file two or more applications, as applicable for each of the inventions. This type of application, divided out of the parent one, is called a

Divisional Application. The priority date for all the divisional applications will be same as that claimed by the Parent Application (Ante-dating).

4.14.2 The Complete Specification of a divisional application should not include any matter not in substance disclosed in the complete specification of the first application. The reference of parent application should be made in the body of the specification. A divisional application has to be filed before the grant for a Parent application,

6.2.14 Example: In Imperial Chemical Industries Ltd. v. Controller of Patents, (AIR 1978 Cal *77)* An Appellant was granted patent in respect of an invention of a catalyst which is used in the steam reforming of hydrocarbons and achieved results which were not, according to the appellant, possible before the invention. The said invention, as the patent certificate stated, related to the catalyst suitable for use in hydrocarbons steam reforming process.

The High Court considered the following well settled propositions of law:—

(i) A patent must be in respect of an invention and not a discovery.
(ii) There must be one single patent in respect of one single invention.
(iii) A patent may be in respect of a substance or in respect of a-process.
(iv) It is not possible to bifurcate a patent and state that one relates to the substance and the other to the process.
(v) In order to have a complete patent the specifications and claims must be clearly and distinctly mentioned.

~~(iii)~~ (vi) It is the claims and claims, alone which constitute the patent. The High Court held that one cannot bifurcate from the processes, the result produced from such processes. A person having the right to use a process patented under the Act, he also has the right to the product of such process.

~~4.14.3~~6.2.15 Divisional Application : Case Study

Patent Application **No. 251/MUMNP/2005** filed by M/s. BHA Holdings Inc. USA for the *"Retention Device engaged with the filter cartridge for limiting the radial movement of the pleats in the filter media"* as a divisional application of the parent application No. 490/MUMNP/2003.

The said divisional application was rejected by the Controller of Patents vide his order dated 11.01.2007 u/s 15 of the Patents Act, 1970 (as amended).

In the parent case, the *prima facie* objection for plurality of distinct inventions was raised by the Patent Office due to multiple sets of independent claims.

However, the Applicants contested this objection by claiming that these claims relate to a single inventive concept as required under Section 16 (3) of the Act. it was pointed out to the Agents that the same features claimed in claims 1-6 of divisional application were claimed in multiple sets of claims in claims 7-33 of a parent application, which were thus redundant and

accordingly they agreed to delete them. Thus, claims 1-6 only were allowed in the parent case.

Later, in the instant divisional patent application No.251/MUMNP/2005, the Applicants again filed claims 1-33 as were filed in the parent case, which attracted objection under Section 16 of the Act. The Patent Office asked to pinpoint differentiating features claimed in this divisional application with respect to the claims finally allowed in the parent application. The Applicants neither provided a proper reasoning to remove this objection raised under Section 16 (3) nor pinpointed the differentiating features of instantly claimed invention with respect to those allowed in the parent case. The Apparatus claims 1-12 of the instant divisional application correspond to claims 1-6 of the parent application and Method claims 13-19 of the instant divisional application correspond to claims 7-12 of the parent application.

Therefore, the divisional application did not meet the requirement of Section 16 (3) of the Act.

Accordingly, the Controller of Patents ordered refusal to grant letters of Patent for the aforesaid patent application No. 251/MUMNP/2005.

6.2.16 POST DATING OF THE APPLICATION (S. 17)

a) The application for patent may be post-dated to a date not later than six months from the date of application on a request made by the applicant at any time before the grant of patent along with the prescribed fee as given in first schedule. However this provision will not apply if the application is deemed to be abandoned

b) If the application or specification (or drawings if any) is amended under section 15 to comply with the requirements of the Act or the Rules and the Controller feels that post-dating is required, he may direct that application or specification or other documents related thereto be deemed to have been made on the date on which the requirements are complied with or the date on which it is re-filed after complying with the requirements. (S. 17(2)).

6.2.17 Example: *In case of* Standipack Private Limited v. *Oswal Trading Co. Ltd.(*,1999 PTC (19) 479 (Del)). Post-dating of the patent can be done only to the date of filing of the complete specifications. In the present case the Controller of Patents has filed the original records relating to the grant of patent in favour of the plaintiff. The said records reveal that the application for the grant of patent was originally filed by plaintiff on 11-4-1989 and the complete specification was filed on 11-10-1990. The Controller of Patents, however, post-dated the patent to 11-7-1989 although complete specifications followed by the provisional specification was filed on 11-10-1990. Thus the post-dating of the patent by the Controller to 11-7-1989 *prima facie* appears to be in violation of the provisions of section 9 of the Act. The date of the patent, therefore, should have been 11-10-1990. The patent documents referred the validity of the patent for 14 years from 11-7-1990. Thus the validity of the patent has also been ignored by the Controller of Patents. The plaintiff also, during the course of arguments, admitted that complete specifications were submitted on 11-10-1990, which is the date from which the

patent granted would be effective. Thus post-dating the patent to 11-7-1989 appears to be illegal in view of the provisions of section 9(4) of the Patents Act and the provisions of section 17 are subject to section 9.

~~4.166~~.3 ACTIONS TO BE TAKEN IN CASES OF ANTICIPATION [Section: 18]

Relevant Section and Rules

Section 18.

Powers of Controller in cases of anticipation;

(1) Where it appears to the Controller that the invention so far as claimed in any claim of the complete specification has been anticipated in the manner referred to in clause (a) of subsection (1) or sub-section (2) of section 13, he may refuse the application unless
the applicant—

(a) shows to the satisfaction of the Controller that the priority date of the claim of his complete specification is not later than the date on which the relevant document was published; or

(b) amends his complete specification to the satisfaction of the Controller.

(2) If it appears to the Controller that the invention is claimed in a claim of any other complete specification referred to in clause (b) of sub-section (1) of section 13, he may, subject to the provisions hereinafter contained, direct that a reference to that other specification shall be inserted by way of notice to the public in the applicant's complete specification unless within such time as may be prescribed,—

(a) the applicant shows to the satisfaction of the Controller that the priority date of his claim is not later than the priority date of the claim of the said other specification; or

(b) the complete specification is amended to the satisfaction of the Controller.

(3) If it appears to the Controller, as a result of an investigation under section 13 or otherwise,—

(a) that the invention so far as claimed in any claim of the applicant's complete specification has been claimed in any other complete

specification referred to in clause (a) of sub-section (1) of section 13; and

(b) that such other complete specification was published on or after the priority date of the applicant's claim,

then, unless it is shown to the satisfaction of the Controller that the priority date of the applicant's claim is not later than the priority date of the claim of that specification, the provisions of sub-section (2) shall apply thereto in the same manner as they apply to a specification published on or after the date of filing of the applicant's complete specification.

Rule 29:

Procedure in case of anticipation by prior claiming.;

(1) When it is found that the invention so far as claimed in any claim of the complete specification, is claimed in any claim of any other specification falling within clause (b) of sub-section (1) of section 13, the applicant shall be so informed and shall be afforded an opportunity to amend his specification.

(2) If the applicant's specification is otherwise in order for grant and an objection under clause (b) of sub-section (1) of section 13 is outstanding, the Controller may postpone the grant of patent and allow a period of two months for removing the objection.

6.3.1 If the invention is anticipated by prior publication *as per S.13 (1) (a) or S.13(2),* the Controller may refuse the complete specification unless the applicant shows that the priority date of his claim is not later than that of the cited document or amends his complete specification to the satisfaction of the Controller. [S.18 (1) & Rule 28]

6.3.2 If the invention is anticipated by prior claiming as per S.13 (1) (b), the Controller may direct that a reference to that other specification be inserted in the applicant's specification by way of notice to the public unless the applicant shows that the priority date of his claim is not later than that of the claim of cited document or amends the specification to the satisfaction of the Controller. (The Controller need not consider the validity of the prior specification when directing such a reference) [S. 18(2) & Rule29, 30, 31]

Format for incorporation of reference is *"Reference has been directed, in pursuance of section 18(2) of the Patents Act 1970, to the specification filed in pursuance of application no..."* **[Rule 31]**

If the invention is anticipated by prior publication as per S.13(1) (a) and the other complete specification was published on or after the priority date of the applicant's claim, the remedy for the anticipation by prior claiming as explained above will equally apply to this case **(S.18(3)).**

6.4 Actions to be taken in case of potential infringement S.19

Section 19:

Powers of Controller in case of potential infringement;

(1) If, in consequence of the investigations required under this Act, it appears to the Controller that an invention in respect of which an application for a patent has been made cannot be performed without substantial risk of infringement of a claim of any other patent, he may direct that a reference to that other patent shall be inserted in the applicant's complete specification by way of notice to the public, unless within such time as may be prescribed-

(a) the applicant shows to the satisfaction of the Controller that there are reasonable grounds for contesting the validity of the said claim of the other patent; or

(b) the complete specification is amended to the satisfaction of the Controller.

(2) Where, after a reference to another patent has been inserted in a complete specification in pursuance of a direction under sub-section (1)—

(a) that other patent is revoked or otherwise ceases to be in force; or

(b) the specification of that other patent is amended by the deletion of the relevant claim; or

(c) it is found, in proceedings before the court or the Controller, that the relevant claim of that other patent is invalid or is not infringed by any working of the applicant's invention,

the Controller may, on the application of the applicant, delete the reference to that other patent.

Rule 32:
Procedure in case of potential infringement;

If in consequence of an investigation made under section 13, it appears to the Controller that the applicant's invention cannot be performed without substantial risk of infringement of a claim of another patent, the applicant shall be so informed and the procedure provided in rule 29 shall, so far as may be necessary, be applicable.

6.4.1 Also, the Controller has power to direct the insertion (in the specification) of the reference to another patent, which could be infringed in the event of performing the invention of the application, and also for the deletion of such reference from there, on the request from the applicant, when the said referred patent ceases, or revoked or relevant conflicting claim is deleted from the other patent. [S. 19, Rules 32 and 33]

6.4.2 The investigation made under Section 13 is not deemed to be conclusive on the question of anticipation and the Central Government or its Officers incur no liability (S.13(4)).

~~4.17~~6.5 Power of the controller to make orders regarding substitution of applicant

Section 20:

Powers of Controller to make orders regarding substitution of applicants, etc;

(1) If the Controller is satisfied, on a claim made in the prescribed manner at any time before a patent has been granted, that by virtue of any assignment or agreement in writing made by the applicant or one of the applicants for the patent or by operation of law, the claimant would, if the patent were then granted, be entitled thereto or to the interest of the applicant therein, or to an undivided share of the patent or of that interest, the Controller may, subject to the provisions of this section, direct that the application shall proceed in the name of the claimant or in the names of the claimants and the applicant or the other joint applicant or applicants, accordingly as the case may require.

(2) No such direction as aforesaid shall be given by virtue of any assignment or agreement made by one of two or more joint applicants for a patent except with the consent of the other joint applicant or applicants.

(3) No such direction as aforesaid shall be given by virtue of any assignment or agreement for the assignment of the benefit of an invention unless—

(a) the invention is identified therein by reference to the number of the application for the patent; or

(b) there is produced to the Controller an acknowledgement by the person by whom the assignment or agreement was made that the assignment or agreement relates to the invention in respect of which that application is made; or

(c) the rights of the claimant in respect of the invention have been finally established by the decision of a court; or

(d) the Controller gives directions for enabling the application to proceed or for regulating the manner in which it should be proceeded with under sub-section (5).

(4) Where one of two or more joint applicants for a patent dies at any time before the patent has been granted, the Controller may, upon a request in that behalf made by the survivor or survivors, and with the consent of the legal representative of the deceased, direct that the application shall proceed in the name of the survivor or survivors alone.

(5) If any dispute arises between joint applicants for a patent whether or in what manner the application should be proceeded with, the Controller may, upon application made to him in the prescribed manner by any of the parties, and after giving to all parties concerned an opportunity to be heard, give such direction as he thinks fit enabling the application to proceed in the name of one or more of the parties alone or for regulating the manner in which it should be proceeded with, or for both those purposes, as the case may require.

Rule 34:

Manner in which a claim under section 20(1) shall be made;

(1) A claim under sub-section (1) of section 20 shall be made in Form 6.

~~(3)~~(2) The original assignment or agreement or an official copy or notarized copy thereof shall also be produced for the Controller's inspection and the Controller may call for such other proof of title or written consent as he may require.

Rule 35:

Manner in which a request may be made under section 20(4);

(1) A request under sub-section (4) of section 20 shall be made in Form 6.

(2) The request shall be accompanied by proof of death of the joint applicant and a certified copy of the probate of the will of the deceased or letters of administration in respect of his estate or any other document to prove that the person who gives the consent is the legal representative of the deceased applicant.

Rule 36:

Manner of application under section 20(5);

(1) An application under sub-section (5) of section 20 shall be made in Form 6 in duplicate and shall be accompanied by a statement setting out fully the facts upon which the applicant relies and the directions which he seeks.

~~(4)~~(2) *A copy of the application and statement shall be sent by the Controller to every other joint applicant.*

~~a)~~6.5.1 A claim for substituting an applicant(s) has to be made in **Form 6** with the prescribed fee as given in the First schedule along with the original assignment/agreement or an official copy or notarized copy thereof. The Controller may call for other proof of title or written consent of the assignor(s), if required (Rule 34). Accordingly, the Controller, if satisfied, may direct that the application shall proceed in the name of the claimant(s)

~~b)~~6.5.2 By virtue of a written assignment or agreement from the applicant or by operation of law, if the claimant(s) makes the claim that, as and when the patent is granted, he may become entitled to any of the following :-

~~1.~~a. The patent :If there is only one applicant and he assigns the title in the patent, then the Controller, if satisfied, may direct that the application shall proceed in the name of the claimant(s).[S.20(1)]

~~2.~~b. A specific interest in the patent : If there is only one applicant and he passes any of the interests in the patent by way of agreement, then the Controller, if satisfied, may direct that the application shall proceed in the name of the applicant and the claimant(s).

~~3.~~c. An undivided share of the patent :if there are more than one applicants and one applicant assigns his title, then the Controller, if satisfied, may direct that the application shall proceed in the name of the claimant(s) and the other joint applicant(s).

4.d. A specific interest in the undivided share of the patent : If there are more than one applicants and one applicant passes any of the interests in the patent by way of agreement, then the Controller, if satisfied, may direct that the application shall proceed in the name of the claimant(s), that applicant and the other joint applicant(s). (S.20(1).

e)**The claimant may become entitled to any of the above by operation of law also.**

6.5.3The direction to substitute an applicant will not be given unless all the applicants have consented to assign the said rights to the claimant **[S.20(2)].**

6.5.4 Legal assignments **(Rule 34(2))** produced along with Form 6 to make the Controller to give directions, should either have a reference of the patent application number in the assignment or in its absence a separate statement of the assignor that it relates to the same invention for which the patent has been filed **[S.20(3)].**

4.6.5.6 The request by the survivor/survivors for the application for Patent to proceed in their name, when one or more of the joint applicants is dead, has to be in form 6, with the consent of the legal representative(s) of the deceased applicant(s) endorsed on the request, along with a prescribed fee and a proof of death of the joint applicant/s and a document to prove the standing of the person as a legal representative who has signed the endorsement **[S. 20(4) & Rule 35) Also see S. 20(5) & Rule 36]**

6.5.7 In case of opposition proceeding before the controller ,the opposition prove the ground of obtaining then the controller has the power to substitute the name of the opponent instead of the name of the applicant and issue an order to proceed with the application

6.6 Time for putting the application in order for grant in case when there is no pre-grant opposition, Sec.(21)

Relevant Section and Rules

Section 21.

Time for putting application in order for grant;

(1) An application for a patent shall be deemed to have been abandoned unless, within such period as may be prescribed, the applicant has complied with all the requirements imposed on him by or under this Act, whether in connection with the complete specification or otherwise in relation to the application from the date on which the first statement of objections to the application or complete specification or other documents related thereto is forwarded to the applicant by the Controller.

Explanation.;

Where the application for a patent or any specification or, in the case of a convention application or an application filed under the Patent Cooperation Treaty designating India any document filed as part of the application has been returned to the applicant by the Controller in the course of the proceedings, the applicant shall not be deemed to have complied with such requirements unless and until he has re-filed it or the applicant proves to the satisfaction of the Controller that for the reasons beyond his control such document could not be re-filed.

(2) If at the expiration of the period as prescribed under sub section (1);

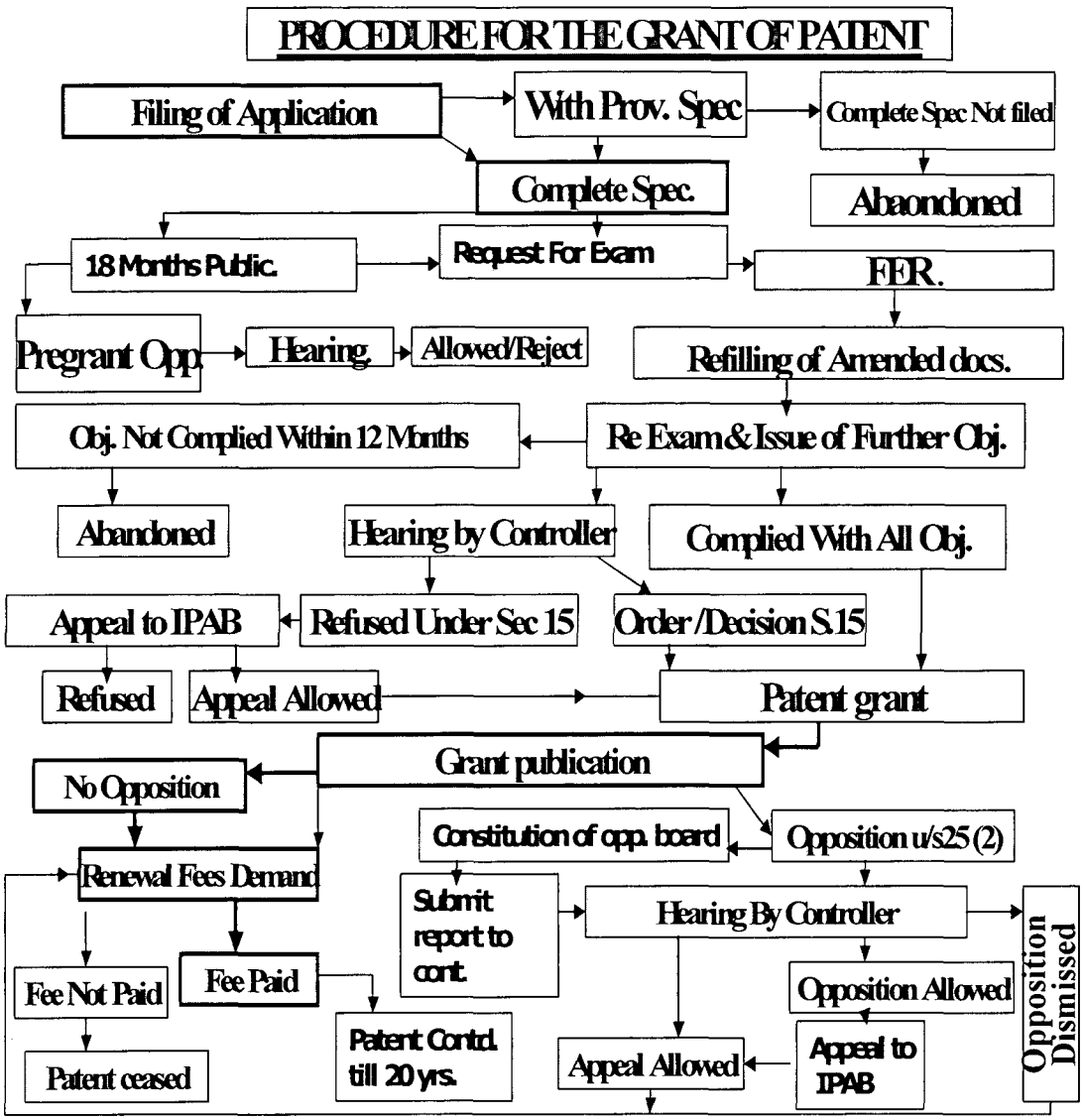
(a) an appeal to the High Court is pending in respect of the application for the patent for the main invention; or

(b) in the case of an application for a patent of addition, an appeal to the High Court is pending in respect of either that application or the application for the main invention, the time within which the requirements of the Controller shall be complied with shall, on an application made by the applicant before the expiration of the period as prescribed under sub-section (1), be extended until such date as the High Court may determine.

(3) If the time within which the appeal mentioned in sub-section (2) may be instituted has not expired, the Controller may extend the period as prescribed under sub-section (1), to such further period as he may determine:
Provided that if an appeal has been filed during the said further period, and the High Court has granted any extension of time for complying with the requirements of the Controller, then the requirements may be complied with within the time granted by the Court.

6.6.1The Patent may be granted and the Letters Patent may be issued by the Controller as soon as possible after the applicant has met with all the official requirements within the period specified in section 21 .If there is an opposition, by way of representation u/s 25(1) and the opposition is disposed off with a direction to amend the application within the time prescribed under the order then the applicant is entitled to amend the specification as required by the controller within the prescribed time.

In case, the applicant fails to meet the requirements as above, the application may be abandoned


PROCEDURE FOR THE GRANT OF PATENT
Filing of Application
With Prov. Spec
Complete Spec Not filed
Complete Spec.
Abaondoned
18 Months Public.
Request For Exam
FER.
Pregrant Opp
Hearing
Allowed/Reject
Refilling of Amended docs.
Obj. Not Complied Within 12 Months
Re Exam & Issue of Further Obj.
Abandoned
Hearing by Controller
Complied With All Obj.
Appeal to IPAB
Refused Under Sec 15
Order /Decision S.15
Refused
Appeal Allowed
Patent grant
Grant publication
No Opposition
Constitution of opp. board
Opposition u/s25 (2)
Renewal Fees Demand
Submit report to cont.
Hearing By Controller
Opposition Dismissed
Fee Not Paid
Fee Paid
Opposition Allowed
Patent Contd. till 20 yrs.
Appeal Allowed
Appeal to IPAB
Patent ceased

CHAPTER VII

OPPOSITION PROCEEDINGS TO GRANT OF PATENT

7.1 PRE-GRANT OPPOSITION BY REPRESENTATION [S. 25(1)]

Relevant Section and Rules :

Section 25: Opposition to the patent –

(1): Where an application for a patent has been published but a patent has not been granted, any person may, in writing, represent by way of opposition to the Controller against the grant of patent on the ground -

~~a.~~(a)that the applicant for the patent or the person under or through whom he claims, wrongfully obtained the invention or any part thereof from him or from a person under or through whom he claims;

~~b.~~(b)that the invention so far as claimed in any claim of complete specification has been published before the priority date of the claim –

i) in any specification filed in pursuance of an application for a patent made in India on or after the 1st day of January, 1912; or

ii) in India or elsewhere, in any other document

iii) Provided that the ground specified in sub-clause (ii) shall not be available where such publication does not constitute an anticipation of the invention by virtue of sub-section (2) or sub-section (3) of section 29;

~~c.~~(c)That the invention so far as claimed in any claim of the complete specification is claimed in a claim of a complete specification published on or after the priority date of the applicant's claim and filed in pursuance of an application for a patent in India, being a claim of which the priority date is earlier than that of the applicant's claim

~~d.~~(d)That the invention so far as claimed in any claim of the complete specification was publicly known or publicly used in India before the priority date of that claim

Explanation: - For the purpose of this clause, an invention relating to a process for which a patent is claimed shall be deemed to have been publicly known or publicly used in India before the priority date of the claim if a product made by that process has already been imported into India before that date except where such importation has been for the purpose of reasonable trial or experiment only;

~~e.~~(e)*That the invention so far as claimed in any claim of the complete specification is obvious and clearly does not involve any inventive step having regard to the matter published as mentioned in clause (b) or having regard to what was used in India before the priority date of the applicant's claim;*

~~f.~~(f) *That the subject matter of any claim of the complete specification is not an invention within the meaning of this Act, or is not patentable under this Act*

~~g.~~(g)*That the complete specification does not sufficiently and clearly describe the invention or the method by which it is to be performed*

~~h.~~(h)*That the applicant has failed to disclose to the Controller the information required by section 8 or has furnished the information which in any material particular was false to his knowledge*

~~i.~~(i) *That in the case of convention application, the application was not made within twelve months from the date of the first application for protection for the invention made in a convention country by the applicant or a person from whom he derives title*

~~j.~~(j) *That the complete specification does not disclose or wrongly mentions the source or geographical origin of biological material used for the invention*

~~k.~~(k)*That the invention so far as claimed in any claim of the complete specification is anticipated having regard to the knowledge, oral or otherwise, available within any local or indigenous community in India or elsewhere*

Rule 55:

(1) Representation for. opposition under sub-section '[(!) of section 25 shall be filed at the appropriate office and shall include a statement and evidence, if any, in support of the representation and a request for hearing if so desired.

(1A) Notwithstanding anything contained in sub-rule (1), no patent shall be granted before the expiry of a period of six months from the date of publication of the application under section 11A.

(2) The Controller shall consider such representation only when a request for examination of the application has been filed.

(3) On consideration of the representation if the Controller is of the opinion that application for patent shall be refused or the complete specification requires amendment, he shall give a notice to the applicant to that effect along with a copy of such representation.

(4) On receiving the notice under sub-rule (3), the applicant shall, if he so desires, file his statement and evidence, if any in support of his application within three months from the date of the notice.

(5) On consideration of the statement and evidence filed by the applicant, the Controller may either refuse to grant a patent on the application or require the complete specification to be amended to his satisfaction before the patent is granted.

(6) After considering the representation and submission made during the hearing if so requested, the Controller shall proceed further simultaneously either rejecting the representation and granting the

patent or accepting the representation and refusing the grant of patent on that application, ordinarily within one month from the completion of above proceedings

7.1.1 Grounds for Pre-grant Opposition by way of Representation u/s 25(1) are summarized as follows:

a) Wrongfully obtaining

b) Prior publication / prior claiming

c) Prior claiming in India

d) Prior public knowledge or public use in India

e) Obviousness and lack of inventive step

f) Not an invention or the invention not patentable

g) Insufficient description of the invention

h) Failure to disclose information or furnishing false information relating to foreign filing

i) Convention application not filed within the prescribed time

j) Incorrect mention of source/geographical origin of biological material

k) Invention anticipated with regard to traditional knowledge of any community , anywhere in the world

No ground other than the statutory grounds as above can be taken for opposing the Grant of Patent under section 25(1)

7.1.2. Proceedings under Pre-Grant Opposition:

1. Any person can file opposition by way of representation to the Controller against the grant of patent, at the appropriate office, before the grant of patent on any of the above-mentioned grounds.

2. The Controller shall not grant the patent before the expiry of 6 months from the date of publication under section 11 A. Therefore, a person should try to file such representation within the assured period of 6 months from the date of publication under section 11 A.

3.The representation shall include a statement and evidence, if any, in support of such representation and a request for hearing, if so desired

4.The Controller shall consider the representation only after a Request for Examination for that application has been filed.

5.On consideration of representation, if the Controller is of the opinion that the application shall be refused or the complete specification requires amendment, he shall give notice to the applicant to that effect along with the copy of such representation.

6.The applicant shall, if he so desires, give reply to that representation along with his statement and evidence, if any, in support of his application within three months form the date of the notice.

7.The Controller shall consider the statement and evidence filed by the applicant and may either refuse the grant of patent or ask for amendment of the complete specification to his satisfaction before the grant of patent.

8.After considering the representation and submission made during the hearing, if so requested, the Controller shall proceed further simultaneously, either rejecting the representation and granting the patent or accepting the representation and refusing the grant, ordinarily **within one month** from the completion of the above proceedings.

Example1:

Case study of Pre-Grant Opposition under section 25(1) :

- **Application No.1602/MAS/1998**
- **M/s Novartis AG, Switzerland v. Controller of Patents, India**

1. **An application for patent was filed in India on July 17, 1998 (at Patent Office, Chennai) by M/s Novartis AG, Switzerland**, claiming Switzerland priority date of July 18,1997 for an invention titled **"Crystal Modification of A N-Phenyl-2-Pyrimidineamine derivative, processes for its manufacture and its use"** and the same was allotted the **Application No.1602/MAS/1998**.

2. Upon publication, the grant of patent was opposed by way of representation u/s 25(1) by M/s Natco Pharma Ltd., India on 26/05/2005 and they also requested for hearing. The grounds for opposition were i) Anticipation by Prior Publication ii) Lack of inventive step iii) Non-patentability u/s 3(d) of the Patents Act and iv) Wrongfully claiming the Priority.

3. Applicant filed the reply statement with evidence on 25/07/2005 and also asked for hearing.

4. The Controller conducted the hearing and considered various grounds for opposition in the light of submissions by both the parties and concluded as follows:

5 (i) **Anticipation by Prior Publication**:

The title compound commercially, called imatinib mesylate, which has been claimed by the applicant is already known in the US Patent No.5521184 (1993 Patent) The 1993 Patent discloses methanesulphonic acid as one of the

salt –forming groups and also states that the required acid additions salts are obtained in a customary manner. Further ,claims 6to 23 of the 1993 Patent claim a pharmaceutically acceptable salt of the base compound.. Another Document, "Nature Medicine" (May 5, 1996) also describes the title compound. Also the compound , imatinib mesylate salt inherently existed in the β-crystalline form, which is most stable form of the salt. This fact is also clear from the results of laboratory experiments conduced by two reputed government institutions, namely, Indian Institute of Chemical Technology, Hyderabad and Indian Institute of Technology, Delhi, . Hence, the claims of the present application for the product and process in respect of the title compound stand anticipated by Prior Publication

ii) **Lack of inventive step:**

Since the 1993 Patent disclosed the free base of the base compound, it was obvious for a person skilled in the art to prepare the corresponding pharmaceutically acceptable salts. The studies by the two laboratories mentioned above clearly demonstrated that the salt prepared using teachings and instructions of the 1993 Patent inherently exists in β-crystalline form. Hence the product claims are obvious over the aforesaid disclosure in the prior art.

iii) **Non-patentability u/s 3(d) of the Patents Act:** As per section 3(d), any salt or polymorph or derivative of the known substance is not patentable unless such salt or polymorph or derivative shows enhanced efficacy of the substance. As regards efficacy, the patent specification itself states that, wherever β-crystals are used, the imatinib free base or other salts can be used. The affidavit submitted by the technical expert on behalf of the applicant demonstrated that the relative bioavailability of the free salt with that of β-crystal form of imatinib mesylate differ only by 30% and accounted this difference to their solubility in water. Thus, the present specification does not bring out any improvement in the efficacy of the β-crystal form over the known substances ; rather its states that the base compound can be used equally in the treatment of diseases or in the preparation of pharmacological agents wherever the β-form is used. Thus, the product claim amounts to a mere discovery of the new form of the known substance. Hence, the subject matter of this application is not patentable u/s 3(d) of the Patents Act, 1970, as amended by Patents (Amendment) Act, 2005.

iv) **Wrongfully claiming the Priority**:

The application filed in India has claimed the Swiss priority dated 18/07/1997, but Switzerland was not an convention country on that date. It became the convention country only in September,1998. Hence, no priority of Swiss application can be claimed in respect of the present application.

Decision:

In view of the above findings and arguments made by both the parties during the hearing , the Learned Controller ruled that the Patent Application no.1602/MAS/1998 cannot proceed for grant of patent.

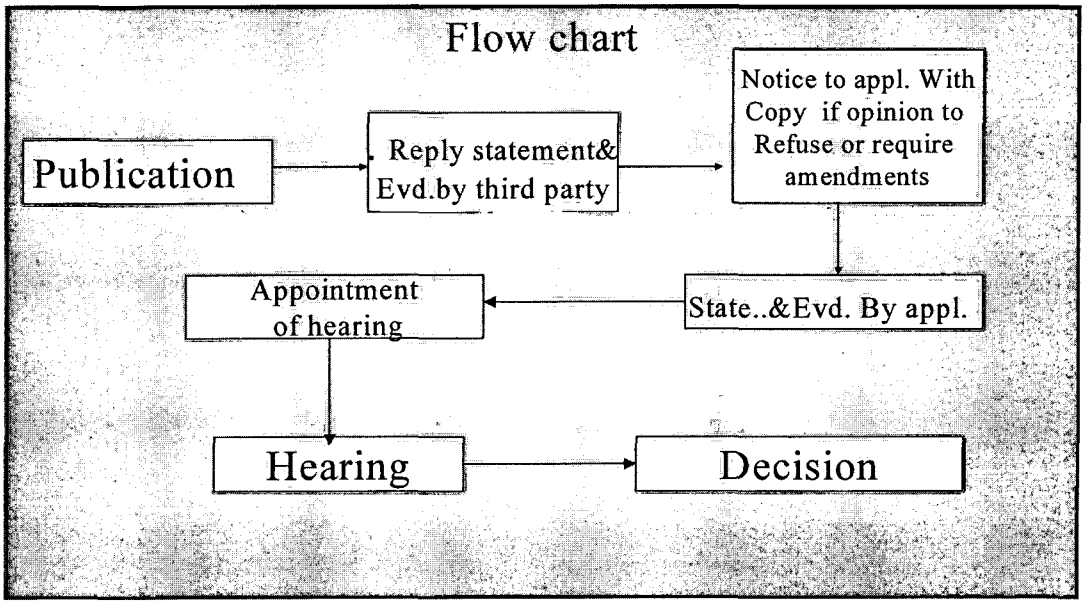
Example 2:

In case of application *No. IN/PCT/2002/00020/DEL, U/S 25(1)* , it was concluded that invention as claimed in finally revised claims 1 to 49 in the Patent application no. IN/PCT/2002/00020/Del does not involve any "inventive step" having regard to the prior art citations JP-8059512 published on 05/03/1996 and US Patent 5,885,617 published on 23/03/1999. Therefore it cannot be considered as an invention under section 2(l)(j) of the Patents Act. As it is a mere admixture and therefore not patentable under section 3(e) of the Patents Act.

It was held that "the selection of particular range of ingredients from the ranges already known prior art in this case cannot amount to establish the inventive step and The variations in the amounts of the known ingredients appear merely workshop improvements achieved by a person skilled in the art without performing any substantial experiments and can not be said a technical advancement of an existing knowledge which is required by the definition of the "inventive step" as mentioned in section 2(l)(ja) of the Patents Act, 2005." and for the ground u/s 3(e) that
"The existence of already known characteristics of composition with known ingredients cannot be termed as synergy among the ingredients of claimed composition"

Further Patent Application Nos. 1903/MAS/1996, 1904/MAS/1996 and 912/MAS/1997, were refused under the proceedings of section 25(1) on the grounds of prior publication and patent application no. 1903/MAS/1996 was refused on additional ground of insufficiency of disclosure.

Procedure for Opposition U/S 25(1)



7.2 POST-GRANT OPPOSITION [S. 25(2)]

Relevant Section and Rules :

Section 25: Opposition to the patent. -

(2): *At any time after the grant of patent but before the expiry of a period of one year from the date of publication of grant of a patent, any person interested may give notice of opposition to the Controller in the prescribed manner on any of the following grounds, namely:--*

(a) that the patentee or the person under or through whom he claims, wrongfully obtained the invention or any part thereof from him or from a person under or through whom he claims;

(b) that the invention so far as claimed in any claim of the complete specification has been published before the priority date of the claim;

(i) in any specification filed in pursuance of an application for a patent made in India on or after the 1st day of January, 1912; or

(ii) in India or elsewhere, in any other document:

Provided that the ground specified in sub-clause (ii) shall not be available where such publication does not constitute an anticipation of

the invention by virtue of sub-section (2) or sub-section (3) of section 29;

(c) that the invention so far as claimed in any claim of the complete specification is claimed in a claim of a complete specification published on or after the priority date of the claim of the patentee and filed in pursuance of an application for a patent in India, being a claim of which the priority date is earlier than that of the claim of the patentee;

(d) that the invention so far as claimed in any claim of the complete specification was publicly known or publicly used in India before the priority date of that claim.

Explanation.—For the purposes of this clause, an invention relating to a process for which a patent is claimed shall be deemed to have been publicly known or publicly used in India before the priority date of the claim if a product made by that process had already been imported into India before that date except where such importation has been for the purpose of reasonable trial or experiment only;

(e) that the invention so far as claimed in any claim of the complete specification is obvious and clearly does not involve any inventive step, having regard to the matter published as mentioned in clause (b) or having regard to what was used in India before the priority date of the applicant's claim;

(f) that the subject of any claim of the complete specification is not an invention within the meaning of this Act, or is not patentable under this Act;

(g) that the complete specification does not sufficiently and clearly describe the invention or the method by which it is to be performed;

(h) that the patentee has failed to disclose to the Controller the information required by section 8 or has furnished the information which in any material particular was false to his knowledge;

(i) that in the case of a patent granted on a convention application, the application for patent was not made within twelve months from the date of the first application for protection for protection for the invention made in a convention country or in India by the patentee or a person from whom he derives the title

(j) that the complete specification does not disclose or wrongly mentions the source and geographical origin of biological material used for the invention

(k) that the invention so far as claimed in any claim of the complete specification was anticipated having regard to the knowledge, oral or

otherwise, available within any local or indigenous community in India or elsewhere,

but on no other ground.

(3): (a) Where any such notice of opposition is duly given under sub-section (2), the Controller shall notify the patentee.

(b) On receipt of such notice of opposition, the Controller shall, by order in writing, constitute a Board to be known as the Opposition Board consisting of such officers as he may determine and refer such notice of opposition along with the documents to that Board for examination and submission of its recommendations to the Controller.

(c) Every Opposition Board constituted under clause (b) shall conduct the examination in accordance with such procedure as may be prescribed.

(4) On receipt of the recommendation of the Opposition Board and after giving the patentee and the opponent an opportunity of being heard, the Controller shall order either to maintain or to amend or to revoke the patent.

(5) While passing an order under sub-section (4) in respect of the ground mentioned in clause (d) or clause (e) of sub-section (2), the Controller shall not take into account any personal document or secret trial or secret use.

(6) In case the Controller issues an order under sub-section (4) that the patent shall be maintained subject to amendment of the specification or any other document, the patent shall stand amended accordingly.

Rule 55A:

The notice of opposition to be given under sub-section (2) of section 25 shall be made in Form 7 and sent to the Controller in duplicate at the appropriate office.

Rule 56:

(1) On receipt of' notice of opposition under rule 55A, the Controller shall, by order, constitute an Opposition Board consisting of three members and nominate one of the members as the Chairman of the Board.

(2) An examiner appointed under sub-section (2) of section 73 shall be eligible to be a member of the Opposition Board.

(3) The examiner, who has dealt with the application for patent during the proceeding for grant of patent thereon shall not be eligible as member of Opposition Board as specified in sub-rule (2) for that application.

(4) The Opposition Board shall conduct the examination of the notice of opposition along with documents filed under rules 57 to 60 referred to under sub-section (3) of section 25, submit a report with reasons on each ground taken in the notice of opposition with its joint recommendation within three months from the date on which the documents were forwarded to them.

Rule 57:

The opponent shall send a written statement in duplicate setting out the nature of the opponent's interest, the facts upon which he bases his case and relief which he seeks and evidence, if any, along with notice of opposition and shall deliver to the patentee a copy of the statement and the evidence, if any.

Rule 58:

(1) If the patentee desires to contest the opposition, he shall leave at the appropriate office a reply statement setting out fully the grounds upon which the opposition is contested and evidence if any, in support of his case within a period of two months from the date of receipt of the copy of the written statement and opponent's evidence if any by him under rule 57 and deliver to the opponent a copy thereof.

(2) If the patentee does not desire to contest or leave his reply and evidence within the period as specified in sub-rule (1), the patent shall be deemed to have been revoked.

Rule 59:

The opponent may, within one month from the date of delivery to him of a copy of the patentee's reply statement and evidence under rule 58, leave at the appropriate office evidence in reply strictly confined to matters in the patentee's evidence and shall deliver to the patentee's a copy of such evidence.

Rule 60:

No further evidence shall be delivered by either party except with the leave or directions of the Controller :
Provided that such leave or direction is prayed before the Controller has fixed the hearing under rule 62.

Rule 61:

~~(2)~~(1) Copies of all documents are referred to in the notice of opposition or in any statement or evidence filed in connection with the opposition and authenticated to the satisfaction of the Controller, shall be simultaneously furnished in duplicate unless the Controller otherwise directs
~~(3)~~(2) Where a specification or other document in a language other than English is referred to in the notice, statement or evidence, an attested translation

thereof, in duplicate, in English shall be furnished along with such notice, statement or evidence, as the case may be.

Rule 62:

(l) On the completion of the presentation of evidence, if any, and on receiving the recommendation of Opposition Board or at such other time as the Controller may think fit, he shall fix a date and time for the hearing of the opposition and shall give the parties not less than ten days' notice of such hearing and may require members of Opposition Board to be present in the hearing.

(2) If either party to the proceeding desires to be heard, he shall inform the Controller by a notice along with the fee as specified in the First Schedule.

(3) The Controller may refuse to hear any party who has not given notice under sub-rule (2).

(4) If either party intends to rely on any publication at the hearing not already mentioned in the notice, statement or evidence, he shall give to the other party and to the Controller not less than five days' notice of his intention, together with details of such publication.

(5) After hearing the party or parties desirous of being heard, or if neither party desires to be heard, then without a hearing, and after taking into consideration the recommendation of Opposition Board, the Controller shall decide the opposition and notify his decision to the parties giving reasons there for.

Rule 63:

If the patentee notifies the Controller that he desires to withdraw the patent after notice of opposition is given, the Controller, depending on the merits of the case, may decide whether costs should be awarded to the opponent.

Section 150:

If any party by whom notice of any opposition is given under this Act or by whom application is made to the Controller for the grant of a licence under a patent neither resides nor carries on business in India, the Controller may require him to give security for the costs of the proceedings, and in default of such security being given may treat the opposition or application as abandoned.

7.2.1 Grounds for Post-grant Opposition u/s 25(2) are summarized as follows:

a) Wrongfully obtaining

b) Prior publication / prior claiming

c) Prior claiming in India

d) Prior public knowledge or public use in India

e) Obviousness and lack of inventive step

f) Not an invention or the invention not patentable

g) Insufficient description of the invention

h) Failure to disclose information or furnishing false information relating to foreign filing

i) Convention application not filed within the prescribed time

j) Incorrect mention of source/geographical origin of biological material

k) Invention anticipated with regard to traditional knowledge of any community , anywhere in the world

7.2. 2 Proceedings under Post Grant Opposition [S 25(2)]

1. Any interested person can oppose the grant of Patent under section 25(2) by giving a notice to the Controller, within one year form the date of publication of grant of a patent in the official journal.

   Person interested [S. 2(1) (t)] includes a person engaged in, or in promoting research in the same field as that to which the invention relates. Any person including an organization that has a manufacturing or trading interest in the goods connected with the patented article or who has a financial interest in manufacturing such goods or who possesses patents relating to the same subject, is considered as person interested

2. The notice of opposition shall be made in Form 7 and sent to the Controller in duplicate at the appropriate office along with the prescribed fee given in first schedule. The notice of opposition shall be accompanied by a written statement (in duplicate) stating out the nature of opponent's interest, the facts upon which he bases his case and the relief which he seeks and evidence, if any, in duplicate in support of his case. **(Rule 57).** The opponent shall deliver to the patentee a copy of the statement and the evidence, if any, filed by him along with the notice of opposition.

3. The Controller shall notify the patentee regarding the filing of the opposition.

4. **Opposition Board:** On receipt of the notice of opposition under rule 55A, the Controller, by order, shall constitute an Opposition Board which will consist of three examiners as members, other than the examiner who has examined the application. The Controller shall nominate one of the members as the chairman of the Board.

5. If the patentee desires to contest the opposition, he shall send the reply statement at the appropriate office giving grounds for contesting the opposition and evidence, if any, in support of his case within a period of 2 months from the date of receipt of a copy of the written statement and opponent's evidence

by him **[Rule 58]**. The patentee shall deliver to the opponent a copy of reply statement and evidence. **(Rule 58).**

6. If the patentee does not desire to contest or fails to send his reply and evidence within the specified period as above, the patent shall be deemed to have been revoked **[Rule 58 (2)].**

7. The opponent may file the evidence in reply within one month form the date of delivery to him a copy of reply statement and the evidence by the patentee; such a reply evidence by the opponent must be strictly confined to the matters in the patentee's evidence **(Rule 59).** Also, the opponent shall deliver to the patentee a copy of his reply evidence.

8. No further evidence shall be delivered by either party except with the leave or direction of Controller **(Rule 60).** Such a leave or direction shall be prayed before the date of the hearing has been fixed by the Controller.

9. The Opposition Board shall examine the notice of opposition and documents filed under **Rules 57 to 60** and submit a report with reasons on each ground within 3 months from the date on which the documents were forwarded to them with its joint recommendation.

10. On receipt of the recommendations of the opposition board along with all evidence filed by both the parties, the Controller shall fix a hearing but at least ten days notice should be given to both the parties **(Rule 62)**. The Controller may require members of the Opposition Board to be present in the hearing.

11. If any party desires to be heard he shall make a request to the Controller along with prescribed fees given in first scheduled.

12. After hearing and taking in to account the recommendations of opposition board, the Controller will decide whether costs should be awarded to the opponent.

7.2.3 Cases reported for the post-grant opposition held on various grounds of section 25 (2) of Indian Patents Act are as mentioned below :

Example: 1

In the matter of Patent No.187163, (581/BOM/1999), the opposition was lodged on the ground of obtaining and request was made to mention the opponent's name as an inventor. The opponents who was working as a Research Assistant and whose job was that of laboratory technician and not as scientist did not produce any substantial evidence or witnesses to substantiate his claim as an inventor. For naming the inventor, he must have provided ideas to produce 'germ of invention' and made intellectual contribution in achieving the final result of research leading to a patent. One or more person involved to arrive at the conception or realization

of the final product or process or merely involved in carrying out experiments does not mean that they are inventors. The inventor for the purpose of Patent law is the actual deviser of what is being claimed. So the opponent failed to prove this ground. (Wrongfully Obtaining)

Example 2 :

In the matter of Patent No.- 173953 (223/BOM/1991), the invention related to "Process for making a soap composition containing glycerol". The opposition was lodged on the ground of prior publication u/s 25 (1)(b), prior public knowledge 25 (1)(d), obviousness, u/s 25 (1)(e), not an invention within the meaning of the Act u/s 25 (1)(f) and does not sufficiently define the invention u/s 25 (1)(g).

It was held that the ingredients recited in the principal claim have a very specific and narrow range of proportions, which are not taught by cited documents. Cited document also do not teach how to obtain the right balance of salt and glycerol in order to avoid a soap which is too hard or too soft and also do not mention about balancing quantities of glycerol or salt against the quantities of total fatty matter. The alleged invention mentions the prior art, problems associated with it, results of various experiments, and best method of working examples. Considering all these factors it was judged that the opponents had failed to establish the above grounds and opposition was rejected

Example3 :

In the matter of Patent No.- 183458 (454/BOM/1998); the invention related to "A process for the preparation of a therapeutic Anti-inflammatory and analgesic composition containing Nimesulide for use transdermally" Opposition was lodged on the ground of prior publication Under Section 25 (1)(b), prior public knowledge Under Section 25(1)(d), Obviousness Under Section 25 (1)(e), not an invention within the meaning of the Act Under Section 25 (1)(f).

Comparison of the alleged invention 183458 with the Sri Lanka's Patent 11012 & Nigerian Patent RP 12829 clearly shown that it does not pass the test of the novelty It is sufficient to destroy the novelty of the claimed process that this process and the known process are identical with respect to the starting material and reaction condition since process as identical in these features must inevitably yield identical products. It was held that in view of the cited Srilanakan & Nigerian Patents the alleged invention stand anticipated as cited document has disclosed the invention or disclosed information in such a way as to make it part of the state of the art.

Grant of Patent was refused on the above grounds.

Example 4 :

In the case of Gujrat Reclaim & Rubber Products Ltd V Kamani Metallic Oxides Ltd1983 (3) PTC 105 (PO), a notice of opposition to the grant of a patent to M/s. Kamani Metallic Oxides Ltd., Bombay, for their patent No. 145917, application number 43/BOM/1976 , for an invention titled "A process for separation of rayon or nylon fibres from cracked

waste tyres and an apparatus thereof" was filed by M/s. Gujarat Reclaim & Rubber Products Ltd., Bombay, on 15-6-1979 having regard to the prior art citations JP-8059512 published on 05/03/1996 and US Patent 5,885,617 published on 23/03/1999.

Opposition to grant of patent was on the grounds of prior publication, prior public knowledge and prior public use, lack of inventive step and insufficiency of description .

It is held that the opponents being engaged in the manufacture of reclaimed rubber in which cracked waste of automobile tyre and such other rubber waste are used and have a manufacturing unit, the opponent are held as 'persons interested' as stipulated in section 25 of the Act. Opponents deposed in support of the opposition that the types of standard machineries used for carrying out the process of separating the rubber particles from fibrous materials and the alleged invention disclosed in the applicants' complete specification has been anticipated by the Exhibits. In the circumstances, a rubber technologist would know its application to cracking of rubber for separation of fibre from rubber and particularly from waste tyres and in fact it has been used for said purpose for many years.

Applicants contested all the arguments of opponents and argued that the opponents have confused the issue by saying that something used in some point of time in the reclamation industry has been claimed by the applicants. He said that applicants' invention lies in the process and apparatus for the separation of fibre from cracked tyres waste i.e. a narrow aspect of dealing with the wider subject of rubber reclamation. So far as the document relating to reclaim from natural and synthetic rubber scrap is concerned, the original which was a confidential document ,and therefore, it has not been published and which is not open to public. On a scrutiny of this document the court observed that the disclosure related to the general process for reclaiming of rubber from natural and synthetic rubber scrap and slow grinder discs for precracking.

The process consisting of three stage viz. cracking, fabric separation and grinding the details given there are applicable generally in a rubber reclaiming process. The invention disclosed in the applicants' specification related to an improved process for the removal of fibre from cracked automobile tyre wastes i.e. the second aspect of the above said three stages process. The steps involved in the process claimed in the complete specification are not found in the said document. No details have been given in the publication about the process and apparatus for removal of fibre from tyre wastes, as has been disclosed in the applicants' specification. Accordingly, the disclosure contained in the said document, even if it is considered to have been published before the priority date of the applicants, the application does not anticipate the applicants' process and apparatus..

Hence, the opponents failed to establish the ground of prior publication. Similarly the opponents also failed under the ground of prior public knowledge and prior public use as the documents relied upon by the opponents are not relevant as they do not anticipate the applicant's invention. The opponents failure to provide any other evidence in support of their contention as to obviousness and lack of inventive step failed them on this ground also. Hence, there being no force in their other grounds of opposition, the opposition is dismissed .

It was held for the ground under section 2 (1)(j) that "the selection of particular range of ingredients from the ranges already known in the prior art in this case

cannot amount to establish the inventive step and variations in the amounts of the known ingredients appear merely workshop improvements achieved by a person skilled in the art without performing any substantial experiments and can not be said a technical advancement of an existing knowledge which is required by the definition of the "inventive step" as mentioned in section 2(1)(ja) of the Patents Act, 2005."

Example 5 :

In the matter of *Thermax Private Limited* v. *Deccan Sugar Industries,* (1987 PTC 137.) Opponents in their written statement of opposition made certain allegation which can be construed to be in support of this ground of opposition, namely, unfair description. The opponents in their written statement of opposition at page 3 para (j) thereof made certain allegations about description wherein they alleged that the specification contained several process variations. What is stated by the opponents during hearing can be construed as an implication of their written statement. Further, during hearing, the applicants were at liberty to deal with each of the opponents' allegations separately and elaborately which they have not done. The opponents clearly proved the deficiencies in the description. Hence, the ground of unfair description is established. Opponents have therefore succeeded in this ground.

Example 6 :

In the matter of *Jagadish Mohanlal Joshi V/s. Ghodavat Pan Masala Products P. Ltd.*_Patent No. 188090 (application no. 166/BOM/1997) Among other grounds, the "insufficiency of description" was a ground for opposition under Section 25(1)(g), citing "If the applicant does not give prior art details in the specification it would mislead the controller and the public, mouth refreshing preparations with tobacco and without tobacco are known in the art, and the applicant is not entitled for a patent unless he shows that his process is an improvement over the earlier process. For this purpose, when 47 RPC 289 was cited submitting that the patent should justify clearly why a particular selection is made, the applicant submitted that the "Non disclosure of prior art does not result in insufficiency of description, the disclosure should enable the skilled person to exercise the invention which the applicant did, and further he deemed the impugned invention was a selection patent". The Controller agreed with the applicant's submission and upheld the patent and dismissed the opposition.

Example 7 :

In the matter of Patent No. 176382(322/BOM/1992) filed by M/s Hindustan Lever Limited titled " Toilet soap bars and the process of manufacturing the same" on 14/10/1992 having two priorities of GB dated 14/10/1991 and 14/07/1992. The Patent was granted on 18th May, 1996 and was opposed under Section 25 by M/s Godrej Soaps Limited.

~~3.~~2. Grounds of Opposition:

- Prior publication section 25 (1) (b)
- Prior public use and prior public knowledge section 25 (1) (d)
- obviousness and lack of inventive step section 25 (1) (e)
- Not an invention or not a patentable invention section 25 (1) (f)
- insufficiency and clarity of description section 25 (1) (g)
- "The applicant has failed to disclose to the controller the information required by section 8 or has furnished the information which in any material particular was false to his knowledge" section 25 (1) (h)

4.3. Proceedings: The case was heard by the controller on 19th Sep, 2003

Opponents relied upon following documents
i) Exhibit A: Page 214 of soap Technology for the 1990's edited by luis spitz.
ii) Exhibit B: Indian standard Bathing bar specification
iii) European Patent No. EP0363215 and
iv) An expert's evidence

After the hearing it was concluded that that teachings of the exhibits were either not pertinent or insufficient to prove the grounds and the opponents could not prove any of the above grounds of opposition .
Applicants made amendments in the description and claims at the time of hearing to make their point clear and to overcome the opponents allegations. As all the amendments were within the scope of invention and have support in the description, these amendments in the claims were allowed

Decision : After considering notice of opposition, statements of both the parties, evidences from both opponents & applicants and hearing, the opposition was dismissed

Example 8 :

In the matter of Patent No. 179304 (124/Cal/93)filed by M/s. Rickitt & Colman of India Ltd) for "A Mosquito/Insect Repellant Device" was opposed by Godrej Hi Care Ltd under Section 25 of the Act. Hearing was held on 10th January, 2001

The applicants' invention related to a mosquito/insect repellent device comprising the: (i) a bottom cover (ii) a positive temperature co-efficient (PTC) thermister heater assembly and iii) a top cover having opening for insertion of mats for placement on said heater assembly

The proceedings of the opposition took place to decide whether the applicant's devices involve any inventive step and the opponents lead any evidence as to patentability The opponents have challenged the alleged application for Patent No. 179304 on the grounds of Section 25 namely, anticipation by prior publication- clause (b) , anticipation by prior claiming - clause (c), prior public knowledge or public use- clause (d) & obviousness and lack of inventive step- clause (e)

Opponents relied upon citation of Registered Design No.56444, photographs of Registered Design No. 159918 dated 5th July, 1988 and advertisement in News paper with photographs of mosquito repellent with extended cord in the brand name

of 'Good Night' dated 06.08.1990 (Ex-Cl), News paper clipping of cordless 'Good Night' dated 15.12.1989 (Ex-C2), copy of letter with photograph of 'Good Night' of Creative Unit Private Ltd. Advertising & Marketing to Godrej Hi Care Ltd. dated June 7, 1999 regarding launch date of "Good Night Cordless Machines" (Ex-C3). 5th July, 1983 & 5,038,974 dated 6th August, 1991.

Proceedings:

It can not be concluded that the cited documents on Patents and Designs can establish anticipation by prior publication, as by combining the integers of the mosquito repellent from the cited patent & design documents is not resulting the identical article as produced by the alleged invention.

No document has been produced or referred by the opponents regarding any claim made by the applicants containing a subject of a claim of earlier priority date in a complete specification published after the priority date of applicants' claim. The opposition therefore can not stand based on the ground of prior claiming.

While considering ground under Section 25(l)(e) i.e. obviousness and the lack of inventive step, the Tribunal considered and analysed the difference between cited documents and the opposed specification to have any relevance regarding obviousness and lack of inventive step

The device 'Mosquito Repellent' under the brand name of 'Good Night' is under public knowledge and use for more than a decade. The Exhibit Ex-C2 & Ex-C3 reveal that the cordless mosquito repellent having press fit detachable top & bottom portion with arrangement of insertion of mat on heater assembly and twist-n-turn i.e. rotatable two pinned plug fitted with the device, manufactured and marketed by Transelektra Domestic Products Private Ltd. were under public knowledge and use much earlier than the date of the alleged application for Patent No. 179304. For more than a decade the rotatable plug through 90 degree is under public knowledge & use in many domestic electrical appliances and the press fit arrangements are under public knowledge and use even much more than a decade. The press fit arrangement of the top and bottom cover as depicted in Unit (iv) in paragraph 2 wherein the projections of the top cover being press fitted with the corresponding grooves formed on the inside face of bottom cover, is a mere workshop modification. Supposing that in the application for patent in question there is a difference with the cited documents in respect of the matter wherein the plug being adopted in a detachable and rotatable manner by providing on the plug rear portion with a integrally formed tubular portion having radially extending flanges as narrated in feature (v) of the alleged application, even in that case it is mere a workshop modification.

The Applicants' counsel have stated during hearing that the alleged device has produced achievements (1) Maintaining of constant temperature of 150o C (2) can easily assemble and disassemble (3) is a compact and can be conveniently used without the necessity of any extendable cord (4) is a safer construction (5) give a regulated release of active material by regulating temperature at 150o C.

All the above stated achievements of the alleged application have been found and claimed in the cited US documents. In the above background this Tribunal

find that the alleged application has its integers (i) to (v) as narrated in paragraph 2 anti by combining one feature of an earlier specification with another earlier specification and so on to secure no advantage other than addition of their respective merits. The Tribunal therefore concluded that the alleged application No. 179304 titled "A Mosquito/Insect Repellent Device" is obvious and clearly does not involve any inventive step.
The grant of patent was therefore refused.

[Rickett & Colman of India Ltd. V *Godrej Hi Care Ltd.*(2001 PTC 637 (PO)].

Example 9 :

In the matter of *M/s. Crompton Greaves Ltd. Mumbai (Applicant)Vs. M/s. Bharat Heavy Electricals Ltd. Hyderabad* (Opponent) Patent application No. 184657 (221/BOM/96)

This is an opposition under Section 25 of the Patents Act, 1970 to the grant of Patent to M/s. Crompton Greaves Limited, Mumbai on their application for Patent No. 184657 (221/BOM/1996) dated 19th April, 1996 . The invention related to "A single phase traction transformer for AC electric locomotive and a method of manufacturing the same".

Under the ground of prior publicly known or publicly used in India under Section 25(l)(d), the opponent submitted that they are in the field of designing and manufacturing traction transformer and developed traction transformer or 3900 KVA in the year 1974. The opponent has supplied more than 600 single-phase traction transformer of 3900 KVA to Indian Railway against their various purchase orders prior to their Patent Application No. 184657 after approval of prototype design from Indian Railway (RDSO). BHEL (Opponent) was the first to supply 5400 KVA of traction transformer to Indian Railway.

It was held by the Controller that the ground under section 25(1)(d) that the invention was publicly known or publicly used in India was not established by the opponent – since the photo copies submitted by the opponent state mainly the terms and conditions of a contract to supply 3900 KVA & 5400 KVA traction transformers. The photocopies of work order did not define any constructional features of the traction transformer. Only by stating that we are the first in the field of manufacturing the applicant company cannot be stopped from obtaining a patent unless the opponents establish that they are manufacturing an identical product.

Example 10 :

In case of Patent No. *184656 (Patent Application No. 221/BOM/96)* the opponents have submitted on the ground of obviousness that the alleged invention is obvious mechanical equivalent of what been known prior to the date of the impugned application. The opponent pleaded that transformer technology is known in the art and claims as worded do not have inventive steps. The opponent submitted that simply stating that the steps and features involved in the claimed invention are obvious is not sufficient without disclosing any prior art which would make the invention obvious to a person skilled in the art. The Controller held that when the

"invention is obviating certain drawbacks of the conventional traction transformer, it cannot be said that the invention is obvious" in absence of relevant prior art.

Example 11 :
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This is an opposition to the grant of a patent under Section 25 of the Patents Act, 1970 for Patent No. 151977 of M/s. Jaya Hind Industries Limited (Applicants) for "External Rotor Assembly for a Magneto"

The opponent M/s. Scooters India Limited, filed a notice of opposition against the grant of a patent on the above application on 12th January, 1984. The case was heard on 30th June, 1986.

Grounds of opposition were Prior publication section 25 (1) (b) , Prior public use and prior public knowledge section 25 (1) (d), obviousness and lack of inventive step section 25 (1) (e), Not an invention or not a patentable invention section 25 (1) (f) insufficiency and clarity of description section 25 (1) (g)

The invention related to an external rotor assembly for a magneto comprising a ferrous yoke fixed to a nonferrous housing having an angular disc with an even number of lugs projecting there from, ferrite magnets (with or without their respective poleshoes) being fixed to the said yoke the said lugs being adapted to hold securedly between them the said ferrite magnets (with or without their respective poleshoes) and the said housing being adapted to be mounted on to the crankshaft of an engine.

In view of the findings in consideration of all matters stated in the written statement, reply statement and evidence as well as the arguments furnished by the opponents and applicants during the hearings and all the circumstances of the case, it was concluded that the opponents have not proved the ground of prior publication and prior public knowledge and have also not submitted any evidences to the fact that the invention is obvious. Therefore, the opposition filed by the opponents M/s. Scooter India Limited on application No. -151977 is dismissed

[Scooters India Ltd. V Jay Hind Industries Ltd, 1987 (7) PTC 204(PO)]

Example 12

In the matter of Wal Chand Nagar Industries Ltd. v.Thermax Private Ltd.,(1988 PTC 213.) Invention entitled "A process for recovery of potassium sulphate from waste liquids such as distillery spent-wash", which was pposed by the opposition on ground of prior publication and prior public knowledge. However, the opposition could not be established and hence, opposition was dismissed and patent granted

Example 13

In case of *Mechelonic Welders Pvt. Ltd.* v. *Paul Opprecht,* (1988 PTC 126.) Application was filed for invention 'Electrical Resistance Seam Welding

Machines' on the ground of prior use which could not be established. The opposition was dismissed and patent proceeded for grant, subject to the amendment in the applicant's specification.

Example 14

An Application for patent for an invention entitled 'A method for making a plant growth nutrient/stimulant' was filed by Hindustan Lever Limited. The acceptance of the application was notified in the Gazette of India part III, Section 2 dated 14-12-1982 after a serial number, 150203 was accorded to it.

The invention relates to "A method for making a plant growth nutrient/stimulant which comprises subjecting plant waxes like rice bran wax, camauba wax or sugarcane wax to a step of saponification obtain a mixture of saponfied and non saponified matter, whereafter the non-saponified matter is separated and recovered from the said mixture by selective extraction is an organic solvent as the said plant growth nutrient/stimulant, and optionally converting said nutrient/stimulant into a stable aqueous emulsion in a conventional manner.

The alleged method consisted of only two steps and an optional step namely subjecting plant waxes like rice bran wax, camauba wax or sugarcane wax to a step of saphonification to obtain a mixture of saphonified matter is separated and recovered from the said mixture by selective extraction in an organic solvent as the said plant growth nutrient/stimulant, and, optionally converting said nutrient/stimulant into a stable aqueous emulsion in a conventional manner

The opponents relied upon scientific publications and expert's evidence . It is held that properties of unsaponified products is not a fit subject matter for the grant of a valid patent, moreover the ground of prior publication having been established, the opposition succeeds on this ground and it is ordered that the patent shall not be granted.

[Kay Laboratories v. *Hindustan Lever Limited* (1988 PTC 31 Mum)]

Example 15

In the case of Abid Kagalwala v. *Edgar Haddley Co. Pvt. Ltd. (*1984 PTC 234) for an invention relating to 'An improved Electrical Switch', it was held that the Applicant has not described as how the use of a resistor in the circuit would be able to eliminate the use of an amplifier. Also the invention has not been properly and clearly described and will not function in the way claimed by the applicants. Hence the patent grant was refused.

Example 16

In an opposition for the patent no. 194085 [AIR 1961 GUJARAT 120 at Page 125] grounds of opposition included prior disclosure and lack of inventive step.

For the prior disclosure, it was held that "Where prior disclosure is relied upon, it is necessary to point to a clear and specific disclosure of something which can be fairly stated to be the invention of the patentee/applicant. If it is something which is said to be like the patentee's/applicant's invention, there should be a description of its use and the manner in which the patentee/applicant intends it to be used. It is not open to take a packet of prior documents, and, as it were, by means of some process of putting a puzzle together, produce what is said to be a disclosure in the nature of a combination *of* the various elements which have been contained in the prior documents" and that "To anticipate a patent, a prior publication or activity must contain the whole of the invention impugned, i.e. all the features by which the particular claim attacked is limited, for the anticipation must be such as to describe, or be, an infringement of the claim attacked."
[M/s. Teva Pharmaceuticals Industries Ltd. vs. M/s. Torrent Pharmaceuticals Ltd.]

Example 17

In the matter of Patent No.- 173462 (224/BOM/1991) between M/s. Hindustan lever limited (Applicants) vs. M/s. Godrej soaps limited (Opponents). The invention related to "process for making a soap composition containing glycerol". Opposition was on the ground of prior publication Under Section 25 (1)(b), prior public knowledge 25 (1)(d), obviousness Under Section 25 (1)(e), not an invention within the meaning of the Act Under Section 25 (1)(f) and does not sufficiently define the invention Under section 25 (1)(g).

The ingredients recited in the principal claim have a very specific & narrow range of proportions, which are not taught by cited documents. Cited document does not teach how to obtain the right balance of salt & glycerol in order to avoid a soap which is to hard or too soft. Also in cited documents there is no mention of balancing the quantities of glycerol or salt against the quantities of total fatty matter. The present invents offer solution to the problem by retraining glycerol produced during specification of triglycerides in the soap bar composition rather than removing it. Also present invention obtained surprising result that the narrow range of total fatty matter, electrolytes of glycerol been taken together in particular combination by applying combination of three steps lead to soap containing glycerol which has acceptable physical proportion. Alleged invention mention prior art, problems, associated, results of various experiments, all essential components, best method by way of working examples.

Opponent failed to establish the above grounds Hence, the patent proceeded for grant

Example 18

In case of *1972-1987 (7) PTC 137(PO),* opposition to grant of patent in respect of 'system for concentration of distillery spent wash and method of disposal of spent" was on the grounds of prior publication, public knowledge and obviousness under Section 25 of the Patents Act, 1970. As regards preliminary objection of the Opponents regarding locus standi of the Applicants to hold patent in their name, it is held that the

applicants being a society registered under the Act, it enjoys the Status of legal entity and as such is capable of suing or being sued as well as capable of entering into a contract and accordingly the preliminary objection raised by the Opponents is rejected. As regards grounds of opposition as stated in clauses (a) to (h) of Sub-section (1) of Section 25 of the Act, it is held that the Opponents have failed to establish ground (a) regarding wrongful obtaining of invention. Similarly, the Opponents having failed to substantiate grounds (b), (c), (d) and (e) by way of documentary evidence, the same are also rejected. As regards ground (f), it is held that since subsequent claims do not have any independent status and have to be construed in conjunction with claim 1 and the opponents having failed to analyse claim 1 of the Applicants, this ground also fails. Regarding ground (g) relating to unfair description, the opponents having been successful in establishing the deficiencies in the description, it is ordered that no patent should be granted to the Applicants

Example 19

In the matter of Patent No, 119964 between M/s Colgate Palmolive & Co. vs. M/s Hindustan Lever Limited; titled "Process and composition for removing stains from fabrics" Applicant raised the objection that the opponent have merely referred to three Indian Prior Patents by numbers without showing how the claims of any of them anticipate the invention of the opposed application. Controller held that "a mere reference is sufficient as it is my duty to see the matters contained therein and thereafter to take or reject any or all of them if they relate to something not appropriate in the proceeding"

Example 20

In the matter of Patent No.120345 between Ashok Ganesh Joshi vs. Harbans lal Malhotra & Sons Pvt. Ltd. For an invention titled " Improvements in or relating to blades for razor and the like instruments." an opposition to the grant of patent filed taking grounds of prior claiming, unfair description and prior public knowledge and user in India of section 9 of Patents Act' 1911 and after the implementation of Patent Act'1970, it was considered under the corresponding grounds of Section 25 i.e. 25(1)(b)(i), 25(1)(c), 25(1)(d) and 25(1)(g). The Controller held that :

Criteria for "Criteria for prior claiming

In order to establish prior claim it must be shown that the subject matter of a claim in the applicants specification forms the subject matter of a distinct claim in the cited specification. It is not sufficient if the claim is merely comprehended in the subject matter of a claim in the cited specification. This follows from the wording of the section. The comparison must be made between (and limited to) the claims in the relevant specifications that is to say, it does not suffice to support an objection under section 25(1)(e) to show that what is claimed in the application as a subject matter for protection is to be found somewhere comprehended or described in the earlier

specification. For the purpose of justifying a finding of prior claim one must find a distinct claim in the earlier specification, which, as a matter of substance, is equivalent to the claim in the applicants' specification. Before claiming to the conclusion that an invention is claimed in an earlier specification. That invention must be found to be distinctly claimed in the earlier specification. This principle applies to chemical selection patents as well as to patents for mechanical combination. (Para 7, Page 160, 161)

Taking up next the ground of 'unfair description', I would point out that this ground would have a considerable effect in an opposition proceeding if it be clearly established that the specification contains description and claims of the alleged invention which is ambiguous, misleading or cannot be clearly understood. From the full written statement, and the evidences submitted by the opponents it would appear, on the other hand, that what has been understood by the opponents as the alleged invention is fully consistent with the actual alleged invention that has been presented by the applicant in the specification. Furthermore, the description and the claims do not appear to be ambiguous or vague in any way and the invention as has been alleged in the claims can be clearly understood by any man in the art. So there does not appear to be much weight in this ground of 'unfair description' and I have to conclude that the opposition has nothing much to gain on this ground also.

Criteria for "Common General Knowledge"

It would appear therefore that when it is a question of common general knowledge i.e., knowledge available in a country for a long time, which every worker in the area is, expected to know; such knowledge would be sufficient to invalidate a patent. Again such a knowledge need not even be found in a p[particular document. In other words a patent application has to be accessed on the basis of not only what will be available from prior documents but also from the common general knowledge on the subject, which may or may not be available in any such document.....Even the parameters suggested in the various steps of the process as claimed are not supported by an example or discussion to prove their superiority or specialty for consideration as a "selection". Further, the Controller concluded that on the ground of Prior public knowledge in India as available from the documents, the prior specifications and the affidavits submitted by the opponents, the opponents have succeeded.

Example 21

5. In the matter of Patent No, 124171 granted for "Improved traction and hoisting apparatus" and opposed by M/s Pulling and Lifting Machines Private Limited under section 9 of Patents Act' 1911 and after the implementation of Patent Act' 1970, it was considered under the corresponding grounds of Section 25 i.e. 25(1)(d) and 25(1)(g).

The Controller held that

"In an opposition proceeding under section 25 of the Act the responsibility of the opponent does not appear to end with the levelling of certain allegations only against

the applicant's invention but he has the duty under the Act to take adequate interest to diligently pursue the opposition and to establish the grounds he relied upon. However, for not furnishing necessary particulars as aforesaid I am unable to consider the merit of this ground on the basis of what has been merely referred to in the written statement of opposition by the opponents. I hold that the opponents have failed to discharge their onus to establish the ground of "prior public knowledge or public user in India" taken by them". (Para 5, page 179)

Example 22

In the matter of Patent No, 146120 ,the petitioners have prayed to the Controller to direct the opponents to withdraw the evidence or amend the same since the drawings annexed to his affidavit were incorrect and not true and that are accordingly the evidence filed by the opponents under rule 38 is false and further to enable the applicants to adduce their evidence under rule 39. The Controller held that: I cannot force them to amend the affidavits simply because the applicants have doubt on the drawings annexed to the affidavits filed by the opponents. The controller has full power either to reject or to accept the affidavit fully or partly after the final hearing of the parties but cannot force the party to the proceeding to amend the affidavit. I do not agree with applicant counsel's arguments that the Controller is empowered under section 77 and rule 113 to force the party to proceeding to amend their affidavit on merely a doubt raised by the applicants. The expression "any other matter' under section 77(1)(h) means any other matter prescribed under the Act or the Rules allied to what are given in clauses (a) to (g) of sub-section (1) of Section 77. It cannot mean any other matter not prescribed under the Act or the Rules or matters not allied to such as specified in clause (a) to (g) of Section 77(1). Similarly the expression "to perform an act, file a document or produce evidence" of Rule 113 has to be read as allied matters. One cannot assign different meaning to each expression. Under Rule 113, if the Controller is of the opinion that it is necessary, then only he will ask the party to perform an act, file a document or produce evidence. Since the Controller cannot go into the merits of the case at this stage, he cannot form any opinion. Therefore, the question of asking the opponents to perform an act does not arise. Further since I have already said that the expression "to perform an act" is an allied expression to file a document or to produce evidence, it cannot mean that the Controller can force the party to amend the evidence. As regards applicant counsel's argument under the Civil Procedure Code, I would state that the Controller is technically not a Court and the C.P.C. is not applicable before him (A.I.R. 1934 Cal. 725).

Example 23

In the matter of Patent No, 140797 titled: "Electronic area Measuring Machine" with regard to the issue of "Obviousness", the applicant stated that the object of the invention is to devise a reliable, compact and accurate area measuring machine with a simple mechanism, easy to maintain and functioning almost automatically. The Controller held that; It is obvious that the skin must pass over a

rigid surface while its area is being measured and the endless conveyor and two end rollers around which said conveyor passes in the prior art of the said French specification have been replaced by two guide rollers and a slotted table in the present invention. The use of a table in conjunction with such machine has already been disclosed in the extract of Turner Machine .....It is obvious that a table, if used in such a machine has necessarily to be slotted or perforated to allow light rays from the light source to pass there through so as to fall on the light sensitive devices located on the opposite side, otherwise Light sensitive devices will not operate when a skin or any opaque object passes over such table..... The applicant has not made any scintilla of invention in the provision of electronic circuits claimed in the statement of claims, as the same has been admitted in the specification to be known in the art.

Example 24

In the matter of Patent No. 150310 dated 21.06.1978 titled "Electro-erosion method an apparatus for taper cutting an electrically conductive work piece with a wire electro and the work piece so cut". the applicant for patent raised the issue of the locus standi of the opponents on the ground that the opponents are manufacture of electrical & electronic goods for medical and industrial applications are not engaged in any manner on a commercial scale, in a manufacture, lease or sailing of wire cut or travelling wire electrical erosion machine and the applicant invention does not in any way conflict with the subject matter of the opponent business. The Controller held that the opponent justify by their activities that they have locus standi as person interested to file the opposition. This conclusion was reached by the Controller after relying on the 29 RPC(1912" "that it is sufficient for the opponent to be able to show a bonafide and existing interest at the time when the opposition is heard" and also relying on the views of U.K. Controller General that the right to oppose a patent be extended to all those who can show bonafide and satisfactory reason to oppose.

Example 25

In the matter of Patent No. 149901 and in the matter of Substitution of name of the opponent during opposition under section 25, the application was opposed by Board of Tea Research Institute of Ceylon, Sri Lanka & Competent authority the Govt. of Sri Lanka successor of business undertaking of Colombo Commercial Company (Engineering) Ltd., Sri Lanka. The Board of Tea Research Institute of Ceylon was amalgamated with Sri Lanka tea Board by virtue of Law no. 14 of 1975 and all the rights and obligation including property of the Tea Research Board Institute should be deemed to be the right and obligation of the Board. However the provision of this law according to the notification was to come into operation on such date as may be appointed by the Minister and published, There was no proof on the record to prove that any date has been appointed by the Minister in order to

operationalise the said law. Therefore Controller held that the name of Board of Tea Research Institute of Ceylon can not be substituted by its successor namely Sri Lanka Tea Board. It was further held (the Terrel on Law Patent at page no. 171) that " A different opponent can not be substituted by amendment after the expiry of the opposition period even if he acquires and interest from the original opponents . further it is intended to limit opposition proceedings to persons who possess necessary interest in the period laid down for opposition and also excluding a person who only acquired such interest subsequently even if it is acquired from a person who had it an used it at the time lodging opposition and therefore substitution of opponents asked for is not legitimate.

Example 25

With regard to further evidence at the time of hearing of opposition under section 25,In the opposition proceedings in respect of application for patent no. 150113 the opponent filed further evidence at the time of hearing. This was objected by the applicant by filing a petition for not admitting such further evidence of the opponent. It was held by the Controller that in the practice of Patent Office the leave for filing further evidence is freely given right up to the hearing and therefore it is right an proper both in the interest of the public and all concerned that all relevant material should be before the Controller when an opposition cases is tried. However, the applicant would be allowed to file a counter affidavit within the specified time.

Further Patent Application Nos. 369/MAS/1988 and 765/MAS/2000 were refused because of the non prosecution of application by the applicant under opposition proceedings. Whereas application no. 699/MAS/1996 was allowed to proceed for grant because of the failure of opposition. In Patent Application No. 2207/MAS/1997 (183745) the opponents were not allowed to file evidence on expiry of the prescribed time lines and the presumable extension thereof in order to avoid undue delay in the grant proceedings.

7.3 ACTION IN CASE OF WRONGFUL OBTAINING (S. 26)

Relevant Section and Rules:

Section 26;

In cases of "obtaining" Controller may treat the patent as the patent of opponent;

(1) Where in any opposition proceeding under this Act the Controller finds that-

(a) the invention, so far as claimed in any claim of the complete specification, was obtained from the opponent in the manner set out in clause (a) of sub-section (2) of section 25 and revokes the patent on

that ground, he may, on request by such opponent made in the prescribed manner, direct that the patent shall stand amended in the name of the opponent;

(b) a part of an invention described in the complete specification was so obtained from the opponent, he may pass an order requiring that the specification be amended by the exclusion of that part of the invention.

~~2~~*(3) Where an opponent has, before the date of the order of the Controller requiring the amendment of a complete specification referred to in clause (b) of sub-section (1), filed an application for a patent for an invention which included the whole or a part of the invention held to have been obtained from him and such application is pending, the Controller may treat such application and specification in so far as they relate to the invention held to have been obtained from him, as having been filed, for the purposes of this Act relating to the priority dates of claims of the complete specification, on the date on which the corresponding document was or was deemed to have been filed by the patentee in the earlier application but for all other purposes the application of the opponent shall be proceeded with as an application for a patent under this Act.*

Rule 63A:

Request made under section 26(1);

Request under section 26(1) shall be made on Form 12 within three months from the date of the order of the Controller and shall be accompanied by a statement setting out the facts upon which the petitioner relies and relief he claims.

7.3.1 Wrongfully Obtaining :

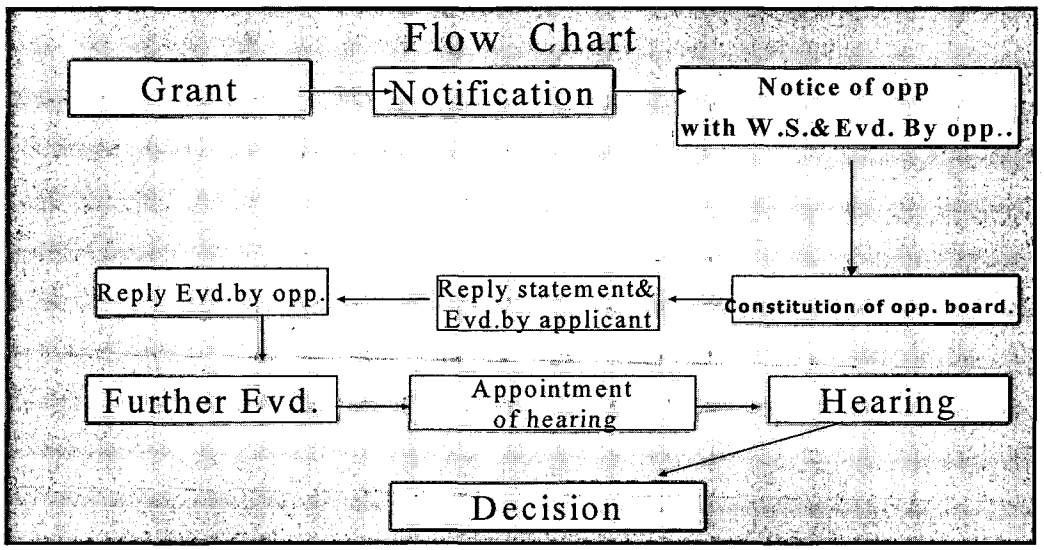
Where the Controller refuses the application on the ground of wrong full obtaining, as a result of proceedings under section 25(2) clause (a), and revokes the patent on this ground, a request can be made by the opponent in Form 12 along with the prescribed fee and in the prescribed manner to allow the patent in the name of the opponent. The controller , upon such request may direct the application to proceed in the name of the opponent with the benefit of priority date attached to the application and order for such an amendment.

However, if only a part of the invention described in the complete specification has been obtained from the opponent, the Controller may allow specification of the patentee to be amended by exclusion of that part.

A special situation is illustrated by Section 26 (2) where the application from opponent containing the whole or a part of the invention held to be obtained from

him has been filed before the order of the controller u/s 26(1) (b) for amendment of patentee's specification on the grounds of obtaining and such application is pending. In such a case, the controller may treat the application and specification filed by opponent containing the whole or apart of invention so excluded from applicant's (patentee's) specification as opponent's application with the same priority date as the earlier application; but for all other purposes the opponent's application will be treated as an independent application under the Act.

Procedure for Opposition U/S 25(2)



7.4 MENTION OF INVENTOR AS SUCH IN PATENT

Relevant Section and Rules

Section 28 :

(1) If the Controller is satisfied, upon a request or claim made in accordance with the provisions of this section,—

(a) that the person in respect of or by whom the request or claim is made is the inventor of an invention in respect of which application for a patent has been made, or of a substantial part of that invention; and

(b) that the application for the patent is a direct consequence of his being the inventor,

the Controller shall, subject to the provisions of this section, cause him to be mentioned as inventor in any patent granted in pursuance of the application in the complete specification and in the register of patents:
Provided that the mention of any person as inventor under this section shall not confer or derogate from any rights under the patent.

(2) A request that any person shall be mentioned as aforesaid may be made in the prescribed manner by the applicant for the patent or (where the person alleged to be the inventor is not the applicant or one of the applicants) by the applicant and that person.

(3) If any person other than a person in respect of whom a request in relation to the application in question has been made under sub-section (2) desires to be mentioned as aforesaid, he may make a claim in the prescribed manner in that behalf.

(4) A request or claim under the foregoing provisions of this section shall be made before the grant of patent.

(6) Where a claim is made under sub-section (3), the Controller shall give notice of the claim to every applicant for the patent (not being the claimant) and to any other person whom the Controller may consider to be interested; and before deciding upon any request or claim made under sub-section (2), or sub section (3), the Controller shall, if required, hear the person in respect of or by whom the request or claim is made, and, in the case of a claim under sub-section (3), any person to whom notice of the claim has been given as aforesaid.

(7) Where any person has been mentioned as inventor in pursuance of this section, any other person who alleges that he ought not to have been so mentioned may at any time apply to the Controller for a certificate to that effect, and the Controller may, after hearing, if required, any person whom he may consider to be interested, issue such a certificate, and if he does so, he shall rectify the specification and the register accordingly.

Rule 66:

A request under subsection (2) of section 28 shall be made in Form 8.

Rule 67:

(1) A claim under subsection (3) of section 28 shall be made in Form 8, and shall be accompanied by a statement setting out the circumstances under which the claim is made.
(2) A copy of the claim and the statement shall be sent by the Controller to every applicant for the patent (not being the claimant) and to any other person whom the Controller may consider to be interested.

Rule 68:

(1) An application under sub-section (7) of section 28 shall be made in Form 8 and shall be accompanied by a statement setting out the circumstances under which the application is made.

(2) A copy of the application and the statement shall be sent by the Controller to each patentee or the applicant for patent, as the case may be, and to any other person whom (he Controller may consider to be interested.

Rule 69:

The procedure specified in rules 55A and 57 to 63 relating to the filing of notice of opposition, written statement, reply statement, leaving evidence, hearing and cost shall, so far as may be, apply to the hearing of a claim or an application under section 28 as they apply to the opposition proceedings subject to the modification that reference to patentee shall be construed as the person making the claim, or an application, as the case may be.

Rule 70:

Any mention of the inventor under sub-section (1) of section 28 shall be made in the relevant documents in the following form namely:-

"The inventor of this invention/substantial part of this invention within the meaning of section 28 of the Patents Act, 1970, is ...of.....".

7.4.1 Procedure under section 28

Mention of Inventor as such in Patent

If the inventor desires to have his name mentioned as such in a patent by virtue of his being the actual inventor of the invention or a substantial part of the invention, he may make an application to that effect. The Controller if satisfied, will cause him to be mentioned as inventor in the complete specification and in the register of patents.

~~e~~(a) The request shall be made at anytime before the grant of patent.

~~e~~(b) The request when made by the applicant for patent alone or jointly with the person alleged to be the inventor, shall be on form 8.

~~e~~(c) If the request is made by the person claiming to be the actual deviser of invention, who is not the applicant for a patent, the claim must be made on Form 8 accompanied by a statement setting out the circumstances under which the claim is made.

~~e~~(d) The Controller will give notice of the claim to every applicant (not being the claimant) and to any other person who is considered to be interested, and decide the case after hearing the parties concerned, if so required. Any person to whom the Controller has sent copies of the request or claim made under Section 28 may oppose such request or claim. The procedure to be followed

in dealing with such opposition is the same as prescribed in rules 55A, 57 to 63 relating to opposition to grant of patent. Where the Controller allows the request, the mention of the inventor will be made in the patent and in the complete specification in the form prescribed in rule 70. Mention of the inventor will also be made in the register of patents

~~e~~(e) If any person alleges that the person who is mentioned as the inventor ought not to have been so mentioned, he may make an application on form 8 accompanied by a statement of case for a certificate to that effect. If the Controller decides the case in favour of the person making the claim , he will issue a certificate and rectify the specification and register accordingly.

CHAPTER VIII

8.1 What Are Not Anticipations (Section 29-34)

Relevant Sections and Rules :

Section 29:

Anticipation by previous publication.—

(1) An invention claimed in a complete specification shall not be deemed to have been anticipated by reason only that the invention was published in a specification filed in pursuance of an application for a patent made in India and dated before the 1st day of January, 1912.

(2) Subject as hereinafter provided, an invention claimed in a complete specification shall not be deemed to have been anticipated by reason only that the invention was published before the priority date of the relevant claim of the specification, if the patentee or the applicant for the patent proves—

(a) that the matter published was obtained from him, or (where he is not himself the true and first inventor) from any person from whom he derives title, and was published without his consent or the consent of any such person; and

(b) where the patentee or the applicant for the patent or any person from whom he derives title learned of the publication before the date of the application for the patent, or, in the case of a convention application, before the date of the application for protection in a convention country, that the application or the application in the convention country, as the case may be, was made as soon as reasonably practicable thereafter:

Provided that this sub-section shall not apply if the invention was before the priority date of the claim commercially worked in India, otherwise than for the purpose of reasonable trial, either by the patentee or the applicant for the patent or any person from whom he derives title or by any other person with the consent of the patentee or the applicant for the patent or any person from whom he derives title.

(4) Where a complete specification is filed in pursuance of an application for a patent made by a person being the true and first inventor or deriving title from him, an invention claimed in that specification shall not be deemed to have been anticipated by reason only of any other application for a patent

in respect of the same invention made in contravention of the rights of that person, or by reason only that after the date of filing of that other application the invention was used or published, without the consent of that person, by the applicant in respect of that other application, or by any other person in consequence of any disclosure of any invention by that applicant.

8.1.1. With regard to Exception to anticipation under Section 29(2)(a), an application for patent 136965 was filed on 29/04/1972. However, a drawing no. P4219 relating to the invention was handed over to M/s. Colliery Mining Machinery company by TISCO on 06.04.1972. The application was opposed on the ground of prior publication in view of the above drawings. It was held by the controller that for seeking protection under section 29(2)(a), it is necessary for the applicant to prove that TISCO obtained the drawing No. P4219 from CFRI (Applicant) and published it without the consent of CFRI and there was no commercial working of the invention before the priory date of the claimed in the complete specification. Since there is no evidence on the record to prove that the drawing was published by TOSCO without the consent of CFRI and TISCO handed over the drawing to M/s. Colliery Mining Machinery Company along with the worked order without any condition. Therefore, this kind of act amount to publication of the drawing prior to date of the filing of the application

Section 30 :
Anticipation by previous communication to Government.—

An invention claimed in a complete specification shall not be deemed to have been anticipated by reason only of the communication of the invention to the Government or to any person authorized by the Government to investigate the invention or its merits, or of anything done, in consequence of such a communication, for the purpose of investigation.

Section 31 :
Anticipation by public display, etc

An invention claimed in a complete specification shall not be deemed to have been anticipated by reason only of—

(d) the display of the invention with the consent of the true and first inventor or a person deriving title from him at an industrial or other exhibition to which the provisions of this section have been extended by the Central Government by notification in the Official Gazette, or the use thereof with his consent for the purpose of such an exhibition in the place where it is held; or

(e) the publication of any description of the invention in consequence of the display or use of the invention at any such exhibition as aforesaid; or

(f) the use of the invention, after it has been displayed or used at any such exhibition as aforesaid and during the period of the exhibition, by any person without the consent of the true and first inventor or a person deriving title from him; or

(g) the description of the invention in a paper read by the true and first inventor before a learned society or published with his consent in the transactions of such a society,

if the application for the patent is made by the true and first inventor or a person deriving title from him not later than twelve months after the opening of the exhibition or the reading or publication of the paper, as the case may be

Section 32:
Anticipation by public working

An invention claimed in a complete specification shall not be deemed to have been anticipated by reason only that at any time within one year before the priority date of the relevant claim of the specification, the invention was publicly worked in India—

(a) by the patentee or applicant for the patent or any person from whom he derives title; or
(b) by any other person with the consent of the patentee or applicant for the patent or any person for whom he derives title,

if the working was effected for the purpose of reasonable trial only and if it was reasonably necessary, having regard to the nature of the invention, that the working for that purpose should be effected in public.

Section: 33 :
Anticipation by use and publication after provisional specification

(1) Where a complete specification is filed or proceeded with in pursuance of an application which was accompanied by a provisional specification or where a complete specification filed along with an application is treated by virtue of a direction under sub-section (3) of section 9 as a provisional specification, then, notwithstanding anything contained in this Act, the Controller shall not refuse to grant the patent, and the patent shall not be revoked or invalidated, by reason only that any matter described in the provisional specification or in the specification treated as aforesaid as a provisional specification was used in India or published in India or elsewhere at any time after the date of the filing of that specification.

(2) Where a complete specification is filed in pursuance of a convention application, then, notwithstanding anything contained in this Act, the Controller shall not refuse to grant the patent, and the patent shall not be revoked or invalidated, by reason only that any matter disclosed in any application for protection in a convention country upon which the convention application is founded was used in India or

published in India or elsewhere at any time after the date of that application for protection.

Section 34 :

No anticipation if circumstances are only as described in Sections 29, 30, 31 and 32

Notwithstanding anything contained in this Act, the Controller shall not refuse to grant a patent, and a patent shall not be revoked or invalidated by reason only of any circumstances which, by virtue of section 29 or section 30 or section 31 or section 32, do not constitute an anticipation of the invention claimed in the specification.

Rule 28 :

Procedure in case of anticipation by prior publication.—

(1) If the Controller is satisfied after investigation under section 13 that the invention so far as claimed in any claim of the complete specification has been published in any specification or other document referred to in clause (a) of sub-section (1) or sub-section (2) of the said section, the Controller shall communicate the gist of specific objections and the basis thereof to the applicant and the applicant shall be afforded an opportunity to amend his specification.

(2) If the applicant contests any of the objections communicated to him by the Controller under sub-rule (1), or if he refiles his specification along with his observations as to whether or not the specification is to be amended, he shall be given an opportunity to be heard in the matter if he so requests:

Provided that such request shall be made on a date earlier than ten days of the final date of the period preferred to under sub-section (1) of section 21:

Provided further that a request for hearing may be allowed to be filed within such shorter period as the Controller may deem fit in the circumstances of the case.

(3) If the applicant requests for a hearing under sub-rule (2) within a period of one month from the date of communication of the gist of objections, or, the Controller, considers it desirable to do so, whether or not the applicant has refiled his application, he shall forthwith fix a date and time for hearing having regard to the period remaining for putting the application in order or to the other circumstances of the case.

(5) The applicant shall be given ten days' notice of any such hearing or such shorter notice as appears to the Controller to be reasonable in the circumstances of the case and the applicant shall, as soon as possible, notify the Controller whether he will attend the hearing.

(6) After hearing the applicant, or without a hearing if the applicant has not attended or has notified that he does not desire to be heard, the Controller may specify or permit such amendment of the specification as he thinks fit to be made and may refuse to grant the patent unless the amendment so specified or permitted is made within such period as may be fixed.

Rule 28A:

Procedure in relation to consideration of report of examiner under section 14.—*In case the applicant contests any of the objections communicated to him, the procedure specified under rule 28 may apply.*

Rule 29:

Procedure in case of anticipation by prior claiming.—

(1) When it is found that the invention so far as claimed in any claim of the complete specification, is claimed in any claim of any other specification falling within clause (b) of sub-section (1) of section 13, the applicant shall be so informed and shall be afforded an opportunity to amend his specification.

(2) If the applicant's specification is otherwise in order for grant and an objection under clause (b) of sub-section (1) of section 13 is outstanding, the Controller may postpone the grant of patent and allow a period of two months for removing the objection.

Rule 30:

Amendment of the complete specification in case of anticipation.—

(1) If the applicant so requests at any time, or if the Controller is satisfied that the objection has not been removed within the period referred to in sub-rule (2) of rule 29, a date for hearing the applicant shall be fixed forthwith and the applicant shall be given at least ten days' notice of the date so fixed. The applicant shall, as soon as possible, notify the Controller whether he will attend the hearing.

(2) After hearing the applicant, or without a hearing if the applicant has not attended or has notified that he does not desire to be heard, the Controller may specify or permit such amendment of the specification as will be to his satisfaction to be made and may direct that reference to such other specification, as he shall mention shall be inserted in the applicant's specification unless the amendment is made or agreed to within such period as he may fix.

Rule 31:

Form of reference to another specification.—

When in pursuance of rule30, the Controller directs that a reference to another specification shall be inserted in the applicant's complete specification, such reference shall be inserted after the claims and shall be in the following form, namely:

"Reference has been directed, in pursuance of section 18(2) of the Patents Act, 1970, to the specification filed in pursuance of application No......"

Rule 32:

Procedure in case of potential infringement.—

If in consequence of an investigation made under section 13 , it appears to the Controller that the applicant's invention cannot be performed without substantial risk of infringement of a claim of another patent, the applicant shall be so informed and the procedure provided in rule 29 shall, so far as may be necessary, be applicable.

Rule 33:

Form of reference to another patent;

Where the Controller directs that a reference to another patent shall be inserted in the applicant's complete specification under sub-section (1) of section 19, such reference shall be inserted, after the claims in the following form, namely:

"Reference has been directed, in pursuance of section 19(1) of the Patents Act, 1970, to Patent No-----"

8.1.2 NOT ANTICIPATIONS: The invention is not anticipated i.e. novelty of an invention is not destroyed in certain exceptional conditions , specially provided in the Act in Sections 29-34

a) Prior Publication (S. 29)

The invention claimed in the complete specification will not be considered as anticipated by a specification accompanying an application in India, which was published before the 1st day of January, 1912.

A prior publication of an invention before its priority date will not be deemed as anticipation, if the patentee or the applicant proves that the matter was obtained from him or the inventor or assignor, and that the publication was done without their knowledge, and the application for patent was therefore made immediately after learning that the publication had happened.

This provision will not apply if the invention was commercially worked in India, otherwise for the purpose of reasonable trial before the priority date of the claim by the inventor, patentee or applicant, their assignor or assignee or some one else having their consent.

An invention claimed in an application made by the inventor or his assignee should not be deemed as anticipated by another application for patent in respect of the same invention made in contravention of the rights of that person, or its publication or use by the other applicant or any other person in consequence of its disclosure by him without the consent of the first mentioned applicant.

b) **Previous communication to Government (S. 30)**

The invention will not be deemed as anticipated by its communication to the government or to any person authorized by the government to investigate the invention or its merits, or of anything done in consequence of such communication for the purpose of the investigation.

c) **Prior Public Display etc. (S. 31)**

If the application for the patent is made by the inventor or his assignee not later than twelve months after the opening of the exhibition (notified by the Central Government) where **the invention is first displayed and published** by the applicant or used with his consent, it will not be deemed as anticipated. The use of the invention (so displayed) by an unauthorized person during the period of exhibition also will be deemed as non-anticipation.

(d) The **description of the invention in a paper read** by the true and first inventor or its publication with his consent in the transactions **before a learned society** also does not constitute anticipation, if the application is made within the period of **twelve months**.

e) **Prior Public Working (S. 32)**

This deals with **public working** of an invention claimed in a complete specification **for a reasonable trial** because the nature of the invention is such that it was necessary to do so. This type of public working will not be deemed as anticipation if performed within one year before the priority date by the patentee, applicant (or assignor) or by any person with their consent.

f) **Use and Publication after provisional specifications (S. 33)**

An invention in an application should not be considered as anticipated by public use and/or publication of the invention in India or elsewhere after the corresponding filing date of the provisional specification or the prior application in a convention country for which a priority is claimed.

Chapter IX

Provisions of Secrecy of Certain Inventions

Section 35:

Secrecy directions relating to inventions relevant for defence purposes.

1) Where, in respect of an application made before or after the commencement of this Act for a patent, it appears to the Controller that the invention is one of a class notified to him by the Central Government as relevant for defence purposes, or, where otherwise the invention appears to him to be so relevant, he may give directions for prohibiting or restricting the publication of information with respect to the invention or the communication of such information.

(2) Where the Controller gives any such directions as are referred to in sub-section (1), he shall give notice of the application and of the directions to the Central Government, and the Central Government shall, upon receipt of such notice, consider whether the publication of the invention would be prejudicial to the defence of India, and if upon such consideration, it appears to it that the publication of the invention would not so prejudice, give notice to the Controller to that effect, who shall thereupon revoke the directions and notify the applicant accordingly.

(3) Without prejudice to the provisions contained in sub-section (1), where the Central Government is of opinion that an invention in respect of which the controller has not given any directions under section (1),is relevant for defence purposes, it may at any time before the grant of patent notify the Government to that effect, and thereupon the provisions of that subsection shall apply as if the invention where one of the class notified by the Central Government, and accordingly the controller shall give notice to the central Government of the directions issued by him.

Section 36:

Secrecy directions to be periodically reviewed;

(1) The question whether an invention in respect of which directions have been given under section 35 continues to be relevant for defence purposes shall be reconsidered by the Central Government at intervals of six months or on a request made by the applicant which is found to be reasonable by the Controller and if, on such reconsideration it appears to the Central Government that the publication of the invention would no longer be prejudicial to the defence of India or in case of an application filed by a foreign applicant it is found that the invention is published outside India it shall forthwith give notice to the Controller to revoke the direction and the Controllers shall thereupon revoke the directions previously given by him.

(2) The result of every re-consideration under sub-section (1), shall be communicated to the applicant within such time and in such manner as may be prescribed.

Section 37.

Consequences of secrecy directions;

(1) So long as any directions under section 35 are in force in respect of an application—

(a) the Controller shall not pass an order refusing to grant the same; and notwithstanding anything contained in this Act, no appeal shall lie from any order of the Controller passed in respect thereof:

Provided that the application may, subject to the directions, proceed up to the stage of grant of the patent, but the application and the specification found to be in order for grant of the patent shall not be published, and no patent shall be granted in pursuance of that application.

(2) Where a complete specification filed in pursuance of an application for a patent for an invention in respect of which directions have been given under section 35 is found to be in order for grant of the patent during the continuance in force of the directions, then—

(a) if, during the continuance in force of the directions, any use of the invention is made by or on behalf of, or to the order of the Government, the provisions of sections 100, 101 and 103 shall apply in relation to that use as if the patent had been granted for the invention; and

(b) if it appears to the Central Government that the applicant for the patent has suffered hardship by reason of the continuance in force of the directions, the Central Government may make to him such payment (if any) by way of solatium as appears to the Central Government to be reasonable having regard to the novelty and utility of the invention and the purpose for which it is designed, and to any other relevant circumstances.

(3) Where a patent is granted in pursuance of an application in respect of which directions have been given under section 35, no renewal fee shall be payable in respect of any period during which those directions were in force.

Section 38.

Revocation of secrecy directions and extension of time.;

When any direction given under section 35 is revoked by the Controller, then, notwithstanding any provision of this Act specifying the time within which any step should be taken or any act done in connection with an application for the patent, the Controller may, subject to such conditions, if any, as he thinks fit to impose, extend the time for doing anything required or authorised to be done by or under this Act in connection with the application whether or not that time has previously expired.

Section 39:

Residents not to apply for patents outside India without prior permission.—

(1) No person resident in India shall, except under the authority of a written permit sought in the manner prescribed and granted by or on behalf of the Controller,

make or cause to be made any application outside India for the grant of a patent for an invention unless—

(a) an application for a patent for the same invention has been made in India, not less than six weeks before the application outside India; and

(b) either no direction has been given under sub-section (1) of section 35 in relation to the application in India, or all such directions have been revoked.

(2) The Controller shall dispose of every such application within such period as may be prescribed:

Provided that if the invention is relevant for defence purpose or atomic energy, the Controller shall not grant permit without the prior consent of the Central Government.

(3) This section shall not apply in relation to an invention for which an application for protection has first been filed in a country outside India by a person resident outside India.]

Section 40:

Liability for contravention of section 35 or section 39.—

Without prejudice to the provisions contained in Chapter XX, if in respect of an application for a patent any person contravenes any direction as to secrecy given

by the Controller under section 35 [or makes or causes to be made an application for grant of a patent outside India in contravention of section 39] the application for patent under this Act shall be deemed to have been abandoned and the patent granted, if any, shall be liable to be revoked under section 64.

Section 41:

Finality of orders of Controller and Central Government.;

All orders of the Controller giving directions as to secrecy as well as all orders of the Central Government under this Chapter shall be final and shall not be called in question in any court on any ground whatsoever.

Section 42:

Savings respecting disclosure to Government.—

Nothing in this Act shall be held to prevent the disclosure by the Controller of information concerning an application for a patent or a specification filed in pursuance thereof to the Central Government for the purpose of the application or specification being examined for considering whether an order under this Chapter should be made or whether an order so made should be revoked.

Rule 71:

Permission for making patent application outside India under section 39;

(1) The request for permission for making patent application outside India shall be made in Form 25.

(2) The time within which the Controller dispose of the request made under sub-rule (1), except in case of inventions relating to defence and atomic energy applications, shall ordinarily be within a period of twenty one days from the date of filing of such request.

Rule 72:
Communication of result of reconsideration under section 36(2);

(1) The result of every reconsideration under sub-section (1) of section 36 shall be communicated lo the applicant for patent within fifteen days of the receipt of the notice by the Controller. (2) ***Extension of time on revocation of secrecy directions under section 3;****The extension of time to be given for doing anything required or authorised to be done under section 38 shall not exceed the period for which directions given by the Central Government under sub-section (1) of section 35 were in force*

9.1 Secrecy Directions For Certain Inventions relevant for defence purposes (S.35)

ɵ9.1.1 There are provisions in the Act for secrecy directions for certain inventions which are relevant for defence purposes **(S. 35).** The respective sections empower the Central Government to prohibit publication of the information relating to such inventions. Section 35(1) provides that the Controller may give direction for prohibiting or restricting the publication of information, relating to certain specific inventions or the communications of such information, if it appears to him that the invention in question is one of a class notified to him by Central Government as relevant for defence purposes or the Controller himself considers it to be so.

ɵ9.1.2 If such directions have been given, the Controller will give notice of the application and of the direction to the Central Government. If the Central Government considers that the publication of the invention in question would not be prejudicial to the defence of India, it will inform the Controller to that effect who, upon receiving such information, will revoke the secrecy direction and inform the applicant (S. 35(2)) accordingly.

ɵ9.1.3 Also, if the Central Government is of the opinion that the invention, in respect of which the Controller has not issued secrecy direction, it may notify to that effect to the Controller before the grant of the patent, who will issue the secrecy direction to the applicant on receipt of such a notice from Central Government and inform the government accordingly about the secrecy directions issued by the Controller.

ɵ9.1.4The Central Government, will review the question on whether the invention continues to be relevant for defence purposes at intervals of 6 months or on a request made by the applicant which is found to be reasonable

by the Controller and, if it is found that the invention is no longer prejudicial for defence of India, the Controller will be given notice to revoke the secrecy direction previously given by him.

ө9.1.5 If the patent application was made by a foreign applicant and the invention was found published out side India the Central Government shall forthwith give notice to the Controller to revoke the secrecy direction **(S. 36)**

ө9.1.6 The result of every reconsideration will be communicated, in writing, to the applicant within fifteen days of the receipt of the notice by the Controller (Rule 72(1)) from Central Government

9.2 CONSEQUENCES OF SECRECY DIRECTION (S.37)

ө9.2.1 During the period when the secrecy direction is in force, the application will not be published.

ө9.2.2 If, during the continuance in force of the directions, any use of the invention is made by or on behalf of, or to the order of the Government, the provisions of Section 100 (Power of Central government to use inventions for the purpose of Government), Sections 101 (Right of Third parties in respect of use of inventions for purposes of Government) and Section 103 (Reference to High Court of disputes as to use for purposes of Government) shall apply in relation to that use, as if the patent has been granted for the invention.

ө9.2.3 If the Central Government finds that the applicant has suffered hardship by reason of continuation of such direction, it may make payment of a suitable sum to the applicant by way of solatium , having regard to novelty and the utility of the invention and the purpose for which it is designed *(S.37 (2) (b))*.

ө9.2.4 If a patent is granted to the invention in respect of which secrecy direction have been issued, no renewal fee is payable in respect of the period during which such direction was in force *(S.37 (3))*.

ө9.2.5 When any direction under section 35 is revoked by the Controller, then, notwithstanding any provision of this Act specifying the time within which any step should be taken or any act done in connection with an application for the patent, the Controller may, subject to such conditions, if any, as he thinks fit to impose, extend the time for doing anything required or authorize to be done by or under this Act in connection with application, whether or not that time has previously expired. **(S.38)**

9.3 Prohibition to Apply for Patent For inventions outside India without permission (S.39)

9.3.1 This provision is made to prevent a person ***resident in India*** to make or cause to be made an application outside India for the grant of a patent for an invention without seeking prior permission from the Controller.

ө9.3.2 If an application has been made in India in respect of the same invention and if six weeks has elapsed and, no secrecy direction is given under

S.35 (or such direction is revoked thereafter), the applicant may proceed with filing outside India.

~~e~~9.3.3 If the invention is relevant for defence purpose & atomic energy, the Controller shall not grant permission without the prior consent of the Central Government.

~~e~~9.3.4 These provisions will not apply if the application for patent was first made outside India by a person resident outside India.

~~e~~9.3.5 The request for permission for making patent application *outside India* should be made in Form 25 with prescribed fee (Rule 71(1)) as given in the first schedule and the Controller shall dispose the said request ordinarily within a period of 21 days from the date of filing such request (Rule 71(2)).

9.4 OTHER PROVISIONS

~~1.~~9.4.1 If any person contravenes any direction as to secrecy issued by the Controller, the application for patent will be deemed to have been abandoned, and the patent if granted, shall be liable to be revoked under section 64 (1) (n) [as provided in section. 40]. It may be noted that these provisions are in addition to the penalty that may be imposed under section 118 of the Act which includes imprisonment for a term which may extend to 2 years or fine or both.

~~2.~~9.4.2 All the orders of the Controller giving directions as to secrecy as well as all orders of the Central Government under this chapter will be final and shall not be called in question in any court on any ground whatsoever. (S.41)

9.4.3 No provisions in the Act shall prevent the Controller to disclose the information concerning an application for patent or the specification thereof to the Central Government for it to be examined for considering whether any secrecy direction or revocation thereof should be issucd. Further, the Central Government may undertake the followings:

~~I.~~

~~II.~~I. The Government may import or make on its own or on its behalf, any patented machine, apparatus or other article or any article made by a patented process, for the purpose of its own use.

~~III.~~II. Similarly, it can use any patented process for its own use.

~~IV.~~III. The patent can be used by any persons for the purpose of experiment or research including the imparting of instruction to pupils.

9.4.4 In case of a patented medicine or drug, the same may be imported by the Government for its own use or for distribution in any dispensary, hospital or other medical institution maintained by or on behalf of the Government or any other dispensary, hospital or other medical institution which the Central Government may, having regard to the public service that such dispensary, hospital or medical institution renders, specify in this behalf by notification in the Official Gazette.

EXHIBIT P6

CHAPTER X

GRANT OF PATENT

Relevant Sections and Rules.

Section 43:

Grant of patents

(1) Where an application for a patent has been found to be in order for grant of the patent and either—

(a) the application has not been refused by the Controller by virtue of any power vested in him by this Act; or

(b) the application has not been found to be in contravention of any of the provisions of this Act,

the patent shall be granted as expeditiously as possible to the applicant or, in the case of a joint application, to the applicants jointly, with the seal of the patent office and the date on which the patent is granted shall be entered in the register.

(2) On the grant of patent, the Controller shall publish the fact that the patent has been granted and thereupon the application, specification and other documents related thereto shall be open for public inspection.

Rule 74:
Form of patent.-

(1) A patent shall be in the form as specified in the Third Schedule with such modifications as the circumstances of each case may require and shall bear the number accorded to the application under rule 37.

(2) The patent certificate shall ordinarily be issued within seven days from the date of grant of patent under section 43.

Rule 74A:
Inspection of documents related to grant of patent.-

After the date of publication of a grant of a patent, the application together with the complete specification and provisional specification, if any, the drawing if any, abstract and other documents related thereto may be inspected at the appropriate office by making a written request to the Controller and on payment of fee and may obtain copies on payment of fee specified in the First Schedule.

EXHIBIT P6

Section 44.

Amendment of patent granted to deceased applicant.-

Where, at any time after a patent has been granted in pursuance of an application under this Act, the Controller is satisfied that the person to whom the patent was granted had died, or, in the case of a body corporate, had ceased to exist, before the patent was granted, the Controller may amend the patent by substituting for the name of that person the name of the person to whom the patent ought to have been granted, and the patent shall have effect, and shall be deemed always to have had effect, accordingly.

Rule 75:

Amendment of patent under section 44.-

An application under section 44 for the amendment of a patent shall be made in Form 10 along with substantiating evidence and be accompanied by the patent.

Section 45:

Date of patent.-

(1) Subject to the other provisions contained in this Act, every patent shall be dated as of the date on which the application for patent was filed.

(2) The date of every patent shall be entered in the register.

(3) Notwithstanding anything contained in this section, no suit or other proceeding shall be commenced or prosecuted in respect of an infringement committed before the date of publication of the application.

Section 46:

Form, extent and effect of patent.-

(1) Every patent shall be in the prescribed form and shall have effect throughout India

(2) A patent shall be granted for one invention only:
Provided that it shall not be competent for any person in a suit or other proceeding to take any objection to a patent on the ground that it has been granted for more than one invention

Section 47:

Grant of patents to be subject to certain conditions.-

The grant of a patent under this Act shall be subject to the condition that;

(1) any machine, apparatus or other article in respect of which the patent is granted or any article made by using a process in respect of which

established a prima facie case on the strength of their two certificates. In such circumstances Section 48 of the Patents Act, 1970 will hold the field according to which a patent granted under this Act shall confer upon the patentee the exclusive right to prevent third parties from the Act of making, using, selling or importing that product in India if the subject matter of the patent is a product. Similarly if the subject matter of the patent is a process the patentee has the exclusive right to prevent 3rd parties from the act of using the process for sale, selling for those purpose the product obtained directly by that process in India.

Section 49:

Patent rights not infringed when used on foreign vessels etc., temporarily or accidentally in India.-

(1) Where a vessel or aircraft registered in a foreign country or a land vehicle owned by a person ordinarily resident in such country comes into India (including the territorial waters thereof) temporarily or accidentally only, the rights conferred by a patent for an invention shall not be deemed to be infringed by the use of the invention—

(a) in the body of the vessel or in the machinery, tackle, apparatus or other accessories thereof, so far as the invention is used on board the vessel and for its actual needs only; or

(b) in the construction or working of the aircraft or land vehicle or of the accessories thereof,

as the case may be.

(2) This section shall not extend to vessels, aircrafts or land vehicles owned by persons ordinarily resident in a foreign country the laws of which do not confer corresponding rights with respect to the use of inventions in vessels, aircraft or land vehicles owned by persons ordinarily resident in India while in the ports or within the territorial waters of that foreign country or otherwise within the jurisdiction of its courts

Section 50:

Rights of co-owners of patents.-

(1) Where a patent is granted to two or more persons, each of those persons shall, unless an agreement to the contrary is in force, be entitled to an equal undivided share in the patent.

(2) Subject to the provisions contained in this section and in section 51, where two or more persons are registered as grantee or proprietor of a patent, then, unless an agreement to the contrary is in force, each of those persons shall be entitled, by himself or his agents, to rights conferred by section 48 for his own benefit without accounting to the other person or persons.

(3) Subject to the provisions contained in this section and in section 51 and to any agreement for the time being in force, where two or more persons are registered as grantee or proprietor of a patent, then, a license under

the patent shall not be granted and share in the patent shall not be assigned by one of such persons except with the consent of the other person or persons.

(4) Where a patented article is sold by one of two or more persons registered as grantee or proprietor of a patent, the purchaser and any person claiming through him shall be entitled to deal with the article in the same manner as if the article had been sold by a sole patentee.

(5) Subject to the provisions contained in this section, the rules of law applicable to the ownership and devolution of movable property generally shall apply in relation to patents; and nothing contained in sub-section (1) or subsection (2) shall affect the mutual rights or obligations of trustees or of the legal representatives of a deceased person or their rights or obligations as such.

(6) Nothing in this section shall affect the rights of the assignees of a partial interest in a patent created before the commencement of this Act.

Section 51:

Power of Controller to give directions to co-owners.-

(1) Where two or more persons are register as grantee or proprietor of a patent, the Controller may, upon application made to him in the prescribed manner by any of those persons, give such directions in accordance with the application as to the sale or lease of the patent or any interest therein, the grant of licenses under the patent, or the exercise of any right under section 50 in relation thereto, as he thinks fit.

(2) If any person registered as grantee or proprietor of a patent fails to execute any instrument or to do any other thing required for the carrying out of any direction given under this section within fourteen days after being requested in writing so to do by any of the other persons so registered, the Controller may, upon application made to him in the prescribed manner by any such other person, give directions empowering any person to execute that instrument or to do that thing in the name and on behalf of the person in default.

(3) Before giving any directions in pursuance of an application under this section, the Controller shall give an opportunity to be heard—

(a) in the case of an application under sub-section (1) to the other person or persons registered as grantee or proprietor of the patent;

(b) In the case of an application under sub-section (2), to the person in default.

(4) No direction shall be given under this section so as to affect the mutual rights or obligations of trustees or of the legal representatives of a deceased person or of their rights or obligations as such, or which is

any renewal fee, if that fee is not paid within the prescribed period or within such extended period as may be prescribed.

(3) Omitted by Act 15 0f 2005

(4) Notwithstanding anything contained in any other law for the time being in force, on cessation of the patent right due to non-payment of renewal fee or on expiry of the term of patent, the subject matter covered by the said patent shall not be entitled to any protection.

Rule 80:

Renewal fees under section 53.-

(1) To keep a patent in force, the renewal fees specified in the First Schedule shall be payable at the expiration of the second year from the date of the patent or of any succeeding year and the same shall be remitted to the patent office before the expiration of the second or the succeeding year.

(1A) The period for payment of renewal fees so specified in sub-rule (1) may be extended to such period not being more than six months if the request for such extension of time is made in Form 4 with the fee specified in the First Schedule.

(2) While paying the renewal fee, the number and date of the patent concerned and the year in respect of which the fee is paid shall be quoted.

(3) The annual renewal fees payable in respect of two or more years may be paid in advance.

(3) The Controller shall, after making such enquiry as he may deem necessary, credit any renewal fee and issue a certificate that the fee has been paid.

Section 142:

Fees. —

(1) There shall be paid in respect of the grant of patents and applications therefor, and in respect of other matters in relation to the grant of patents under this Act, such fees as may be prescribed by the Central Government.

(2) Where a fee is payable in respect of the doing of an act by the Controller, the Controller shall not do that act until the fee has been paid.

(3) Where a fee is payable in respect of the filing of a document at the patent office, the fee shall be paid along with the document or within the prescribed time and the document shall be deemed not to have been filed at the office if the fee has not been paid within such time.

(4) Where a principal patent is granted later than two years from the date of the filing of the application, the fees which have become due in the meantime may be paid within a term of three months from the date of the recording of the patent in the register or within the extended period not later than nine months from the date of recording.

EXHIBIT P6

10.2 Grant of Patent: (Section 43)

The patent is granted when the applicant for patent put the application in order for grant under Section 21 of the Act and when there is no pre-grant representation within the stipulated period or when the pre-grant opposition has been disposed of in favour of the applicant. After a patent is granted in respect of applications made under Section 5(2) of the repealed Act, the patent holder shall only be entitled to receive reasonable royalty from such enterprises which have made significant investment and were producing and marketing the concerned product prior to the 1st day of January 2005, and which continue to manufacture the product covered by the patent on the date of grant of the patent and no infringement proceedings shall be instituted against such enterprises.

10.3 Deletion of the claims at the time of sealing under section 43 and method of tagging of animal ear not an invention under section 2(1)(j): An application for patent no,.149056(149/Bom/77) was made by Pratap Shanker Rao Borade of SPADMA Plastic and Engineering Industry Aurangabad Maharashtra on April 25,1977 for a method and apparatus for tagging an animal ear. The complete specification was accepted by the Patent Office and notification was made in Gazette of India,. Part III, Section-2 dated 29.08.1981. At the time of sealing the method claims relating to tagging of ear were objected by the Parent Office on the ground that the method of tagging is not an invention under section 2(i)(j) and accordingly the amendments in the title and claims and specification were required and therefore the applicant was informed to make such corrections under section 78 (2) &(3) of the Act. It was argued by the applicant that the Controller has no power to delete the claims at the time of sealing of patent particularly Head office. If at all Controller has power to amend the claims, this power should be exercise by the Controller at the appropriate office. The Controller held that under the provision of section 78 (2) and (3) the Controller has powers to amend the specification by providing an opportunity of being heard. Further the method of tagging of ear of the animal was not held an invention under section 2(1)(j) of the patents Act 1970,not being a manner of manufacture. In the present context also such methods can not be considered as an invention due to lack of industrial application of the invention .

10.4 Amendment of Patent granted to deceased applicant (S. 44)

If the patentee had died or ceased to exist in case of a corporate body, the Controller may amend the patent by substituting the name of the Patentee-with the name of the legal representative. An application for such amendment of a patent should be made in Form 10 with the prescribed fee as given in the First schedule and should be accompanied by evidence verifying the statements made therein and accompanied by the letters patent.

EXHIBIT P6

10.5 Date of patent (S. 45)

1. The date of patent is the date of filing of the application. The date will be entered in the register of Patents. The purpose of "date of patent" is for calculating the duration of a patent and reckoning the time for payment of renewal fee.

2. In spite of date of filing being the date of patent, a suit or proceeding cannot be commenced or prosecuted against infringement committed before the date of publication.

10.6 Form, Extent and Effect of Patent (S. 46)

Every patent shall be in the prescribed form and shall have effect throughout India and shall be granted for one invention only,

A patent shall be in the form as specified in the Third Schedule with such modification as the circumstances of each case may require and shall bear the number accorded to the application after the grant of a complete specification. i.e. ,the number of the patent so granted.

10.7 Conditions under which patent is granted (S. 47)

The patent right is not an obsolete right. It is fettered right and it is subjected the following constraints: any machine, apparatus or other article in respect of which the patent is granted or any article made in respect of which the patent is granted may be used, by any person, for the purpose merely of experiment or research including the imparting of instructions to the students.

10.8 Rights of Patentee (S. 48)

The patent granted under the Act confer upon patentee the following rights, (subject to the provisions of S. 47 and other provisions in the Act)

a) In case of a patented product, the patentee shall have the exclusive right to prevent third parties, from the act of making, using, offering for sale, selling or importing for those purposes that product in India;

b) In case of a patented process, the patentee has the exclusive right to prevent third parties, from the act of using that process, and from the act of using, offering for sale, selling or importing for those purposes the product obtained directly by that process in India;

EXHIBIT P6

8.710.9 Patent rights not infringed when used on foreign vessels, etc., temporarily or accidentally in India (S. 49)

The use of the invention on board a vessel or aircraft registered in a foreign country or a land vehicle owned by a person ordinarily resident in such country, which comes to India (including the territorial waters thereof) temporarily or accidentally, will not infringe the rights of the Patentee. However this will not apply to vessels, aircraft or land vehicles owned by persons ordinarily resident in a foreign country the laws of which do not confer corresponding rights with respect to the use of inventions in vessels, aircraft or land vehicles owned by person, ordinarily resident in India while in the ports or within the territorial water of that foreign country or otherwise within the jurisdiction of its courts. As there is no commercial intention, there is no violation of patent right.

10.10 Rights of Co-owners of Patents (S. 50)

The patent right is a unitary right shared equally among the patent holders

~~a~~a) When a patent is granted to two or more persons, each of those persons will be entitled to an equal undivided share in the patent, unless an agreement to the contrary is in force. All of them can enjoy their rights for his own benefit without accounting to the other person or persons, but license or assignment of their share to any other person should not be made with out the consent of others.

~~b~~b) When a patented article is sold by one of two or more persons registered as grantee or proprietor of a patent, the purchaser and any person claiming through him shall deal with the article in the same manner as if the article had been sold by a sole patentee.

~~c~~c) For the purpose of property right, patent right is treated as movable property. The rules of law applicable to the ownership and devolution of movable property are applicable to patents. The mutual rights or obligations of trustees or of the legal representatives of a deceased person or their rights or obligations as such are not affected by the provisions in sub section (1) or (2).

10.11 Power of Controller to give directions to co-owners (S. 51)

i) Where two or more persons are registered as grantee or proprietor of a patent, the Controller may, upon application made to him in the prescribed manner by any of those persons, give such directions in accordance with the application as to the sale or lease of the patent or any interest therein, the grant of licenses under the patent, or the exercise of any right under section 50 in relation thereto, as he thinks fit [S.51(1)].

ii) If any person registered as grantee or proprietor of a patent fails to execute any instrument or to do any other thing required for the carrying out of any direction given under this section within fourteen days after being requested

in writing so to do by any of the other persons so registered, the Controller may, upon application made to him in the prescribed manner by any such other person, give directions empowering any person to execute that instrument or to do that thing in the name and on behalf of the person in default [S.51(2)].

(iii) An application for directions under sub-section (1) of section 51 shall be made in Form 11, in duplicate, and shall be accompanied by a statement setting out the facts upon which the applicant relies. A copy of the application and of the statement should be sent by the Controller to every other person registered as grantee or proprietor of the patent[S.51(1)], or to the person in default [S.51(2)], as the case may be , and the applicant shall supply sufficient number of copies for that purpose.

iii) Before giving any directions in pursuance of an application under this section, the Controller shall give an opportunity to be heard to the other person or persons registered as grantee or proprietor of the patent or to the person in default. No direction will be given under this section so as to affect the mutual rights or obligations of trustees or of the legal representatives of a deceased person or of their rights or obligations as such, or which is inconsistent with the terms of any agreement between person registered as grantee or proprietor of the Patent.

iv) Also the Controller has the power to grant a patent to the true and first inventor with the same date and number of a patent which has been revoked on the ground that it had been obtained by the patentee in fraud **S.52**

~~8.10~~10.12 TERM OF PATENT (S. 53)

i) The Term of Patent is 20 years from the date of the application in respect of all the patents including those for which the term has not expired on 20th May, 2003, when Patents (Amendment) Act 2002 came into force; provided that the renewal fee is paid every year before the due date or within the extended period (maximum six months).

ii) In order to keep the patent in force, renewal fee as given in the First Schedule (entry no. **17**) should be paid before the expiration of the second year from the date of patent and , subsequently, before the expiration of the succeeding year (Rule 80 (1)). The annual fee payable in respect of two or more years may be paid in advance.

iii) The term of patent and renewal fee in general shall be governed by the provisions of sec. 53, whereas the renewal fees, which has become due at the time of grant of Patent (grant), will be governed by section 142(4). It says that when the patent is granted later than two years from the date of filing of the application, the fee that has become due in the meantime might be paid within three months from the date of recording of the patent in the Register or within the extended period not later than nine months from the date of recording. (S. 142(4)). In the cases where the renewal fees, which has became due at the time of grant and which has become due after the grant are very close, they may be paid together along with required extension under section 53.

term for the patent for the main invention and thereupon the patent shall continue in force as an independent patent accordingly.

(2) No renewal fees shall be payable in respect of a patent of addition, but, if any such patent becomes an independent patent under sub-section (1) the same fees shall thereafter be payable, upon the same dates, as if the patent had been originally granted as an independent patent.

Section 56:

Validity of patents of addition.—

(1) The grant of a patent of addition shall not be refused, and a patent granted as a patent of addition shall not be revoked or invalidated, on the ground only that the invention claimed in the complete specification does not involve any inventive step having regard to any publication or use of—

(a) the main invention described in the complete specification relating thereto; or

(b) any improvement in or modification of the main invention described in the complete specification of a patent of addition to the patent for the main invention or of an application for such a patent of addition,

and the validity of a patent of addition shall not be questioned on the ground that the invention ought to have been the subject of an independent patent.

(2) For the removal of doubts it is hereby declared that in determining the novelty of the invention claimed in the complete specification filed in pursuance of an application for a patent of addition regard shall be had also to the complete specification in which the main invention is described.

11.1 Patent of Addition: Important Features

i) When an applicant feels that he has come across an invention which is a slight modification of the invention for which he has already applied for or has obtained patent, the applicant can go for patent of addition since the invention does not involve a substantial inventive step. It is also possible to convert an independent patent to a patent of addition at a later date if the subject matter was an improvement in or modification to a main invention for which he holds a patent. There is no need to pay separate renewal fee for the patent of addition during the term of the main patent. A Patent of Addition expires along with the main patent unless it is made independent according to the provisions in Section 54.

ii) However a Patent of Addition will not be granted unless the date filing of Application was the same or later than the date of filing of the complete specification in respect of the main invention *(S. 54(1),S. 54 (2) & S. 54(3))*.

iii) It should be noted that a patent of addition will not be granted before granting of the patent for the main invention.

iv) In an application for a patent of addition, the determination as to whether the invention proposed is or is not an improvement or modification of the applicant's previous invention, has to be done by the proper comparison between the novel contributions which each specification has made to the art and not between the sum of the characteristics claimed in the respective main invention and proposed patent of addition. In other words mere presence of a number of elements common to both inventions, is not sufficient to make one invention an improvement of or addition to the other

iv) The validity of a patent of addition will not be questioned on the ground that invention ought to have been the subject of an independent patent and on the ground that the invention claimed in the complete specification does not involve any inventive step having regard to the publication and use of the main invention (Section 56)

v) For determining the novelty of the invention claimed in the complete specification filed in pursuance of an application for patent of addition, regard should be had to the complete specification in which the main invention is described. Thus the complete specification of the main invention could be cited for novelty as an anticipatory publication.

vi) The Complete Specification of application for the patent of addition shall include specific reference to the number of main patent or the application number of main patent, as the case may be, and a definite statement that the invention comprises an improvement in, or a modification of the invention claimed in the specification of the main patent, granted or applied for.

vii) When improvement is patentable:

It is important to bear in mind that in order to be patentable an improvement on something known before or a combination or different matters already known, should be something more than a mere workshop improvement; and must independently satisfy, the test of invention or an "inventive step". To be patentable the improvement or the combination must produce a new result, or a new article or a better or cheaper article than before. The combination of old known integers may be so combined that by their working inter-relation they produce a new process or improved result. Mere collection of more than one integers or things, not involving the exercise of any inventive faculty, does not qualify for the grant to a patent; *Biswanath Prasad Radhey Shyam v. Hindustan Metal Industries,* AIR 1982 SC 1444.

11.2 Term of Patent of Addition (S.55)

The term of the patent of addition will run for a term equal to that of the patent for main invention. If the patent for the main invention is revoked under the Act, the patent of addition shall become an independent patent for the remainder of the term of patent for the main invention if the court or Controller so orders on the request made by the patentee.

EXHIBIT P6

No renewal fee is payable in respect of a patent of addition so long as the main patent remain in force. However if patent of addition becomes an independent patent, the same fee shall be payable upon the same dates as if the patent has been originally granted as an independent patent.

EXHIBIT P7

Experimental Parasitology 185 (2018) 107–114

Contents lists available at ScienceDirect

Experimental Parasitology

journal homepage: www.elsevier.com/locate/yexpr

Novel arylidene derivatives of quinoline based thiazolidinones: Synthesis, *in vitro*, *in vivo* and *in silico* study as antimalarials

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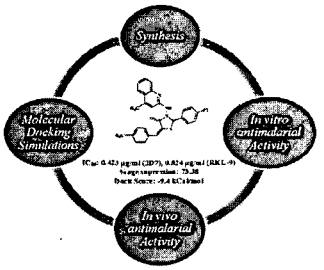
HIGHLIGHTS

- Synthesis and characterization of arylidene derivatives of quinoline based thiazolidinones.
- Evaluation for *in vitro* antimalarial potential against CQ-sensitive and CQ-resistant strains of *P. falciparum*.
- Top five potent compounds were further evaluated *in vivo* against *P. berghei*.
- Docking studies have been performed in the active site of *P. falciparum* lactate dehydrogenase.
- **5g** was found to be most promising candidate with 73.38% of suppression.

GRAPHICAL ABSTRACT



ARTICLE INFO

Article history:
Received 19 April 2017
Received in revised form
3 January 2018
Accepted 14 January 2018

1. Introduction

Malaria is a common and life-threatening disease transmitted via the bites of infected female *Anopheles* mosquitoes and caused by protozoan parasites of the genus *Plasmodium*. The prevalent species responsible for it are *Plasmodium falciparum* and *Plasmodium vivax* and the most lethal parasite is former one. The parasitic multiplication begins in the liver, infecting erythrocytes where a cyclic asexual replication begins with the cycles of fever and chills as symptoms of malaria. This infected person with severe illness can result to death within hours to days; if untreated (Warhurst et al., 2003; Mishra et al., 2017). According to the World Health Organisation (WHO) report, 212 million new cases of malaria worldwide in 2015 were reported (range 148–304 million). The WHO African Region accounted for most global cases of malaria (90%), followed by the South-East Asia Region (7%) and the Eastern Mediterranean Region (2%) (WHO, World Malaria Report, 2016). The surge in resistance of malaria parasites particularly in *P. falciparum* is an important factor in the persistence of this disease as a major worldwide public health threat (Sinha et al., 2014). The existing chemotherapy lacks satisfaction and effectiveness due to the side effects associated to long-term treatments. The existing drugs come across shortcomings like drug resistance and strain sensitivity for the clinically accessible chemotherapy (Sahu et al., 2016; Manohar et al., 2014; Teixeira et al., 2014).

Quinoline derived drugs like chloroquine, amodiaquine, quinine, quinidine, mefloquine, primaquine, lumefantrine, and halofantrine have long been used against malaria and all these shows

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https://doi.org/10.1016/j.exppara.2018.01.015

potent activity against the erythrocytic stage of infection (Olson et al., 1999). Primaquine also kills intrahepatic forms and gametocytes. The drugs act by accumulating in the parasite food vacuole and forming a complex with heme that prevents crystallization in the *Plasmodium* food vacuole. Heme polymerase activity is restraint, resulting in accumulation of cytotoxic-free heme (Foley and Tilley, 1998; Bekhit et al., 2012). The appearance of drug-resistant strains of the malaria parasite was the distressing outcome of efforts for the development of insecticide-resistant mosquitos (Kumar et al., 2015).

Several biological activities are associated with a five-membered ring thiazolidine which is an important pharmacophore. 4-Thiazolidinones having wide range of biological activities are evolved from thiazolidine with a carbonyl group at the position 4. Substitution of group to the carbon atom present at position 2 shows marked difference in structure and physicochemical properties of 4-thiazolidones (Singh et al., 2010; Dorn et al., 1995). Rigid molecules present in the nitrogen containing heterocyclic skeleton (thiazolidine-4-one) show biologically active scaffold for the design of new antimalarial drugs active against *Plasmodium* malaria parasite (Rojas Ruiz et al., 2011; Kumar et al., 2014; Rosenthal et al., 2002). In the current study, novel thiazolidinone-quinoline hybrids and their corresponding arylidene derivatives were prepared in good yield. Structure-Activity relationship has also been established to get a deep insight into the effect of different substitutions on antimalarial potential of the series. This work also includes the docking simulation of the active agents among the series to get an idea about the ligand receptor interaction. We, herein present study, reported the synthesis, *in vitro*, *in vivo* and *in silico* screening of synthesized series for antimalarial potential.

2. Experimental

2.1. Synthetic strategy adopted

The synthetic protocol followed for the synthesis of compounds under study has been outlined in Scheme 1.

2.1.1. General experimental procedure for synthesis of hydrazone (3a-e)

The whole synthesis is outlined in Scheme 1. To a mixture of 2-hydrazino-4-methylquinoline, **compound 2** in EtOH (20 ml) was added in an equimolar amount of various aromatic aldehyde and refluxed in the presence of 1–2 drop of glacial acetic acid for 6 h. The resulting solution was poured on crushed ice to yield hydrazones in high yield (Unsal-Tan et al., 2012; Kumar et al., 2007).

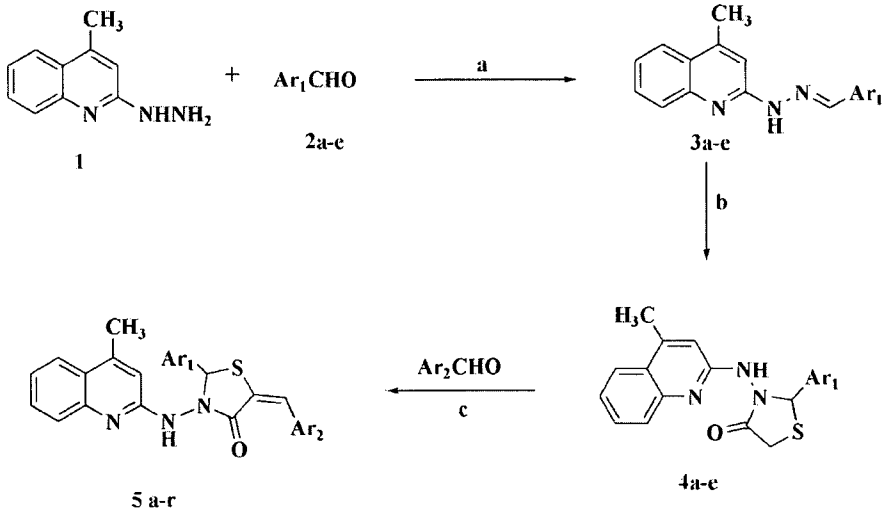
2.1.1.1. 1-Benzylidene-2-(4-methylquinolin-2-yl)hydrazine ***(3a).*** Yield 73%, mp 153–154 °C IR (υ, cm^{-1}): 3354.20 (N-H), 2919.50 (C-H), 1612.10 (C=N); ^1H NMR (400 MHz, $CDCl_3$, δ): 8.59 (s, br, 1H, NH), 8.23 (s, 1H, quinoline ring), 7.43–7.89 (m, 9H, aromatic), 7.28 (s, 1H, -N=CH), 2.74 (s, 3H, CH_3 of Qu-ring).

2.1.1.2. 1-(4-chlorobenzylidene)-2-(4-methylquinolin-2-yl)hydrazine ***(3b).*** Yield 71%, mp 166–168 °C IR (υ, cm^{-1}): 3361.12 (N-H), 2921.17 (C-H), 1613.24 (C=N), 653.27 (C-Cl); ^1H NMR (400 MHz, $CDCl_3$, δ): 8.61 (s, br, 1H, NH), 8.26 (s, 1H, quinoline ring), 7.83 (d, 2H), 7.65–7.89 (m, 4H), 7.29 (s, 1H, -N=CH), 6.98 (d, 2H), 2.78 (s, 3H, CH_3).

2.1.1.3. 1-(4-methylbenzylidene)-2-(4-methylquinolin-2-yl)hydrazine ***(3c).*** Yield 79%, mp 172–174 °C IR (υ, cm^{-1}): 3349.11 (N-H), 2929.41 (C-H), 1609.81 (C=N); ^1H NMR (400 MHz, $CDCl_3$, δ): 8.61(s, br, 1H, NH), 8.23 (s, 1H, quinoline ring), 7.86 (d, 2H), 7.55–7.78 (m, 4H), 7.26 (s, 1H, -N=CH), 6.99 (d, 2H), 2.73 (s, 3H, CH_3 of Qu-ring), 2.31 (s, 3H, CH_3).

2.1.1.4. 1-(4-methoxybenzylidene)-2-(4-methylquinolin-2-yl)hydrazine ***(3d).*** Yield 81%, mp 151–153 °C IR (υ, cm^{-1}): 3327.33 (N-H), 2932.45 (C-H), 1615.11 (C=N); ^1H NMR (400 MHz, $CDCl_3$, δ): 8.64 (s, br, 1H, NH), 8.23 (s, 1H, quinoline ring), 7.81 (d, 2H), 7.68–7.90 (m, 4H), 7.28 (s, 1H, -N=CH), 6.98 (d, 2H), 3.89 (s, 3H, OCH_3), 2.79 (s, 3H, CH_3).

2.1.1.5. 1-(4-methylquinolin-2-yl)-2-(thiophen-2-ylmethylene)hydrazine ***(3e).*** Yield 69%, mp 140–142 °C IR (υ, cm^{-1}): 3341.29 (N-H), 2922.17 (C-H), 1613.62 (C=N); ^1H NMR (400 MHz, $CDCl_3$, δ): 8.59 (s, br, 1H, NH), 8.17 (s, 1H, quinoline ring), 7.21 (s, 1H, -N=CH), 6.83–7.56 (m, 7H), 2.70 (s, 3H, CH_3).



Scheme 1. Synthesis of arylidene derivatives (**5 a-r**): **a)** 1–2 drops Glacial acetic acid, Ethanol, reflux, 6 h. **b)** Thioglycolic acid, 1,4-Dioxane, $ZnCl_2$, reflux, 8–10 h. **c)** Glacial acetic acid, Sodium acetate, reflux, 12 h.

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*2.1.2. General experimental procedure for synthesis of thiazolidinone **(4a-e)***

To a solution of compound (3) (0.01 mol) in 1,4 dioxane (50 ml) was added mercapto acetic acid (0.015 mol) with stirring and a little amount of anhydrous $ZnCl_2$ was added. The mixture was refluxed for 10–12 h, after the completion of reaction, it was cooled and the excess solvent distilled and poured into sodium bicarbonate solution to neutralize it. The solid product was filtered and washed with cold water. The resulting solid was recrystallized in ethanol (99%) (Desai and Dodiya, 2014; Nagalakshmi et al., 2013).

*2.1.2.1. 3-(4-methylquinolin-2-ylamino)-2-phenylthiazolidin-4-one **(4a)**.* Yield 51%, mp 202–204 °C IR (υ, cm^{-1}): 3406.34 (N-H), 1656.17 (C=O); ^1H NMR (400 MHz, DMSO-d_6, δ): 8.46 (s, 1H, NH), 8.16 (s, 1H, H_3 of quinoline), 7.33–7.90 (m, 9H), 6.77 (s, 1H, thiazolidinone, 2nd position), 5.29 (s, 2H, Thiazolidinone, 4th position), 2.63 (s, 3H, CH_3 of quinoline).

*2.1.2.2. 2-(4-chlorophenyl)-3-(4-methylquinolin-2-ylamino)thiazolidin-4-one **(4b)**.* Yield 54%, mp 230–232 °C IR (υ, cm^{-1}): 3409.46 (N-H), 1659.32 (C=O); ^1H NMR (400 MHz, DMSO-d_6, δ): 8.52 (s, 1H, NH), 8.14 (s, 1H, H_3 of quinoline), 7.20–7.85 (m, 8H), 6.65 (s, 1H, thiazolidinone, 2nd position), 5.33 (s, 2H, Thiazolidinone, 4th position), 2.68 (s, 3H, CH_3 of-quinoline).

*2.1.2.3. 3-(4-methylquinolin-2-ylamino)-2-p-tolylthiazolidin-4-one **(4c)**.* Yield 49%, mp 236–238 °C IR (υ, cm^{-1}): 3411.43 (N-H), 1659.22 (C=O); ^1H NMR (400 MHz, DMSO-d_6, δ):8.41 (s, 1H, NH), 8.19 (s, 1H, H_3 of quinoline), 7.15–7.95 (m, 8H), 6.73 (s, 1H, thiazolidinone, 2nd position), 5.06 (s, 2H, Thiazolidinone, 4th position), 2.65 (s, 3H, CH_3 of quinoline), 2.35 (s, 3H, CH_3 of phenyl).

*2.1.2.4. 2-(4-methoxyphenyl)-3-(4-methylquinolin-2-ylamino)thiazolidin-4-one **(4d)**.* Yield 57%, mp 220–222 °C IR (υ, cm^{-1}): 3410.58 (N-H), 1654.63 (C=O); ^1H NMR (400 MHz, DMSO-d_6, δ): 8.42 (s, 1H, NH), 8.26 (s, 1H, H_3 of quinoline), 7.06–7.80 (m, 8H), 6.54 (s, 1H, thiazolidinone, 2nd position), 5.15 (s, 2H, Thiazolidinone, 4th position), 4.35 (s, 3H, OCH_3 of phenyl), 2.67 (s, 3H, CH_3 of quinoline).

*2.1.2.5. 3-(4-methylquinolin-2-ylamino)-2-(thiophen-2-yl)thiazolidin-4-one **(4e)**.* Yield 42%, mp 200–202 °C IR (υ, cm^{-1}): 3399.18 (N-H), 1659.47 (C=O); ^1H NMR (400 MHz, DMSO-d_6, δ): 8.48 (s, 1H, NH), 8.21 (s, 1H, H_3 of quinoline), 7.16–7.85 (m, 7H), 5.23 (s, 2H, Thiazolidinone, 4th position), 6.67 (s, 1H, thiazolidinone, 2nd position), 2.56 (s, 3H, CH_3 of quinoline).

2.1.3. General experimental procedure for synthesis of arylidine derivatives

A well-stirred solution of 3-(4-methylquinolin-2-ylamino)-2-arylthiazolidin-4-ones **(4a-e)** in 20 ml glacial acetic acid was buffered with sodium acetate, 0.66 g (8 mmol) followed by addition of substituted arylaldehyde (6 mmol). The solution was refluxed for 12 h and then poured into ice-cold water to yield titled compounds, **5a-r**. The resulting product was purified by recrystallization from dioxane (Omar et al., 2010; Deep et al., 2014).

*2.1.3.1. 5-Benzylidene-3-(4-methylquinolin-2-ylamino)-2-phenylthiazolidin-4-one **(5a)**.* Yield 62%, mp 212–214 °C IR (υ, Cm^{-1}): 1527 (=C-H), 2974 (=C-H), 1565 (C=N); ^1H NMR (400 MHz, DMSO-d_6, δ): 8.25 (s, 1H, NH), 8.11 (s, 1H, H_3 of quinoline), 6.82 (s, 1H, thiazolidinone, 2nd position), 6.9–7.85 (m, 14H), 5.88 (s, 1H, =CH-Ar), 2.70 (s, 3H, CH_3 of quinoline); MS: m/z = 424.35 (M+1); Anal. Calcd for $C_{26}H_{21}N_3OS$: C, 73.73; H, 5.00; N, 9.92. Found: C, 73.81; H, 5.02; N, 9.89.

*2.1.3.2. 5-(4-chlorobenzylidene)-3-(4-methylquinolin-2-ylamino)-2-phenylthiazolidin-4-one **(5b)**.* Yield 56%, mp 219–221 °C IR (υ, cm^{-1}): 1525 (=C-H), 2975 (=C-H), 1569 (C=N); ^1H NMR (400 MHz, DMSO-d_6, δ): 8.24 (s, 1H, NH), 8.13 (s, 1H, H_3 of quinoline), 6.88 (s, 1H, thiazolidinone, 2nd position), 6.78–7.67 (m, 13H), 5.82 (s, 1H, =CH-Ar), 2.73 (s, 3H, CH_3 of quinoline); MS: m/z = 458.73 (M+1); Anal. Calcd for $C_{26}H_{20}ClN_3OS$: C, 68.19; H, 4.40; N, 9.18. Found: C, 68.21; H, 4.46; N, 9.25.

*2.1.3.3. 5-(4-methylbenzylidene)-3-(4-methylquinolin-2-ylamino)-2-phenylthiazolidin-4-one **(5c)**.* Yield 60%, mp 199–201 °C IR (υ, cm^{-1}): 1526 (=C-H), 2972 (=C-H), 1571 (C=N); ^1H NMR (400 MHz, DMSO-d_6, δ):8.23 (s, 1H, NH), 8.11 (s, 1H, H_3 of quinoline), 6.92–7.83 (m, 13H), 6.86 (s, 1H, thiazolidinone, 2nd position), 5.80 (s, 1H, =CH-Ar), 2.69 (s, 3H, CH_3 of quinoline), 2.45 (s, 3H, CH_3 of phenyl). MS: m/z = 438.47 (M+1); Anal. Calcd for $C_{27}H_{23}N_3OS$: C, 74.11; H, 5.30; N, 9.60. Found: C, 74.19; H, 5.37; N, 9.71.

*2.1.3.4. 5-(4-methoxybenzylidene)-3-(4-methylquinolin-2-ylamino)-2-phenylthiazolidin-4-one **(5d)**.* Yield 63%, mp 205–206 °C IR (υ, cm^{-1}): 1529 (=C-H), 2976 (=C-H), 1573 (C=N); ^1H NMR (400 MHz, DMSO-d_6, δ): 8.23 (s, 1H, NH), 8.17 (s, 1H, H_3 of quinoline), 6.83 (s, 1H, thiazolidinone, 2nd position), 6.77–7.69 (m, 13H), 5.83 (s, 1H, =CH-Ar), 4.03 (s, 3H, OCH_3 of phenyl), 2.67 (s, 3H, CH_3 of quinoline); MS: m/z = 454.35 (M+1); Anal. Calcd for $C_{27}H_{23}N_3O_2S$: C, 71.50; H, 5.11; N, 9.26. Found: C, 71.53; H, 5.16; N, 9.21.

*2.1.3.5. 5-Benzylidene-2-(4-chlorophenyl)-3-(4-methylquinolin-2-ylamino)thiazolidin-4-one **(5e)**.* Yield 63%, mp 205–206 °C IR (υ, cm^{-1}): 1531 (=C-H), 2972 (=C-H), 1571 (C=N); ^1H NMR (400 MHz, DMSO-d_6, δ): 8.27 (s, 1H, NH), 8.19 (s, 1H, H_3 of quinoline), 7.1–7.92 (m, 13H), 6.79 (s, 1H, thiazolidinone, 2nd position), 5.84 (s, 1H, =CH-Ar), 2.65 (s, 3H, CH_3 of quinoline); MS: m/z = 458.35 (M+1); Anal. Calcd for $C_{26}H_{20}ClN_3OS$: C, 68.19; H, 4.40; N, 9.18. Found: C, 68.21; H, 4.46; N, 9.25.

*2.1.3.6. 5-(4-chlorobenzylidene)-2-(4-chlorophenyl)-3-(4-methylquinolin-2-ylamino) thiazolidin -4-one **(5f)**.* Yield 61%, mp 217–218 °C IR (υ, cm^{-1}): 1527 (=C-H), 2971 (=C-H), 1573 (C=N); ^1H NMR (400 MHz, DMSO-d_6, δ): 8.29 (s, 1H, NH), 8.18 (s, 1H, H_3 of quinoline), 7.12–7.97 (m, 12H), 6.75 (s, 1H, thiazolidinone, 2nd position), 5.87 (s, 1H, =CH-Ar), 2.68 (s, 3H, CH_3 of quinoline). MS: m/z = 492.45 (M+1); Anal. Calcd for $C_{26}H_{19}Cl_2N_3OS$: C, 63.42; H, 3.89; N, 8.53. Found: C, 63.52; H, 3.93; N, 8.55.

*2.1.3.7. 5-(4-methylbenzylidene)-2-(4-chlorophenyl)-3-(4-methylquinolin-2-ylamino) thiazolidin-4-one **(5g)**.* Yield 59%, mp 221–223 °C IR (υ, cm^{-1}): 1528 (=C-H), 2968 (=C-H), 1571 (C=N); ^1H NMR (400 MHz, DMSO-d_6, δ): 8.33 (s, 1H, NH), 8.17 (s, 1H, H_3 of quinoline), 7.14–7.93 (m, 12H), 6.79 (s, 1H, thiazolidinone, 2nd position), 5.80 (s, 1H, =CH-Ar), 2.65 (s, 3H, CH_3 of quinoline), 2.47 (s, 3H, CH_3 of phenyl); MS: m/z = 492.45 (M+1); Anal. Calcd for $C_{27}H_{22}ClN_3OS$ C, 68.71; H, 4.70; N, 8.90. Found: C, 68.76; H, 4.73; N, 8.94.

*2.1.3.8. 5-(4-methoxybenzylidene)-2-(4-chlorophenyl)-3-(4-methylquinolin-2-ylamino) thiazolidin-4-one **(5h)**.* Yield 65%, mp 198–201 °C IR (υ, cm^{-1}): 1532 (=C-H), 2976 (=C-H), 1577 (C=N); ^1H NMR (400 MHz, DMSO-d_6, δ): 8.31 (s, 1H, NH), 8.20 (s, 1H, H_3 of quinoline), 6.88–7.87 (m, 12H), 6.72 (s, 1H, thiazolidinone, 2nd position), 5.84 (s, 1H, =CH-Ar), 4.12 (s, 3H, OCH_3 of phenyl), 2.71 (s, 3H, CH_3 of quinoline); MS: m/z = 488.34 (M+1); Anal. Calcd for $C_{27}H_{22}ClN_3O_2S$; C, 66.45; H, 4.54; N, 8.61. Found: C, 66.47; H, 4.53; N, 8.64.

*2.1.3.9. 5-Benzylidene-3-(4-methylquinolin-2-ylamino)-2-p-tolylthiazolidin-4-one **(5i)**.* Yield 54%, mp 213–215 °C IR (*v*, cm^{-1}): 1530 (=C-H), 2974 (=C-H), 1573 (C=N); ^1H NMR (400 MHz, DMSO-d_6, δ): 8.26 (s, 1H, NH), 8.15 (s, 1H, H_3 of quinoline), 7.1–7.92 (m, 13H), 6.71 (s, 1H, thiazolidinone, 2nd position), 5.87 (s, 1H, =CH-Ar), 2.66 (s, 3H, CH_3 of quinoline), 2.34 (s, 3H, CH_3 of phenyl). MS: *m/z* = 438.47 (M+1); Anal. Calcd for $C_{27}H_{23}N_3OS$: C, 74.11; H, 5.30; N, 9.60. Found: C, 74.19; H, 5.37; N, 9.71.

*2.1.3.10. 5-(4-chlorobenzylidene)-3-(4-methylquinolin-2-ylamino)-2-p-tolylthiazolidin-4-one **(5j)**.* Yield 61%, mp 219–220 °C IR (*v*, cm^{-1}): 1529 (=C-H), 2967 (=C-H), 1569 (C=N); ^1H NMR (400 MHz, DMSO-d_6, δ): 8.28 (s, 1H, NH), 8.12 (s, 1H, H_3 of quinoline), 7.12–7.96 (m, 12H), 6.72 (s, 1H, thiazolidinone, 2nd position), 5.80 (s, 1H, =CH-Ar), 2.64 (s, 3H, CH_3 of quinoline), 2.32 (s, 3H, CH_3 of phenyl). MS: *m/z* = 492.45 (M+1); Anal. Calcd for $C_{27}H_{22}ClN_3OS$ C, 68.71; H, 4.70; N, 8.90. Found: C, 68.76; H, 4.73; N, 8.94.

*2.1.3.11. 5-(4-methylbenzylidene)-3-(4-methylquinolin-2-ylamino)-2-p-tolylthiazolidin-4-one **(5k)**.* Yield 49%, mp 209–211 °C IR (*v*, cm^{-1}): 1525 (=C-H), 2965 (=C-H), 1567 (C=N); ^1H NMR (400 MHz, DMSO-d_6, δ): 8.36 (s, 1H, NH), 8.12 (s, 1H, H_3 of quinoline), 6.98–7.81 (m, 12H), 6.59 (s, 1H, thiazolidinone, 2nd position), 5.68 (s, 1H, =CH-Ar), 2.68 (s, 3H, CH_3 of quinoline), 2.41 (s, 3H, CH_3 of phenyl), 2.34 (s, 3H, CH_3 of phenyl). MS: *m/z* = 452.35 (M+1); Anal. Calcd for $C_{28}H_{25}N_3OS$; C, 74.47; H, 5.58; N, 9.31. Found: C, 74.56; H, 5.62; N, 9.36.

*2.1.3.12. 5-(4-methoxybenzylidene)-3-(4-methylquinolin-2-ylamino)-2-p-tolylthiazolidin-4-one **(5l)**.* Yield 54%, mp 206–207 °C IR (*v*, cm^{-1}): 1526 (=C-H), 2969 (=C-H), 1572 (C=N); ^1H NMR (400 MHz, DMSO-d_6, δ): 8.29 (s, 1H, NH), 8.15 (s, 1H, H_3 of quinoline), 7.12–7.96 (m, 12H), 6.61 (s, 1H, thiazolidinone, 2nd position), 5.73 (s, 1H, =CH-Ar), 4.25 (s, 3H, OCH_3 of phenyl), 2.71 (s, 3H, CH_3 of quinoline), 2.38 (s, 3H, CH_3 of phenyl). MS: *m/z* = 468.53 (M+1); Anal. Calcd for $C_{28}H_{25}N_3O_2S$; C, 71.92; H, 5.39; N, 8.99. Found: C, 71.99; H, 5.45; N, 9.02.

*2.1.3.13. 5-Benzylidene-2-(4-methoxyphenyl)-3-(4-methylquinolin-2-ylamino)thiazolidin-4-one **(5m)**.* Yield 61%, mp 202–203 °C IR (*v*, cm^{-1}): 1527 (=C-H), 2974 (=C-H), 1576 (C=N); ^1H NMR (400 MHz, DMSO-d_6, δ): 8.37 (s, 1H, NH), 8.20 (s, 1H, H_3 of quinoline), 7.1–7.92 (m, 13H), 6.71 (s, 1H, thiazolidinone, 2nd position), 5.74 (s, 1H, =CH-Ar), 4.27 (s, 3H, OCH_3 of phenyl), 2.68 (s, 3H, CH_3 of quinoline), MS: *m/z* = 454.35 (M+1); Anal. Calcd for $C_{27}H_{23}N_3O_2S$: C, 71.50; H, 5.11; N, 9.26. Found: C, 71.53; H, 5.16; N, 9.21.

*2.1.3.14. 5-(4-chlorobenzylidene)-2-(4-methoxyphenyl)-3-(4-methylquinolin-2-ylamino) thiazolidin-4-one **(5n)**.* Yield 56%, mp 199–201 °C IR (*v*, cm^{-1}): 1526 (=C-H), 2972 (=C-H), 1575 (C=N); ^1H NMR (400 MHz, DMSO-d_6, δ): 8.33 (s, 1H, NH), 8.21 (s, 1H, H_3 of quinoline), 6.92–7.94 (m, 12H), 6.74 (s, 1H, thiazolidinone, 2nd position), 5.79 (s, 1H, =CH-Ar), 4.27 (s, 3H, OCH_3 of phenyl), 2.67 (s, 3H, CH_3 of quinoline). MS: *m/z* = 488.34 (M+1); Anal. Calcd for $C_{27}H_{22}ClN_3O_2S$; C, 66.45; H, 4.54; N, 8.61. Found: C, 66.47; H, 4.53; N, 8.64.

*2.1.3.15. 5-(4-methylbenzylidene)-2-(4-methoxyphenyl)-3-(4-methylquinolin-2-ylamino)thiazolidin-4-one **(5o)**.* Yield 53%, mp 210–211 °C IR (*v*, cm^{-1}): 1522 (=C-H), 2976 (=C-H), 1577 (C=N); ^1H NMR (400 MHz, DMSO-d_6, δ): 8.38 (s, 1H, NH), 8.16 (s, 1H, H_3 of quinoline), 6.98–7.90 (m, 12H), 6.72 (s, 1H, thiazolidinone, 2nd position), 5.72 (s, 1H, =CH-Ar), 4.18 (s, 3H, OCH_3 of phenyl), 2.62 (s, 3H, CH_3 of quinoline), 2.38 (s, 3H, CH_3 of phenyl). MS: *m/z* = 468.53 (M+1); Anal. Calcd for $C_{28}H_{25}N_3O_2S$; C, 71.92; H, 5.39; N, 8.99. Found: C, 71.99; H, 5.45; N, 9.02.

*2.1.3.16. 5-(4-methoxybenzylidene)-2-(4-methoxyphenyl)-3-(4-methylquinolin-2-ylamino)thiazolidin-4-one **(5p)**.* Yield 52%, mp 229–231 °C IR (*v*, cm^{-1}): 1527 (=C-H), 2976 (=C-H), 1573 (C=N); ^1H NMR (400 MHz, DMSO-d_6, δ):8.26 (s, 1H, NH), 8.12 (s, 1H, H_3 of quinoline), 6.98–7.88 (m, 12H), 6.69 (s, 1H, thiazolidinone, 2nd position), 5.68 (s, 1H, =CH-Ar), 4.26 (s, 3H, OCH_3 of phenyl), 4.17 (s, 3H, OCH_3 of phenyl), 2.72 (s, 3H, CH_3 of quinoline). MS: *m/z* = 484.25 (M+1); Anal. Calcd for $C_{28}H_{25}N_3O_3S$; C, 69.54; H, 5.21; N, 8.69. Found: C, 69.58; H, 5.28; N, 8.73.

*2.1.3.17. 5-Benzylidene-3-(4-methylquinolin-2-ylamino)-2-(thiophen-2-yl)thiazolidin-4-one **(5q)**.* Yield 67%, mp 189–191 °C IR (*v*, cm^{-1}): 1526 (=C-H), 2979 (=C-H), 1569 (C=N); ^1H NMR (400 MHz, DMSO-d_6, δ): 8.34 (s, 1H, NH), 8.13 (s, 1H, H_3 of quinoline), 6.93–7.75 (m, 12H), 6.72 (s, 1H, thiazolidinone, 2nd position), 5.81 (s, 1H, =CH-Ar), 2.76 (s, 3H, CH_3 of quinoline). MS: *m/z* = 430.19 (M+1); Anal. Calcd for $C_{24}H_{19}N_3OS_2$; C, 67.11; H, 4.46; N, 9.78. Found: C, 67.18; H, 4.51; N, 9.83.

*2.1.3.18. 5-(4-methylbenzylidene)-3-(4-methylquinolin-2-ylamino)-2-(thiophen-2-yl)thiazolidin-4-one **(5r)**.* Yield 54%, mp 182–183 °C IR (*v*, cm^{-1}): 1531 (=C-H), 2971 (=C-H), 1573 (C=N); ^1H NMR (400 MHz, DMSO-d_6, δ): 8.36 (s, 1H, NH), 8.17 (s, 1H, H_3 of quinoline), 6.98–7.96 (m, 12H), 6.92 (s, 1H, thiazolidinone, 2nd position), 5.84 (s, 1H, =CH-Ar), 2.78 (s, 3H, CH_3 of quinoline), 2.36 (s, 3H, CH_3 of phenyl). MS: *m/z* = 444.61 (M+1); Anal. Calcd for $C_{25}H_{21}N_3OS_2$; C, 67.69; H, 4.77; N, 9.47. Found: C, 67.68; H, 4.77; N, 9.51.

2.2. In vitro antimalarial activity

Schizont Maturation Inhibition (SMI) assay was performed against Chloroquine sensitive strain, 3D7 and Chloroquine resistant strain, RKL9 of *Plasmodium falciparum* in RPMI medium (Rieckmann et al., 1978). The cultures of both strains were synchronized using 5% aqueous sorbitol solution. All stages except trophozoites (ring form) of parasite were degenerated and removed by centrifugation at 1500 rpm for 5 min. The test solutions were prepared in 0.1 ml DMSO and further diluted to produce concentration of 1.98–500 μg/ml with RPMI 1640 medium. 96 well plates were used for both cultures and inoculated with synchronized parasites. The plates were kept for 24–30 h in 5% CO_2 incubator at 37 °C. Thick smear was prepared for each well, stained with Giemsa stain and examined microscopically. EC_{50} was calculated for evaluation of antimalarial potential (Saini et al., 2016).

2.3. In vivo antimalarial screening

Acute toxicity study was performed by following OECD guidelines 423. Overnight fasted 4–6 week old using Swiss Albino Mice were used. The mice was observed for any symptom of toxicity such as change in colour of eyes, fur, urination, defecation, posture alteration, aggressiveness or any lethal response for first 4 h and examined for 24 h. If no lethal response was found, then second animal was administered with higher dose and observed as earlier. The animal were given dose for 14 days and kept under observation for the calculation of LD_{50} (Ecobichon, 1977).

In vivo antimalarial potential was investigated by 4-day suppressive test using Swiss Albino Mice of 4–6 week (22±5 g, 5 animal/group) against *P. berghei*. Each mice was inoculated with 0.2 ml of 1×10^6 parasitized RBC (from donor mice) intraperitoneally on day 0. Two hour post-infection, all the test groups were

administered with test drug at 200 mg/kg and standard at 5 mg/kg for 4 consecutive days. On day 4, thin smears were prepared from tail vein and were stained using Giemsa stain for evaluation of parasitemia microscopically. The mortality was observed for 7 days to check the survival rate. Percentage of parasitemia inhibition was calculated by (A-B)/A × 100, where A is the parasitemia of negative control (without any treatment) and B is the parasitemia of each test group (Devi et al., 2001; Manohar et al., 2012).

2.4. Docking study

In an effort to get insight the factors determining the bioactivity of novel arylidene derivatives of thiazolidinone-quinoline hybrids, docking simulations were performed in the active sight of *Plasmodium falciparum* lactate dehydrogenase (Singh et al., 2016; Prathiban et al., 2015). The molecular docking study was done by AutodockVina and autodock tools using Lamarckian Genetic Algorithm (Trott and Olson, 2010). The crystal structure of protein (PDB ID: 1CET) was obtained from Protein Data Bank (www.rcsb.org) (Kaushik et al., 2015). The structures of five ligands were prepared using ChemDrawUltra 8.0.3. Then the structures were converted into required. pdbqt format using ADT 1.5.6. During protein preparation, all the water molecules were removed; polar hydrogen and partial charges were added and saved as. pdbqt. The active grid was generated for docking with size 40 × 40 × 40 along x, y & z centres, 25.8, 26.829 & 9.405 respectively with 0.375 Å grid spacing. Further, ADT and Python were used for visualisation and identification of residues involved in binding.

3. Result and discussion

3.1. Chemistry

The synthetic protocol was successfully followed for the synthesis of thiazolidinone and their respective arylidene derivatives. The first step, compounds **(3a-e)** were prepared in good yield by condensation of 2-hydrazino-4-methylquinoline with different aromatic aldehyde in acidic conditions. In next step, hydrazone intermediates were converted into thiazolidinone **(4a-e)** by reacting with thioglycolic acid in dioxane. Finally the target compounds, 5-Arylidene-3-(4-methylquinolin-2-ylamino)-2-arylthiazolidin-4-one, were obtained by reacting equimolar amount of **(4a-e)** and aryl aldehyde in Glacial acetic acid.

Characteristic data from FTIR and ^{1}H NMR was studied for the progression of reaction. A strong band in range of 3200–3400 cm^{-1} is attributed to secondary amine present in all the intermediates and final compounds. Similarly, ^{1}H NMR of all the derivatives were supported by the presence of one broad singlet corresponding to NH nearly at δ 8.3–8.6 and a sharp singlet for proton at 3rd position in quinoline ring around δ 8.2. Characteristic peak in FTIR of compounds **(4a-e)** was observed in range of 1650–1660 cm^{-1} due to the presence of carbonyl group. In ^{1}H NMR, two distinct singlets corresponding to C-CH_2-S and N-CH-S at δ 5.29 and 6.77 ppm respectively, confirmed the synthesis of thiazolidinone ring. Further, disappearance of singlet at δ 5.29 for two protons with emergence of new singlet in δ 5.88 for single proton authenticated the progression of reaction from thiazolidinone to target arylidene derivatives. Eventually, all the structures of synthesized compounds were found in accordance with mass and elemental analysis.

3.2. In vitro antimalarial evaluation and structure-activity relationship

The antimalarial potential of entire set of synthesized analogues was assessed by *in vitro* antimalarial assay against Chloroquine-sensitive, 3D7 and Chloroquine-resistant, RKL9 strains of *Plasmodium falciparum*. The activity results of the target molecules have been displayed in Table 1. All compounds exhibited good antimalarial potency with EC_{50} range 0.432–2.672 μg/ml against 3D7 while against RKL-9 EC_{50} varies from 0.824 to 11.451 μg/ml. EC_{50} value for all the synthesized derivatives against both Chloroquine sensitive and Chloroquine resistant strain has also been represented graphically in Fig. 1. Compound **5g** was found to be most potent among the series with EC_{50} of 0.423 μg/ml and 0.824 μg/ml against 3D7 and RKL-9 respectively. Compound **5r** displayed maximum EC_{50} against both the strains and hence considered as least active compound of the series. Compounds **5b, 5e, 5g, 5j** and **5n** were found to be five most potent analogues among the series with EC_{50} (3D7/RKL-9) values of 0.731/1.617, 0.734/2.011, 0.423/0.824, 0.562/0.992 and 0.632/1.211 μg/ml respectively. From *in vitro* study, we have concluded the results in structure-activity relationship.

3.2.1. Structure-activity relationship

It has been revealed that the presence of chloro group at *p*-position of either ring led to the development of best candidate for malaria as compounds **5b, 5c, 5g, 5h, 5j** and **5n** were found to have EC_{50} less than 1 μg/ml. Unfortunately, 5f, substitution of both rings with chloro group didn't meet the expectation of enhanced potency and was found to be less active than above given (substitution with chloro group at one ring only) derivatives. Incorporation of methyl group along with chloro group was proven to be best match and hence **5g** was the most potent derivative among the series. Furthermore, it was also indicated that the presence of methyl group was more preferred as compared to methoxy group at *p*-position of phenyl rings. The effect of ring size was also established by replacing phenyl ring with five membered sulphur containing thienyl ring, the activity was reduced by many folds, even compound **5r**, least active among the series, belongs to this category. The complete Structure-activity relationship study regarding various substitution around arylidene derivatives suggested that *p*-position of rings should be occupied by chloro group at one ring while methyl ring at another to get remarkable antimalarial activity. The SAR study of series is depicted in Fig. 2.

3.3. In vivo antimalarial activity

No mortality was observed during acute toxicity study. At the end of study, the dose calculated for all the synthetic derivatives was 200 mg/kg. Among the synthesized analogues **5 a-r**, five most potent compounds, **5b, 5e, 5g, 5j** and **5n**, were further selected for *in vivo* antimalarial evaluation. Compounds were screened against *P. berghei* in swiss albino mice using 4-day suppressive test. Compound **5g**, bearing *p*-chloro group in one ring and *p*-methyl group in another, showed best activity with 73.38% of parasitemia inhibition. Four mice out of five were found to be alive on 7th day. Antimalarial potential displayed by 5 selected compounds has been presented in Table 2. Microscopic examination of thin smears of control group, standard (Chloroquine), **5g** (most active) and **5e** (least active) from *in vivo* study has been displayed in Fig. 3. Further the plausible route for antimalarial activity of compounds was studied through *in-silico* approach.

EXHIBIT P7

Table 1
In vitro antimalarial activity of synthetic derivatives **5(a-r)** against CQ-sensitive (3d7) and CQ-resistant (RKL-9) strain of *P. falciparum*.

S. No.	Compounds	Ar_1	Ar_2	EC_{50} (3D7, μg/ml)	EC_{50} (RKL-9, μg/ml)
1.	5a	C_6H_5-	C_6H_5-	1.012	3.121
2.	5b	C_6H_5-	*p*-Cl C_6H_4-	0.731	1.617
3.	5c	C_6H_5-	*p*-$CH_3C_6H_4$-	1.212	4.723
4.	5d	C_6H_5-	*p*-$OCH_3C_6H_4$-	1.230	5.123
5.	5e	*p*-Cl C_6H_4-	C_6H_5-	0.734	2.011
6.	5f	*p*-Cl C_6H_4-	*p*-Cl C_6H_4-	0.783	2.026
7.	5g	*p*-Cl C_6H_4-	*p*-$CH_3C_6H_4$-	0.423	0.824
8.	5h	*p*-Cl C_6H_4-	*p*-$OCH_3C_6H_4$-	0.791	2.114
9.	5i	*p*-$CH_3C_6H_4$-	C_6H_5-	1.501	6.726
10.	5j	*p*-$CH_3C_6H_4$-	*p*-Cl C_6H_4-	0.562	0.992
11.	5k	*p*-$CH_3C_6H_4$-	*p*-$CH_3C_6H_4$-	1.732	9.001
12.	5l	*p*-$CH_3C_6H_4$-	*p*-$OCH_3C_6H_4$-	1.621	7.992
13.	5m	*p*-$OCH_3C_6H_4$-	C_6H_5-	1.414	6.023
14.	5n	*p*-$OCH_3C_6H_4$-	*p*-Cl C_6H_4-	0.632	1.211
15.	5'	*p*-$OCH_3C_6H_4$-	*p*-$CH_3C_6H_4$-	1.536	7.231
16.	5p	*p*-$OCH_3C_6H_4$-	*p*-$OCH_3C_6H_4$-	1.801	9.373
17.	5q	2-thienyl	C_6H_5-	1.931	9.921
18.	5r	2-thienyl	*p*-$CH_3C_6H_4$-	2.672	11.451
19.	CQ	–	–	0.375	0.80

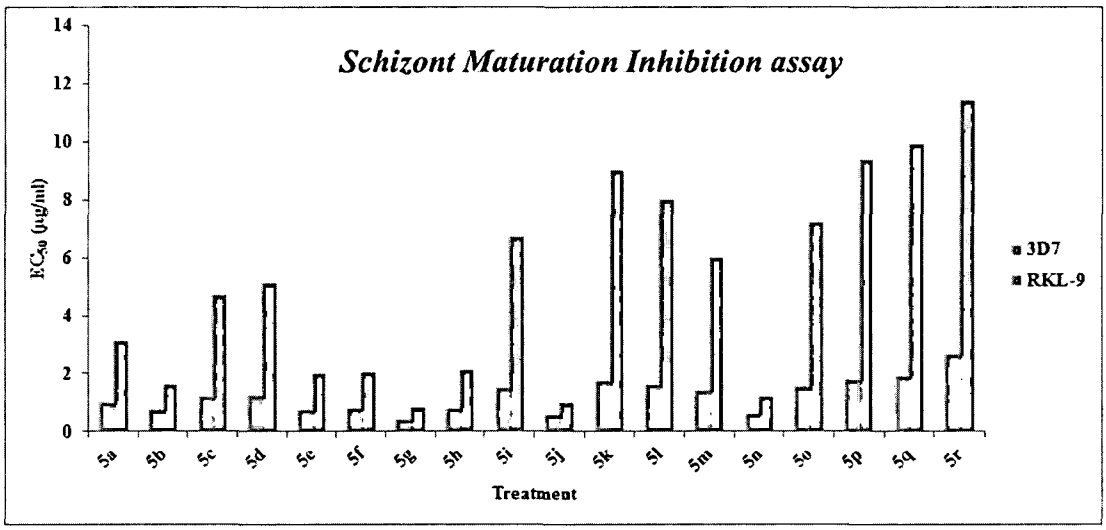

Fig. 1. EC_{50} of synthesized derivatives, **5a-r**, against 3D7 and RKL-9 of *Plasmodium falciparum*.

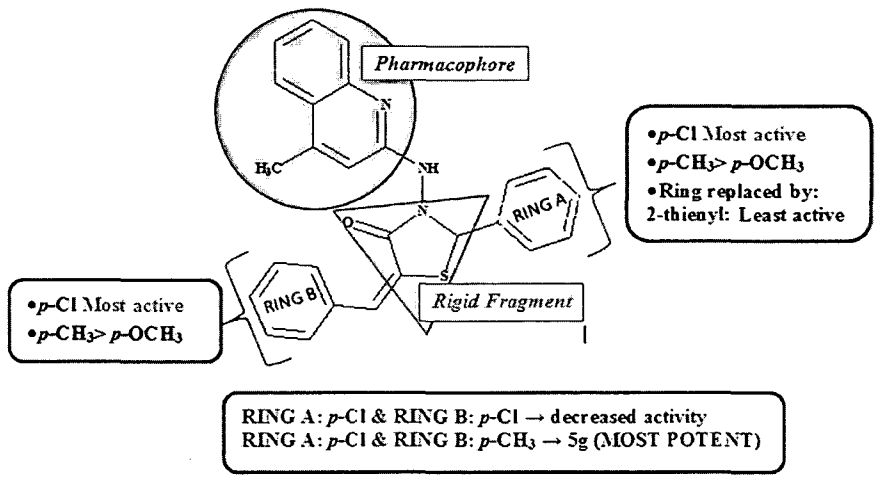

Fig. 2. Structure-Activity Relationship of Arylidene derivatives of Thiazolidinone-quinoline hybrids.

Table 2
Effect of five selected compounds on parasitemia of *P. berghei* infected mice.

S. No.	Drug treatment	Dose\kg	No. Of animals	%parasitemia	Percentage inhibition	Survival on 7th day
1.	Control	–	5	49.62 ± 0.304	–	0/5
2.	Standard	5 mg/kg	5	–	100	5/5
3.	5b	200 mg/kg[a]	5	29.43 ± 0.312	40.68**	2/5
4.	5e	200 mg/kg[a]	5	35.72 ± 0.403	28.01	3/5
5.	5g	200 mg/kg[a]	5	13.21 ± 0.126	73.38**	4/5
6.	5j	200 mg/kg[a]	5	17.34 ± 0.301	65.05**	4/5
7.	5n	200 mg/kg[a]	5	21.21 ± 0.116	57.26**	3/5

N = 5. Values are expressed as Mean ± SEM and analyze by ANOVA. **p < .01(significant). Values are compared with control group.
[a] Dose calculated by acute toxicity method.

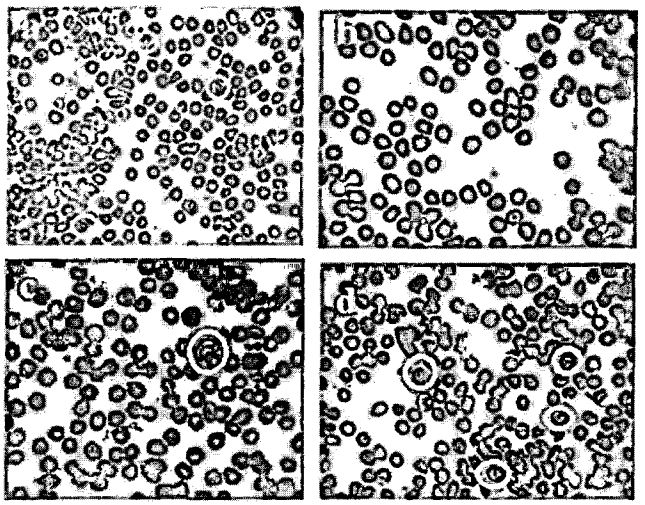

Fig. 3. Photomicrographs of blood smears of different groups showing parasitemia (encircled) (a) parasite infected RBCs in control group (b) parasitemia after treatment with standard drug, chloroquine c) parasitemia after treatment with **5g** (Most active) c) parasitemia after treatment with **5e** (Least active).

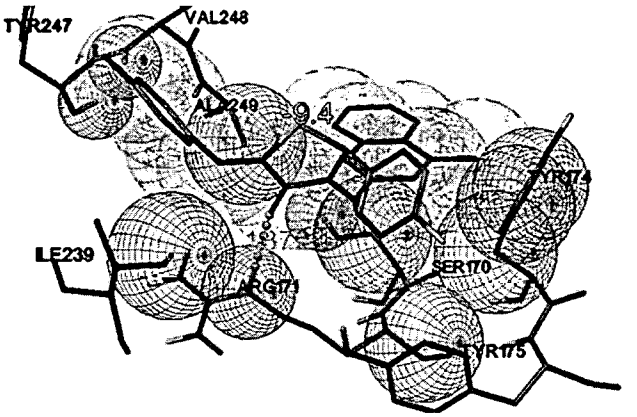

Fig. 4. Binding interaction of most potent synthesized ligand, **5g**, with active site of Lactate dehydrogenase (PDB ID: 1CET).

3.4. Docking study

Anaerobic life cycle of parasite *Plasmodium falciparum* is supported by *Plasmodium falciparum* Lactate Dehydrogenase (*Pf*LDH), being the terminal enzyme that leads the regeneration of NAD^+ from NADH for continual glycolysis. From the literature, it has been revealed that inhibition of *Pf*LDH may lead a pathway for designing of antimalarial agents and this has been illustrated in the present study by docking simulations using 1CET, *Pf* Lactate dehydrogenase enzyme complex as target protein. The docked confirmation and results of ligands in binding pocket is demonstrated in Table 3. The main amino acid residue that has played a vital role in interaction of ligands with target protein was ARG171. The biological evaluation was corroborated by *in silico* study as compound **5g** formed a stable interaction with *Pf*LDH enzyme having binding affinity −9.4 kCal/mol and hydrogen bond as well, depicted in Fig. 4. The results from docking study justified our preceding research of arylidene derivatives of quinoline-thiazolidinone hybrids as antimalarial agents.

4. Conclusion

In summary, we have synthesized novel series comprised of arylidene derivatives of quinoline-thiazolidinone hybrids, where compound **5g** exhibited promising *in vitro* antimalarial potency against both 3D7 and RKL-9 strains of *Plasmodium falciparum*. It also showed highest suppression of parasitemia against *P. berghei* during *in vivo* antimalarial screening. The present study also portrayed the utility of docking simulations to get a deep insight of interaction of synthesized scaffold with target proteins. From structure-activity relationship, **5g** may be utilised as a lead molecule for further investigation to improve their pharmacological potential. Thus, the current study serves as an encouragement for the development of new hybrids of thiazolidinone pharmacophore as antimalarial agent.

Conflicts of interest

The authors report no conflict of interest.

Table 3
Docking simulations of **5b**, **5e**, **5g**, **5j** and **5n** in active site of Lactate dehydrogenase receptor (PDB ID: 1CET).

S. No.	Compound	Dock Score (kCal/mol)	Number of hydrogen bonds	Amino Acid involved	Group of ligand involved
1.	5b	−9.0	1	ARG171	O of C=O (thiazolidinone)
2.	5e	−9.0	–	–	–
3.	5g	−9.4	1	ARG171	O of C=O (thiazolidinone)
4.	5j	−9.2	1	ARG171	O of C=O (thiazolidinone)
5.	5n	−9.2	–	–	–

EXHIBIT P7

Acknowledgement

The authors gratefully acknowledge financial assistance from Department of Science and Technology, New Delhi (Letter no. DST/INSPIRE Fellowship/2013/480).

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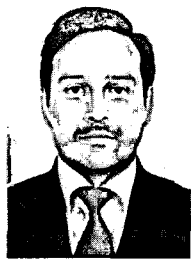

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EXHIBIT P8

December 2, 2004

DRAFT

"ENLARGED" CONCEPT OF NOVELTY: INITIAL STUDY CONCERNING NOVELTY AND THE PRIOR ART EFFECT OF CERTAIN APPLICATIONS UNDER DRAFT ARTICLE 8(2) OF THE SPLT

prepared by the International Bureau

I. SUMMARY

1. The present initial study is submitted upon request of the Standing Committee on the Law of Patents (SCP) at its tenth session, held in Geneva from May 10 to 14, 2004, in order to provide a basis for discussion concerning a possible new novelty concept applicable to the prior art effect of unpublished earlier applications under Article 8(2) of the draft Substantive Patent Law Treaty (SPLT). The study aims at providing broad background information and at facilitating further substantive discussion in the SCP, and thus addresses not only national and regional laws and practices regarding the prior art effect of earlier applications, but also the policy objectives underlying these different practices.

2. The divergences among national laws and practices in respect of the prior art effect of unpublished earlier applications seem to reflect different principles and objectives underlying the prevention of double patenting. Examining a number of national and regional laws and practices, it appears that those different practices correspond mainly to one or more of the following three models:

(i) Strict novelty: if a claimed invention is explicitly or inherently disclosed in an earlier application, the earlier application defeats the patentability of the claimed invention;

(ii) Broader novelty: even if the claimed invention is not fully disclosed (explicitly or inherently) in the earlier application, the earlier application defeats the patentability of the claimed invention if the differences between the two are minor (for example, a replacement with a well-known equivalent element);

(iii) Novelty and inventive step (non-obviousness): the earlier application defeats the patentability of the claimed invention if the latter lacks either novelty or inventive step (non-obviousness) compared to the earlier application.

consideration, and which are published on or after the filing date (or priority date) of that latter application. Although at the time of filing, the applicant of the later application would not, in general, know that an earlier application had been filed (since the earlier application would not yet be available to the public), such an earlier application forms part of the prior art in respect of the later application in many jurisdictions.

8. Since the very beginning of the discussions on the draft SPLT in May 2001, the draft texts submitted to the SCP have included provisions on the prior art effect of earlier applications.[1] In addition to other issues discussed in the Committee, such as the question of the prior art effect of unpublished earlier filed international applications under the Patent Cooperation Treaty (PCT), the issue of the extent of the prior art effect of earlier applications (namely whether such effect should extend to novelty only or to both novelty and inventive step/non-obviousness) has been on the table since the beginning of the relevant discussions. The report of the fifth session of the SCP reflects the split of opinions among delegations on this matter[2] which first appeared at an early stage of the discussions on the draft SPLT.

9. While the text relating to the prior art effect of earlier applications contained in the draft SPLT has evolved over several sessions of the SCP, the main question of the extent of such a prior art effect as mentioned above has not yet been solved due to fundamental differences in approach among delegations. Although the latest versions of the draft SPLT apply the prior art effect of earlier applications to novelty only,[3] the debate on whether such prior art effect should also apply to inventive step/non-obviousness is still going on.[4]

10. At the eighth session of the SCP held in November 2002, some delegations pointed out that the question of the difference in practice between applying the prior art effect of earlier applications to novelty only and applying it to both novelty and obviousness would depend on the criteria for determining novelty.[5] Similar arguments were put forward at the ninth session of the SCP held in May 2003.[6] At the tenth session of the SCP in May 2004, a number of delegations suggested that, instead of extending the prior art effect of earlier applications to inventive step/non-obviousness, a concept of "enlarged novelty" could be considered as a compromise. In response to a request for clarification by one delegation, the Chair explained that a concept of "enlarged novelty" could include inherent disclosures and equivalents in addition to a strictly "photographic" concept of novelty.[7] Following that suggestion, the SCP agreed to a proposal by the Chair that the International Bureau should prepare a study on this subject, focussing initially on the prior art effect of earlier applications, but also considering the implications of extending the concept of "enlarged novelty" to novelty in general. The present document addresses a number of issues related to this question, and further gives some consideration to the application of such a concept to novelty in general.

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1 See for example the first draft of the SPLT, Article 9 of document SCP/5/2 and Rule 7 of document SCP/5/3.

2 See, in particular, paragraph 88 of document SCP/5/6.

3 The texts of relevant draft SPLT provisions are reproduced in Annexes I and II.

4 See for example paragraphs 136 and 137 of document SCP/6/9; paragraph 74 ff. of document SCP/7/8; paragraphs 173 to 175 of document SCP/8/9; paragraph 173 of document SCP/9/8; paragraph 88 of document SCP/10/11 Prov.2.

5 See paragraphs 173 and 174 of document SCP/8/9.

6 See paragraph 173 of document SCP/9/8.

7 See paragraph 89 of document SCP/10/11 Prov.2. See also Chapter VI.

11. Pursuant to the mandate of the SCP, the International Bureau requested, through the SCP Electronic Forum, members and observers of the SCP to provide information concerning the "novelty" criterion and the prior art effect of earlier filed, but later published applications under draft Article 8(2) of the SPLT as applied under national laws and practices. The information received by the members of the SCP was taken into account in preparing this study.

12. Against this background, this document constitutes an initial response to the request by the SCP, aiming at providing broad background information and at facilitating further substantive discussion in the SCP. Thus, it addresses not only national and regional laws and practices regarding the prior art effect of earlier applications, but also the policy objectives underlying these different practices. The document first describes the general rules governing novelty and inventive step and then addresses the prior art effect of earlier applications as well as the policy objectives behind such rules (Chapters III and IV). Chapter V portrays various national/regional laws and practices regarding the prior art effect of earlier applications with an emphasis on the applicable notion of "novelty", and Chapter VI outlines the concept of "enlarged novelty" described by Samson Helfgott, Director of Patents, KMZ Rosenman, New York, Heinz Bardehle, European Patent Attorney, Bardehle Pagenberg Dost Altenberg Geissler, Munich and John Hornickel, Intellectual Property Counsel, PolyOne Corp., Avon Lake, Ohio.[8] Chapter VII provides the concept of novelty applied to earlier applications under the SPLT. Chapter VIII portrays a range of various concepts, including the feasibility of broadening the concept of "novelty", and provides an analysis of the commonalities and differences characterizing them. Chapter IX considers a number of implications to other novelty-related issues. Chapter X draws some provisional conclusions from the previous chapters.

III. GENERAL CONSIDERATIONS REGARDING NOVELTY AND INVENTIVE STEP

(a) Novelty

13. The patent system confers on a patentee the exclusive right to prevent others from commercially using the patented invention in return for the public disclosure of the invention in order to enrich the existing body of technical knowledge in the world. It is a fundamental objective of the patent system that nothing be alienated from society which already belongs to it. Indeed, granting a patent on an invention already known would impose constraints on society in respect of the use of known information without offering any return or benefit. The line between what belongs to society and what can be withheld from it is, to a large extent, drawn by the notion of novelty. Accordingly, the novelty requirement is one of the most important internationally recognized principles provided under patent law.

14. The term "novelty" does not necessarily coincide with its recognized understanding in the general usage of the language. In general, patent law requires an invention to be new in the sense that it does not form part of the prior art, prior art being defined as information that, in some form, has been made available to the public (although the same form(s) are not necessarily recognized as relevant in all jurisdictions). Since the determination of novelty involves the factual question of whether the same invention has already been made available to the public before the filing or the priority date, in considering novelty, it is not permissible

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[8] See Annex III.

only issue to bear in mind: the rights of the applicant of the later application and the rights of the public require consideration as well.

22. Where the claimed invention in the later application is not the same as the invention contained in the earlier application, but is an obvious variant of the invention contained in the earlier application, there is no risk of double patenting *stricto sensu* by virtue of the grant of a patent in respect of the later application. However, some argue that according an exclusive right to the applicant of the later application for merely an obvious variant of what has been invented by the applicant of the earlier application disrupts the delicate balance between the interests of the applicant of the earlier application and those of the applicant of the later application and of the public. In other words, granting a patent to such a later application could result in preventing non-value-added subject matter from entering the public domain. Following this line of thinking, some conclude that the later application claiming different, but (in respect of an earlier application) obvious, subject matter should not be patentable vis-à-vis that earlier application.

(b) Main approaches in detail

Prior art effect applied to novelty only

23. As described above, the *rationale* for applying the novelty-only approach to the prior art effect of earlier applications is mainly to avoid granting two or more patents for the same invention, a governing principle which is common to many patent systems. If that is the main objective, the novelty-only approach is sufficient to address the issue. It allows, in particular, to avoid that more than one patent is granted in respect of the same subject matter. Some argue that, with respect to the prior art available to the public, the later applicant's invention must involve an inventive step in order to justify an exclusive right. However, as regards the non-published earlier applications already pending, the later applicant does not have to make an inventive contribution over the first invention in order to prevent double patenting. In addition, the ban on double patenting seeks to ensure that no unjustified extension of the exclusive right is obtained for the same invention. The effect of applying the novelty only approach is that, without any additional rule, both the applicant of the invention contained in the earlier application and third parties who have developed improvements or variants of the invention contained in the earlier application can obtain a patent for those developments, even if they are considered obvious.

24. This approach offers the possibility of patenting new, but obvious developments during a limited time period, that is, between the filing date of the earlier application and its publication. It is therefore rather favorable to the granting of rights to further developments of earlier inventions, even if such developments are obvious, minor technical achievements. On the other hand, it may result in the granting of a number of patents in respect of subject mater that are, although not identical, nevertheless obvious. Such a thicket of overlapping patent claims may lead to complexity in terms of the number of co-existing rights, and also with regard to the relationship of those rights among themselves, in particular, where they are owned by different persons. Consequently, the exploitation of those rights may become more complex. Further, it may be more complicated for third parties to obtain licenses from the various patentees. In addition, a patent granted in respect of a later invention containing only a minor variation compared to the earlier invention might, in effect, extend the term of patent protection with respect to the earlier invention.

Prior art effect applied to novelty and inventive step

25. The main objective of applying the prior art effect of earlier applications to both novelty and inventive step is, in addition to avoiding strict double patenting, to prevent a proliferation of patents in respect of new, but nevertheless similar inventions. One additional argument sometimes put forward is that there is no reason for treating the novelty and the inventive step/non-obviousness aspects differently, since, once an earlier applicant has filed an application before the Office, he has taken the necessary step to communicate his invention to the public. Therefore, he should be able to rely on the filing of the earlier application to prevent any later applicant from obtaining a patent for a later invention which is obvious in respect of the invention he had disclosed (even though it may not yet have been published).

26. This second approach aims to prevent the patenting of developments which are new and obvious vis-à-vis an earlier application, even if the applicant of the later application could not know that an earlier application was pending at the time of his later filing. It is further intended to prevent the extension of the patent term by prohibiting claims in a second patent that are not inventive over claims in the first patent. This approach also raises some issues: one of them relates to the fact that, in practice, inventors often file a first application and later improve the invention contained in that first application. Where such improvements are obvious in respect of the invention contained in the earlier filed application, there is no possibility for the inventor himself to obtain a patent for his own developments.

27. One of the counter-arguments to the above conclusion that later obvious inventions should not obtain a patent in view of patentable earlier applications is based on the ground that, at the time of filing of the later application, the earlier application was not available to the public, that is, that the applicant of the later application arrived at the obvious variant independently without knowledge of the subject matter contained in the earlier application. Focusing on the individual and independent achievement by the applicant of the later application, it is thus sometimes argued that his achievement should be reviewed against the published state of the art which was available at the time of filing, but not against information of which the applicant could not have been aware of.

28. In sum, this approach bars the possibility to patent obvious improvements/developments of an invention contained in an earlier application, even if they were made independently and are not derived from that first invention.

Measures to adjust the system

29. The above two main approaches inherently contain some practical issues which may not be in line with some of the underlying policy objectives. The first issue relates to the fact that it is the whole contents of an earlier application that eventually became part of the prior art. It may happen that, shortly after filing an earlier application, the applicant realizes that subject matter disclosed, but not claimed, in his earlier application is worth obtaining patent protection. Under the whole contents approach, however, where the applicant disclosed subject matter in the description of an earlier application, but did not claim such subject matter, the same applicant can no longer claim that same subject matter in a later application (so-called "self-collision"). In this case, although the applicant may file a divisional application on the basis of his earlier application or claim internal priority from the earlier application, he must comply with the procedural and substantive requirements under the applicable law in order to enjoy the benefits of divisional applications or of claiming internal priority. Further, since inventive activities are often carried out in a corporation by a group of

inventors working together, the corporation may file[10] more than one application containing the same disclosure of a particular subject matter, but each of which claims a different invention by different inventor(s). In particular, where the prior art effect of earlier applications applies to both novelty and inventive step, if one inventor of the group made an obvious development to the invention contained in the earlier application which had been made by colleagues in the same company, the corporation could not obtain a patent on the later invention. Some patent systems therefore provide remedies for these cases, such as provisions that avoid the self-collision (so called "anti-self-collision"), providing that earlier unpublished applications do not constitute prior art in respect of applications filed later by the same inventor or applicant.

30. A second issue relates to the concerns about extending the term of patent protection through the issuance of a second patent claiming a variation or obvious development of the first patent. Some patent systems thus require that the term of the second patent may not go beyond the term of protection of the first patent, and that both patents have to remain in the hands of the same owner (or at least related owners). Combined with the anti-self-collision rule, this aims to ensure that the inventor (or the assignee) of the first patent does not effectively extend the term of his exclusive rights via the second patent.

A possible way forward

31. The two approaches as well as measures to respond to certain concerns outlined above reflect, at least in part, conflicting underlying policy objectives. Should the patent system encourage later applications containing minor or obvious variants, thereby accepting a potential proliferation of patents related to at least similar subject matter, or should it rather aim to limit the number of such patents and primarily reward the contribution to the art by the first inventor (the applicant of the earlier application)? The divergence in the discussions in the SCP have shown that this issue is deeply rooted in the different patent cultures of the various countries.

32. As rightly pointed out by some delegations in the SCP (see paragraph 10 above), the issue depends also on the definition of the notion of "novelty" vis-à-vis unpublished earlier applications. One possible avenue to explore might thus consist in the further elaboration of that concept. Does "novelty" mean that a claimed invention shall be strictly identical to what was explicitly disclosed in the earlier application? Is subject matter that is inherently or implicitly disclosed in the earlier application also considered "disclosed" in the earlier application? If the difference between the claimed invention and what is disclosed in the earlier application is a mere replacement by a well-known equivalent element, is the claimed invention anticipated by the contents of the earlier application? The following chapter provides information concerning different national/regional practices as regards the prior art effect of earlier applications, emphasizing the notion of applicable "novelty".

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[10] In the United States of America, since the applicant has to be the inventor, the right to the patent has to be assigned to the corporation from each inventor.

V. EXAMPLES OF NATIONAL/REGIONAL LAWS AND PRACTICES CONCERNING THE PRIOR ART EFFECT OF EARLIER APPLICATIONS

33. This chapter is based essentially on the submissions to the SCP Electronic Forum by the SCP members concerning the "novelty" criterion and the prior art effect of earlier applications (see paragraph 11). All of the submissions received from members of the SCP can be found on the SCP Electronic Forum's website.

(a) Bulgaria

34. According to Article 8 of the Bulgarian Patent Law 1993, for the purpose of determining novelty, applications the filing date (or the priority date) of which is earlier than the filing date (or priority date) of the application under examination, but which are published after the filing date (or priority date) of that latter application, also form part of prior art. Such earlier applications include earlier national, European and international applications designating the Republic of Bulgaria. The examination practice of the Bulgarian Patent Office is that a conclusion of lack of novelty may be made only when full coincidence exists between the claimed invention and the subject matter of the prior art. In addition to features expressly mentioned in the prior art, features which are implicit to a person skilled in the art are also taken into account.

(b) France

35. The concept of novelty is laid down in Article L.611-11 of the Intellectual Property Code (*Code de la propriété intellectuelle (CPI)*). Paragraph (1) of that Article provides that an invention shall be considered novel if it does not form part of the prior art. The prior art is defined in paragraph (2) as everything accessible to the public before the filing date of the application in writing, by oral disclosure, through use or in any other form. Paragraph (3) provides that, for the purpose of determining novelty, prior art also consists of certain earlier applications (national applications as well as European applications and international applications under the PCT designating France) the filing dates (priority dates) of which are earlier, but the publication dates of which are later, than the filing (priority) date of the application under consideration.

36. As regards the practice by the National Industrial Property Institute (INPI), according to the Directives concerning the examination of patent applications, Title I, Section C, Chapter VIII, p.25 and 26, lack of novelty can be determined in case where "there is identity between the claimed invention and the item of prior art, that is, when they are exact copies, the effect of the prior art being flagrant and indisputable. The disclosure of specific technical means in the prior art destroys the novelty of general means". On the other hand, there is no manifest lack of novelty where "the claimed invention, although it is not an exact copy of the item of prior art, only differs from that item in details, forming part of a whole which is more complex, or where there is a doubt concerning the identity of the two. In that case, a patent is granted with a search report citing that item of prior art".[11]

37. As regards court decisions concerning novelty determination in France, the courts apply novelty in a strict sense. An item of prior art can destroy novelty only where it is one single

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[11] The INPI rejects a patent application on the basis of a lack of novelty, but not of a lack of inventive step.

piece that is, it is found entirely in the patent (TGI Toulouse, October 31, 1996, PIBD 1997 III, p.92). In principle, in order to form part of the prior art, an item of prior art shall contain all the elements of the claimed invention, with definite character, with the elements which constitute the same form, the same arrangement and the same function in view of the same technical result; the item of prior art destroys novelty only where the essential characteristics are represented (*Cour de cassation*, March 12, 1996, PIBD 1996 611 III p.273; CA Paris February 28, 1991, PIBD 1991 506 III p.497). Consequently, it is not sufficient for the characterization of lack of novelty that the patent recapture a major part of the item of prior art (TGI Paris March 19, 2002). On the contrary, an invention is considered novel because of the only fact that, for example, it claims a function different from that of the item of prior art, even if its structure, its form and its arrangement are identical (*Cour d'appel de Paris*, February 9, 2001, PIBD 2001 725 III p.389).

38. With respect to the effect of equivalent means, the French Law of 1844 took into account the equivalents for the determination of novelty. Thus, a patent was revoked due to lack of novelty if the claimed invention was found equivalent to the state of the art. This practice was abandoned by the Law of January 2, 1968 which applies a stricter novelty due to the integration of the requirement of inventive step in addition to novelty and industrial applicability. According to the decision of December 1, 1993, the Appeal Court of Paris considered that an equivalent means should not be considered for the determination of novelty (*Cour d'appel de Paris*, December 1, 1993, PIBD 562 III p.139). In the same sense, in a decision of March 19, 2002, the Paris High Court rejected the argument that a patent should be revoked on the basis of a lack of novelty because one part of the patent was found equivalent to the prior art. The Court considered that "the prior art should present all the technical characteristics of the claimed invention. Since the novelty of the claimed invention should be considered strictly, the equivalents invoked by the plaintiff cannot be taken into account for the determination of novelty" (TGI Paris, March 19, 2002). Such practice, therefore, seems to be well-established under the French law, although there are certain isolated cases that still apply the principles that were valid before 1968 (for example, TGI Lyon, September 29, 1986, PIBD 1986 405 III p.52 and *Cour d'appel de Lyon*, September 10, 1998, PIBD 1999 669 III p.42).

(c) Germany

39. Section 3(2) of the German Patent Law provides that, for the purpose of the determination of novelty, the contents of applications which have earlier priority and which were published only on or after the date relevant for the priority of the later application, shall also be considered to form part of the prior art. According to the submission by the Delegation of Germany, essentially, this provision aims at preventing double patenting. This is in the interest of the public, and of the earlier applicant who should be able to trust that the inventions that he has disclosed will not be protected by another person. The restriction to the novelty examination also contributes to safeguarding the interests of the later applicant: the contents of the earlier application, which is published only after the priority date of the later application, as a rule, cannot be known to the later applicant. Therefore, he is not able to incorporate the contents of the earlier application into his considerations when further developing the known state of the art.

40. As regards the interpretation of the term "novelty", according to German case law, the content of disclosure of a written citation is not limited to its wording (so-called "photographic novelty"). Rather, the relevant criterion for understanding the invention is the general expert knowledge of a person skilled in the art who considers the citation. The prior

art of a citation comprises everything - even if not expressly mentioned - which the skilled person, in the light of his general expert knowledge, deems to be obvious or nearly indispensable from the whole contents of the single item of prior art for executing the teaching. Likewise, it also includes evident variations that are obvious from the general context of the document, that is variations which the skilled person will automatically realise and take as read, if he studies the documents carefully and focuses on the discernible meaning rather than on the wording. The Federal Court of Justice has expressly confirmed that these principles apply as well to novelty evaluation in relation to documents made available to the public under Section 3(2) of the German Patent Law.

(d) Japan

41. Under the Japanese Patent Law, the general novelty requirement and the prior art effect of the earlier applications are regulated separately. Section 29(1) deals with the novelty requirement with respect to publicly available prior art. The prior art effect of earlier applications is described in Section 29*bis*, which regulates, together with Section 39, the priority over two or more competing applications. Section 29*bis* provides, in essence, that where an invention claimed in a patent application is identical with an invention disclosed in the specification or drawings originally attached to the request of another patent or utility model application the filing date (priority date) of which was prior to the filing date (priority date) of the patent application and which was laid open to the public after the filing date (priority date) of the patent application, a patent shall not be granted for that invention.

42. Where the inventor or the applicant of the earlier application and the application under examination are the same, Section 29*bis* does not apply. In other words, the so-called anti-self-collision rule is applicable. Therefore, where an invention claimed in the second application is disclosed, but not claimed, in the earlier application and the inventor or the applicant of both applications are the same, the claimed invention is patentable, provided the other requirements for patentability are also complied with.

43. According to the Examination Guidelines, the expression "an invention [...] disclosed in [...] another application" in Section 29*bis* means an invention identified by the "matters described" or "matters essentially described, though not literally" in the other application on the filing date.[12] It is explained that the expression "matters essentially described, though not literally" means those matters that are directly derivable from the matters described, taking into consideration the common general knowledge at the time of the filing of the other application. The term "common general knowledge" means technologies generally known to a person skilled in the art or matters clear from empirical rules. The common general knowledge includes "well-known art", which is generally known technologies in the relevant technical field, such as the existence of many prior art documents describing those technologies, technologies widely known throughout the industry, or well-known technologies which are not necessary to be explained in details. It also includes "commonly used art" which means well-known and widely used art. In sum, the scope of the disclosure in the other application is determined by the subject matter which a person skilled in the art can identify on the basis of the explicit disclosure as well as the implicit disclosure that can be directly derivable from the matters described in the other application taking into account the common general knowledge of a person skilled in the art.

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[12] Examination Guidelines, Chapter II-3, 2.3.

55. As regards the practice followed by the Spanish Patents and Trademarks Office (OEPM) in examining the novelty of an invention which is the subject of a patent application, the following aspects are taken into account:

- the novelty of the invention as it is claimed is examined, not the different embodiments;

- an invention is not novel where the prior art (one single document) has all the technical features of the application and is suitable for solving the same problem as the invention being examined.

56. To sum up, Spanish legislation and practice provide for the requirement of novelty as an absolute requirement:

- at the global level;

- in terms of identity: if a previous document contains the same features as the claimed invention, be it explicitly or implicitly, it destroys the novelty. Minimal differences in the technical features between both documents imply that the claimed invention is considered novel, apart from where such minimal technical differences are irrelevant, obvious or matters of detail;

- a particular embodiment annuls the novelty of the general concept, but not vice versa, mainly in the case of ranges or parameters.

The OEPM indicated that, in any case, it followed the practice and guidelines of the European Patent Office, mainly in order to achieve harmonization in Europe.

(h) United Kingdom

57. Under the patent law of the United Kingdom (UK), the requirement for novelty is defined by Section 2 of the Patents Act 1977 which corresponds closely with Article 54 of the European Patent Convention (EPC). Section 130(7) of the Act states that this section is amongst those which are framed to have, as nearly as practicable, the same effects in the UK as the corresponding provision of the EPC. The policy considerations underlying this Article and the jurisprudence of the Boards of Appeal at the European Patent Office (EPO) are therefore also of relevance to the application of the novelty requirement under UK law.

58. Section 2(3) of the Act defines the state of the art as also including matter contained in an application for another patent having a priority date earlier than the application in suit, but which was published on or after the priority date of the application in suit. In order to form part of the state of the art under Section 2(3), the matter must be contained in the application for that other patent both as filed and as published, and the priority date of that matter must be earlier than that of the invention of the application in suit.

59. Details of the practice followed under the Patents Act 1977 to assess novelty of a patent application are described in paragraphs 2.01 to 2.56 of the Manual of Patent Practice.[19] When

[19] http://www.patent.gov.uk/patent/reference/mpp/index.htm.

considering whether a patent claim lacks novelty, in addition to information that is explicitly disclosed, the teaching that is implicit in the prior publication may be taken into account. In other words, the skilled person may use his common general knowledge to deduce that certain standard features of a system, product, method, etc. must be a necessary part of the disclosure and are thus implicitly present. The concept of novelty therefore has a broader extent than "photographic novelty". However, the skilled person may not go so far as to assume that certain common but non-universal features are present; this would be a matter for obviousness instead. This distinction is emphasized in *General Tire v Firestone* [1972] RPC 457, which sets out the generally-held principle in UK patent law that a disclosure which would infringe a claim in a patent application if the application was granted demonstrates a lack of novelty in the same claim before grant (the "post-infringement" or "right to work" test). In this judgment, on pages 485 to 486, it is stated: "If the prior inventor's publication contains a clear description of, or clear instructions to do or make, something that would infringe the patentee's claim if carried out after the grant of the patentee's patent, the patentee's claim will have been shown to lack the necessary novelty, that is to say, it will have been anticipated. The prior inventor, however, and the patentee may have approached the same device from different starting points... but if carrying out the directions contained in the prior inventor's publication will inevitably result in something being made or done which, if the patentee's patent were valid, would constitute an infringement of the patentee's claim, this circumstance demonstrates that the patentee's claim has in fact been anticipated. If, on the other hand, the prior publication contains a direction which is capable of being carried out in a manner which would infringe the patentee's claim, but would be at least as likely to be carried out in a way which would not do so, the patentee's claim will not have been anticipated, although it may fail on the grounds of obviousness".

60. The *General Tire* judgment continues: "To anticipate the patentee's claim, a prior publication must contain clear and unmistakable directions to what the patentee claims to have invented... A signpost, however clear, upon the road to the patentee's invention will not suffice. The prior inventor must be clearly shown to have planted his flag at the precise destination before the patentee". This requirement was applied in *Asahi's Application* [1991] RPC 485, where it was held that a prior disclosure had to have an enabling character in order to anticipate an invention. An invention was not made available to the public merely by a published statement of its existence, unless the method of working is so self-evident as to require no explanation.

61. The test to determine whether matter in a patent application unpublished at the priority date of the application in suit forms part of the state of the art under section 2(3) of the Act is the same as the test for whether matter in a prior publication made available to the public forms part of the state of the art under section 2(2) of the Act, as held in the*Asahi* judgment. In both cases, the matter has to be enabling. Furthermore, when considering novelty, matter which forms part of the state of the art under section 2(3) is considered in exactly the same way as matter that is part of the state of the art under section 2(2), as was confirmed in *SmithKline Beecham's Patent* [2003] RPC 6.

(i) United States of America

62. In the United States of America, novelty and non-obviousness are determined in accordance with 35 U.S.C. §102 and 35 U.S.C. §103, respectively.[20] Further, guidance on

[20] http://www.uspto.gov/web/offices/pac/mpep/consolidates_laws.pdf.

novelty and non-obviousness practice concerning prosecution of patent applications before the United States Patent and Trademark Office (USPTO) is found in Chapters 700 and 2100 of the USPTO Manual of Patent Examining Procedure (MPEP).[21]

63. The prior art effect of prior-filed but later-published applications is determined in accordance with 35 U.S.C. §102(e), which reads as follows:

> "A person shall be entitled to a patent unless –
>
> [...]
>
> (e) the invention was in — (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for the purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language; or
>
> [...]"

According to MPEP 2136.04, the term "another" means persons other than the applicant (*In re Land*, 368 F.2d 866, 151 USPQ 621 (CCPA 1966)), in other words, a different inventive entity. The inventive entity is different if not all inventors are the same.

64. In accordance with 35 U.S.C. §103(a), in order to determine whether a claimed invention is obvious from the prior art, all subject matter that is prior art under U.S.C. §102 can be used. Thus, the prior art effect of prior-filed but later-published applications is applicable to the determination of both novelty and non-obviousness. However, 35 U.S.C. §103(c) provides that subject matter developed by another person, which qualifies as prior art under section 102(e), (f) or (g), shall not be considered when determining whether an invention sought to be patented is obvious under 35 U.S.C. §103, provided the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person. The subject matter and the claimed invention were owned by the same person if the subject matter, which would otherwise be prior art in respect of the claimed invention, and the claimed invention are entirely or wholly owned by the same person(s) or organization(s)/business entity(ies) at the time the claimed invention was made.[22] Therefore, for example, if employees A and B work for a company C, each with knowledge of the other's work, and with obligation to assign inventions to C while employed, a so called "earlier application" under 35 U.S.C. §102(e), the applicant of which is A, would not be considered when examining the obviousness of the subsequent claimed invention made by applicant B.

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21 http://www.uspto.gov/web/offices/pac/mpep/index.html.

22 MPEP 706.02(l)(2). It is explained that the requirement for common ownership at the time the claimed invention was made is intended to preclude obtaining ownership of subject matter after the claimed invention was made in order to disqualify that subject matter as prior art against the claimed invention.

65. Even if the claimed invention complies with the conditions laid down in 35 U.S.C. §102(e) and §103(a) and (c) and thus the claimed invention is considered novel and non-obvious vis-à-vis earlier applications and patents, the question as to whether the doctrine of double patenting applies is examined.[23] The doctrine of double patenting seeks to prevent the unjustified extension of patent exclusivity beyond the term of the patent. The public policy behind this doctrine is that the public should be able to act on the assumption that upon the expiration of the patent it will be free to use not only the invention claimed in the patent but also modifications or variants which would have been obvious to those of ordinary skill in the art at the time the invention was made, taking into account the skill in the art and prior art other than the invention claimed in the issued patent. Before consideration can be given to the issue of double patenting, there must be some common relationship of inventorship and/or ownership of two or more patents or applications. Since the doctrine of double patenting seeks to avoid unjustly extending patent rights at the expense of the public, the focus of any double patenting analysis is on the claims in the multiple patents or patent applications involved in the analysis.

66. There are generally two types of double patenting rejection. One is the "same invention" type of double patenting rejection based on 35 U.S.C. §101. Where the claims of an application are subsequently the same as those of a first patent, they are barred under 35 U.S.C. §101 – the statutory basis for a double patenting rejection. The term "same invention" in this context means an invention drawn to identical subject matter. A reliable test for double patenting under 35 U.S.C. §101 is whether a claim in the application could be literally infringed without literally infringing a corresponding claim in the patent.

67. The second is the "non-statutory-type" double patenting rejection based on a judicially created doctrine grounded in public policy and which is primarily intended to prevent prolongation of the patent term by prohibiting claims in a second patent not patentably distinct from claims in a first patent. In determining whether a non-statutory basis exists for a double patenting rejection, the first question to be asked is – does any claim in the application define an invention that is merely an obvious variation of an invention claimed in the patent? If the answer is yes, then an "obvious-type" non-statutory double patenting rejection may be appropriate. A double patenting rejection of the obvious-type is analogous to a failure to meet the non-obviousness requirement of 35 U.S.C. §103, except that the patent principally underlying the double patenting rejection is not considered prior art. In addition to the "obvious-type" rejection, there are some unique circumstances where it has been recognized that another type of non-statutory double patenting rejection is applicable even where the inventions claimed in two or more applications/patents are considered non-obvious over each other.[24]

68. A rejection based on a non-statutory type of double patenting can be avoided by filing a terminal disclaimer in the application or proceeding in which the rejection is made. A terminal disclaimer is a statement filed by an owner of a patent or a patent to be granted that disclaims the terminal portion of the term of the later patent and includes in the disclaimer a provision that the patent shall be enforceable only for and during the period the patent is commonly owned with the application or patent which formed the basis of the double patent rejection, thereby eliminating the problem of extending patent life. For example, if

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[23] MPEP 804 provides the details concerning prohibition of double patenting.

[24] For example, *In re Schneller*, 397 F.2d 350, 158 USPQ 210 (CCPA 1968) and *In re Kaplan*, 789 F.2d 1574, 229 USPQ 678 (Fed. Cir. 1986).

72. Alternatively, in particular in the case of properties or parameters, there can be features which can be seen to be present automatically if the teaching of the prior art is put into practice. This interpretation also has the consequence that a specific disclosure can take away the novelty of a generic claim embracing that specific disclosure (e.g. a disclosed value takes away the novelty of a range including that value), but that the converse is not the case (see T 651/91 and T 508/91).

73. Moreover, well-known equivalents of features which are explicitly or implicitly disclosed in the prior art document are not considered to be "derivable directly and unambiguously" from the prior art document, and are therefore to be taken into account only for the assessment of inventive step (see T 517/90). This narrow concept of novelty, which excludes equivalents, is of particular importance for the application of Article 54(3) EPC. In T 167/84 (OJ 1987, 369) the board commented that conflicting applications within the meaning of Article 54(3) EPC were included in the state of the art solely from the point of view of novelty, but were considered in the light of their "whole contents". In order to mitigate the harsh effects of the "whole contents approach", its application was confined to novelty (see Article 56 EPC, second sentence). Further, in order to reduce the risk of "self-collision", it had always been considered justified to adopt a strict approach to novelty. Accordingly, the board held that the "whole contents" of an earlier document did not also comprise features which were equivalents of features in the later document (see also T 928/93).

VI. PROPOSAL CONCERNING "ENLARGED NOVELTY" APPLIED TO EARLIER APPLICATIONS BY HELFGOTT, BARDEHLE AND HORNICKEL

74. In view of the different laws and practices at the national/regional level described above and the divergent views expressed on this matter in the SCP, Helfgott, Bardehle, and Hornickel, published an article outlining a concept of "enlarged novelty" which could be applied to the determination of patentability vis-à-vis prior filed, but subsequently published conflicting earlier applications in the international context, so as to overcome existing differences. The following paragraphs provide a summary of the article, is reproduced in its entirety in Annex III.

75. According to that proposal, conceptually, the concept of enlarged novelty is located somewhere between "photographic novelty" (no difference whatsoever between the earlier application and the claimed invention) and obviousness. The concept of enlarged novelty covers not only the subject matter explicitly disclosed in the earlier application but also all that one skilled in the art usually understands when reading the earlier application. Further, where the difference between the claimed invention and the contents of the earlier application consists of a substitution with equivalent means which is well known to a person skilled in the art reading the original disclosure, the claimed invention should also be precluded from obtaining a patent. Similarly, if a generic invention is disclosed in the secret prior art, it should preclude a subsequent application from covering a species not particularly identified within the generic disclosure (unless the "species" is in the nature of a "selection" which could give rise to patentability). To the extent that the second applicant can show that his particular species, equivalent, substitute, etc., would not have been within the original "enlarged" disclosure, because it provides unexpected benefits, unusual results or the like, he may present arguments to overcome the rejection. Also, as the earlier application can only be

used for (enlarged) novelty defeating purposes, it cannot be combined with any other references or any other material to provide an obviousness type rejection.

76. This approach of applying an enlarged novelty to the prior art effect of earlier applications aims to give the full benefit of the invention to the applicant who is the first to file. Although the first applicant may have only described his invention and given some examples, someone else should not be able to come up with another equivalent or well known substitute and get a separate patent for such modified invention. The first applicant should be given protection for the full breadth of his invention and be able to prevent others from getting patents on anything falling within the scope of his invention. The first applicant, however, should not be able to hinder others from making use of his invention if combined with other independent ideas. Thus, earlier applications should not be used for the determination of non-obviousness.

77. In accordance with the above principle that the first applicant should be given protection for the full breadth of his invention, the paper proposes that the applicant should be able to claim anything disclosed in his first application from an "enlarged" viewpoint. In other words, where the applicants of both the earlier application and the application under examination are the same, the earlier application does not take away the patentability of the claimed invention contained in the latter application even if the claimed invention is not novel (in the enlarged sense) vis-à-vis the contents of the earlier application. It makes no difference whether two applications are filed by a common inventor or by a common applicant (the inventors of each application are not the same but they had an obligation to assign their inventions to the same applicant). However, with a view to achieve fairness in respect of the public, in cases where a common applicant files both applications, it is proposed that the second application be subject to a terminal disclaimer. Such a terminal disclaimer, however, should be limited to the "enlarged novelty" of the invention. If a claimed invention in the second application complies with the enlarged novelty requirement, but is obvious from the contents of the earlier application, the common inventor/applicant would be entitled to the full term of protection as regards the second application, provided that no other grounds of refusal apply.

VII. CONCEPT OF NOVELTY APPLIED TO EARLIER APPLICATIONS UNDER THE SPLT

78. Before further exploring possible concepts of "novelty", "enlarged novelty" and "inventive step" applied to earlier applications, it is first necessary to examine in detail how the SPLT applies the "novelty" standard to earlier applications.

79. As reproduced in Annex I, Article 8(2) and Rule 9 provide for the prior art effect of certain applications which are filed before, but published after, the filing date (or priority date) of the application under examination. According to Article 8(2)(a), earlier applications form part of the prior art for the purpose of determining novelty, but not of determining inventive step. Rule 9(1)(a) regulates the principle of the "whole contents" approach, and Rule 9(3), which provides the principle of anti-self-collision, is included within square brackets in the draft SPLT.

80. The requirement of novelty is provided in Article 12(2) and Rule 14, as reproduced in Annex II. Article 12(2) provides for the principle that the novelty requirement is complied with where the invention does not form part of the prior art. According to paragraph 157 of

the draft Practice Guidelines (as contained in document SCP/11/4), the following three steps shall be applied to the assessment of novelty:

(i) determination of the [scope][elements] of the claimed invention;

(ii) determination of the [disclosure in][elements of] the relevant item of prior art;

(iii) assessment of whether every and each element or step of the claimed invention is found in the scope of the item of prior art.

81. Rule 14 provides more detailed rules concerning the determination of the relevant item of prior art when assessing novelty. In particular, Rule 14(1)(b) states that a "mosaic" approach to assessing novelty, whereby a plurality of items in the prior art are combined to defeat the novelty of an invention, may not be applied. Further, Rule 14(2) provides that the scope of the item of prior art shall be determined by what was explicitly or inherently disclosed to a person skilled in the art.

82. The following explanations regarding the inherent disclosure in the item of prior art are given in paragraph 156 of the draft Practice Guidelines:

> "As regards the words "inherently disclosed", even if a certain characteristic is not disclosed explicitly in the item of prior art, such characteristic is inherent, where it could be recognized by a person skilled in the art that, taking into account his/her general knowledge, the characteristic is necessarily contained in the disclosure. Inherency requires that the extrinsic evidence should make it clear that the missing descriptive matter is necessarily present in the information described in the item of prior art, and that it would be so recognized by a person skilled in the art. Inherency, however, may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient".

83. In sum, according to the SPLT provisions, the scope of the disclosure of an earlier application under Article 8(2) for the purpose of the assessment of novelty is not limited to what is explicitly disclosed, but also includes subject matter inherently disclosed in the earlier application when a person skilled in the art reads the earlier application.

84. In addition to the scope of the disclosure, currently, divergent practices apply in national/regional systems with regard to the relevant date for determining the scope of the disclosure of earlier applications under Article 8(2). In some systems, the filing date (or priority date) of the earlier application is the relevant date for determining what the earlier application discloses and whether the disclosure is enabling. In other systems, the relevant date is the filing date (or priority date) of the claimed subject matter. Under the SPLT, these two positions are reflected as alternatives under Rule 14(2). This issue may also be addressed in the context of the discussions on harmonization.

85. Paragraphs 158 and 159 of the draft Practice Guidelines deal with the novelty assessment in respect of generic vs. specific disclosures. They provides that:

> "An item of prior art that discloses a genus does not always anticipate a claim to a species within the genus. In other words, where a claim contains a specific disclosure, for the determination of novelty, a generic disclosure in the item of prior art does not always anticipate the claim to a specific example falling within that generic disclosure.

However, where the specific example is identified with sufficient specificity in the scope of the item of prior art, the species claim is anticipated no matter how many other species are additionally described in the item of prior art.

"On the other hand, where a claim contains generic disclosure, for the determination of novelty, the disclosure of a specific example in the item of prior art falling within a claimed generic disclosure anticipates that generic disclosure. For example, the disclosure of "copper" in the item of prior art defeats the novelty of a claim comprising "metal" as a generic concept. Similarly, where a claim defines the genus of specific species in the alternatives, for example, Markush claims (P1, P2, P3 ... Pn), and if at least one of the alternatives (P1) is described in the item of prior art, the whole claim would be rejected unless the applicant delete the alternative P1 from the scope of that claim".

Therefore, in connection with the prior art effect of earlier applications, the SPLT provides that a claim containing generic disclosure lacks novelty where an earlier application discloses a specific example falling within the claimed generic disclosure. On the other hand, where an earlier application contains a generic disclosure, a claim under examination with a specific disclosure is not always anticipated by the earlier application (for example, such a species may be a so-called "selection invention" which could be patentable).

86. In addition, the novelty assessment regarding the disclosure of a claimed range is provided for in paragraph 160 of the draft Practice Guidelines, which reads as follows:

"A specific example in the item of prior art which is within a claimed range anticipates the range claimed. Therefore, where, as by a recitation of ranges or otherwise, a claim covers several compositions, the claim is anticipated if one of them is described in the item of prior art. For example, a claim to titanium (Ti) alloy with 0.6 to 0.7% nickel (Ni) and 0.2 to 0.4% Molybdenum (Mo) would be anticipated by an item of prior art that describes a Ti alloy containing 0.65% Ni and 0.3% Mo. Where an item of prior art discloses a range which touches, overlaps or is within the claimed range, but no specific examples falling within the claimed range was disclosed, a case-by case determination must be made as to the novelty of the claim. In order to anticipate the claims, the claimed subject matter should be disclosed with sufficient specificity in the item of prior art. If the claims are directed to a narrow range and the item of prior art discloses a broad range, and if the selected narrow range is not merely one way of carrying out the teaching of the item of prior art (for example, there is evidence that the effect of the selection (e.g., unexpected results) occurred in all probability only within the claimed narrow range), depending on the other facts of the case, it may be reasonable to conclude that the narrow range is not disclosed with sufficient specificity in the item of prior art in order to anticipate the claims (a selection invention). The unexpected results may also render the claims unobvious".

Applying the above assessment to the prior art effect of earlier applications, a claimed invention lacks novelty where the earlier application provides a specific example which is within a claimed range. On the other hand, where an earlier application discloses a range which touches, overlaps or is within the claimed range, the novelty of the claim should be assessed on a case-by case basis.

87. In sum, according to the provisions under the draft SPLT and to its Practice Guidelines, the novelty requirement under the draft SPLT does not require a photographic identity

between the relevant item of prior art and the claimed invention. Not only the explicit disclosure in the item of prior art, but also the disclosure inherent to a person skilled in the art, should be considered when assessing novelty. Taking into account the draft Practice Guidelines, the draft SPLT also provides guiding principles when assessing the novelty of special types of claims, such as claims formulated in generic/specific terms and claims defining ranges. Those general rules concerning novelty are also applicable for the prior art effect of earlier applications under Article 8(2).

VIII. POSSIBLE CONCEPTS OF "NOVELTY", "ENLARGED NOVELTY" AND "INVENTIVE STEP" APPLIED TO EARLIER APPLICATIONS AND THEIR EFFECTS

(a) Objectives: commonalties and differences

88. Many patent systems provide that, in addition to the publicly available prior art, so-called earlier applications should form part of the prior art in order to avoid "double patenting". The divergences among national laws and practices, as described above, do not contradict with this standpoint. Rather, the different practices seem to reflect different principles and objectives underlying the prevention of double patenting. It appears that one of the key policy questions is: where there is a granted patent, to what extent should the said patent prevent the issuance of later patents which cover the same or at least similar subject matter? Since a patent grants an exclusive right to carry out the claimed invention for a certain period of time, granting two or more patents for the same invention would reward later applicants with the same exclusive right as well, and would allow an unfair extension of the patent term with respect to the same invention. Beyond this general concept, however, the question arises as to the definition of the term "same invention" covered by more than one patent, and whether a somewhat "different" invention filed later, for example, a later invention which is obvious from the earlier patented invention, should be precluded from also obtaining an exclusive right.

89. Clearly, the issue of "double patenting" as such concerns the relationship between two claimed inventions, and it is not, strictly speaking, a matter of prior art. However, as described in Chapters IV and V, the *raison d'être* of the prior art effect of earlier applications cannot be considered in isolation, that is, without understanding the different principles underlying the double patenting bar. Each of those principles mirrors a certain social and cultural environment, but they all attempt, in their own way, to strike a balance among the first applicant, later applicants and the general public, and to guarantee a sound, reliable and predictable legal system.

(b) Different notions of novelty and inventive step applied to the prior art effect of earlier applications

90. Examining the concept of novelty under the draft SPLT as well as various national/regional laws and practices as described in Chapter V, it appears that the prior art effect of earlier applications under the SPLT is in line with the laws and practices of many national/regional systems. However, there are other systems that adopt different criteria for such a determination. Generally speaking, those different practices correspond mainly to one or other of the following three models:

(i) The first model (Model A) suggests that, if a claimed invention is explicitly or inherently disclosed in an earlier application, the earlier application defeats the patentability

of the claimed invention. This assessment is in line with the draft SPLT and corresponds to the practices which apply in, for example, France and the Russian Federation and under the EPC.

(ii) The second model (Model B) is located somewhere between the first model and the third model (below). An earlier application defeats the patentability of a claimed invention even if the claimed invention is not entirely disclosed (explicitly or inherently) in the earlier application. However, it is not permissible to combine the earlier application with another item of prior art. The difference between the claimed invention and the disclosure in the earlier application should be minor in the sense that it could be envisaged either by employing the general common knowledge in the relevant field of the art or by a person skilled in the art reading the earlier application with his general knowledge and ordinary skill in the relevant field of the art. Such a concept can be found in the practices of, for example, Germany, Japan and the Netherlands. The "enlarged novelty" proposal made by Helfgott, Bardehle and Hornickel[25] can be considered to form part of this category.

(iii) The third model (Model C) provides that, if a claimed invention also lacks inventive step (non-obviousness) in respect of the disclosure in an earlier application, the earlier application defeats the patentability of the claimed invention. This practice is applied in the United States of America, in particular.

91. The above models may be illustrated as follows:

	Prior Art Effect of Earlier Applications
Model A	Broader Novelty: Explicit or inherent disclosure in earlier applications. No combination of earlier applications and other items of prior art.
Model B	Broader Novelty: Explicit or inherent disclosure in earlier applications + general common knowledge in the relevant field (for example, replacing with a well-known equivalent element). No combination of earlier applications and other items of prior art. --- Broader Novelty: Explicit or inherent disclosure in earlier applications + what a person skilled in the art can understand and envisage from the disclosure (for example, evident modifications such as a mere optimization of a size or a mere re-arrangement of elements). No combination of earlier applications and other items of prior art.
Model C	Novelty and Inventive Step: Combination of earlier applications and other items of prior art.

[25] See Chapter VI and Annex III.

92. Comparing the above three models, Model A offers the possibility of patenting a later invention that goes beyond the explicit or inherent disclosure in the earlier application. It therefore avoids the potential risk of granting a patent to a later invention which is identical to subject matter disclosed in the earlier application. On the other hand, it allows later patents to be granted in respect of subject matter that is, although not "disclosed" in the earlier application, nevertheless apparent to a person skilled in the art applying the general common knowledge in the relevant field of art. It will encourage the patenting of further developments of earlier inventions, even if such developments are minor, thereby offering the opportunity to later inventors (including the applicant of the earlier invention himself) to obtain patents in respect of later inventions. At the same time, this model increases the risk of a thicket of overlapping patents.

93. Model B is characterized by the fact that certain matters that go beyond the explicit or inherent disclosure in the earlier application can be taken into account when determining lack of novelty.[26] However, it does not go so far as to allow the combination of the earlier application with any other piece of prior art which would render the claimed invention obvious. Under this model, different degrees of other "matters that go beyond explicit or inherent disclosure in the earlier applications" can be explored. The first variation can be described in a way that if a person skilled in the art, having read the earlier application, can arrive at the claimed invention by applying his/her general common knowledge, the earlier application destroys the novelty of the claimed invention. The person skilled in the art can only refer to the general common knowledge in the relevant field, such as the addition/deletion of, or the replacement with, well-known or conventionally and widely used art which does not generate any substantial effect. In other words, if the difference between the claimed invention and the disclosure in the earlier application provides unexpected benefits or unusual results, the claimed invention is indeed a separate invention as in the case of so-called selection inventions, and would thus not be anticipated by the earlier application. A typical situation where a person skilled in the art would take into account the general common knowledge may be replacing an element disclosed in the earlier application with a well-known or common equivalent element which does not generate any substantial difference in effect.

94. The second variation under Model B can be described in a way that, based on the teaching of the earlier application, everything that can be understood by a person skilled in the art could be taken into account. In other words, the scope of the earlier application is extended to what a person skilled in the art with his general knowledge and ordinary skill might understand and envisage from the teaching of the earlier application. The difference between the claimed invention and the disclosure in the earlier application should be able to be, in some way, filled by a person skilled in the art when he reads the earlier application. In order to fill such a difference, the person skilled in the art can utilize his full capacity, not just the general common knowledge. For example, evident modifications to the prior art, such as the mere optimization of a size or a shape or the mere re-arrangement of elements, could evidently be made by the person skilled in the art when he reads and understands the teaching of the earlier application. However, unlike Model C, the prior art effect of earlier applications

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[26] In certain countries, the same novelty test applies to both publicly disclosed prior art and earlier applications. In other countries, the "identity" of the claimed invention and the disclosure in the prior art is not considered in the same manner between the publicly available prior art and earlier applications. This issue will be discussed in Chapter IX.

is limited to what a person skilled in the art can derive from such earlier applications, and the difference between the claimed invention and the earlier application should not be so wide that it could only by filled by combining the earlier application with other items of prior art.

95. The consequence of Model B is that the earlier application prevents later minor developments from being patented, but allows patent protection for later developments which are new but obvious. Therefore, in addition to avoiding strict double patenting, it prevents a proliferation of later patents claiming inventions providing only minor technical improvements, such as a mere substitution with well-known equivalent means with no substantial effects. In the absence of an anti-self-collision provision, this means that no one, including the applicant of the earlier application himself, may obtain a patent in respect of subject matter going beyond the disclosure in the earlier application but having a similar scope. Consequently, that subject matter either falls into the public domain or, depending on how broad the doctrine of equivalents is applied under the applicable law, is considered as infringing the earlier patent. At the same time, it leaves room for later applicants to obtain patents in respect of later inventions that are not just minor variants, but are obvious developments from earlier inventions. It allows the co-existence of later patents which do not comply with the inventive step requirement and which are not making a sufficient contribution to the state of the art.

96. If Model B was considered to be the best practice, it would need further elaboration as to the extent to which other "matters" can be taken into account in addition to the disclosure in the earlier application. Without a clear definition in this respect, it will be difficult to ensure legal certainty and predictability at the international level.

97. Model C completely bars the possibility of patenting obvious improvements or developments of an invention contained in the earlier application, even if they were made independently and are not derived from the first invention. In effect, the earlier application prevents any person, including the applicant of the earlier application himself, from obtaining a later patent which claims obvious developments, unless there is a special rule avoiding self-collision. Consequently, such obvious improvements or developments fall into the public domain. Theoretically, different variations can be considered under this model. One variation could be that, in order to deny the patentability of the claimed invention, an earlier application could be combined with other items of prior art only where they were made available to the public before the filing (priority) date. In effect, it would not be possible to combine two or more earlier applications to render the claimed invention obvious. However, such a distinction between the combination of earlier applications and the combination between an earlier application and publicly available prior art may be an artificial one, since it appears that there is no substantial reason to treat earlier applications and publicly available prior art differently in this context.

98. The above three models require different degrees of identity or similarity between the subject matter disclosed in the earlier application and a later invention in order for the later invention not to be patentable. They also clearly reflect different underlying policy choices. At the one end of the spectrum, later applications including only minor or obvious variants are rather encouraged. At the other end, certain systems prevent, in principle, issuing patents to any later developments that do not fulfil the novelty and inventive step (non-obviousness) requirements. In between, a number of patent systems found some form of a balance that they considered appropriate.

99. As regards Model B, a clarification should be made with respect to the time as at which the general common knowledge must be assessed. Should a person skilled in the art apply the general common knowledge as of the filing date (or priority date) of the later application, or should the relevant date be the filing date (or priority date) of the earlier application? Under those systems which publish applications 18 months after their filing date (or priority date), the difference between the two relevant dates will not exceed 18 months. Nevertheless, in areas of quickly advancing technologies, the evolution of the general common knowledge might be fast, and the choice of the relevant date might have serious implications. It appears, though, that such a date determining the general common knowledge should be the same as the relevant date for the determination of the scope of the earlier application (see paragraph 84).

(c) Anti-self-collision

100. As described in Chapter V, some patent systems apply anti-self-collision in conjunction with determining the prior art effect of earlier applications. At first sight, the provision of anti-self-collision does not depend on the three different models above. For each model, there is at least one country that provides anti-self-collision.

101. Anti-self-collision provides that, if the inventor or the applicant of the earlier application and the application under examination are the same, such an earlier application does not become part of the prior art. Combined with Model A, anti-self-collision would allow the same inventor or applicant to later claim an invention that was originally disclosed (either explicitly or inherently) in the earlier application.[27] As described in paragraph 29, the applicant may achieve a similar result[28] by way of fling a divisional application or claiming internal priority, or simply amending the claims of the earlier application, if the applicable law so permits. Therefore, anti-self-collision may provide an additional safety net for inventors/applicants who wish to seek a patent in respect of subject matter that they inadvertently disclosed in the earlier application. However, as correctly pointed out by the Boards of Appeal of the EPO, a strict approach to novelty essentially reduces the risk of "self-collision" (see paragraph 73). Therefore, it appears that anti-self-collision may not be a critical factor for the operation of Model A.

102. On the other hand, under Model B, a patent may not be granted to a later application claiming subject matter that is not disclosed in the earlier application, but is a minor modification (such as well-known equivalents). Combined with an anti-self-collision clause, Model B would operate in such a way as to allow the inventor or the applicant of the earlier application, but not third parties, to obtain a patent on such a later invention with minor modifications compared to his own earlier invention. The underlying consideration seems to be that, particularly under a first-to-file system where an early filing date plays a crucial role for obtaining a patent, an applicant may first file an application with certain claims and embodiments, and later seek patent protection for another embodiment, which was not disclosed in his earlier application, but is nothing more than, for example, a substitution with well-known equivalents. In effect, anti-self-collision provides a certain safeguard for the

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[27] Even in this case, in general, the ban of double patenting applies to the claimed invention in the earlier application and the claimed invention in the later application.

[28] In fact, filing a divisional application or claiming internal priority would preserve the benefit of filing date/priority date of the earlier application, which is more advantageous than filing a separate later application.

inventor/applicant who first made a contribution to the art, while leaving room for third parties, who do not know the contents of the earlier application at the time they file a later application, to obtain a patent on a later invention developed independently even if that invention is obvious in respect of the earlier invention.

103. As regards Model C, its strict application leads to the situation that, even if the earlier applications are not published, they defeat the patentability of later inventions which are not novel or obvious from the subject matter disclosed in the earlier applications. Combined with anti self-collision, this model provides the possibility for the inventor/applicant of the earlier application to obtain a patent in respect of subject matter that is not novel or obvious vis-à-vis the earlier application, provided that double patenting rejection does not apply. The underlying consideration of combining anti-self-collision with Model C appears to be similar to the reasoning in respect of Model B. In the case of Model C, however, a mechanism without anti-self-collision provision may give rise to greater concerns, since anyone, including the inventor/applicant of the earlier application himself, would be prevented from obtaining a patent in respect of later new, but obvious improvements. On the other hand, anti self-collision, when combined with Model C, may put the inventor/applicant of the earlier application in a relatively strong position, since, once an earlier application is filed, third parties will not be able to obtain a patent in respect of subject matter similar or obvious from the earlier invention.

(d) Adjustment of the term of protection

104. The practice in at least one country, namely the United States of America, addresses the issue of effectively extending the term of patent protection by granting patents for similar or obvious variations. The American Intellectual Property Law Association (AIPLA) expressed its concerns on this matter in its submission to the International Bureau as follows:

> "The issuance of patents for obvious variations of what is, in actuality, a single invention, would subject consumers to extended patent terms for potentially every invention. This can result in an improper burden on the public at large, bringing discredit on patent systems for placing the interests of patent applicants and patentees first, and failing to take the public's interest into account".

Accordingly, as described in paragraph 68, so-called terminal disclaimers play a key role in the United States of America in view of eliminating public concerns about the potential risk of extending the term of a patent. However, the International Bureau is not aware of any other countries raising such concern or providing specific mechanisms to respond to such concerns in their submissions.

105. It may be noted that the above concern is raised by the United States of America, which applies to Model C, while no concerns in this respect have been expressed by any other countries that belong to Model A or C. From a purely theoretical point of view, comparing Models A to C without anti-self-collision, the probability of granting multiple patents covering similar subject matter is the highest in the case of Model A and the lowest in the case of Model C, since only what is explicitly or inherently disclosed in earlier applications becomes part of the prior art under Model A. If that is the case, theoretically, the above concerns should be higher under Models A and B than under Model C. However, if these models apply anti-self-collision, as described in paragraph 103, Model C strengthens the relative position of the inventor/applicant of the earlier application by way of retaining his possibility of obtaining a patent in respect of obvious improvements in respect of his earlier

invention, while third parties would be excluded from such possibility. On the other hand, under Models A and B, the inventor/applicant of the earlier application could obtain marginal advantage over third parties through anti-self-collision, since any person may obtain a patent in respect of obvious improvements compared to the earlier application. Therefore, it may be said that terminal disclaimers are applied under Model C together with the anti-self-collision system in order to balance the relatively strong position of the earlier inventor/applicant with a limitation of the term of protection.

106. In any case, the adjustment of the term of protection *per se* or terminal disclaimers as such are neither a matter of the definition of prior art nor of the definition of novelty. Although public concerns about extended patent terms may merit further examination,[29] discussions on terminal disclaimers or any other mechanism for the adjustment of the term of protection should be isolated from the determination of the prior art effect of earlier applications.

IX. SHOULD THE SAME NOVELTY STANDARD BE APPLIED THROUGHOUT THE PATENT SYSTEM?

107. In connection with reviewing the novelty standard applicable to the prior art effect of earlier applications, one related issue that remains to be examined is whether the novelty standard applicable to the prior art effect of earlier applications should necessarily be the same as the novelty standard applicable to publicly available prior art as well as to a number of other situations occurring in the patent system. As described in Chapter V, different countries take different approaches in this respect: some apply the same novelty standard to both publicly available prior art and prior art consisting of earlier applications; others apply a strict novelty standard to publicly available prior art and a broader novelty concept to prior art consisting of earlier applications.

108. A question which arises is whether a "broader" novelty standard, if accepted, should necessarily apply to all types of prior art. In this regard, a comparison of two possible scenarios provide a clearer picture of the consequences of applying the same or different novelty standards to different types of prior art: the first scenario would apply the same broader novelty standard to publicly available prior art, and the second scenario would apply, a much stricter novelty concept to the publicly available prior art. It would seem that, in practice, the difference between the two scenarios has no significant consequences on the result of substantive examination because, as far as publicly available prior art is concerned, not only lack of novelty, but also lack of inventive step is examined. If a claimed invention under examination is not explicitly or inherently disclosed in the publicly available prior art, but the difference between the two consists in, for example, a substitution by well-known equivalents, such a claimed invention would not be patentable on the grounds of lack of novelty vis-à-vis the publicly available prior art under the first scenario. Under the second scenario, although the novelty requirement would be complied with, since the claimed invention would be considered obvious for a person skilled in the art through combining the publicly available prior art and well-known equivalent means, it would not be patentable on the grounds of lack of inventive step. Therefore, under both scenarios, the claimed invention would not be patentable.

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[29] It should be noted that neither double patenting nor the term of protection are covered by the current draft SPLT.

109. The adoption of different approaches, therefore, may result only in theoretical differences leading to the same end, since there is no contradiction in respect of the fate of the application between the two. In this respect, the historical development of national laws as described in the French submission (see paragraph 38) issuggestive. It may well be that one of the reasons for applying a strict novelty standard is a consequence of introducing the concept of inventive step in the 20th century.

110. Among those that apply a strict novelty standard, the EPC, for example, applies that same novelty test to other matters, such as determining whether the "same invention" is contained in a previous application the priority of which is claimed, examining whether a divisional application is permissible or the assessment of the admissibility of amendments. Since the strict novelty standard requires an identity with the explicit or inherent disclosure in the document concerned, obviously, the same test could be extended to the above matters where it is indispensable to preserve the contents of the original application, be it a previous application the priority of which is claimed or a parent application in the case of divisional applications.

111. It would seem, however, that the objectives underlying the novelty requirement and those relating to the validity of a priority right, divisional applications or amendments are different. The objective relating to the novelty requirement is to avoid the grant of an exclusive right to what already belongs to the public domain. Granting a patent to an invention already known is not justified. The key issue is, therefore, to define the boundary between existing prior art which belongs to society and subject matter that can be subject to an exclusive right. What constitutes the "existing prior art" in the context of novelty determination should be considered against this backdrop. On the other hand, the validity of a priority right, divisional applications, and amendments are based on the principle that an applicant should not obtain patent protection in respect of subject matter which he did not disclose in the application on the filing date (priority date). An exclusive right cannot be extended to subject matter that the applicant had not invented before filing an application, and which he had not described in the application as filed. On the basis of this assumption, the key issue in these cases is the determination of the scope of the original disclosure (disclosure in the application the priority of which is claimed, the parent application for divisional application or the application as filed in the case of amendments), and no priority claim, division or amendment that goes beyond the original disclosure should be allowed. Therefore, in those systems that apply a novelty standard that is broader than a concept covering solely the explicit or inherent disclosure in the earlier application, such a standard may not easily be applied to those other matters in respect of which the preservation of the contents is important.

112. In sum, in connection with the prior art effect of earlier applications, where a novelty standard goes beyond the explicit or inherent disclosure contained in the earlier applications, whether applying the same novelty standard to publicly available prior art or imposing a stricter novelty standard to such prior art does not seem to lead to significant practical problems. In certain cases, the same invention may be refused on the grounds of lack of novelty in one system, and on the grounds of lack of inventive step in another. In any case, however, the outcome regarding the patentability of the same invention remains the same. If the novelty standard with respect to earlier applications is determined by the explicit or inherent disclosure in the earlier application, it might be convenient to apply the same standard for other type of determination, such as claiming priority, divisional applications and

– Finally, consideration might be given to limiting the discussion to those elements that appear to be necessary to achieve a common prior art basis, while leaving aside those elements that, while applied in certain systems in the context of the prior art effect of earlier applications, do not seem to relate directly to prior art (such as, for example, terminal disclaimers).

116. The Committee is invited to note the contents of, and to consider possible approaches to address the issues raised in, this document.

[Annexes follow]

EXHIBIT P8

ANNEX I

ARTICLE 8(2) AND RULE 9 OF THE
DRAFT SUBSTANTIVE PATENT LAW TREATY (SPLT)

Article 8

Prior Art

...

(2) [*Prior Art Effect of Certain Applications*] (a) The following subject matter in another application ("the other application") shall also form part of the prior art for the purpose of Article 12(2), provided that the other application or the specification of the patent granted thereon is made available to the public on or after the priority date of the claimed invention by the Office[, as prescribed in the Regulations]:

(i) if the filing date of the other application is prior to the priority date of the claimed invention, the whole contents of the other application;

(ii) if the other application has a filing date that is the same as, or later than, the priority date of the claimed invention, but claims, in accordance with the applicable law, the priority of a previous application having a filing date that is earlier than the priority date of the claimed invention, subject matter that is contained in both the other application and that previous application.

(b) For the purpose of this provision, "the other application" means:

[Alternative A]

(i) where the Contracting Party is a State, an application referred to in Article 3(1)(i) and (iii) and, if that Contracting Party is a member of a regional patent organization, [subject to the applicable law,] a regional application filed with or for the Office of that regional patent organization through which patent protection in the said Contracting Party is sought and an international application the processing and examination of which has started before the Office of that regional patent organization in its capacity as a designated Office under the PCT;

(ii) where the Contracting Party is a regional patent organization, an application referred to in Article 3(1)(ii) and (iii).

[End of Alternative A]

Rule 9

Prior Art Effect of Certain Applications Under Article 8(2)

(1) [*Principle of "Whole Contents"*] (a) The whole contents of another application referred to in Article 8(2) shall consist of the description, claims and drawings as of the filing date.

(b) The other application referred to in subparagraph (a) shall also include an application for a utility model or any other title protecting an invention under the applicable law, except where the applicable law allows for a patent and another such title to be validly granted with effect for a Contracting Party for the same claimed invention.

(2) [*Applications That Should Not Have Been Made Available*] Where the other application has been made available to the public in accordance with Article 8(2) in spite of the fact that it should not have been made available to the public under the applicable law, it shall not be considered as prior art for the purposes of Article 8(2).

[(3) [*Anti-Self Collision*] Article 8(2) and paragraph (1) shall not apply when the applicant in respect of, or the inventor identified in, the other application and the applicant in respect of, or the inventor identified in, the application under examination, are, at the filing date of the application under examination, one and the same person, provided that only one patent may be validly granted with effect for a Contracting Party for the same claimed invention.]

[Annex II follows]

EXHIBIT P8

ANNEX II

ARTICLE 12(2) AND RULE 14 OF THE
DRAFT SUBSTANTIVE PATENT LAW TREATY (SPLT)

Article 12

Conditions of Patentability

...

(2) [*Novelty*] A claimed invention shall be novel. It shall be considered novel if it does not form part of the prior art[, as prescribed in the Regulations].

...

EXHIBIT P8

ANNEX III

A Harmonized Approach To Applying Secret Prior Art

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Abstract

As patent harmonization discussions proceed, one of the major issues to be harmonized concerns the citation of secret prior art. Previously filed, subsequently published applications can be utilized as prior art both against third-party applicants and the later-filing applicant himself.

In the United States, Japan, and Europe, such secret prior art is currently used in different ways. A new proposal is herein suggested which reintroduces the concept of "enlarged novelty" as applying to both third-party rejections and the later-filing applicant. This new system inherently results in a compromise of the three existing Patent Systems.

I. Patent Harmonization Discussions

Patent harmonization discussions have been going on for at least 25 years. Initial activities taking place at Geneva under the sponsorship of the World Intellectual Property Organization (WIPO) yielded hope for a substantive treaty but were ultimately stymied by lack of progress on the "first-to-file" issue. However, the discussions did result in the passage of a procedural Patent Law Treaty (PLT), which has already been successful. While not yet ratified, it has served as a model for changing all other patent laws, including the Patent Cooperation Treaty (PCT), to conform with the PLT.

Continued discussions on substantive patent law harmonization have proceeded on a rather slow basis. Confronted by a number of political obstacles, patent harmonization has been an elusive goal. Conflicting views between "east and west" on major patent issues such as patentable subject matter, technical effect, and first-to-file have slowed the pace towards any compromise solution. Likewise, "north-south" issues on protecting genetic resources and traditional folklore have likewise stymied progress on harmonization talks.

However, it appears that Non-Governmental Organizations (NGOs) are actively trying to eliminate duplication of effort by patent offices around the world to ultimately reduce the cost of patent protection globally, while maintaining high quality. As a result, a flurry of efforts has recently taken place to revive the stymied WIPO talks and attempt to give patent harmonization a "jump start".

On the one hand, the Trilateral Patent Offices (European Patent Office, Japan Patent Office, and U.S. Patent and Trademark Office) have proceeded by prioritizing the issues into primary and secondary groups and to address those issues in the primary list, while keeping the most difficult subjects as part of a secondary list. At the same time, the NGOs have met, and in a similar approach have put together a "mini basket" of issues which should be initially addressed in an attempt to achieve harmonization on these issues as a first step.

In both lists of issues, the main areas being addressed relate to those laws requiring harmonization in order to achieve an equal basis for an international-type search. At present, one of the difficulties in providing "good faith and credit" to an international search from one organization to another is the differences in substantive patent laws.

The grace period in the United States eliminates references which Europe and Japan would accept. Different interpretation of prior art, for example, local versus absolute, also provides differences in the utilization of prior art. Finally, one of the most difficult and distinct areas preventing uniform searching relates to the use of previously filed, subsequently published applications, typically referred to as "secret prior art".

To the extent that a common legal approach can be achieved in uniformly addressing such "secret prior art", great progress might be achieved toward ultimately obtaining harmonization on the "mini-basket" of issues presently being considered.

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II. What is "Secret Prior Art"?

Secret prior art refers to patent applications that have been previously filed but subsequently published with respect to a particular application that is being examined. Such secret prior art presents conceptual problems when utilizing it as prior art. On the one hand, as it was "secret" and not available to the public, it is difficult to utilize as information that was in the public domain, since no one could get access to that information and no one, except the inventor of the first-filed application, was aware of it.

At the same time, it cannot be totally disregarded, since it does show that someone else had previously invented that concept, described it, and satisfied the requirements of the patent system by disclosing it at least to the Patent Office in a patent application. In a first-to-invent system, it shows that someone else invented that information, at least to the extent that they established a previous filing date. In a first-to-file system, it shows that someone else had filed that invention previously. Accordingly, the prior-filed application cannot be totally disregarded as a prior art for the later-filed application.

Secret prior art can then be utilized against all third parties, as well as against the applicant in certain circumstances, which *differ from country to country. Against third parties, it presents* prior art conceived of by another. Even as against the applicant, however, it presents an indication that all of the material was previously disclosed by the applicant himself and constitutes a prior official disclosure for the later submission into the public domain.

The extent of utilization of such secret prior art has two possibilities. One is the "prior claim approach", which only utilizes the specific claims of the first patent application against a later-filed application. The difficulty with this approach is that it takes many years until the claims of the first application are fully known. As a result, it may delay the prosecution of the second application, since the second application cannot move forward until the claims of the first patent application have been defined.

The more widely accepted approach is the "whole contents approach". In this case, the entire text of the first patent application is utilized as prior art to be applied against what is being claimed in the second application.

III. Current Systems Applying Secret Prior Art

At present, the U.S., Europe, and Japan each have different approaches to utilizing secret prior art as a reference against third parties, as well as against the applicant himself. Each of these approaches defines a workable system that has been utilized for years, and each approach presents a viable possibility that can be the basis for a harmonized system. However, each of these approaches also presents some conceptual contradictions and often does not appear to be logical or equitable in applying such secret prior art. Each of these approaches actually has two parts. One is applying the secret prior art against third parties, and the other is applying the secret prior art against the applicant himself. Each of these will be analyzed below.

A. Secret Prior Art Utilized Against Third Parties

i. European Approach

The European approach is to use the whole contents of the *secret prior art against a third-party pending application. How*ever, it only utilizes the whole contents for strict novelty-defeating purposes. Such strict novelty is sometimes referred to as "photographic novelty". Thus, to the extent that the later-filed application differs even slightly from what is contained in the secret prior art, a patent will issue to the second applicant. Consequently, to the extent the second applicant claims something which is not directly within the secret prior art disclosure but might be obvious from it, he would also get a patent. This can best be described below in Fig. 1.[1]

FIG 1 – Europe applying Secret Prior Art against another applicant

	Disclosure		
Applicant 1	A, B, C		
	Applicant 2 -	Claims B	- No Patent
	Applicant 2 -	Claims B'	- Patent
	Applicant 2 -	Claims BD	- Patent

ii. Japanese Approach[2]

The Japanese system generally is similar to the European system in applying the whole contents of the secret prior art only for novelty-defeating purposes against a third-party applicant who files later. However, according to the Japanese Patent Office, the whole contents of the first application is applied not only for what is "photographically" presented, but also for information that one could understand or grasp from the disclosure or from the matters which can be said to be substantially disclosed in the secret prior art – specifically, anything that can be derived by considering the common technical knowledge in the arts at the time of filing of the secret prior art.

Such common technical knowledge in the arts is the matter which is apparent on the basis of arts well known to the person having ordinary skill in the art. Thus, in Japan the concept of "novelty" is broader than just "photographic novelty". The situation in Japan would be as shown in Fig. 2 below.

FIG 2 – Japan applying Secret Prior Art against another applicant

	Disclosure		
Applicant 1	A, B, C		
	Applicant 2 -	Claims B	- No Patent
	Applicant 2 -	Claims B'	- No Patent
	Applicant 2 -	Claims BD	- Patent

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iii. U.S. Approach

The U.S. approach also applies the whole contents of the secret prior art. However, it utilizes it both for novelty-defeating purposes and for obviousness purposes. Accordingly, in the U.S. they will apply everything that is disclosed in the secret prior art directly, as well as combining it with any other reference which may either have been published or may also have been part of the secret prior art. This situation is described in Fig. 3 below.

FIG 3 – U.S. applying Secret Prior Art against another applicant

	Disclosure		
Applicant 1	A, B, C		
	Applicant 2 -	Claims B	- No Patent
	Applicant 2 -	Claims B'	- No Patent
	Applicant 2 -	Claims BD	- No Patent (assume D is known in that art)

B. Against the Applicant Himself

i. European Approach

In Europe, they utilize the same whole-contents approach for novelty-defeating purposes against the applicant exactly as against a third party. This is typically referred to as "self-collision" or "internal collision". Namely, to the extent that the applicant has disclosed an invention in a secret prior art, he can no longer claim that same invention in a later application, the concept being that once he disclosed it in the first application, he must claim it there and cannot claim it elsewhere. He can file a divisional on that first application, but he cannot claim it in any other application.

However, again, this novelty is only "photographic novelty", so that should he claim a slight variation, an equivalent, a species, or some other slightly different invention in a later application, the earlier, secret prior art application will not be used against him. Clearly, if he claims in a later-filed application an invention that is only obvious over the first disclosure, he will definitely get a patent, since the first application is only utilized for very narrow novelty-defeating purposes. This is shown below in Fig. 4. It should be noted that it is a similar situation to applying the secret prior art against third parties.

FIG 4 – Europe applying Secret Prior Art against same applicant

	Disclosure		
Applicant 1	A, B, C		
	Applicant 1 -	Claims B	- No Patent
	Applicant 1 -	Claims B'	- Patent
	Applicant 1 -	Claims BD	- Patent

ii. Japanese Approach

In Japan, however, they do not care about self-collision. Specifically, the prior art cannot be used against the applicant himself, or even the same inventor of the claimed invention and different assignees, even for novelty-defeating purposes. One of the reasons for this is that in Japan, large industry files many applications. Typically, the applications may be initially prepared by the inventor himself and reviewed by a patent attorney before filing. The disclosure put together by the inventor, or even a patent attorney, may often overlap another disclosure, since large groups of inventors typically work together. Accordingly, the same disclosure of a particular invention may be found in a number of different applications, all being filed around the same time, although not on the same day.

As a result, the particular application which claims that invention may be later than an earlier application that already described that invention. Accordingly, the situation in Japan is shown below in Fig. 5.

FIG 5 – Japan applying Secret Prior Art against same applicant

	Disclosure		
Applicant 1	A, B, C		
	Applicant 1 -	Claims B	- Patent
	Applicant 1 -	Claims B'	- Patent
	Applicant 1 -	Claims BD	- Patent

iii. U.S. Approach

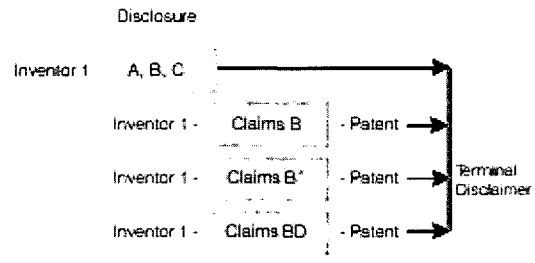
The U.S. situation is much more complicated. Firstly, it makes a distinction whether the secret prior art and the later application were filed by the same inventor[3] or not, and also makes a distinction whether there is an obligation to assign the secret prior art invention and the later invention to a single applicant, at the time each was filed. Furthermore, it makes a distinction between applying the reference for novelty-defeating purposes and for obviousness purposes.

Additionally, U.S. law includes terminal disclaimers. Should the same inventor claim the same invention twice, this is absolutely prohibited as being statutory double-patenting. On the other hand, should the applicant be claiming an invention that is obvious over a previously disclosed invention, such would be considered obvious double- patenting and would require a terminal disclaimer so that both patents must remained owned by the same inventive entity or its assignee and would terminate at the same time to avoid any extension of the patent grant beyond the expiration date of the patent issuing from the original invention.

Shown below in Fig. 6 is U.S. application of secret prior art applied against the same inventor. In this case, there would actually be no application of the secret prior art against the inventor himself. However, a terminal disclaimer would be re-

quired even though the secret prior art is not a reference. (It is understood that the same invention is not being claimed twice, namely it is not being claimed in the first application, although it is disclosed in that first application).

FIG 6 – U.S. applying Secret Prior Art against same inventor

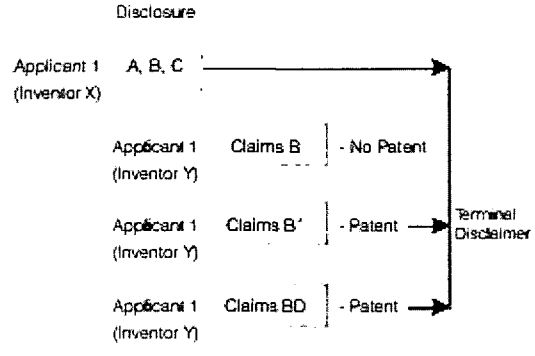


In connection with applying the secret prior art where there are different inventive entities of claims in the later application compared with the first application, although at the time of their *respective inventions all inventors had an obligation to assign* to the same assignee, a different situation occurs. In this case, if the same invention is disclosed in the secret prior art, the secret prior art will be applied for novelty purposes. In this case, no patent will issue unless the second inventive entity was the same inventive entity of the invention disclosed in the first application.

However, the secret prior art will not be applied for obviousness purposes, since U.S. law has been changed to acknowledge the fact that groups work together, and therefore one inventor may learn an invention from another and improve upon it within the same group, working for the same company, and therefore the company should not be deprived of those inventions coming from the group when one inventor improves upon the other.

Accordingly, applying secret prior art in the U.S. against the same assignee but different inventors will result in the following as shown in Fig. 7.

FIG 7 – U.S. applying Secret Prior Art against different inventors but common assignee



III. Logical Inconsistencies With Existing Approaches

Although each of the European, Japanese, and U.S. approaches provides a workable system, there are logical inconsistencies with each of these systems producing contradictions and logically difficult results.

By way of example, the European approach fails to provide adequate protection to an applicant who comes up with a basic idea. Since the secret prior art will only be utilized against third parties for "photographic novelty" to the extent the first applicant makes a basic contribution, a later applicant can come along and make a very slight or equivalent modification or substitution and get his own patent.[4] Sometimes this can deprive the original applicant of any of the practical, commercial benefits of his first invention.

Especially in a first-to-file system, where there is a rush to get the application on file, there may not be adequate time to include every variation. However, once the first applicant files the application, he locks in his rights. Although he had been the first to file for the invention, someone else may come up with a very minor change and gain independent patent rights of a much more significantly commercial invention.

Furthermore, limiting the applicant to the specific wording of the patent application places his invention as the "sacrificial lamb" to the linguistic capabilities of a patent attorney. Since Europe only precludes "photographic novelty" to the extent the patent attorney used a particular word or phrase rather than a different phrase, someone with a slightly different wording would be able to get an independent patent thwarting the rights of the true first-to-file inventor.

Additionally, while the applicant himself can always file divisionals and claim all aspects of his original disclosure to the extent of the linguistic capabilities of the patent attorney, should he fail to do so until grant of his first application as a result of self-collision, he is precluded from recovering what he originally disclosed should he file a second application. If he filed the divisional shortly before grant, he would be able to cover what he had disclosed. If he files it after grant, he is now precluded, although he was the one who originally disclosed it.

Additionally, since the European and Japanese approaches do not have terminal disclaimers, although it is not an identical invention as disclosed, the public is subjected to extending the monopoly for what are essentially minor variations of the same invention, because "photographic novelty" will not prevent the same applicant from extending the monopoly with minor variations. This problem would be further exacerbated if there were to be a grace period where the applicant's own publication would not be prior art against the applicant for the time limit of the grace period.

The U.S. system likewise presents logical inconsistencies. Under the U.S. system, a "secret prior art" is utilized and combined with other references, in some cases also other "*secret prior art*". *This is effectively saying that one skilled in*

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the art would find it obvious to take what is not known to anyone publicly and combine it with something else which is known or even not known to anyone publicly, in order to make the invention obvious on the date the second application was filed.

In truth, the only one privy to the "obvious combination" of two items of "secret prior art" is the patent examiner, who must decide what is obvious to one of ordinary skill in the art and not be that skilled artisan himself.

Furthermore, the anomaly of applying the U.S. law against inventors, as compared to applicants, also presents inconsistencies. Should there be a common applicant (assignee) with different inventors, no patent will issue if it was previously disclosed (applying 102(e)) but a patent will issue on an obvious variant (not applying 102(e)/103), as the group works together. The law thus recognizes a group working together but not a patent attorney writing an application based upon the work of the group and incorporating more than one idea, although not claiming it.

Moreover, the "working group" concept fails if the working group is a corporation and a university that work in joint development, two corporations working in joint development, etc. Innovation often occurs where two different legal entities not under common control are engaged in research and development.

Accordingly, although all of the various existing systems have functioned and operate effectively, none of them provides a perfect logic to all aspects of utilizing "secret prior art".

IV. New Proposal For Applying Secret Prior Art

Although, in a harmonized treaty, any of the existing approaches could be utilized as the accepted standard, in order to do so there would have to be full concessions on the part of one approach to accept the other approach. While concessions are always available in negotiating harmonization treaties, compromise often is preferable. However, in compromising, what is often done is to take one of the existing approaches and "tailor" or modify it in certain aspects.

As has been frequently pointed out, an existing approach may have been proven effective for many years. It is built on numerous other intertwined aspects. "Tinkering" with one aspect and modifying it often has detrimental effects on another aspect, and it is not that easy to take an existing approach and simply modify it in one or two aspects. It is often preferable to come up with a totally new approach which provides a compromise in its effect, and at the same time is one that can be accepted based upon logical principles of law and equity, and fairness for all systems involved and their applicants.

In this regard, a new proposal is presented for dealing with secret prior art which effectively provides a compromise and, at the same time, provides a new approach which differs from all existing approaches. The new approach is based upon applying the whole contents of secret prior art for what is referred to as "enlarged novelty" purposes.[5] To some extent, it is not a new concept but reverts back to an old understanding of the concept of novelty.

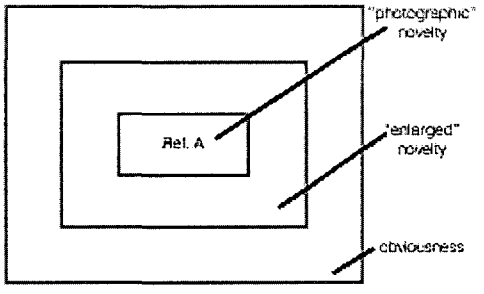
For example, under the German national patent system this is a concept of novelty, which covers all that one skilled in the art usually understands from a document and which is broader than the photographic novelty approach that is currently being utilized by the European Patent Office and by most of its Member States. By way of example, if a generic invention is disclosed in the secret prior art, it should preclude a subsequent application from covering a species not particularly identified within the generic disclosure (unless the "species" is in the nature of a "selection" which could give rise to patentability).

Likewise, later equivalents should be precluded. Later well-known substitutes should be precluded. Anything that would be well known to one skilled in the art reading the original disclosure should also be precluded. Thus, the first disclosure should not only provide novelty-defeating from a "photographic" viewpoint, but from an "enlarged novelty" viewpoint. To some extent, this is similar (although perhaps broader) than the present Japanese understanding of "novelty". Moreover, this German concept of novelty is similar to the American concept of "inherency" found in a single prior art reference.

To the extent that the second inventor can show that his particular species, equivalent, substitute, etc. would not have been within the original "enlarged" disclosure, as it provides unexpected benefits, unusual results, or the like, he may present arguments to overcome such secret prior art rejection. Also, as the secret prior art can only be used for novelty (enlarged) defeating purposes, it cannot be combined with any other reference or any other material to provide an obviousness type rejection.

By way of example, Fig. 8 indicates schematically what constitutes the "enlarged novelty" beyond the "photographic novelty" of the secret prior art Reference A and the potential for combining it with other references to provide an "obviousness" rejection from that Reference A. It is only the "enlarged novelty" that would be utilized for applying such secret prior art.

FIG 8



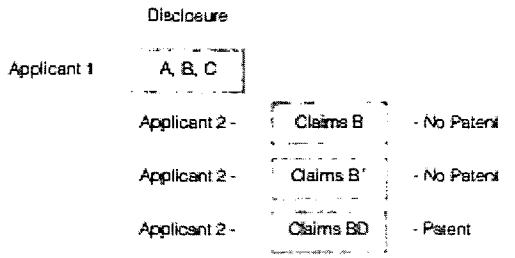
Conceptually, the approach of using the "enlarged" novelty for applying secret prior art is to give the full benefit of the invention to the inventor who is the first to file. Although he may have rushed to file his application first, and his patent attorney

may have used specific words, he should still be entitled to the full benefit of his invention. Thus, to the extent that he covered a generic concept and listed some but not all species, someone else should not be able to come up with another species falling within the generic class and get a separate patent on it (except for the "selection" concept indicated above, which should be held to high standards of proof).

Likewise, although he may have described his invention and given some examples, someone else should not be able to come up with one other equivalent or well-known substitute and get a separate patent on that. The inventor should be given the full breadth of his invention and be able to stop others from getting patents on anything falling within the scope of his invention. However, he should not be able to stop others from making use of his invention and combining it with other independent ideas. Thus, he should not be able to utilize his secret prior art for obviousness purposes where it is necessary to combine the secret prior art with other references.

In connection with applying "secret prior art" in an "enlarged" novelty approach, the result applying it against third parties would be as shown in Fig. 9 as follows.

FIG 9 – Applying Secret Prior Art against another applicant in "Enlarged Novelty" system



It should be noted that the effective result of using the "enlarged novelty" approach is effectively a compromise between the European approach (Fig. 1) and the U.S. approach (Fig. 3), and rather similar to the Japanese approach (Fig. 2).

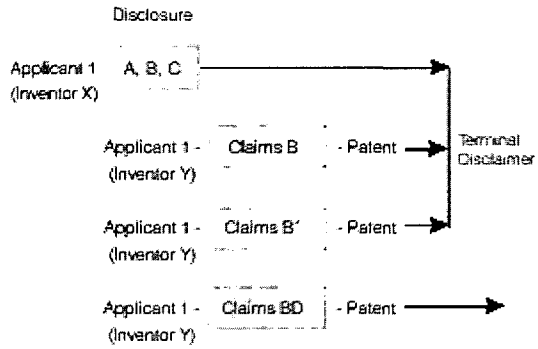
It is also believed that this same "enlarged novelty" concept can be utilized in connection with the applicant himself. The applicant should be able to ultimately claim anything disclosed in his first application from an "enlarged" viewpoint. Specifically, the applicant should be able to claim both his "photographic" disclosure and an "enlarged" version of that disclosure in his second application.

Furthermore, it should not make a difference whether it is the inventor himself who filed the second application or whether it is another inventor within the same applicant group. So long as both inventors were part of the applicant, in the sense that they had an obligation to assign it to the same applicant, we must recognize the group aspect of inventions and grant patents to the applicant whether the invention was disclosed in the first application and claimed in the second, or claimed in the first, so long as the true inventor is named in the application claiming his invention.

However, in all fairness to the public, in cases where it is a common applicant that is working with members of a single group expanding the invention, a terminal disclaimer should be applied. However, such terminal disclaimer should only be limited to the "enlarged novelty" of the invention, not to anything that results from obvious advances of the invention.

Accordingly, in the proposed system the following Fig. 10 would result when applying secret prior art against an applicant, regardless of who is the inventor.

FIG 10 – Applying Secret Prior Art against different inventors but common assignee



It will be noted that this approach again results in a compromise between Japan, Europe, and the U.S. It provides anti-collision features, terminal disclaimer features, equates applicants and inventors, and provides a logical and equitable compromised system.

Conclusion

It is therefore seen that using the "enlarged novelty" approach for applying secret prior art, both against other applicants and in connection with the applicant himself, there is provided a new compromise type of system that provides a logical and equitable approach to the applicant, other inventors, and the public at large. It also happens to provide a mid-way position between the existing approaches currently employed in Japan, Europe, and the United States.

Furthermore, it avoids the necessity of "tinkering" with any existing approach which may cause problems, and instead comes up with a new overall approach. Also, it avoids the political problem of having any one country or region "conceding" to the approach of the other, but instead creates a totally new approach and consistent logic to reach an effective compromise position.

Notes

1 In the examples that follow, "disclosure A, B, C," means that the application discloses these three inventions but does not claim them. "Claims B" means that the application claims invention B. "Claim B´" means the application claims an invention slightly different than invention B disclosed. "Claims BD" means the application combines invention B with another known idea such that the combination BD is an obvious variation of B but requires combining the teaching of B with another reference.

2 The Japanese information has been provided by Shinji Kato, Japanese Patent Attorney, Partner of PROSPEC Patent Firm, Tokyo Branch Office, Japan.

3 In the USA only, the applicant is the inventor, not an assignee of the inventor. Because inventorship can vary from claim to claim, the "inventive entity" of each claim needs identification in both the prior application and the later application for prior art purposes.

4 The later applicant's work is done and filed without knowledge of the earlier applicant's work. But in rapidly emerging technologies, parallel innovation paths often occur.

5 In some respects this concept has been suggested informally in the past. Among those who had considered this concept in the past, in addition to the authors of this paper, was Mike Pantuliano of Clifford Chance. On behalf of the IIPS at the London "Roundtable" of NGOs on November 10 and 11, 2003, he advanced, in general terms, the proposal being formally presented here in this paper. He also endorsed the notion that under an "enlarged novelty" concept, for citation purposes a first-filed, later published application would not be combinable with other known or unknown references. His proposal was submitted only with respect to the application of secret prior art to third parties. However, in this paper it is now extended to apply also with respect to an applicant.

[End of Annex III and of document]

EXHIBIT P9

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
23 February 2012 (23.02.2012)

PCT

(10) International Publication Number
WO 2012/024620 A2

(51) International Patent Classification:
C07D 209/30 (2006.01) *A61K 31/4439* (2006.01)
C07D 401/04 (2006.01) *A61P 11/00* (2006.01)
C07D 401/06 (2006.01) *A61P 35/00* (2006.01)
A61K 31/404 (2006.01)

(21) International Application Number:
PCT/US2011/048477

(22) International Filing Date:
19 August 2011 (19.08.2011)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
61/375,688 20 August 2010 (20.08.2010) US

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(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PE, PG, PH, PL, PT, QA, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:

— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))*

— *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))*

Published:

— *without international search report and to be republished upon receipt of that report (Rule 48.2(g))*

(54) Title: AUTOTAXIN INHIBITORS AND USES THEREOF

(57) Abstract: Described herein are compounds that are inhibitors of autotaxin. Also described are pharmaceutical compositions and medicaments that include the compounds described herein, as well as methods of using such inhibitors, alone and in combination with other compounds, for treating autotaxin-dependent or autotaxin-mediated conditions or diseases.

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AUTOTAXIN INHIBITORS AND USES THEREOF

RELATED APPLICATIONS

[0001] This application claims the benefit of U.S provisional patent application no. 61/375,688 entitled "AUTOTAXIN INHIBITORS AND USES THEREOF" filed on August 20, 2010, which is incorporated by reference in its entirety.

FIELD OF THE INVENTION

[0002] Described herein are compounds, methods of making such compounds, pharmaceutical compositions and medicaments comprising such compounds, and methods of using such compounds to treat, prevent or diagnose diseases, disorders or conditions associated with autotaxin activity.

BACKGROUND OF THE INVENTION

[0003] Autotaxin (ATX) is a secreted enzyme that is important for generating the lipid signaling molecule lysophosphatidic acid (LPA). Autotaxin has lysophospholipase D activity that converts lysophosphatidylcholine to LPA. LPA is a lipid mediator that functions, for example, as a mitogen, chemoattractant, and survival factor for many cell types. The ATX-LPA signaling axis is implicated in, for example, angiogenesis, chronic inflammation, autoimmune diseases, fibrotic diseases, neurodegenerative diseases, reperfusion injury post stroke or myocardial ischemia, reproduction and tumor progression.

SUMMARY OF THE INVENTION

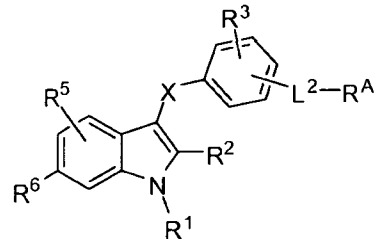
[0004] In one aspect, presented herein are compounds of Formula (I) that inhibit autotaxin activity. In some embodiments, autotaxin inhibitors described herein are useful as agents for the treatment or prevention of diseases or conditions in which ATX and/or LPA participates, is involved in the etiology or pathology of the disease, or is otherwise associated with at least one symptom of the disease. Inhibition of the physiological activity of ATX and/or LPA is useful in a variety of diseases or conditions. The ATX-LPA signaling pathway has been implicated in angiogenesis, chronic inflammation, autoimmune diseases, fibrotic diseases, reproduction and tumor progression.

[0005] In one aspect, the compounds of Formula (I) are useful for the treatment of fibrosis, cell proliferative disease (cancer and invasive metastasis of cancer cells, and the like), inflammatory disease, autoimmune diseases (e.g. arthritis), reproductive diseases, abnormal angiogenesis-associated disease, scleroderma, brain or heart reperfusion injury (cerebral infarction, cerebral hemorrhage, and the like), neurodegenerative diseases, neuropathic pain, peripheral neuropathy, ocular disease (age-related macular degeneration (AMD), diabetic retinopathy, proliferative vitreoretinopathy (PVR), cicatricial pemphigoid, glaucoma filtration surgery scarring, and the like).

[0006] In one aspect, described herein are compounds of Formula (I), pharmaceutically acceptable salts, pharmaceutically acceptable solvates, and prodrugs thereof.

[0007] Compounds of Formula (I) are used in the treatment of diseases or conditions in which autotaxin activity contributes to the symptomology or progression of the disease, disorder or condition. These diseases, disorders, or conditions may arise from one or more of a genetic, iatrogenic, immunological, infectious, metabolic, oncological, toxic, surgical, and/or traumatic etiology. In one aspect, the methods, compounds, pharmaceutical compositions, and medicaments described herein comprise autotaxin inhibitors.

[0008] In one aspect, provided herein is a compound having the structure of Formula (I), pharmaceutically acceptable salt, pharmaceutically acceptable solvate, or prodrug thereof:



Formula (I)

wherein,

R^1 is H, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6fluoroalkyl, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted C_3-C_6cycloalkyl, substituted or unsubstituted phenyl, substituted or unsubstituted monocyclic heteroaryl, or $-L^1$-R^4;

L^1 is substituted or unsubstituted C_1-C_6alkylene, substituted or unsubstituted phenylene, or substituted or unsubstituted monocyclic heteroarylene;

R^4 is substituted or unsubstituted C_3-C_6cycloalkyl, substituted or unsubstituted phenyl, substituted or unsubstituted benzyl, substituted or unsubstituted naphthyl, or substituted or unsubstituted monocyclic heteroaryl;

R^2 is H, C_1-C_4alkyl or C_1-C_4fluoroalkyl;

X is -O-, -S-, -S(O)-, $-S(O)_2$-, $-CH_2$-, $-CH_2CH_2$-, $-OCH_2$-, $-CH_2O$-, $-SCH_2$-, $-CH_2S$-, -C(=O)-, $-C(=O)CH_2$-, or $-CH_2C(=O)$-;

L^2 is absent, C_1-C_6alkylene or C_3-C_6cycloalkylene;

R^A is $-CO_2H$, $-CO_2(C_1$-C_6alkyl), -OH, -CN, $-B(OH)_2$, $-C(=O)NHSO_2R^9$, $-C(=O)N(R^{10})_2$, $-C(=O)NHCH_2CH_2N(CH_3)_2$, $-C(=O)NHCH_2CH_2N(CH_3)_3$, -C(=O)NH-OH, -C(=O)NH-CN, $-NHSO_2C(=O)R^9$, -CN, tetrazolyl or carboxylic acid bioisostere;

R^3 and R^5 are each independently H, halogen, -CN, -OH, C_1-C_4alkyl, C_1-C_4alkoxy, -S-C_1-C_4alkyl, C_1-C_4fluoroalkyl, C_1-C_4fluoroalkoxy, and C_1-C_4heteroalkyl;

R^6 is H, halogen, -CN, $-NO_2$, -OH, $-OR^9$, $-SR^9$, $-S(=O)R^9$, $-S(=O)_2R^9$, $-S(=O)_2N(R^{10})_2$, $-NR^{10}S(=O)_2R^9$, $-C(=O)R^9$, $-OC(=O)R^9$, $-CO_2R^{10}$, $-OCO_2R^9$, $-N(R^{10})_2$, $-C(=O)N(R^{10})_2$, $-OC(=O)N(R^{10})_2$, $-NHC(=O)R^9$, $-NHC(=O)OR^9$, C_1-C_4alkyl, C_1-C_4alkoxy, -S-C_1-C_4alkyl, $-S(O)_2$-C_1-C_4alkyl, C_1-C_4fluoroalkyl, C_1-C_4fluoroalkoxy, C_1-C_4heteroalkyl, C_3-

C_6cycloalkyl, substituted or unsubstituted phenyl, substituted or unsubstituted monocyclic heteroaryl,

R^9 is C_1-C_6alkyl, C_3-C_6cycloalkyl, a substituted or unsubstituted phenyl, or a substituted or unsubstituted monocyclic heteroaryl;

each R^{10} is independently selected from H, C_1-C_6alkyl, C_3-C_6cycloalkyl, a substituted or unsubstituted phenyl, or a substituted or unsubstituted monocyclic heteroaryl; or

two R^{10} groups attached to the same N atom are taken together with the N atom to which they are attached to form a substituted or unsubstituted heterocycle;

[0009] For any and all of the embodiments, substituents are selected from among a subset of the listed alternatives. For example, in some embodiments, R^A is $-CO_2H$, $-CO_2(C_1$-C_6alkyl), -OH, -CN, -$B(OH)_2$, $-C(=O)NHSO_2R^9$, $-C(=O)N(R^{10})_2$, $-C(=O)NHCH_2CH_2N(CH_3)_2$, $-C(=O)NHCH_2CH_2N(CH_3)_3$, $-C(=O)NH$-OH, $-C(=O)NH$-CN, $-NHSO_2C(=O)R^9$, -CN, tetrazolyl or carboxylic acid bioisostere. In some embodiments, R^A is $-CO_2H$, $-CO_2(C_1$-C_6alkyl), -$B(OH)_2$, $-C(=O)NHSO_2R^9$, $-C(=O)N(R^{10})_2$, $-C(=O)NHCH_2CH_2N(CH_3)_2$, $-C(=O)NHCH_2CH_2N(CH_3)_3$, $-NHSO_2C(=O)R^9$, -CN, tetrazolyl or carboxylic acid bioisostere. In some embodiments, R^A is $-CO_2H$, $-CO_2(C_1$-C_6alkyl), or -$B(OH)_2$. In some embodiments, R^A is $-CO_2H$ or $-CO_2(C_1$-C_6alkyl). In some embodiments, R^A is $-CO_2H$.

[0010] In some embodiments, R^1 is C_1-C_6alkyl, C_1-C_6heteroalkyl, substituted or unsubstituted C_3-C_6cycloalkyl, substituted or unsubstituted phenyl, substituted or unsubstituted monocyclic heteroaryl, or $-L^1$-R^4; L^1 is C_1-C_4alkylene, substituted or unsubstituted phenylene, or substituted or unsubstituted monocyclic heteroarylene; R^4 is substituted or unsubstituted C_3-C_6cycloalkyl, substituted or unsubstituted phenyl, substituted or unsubstituted naphthyl, substituted or unsubstituted monocyclic heteroaryl; R^2 is C_1-C_4alkyl or C_1-C_4fluoroalkyl; R^6 is halogen, -CN, -OH, C_1-C_4alkyl, C_1-C_4alkoxy, -S-C_1-C_4alkyl, C_1-C_4fluoroalkyl, C_1-C_4fluoroalkoxy, or C_1-C_4heteroalkyl; X is -O- or -S-.

[0011] In some embodiments, X is -O- or -S-. In some embodiments, X is -S-. In some embodiments, X is -O-.

[0012] In some embodiments, R^1 is a substituted or unsubstituted phenyl, or a substituted or unsubstituted monocyclic heteroaryl. In some embodiments, R^1 is a substituted or unsubstituted phenyl, or a substituted or unsubstituted monocyclic heteroaryl with at least 1 N atom in the heteroaryl ring. In some embodiments, R^1 is a substituted or unsubstituted monocyclic heteroaryl with at least 1 N atom in the heteroaryl ring.

[0013] In some embodiments, R^2 is H, $-CH_3$, $-CH_2CH_3$, $-CH_2CH_2CH_3$, $-CH(CH_3)_2$, $-CH_2CH_2CH_2CH_3$, $-C(CH_3)_3$, or $-CF_3$. In some embodiments, R^2 is H, $-CH_3$, $-CH_2CH_3$, $-CH(CH_3)_2$, or $-CF_3$. In some embodiments, R^2 is $-CH_3$, or $-CF_3$. In some embodiments, R^2 is $-CH_3$.

[0014] In some embodiments, L^2 is absent, $-CH_2$-, $-CH_2CH_2$-, $-CH_2CH_2CH_2$-, $-CH(CH_3)$-, $-CH(CH_2CH_3)$-, $C(CH_3)_2$-, $-C(CH_2CH_3)_2$-, cyclopropyl-1,1-diyl, cyclobutyl-1,1-diyl, or cyclopentyl-

1,1-diyl. In some embodiments, L^2 is absent, -CH_2-, or -CH_2CH_2-. In some embodiments, L^2 is absent.

[0015] In some embodiments, L^2 is absent, -CH_2-, -CH_2CH_2-, -$CH_2CH_2CH_2$-, -$CH(CH_3)$-, -$CH(CH_2CH_3)$-, $C(CH_3)_2$- ,-$C(CH_2CH_3)_2$- , cyclopropyl-1,1-diyl, cyclobutyl-1,1-diyl, or cyclopentyl-1,1-diyl; R^6 is F, Cl, Br, I, -CN, -OH, $-CH_3$, -CH_2CH_3, -$CH(CH_3)_2$, $-OCH_3$, $-OCH_2CH_3$, $-CF_3$, $-OCF_3$, -S-CH_3 or $-S(O)_2$-CH_3.

[0016] In some embodiments, R^2 is $-CH_3$, -CH_2CH_3, -$CH_2CH_2CH_3$, -$CH(CH_3)_2$, -$CH_2CH_2CH_2CH_3$, -$C(CH_3)_3$, or $-CF_3$; L^2 is absent, -CH_2-, -CH_2CH_2-, -$CH_2CH_2CH_2$-, -$CH(CH_3)$-, -$CH(CH_2CH_3)$-, $C(CH_3)_2$- ,-$C(CH_2CH_3)_2$- , cyclopropyl-1,1-diyl, cyclobutyl-1,1-diyl, or cyclopentyl-1,1-diyl; R^6 is F, Cl, Br, I, -CN, -OH, $-CH_3$, -CH_2CH_3, -$CH(CH_3)_2$, $-OCH_3$, $-OCH_2CH_3$, $-CF_3$, $-OCF_3$, -S-CH_3 or $-S(O)_2$-CH_3.

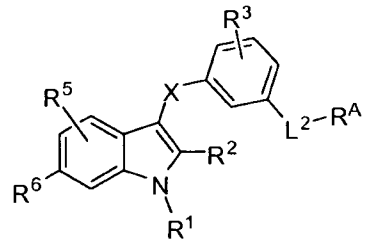
[0017] In some embodiments, R^3 and R^5 are each independently H, halogen, -CN, -OH, C_1-C_4alkyl, C_1-C_4alkoxy, -S-C_1-C_4alkyl, C_1-C_4fluoroalkyl, and C_1-C_4fluoroalkoxy.

[0018] In some embodiments, R^3 is H, F, Cl, -CN, -OH, $-CH_3$, $-OCH_3$, $-CF_3$, or $-OCF_3$; R^5 is H, F, Cl, -CN, -OH, $-CH_3$, $-OCH_3$, $-CF_3$, or $-OCF_3$.

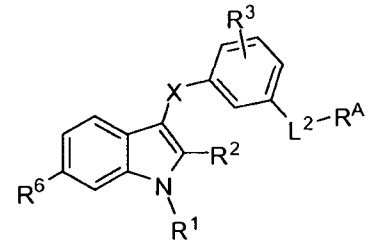
[0019] In some embodiments, R^6 is not H. In some embodiments R^5 is not H.

[0020] In some embodiments, R^5 is H.

[0021] In some embodiments, the compound of Formula (I) has the following structure:



[0022] In some embodiments, the compound of Formula (I) has the structure of Formula (II):



Formula (II).

[0023] In some embodiments, R^A is $-CO_2H$, $-CO_2(C_1$-C_6alkyl), -$B(OH)_2$, or tetrazolyl; X is -S-.

[0024] In some embodiments, R^2 is $-CH_3$, -CH_2CH_3, or $-CF_3$; L^2 is absent, -CH_2-, or -CH_2CH_2-; R^A is $-CO_2H$ or $-CO_2(C_1$-C_6alkyl).

[0025] In some embodiments, R^1 is C_1-C_6alkyl, C_1-C_6heteroalkyl, C_3-C_6cycloalkyl, substituted or unsubstituted phenyl, substituted or unsubstituted monocyclic heteroaryl, or $-L^1$-R^4; L^1 is -CH_2-, substituted or unsubstituted phenylene, or substituted or unsubstituted monocyclic heteroarylene; R^4

is C_3-C_6cycloalkyl, substituted or unsubstituted phenyl, substituted or unsubstituted naphthyl, substituted or unsubstituted monocyclic heteroaryl.

[0026] In some embodiments, R^1 is C_1-C_6alkyl, C_1-C_6heteroalkyl, or $-L^1$-R^4; L^1 is $-CH_2-$; R^4 is substituted or unsubstituted phenyl, substituted or unsubstituted naphthyl, substituted or unsubstituted monocyclic heteroaryl.

[0027] In some embodiments, R^1 is substituted or unsubstituted phenyl, substituted or unsubstituted monocyclic heteroaryl, or $-L^1$-R^4; L^1 is substituted or unsubstituted phenylene, or substituted or unsubstituted monocyclic heteroarylene; R^4 is substituted or unsubstituted phenyl, substituted or unsubstituted naphthyl, substituted or unsubstituted monocyclic heteroaryl.

[0028] In some embodiments, R^1 is substituted or unsubstituted phenyl, substituted or unsubstituted monocyclic heteroaryl.

[0029] In some embodiments, R^1 is a substituted or unsubstituted phenyl, substituted or unsubstituted furanyl, substituted or unsubstituted pyrrolyl, substituted or unsubstituted oxazolyl, substituted or unsubstituted thiazolyl, substituted or unsubstituted imidazolyl, substituted or unsubstituted pyrazolyl, substituted or unsubstituted triazolyl, substituted or unsubstituted tetrazolyl, substituted or unsubstituted isoxazolyl, substituted or unsubstituted isothiazolyl, substituted or unsubstituted oxadiazolyl, substituted or unsubstituted thiadiazolyl, substituted or unsubstituted pyridinyl, substituted or unsubstituted pyrimidinyl, substituted or unsubstituted pyrazinyl, substituted or unsubstituted pyridazinyl, or substituted or unsubstituted triazinyl.

[0030] In some embodiments, R^1 is a substituted or unsubstituted phenyl.

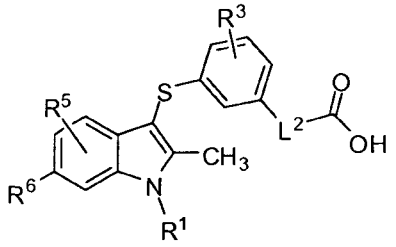
[0031] In some embodiments, R^1 is a substituted or unsubstituted monocyclic 5-membered heteroaryl.

[0032] In some embodiments, R^1 is a substituted or unsubstituted pyrrolyl, substituted or unsubstituted oxazolyl, substituted or unsubstituted thiazolyl, substituted or unsubstituted imidazolyl, substituted or unsubstituted pyrazolyl, substituted or unsubstituted triazolyl, substituted or unsubstituted isoxazolyl, substituted or unsubstituted isothiazolyl, substituted or unsubstituted oxadiazolyl, or substituted or unsubstituted thiadiazolyl.

[0033] In some embodiments, R^1 is a substituted or unsubstituted monocyclic 6-membered heteroaryl.

[0034] In some embodiments, R^1 is a substituted or unsubstituted pyridinyl, substituted or unsubstituted pyrimidinyl, substituted or unsubstituted pyrazinyl, or substituted or unsubstituted pyridazinyl.

[0035] In some embodiments, R^1 is a substituted or unsubstituted monocyclic heteroaryl; R^2 is H or C_1-C_4alkyl; X is -O-, -S-, -S(O)-, or $-S(O)_2-$; L^2 is absent, C_1-C_6alkylene or C_3-C_6cycloalkylene; R^A is $-CO_2H$; R^3 and R^5 are each independently H, halogen, -CN, -OH, C_1-C_4alkyl, C_1-C_4alkoxy, -S-C_1-C_4alkyl, C_1-C_4fluoroalkyl, and C_1-C_4fluoroalkoxy; R^6 is halogen, -CN, -OH, C_1-C_4alkyl, C_1-C_4alkoxy, -S-C_1-C_4alkyl, C_1-C_4fluoroalkyl, C_1-C_4fluoroalkoxy, or C_1-C_4heteroalkyl.



Formula (IV)

wherein,

R^1 is a substituted or unsubstituted monocyclic heteroaryl;

L^2 is absent, $-CH_2-$, or $-CH_2CH_2-$;

R^3 is H, halogen, -CN, -OH, C_1-C_4alkyl, C_1-C_4alkoxy, -S-C_1-C_4alkyl, C_1-C_4fluoroalkyl, or C_1-C_4fluoroalkoxy;

R^5 is H, halogen, -CN, -OH, C_1-C_4alkyl, C_1-C_4alkoxy, -S-C_1-C_4alkyl, C_1-C_4fluoroalkyl, or C_1-C_4fluoroalkoxy;

R^6 is H, halogen, -CN, -OH, C_1-C_4alkyl, C_1-C_4alkoxy, -S-C_1-C_4alkyl, C_1-C_4fluoroalkyl, or C_1-C_4fluoroalkoxy;

each substituted group is substituted with 1 or more groups independently selected from halogen, -CN, -OH, C_1-C_4alkyl, C_1-C_4alkoxy, -S-C_1-C_4alkyl, C_1-C_4fluoroalkyl, C_1-C_4fluoroalkoxy, and C_1-C_4heteroalkyl.

[0043] In some embodiments, R^1 is a substituted or unsubstituted monocyclic 5-membered heteroaryl; L^2 is absent or $-CH_2-$; R^3 is H, F, Cl, Br, I, -CN, -OH, $-CH_3$, $-OCH_3$, $-OCH_2CH_3$, $-CF_3$, $-OCF_3$, or -S-CH_3; R^5 is H, F, Cl, Br, I, -CN, -OH, $-CH_3$, $-OCH_3$, $-OCH_2CH_3$, $-CF_3$, $-OCF_3$, or -S-CH_3; R^6 is F, Cl, Br, I, -CN, -OH, $-CH_3$, $-OCH_3$, $-OCH_2CH_3$, $-CF_3$, $-OCF_3$, or -S-CH_3.

[0044] In some embodiments, R^1 is a substituted or unsubstituted pyrrolyl, substituted or unsubstituted oxazolyl, substituted or unsubstituted thiazolyl, substituted or unsubstituted imidazolyl, substituted or unsubstituted pyrazolyl, substituted or unsubstituted triazolyl, substituted or unsubstituted isoxazolyl, substituted or unsubstituted isothiazolyl, substituted or unsubstituted oxadiazolyl, or substituted or unsubstituted thiadiazolyl; each substituted group is substituted with 1 or more groups independently selected from halogen, -OH, C_1-C_4alkyl, C_1-C_4alkoxy, and C_1-C_4fluoroalkyl; L^2 is absent or $-CH_2-$; R^3 is H, F, Cl, $-CH_3$, $-OCH_3$, $-CF_3$, $-OCF_3$, or -S-CH_3; R^5 is H, F, or Cl; R^6 is Cl.

[0045] In some embodiments, R^1 is a substituted or unsubstituted pyrazolyl; each substituted group is substituted with C_1-C_4alkyl; R^3 is H, F, Cl, $-CH_3$, $-OCH_3$, $-CF_3$, $-OCF_3$, or -S-CH_3; R^5 is H, F, or Cl; R^6 is Cl. In some embodiments, R^1 is a substituted or unsubstituted pyrazolyl; each substituted group is substituted with C_1-C_4alkyl; R^3 is H, F, or Cl; R^5 is H, F, or Cl; R^6 is Cl.

[0046] Any combination of the groups described above for the various variables is contemplated herein. Throughout the specification, groups and substituents thereof are chosen by one skilled in the field to provide stable moieties and compounds.

[0047] In one aspect, compounds of Formula (I) include compounds described in Table 1, Table 2, Table 3, and Table 4, or a pharmaceutically acceptable salt thereof.

[0048] In one aspect, compounds of Formula (I), or a pharmaceutically acceptable salt thereof, are autotaxin inhibitors.

[0049] In some embodiments, presented herein are compounds selected from active metabolites, tautomers, pharmaceutically acceptable solvates, pharmaceutically acceptable salts or prodrugs of a compound of Formula (I).

[0050] In some embodiments, provided is a pharmaceutical composition comprising a compound of Formula (I), or a pharmaceutically acceptable salt thereof, and at least one pharmaceutically acceptable inactive ingredient. In some embodiments, the pharmaceutical composition comprises a therapeutically effective amount of a compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, the pharmaceutical composition is formulated for intravenous injection, subcutaneous injection, oral administration, inhalation, nasal administration, topical administration, ophthalmic administration or otic administration. In some embodiments, the pharmaceutical composition is a tablet, a pill, a capsule, a liquid, an inhalant, a nasal spray solution, a suppository, a suspension, a gel, a colloid, a dispersion, a suspension, a solution, an emulsion, an ointment, a transdermal patch, a lotion, an eye drop or an ear drop.

[0051] In some embodiments, the pharmaceutical composition further comprises one or more additional therapeutically active agents selected from: corticosteroids, immunosuppressants, analgesics, anti-cancer agents, anti-inflammatories, non-steroidal anti-inflammatories, dual cyclooxygenase-1 and -2 inhibitors, cyclooxygenase-2 selective inhibitors, TNFα blockers, kinase inhibitors, chemokine receptor antagonists, bronchodilators, leukotriene receptor antagonists, leukotriene formation inhibitors, prostaglandin receptor antagonists, prostaglandin formation inhibitors, monoacylglycerol kinase inhibitors, phospholipase A_1 inhibitors, phospholipase A_2 inhibitors, lysophospholipase D (lysoPLD) inhibitors, autotaxin inhibitors, and LPA receptor antagonists.

[0052] Pharmaceutical compositions described herein are administerable to a subject in a variety of ways by multiple administration routes, including but not limited to, oral, parenteral (e.g., intravenous, subcutaneous, intramuscular), intranasal, buccal, topical or transdermal administration routes. The pharmaceutical formulations described herein include, but are not limited to, aqueous liquid dispersions, self-emulsifying dispersions, solid solutions, liposomal dispersions, aerosols, solid dosage forms, powders, immediate release formulations, controlled release formulations, fast melt formulations, tablets, capsules, pills, delayed release formulations, extended release formulations, pulsatile release formulations, multiparticulate formulations, and mixed immediate and controlled release formulations.

[0053] In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered orally.

[0054] In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered topically. In such embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is formulated into a variety of topically administrable compositions, such as solutions, suspensions, lotions, gels, pastes, shampoos, scrubs, rubs, smears, medicated sticks, medicated bandages, balms, creams or ointments. Such pharmaceutical compounds can contain solubilizers, stabilizers, tonicity enhancing agents, buffers and preservatives. In one aspect, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered topically to the skin.

[0055] In another aspect, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered by inhalation. In one embodiment, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered by inhalation that directly targets the pulmonary system.

[0056] In another aspect, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is formulated for intranasal adminstration. Such formulations include nasal sprays, nasal mists, and the like.

[0057] In another aspect, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is formulated as eye drops.

[0058] In another aspect is the use of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, in the treatment or prevention of a disease, disorder or conditions in which the activity of autotaxin and/or at least one LPA receptor contributes to the pathology and/or symptoms of the disease or condition. In one aspect, the disease or condition is any of the diseases or conditions specified herein.

[0059] In any of the aforementioned aspects are further embodiments in which: (a) the effective amount of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is systemically administered to the mammal; and/or (b) the effective amount of the compound is administered orally to the mammal; and/or (c) the effective amount of the compound is intravenously administered to the mammal; and/or (d) the effective amount of the compound is administered by inhalation; and/or (e) the effective amount of the compound is administered by nasal administration; or and/or (f) the effective amount of the compound is administered by injection to the mammal; and/or (g) the effective amount of the compound is administered topically to the mammal; and/or (h) the effective amount of the compound is administered by ophthalmic administration; and/or (i) the effective amount of the compound is administered rectally to the mammal; and/or (j) the effective amount is adminstered non-systemically or locally to the mammal.

[0060] In any of the aforementioned aspects are further embodiments comprising single administrations of the effective amount of the compound, including further embodiments in which (i) the compound is administered once; (ii) the compound is administered to the mammal multiple times over the span of one day; (iii) continually; or (iv) continuously.

[0061] In any of the aforementioned aspects are further embodiments comprising multiple administrations of the effective amount of the compound, including further embodiments in which (i) the compound is administered continuously or intermittently: as in a a single dose; (ii) the time between multiple administrations is every 6 hours; (iii) the compound is administered to the mammal every 8 hours; (iv) the compound is administered to the mammal every 12 hours; (v) the compound is administered to the mammal every 24 hours. In further or alternative embodiments, the method comprises a drug holiday, wherein the administration of the compound is temporarily suspended or the dose of the compound being administered is temporarily reduced; at the end of the drug holiday, dosing of the compound is resumed. In one embodiment, the length of the drug holiday varies from 2 days to 1 year.

[0062] In some embodiments, provided is a method of treating or preventing a disease or condition in which the activity of autotaxin is involved in the etiology of the disease or condition comprising administering a compound of Formula (I), or a pharmaceutically acceptable salt thereof, to the human in need thereof. In some embodiments, the human is already being administered one or more additional therapeutically active agents other than a compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, the method further comprises administering one or more additional therapeutically active agents other than a compound of Formula (I), or a pharmaceutically acceptable salt thereof.

[0063] In some embodiments, the one or more additional therapeutically active agents other than a compound of Formula (I), or a pharmaceutically acceptable salt thereof, are selected from: corticosteroids, immunosuppressants, analgesics, anti-cancer agents, anti-inflammatories, non-steroidal anti-inflammatories, dual cyclooxygenase-1 and -2 inhibitors, cyclooxygenase-2 selective inhibitors, TNF-α blockers, kinase inhibitors, chemokine receptor antagonists, bronchodilators, leukotriene receptor antagonists, leukotriene formation inhibitors, prostaglandin receptor antagonists, prostaglandin formation inhibitors, monoacylglycerol kinase inhibitors, phospholipase A_1 inhibitors, phospholipase A_2 inhibitors, lysophospholipase D (lysoPLD) inhibitors, autotaxin inhibitors, and LPA receptor antagonists.

[0064] Also provided is a method of inhibiting the physiological activity of ATX in a mammal comprising administering a therapeutically effective amount of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, to the mammal in need thereof.

[0065] In some embodiments, compounds described herein are used for the treatment or prevention of a disease or condition in a mammal that is mediated by or dependent upon increased lysophosphatidic acid levels or the activation of autotaxin.

[0066] In some embodiments, compounds described herein are used for inhibiting the physiological activity of autotaxin in a mammal.

[0067] In some embodiments, compounds described herein are used for controlling an abnormal production of lysophosphatidic acid in a mammal.

[0068] In some embodiments, compounds described herein are used for the treatment or prevention of a disease or condition in a mammal that is characterized by an abnormal production of lysophosphatidic acid. In some embodiments, the disease or condition involves excessive fibrosis, angiogenesis, inflammation or cell proliferation.

[0069] In some embodiments, compounds described herein are used for the treatment or prevention of fibrosis, inflammation, cancer, angiogenesis, or pain in a mammal.

[0070] In some embodiments, compounds described herein are used for the treatment or prevention of lung fibrosis, asthma, chronic obstructive pulmonary disease (COPD), renal fibrosis, acute kidney injury, chronic kidney disease, liver fibrosis, skin fibrosis, fibrosis of the gut, breast cancer, pancreatic cancer, ovarian cancer, prostate cancer, glioblastoma, bone cancer, colon cancer, bowel cancer, head and neck cancer, melanoma, multiple myeloma, chronic lymphocytic leukemia, B cell lymphoma, T cell lymphoma, cancer pain, tumor metastasis, transplant organ rejection, scleroderma, ocular fibrosis, age related macular degeneration (AMD), diabetic retinopathy, collagen vascular disease, atherosclerosis, Raynaud's phenomenom, rheumatoid arthritis, osteoarthritis or neuropathic pain in a mammal.

[0071] In some embodiments, compounds described herein are used for reducing or inhibiting angiogenesis in a mammal. In some embodiments, reducing or inhibiting angiogenesis in the mammal treats atherosclerosis, hypertension, tumor growth, inflammation, rheumatoid arthritis, wet-form macular degeneration, choroidal neovascularization, retinal neovascularization, or diabetic retinopathy.

[0072] In some embodiments, compounds described herein are used for the treatment or prevention of an inflammatory disease or condition in a mammal. In some embodiments, the inflammatory disease or condition is psoriasis, rheumatoid arthritis, vasculitis, inflammatory bowel disease, dermatitis, osteoarthritis, asthma, inflammatory muscle disease, allergic rhinitis, vaginitis, interstitial cystitis, scleroderma, eczema, lupus erythematosus, dermatomyositis, Sjogren's syndrome, thyroiditis, myasthenia gravis, autoimmune hemolytic anemia, multiple sclerosis, cystic fibrosis, chronic relapsing hepatitis, primary biliary cirrhosis, allergic conjunctivitis or atopic dermatitis.

[0073] In one aspect, provided is a medicament for treating an ATX-dependent or ATX-mediated disease or condition in a mammal comprising a therapeutically effective amount of a compound of Formula (I), or a pharmaceutically acceptable salt thereof. In one some embodiments, compounds disclosed herein inhibit ATX-mediated LPA production in a mammal. In some cases disclosed herein is the use of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, in the treatment or prevention of a LPA-dependent or LPA-mediated disease or condition. In some embodiments, LPA-dependent or LPA-mediated diseases or conditions include, but are not limited to, fibrosis of organs or tissues, scarring, liver diseases, dermatological conditions, cancer, cardiovascular disease, respiratory diseases or conditions, inflammatory disease, autoimmune diseases, gastrointestinal tract disease, renal disease, urinary tract-associated disease, inflammatory

disease of lower urinary tract, dysuria, frequent urination, reproductive diseases, pancreatic disease, arterial obstruction, cerebral infarction, cerebral hemorrhage, pain, peripheral neuropathy, myalgic encephylitis and fibromyalgia.

[0074] In one aspect, a compound of Formula (I), or a pharmaceutically acceptable salt thereof, is used in the treatment or prevention of a respiratory disease or condition in mammal. In some embodiments, the respiratory disease or condition is asthma, chronic obstructive pulmonary disease (COPD), interstitial lung disease, pulmonary fibrosis, pulmonary arterial hypertension or acute respiratory distress syndrome.

[0075] In one aspect, a compound of Formula (I), or a pharmaceutically acceptable salt thereof, is used in the treatment or prevention of autoimmune diseases or condition in a mammal. In some embodiments, the autoimmune disease is is rheumatoid arthritis, osteoarthritis juvenile arthritis, spondylarthritis, ankylosing spondylitis polymyalgia rheumatica, psoriasis, giant cell arteritis, Sjogren's syndrome, or systemic Lupus erythematosus.

[0076] In one aspect, a compound of Formula (I), or a pharmaceutically acceptable salt thereof, is used in the treatment or prevention of a pain in a mammal. In one aspect, a compound of Formula (I), or a pharmaceutically acceptable salt thereof, is used in the treatment or prevention of a neuropathic pain in a mammal. In some embodiments, the pain condition is associated with rheumatoid arthritis, osteoarthritis juvenile arthritis, spondylarthritis, ankylosing spondylitis, lower back pain, neck pain, neuropathic pain, sickle cell pain, carpal tunnel syndrome, myalgic encephylitis or fibromyalgia.

[0077] In some embodiments, a compound of Formula (I), or a pharmaceutically acceptable salt thereof, is used in the treatment or prevention of idiopathic pulmonary fibrosis; other diffuse parenchymal lung diseases of different etiologies including iatrogenic drug-induced fibrosis, occupational and/or environmental induced fibrosis, granulomatous diseases (sarcoidosis, hypersensitivity pneumonia), collagen vascular disease, alveolar proteinosis, langerhans cell granulomatosis, lymphangioleiomyomatosis, inherited diseases (Hermansky-Pudlak Syndrome, tuberous sclerosis, neurofibromatosis, metabolic storage disorders, familial interstitial lung disease); radiation induced fibrosis; chronic obstructive pulmonary disease (COPD); scleroderma; bleomycin induced pulmonary fibrosis; chronic asthma; silicosis; asbestos induced pulmonary fibrosis; acute respiratory distress syndrome (ARDS); kidney fibrosis; tubulointerstitium fibrosis; glomerular nephritis; focal segmental glomerular sclerosis; IgA nephropathy; hypertension; Alport; gut fibrosis; liver fibrosis; cirrhosis; alcohol induced liver fibrosis; toxic/drug induced liver fibrosis; hemochromatosis; nonalcoholic steatohepatitis (NASH); biliary duct injury; primary biliary cirrhosis; infection induced liver fibrosis; viral induced liver fibrosis; and autoimmune hepatitis; corneal scarring; hypertrophic scarring; Dupuytren disease, keloids, cutaneous fibrosis; cutaneous scleroderma; systemic sclerosis, spinal cord injury/fibrosis; myelofibrosis; vascular restenosis; atherosclerosis; arteriosclerosis; Wegener's granulomatosis; Peyronie's disease, chronic lymphocytic

leukemia, tumor metastasis, transplant organ rejection, endometriosis, neonatal respiratory distress syndrome or neuropathic pain.

[0078] In some embodiments, a compound of Formula (I), or a pharmaceutically acceptable salt thereof, is used in the treatment or prevention of cancer. In some embodiments, the cancer is bone cancer (osteosarcoma and malignant fibrous histiocytoma), brain stem glioma, brain tumors, brain and spinal cord tumors, breast cancer, Burkitt lymphoma, prostate cancer, B cell lymphomas, ovarian cancers, pancreatic cancer, and colon cancer. In some embodiments, the cancer is a cancer described herein.

[0079] In one aspect, a compound of Formula (I), or a pharmaceutically acceptable salt thereof, is used in the treatment or prevention of a disease or condition that is described herein.

[0080] In one aspect, a compound of Formula (I), or a pharmaceutically acceptable salt thereof, is used in the treatment or prevention of fibrosis in a mammal. In some embodiments, the fibrosis comprises lung fibrosis, renal fibrosis, hepatic fibrosis or cutaneous fibrosis.

[0081] In one aspect, a compound of Formula (I), or a pharmaceutically acceptable salt thereof, is used in the treatment or prevention of organ fibrosis in a mammal. In one aspect, the organ fibrosis comprises lung fibrosis, renal fibrosis, or hepatic fibrosis.

[0082] In one aspect, provided is a method of improving lung function in a mammal comprising administering a therapeutically effective amount of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, to the mammal in need thereof. In one aspect, the mammal has been diagnosed as having lung fibrosis.

[0083] In one aspect, compounds disclosed herein are used to treat idiopathic pulmonary fibrosis (usual interstitial pneumonia) in a mammal.

[0084] In some embodiments, compounds disclosed herein are used to treat diffuse parenchymal interstitial lung diseases in mammal: iatrogenic drug induced, occupational/environmental (Farmer lung), granulomatous diseases (sarcoidosis, hypersensitivity pneumonia), collagen vascular disease (scleroderma and others), alveolar proteinosis, langerhans cell granulonmatosis, lymphangioleiomyomatosis, Hermansky-Pudlak Syndrome, Tuberous sclerosis, neurofibromatosis, metabolic storage disorders, familial interstitial lung disease.

[0085] In some embodiments, compounds disclosed herein are used to treat post-transplant fibrosis associated with chronic rejection in a mammal: Bronchiolitis obliterans for lung transplant.

[0086] In some embodiments, compounds disclosed herein are used to treat cutaneous fibrosis in a mammal: cutaneous scleroderma, Dupuytren disease, keloids.

[0087] In one aspect, compounds disclosed herein are used to treat hepatic fibrosis with or without cirrhosis in a mammal: toxic/drug induced (hemochromatosis), alcoholic liver disease, viral hepatitis (hepatitis B virus, hepatitis C virus, HCV), nonalcoholic liver disease (NASH), metabolic and auto-immune.

[0088] In one aspect, compounds disclosed herein are used to treat renal fibrosis in a mammal: tubulointerstitium fibrosis, glomerular sclerosis.

[0089] In any of the aforementioned aspects involving the treatment of LPA dependent diseases or conditions are further embodiments comprising administering at least one additional agent in addition to the administration of a compound having the structure of Formula (I), or a pharmaceutically acceptable salt thereof. In various embodiments, each agent is administered in any order, including simultaneously.

[0090] In any of the embodiments disclosed herein, the mammal is a human.

[0091] In some embodiments, compounds provided herein are administered to a human.

[0092] In some embodiments, compounds provided herein are orally administered.

[0093] Articles of manufacture, which include packaging material, a compound of Formula (I), or a pharmaceutically acceptable salt thereof, within the packaging material, and a label that indicates that the compound or composition, or pharmaceutically acceptable salt, tautomers, pharmaceutically acceptable N-oxide, pharmaceutically active metabolite, pharmaceutically acceptable prodrug, or pharmaceutically acceptable solvate thereof, is used for inhibiting the activity of autotaxin, or for the treatment, prevention or amelioration of one or more symptoms of a disease or condition that would benefit from inhibition of the activity of autotaxin, are provided.

[0094] Other objects, features and advantages of the compounds, methods and compositions described herein will become apparent from the following detailed description. It should be understood, however, that the detailed description and the specific examples, while indicating specific embodiments, are given by way of illustration only, since various changes and modifications within the spirit and scope of the instant disclosure will become apparent to those skilled in the art from this detailed description.

DETAILED DESCRIPTION OF THE INVENTION

[0095] Autotaxin (ATX or NPP2) is a secreted nucleotide pyrophosphatase/phosphodiesterease (NPP) originally isolated from melanoma cells. ATX, a ~120 kDa glycoprotein, is unique amongst the NPPs in that it functions as a lysophospholipase D (lysoPLD) that converts extracellular lysophophatidylcholine (LPC) to LPA. ATX is widely expressed, with mRNA detected in many tissues, such as, brain, ovary, lung, intestine, and kidney. ATX expression is controlled by growth factors acting through transcriptional activation of the autotaxin gene.

[0096] Lysophospholipids, such as lysophosphatidic acid (LPA), sphingosine 1-phosphate (S1P), lysophosphatidylcholine (LPC), and sphingosylphosphorylcholine (SPC), are membrane-derived bioactive lipid mediators that affect fundamental cellular functions that include cellular proliferation, differentiation, survival, migration, adhesion, invasion, and morphogenesis. These functions influence many biological processes that include neurogenesis, angiogenesis, wound healing, reproduction, inflammation, immunity, and carcinogenesis.

[0097] LPA has a role as a biological effector molecule, and has a diverse range of physiological actions such as, but not limited to, effects on platelet activation, blood pressure, and smooth muscle contraction, and a variety of cellular effects, which include cell growth, cell rounding, neurite retraction, and actin stress fiber formation and cell migration. The effects of LPA are predominantly receptor mediated.

[0098] LPA acts through sets of specific G protein-coupled receptors (GPCRs) in an autocrine and paracrine fashion. LPA binding to its cognate GPCRs (LPA_1, LPA_2, LPA_3, LPA_4, LPA_5, LPA_6, LPA_7, LPA_8) activates intracellular signaling pathways to produce a variety of biological responses.

[0099] Activation of the LPA receptors (LPA_1, LPA_2, LPA_3, LPA_4, LPA_5, LPA_6, , LPA_7, LPA_8) by LPA mediates multiple downstream signaling pathways. These include, but are not limited to, mitogen-activated protein kinase (MAPK) activation, adenylyl cyclase (AC) inhibition/activation, phospholipase C (PLC) activation/Ca^{2+} mobilization, arachidonic acid release, Akt/PKB activation, and the activation of small GTPases, Rho, ROCK, Rac, and Ras. Other pathways that are affected by LPA receptor activation include, but are not limited to, cell division cycle 42/GTP-binding protein (Cdc42) , proto-oncogene serine/threonine-protein kinase Raf (c-RAF), proto-oncogene tyrosine-protein kinase Src (c-src), extracellular signal-regulated kinase (ERK), focal adhesion kinase (FAK), guanine nucleotide exchange factor (GEF), glycogen synthase kinase 3b (GSK3b), c-jun amino-terminal kinase (JNK), MEK, myosin light chain II (MLC II), nuclear factor kB (NF-kB), N-methyl-D-aspartate (NMDA) receptor activation, phosphatidylinositol 3-kinase (PI3K), protein kinase A (PKA), protein kinase C (PKC), ras-related C3 botulinum toxin substrate 1 (RAC1). The actual pathway and realized end point are dependent on a range of variables that include receptor usage, cell type, expression level of a receptor or signaling protein, and LPA concentration. Nearly all mammalian cells, tissues and organs co-express several LPA receptor subtypes, which indicates that LPA receptors signal in a cooperative manner.

[00100] LPA is produced both in cells and biological fluids, where multiple synthetic reactions occur. In serum or plasma, LPA is predominantly produced by a plasma enzyme called autotaxin (ATX). ATX is a multifunctional ectoenzyme and is involved in many patho-physiological conditions such as, but not limited to, cancer, neuropathic pain, inflammation, autoimmune diseases (e.g. arthritis), fibrosis, lymphocyte tracking in lymph nodes, obesity, diabetes, and embryonic blood vessel formation.

[00101] ATX is essential for vascular development and is found overexpressed in various human cancers. In certain instances, forced over-expression of ATX or individual LPA receptors promotes tumor progression in mouse models, while certain LPA receptor deficiencies protect from cancer. In addition to its role in cancer, ATX-LPA signaling is implicated in lymphocyte homing and (chronic) inflammation, fibrotic diseases, and thrombosis.

[00102] Because enhanced expression of ATX is frequently observed in tumor tissues, ATX is implicated in metastatic and invasive potential of tumor cells. In certain instances, ATX stimulates

cell migration of mouse fibroblasts and various cancer cells in an LPA_1-dependent manner. ATX is abundantly present in blood and produces LPA. In some instances, ATX and LPA levels are strongly correlated. In addition, in ATX-depleted serum and plasma, LPA production is completely absent. Thus, ATX is considered to be responsible for LPA production, at least, in blood.

[00103] ATX and LPA have been detected in various biological fluids such as serum, plasma, cerebrospinal fluid, seminal fluid, urine, and saliva, both in animals and human, suggesting that they are potential biomarkers to predict certain diseases. In some instances, serum ATX concentration and activity is elevated in patients with chronic liver diseases and pregnant women. In certain instances, ATX concentration is lower in postoperative cancer patients as a result of postoperative damage or poor nutritional state. In addition, ATX is present in urine of nephrosis patients. Further, ATX activity is found to increase in normal pregnant women in the third trimester of pregnancy and to be even higher in pregnant women threatened with preterm delivery. A. Tokumura, *Biochim. Biophys. Acta* (2002), 1582(1-3), 18-25. In some instances, lysoPLD activity is also significantly elevated in human peritoneal fluid from patients with ovarian cancer, dermoid cyst, or mucinous cystademnoma.

Angiogenesis

[00104] In certain instances, ATX-deficient mice die at embryonic day 9.5 with profound vascular defects in yolk sac and embryo. Furthermore, at embryonic day 8.5 ATX-deficient embryos showed allantois malformation, neural tube defects, and asymmetric headfolds. The onset of these abnormalities coincided with increased expression of ATX and LPA receptors in normal embryos. LPA has multiple effects on endothelial cells, including stimulation of cell migration and invasion, which are critical events during angiogenesis, and an increase in endothelial monolayer permeability. LPA also exerts migratory and contractile effects on vascular smooth muscle cells. Thus, in some instances, ATX-mediated LPA production and subsequent LPA signaling contributes to vascular development by stimulating endothelial cell migration and invasion as well as regulating adhesive interactions with the extracellular matrix and smooth muscle cells. The vascular defects observed in ATX-deficient mice resemble those in mice lacking genes involved in cell migration and adhesion such as fibronectin and focal adhesion kinase. L.A. vanMeeteren *et al.*, *Mol. Cell. Biol.* (2006) 26(13), 5015-5022. Therefore an ATX inhibitor may have benefit in some diseases involving dysregulated angiogenesis.

[00105] In some instances, vascular endothelial growth factor (VEGF) stimulates expression of ATX and the LPA receptor LPA_1 in human umbilical vein endothelial cells. Knockdown of ATX expression significantly decreases mRNA levels for the receptors LPA_1, LPA_2, S1P1, S1P2, S1P3, and VEGFR2 and abolishes cell migration to LPC, LPA, recombinant ATX, and VEGF. Migration to sphingosylphosphorylcholine and sphinogosine-1-phosphate is also reduced in ATX knockdown cells, whereas migration to serum remains unchanged. Furthermore, ATX knockdown decreased Akt2 mRNA levels, whereas LPA treatment strongly stimulates Akt2 expression. In certain instances, VEGF stimulates LPA production by inducing ATX expression. VEGF also increases

LPA_1 signaling, which in turn increases Akt2 expression. Akt2 is strongly associated with cancer progression, cellular migration, and promotion of epithelial-mesenchymal transition. In some instances, ATX plays a role in maintaining expression of receptors required for VEGF and lysophospholipids to accelerate angiogenesis. M.M. Ptaszynska *et al.*, *Mol. Cancer Res.* (2010) 8(3), 309-321.

[00106] In one aspect, dysregulation of the processes mediating angiogenesis leads to atherosclerosis, hypertension, tumor growth, inflammation, rheumatoid arthritis, wet-form macular degeneration, choroidal neovascularization, retinal neovascularization, and diabetic retinopathy. In some embodiments, autotaxin inhibitors are useful in the treatment or prevention of the aforementioned diseases or conditions.

[00107] In one aspect, an autotaxin inhibitor described herein is used to treat or prevent cardiovascular disease in mammal. The term "cardiovascular disease," as used herein refers to diseases affecting the heart or blood vessels or both, including but not limited to: arrhythmia (atrial or ventricular or both); atherosclerosis and its sequelae; angina; cardiac rhythm disturbances; myocardial ischemia; myocardial infarction; cardiac or vascular aneurysm; vasculitis, stroke; peripheral obstructive arteriopathy of a limb, an organ, or a tissue; reperfusion injury following ischemia of the brain, heart, kidney or other organ or tissue; endotoxic, surgical, or traumatic shock; hypertension, valvular heart disease, heart failure, abnormal blood pressure; shock; vasoconstriction (including that associated with migraines); vascular abnormality, inflammation, insufficiency limited to a single organ or tissue.

Inflammation

[00108] Significant amounts of LPA have been detected in various biological fluids, including serum, saliva, and bronchoalveolar lavage fluid (BALF). The most significant effects of LPA appear to be through activation of the G-protein-couple receptors LPA_{1-8}. LPA regulates gene expression through activation of several transcriptional factors, such as nuclear factor κB (NF-κb), AP-1, and C/EBPβ. In addition to GPCRs, cross-talk between LPA receptors and receptor tyrosine kinases (RTKs) partly regulates LPA-induced intracellular signaling and cellular responses. Airway epithelial cells participate in innate immunity through the release of cytokines, chemokines, lipid mediators, other inflammatory mediators and an increase in barrier function in response to a variety of inhaled stimuli. Expression of LPA receptors have been demonstrated in airway epithelial cells. Y. Zhao, Lysophophatidic Acid Signaling in Airway Epithelium: Role in Airway Inflammation and Remodeling, *Cell Signal.* (2009) 21(3), 367-377.

[00109] In some instances, the ATX-LPA axis is upregulated in a variety of inflammatory conditions. In human rheumatoid arthritis (RA) the autotaxin gene is upregulated in fibroblasts from RA patients. Further, ATX protein is present in synovial fluid from RA patients and LPA_1 is upregulated in synovial fibroblasts from RA patients. In addition, autotaxin is one of four proteins upregulated in multiple sclerosis patients. In some instances, both plasma and air pouch LPA was reduced in a rat air pouch model by an ATX inhibitor, indicating that ATX is a major source of LPA during

inflammation. Inhibition of plasma ATX activity correlated with inhibition of ATX at the site of inflammation and in *ex vivo* whole blood. J. Gierse, A Novel Autotaxin Inhibitor Reduces Lysophosphatidic Acid Levels in Plasma and the Site of Inflammation, *JPET* (2010).

[00110] In certain instances, ATX is highly expressed in high endothelial venules (HEVs) of lymphoid organs and is secreted. Chemokine-activated lymphocytes express enhanced receptors for ATX, providing a mechanism to target the secreted ATX onto lymphocytes undergoing recruitment. LPA induces chemokinesis in T-cells. In some instances, intravenous injection of enzymatically inactive ATX attenuates homing of T-cells to lymphoid tissues, likely by competing with endogenous ATX and exerting a dominant-negative effect. In certain instances, the ectozyme ATX facilitates lymphocyte entry into lymphoid organs. H. Kanda *et al.*, Autotaxin, a lysophosphatidic acid-producing ectozyme, promotes lymphocyte entry into secondary lymphoid organs, *Nat. Immunol.* (2008) 9(4), 415-423. Therefore an ATX inhibitor may block lymphocyte migration into secondary lymphoid organs and be of benefit in autoimmune diseases.

[00111] In one aspect, a compound of Formula (I), or a pharmaceutically acceptable salt thereof, is used to treat or prevent inflammation in a mammal. In one aspect, a compound of Formula (I), or a pharmaceutically acceptable salt thereof, finds use in the treatment or prevention of inflammatory/immune disorders in a mammal.

[00112] Examples of inflammatory/immune disorders include psoriasis, rheumatoid arthritis, vasculitis, inflammatory bowel disease, dermatitis, osteoarthritis, asthma, inflammatory muscle disease, allergic rhinitis, vaginitis, interstitial cystitis, scleroderma, eczema, allogeneic or xenogeneic transplantation (organ, bone marrow, stem cells and other cells and tissues) graft rejection, graft-versus-host disease, lupus erythematosus, inflammatory disease, type I diabetes, pulmonary fibrosis, dermatomyositis, Sjogren's syndrome, thyroiditis (e.g., Hashimoto's and autoimmune thyroiditis), myasthenia gravis, autoimmune hemolytic anemia, multiple sclerosis, cystic fibrosis, chronic relapsing hepatitis, primary biliary cirrhosis, allergic conjunctivitis and atopic dermatitis.

Fibrotic Diseases and Conditions

[00113] In one aspect, a compound of Formula (I), or a pharmaceutically acceptable salt thereof, is used to treat or prevent fibrosis in a mammal. In one aspect, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is used to treat fibrosis of an organ or tissue in a mammal. In one aspect is a method for preventing a fibrosis condition in a mammal, the method comprising administering to the mammal at risk of developing one or more fibrosis conditions a therapeutically effective amount of a compound of Formula (I), or a pharmaceutically acceptable salt thereof. In one aspect, the mammal has been exposed to one or more environmental conditions that are known to increase the risk of fibrosis of an organ or tissue. In one aspect, the mammal has been exposed to one or more environmental conditions that are known to increase the risk of lung, liver or kidney fibrosis. In one aspect, the mammal has a genetic predisposition of developing fibrosis of an organ or tissue. In one aspect, a compound of Formula (I), or a pharmaceutically acceptable salt thereof, is

adminstered to a mammal to prevent or minimize scarring following injury. In one aspect, injury includes surgery.

[00114] The terms "fibrosis" or "fibrosing disorder," as used herein, refers to conditions that are associated with the abnormal accumulation of cells and/or fibronectin and/or collagen and/or increased fibroblast recruitment and include but are not limited to fibrosis of individual organs or tissues such as the heart, kidney, liver, joints, lung, pleural tissue, peritoneal tissue, skin, cornea, retina, musculoskeletal and digestive tract.

[00115] Exemplary diseases, disorders, or conditions that involve fibrosis include, but are not limited to: Lung diseases associated with fibrosis, e.g., idiopathic pulmonary fibrosis, pulmonary fibrosis secondary to systemic inflammatory disease such as rheumatoid arthritis, scleroderma, lupus, cryptogenic fibrosing alveolitis, radiation induced fibrosis, chronic obstructive pulmonary disease (COPD), scleroderma, chronic asthma, silicosis, asbestos induced pulmonary or pleural fibrosis, acute lung injury and acute respiratory distress (including bacterial pneumonia induced, trauma induced, viral pneumonia induced, ventilator induced, non-pulmonary sepsis induced, and aspiration induced); Chronic nephropathies associated with injury/fibrosis (kidney fibrosis), e.g., glomerulonephritis secondary to systemic inflammatory diseases such as lupus and scleroderma, diabetes,, glomerular nephritis, focal segmental glomerular sclerosis, IgA nephropathy, hypertension, allograft and Alport; Gut fibrosis, e.g., scleroderma, and radiation induced gut fibrosis; Liver fibrosis, e.g., cirrhosis, alcohol induced liver fibrosis, nonalcoholic steatohepatitis (NASH), biliary duct injury, primary biliary cirrhosis, infection or viral induced liver fibrosis (e.g., chronic HCV infection), and autoimmune hepatitis; Head and neck fibrosis, e.g., radiation induced; Corneal scarring, e.g., LASIK (laser-assisted in situ keratomileusis), corneal transplant, and trabeculectomy; Hypertrophic scarring and keloids, e.g., burn induced or surgical; and Other fibrotic diseases, e.g., sarcoidosis, scleroderma, spinal cord injury/fibrosis, myelofibrosis, vascular restenosis, atherosclerosis, arteriosclerosis, Wegener's granulomatosis, mixed connective tissue disease, and Peyronie's disease.

[00116] In certain instances, LPA stimulates hepatic stellate cell proliferation and inhibits DNA synthesis in hepatocytes. LPA level and serum ATX activity are increased in patients with chronic hepatitis C. In the blood of rats with various liver injuries, plasma LPA concentrations and serum ATX activity are increased in carbon tetrachloride-induced liver fibrosis correlatively with fibrosis grade, in dimethylnitrosamine-induced acute liver injury correlatively with serum alanine aminotransferase level, or in 70% hepatectomy as early as 3 hours after the operation. The plasma LPA level is correlated with serum ATX activity in rats with chronic and acute liver injury. ATX mRNA in the liver is not altered in carbon tetrachloride-induced liver fibrosis. Plasma LPA concentrations and serum ATX activity are increased in various liver injuries in relation to their severity. N. Watanabe, Plasma lysophosphatidic acid level and serum autotaxin activity are increased in liver injury in rats in relation to its severity, *Life Sci.* (2007) 81(12), 1009-1015.

[00117] In one aspect, a compound of Formula (I), or a pharmaceutically acceptable salt thereof, is adminstered to a mammal with fibrosis of an organ or tissue or with a predisposition of developing fibrosis of an organ or tissue with one or more other agents that are used to treat fibrosis. In one aspect, the one or more agents include corticosteroids. In one aspect, the one or more agents include immunosuppresants. In one aspect, the one or more agents include B-cell antagonists. In one aspect, the one or more agents include uteroglobin.

[00118] In one aspect, a mammal suffering from one of the following non-limiting exemplary diseases, disorders, or conditions will benefit from therapy with a compound of Formula (I), or a pharmaceutically acceptable salt thereof: atherosclerosis, thrombosis, heart disease, vasculitis, formation of scar tissue, restenosis, phlobitis, COPD (chronic obstructive pulmonary disease), pulmonary hypertension, pulmonary fibrosis, scleroderma, pulmonary inflammation, bowel adhesions, bladder fibrosis and cystitis, fibrosis of the nasal passages, sinusitis, inflammation mediated by neutrophils, and fibrosis mediated by fibroblasts.

[00119] In one aspect, a compound of Formula (I), or a pharmaceutically acceptable salt thereof, is used to treat dermatological disorders in a mammal. The term "dermatological disorder," as used herein refers to a skin disorder. Such dermatological disorders include, but are not limited to, proliferative or inflammatory disorders of the skin such as, atopic dermatitis, bullous disorders, collagenoses, psoriasis, psoriatic lesions, dermatitis, contact dermatitis, eczema, urticaria, rosacea, scleroderma, wound healing, scarring, hypertrophic scarring, keloids, Kawasaki Disease, rosacea, Sjogren-Larsso Syndrome, urticaria.

[00120] In some embodiments, provided is a method of reducing lung injury, vascular leakage, inflammation and/or fibrosis in a mammal comprising administering to the mammal a compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, provided is a method of reducing lung injury, vascular leakage, inflammation and fibrosis in a mammal comprising administering to the mammal a compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, provided is a method of attenuating fibrosis in a mammal comprising administering a compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, provided is a method of attenuating tissue remodeling and fibrosis in a mammal comprising administering a compound of Formula (I), or a pharmaceutically acceptable salt thereof.

[00121] In some embodiments, provided is a method of decreasing cytokine production in a mammal comprising administering a compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, the method of decreasing cytokine production in a mammal comprising administering a compound of Formula (I), or a pharmaceutically acceptable salt thereof, results in a reduction of tissue damage and fibrosis in a mammal.

[00122] In some embodiments, provided is a method of treating fibrosis is a mammal comprising administering to the mammal a compound of Formula (I), or a pharmaceutically acceptable salt thereof.

Respiratory and Allergic Diseases and Conditions

[00123] ATX generates LPA and in some embodiments LPA is a contributor to the pathogenesis of respiratory diseases. Proinflammatory effects of LPA include degranulation of mast cells, contraction of smooth-muscle cells and release of cytokines from dendritic cells. Airway smooth muscle cells, epithelial cells and lung fibroblasts all show responses to LPA. LPA induces the secretion of IL-8 from human bronchial epithelial cells. IL-8 is found in increased concentrations in BAL fluids from patients with asthma, chronic obstructive lung disease, pulmonary sarcoidosis and acute respiratory distress syndrome and IL-8 has been shown to exacerbate airway inflammation and airway remodeling of asthmatics.

[00124] The release of LPA from platelets activated at a site of injury and its ability to promote fibroblast proliferation and contraction are features of LPA as a mediator of wound repair. In the context of airway disease, asthma is an inflammatory disease where inappropriate airway "repair" processes lead to structural "remodeling" of the airway. In asthma, the cells of the airway are subject to ongoing injury due to a variety of insults, including allergens, pollutants, other inhaled environmental agents, bacteria and viruses, leading to the chronic inflammation that characterizes asthma.

[00125] In one aspect, in the asthmatic individual, the release of normal repair mediators, including LPA, is exaggerated or the actions of the repair mediators are inappropriately prolonged leading to inappropriate airway remodeling. Major structural features of the remodeled airway observed in asthma include a thickened lamina reticularis (the basement membrane-like structure just beneath the airway epithelial cells), increased numbers and activation of myofibroblasts, thickening of the smooth muscle layer, increased numbers of mucus glands and mucus secretions, and alterations in the connective tissue and capillary bed throughout the airway wall. In one aspect, ATX and/or LPA contributes to these structural changes in the airway. In one aspect, ATX and/or LPA are involved in acute airway hyperresponsiveness in asthma. The lumen of the remodeled asthmatic airway is narrower due to the thickening of the airway wall, thus decreasing airflow. In one aspect, LPA contributes to the long-term structural remodeling and the acute hyperresponsiveness of the asthmatic airway. In one aspect, LPA contributes to the hyper-responsiveness that is a primary feature of acute exacerbations of asthma.

[00126] In one aspect, the fibroblast proliferation and contraction and extracellular matrix secretion stimulated by LPA contributes to the fibroproliferative features of other airway diseases, such as the peribronchiolar fibrosis present in chronic bronchitis, emphysema, and interstitial lung disease. Emphysema is also associated with a mild fibrosis of the alveolar wall, a feature which is believed to represent an attempt to repair alveolar damage. In another aspect, LPA plays a role in the fibrotic interstitial lung diseases and obliterative bronchiolitis, where both collagen and myofibroblasts are increased. In another aspect, LPA is involved in several of the various syndromes that constitute chronic obstructive pulmonary disease.

[00127] Administration of LPA *in vivo* induces airway hyper-responsiveness, itch-scratch responses, infiltration and activation of eosinophils and neutrophils, vascular remodeling, and nociceptive flexor responses. LPA also induces histamine release from mouse and rat mast cells. In an acute allergic reaction, histamine induces various responses, such as contraction of smooth muscle, plasma exudation, and mucus production. Plasma exudation is important in the airway, because the leakage and subsequent airway-wall edema contribute to the development of airway hyperresponsiveness. Plasma exudation progresses to conjunctival swelling in ocular allergic disorder and nasal blockage in allergic rhinitis (Hashimoto *et al.*, *J Pharmacol Sci* 100, 82 – 87, 2006).

[00128] In one aspect, a compound of Formula (I), or a pharmaceutically acceptable salt thereof, is used in the treatment of various allergic disorders in a mammal. In one aspect, a compound of Formula (I), or a pharmaceutically acceptable salt thereof, is used in the treatment of respiratory diseases, disorders or conditions in a mammal. In one aspect, a compound of Formula (I), or a pharmaceutically acceptable salt thereof, is used in the treatment of asthma in a mammal. In one aspect, a compound of Formula (I), or a pharmaceutically acceptable salt thereof, is used in the treatment of chronic asthma in a mammal.

[00129] In some embodiments, provided is a method of treating respiratory disease in a mammal comprising administering to the mammal a compound of Formula (I), or a pharmaceutically acceptable salt thereof.

[00130] The term "respiratory disease," as used herein, refers to diseases affecting the organs that are involved in breathing, such as the nose, throat, larynx, eustachian tubes, trachea, bronchi, lungs, related muscles (e.g., diaphram and intercostals), and nerves. Respiratory diseases include, but are not limited to, asthma, adult respiratory distress syndrome and allergic (extrinsic) asthma, non-allergic (intrinsic) asthma, acute severe asthma, chronic asthma, clinical asthma, nocturnal asthma, allergen-induced asthma, aspirin-sensitive asthma, exercise-induced asthma, isocapnic hyperventilation, child-onset asthma, adult-onset asthma, cough-variant asthma, occupational asthma, steroid-resistant asthma, seasonal asthma, seasonal allergic rhinitis, perennial allergic rhinitis, chronic obstructive pulmonary disease, including chronic bronchitis or emphysema, pulmonary hypertension, interstitial lung fibrosis and/or airway inflammation and cystic fibrosis, and hypoxia.

[00131] The term "asthma" as used herein refers to any disorder of the lungs characterized by variations in pulmonary gas flow associated with airway constriction of whatever cause (intrinsic, extrinsic, or both; allergic or non-allergic). The term asthma may be used with one or more adjectives to indicate cause.

[00132] In one aspect, presented herein is the use of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, in the treatment or prevention of chronic obstructive pulmonary disease in a mammal comprising administering to the mammal at least once an effective amount of at least one compound of Formula (I), or a pharmaceutically acceptable salt thereof. In addition, chronic obstructive pulmonary disease includes, but is not limited to, chronic bronchitis or

emphysema, pulmonary hypertension, interstitial lung fibrosis and/or airway inflammation, and cystic fibrosis.

Cancer

[00133] Lysophospholipid receptor signaling plays a role in the etiology of cancer. Lysophosphatidic acid (LPA) and its G protein-coupled receptors (GPCRs) LPA_1, LPA_2, and/or LPA_3 play a role in the development of several types of cancers. The initiation, progression and metastasis of cancer involve several concurrent and sequential processes including cell proliferation and growth, survival and anti-apoptosis, migration of cells, penetration of foreign cells into defined tissues and/or organs, and promotion of angiogenesis. The control of each of these processes by LPA signaling in physiological and pathophysiological conditions underscores the potential therapeutic usefulness of modulating LPA signaling pathways for the treatment of cancer, especially by LPA receptor antagonism or ATX/lysoPLD enzyme inhibition. Autotaxin is a prometastatic enzyme initially isolated from the conditioned medium of human melanoma cells that stimulates a myriad of biological activities, including angiogenesis and the promotion of cell growth, migration, survival, and differentiation through the production of LPA (*Mol Cancer Ther* 2008;7(10):3352–62).

[00134] LPA signals through its own GPCRs leading to activation of multiple downstream effector pathways. Such downstream effector pathways play a role in cancer. LPA and its GPCRs are linked to cancer through major oncogenic signaling pathways.

[00135] LPA contributes to tumorigenesis by increasing motility and invasiveness of cells. LPA has been implicated in the initiation or progression of ovarian cancer. LPA is present at significant concentrations (2–80 μM) in the ascitic fluid of ovarian cancer patients. Ovarian cancer cells constitutively produce increased amounts of LPA as compared to normal ovarian surface epithelial cells, the precursor of ovarian epithelial cancer. Elevated LPA levels are also detected in plasma from patients with early-stage ovarian cancers compared with controls. LPA has also been implicated in the initiation or progression of prostate cancer, breast cancer, melanoma, head and neck cancer, bowel cancer (colorectal cancer), thyroid cancer, glioblastoma, follicular lymphoma and other cancers (Gardell *et al*, *Trends in Molecular Medicine*, vol. 12, no. 2, p 65-75, 2006; Ishii *et al*, *Annu. Rev. Biochem*, 73, 321-354, 2004; Mills *et al.*, *Nat. Rev. Cancer*, 3, 582-591, 2003; Murph *et al.*, *Biochimica et Biophysica Acta*, 1781, 547-557, 2008; Kishi *et al.*, *J. Biol. Chem.*, 281, 17492-17500, 2006).

[00136] In certain instances, ATX is implicated in the invasive and metastatic process of tumor cells, because ectopic overexpression of ATX is frequently observed in malignant tumor tissues such as breast cancer, renal cancer, Hodgkin lymphoma, hepatocellular carcinoma, and glioblastoma.

[00137] ATX was found to be overexpressed in a variety of tumors such as malignant melanoma, teratocarcinoma, neuroblastoma, non-small-cell lung cancer, renal cell carcinoma. MJJG Stassar *et al.*, *Br. J. Cancer* (2001) 85(9), 1371-1382.

[00138] Furthermore, expression of ATX by cancer cells controls osteolytic bone metastasis formation. In certain instances, LPA stimulates directly cancer growth and metastasis, and osteoclast differentiation. In some instances, targeting the ATX/LPA track improves the outcome of patients with bone metastases. M. David *et al.* (2010), *PLoS One*, 5(3), e9741.

[00139] In some instances, inhibition of ATX production or activity blocks LPC-induced migration of human breast cancer and melanoma cells. LPC alone is unable to stimulate the migration of MDA-MB-231 breast cancer cells, which produce little ATX, and MDA-MB-435 melanoma cells, which secrete significant levels of ATX, unless ATX is present. Knocking down ATX secretion, or inhibiting its catalytic activity, blocks cell migration by preventing LPA production and the subsequent activation of LPA receptors. In certain instances, inhibiting ATX production or activity provides a beneficial adjuvant to chemotherapy for preventing tumor growth and metastasis in patients with high ATX expression in their tumors. C.B. Gaetano *et al.*, Inhibition of autotaxin production or activity blocks lysophosphatidylcholine-induced migration of human breast cancer and melanoma cells, *Mol. Carcinog.* (2009) 48(9) 801-809.

[00140] Aberrant expression of ATX and LPA receptors occurs during the development and progression of breast cancer. In addition, expression of either ATX or LPA in the mammary glands of transgenic mice is sufficient to induce the development of a high frequency of invasive metastatic mammary cancers. N. Panupinthu *et al.*, Lysophosphatidic acid production and action: critical new players in breast cancer initiation and progression, *Br. J. Cancer* (2010) 102(6), 941-946.

[00141] In some instances, metabolically stabilized LPA analogues reduce cell migration and invasion and cause regression of orthotopic breast tumors in vivo. In certain instances, acting as pan-LPA GPCR antagonists and also nanomolar inhibitors of ATX, the analogues reduce tumor burden in orthotopic breast cancer xenografts established in nude mice and are superior to paclitaxel in reducing blood vessel density in tumors. H. Zhang *et al,* Dual activity lysophosphatidic acid receptor pan-antagonist/autotaxin inhibitor reduces breast cancer cell migration in vitro and causes tumor regression in vivo, *Cancer Res.* (2009) 69(13) 5441-5449.

[00142] In certain instances, LPC has no significant effect on paclitaxel-induced apoptosis in MCF-7 breast cancer cells, which do not secrete significant amounts of ATX. Addition of incubation medium from MDA-MB-435 melanoma cells, which secrete ATX, or recombinant ATX enables LPC to inhibit paclitaxel-induced apoptosis of MCF-7 cells. Inhibition of ATX activity blocks this protection against apoptosis. In some instances, LPC has no significant effect in protecting MCF-7 cells against paclitaxel treatment unless it is converted to LPA by ATX. LPA strongly antagonizes paclitaxel-induced apoptosis through stimulating phosphatidylinositol 3-kinase and inhibiting ceramide formation. LPA also partially reverses the paclitaxel-induced arrest in the G2/M phase of the cell cycle. N. Samadi *et al.*, Autotaxin protects MCF-7 breast cancer and MDA-MB-435 melanoma cells against Taxol-induced apoptosis, *Oncogene* (2009) 28(7), 1028-1039.

[00143] In some instances, Epstein-Barr virus (EBV) infection of Hodgkin lymphoma cells results in the induction of ATX. Up-regulation of ATX increases the generation of LPA and leads to enhanced growth and survival of Hodgkin lymphoma cells, whereas specific down-regulation of ATX decreases LPA levels and reduces cell growth and viability. In lymphoma tissues, ATX expression is mainly restricted to $CD30^+$ anaplastic large-cell lymphomas and Hodgkin lymphoma; in the latter, high levels of ATX are strongly associated with EBV positivity. In certain instances, the induction of ATX and the subsequent generation of LPA are key molecular events that mediate the EBV-induced growth and survival of Hodgkin lymphoma cells. K.R.N. Baumforth *et al.*, Induction of autotaxin by the Epstein-Barr virus promotes the growth and survival of Hodgkin lymphoma cells, *Blood* (2005) 106, 2138-2146.

[00144] In some instances, when ATX expression is evaluated in tissues from human hepatocellular carcinoma (HCC) and normal control subjects, ATX is detected mainly in tumor cells within tissue sections and its over-expression in HCC is specifically correlated with inflammation and liver cirrhosis. In addition, when ATX expression is examined in normal human hepatocytes and liver cancer cell lines, hepatoma Hep3B and Huh7 cells display stronger ATX expression than hepatoblastoma HepG2 cells and normal hepatocytes did. Proinflammatory cytokine tumor necrosis factor alpha (TNF-α) promoted ATX expression and secretion selectively in Hep3B and Huh7 cells, which leads to a corresponding increase in lysoPLD activity. Moreover, in hepatoma cells a critical role of nuclear factor-kappa (NF-κB) in basal and TNF-α induced ATX expression is established. In certain instances, ATX plays an important role in inflammation related liver tumorigenesis, because of the link between the TNF-α /NF-κB axis and the ATX-LPA signaling pathway. J.-M. Wu *et al.*, Autotaxin expression and its connection with the TNF-alpha-NF- κB axis in human hepatocellular carcinoma, *Mol. Cancer* 2010), 9, 71.

[00145] In certain instances, ATX is highly expressed in glioblastoma multiforme (GBM). In addition, LPA_1, an LPA receptor responsible for LPA-driven cell motility, is predominantly expressed in GBM. One of the glioblastomas that shows the highest ATX expression (SNB-78), as well as ATX-stable transfectants, showed LPA_1-dependent cell migration in response to LPA in both Boyden chamber and wound healing assays. These ATX-expressing cells also show chemotactic response to LPC. In addition, knockdown of the ATX level using a small interfering RNA technique in SNB-78 cells suppresses their migratory response to LPC. In some instances, the autocrine production of LPA by cancer cell-derived ATX and exogenously supplied LPC contribute to the invasiveness of cancer cells. Y. Kishi, Autotaxin is Overexpressed in Glioblastoma Multiforme and Contributes to Cell Motility of Glioblastoma by Converting Lysophosphatidylcholine to Lysophosphatidic Acid, *J. Biol. Chem.* (2006), 281(25), 17492-17500.

[00146] In certain instances, ATX delays apoptosis induced by carboplatin in ovarian cancer cells. Stable ectopic expression of ATX in OVCAR-3 cells leads to a delay in apoptosis. When serum is withdrawn to remove exogenous LPA, the small molecule inhibitor of ATX, 2-carbacyclic

phosphatidic acid, causes a pronounced potentiation of apoptosis induced by carboplatin in cells expressing ATX. S. Vidot *et al.*, Autotaxin delays apoptosis induced by carboplatin in ovarian cancer cells, *Cell Signal.* (2010) 22(6), 926-935.

[00147] In some instances, ATX is frequently expressed in prostate cancer cells and precancerous high-grade intra-epithelial neoplasia. High expression levels of ATX are associated with both malignant potential and poor outcomes. M.A. Nouh, Expression of autotaxin and acylglycerol kinase in prostate cancer: association with cancer development and progression, *Cancer Sci.* (2009) 100(9), 1631-1638.

[00148] In certain instances, engineered A549 lung tumors regress and lose vascularity in response to LPA receptor antagonism and ATX inhibition. X. Xu *et al.*, Inhibition of Tumor Growth and Angiogenesis by a Lysophosphatidic Acid Antagonist in a Engineered Three-dimensional Lung Cancer Xenograft Model, *Cancer* (2010) 116(7), 1739-1750.

[00149] In some embodiments, a compound of Formula (I), or a pharmaceutically acceptable salt thereof, is used in the treatment of cancer in a mammal. The term "cancer" as used herein refers to an abnormal growth of cells which tend to proliferate in an uncontrolled way and, in some cases, to metastasize (spread). The types of cancer include, but is not limited to, solid tumors (such as those of the bladder, bowel, brain, breast, endometrium, heart, kidney, lung, uterus, lymphatic tissue (lymphoma), ovary, pancreas or other endocrine organ (thyroid), prostate, skin (melanoma or basal cell cancer) or hematological tumors (such as the leukemias and lymphomas) at any stage of the disease with or without metastases.

[00150] Non-limiting examples of cancers include, acute lymphoblastic leukemia, acute myeloid leukemia, adrenocortical carcinoma, anal cancer, appendix cancer, astrocytomas, atypical teratoid/rhabdoid tumor, basal cell carcinoma, bile duct cancer, bladder cancer, bone cancer (osteosarcoma and malignant fibrous histiocytoma), brain stem glioma, brain tumors, brain and spinal cord tumors, breast cancer, bronchial tumors, Burkitt lymphoma, cervical cancer, chronic lymphocytic leukemia, chronic myelogenous leukemia, colon cancer, colorectal cancer, craniopharyngioma, cutaneous T-Cell lymphoma, embryonal tumors, endometrial cancer, ependymoblastoma, ependymoma, esophageal cancer, ewing sarcoma family of tumors, eye cancer, retinoblastoma, gallbladder cancer, gastric (stomach) cancer, gastrointestinal carcinoid tumor, gastrointestinal stromal tumor (GIST), gastrointestinal stromal cell tumor, germ cell tumor, glioma, hairy cell leukemia, head and neck cancer, hepatocellular (liver) cancer, hodgkin lymphoma, hypopharyngeal cancer, intraocular melanoma, islet cell tumors (endocrine pancreas), Kaposi sarcoma, kidney cancer, Langerhans cell histiocytosis, laryngeal cancer, leukemia, Acute lymphoblastic leukemia, acute myeloid leukemia, chronic lymphocytic leukemia, chronic myelogenous leukemia, hairy cell leukemia, liver cancer, non-small cell lung cancer, small cell lung cancer, Burkitt lymphoma, cutaneous T-cell lymphoma, Hodgkin lymphoma, non-Hodgkin lymphoma, lymphoma, Waldenström macroglobulinemia, medulloblastoma, medulloepithelioma,

melanoma, mesothelioma, mouth cancer, chronic myelogenous leukemia, myeloid leukemia, multiple myeloma, nasopharyngeal cancer, neuroblastoma, non-Hodgkin lymphoma, non-small cell lung cancer, oral cancer, oropharyngeal cancer, osteosarcoma, malignant fibrous histiocytoma of bone, ovarian cancer, ovarian epithelial cancer, ovarian germ cell tumor, ovarian low malignant potential tumor, pancreatic cancer, papillomatosis, parathyroid cancer, penile cancer, pharyngeal cancer, pineal parenchymal tumors of intermediate differentiation, pineoblastoma and supratentorial primitive neuroectodermal tumors, pituitary tumor, plasma cell neoplasm/multiple myeloma, pleuropulmonary blastoma, primary central nervous system lymphoma, prostate cancer, rectal cancer, renal cell (kidney) cancer, retinoblastoma, rhabdomyosarcoma, salivary gland cancer, sarcoma, Ewing sarcoma family of tumors, sarcoma, kaposi, Sézary syndrome, skin cancer, small cell Lung cancer, small intestine cancer, soft tissue sarcoma, squamous cell carcinoma, stomach (gastric) cancer, supratentorial primitive neuroectodermal tumors, T-cell lymphoma, testicular cancer, throat cancer, thymoma and thymic carcinoma, thyroid cancer, urethral cancer, uterine cancer, uterine sarcoma, vaginal cancer, vulvar cancer, Waldenström macroglobulinemia, Wilms tumor.

Other Diseases, Disorders or Conditions

[00151] LPA induces neuropathic pain as well as demyelination and pain-related protein expression changes via LPA1. In some instances, ATX heterozygous knockout mice show about 50% recovery of nerve injury-induced neuropathic pain compared to wild type mice. Lysophosphatidylcholine (LPC), also known as lyso-lecithin, is known to induce neuropathic pain. In certain instances, LPC-induced neuropathic pain is partially reduced in ATX heterozygous knockout mice. These results support the idea that LPA is produced by ATX resulting in neuropathic pain.

[00152] LPA and ATX activity are induced by carageenan injection into the mouse air pouch. This model is used to develop anti-inflammatory drugs, including cyclooxygenase inhibitors for arthritis. ATX inhibitors reduce LPA and PGE_2 in the carageenan injected mouse air pouch and also reduce inflammatory pain. These results support the idea that ATX inhibitors would be beneficial in the treatment of arthritis.

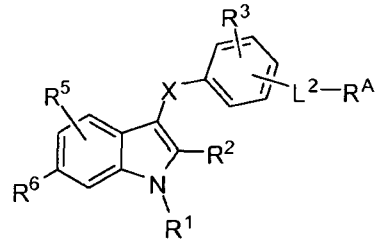
[00153] ATX is also implicated in obesity and diabetes. In some instances, ATX is responsible for the lysoPLD activity released by adipocytes and exerts a paracrine control on preadipocyte growth via an LPA-dependent mechanism. In addition, ATX is up-regulated during adipocyte differentiation and in genetic obesity. In certain instances, ATX mRNA is up-regulated in adipocytes from db/db mice suggesting that the up-regulation of ATX is related to the severe type 2 diabetes phenotype and adipocyte insuline resistance. In some instances, up-regulation of adipocyte ATX is associated with type 2 diabetes in human. J. Boucher *et al.*, *J. Biol. Chem.* (2003) 278(20), 18162-18169.

[00154] In some instances, transgenic overexpression of ATX elevates circulating LPA levels and induces a bleeding diathesis and attenuation of thrombosis in mice. Intravascular administration of exogenous LPA recapitulates the prolonged bleeding time observed in ATX-Tg mice. ATX+/- mice, which have ~50% normal plasma LPA levels, are more prone to thrombosis. Plasma ATX associates

with platelets during aggregation and concentrates in arterial thrombus, and activated but not resting platelets bind recombinant ATX in an integrin-dependent manner. In certain instances, LPA production by ATX regulates murine hemostasis and thrombosis and binding of ATX to activated platelets provides a mechanism to localize LPA production. Z. Pamuklar *et al.*, Autotaxin/lysopholipase D and lysophosphatidic acid regulate murine hemostasis and thrombosis, *J. Biol. Chem.* (2009) 284, 7385-7394.

Compounds

[00155] In one aspect, provided herein is a compound of Formula (I), pharmaceutically acceptable salt, pharmaceutically acceptable solvate, or prodrug thereof:



Formula (I)

wherein,

R^1 is H, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6fluoroalkyl, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted C_3-C_6cycloalkyl, substituted or unsubstituted phenyl, substituted or unsubstituted monocyclic heteroaryl, or $-L^1$-R^4;

L^1 is substituted or unsubstituted C_1-C_6alkylene, substituted or unsubstituted phenylene, or substituted or unsubstituted monocyclic heteroarylene;

R^4 is substituted or unsubstituted C_3-C_6cycloalkyl, substituted or unsubstituted phenyl, substituted or unsubstituted benzyl, substituted or unsubstituted naphthyl, or substituted or unsubstituted monocyclic heteroaryl;

R^2 is H, C_1-C_4alkyl or C_1-C_4fluoroalkyl;

X is -O-, -S-, -S(O)-, -$S(O)_2$-, -CH_2-, -CH_2CH_2-, -OCH_2-, -CH_2O-, -SCH_2-, -CH_2S-, -C(=O)-, -C(=O)CH_2-, or -CH_2C(=O)-;

L^2 is absent, C_1-C_6alkylene or C_3-C_6cycloalkylene;

R^A is $-CO_2H$, $-CO_2(C_1$-C_6alkyl), -OH, -CN, -$B(OH)_2$, $-C(=O)NHSO_2R^9$, $-C(=O)N(R^{10})_2$, $-C(=O)NHCH_2CH_2N(CH_3)_2$, $-C(=O)NHCH_2CH_2N(CH_3)_3$, -C(=O)NH-OH, -C(=O)NH-CN, $-NHSO_2C(=O)R^9$, -CN, tetrazolyl or carboxylic acid bioisostere;

R^3 and R^5 are each independently H, halogen, -CN, -OH, C_1-C_4alkyl, C_1-C_4alkoxy, -S-C_1-C_4alkyl, C_1-C_4fluoroalkyl, C_1-C_4fluoroalkoxy, and C_1-C_4heteroalkyl;

R^6 is H, halogen, -CN, $-NO_2$, -OH, $-OR^9$, $-SR^9$, $-S(=O)R^9$, $-S(=O)_2R^9$, $-S(=O)_2N(R^{10})_2$, $-NR^{10}S(=O)_2R^9$, $-C(=O)R^9$, $-OC(=O)R^9$, $-CO_2R^{10}$, $-OCO_2R^9$, $-N(R^{10})_2$, $-C(=O)N(R^{10})_2$, $-OC(=O)N(R^{10})_2$, $-NHC(=O)R^9$, $-NHC(=O)OR^9$, C_1-C_4alkyl, C_1-C_4alkoxy, -S-C_1-C_4alkyl, -

$S(O)_2$-C_1-C_4alkyl, C_1-C_4fluoroalkyl, C_1-C_4fluoroalkoxy, C_1-C_4heteroalkyl, C_3-C_6cycloalkyl, substituted or unsubstituted phenyl, substituted or unsubstituted monocyclic heteroaryl,

R^9 is C_1-C_6alkyl, C_3-C_6cycloalkyl, a substituted or unsubstituted phenyl, or a substituted or unsubstituted monocyclic heteroaryl;

each R^{10} is independently selected from H, C_1-C_6alkyl, C_3-C_6cycloalkyl, a substituted or unsubstituted phenyl, or a substituted or unsubstituted monocyclic heteroaryl; or

two R^{10} groups attached to the same N atom are taken together with the N atom to which they are attached to form a substituted or unsubstituted heterocycle;

[00156] For any and all of the embodiments, substituents are selected from among a subset of the listed alternatives. For example, in some embodiments, R^A is $-CO_2H$, $-CO_2(C_1$-C_6alkyl), -OH, -CN, $-B(OH)_2$, $-C(=O)NHSO_2R^9$, $-C(=O)N(R^{10})_2$, $-C(=O)NHCH_2CH_2N(CH_3)_2$, $-C(=O)NHCH_2CH_2N(CH_3)_3$, $-C(=O)NH$-OH, $-C(=O)NH$-CN, $-NHSO_2C(=O)R^9$, -CN, tetrazolyl or carboxylic acid bioisostere. In some embodiments, R^A is $-CO_2H$, $-CO_2(C_1$-C_6alkyl), $-B(OH)_2$, $-C(=O)NHSO_2R^9$, $-C(=O)N(R^{10})_2$, $-C(=O)NHCH_2CH_2N(CH_3)_2$, $-C(=O)NHCH_2CH_2N(CH_3)_3$, $-NHSO_2C(=O)R^9$, -CN, tetrazolyl or carboxylic acid bioisostere. In some embodiments, R^A is $-CO_2H$, $-CO_2(C_1$-C_6alkyl), or $-B(OH)_2$. In some embodiments, R^A is $-CO_2H$ or $-CO_2(C_1$-C_6alkyl). In some embodiments, R^A is $-CO_2H$.

[00157] In some embodiments, R^2 is H, C_1-C_4alkyl or C_1-C_4fluoroalkyl. In some embodiments, R^2 is C_1-C_4alkyl or C_1-C_4fluoroalkyl. In some embodiments, R^2 is C_1-C_4alkyl.

[00158] In some embodiments, R^3 is H, halogen, -CN, -OH, C_1-C_4alkyl, C_1-C_4alkoxy, -S-C_1-C_4alkyl, C_1-C_4fluoroalkyl, C_1-C_4fluoroalkoxy, or C_1-C_4heteroalkyl. In some embodiments, R^3 is H, halogen, -CN, -OH, C_1-C_4alkyl, C_1-C_4alkoxy, -S-C_1-C_4alkyl, C_1-C_4fluoroalkyl, or C_1-C_4fluoroalkoxy. In some embodiments, R^3 is H, F, Cl, Br, I, -CN, -OH, $-CH_3$, $-OCH_3$, $-OCH_2CH_3$, $-CF_3$, $-OCF_3$, or -S-CH_3. In some embodiments, R^3 is H, F, Cl, -CN, -OH, $-CH_3$, $-OCH_3$, $-OCH_2CH_3$, $-CF_3$, $-OCF_3$, or -S-CH_3. In some embodiments, R^3 is H, F, or Cl.

[00159] In some embodiments, R^5 is H, halogen, -CN, -OH, C_1-C_4alkyl, C_1-C_4alkoxy, -S-C_1-C_4alkyl, C_1-C_4fluoroalkyl, C_1-C_4fluoroalkoxy, or C_1-C_4heteroalkyl. In some embodiments, R^5 is H, halogen, -CN, -OH, C_1-C_4alkyl, C_1-C_4alkoxy, -S-C_1-C_4alkyl, C_1-C_4fluoroalkyl, or C_1-C_4fluoroalkoxy. In some embodiments, R^5 is H, F, Cl, Br, I, -CN, -OH, $-CH_3$, $-OCH_3$, $-OCH_2CH_3$, $-CF_3$, $-OCF_3$, or -S-CH_3. In some embodiments, R^5 is H, F, Cl, -CN, -OH, $-CH_3$, $-OCH_3$, $-OCH_2CH_3$, $-CF_3$, $-OCF_3$, or -S-CH_3. In some embodiments, R^5 is H, F, or Cl.

[00160] In some embodiments, R^4 is substituted or unsubstituted C_3-C_6cycloalkyl, substituted or unsubstituted phenyl, substituted or unsubstituted naphthyl, or substituted or unsubstituted monocyclic heteroaryl;

[00161] In some embodiments, R^1 is C_1-C_6alkyl, C_1-C_6heteroalkyl, substituted or unsubstituted C_3-C_6cycloalkyl, substituted or unsubstituted phenyl, substituted or unsubstituted monocyclic heteroaryl,

or $-L^1-R^4$; L^1 is C_1-C_4alkylene, substituted or unsubstituted phenylene, or substituted or unsubstituted monocyclic heteroarylene; R^4 is substituted or unsubstituted C_3-C_6cycloalkyl, substituted or unsubstituted phenyl, substituted or unsubstituted naphthyl, substituted or unsubstituted monocyclic heteroaryl; R^2 is C_1-C_4alkyl or C_1-C_4fluoroalkyl; R^6 is halogen, -CN, -OH, C_1-C_4alkyl, C_1-C_4alkoxy, -S-C_1-C_4alkyl, C_1-C_4fluoroalkyl, C_1-C_4fluoroalkoxy, or C_1-C_4heteroalkyl; X is -O- or -S-.

[00162] In some embodiments, R^1 is C_1-C_6alkyl, C_1-C_6fluoroalkyl, C_1-C_6heteroalkyl, C_3-C_6cycloalkyl, substituted or unsubstituted phenyl, or substituted or unsubstituted monocyclic heteroaryl, or $-L^1-R^4$; L^1 is C_1-C_4alkylene, phenylene, or monocyclic heteroarylene; R^4 is substituted or unsubstituted C_3-C_6cycloalkyl, substituted or unsubstituted phenyl, substituted or unsubstituted benzyl, substituted or unsubstituted naphthyl, or substituted or unsubstituted monocyclic heteroaryl.

[00163] In some embodiments, R^1 is $-L^1-R^4$; L^1 is C_1-C_4alkylene, phenylene, or monocyclic heteroarylene; R^4 is substituted or unsubstituted C_3-C_6cycloalkyl, substituted or unsubstituted phenyl, substituted or unsubstituted benzyl, substituted or unsubstituted naphthyl, or substituted or unsubstituted monocyclic heteroaryl.

[00164] In some embodiments, R^1 is $-L^1-R^4$; L^1 is monocyclic heteroarylene; R^4 is substituted or unsubstituted C_3-C_6cycloalkyl, substituted or unsubstituted phenyl, substituted or unsubstituted benzyl, or substituted or unsubstituted monocyclic heteroaryl.

[00165] In some embodiments, R^6 is H, halogen, -CN, $-NO_2$, -OH, $-OR^9$, C_1-C_4alkyl, C_1-C_4alkoxy, -S-C_1-C_4alkyl, $-S(O)_2$-C_1-C_4alkyl, C_1-C_4fluoroalkyl, C_1-C_4fluoroalkoxy, C_1-C_4heteroalkyl, C_3-C_6cycloalkyl, substituted or unsubstituted phenyl, substituted or unsubstituted monocyclic heteroaryl.

[00166] In some embodiments, R^6 is halogen, -CN, $-NO_2$, -OH, $-OR^9$, C_1-C_4alkyl, C_1-C_4alkoxy, -S-C_1-C_4alkyl, $-S(O)_2$-C_1-C_4alkyl, C_1-C_4fluoroalkyl, C_1-C_4fluoroalkoxy, C_3-C_6cycloalkyl, substituted or unsubstituted phenyl, substituted or unsubstituted monocyclic heteroaryl. In some embodiments, R^6 is halogen. In some embodiments, R^6 is Cl.

[00167] In some embodiments, X is -O- or -S-. In some embodiments, X is -S-. In some embodiments, X is -O-.

[00168] In some embodiments, R^1 is a substituted or unsubstituted phenyl, or a substituted or unsubstituted monocyclic heteroaryl. In some embodiments, R^1 is a substituted or unsubstituted phenyl, or a substituted or unsubstituted monocyclic heteroaryl with at least 1 N atom in the heteroaryl ring. In some embodiments, R^1 is a substituted or unsubstituted monocyclic heteroaryl with at least 1 N atom in the heteroaryl ring.

[00169] In some embodiments, R^2 is H, $-CH_3$, $-CH_2CH_3$, $-CH_2CH_2CH_3$, $-CH(CH_3)_2$, $-CH_2CH_2CH_2CH_3$, $-C(CH_3)_3$, or $-CF_3$. In some embodiments, R^2 is H, $-CH_3$, $-CH_2CH_3$, $-CH(CH_3)_2$, or $-CF_3$. In some embodiments, R^2 is $-CH_3$, or $-CF_3$. In some embodiments, R^2 is $-CH_3$.

[00170] In some embodiments, L^2 is absent or C_1-C_6alkylene. In some embodiments, L^2 is absent. In some embodiments, L^2 is C_1-C_6alkylene. In some embodiments, L^2 is C_3-C_6cycloalkylene. In some embodiments, L^2 is absent, $-CH_2-$, $-CH_2CH_2-$, $-CH_2CH_2CH_2-$, $-CH(CH_3)-$, $-CH(CH_2CH_3)-$, $C(CH_3)_2$-

,-$C(CH_2CH_3)_2$- , cyclopropyl-1,1-diyl, cyclobutyl-1,1-diyl, or cyclopentyl-1,1-diyl. In some embodiments, L^2 is absent, -CH_2-, or -CH_2CH_2-. In some embodiments, L^2 is absent, or -CH_2-. In some embodiments, L^2 is -CH_2-. In some embodiments, L^2 is absent.

[00171] In some embodiments, L^2 is absent, -CH_2-, -CH_2CH_2-, -$CH_2CH_2CH_2$-, -$CH(CH_3)$-, -$CH(CH_2CH_3)$-, $C(CH_3)_2$- ,-$C(CH_2CH_3)_2$- , cyclopropyl-1,1-diyl, cyclobutyl-1,1-diyl, or cyclopentyl-1,1-diyl; R^6 is F, Cl, Br, I, -CN, -OH, –CH_3, -CH_2CH_3, -$CH(CH_3)_2$, –OCH_3, –OCH_2CH_3, –CF_3, –OCF_3, -SCH_3 or –$S(O)_2$-CH_3.

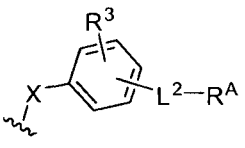
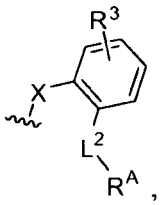
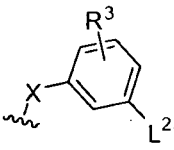
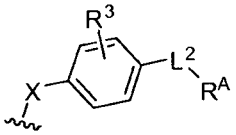
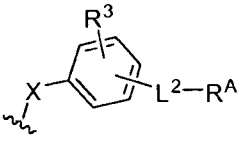
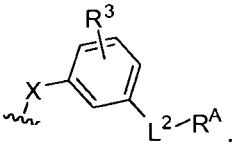
[00172] In some embodiments, R^2 is –CH_3, -CH_2CH_3, -$CH_2CH_2CH_3$, -$CH(CH_3)_2$, -$CH_2CH_2CH_2CH_3$, -$C(CH_3)_3$, or –CF_3; L^2 is absent, -CH_2-, -CH_2CH_2-, -$CH_2CH_2CH_2$-, -$CH(CH_3)$-, -$CH(CH_2CH_3)$-, $C(CH_3)_2$- ,-$C(CH_2CH_3)_2$- , cyclopropyl-1,1-diyl, cyclobutyl-1,1-diyl, or cyclopentyl-1,1-diyl; R^6 is F, Cl, Br, I, -CN, -OH, –CH_3, -CH_2CH_3, -$CH(CH_3)_2$, –OCH_3, –OCH_2CH_3, –CF_3, –OCF_3, -S-CH_3 or –$S(O)_2$-CH_3.

[00173] In some embodiments, R^3 and R^5 are each independently H, halogen, -CN, -OH, C_1-C_4alkyl, C_1-C_4alkoxy, -S-C_1-C_4alkyl, C_1-C_4fluoroalkyl, and C_1-C_4fluoroalkoxy.

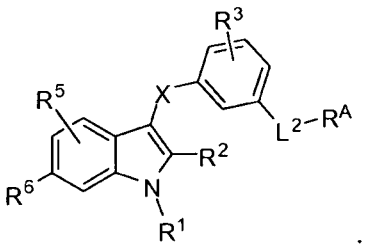
[00174] In some embodiments, R^3 is H, F, Cl, -CN, -OH, –CH_3, –OCH_3, –CF_3, or –OCF_3; R^5 is H, F, Cl, -CN, -OH, –CH_3, –OCH_3, –CF_3, or –OCF_3.

[00175] In some embodiments, R^6 is not H. In some embodiments R^5 is not H.

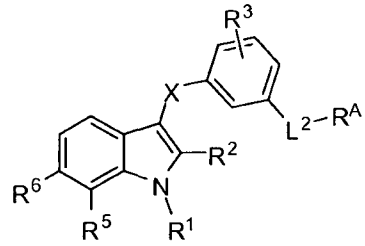
[00176] In some embodiments, R^5 is H.

[00177] In some embodiments,  is  ,  , or  . In some embodiments,  is  .

[00178] In some embodiments, the compound of Formula (I) has the following structure:

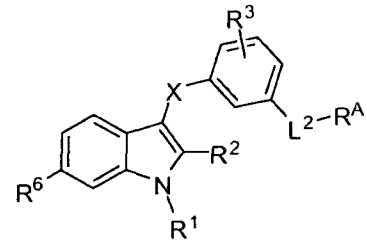


[00179] In some embodiments, the compound of Formula (I) has the following structure:



[00180] In some embodiments, R^A is $-CO_2H$; L^2 is absent, or $-CH_2-$; R^2 is $-CH_3$; R^3 and R^5 are each independently H, halogen, -CN, -OH, C_1-C_4alkyl, C_1-C_4alkoxy, -S-C_1-C_4alkyl, C_1-C_4fluoroalkyl, and C_1-C_4fluoroalkoxy; R^6 is halogen. In some embodiments, R^A is $-CO_2H$; L^2 is absent, or $-CH_2-$; R^2 is $-CH_3$; R^3 and R^5 are each independently H, halogen, -CN, -OH, C_1-C_4alkyl, C_1-C_4alkoxy, -S-C_1-C_4alkyl, C_1-C_4fluoroalkyl, and C_1-C_4fluoroalkoxy; R^6 is halogen; X is -S-. In some embodiments, R^A is $-CO_2H$; L^2 is absent, or $-CH_2-$; R^2 is $-CH_3$; R^3 is H, F, Cl, -CN, -OH, $-CH_3$, $-OCH_3$, $-CF_3$, or $-OCF_3$; R^5 is H, F, Cl, -CN, -OH, $-CH_3$, $-OCH_3$, $-CF_3$, or $-OCF_3$; R^6 is Cl. In some embodiments, R^A is $-CO_2H$; L^2 is absent, or $-CH_2-$; R^2 is $-CH_3$; R^3 is H, F, Cl, -CN, -OH, $-CH_3$, $-OCH_3$, $-CF_3$, or $-OCF_3$; R^5 is H, F, or Cl; R^6 is Cl.

[00181] In some embodiments, the compound of Formula (I) has the structure of Formula (II):



Formula (II).

[00182] In some embodiments, R^A is $-CO_2H$, $-CO_2(C_1$-C_6alkyl), $-B(OH)_2$, or tetrazolyl; X is -S-.

[00183] In some embodiments, R^2 is $-CH_3$, $-CH_2CH_3$, or $-CF_3$; L^2 is absent, $-CH_2-$, or $-CH_2CH_2-$; R^A is $-CO_2H$ or $-CO_2(C_1$-C_6alkyl).

[00184] In some embodiments, R^1 is C_1-C_6alkyl, C_1-C_6heteroalkyl, C_3-C_6cycloalkyl, substituted or unsubstituted phenyl, substituted or unsubstituted monocyclic heteroaryl, or $-L^1$-R^4; L^1 is $-CH_2-$, substituted or unsubstituted phenylene, or substituted or unsubstituted monocyclic heteroarylene; R^4 is C_3-C_6cycloalkyl, substituted or unsubstituted phenyl, substituted or unsubstituted naphthyl, substituted or unsubstituted monocyclic heteroaryl.

[00185] In some embodiments, R^1 is C_1-C_6alkyl, C_1-C_6heteroalkyl, or $-L^1$-R^4; L^1 is $-CH_2-$; R^4 is substituted or unsubstituted phenyl, substituted or unsubstituted naphthyl, substituted or unsubstituted monocyclic heteroaryl.

[00186] In some embodiments, R^1 is substituted or unsubstituted phenyl, substituted or unsubstituted monocyclic heteroaryl, or $-L^1$-R^4; L^1 is substituted or unsubstituted phenylene, or substituted or unsubstituted monocyclic heteroarylene; R^4 is substituted or unsubstituted phenyl, substituted or unsubstituted naphthyl, substituted or unsubstituted monocyclic heteroaryl.

[00187] In some embodiments, R^1 is substituted or unsubstituted phenyl, substituted or unsubstituted monocyclic heteroaryl.

[00188] In some embodiments, R^1 is a substituted or unsubstituted phenyl, substituted or unsubstituted furanyl, substituted or unsubstituted pyrrolyl, substituted or unsubstituted oxazolyl, substituted or unsubstituted thiazolyl, substituted or unsubstituted imidazolyl, substituted or unsubstituted pyrazolyl, substituted or unsubstituted triazolyl, substituted or unsubstituted tetrazolyl, substituted or unsubstituted isoxazolyl, substituted or unsubstituted isothiazolyl, substituted or unsubstituted oxadiazolyl, substituted or unsubstituted thiadiazolyl, substituted or unsubstituted pyridinyl, substituted or unsubstituted pyrimidinyl, substituted or unsubstituted pyrazinyl, substituted or unsubstituted pyridazinyl, or substituted or unsubstituted triazinyl.

[00189] In some embodiments, R^1 is a substituted or unsubstituted phenyl.

[00190] In some embodiments, R^1 is a substituted or unsubstituted monocyclic 5-membered heteroaryl.

[00191] In some embodiments, R^1 is a substituted or unsubstituted pyrrolyl, substituted or unsubstituted oxazolyl, substituted or unsubstituted thiazolyl, substituted or unsubstituted imidazolyl, substituted or unsubstituted pyrazolyl, substituted or unsubstituted triazolyl, substituted or unsubstituted isoxazolyl, substituted or unsubstituted isothiazolyl, substituted or unsubstituted oxadiazolyl, or substituted or unsubstituted thiadiazolyl. In some embodiments, R^1 is a substituted or unsubstituted oxazolyl, substituted or unsubstituted thiazolyl, substituted or unsubstituted imidazolyl, substituted or unsubstituted pyrazolyl, substituted or unsubstituted isoxazolyl. In some embodiments, R^1 is a substituted or unsubstituted pyrazolyl.

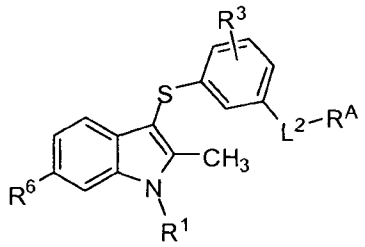
[00192] In some embodiments, R^1 is a substituted or unsubstituted monocyclic 6-membered heteroaryl.

[00193] In some embodiments, R^1 is a substituted or unsubstituted pyridinyl, substituted or unsubstituted pyrimidinyl, substituted or unsubstituted pyrazinyl, or substituted or unsubstituted pyridazinyl.

[00194] In some embodiments, R^1 is a substituted or unsubstituted monocyclic heteroaryl; R^2 is H or C_1-C_4alkyl; X is -O-, -S-, -S(O)-, or -$S(O)_2$-; L^2 is absent, C_1-C_6alkylene or C_3-C_6cycloalkylene; R^A is $-CO_2H$; R^3 and R^5 are each independently H, halogen, -CN, -OH, C_1-C_4alkyl, C_1-C_4alkoxy, -S-C_1-C_4alkyl, C_1-C_4fluoroalkyl, and C_1-C_4fluoroalkoxy; R^6 is halogen, -CN, -OH, C_1-C_4alkyl, C_1-C_4alkoxy, -S-C_1-C_4alkyl, C_1-C_4fluoroalkyl, C_1-C_4fluoroalkoxy, or C_1-C_4heteroalkyl.

[00195] In some embodiments, R^1 is a substituted or unsubstituted monocyclic heteroaryl; R^2 is C_1-C_4alkyl; X is -S-; L^2 is absent, or C_1-C_4alkylene; R^A is $-CO_2H$; R^3 is H, halogen, C_1-C_4alkyl, C_1-C_4alkoxy, or C_1-C_4fluoroalkyl; R^5 is H, or halogen; R^6 is halogen.

[00196] In some embodiments, the compound of Formula (I) has the structure of Formula (III):



Formula (III)

wherein

R^1 is a substituted or unsubstituted phenyl or a substituted or unsubstituted monocyclic heteroaryl;

L^2 is absent, $-CH_2-$, or $-CH_2CH_2-$;

R^A is $-CO_2H$ or $-CO_2(C_1\text{-}C_6\text{alkyl})$;

R^3 is H, halogen, -CN, -OH, $C_1\text{-}C_4$alkyl, $C_1\text{-}C_4$alkoxy, -S-$C_1\text{-}C_4$alkyl, $C_1\text{-}C_4$fluoroalkyl, $C_1\text{-}C_4$fluoroalkoxy, and $C_1\text{-}C_4$heteroalkyl;

R^6 is H, halogen, -CN, -OH, $C_1\text{-}C_4$alkyl, $C_1\text{-}C_4$alkoxy, -S-$C_1\text{-}C_4$alkyl, $C_1\text{-}C_4$fluoroalkyl, or $C_1\text{-}C_4$fluoroalkoxy;

each substituted group is substituted with 1 or more groups independently selected from halogen, -CN, -OH, $C_1\text{-}C_4$alkyl, $C_1\text{-}C_4$alkoxy, -S-$C_1\text{-}C_4$alkyl, $C_1\text{-}C_4$fluoroalkyl, $C_1\text{-}C_4$fluoroalkoxy, and $C_1\text{-}C_4$heteroalkyl.

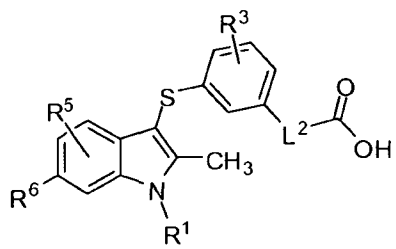
[00197] In some embodiments, R^1 is a substituted or unsubstituted monocyclic 5-membered heteroaryl. In some embodiments, R^1 is a substituted or unsubstituted monocyclic 5-membered heteroaryl with at least 1 N atom in the heteroaryl ring.

[00198] In some embodiments, R^1 is a substituted or unsubstituted monocyclic 6-membered heteroaryl. In some embodiments, R^1 is a substituted or unsubstituted monocyclic 6-membered heteroaryl with at least 1 N atom in the heteroaryl ring.

[00199] In some embodiments, L^2 is absent or $-CH_2-$; R^A is $-CO_2H$.

[00200] In some embodiments, R^6 is F, Cl, Br, I, -CN, -OH, $-CH_3$, $-OCH_3$, $-OCH_2CH_3$, $-CF_3$, $-OCF_3$, or -S-CH_3. In some embodiments, R^6 is Cl.

[00201] In some embodiments, the compound of Formula (I) has the structure of Formula (IV):



Formula (IV)

wherein,

R^1 is a substituted or unsubstituted monocyclic heteroaryl;

L^2 is absent, -CH_2-, or -CH_2CH_2-;

R^3 is H, halogen, -CN, -OH, C_1-C_4alkyl, C_1-C_4alkoxy, -S-C_1-C_4alkyl, C_1-C_4fluoroalkyl, or C_1-C_4fluoroalkoxy;

R^5 is H, halogen, -CN, -OH, C_1-C_4alkyl, C_1-C_4alkoxy, -S-C_1-C_4alkyl, C_1-C_4fluoroalkyl, or C_1-C_4fluoroalkoxy;

R^6 is H, halogen, -CN, -OH, C_1-C_4alkyl, C_1-C_4alkoxy, -S-C_1-C_4alkyl, C_1-C_4fluoroalkyl, or C_1-C_4fluoroalkoxy;

each substituted group is substituted with 1 or more groups independently selected from halogen, -CN, -OH, C_1-C_4alkyl, C_1-C_4alkoxy, -S-C_1-C_4alkyl, C_1-C_4fluoroalkyl, C_1-C_4fluoroalkoxy, and C_1-C_4heteroalkyl.

[00202] In some embodiments, R^1 is a substituted or unsubstituted monocyclic 5-membered heteroaryl; L^2 is absent or -CH_2-; R^3 is H, F, Cl, Br, I, -CN, -OH, –CH_3, –OCH_3, –OCH_2CH_3, –CF_3, –OCF_3, or -S-CH_3; R^5 is H, F, Cl, Br, I, -CN, -OH, –CH_3, –OCH_3, –OCH_2CH_3, –CF_3, –OCF_3, or -S-CH_3; R^6 is F, Cl, Br, I, -CN, -OH, –CH_3, –OCH_3, –OCH_2CH_3, –CF_3, –OCF_3, or -S-CH_3.

[00203] In some embodiments, R^1 is a substituted or unsubstituted pyrrolyl, substituted or unsubstituted oxazolyl, substituted or unsubstituted thiazolyl, substituted or unsubstituted imidazolyl, substituted or unsubstituted pyrazolyl, substituted or unsubstituted triazolyl, substituted or unsubstituted isoxazolyl, substituted or unsubstituted isothiazolyl, substituted or unsubstituted oxadiazolyl, or substituted or unsubstituted thiadiazolyl; each substituted group is substituted with 1 or more groups independently selected from halogen, -OH, C_1-C_4alkyl, C_1-C_4alkoxy, and C_1-C_4fluoroalkyl; L^2 is absent or -CH_2-; R^3 is H, F, Cl, –CH_3, –OCH_3, –CF_3, –OCF_3, or -S-CH_3; R^5 is H, F, or Cl; R^6 is Cl.

[00204] In some embodiments, R^3 is H, F, Cl, Br, I, -CN, -OH, –CH_3, –OCH_3, –OCH_2CH_3, –CF_3, –OCF_3, or -S-CH_3; R^5 is H, F, Cl, Br, I, -CN, -OH, –CH_3, –OCH_3, –OCH_2CH_3, –CF_3, –OCF_3, or -S-CH_3. In some embodiments, R^3 is H, F, Cl, –CH_3, –OCH_3, –OCH_2CH_3, –CF_3, –OCF_3, or -S-CH_3; R^5 is H, F, Cl, –CH_3, –OCH_3, –OCH_2CH_3, –CF_3, –OCF_3, or -S-CH_3. In some embodiments, R^3 is H, F, Cl, –CH_3, or –CF_3; R^5 is H, F, Cl, –CH_3, or –CF_3. In some embodiments, R^3 is H, F, or Cl; R^5 is H, F, or Cl.

[00205] In some embodiments, R^1 is a substituted or unsubstituted pyrazolyl; each substituted group is substituted with C_1-C_4alkyl; R^3 is H, F, Cl, –CH_3, –OCH_3, –CF_3, –OCF_3, or -S-CH_3; R^5 is H, F, or Cl; R^6 is Cl. In some embodiments, R^1 is a substituted or unsubstituted pyrazolyl; each substituted group is substituted with C_1-C_4alkyl; R^3 is H, F, or Cl; R^5 is H, F, or Cl; R^6 is Cl.

[00206] In some embodiments, R^1 is as described in Table 1, Table 2, Table 3 and/or Table 4.

[00207] In some embodiments, R^6 is as described in Table 1, Table 2, Table 3 and/or Table 4.

[00208] In some embodiments, L^2 is as described in Table 1, Table 2, Table 3 and/or Table 4.

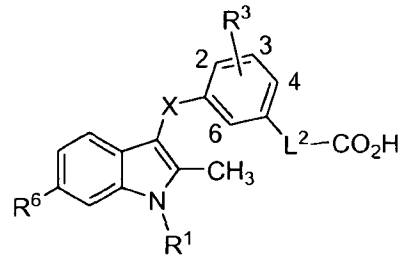
[00209] In some embodiments, R^A is as described in Table 2, Table 3 and/or Table 4.

[00210] In some embodiments, X is as described in Table 1, Table 2 and/or Table 3.

[00211] Any combination of the groups described above for the various variables is contemplated herein. Throughout the specification, groups and substituents thereof are chosen by one skilled in the field to provide stable moieties and compounds.

[00212] Representative compounds of Formula (I) include, but are not limited to, those described in Table 1, Table 2, Table 3 and Table 4.

Table 1.

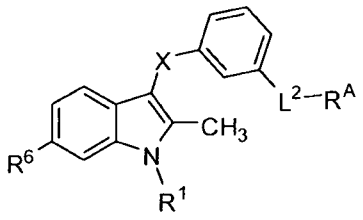


Cmpd No	R^1	R^6	R^3	R_3 position	X	L^2
1-1	H	H	H	-	S	$-CH_2-$
1-2	H	F	H	-	S	$-CH_2-$
1-3	H	Methoxy	H	-	S	$-CH_2-$
1-4	Methyl	H	H	-	S	$-CH_2-$
1-5	Methyl	Cl	H	-	S	$-CH_2-$
1-6	Methyl	Cl	H	-	S	-
1-7	*iso*-Butyl	Cl	H	-	S	$-CH_2-$
1-8	Methoxyethyl	Cl	H	-	S	$-CH_2-$
1-9	Benzyl	H	H	-	S	$-CH_2-$
1-10	Benzyl	Br	H	-	S	-
1-11	Benzyl	Phenyl	H	-	S	-
1-12	Benzyl	3-Pyridinyl	H	-	S	-
1-13	Benzyl	Benzyl	H	-	S	-
1-14	Benzyl	Cl	H	-	S	$-CH_2-$
1-15	Benzyl	Cl	H	-	S	-
1-16	Benzyl	Cl	H	-	O	$-CH_2-$
1-17	Benzyl	Cl	H	-	S	$-CH_2CH_2-$
1-18	4-Fluorobenzyl	Cl	H	-	S	-
1-19	α-Methylbenzyl	Cl	H	-	S	-
1-20	Naphth-2-ylmethyl	Cl	H	-	S	-
1-21	Pyridin-3-ylmethyl	Cl	H	-	S	-
1-22	6-Trifluoromethyl-pyridin-3-ylmethyl	Cl	H	-	S	-
1-23	Pyridin-4-ylmethyl	Cl	H	-	S	-
1-24	Pyridin-2-ylmethyl	Cl	H	-	S	-
1-25	3,5-Dimethyl-4-methoxy-pyridin-2-ylmethyl	Cl	H	-	S	-
1-26	Phenyl	Cl	H	-	S	-
1-27	Biphenyl	Cl	H	-	S	-
1-28	Biphenyl-3-yl	Cl	H	-	S	-
1-29	3-Chlorophenyl	Cl	H	-	S	-
1-30	3-Pyridinyl	Cl	H	-	S	-
1-31	2-Pyridinyl	Cl	H	-	S	-
1-32	6-Trifluoromethyl-3-pyridinyl	Cl	H	-	S	-

Cmpd No	R^1	R^6	R^3	R_3 position	X	L^2
1-33	6-Methoxy-3-Pyridinyl	Cl	H	-	S	-
1-34	6-Methyl-3-Pyridinyl	Cl	H	-	S	-
1-35	3-Pyridinyl	Cl	H	-	S	$-CH_2-$
1-36	6-Ethoxy-3-Pyridinyl	Cl	H	-	S	-
1-37	5-Methoxy-3-Pyridinyl	Cl	H	-	S	-
1-38	3-Pyrimidinyl	Cl	H	-	S	-
1-39	N-Methyl-4-pyrazolyl	Cl	H	-	S	-
1-40	3-Pyridinyl	Cl	OCH_3	2	S	-
1-41	N-Methyl-4-pyrazolyl	Cl	OCH_3	2	S	-
1-42	4-Isothiazolyl	Cl	H	-	S	-
1-43	1-Ethyl-4-pyrazolyl	Cl	H	-	S	-
1-44	1-Isopropyl-4-pyrazolyl	Cl	H	-	S	-
1-45	1-Methyl-4-pyrazolyl	Cl	H	-	S	$-CH_2-$
1-46	3-Pyridinyl	Cl	CF_3	3	S	-
1-47	1-Methyl-4-pyrazolyl	Cl	OCH_3	2	S	$-CH_2-$
1-48	3-Methyl-5-pyridinyl	Cl	H	-	S	$-CH_2-$
1-49	3-pyridinyl	Cl	H	-	S	$-CH(CH_2CH_3)-$
1-50	1-Methyl-4-pyrazolyl	Cl	CH_3	2	S	-
1-51	1-Ethyl-4-pyrazolyl	Cl	Br	3	S	-
1-52	1-Ethyl-4-pyrazolyl	Cl	Me	3	S	-
1-53	1-Methyl-4-pyrazolyl	Cl	CF_3	3	S	-
1-54	3-pyridinyl	Cl	CH_3	2	S	-
1-55	1-Trifluoroethyl-4-pyrazolyl	Cl	-	-	S	-
1-56	3-Methyl-5-pyridinyl	Cl	H	-	S	-
1-57	1-Propyl-4-pyrazolyl	Cl	-	-	S	-
1-58	1-Phenyl-4-pyrazolyl	Cl	-	-	S	-
1-59	1-Benzyl-4-pyrazolyl	Cl	-	-	S	-
1-60	1,3-Dimethyl-4-pyrazolyl	Cl	-	-	S	-
1-61	1-Methyl-4-pyrazolyl	Cl	OMe	6	S	-
1-62	1-Ethyl-4-pyrazolyl	Cl	OMe	6	S	-
1-63	1-Methyl-4-pyrazolyl	Cl	CH_3	6	S	-
1-64	1-Ethyl-4-pyrazolyl	Cl	CH_3	6	S	-
1-65	3-Methyl-5-pyridinyl	Cl	CH_3	6	S	-
1-66	3-Methyl-5-pyridinyl	Cl	F	6	S	-
1-67	1-Ethyl-4-pyrazolyl	Cl	F	6	S	-
1-68	3-Methyl-6-pyridazinyl	Cl	H	-	S	-
1-69	1-Ethyl-4-pyrazolyl	Cl	H	-	S	$-CH_2-$
1-70	1-Propyl-4-pyrazolyl	Cl	H	-	S	$-CH_2-$
1-71	1-(4-Fluorophenyl)-4-pyrazolyl	Cl	H	-	S	-
1-72	1-Butyl-4-pyrazolyl	Cl	H	-	S	-
1-73	3-Ethyl-5-pyridinyl	Cl	F	6	S	-
1-74	1-Ethyl-4-pyrazolyl	Cl	H	-	S	Cyclopropyl-1,1-diyl
1-75	1-Ethyl-4-pyrazolyl	CH_3SO_2-	H	-	S	-
1-76	1-Ethyl-4-pyrazolyl	Cl	F	4	S	-
1-77	3-Ethyl-5-isoxazolyl	Cl	H	-	S	-
1-78	3-Ethyl-5-isoxazolyl	Cl	H	-	S	$-CH_2-$
1-79	5-Ethyl-3-isoxazolyl	Cl	H	-	S	-
1-80	5-Ethyl-3-isoxazolyl	Cl	H	-	S	$-CH_2-$
1-81	3-Ethyl-5-isoxazolyl	Cl	F	6	S	-
1-82	3-Ethyl-5-isoxazolyl	Cl	F	6	S	$-CH_2-$

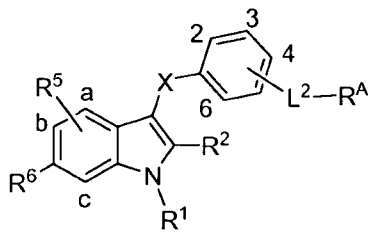
Cmpd No	R^1	R^6	R^3	R_3 position	X	L^2
1-83	5-Ethyl-3-isoxazolyl	Cl	F	6	S	-
1-84	5-Ethyl-3-isoxazolyl	Cl	F	6	S	$-CH_2-$
1-85	3-Ethyl-5-isothiazolyl	Cl	H	-	S	-
1-86	3-Ethyl-5-isothiazolyl	Cl	H	-	S	$-CH_2-$
1-87	5-Ethyl-3- isothiazolyl	Cl	H	-	S	-
1-88	5-Ethyl-3- isothiazolyl	Cl	H	-	S	$-CH_2-$
1-89	3-Ethyl-5- isothiazolyl	Cl	F	6	S	-
1-90	3-Ethyl-5- isothiazolyl	Cl	F	6	S	$-CH_2-$
1-91	5-Ethyl-3- isothiazolyl	Cl	F	6	S	-
1-92	5-Ethyl-3- isothiazolyl	Cl	F	6	S	$-CH_2-$
1-93	4-Ethyl-2-pyrimidinyl	Cl	H	-	S	-
1-94	4-Ethyl-2-pyrimidinyl	Cl	H	-	S	$-CH_2-$
1-95	4-Ethyl-2-pyrimidinyl	Cl	F	6	S	-
1-96	4-Ethyl-2-pyrimidinyl	Cl	F	6	S	$-CH_2-$
1-97	2-Ethyl-4-pyrimidinyl	Cl	H	-	S	-
1-98	2-Ethyl-4-pyrimidinyl	Cl	H	-	S	$-CH_2-$
1-99	2-Ethyl-4-pyrimidinyl	Cl	F	6	S	-
1-100	2-Ethyl-4-pyrimidinyl	Cl	F	6	S	$-CH_2-$
1-101	2-Methoxy-4-pyridinyl	Cl	H	-	S	-
1-102	2-Methoxy-4-pyridinyl	Cl	H	-	S	$-CH_2-$
1-103	2-Methoxy-4-pyridinyl	Cl	F	6	S	-
1-104	2-Methoxy-4-pyridinyl	Cl	F	6	S	$-CH_2-$
1-105	2-Methoxy-6-pyridinyl	Cl	H	-	S	-
1-106	2-Methoxy-6-pyridinyl	Cl	H	-	S	$-CH_2-$
1-107	2-Methoxy-6-pyridinyl	Cl	F	6	S	-
1-108	2-Methoxy-6-pyridinyl	Cl	F	6	S	$-CH_2-$
1-109	1-Ethyl-4-pyrazolyl	Cl	H	-	SCH_2	-
1-110	1-Ethyl-4-pyrazolyl	Cl	H	-	SCH_2	$-CH_2-$
1-111	1-Ethyl-4-pyrazolyl	Cl	F	6	SCH_2	-
1-112	1-Ethyl-4-pyrazolyl	Cl	F	6	SCH_2	$-CH_2-$
1-113	1-Ethyl-4-pyrazolyl	Cl	H	-	OCH_2	-
1-114	1-Ethyl-4-pyrazolyl	Cl	H	-	OCH_2	$-CH_2-$
1-115	1-Ethyl-4-pyrazolyl	Cl	F	6	OCH_2	-
1-116	1-Ethyl-4-pyrazolyl	Cl	F	6	OCH_2	$-CH_2-$
1-117	1-Ethyl-4-pyrazolyl	Cl	H	-	CH_2O	-
1-118	1-Ethyl-4-pyrazolyl	Cl	H	-	CH_2O	$-CH_2-$
1-119	1-Ethyl-4-pyrazolyl	Cl	F	6	CH_2O	-
1-120	1-Ethyl-4-pyrazolyl	Cl	F	6	CH_2O	$-CH_2-$
1-121	1-Ethyl-4-pyrazolyl	Cl	H	-	CH_2S	-
1-122	1-Ethyl-4-pyrazolyl	Cl	H	-	CH_2S	$-CH_2-$
1-123	1-Ethyl-4-pyrazolyl	Cl	F	6	CH_2S	-
1-124	1-Ethyl-4-pyrazolyl	Cl	F	6	CH_2S	$-CH_2-$
1-125	1-Ethyl-4-pyrazolyl	Cl	H	-	CH_2CH_2	-
1-126	1-Ethyl-4-pyrazolyl	Cl	H	-	CH_2CH_2	$-CH_2-$
1-127	1-Ethyl-4-pyrazolyl	Cl	F	6	CH_2CH_2	-
1-128	1-Ethyl-4-pyrazolyl	Cl	F	6	CH_2CH_2	$-CH_2-$
1-129	1-Ethyl-4-pyrazolyl	Cl	F	3	S	-
1-130	1-(*p*-Tolyl)-4-pyrazolyl	Cl	H	-	S	-
1-131	1-Propyl-4-pyrazolyl	Cl	F	6	S	-
1-132	1-Ethyl-4-pyrazolyl	Cl	Me	4	S	-

Table 2.



Cmpd No	R^6	R^1	X	L^2	R^A
2-1	Cl	H	S	-	$-B(OH)_2$
2-3	Cl	Benzyl	O	-	CO_2CH_3
2-4	Cl	Benzyl	O	$-CH_2-$	-OH
2-5	Cl	Benzyl	O	$-CH_2-$	-CN
2-6	Cl	Benzyl	O	$-CH_2-$	5-Tetrazolyl
2-7	Cl	Benzyl	S	-CH=CH-	$-CO_2H$
2-8	Cl	Benzyl	S	$-CH_2-$	5-Tetrazolyl
2-9	Cl	Benzyl	S	-	5-Tetrazolyl
2-10	Br	Benzyl	S	-	$-C(O)NH(CH_2)_2N(CH_3)_3^+$
2-11	Br	Benzyl	S	-	$-C(O)NH(CH_2)_2N(CH_3)_2$
2-12	Cl	3-Pyridinyl	S	-	$-B(OH)_2$

Table 3.

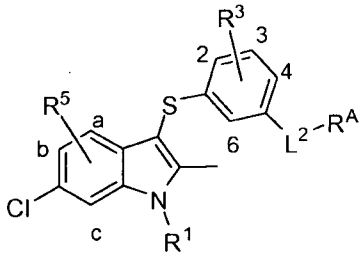


Cmpd No	R^1	R^2	X	L^2	R^A	Position of $-L^2R^A$	R^5	Position of R^5	R^6
3-1	H	$-CH_3$	S	$-CH_2-$	$-CO_2H$	2	H	-	Cl
3-2	H	$-CH_3$	S	$-CH_2-$	$-CO_2H$	4	H	-	Cl
3-3	H	$-CH_3$	S	$-CH_2-$	$-CO_2H$	3	Cl	b	H
3-4	H	$-CH_3$	S	$-CH_2-$	$-CO_2H$	3	Cl	c	H
3-5	H	$-CH_3$	S	$-CH_2-$	$-CO_2H$	3	F	a	H
3-6	H	$-CH_3$	S	$-CH_2-$	$-CO_2H$	3	$-OCH_3$	a	H
3-7	H	$-CF_3$	S	-	$-CO_2H$	3	H	-	Cl
3-9	H	$-CH_3$	S	-	$-B(OH)_2$	3	Cl	a	H
3-10	Methyl	$-CH_3$	S	$-CH_2-$	$-CO_2H$	2	H	-	Cl
3-11	Methyl	$-CH_3$	S	$-CH_2-$	$-CO_2H$	4	H	-	Cl
3-12	Methyl	$-CH_3$	S	$-CH_2-$	$-CO_2H$	3	Cl	b	H
3-13	Benzyl	$-CF_3$	S	-	$-CO_2H$	3	H	-	Cl
3-15	Benzyl	$-CH_2CH_3$	S	-	$-CO_2H$	3	H	-	Cl
3-16	1-Ethyl-4-pyrazolyl	$-CH_3$	S	-	$-CO_2H$	3	F	c	Cl
3-17	Benzyl	H	S	-	$-CO_2H$	3	H	-	Cl
3-19	3-Pyridinyl	H	S	-	$-CO_2H$	3	H	-	Cl
3-20	3-Pyridinyl	$-CH_3$	S	$-CH(CH_3)$	$-CO_2H$	3	H	-	Cl

Cmpd No	R^1	R^2	X	L^2	R^A	Position of $-L^2R^A$	R^5	Position of R^5	R^6
				-					
3-21	1-Ethyl-4-pyrazolyl	$-CH_3$	S	-	$-CO_2H$	3	Me	c	Cl
3-22	3-Methyl-5-pyridinyl	$-CH_3$	S	-	$-CO_2H$	3	F	c	Cl
3-23	1-Phenyl-4-pyrazolyl	$-CH_3$	S	-	$-CO_2H$	3	F	c	Cl
3-24	1-Propyl-4-pyrazolyl	$-CH_3$	S	-	$-CO_2H$	3	F	c	Cl
3-25	3-Ethyl-5-pyridinyl	$-CH_3$	S	-	$-CO_2H$	3	F	c	Cl
3-26	1-Ethyl-4-pyrazolyl	$-CH_3$	S	-	$-CO_2H$	3	F	b	Cl
3-27	1-Propyl-4-pyrazolyl	$-CH_3$	S	-	$-CO_2H$	3	F	b	Cl
3-28	1-Ethyl-4-pyrazolyl	$-CH_3$	S	$-CH_2-$	$-CO_2H$	3	F	c	Cl
3-29	1-Ethyl-4-pyrazolyl	$-CH_3$	S	-	$-CONH-SO_2CH_3$	3	F	c	Cl
3-30	1-Ethyl-4-pyrazolyl	$-CH_3$	S	$-CH_2-$	$-CO_2H$	4	H	-	Cl
3-31	1-Ethyl-4-pyrazolyl	$-CH_3$	S	-	$-CO_2H$	3	H	-	CN
3-32	1-(4-methyphenyl)-4-pyrazolyl	$-CH_3$	S	-	$-CO_2H$	3	F	c	Cl
3-33	1-(3-chlorophenyl)-4-pyrazolyl	$-CH_3$	S	-	$-CO_2H$	3	F	c	Cl
3-34	1-(cyclopropylmethyl)-4-pyrazolyl	$-CH_3$	S	-	$-CO_2H$	3	F	c	Cl
3-35	1-cyclopentyl-4-pyrazolyl	$-CH_3$	S	-	$-CO_2H$	3	F	c	Cl
3-36	1-cyclobutyl-4-pyrazolyl	$-CH_3$	S	-	$-CO_2H$	3	F	c	Cl
3-37	1-propyl-4-pyrazolyl	$-CH_3$	S	$-CH_2-$	$-CO_2H$	3	F	c	Cl
3-38	1-Ethyl-4-pyrazolyl	$-CH_3$	S	-	$-CONH-SO_2CH_3$	3	H	-	Cl
3-39	1-Ethyl-4-pyrazolyl	$-CH_3$	S	-	$-CONH-SO_2CH_2CH_3$	3	H	-	Cl
3-40	1-Ethyl-4-pyrazolyl	$-CH_3$	S	-	$-CONH-SO_2CH_2CH_3$	3	F	c	Cl
3-41	1-Ethyl-4-pyrazolyl	$-CH_3$	S	-	$-CONH-SO_2Ph$	3	H	-	Cl
3-42	1-Ethyl-4-pyrazolyl	$-CH_3$	S	-	$-CONH-SO_2Ph$	3	F	c	Cl
3-43	1-Ethyl-4-pyrazolyl	$-CH_3$	S	-	$-NH-SO_2COCH_3$	3	H	-	Cl
3-44	1-Ethyl-4-	$-CH_3$	S	-	-NH-	3	F	c	Cl

Cmpd No	R^1	R^2	X	L^2	R^A	Position of $-L^2R^A$	R^5	Position of R^5	R^6
	pyrazolyl				SO_2COCH_3				
3-45	1-Ethyl-4-pyrazolyl	$-CH_3$	S	-	- NH-SO_2COPh	3	H	-	Cl
3-46	1-Ethyl-4-pyrazolyl	$-CH_3$	S	-	- NH-SO_2COPh	3	F	c	Cl
3-47	1-Cyclopropyl-4-pyrazolyl	$-CH_3$	S	-	$-CO_2H$	3	F	c	Cl
3-48	1-(4-Methoxybenzyl)-4-pyrazolyl	$-CH_3$	S	-	$-CO_2H$	3	F	c	Cl
3-49	1-H-4-Pyrazolyl	$-CH_3$	S	-	$-CO_2H$	3	F	c	Cl
3-50	1-(2-Hydroxyethyl)-4-pyrazolyl	$-CH_3$	S	-	$-CO_2H$	3	F	c	Cl
3-51	1-Ethyl-4-pyrazolyl	$-CH_3$	S	-	-CONH-SO_2cyPr	3	F	c	Cl
3-52	1-Ethyl-4-pyrazolyl	$-CH_3$	S	-	$-CO_2H$	3	Cl	c	Cl
3-53	1-Propyl-4-pyrazolyl	$-CH_3$	S	$-CH_2-$	-CONH-SO_2CH_3	3	H	-	Cl
3-54	1-Propyl-4-pyrazolyl	$-CH_3$	S	$-CH_2-$	-CONH-SO_2cyPr	3	H	-	Cl
3-55	1-Propyl-4-pyrazolyl	$-CH_3$	S	$-CH_2-$	-CONH-SO_2Ph	3	H	-	Cl
3-56	1-Isopropyl-4-pyrazolyl	$-CH_3$	S	-	$-CO_2H$	3	F	c	Cl
3-57	1-Methyl-4-pyrazolyl	$-CH_3$	S	-	$-CO_2H$	3	F	c	Cl
3-58	1-Methyl-3-pyrazolyl	$-CH_3$	S	-	$-CO_2H$	3	F	c	Cl
3-59	5-Propyl-[1,2,4]oxadiazol-3-yl	$-CH_3$	S	-	$-CO_2H$	3	F	c	Cl
3-60	1-*tert*Butyl-4-pyrazolyl	$-CH_3$	S	-	$-CO_2H$	3	F	c	Cl
3-61	5-Methyl-thiopen-3-yl	$-CH_3$	S	-	$-CO_2H$	3	F	c	Cl
3-62	5-Methyl-thiopen-2-yl	$-CH_3$	S	-	$-CO_2H$	3	F	c	Cl

Table 4.



Cmpd No	R^1	L^2	R^A	R^3	Position of R^3	R^5	Position of R^5
4-1	1-Ethyl-4-pyrazolyl	-	$-CO_2H$	F	4	F	c
4-2	1-Ethyl-4-pyrazolyl	-	$-CO_2H$	F	3	F	c
4-3	1-Ethyl-4-pyrazolyl	-	$-CO_2H$	F	6	F	c
4-4	1-Propyl-4-pyrazolyl	-	$-CO_2H$	F	6	F	c
4-5	1-Propyl-4-pyrazolyl	-	$-CO_2H$	F	3	F	c
4-6	1-Isopropyl-4-pyrazolyl	-	$-CO_2H$	F	3	F	c
4-7	1-Ethyl-4-pyrazolyl	-	$-CONH-SO_2Ph$	F	6	F	c
4-8	1-Propyl-4-pyrazolyl	-	$-CONH-SO_2Ph$	F	6	F	c
4-9	1-Ethyl-4-pyrazolyl	-	$-CO_2H$	Me	4	F	c
4-10	1-Propyl-4-pyrazolyl	-	$-CO_2H$	OMe	4	F	c
4-11	1-Ethyl-4-pyrazolyl	-	$-CO_2H$	F	6	F	a
4-12	1-Propyl-4-pyrazolyl	$-CH_2-$	$-CO_2H$	F	6	F	c
4-13	1-Propyl-4-pyrazolyl	-	$-CO_2H$	Me	4	F	c
4-14	1-Propyl-4-pyrazolyl	$-CH_2-$	$-CO_2H$	CF_3	4	F	c
4-15	1-Ethyl-4-pyrazolyl	$-CH_2-$	$-CO_2H$	F	6	F	c

[00213] Throughout the specification, groups and substituents thereof are chosen by one skilled in the field to provide stable moieties and compounds. Any combination of the groups described above for the various variables is contemplated herein.

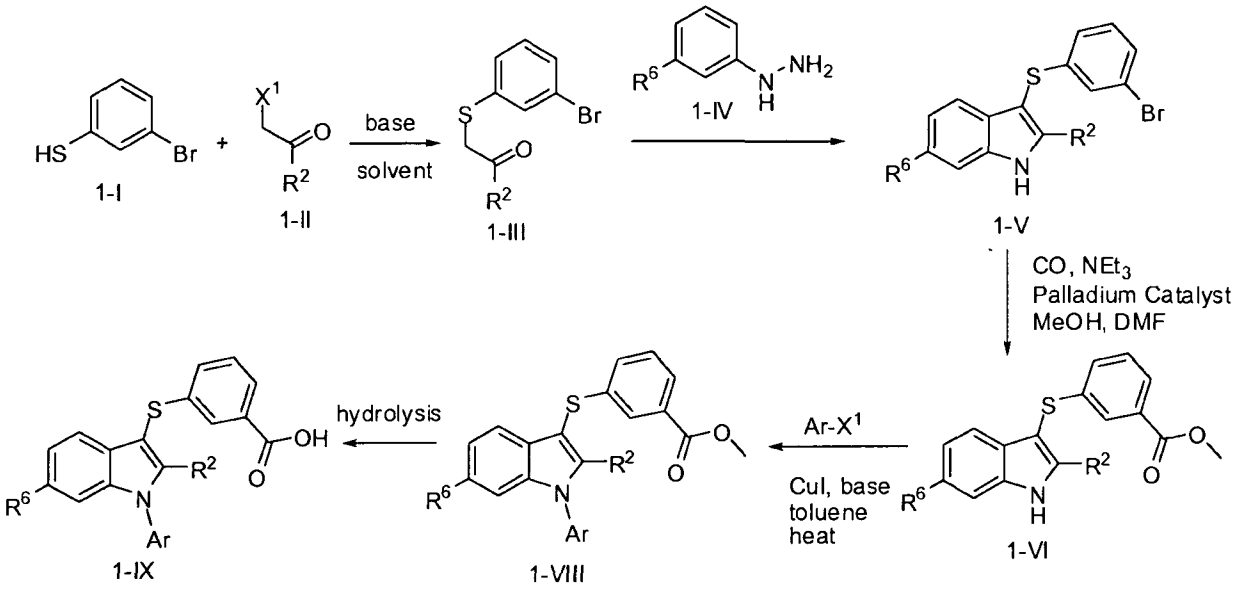
Synthesis of Compounds

[00214] Compounds of Formula (I) described herein are synthesized using standard synthetic techniques or using methods described herein (see, e.g. March, ADVANCED ORGANIC CHEMISTRY 4th Ed., (Wiley 1992); Carey and Sundberg, ADVANCED ORGANIC CHEMISTRY 4th Ed., Vols. A and B (Plenum 2000, 2001), and Green and Wuts, PROTECTIVE GROUPS IN ORGANIC SYNTHESIS 3rd Ed., (Wiley 1999)). General methods for the preparation of compounds can be modified by the use of appropriate reagents and conditions for the introduction of the various moieties found in the formulae as provided herein. In additions, solvents, temperatures and other reaction conditions presented herein may vary.

[00215] The starting material used for the synthesis of the compounds of Formula (I) are either synthesized or obtained from commercial sources, such as, but not limited to, Sigma-Aldrich, Fluka, Acros Organics, Alfa Aesar, and the like. General methods for the preparation of compounds can be modified by the use of appropriate reagents and conditions for the introduction of the various moieties found in the formulae as provided herein.

[00216] In some embodiments, compounds described herein are prepared according to Scheme 1.

Scheme 1.



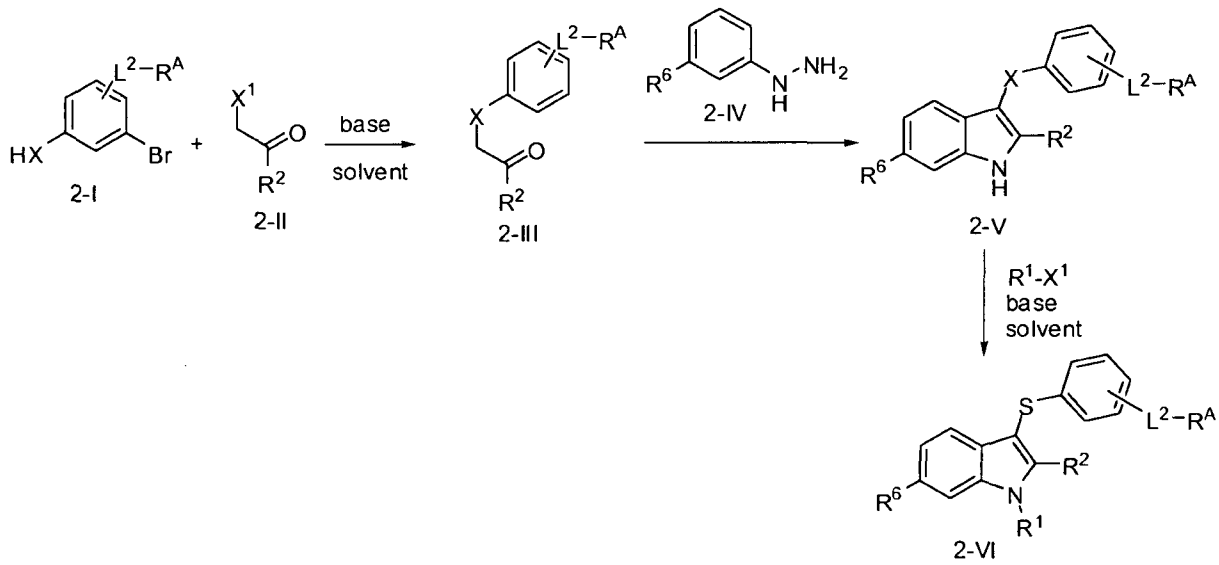
[00217] In some embodiments, the synthesis of compounds of Formula (I) described herein begins with the reaction of an aromatic thiol 1-I with an alpha-halo ketone (e.g. 1-II where X^1 = Br or Cl) to provide a compound of structure 1-III. Fischer indole synthesis is carried out with compounds of structure 1-III and substituted phenyl hydrazines of structure 1-IV to provide indole of structure 1-V. Treatment of indole of structure 1-V with carbon monoxide in the presence of a base such as triethylamine, methanol and palladium (II) catalyst provides esters of structure 1-VI. In some embodiments, the palladium catlayst is $PdCl_2(dppf)$. A copper mediated cross-coupling reaction of compounds 1-VI with aryl halides ArX^1 (where X^1 is Br or I) provides N-arylated indoles of structure 1-VIII. Hydrolysis of the ester group of indoles of structure 1-VIII provides the Formula (I) compound as the carboxylic acids of structure 1-IX.

[00218] Replacement of the aryl iodide 1-VII with a heteroaryl halide allows for the preparation of compounds of Formula (I) that contain an indole N-heteroaryl substituent.

[00219] Additional non-limiting examples of synthetic strategies toward the synthesis of indole compounds of Formula (I), include modifications to various syntheses of indoles, including, but not limited to: Batcho-Leimgruber Indole Synthesis, Reissert Indole Synthesis, Hegedus Indole Synthesis, Fukuyama Indole Synthesis, Sugasawa Indole Synthesis, Bischler Indole Synthesis, Gassman Indole Synthesis, Fischer Indole Synthesis, Japp-Klingemann Indole Synthesis, Buchwald Indole Synthesis, Larock Indole Synthesis, Bartoli Indole Synthesis, Castro Indole Synthesis, Hemetsberger Indole Synthesis, Mori-Ban Indole Synthesis, Madelung Indole Synthesis, Nenitzescu Indole Synthesis, and other unnamed reactions.

[00220] In some embodiments, compounds described herein are prepared according to Scheme 2.

Scheme 2.

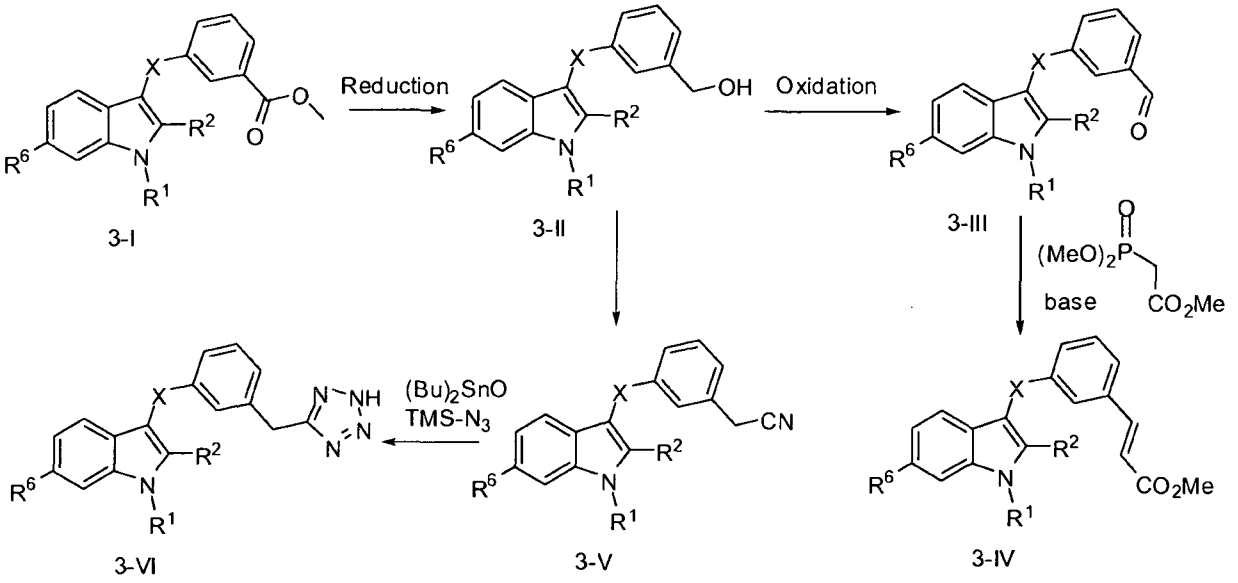


[00221] In some embodiments, the synthesis of compounds of Formula (I) described herein begins with the reaction of a compound of structure 2-I with an alpha-halo ketone (e.g. 2-II where X^1 is a leaving group such as Br or I) to provide a compound of structure 2-III. In some embodiments, X = S or O. Compounds of structure 2-III are reacted with a substituted aromatic hydrazine of structure 2-IV to provide compounds of structure 2-V via the Fischer indole synthesis. Treatment of indoles of structure 2-V with a base followed by R^1-X^1 provides compounds of Formula (I). In some embodiments, R^1 is a susbtituted or unsubtituted alkyl. In some embodiments, R^1 is a substituted or unsubstituted benzyl. In some embodiments, X^1 is a leaving group. In some embodiments, X^1 is Br or I.

[00222] In the case where R^A is an alkyl ester, hydrolysis of the ester group of indoles of structure 2-VI provides compounds of Formula (I) where R^A is a carboxylic acid.

[00223] In some embodiments, compounds described herein are prepared according to Scheme 3.

Scheme 3.



[00224] In some embodiments, the synthesis of compounds of Formula (I) begins with the reaction of indoles of structure 3-I. Compounds 3-I are reduced to the corresponding benzyl alcohols of structure 3-II upon treatment with diisobutylaluminum hydride. In some embodiments, benzyl alcohols of structure 3-II are then oxidized to provide aldehydes of structure 3-III. In some embodiments, suitable oxidizing agents include, but are not limited to tetrapropylammonium perruthenate and Dess-Martin periodinane. Compounds of structure 3-III are transformed to alkenes of structure 3-IV utilizing Horner-Wadsworth-Emmons reaction conditions. In some embodiements, benzyl alcohols of structure 3-II are treated with methanesulfonyl chloride and a base such as Hunig's base to produce the corresponding mesylate which is treated with sodium cyanide in a suitable solvent to produce compounds of structure 3-V. In some embodiments, compounds of structure 3-V are reacted with trimethylsilyl azide in a tin-catalyzed cyclization reaction to afford the tetrazoles 3-VI.

[00225] A detailed description of techniques applicable to the creation of protecting groups and their removal are described in Greene and Wuts, Protective Groups in Organic Synthesis, 3rd Ed., John Wiley & Sons, New York, NY, 1999, and Kocienski, Protective Groups, Thieme Verlag, New York, NY, 1994, which are incorporated herein by reference for such disclosure.

[00226] In one aspect, compounds of Formula (I) are synthesized as outlined in the Examples section.

Further Forms of Compounds

[00227] In one aspect, compounds of Formula (I) may possess one or more stereocenters and each stereocenter exists independently in either the R or S configuration. The compounds presented herein include all diastereomeric, enantiomeric, and epimeric forms as well as the appropriate mixtures thereof. The compounds and methods provided herein include all cis, trans, syn, anti, entgegen (E), and zusammen (Z) isomers as well as the appropriate mixtures thereof. In certain embodiments, compounds of Formula (I) are prepared as their individual stereoisomers by reacting a racemic mixture of the compound with an optically active resolving agent to form a pair of diastereoisomeric

compounds/salts, separating the diastereomers and recovering the optically pure enantiomers. In some embodiments, resolution of enantiomers is carried out using covalent diastereomeric derivatives of the compounds described herein. In another embodiment, diastereomers are seprated by separation/resolution techniques based upon differences in solubility. In other embodiments, separation of steroisomers is performed by chromatography or by the forming diastereomeric salts and separation by recrystallization, or chromatography, or any combination thereof. Jean Jacques, Andre Collet, Samuel H. Wilen, "Enantiomers, Racemates and Resolutions", John Wiley And Sons, Inc., 1981. In one aspect, stereoisomers are obtained by stereoselective synthesis.

[00228] The methods and compositions described herein include the use of amorphous forms as well as crystalline forms (also known as polymorphs). In one aspect, compounds described herein are in the form of pharmaceutically acceptable salts. As well, active metabolites of these compounds having the same type of activity are included in the scope of the present disclosure. In addition, the compounds described herein can exist in unsolvated as well as solvated forms with pharmaceutically acceptable solvents such as water, ethanol, and the like. The solvated forms of the compounds presented herein are also considered to be disclosed herein.

[00229] In some embodiments, compounds described herein are prepared as prodrugs. A "prodrug" refers to an agent that is converted into the parent drug *in vivo*. Prodrugs are often useful because, in some situations, they may be easier to administer than the parent drug. They may, for instance, be bioavailable by oral administration whereas the parent is not. The prodrug may also have improved solubility in pharmaceutical compositions over the parent drug. In some embodiments, the design of a prodrug increases the effective water solubility. An example, without limitation, of a prodrug is a compound described herein, which is administered as an ester (the "prodrug") to facilitate transmittal across a cell membrane where water solubility is detrimental to mobility but which then is metabolically hydrolyzed to the carboxylic acid, the active entity, once inside the cell where water-solubility is beneficial. A further example of a prodrug might be a short peptide (polyaminoacid) bonded to an acid group where the peptide is metabolized to reveal the active moiety. In certain embodiments, upon *in vivo* administration, a prodrug is chemically converted to the biologically, pharmaceutically or therapeutically active form of the compound. In certain embodiments, a prodrug is enzymatically metabolized by one or more steps or processes to the biologically, pharmaceutically or therapeutically active form of the compound.

[00230] In one aspect, prodrugs are designed to alter the metabolic stability or the transport characteristics of a drug, to mask side effects or toxicity, to improve the flavor of a drug or to alter other characteristics or properties of a drug. By virtue of knowledge of pharmacokinetic, pharmacodynamic processes and drug metabolism *in vivo*, once a pharmaceutically active compound is known, the design of prodrugs of the compound is possible. (see, for example, Nogrady (1985) *Medicinal Chemistry A Biochemical Approach*, Oxford University Press, New York, pages 388-392; Silverman (1992), The Organic Chemistry of Drug Design and Drug Action, Academic Press, Inc.,

San Diego, pages 352-401, Rooseboom *et al.*, *Pharmacological Reviews*, 56:53–102, 2004; Aesop Cho, "Recent Advances in Oral Prodrug Discovery", *Annual Reports in Medicinal Chemistry*, Vol. 41, 395-407, 2006; T. Higuchi and V. Stella, *Pro-drugs as Novel Delivery Systems*, Vol. 14 of the A.C.S. Symposium Series).

[00231] Prodrug forms of the herein described compounds, wherein the prodrug is metabolized *in vivo* to produce a compound of Formula (I) as set forth herein, are included within the scope of the claims. In some cases, some of the herein-described compounds may be a prodrug for another derivative or active compound.

[00232] In some embodiments, sites on the aromatic ring portion of compounds of Formula (I) are susceptible to various metabolic reactions Therefore incorporation of appropriate substituents on the aromatic ring structures will reduce, minimize or eliminate this metabolic pathway. In specific embodiments, the appropriate substituent to decrease or eliminate the susceptibility of the aromatic ring to metabolic reactions is, by way of example only, a halogen, or an alkyl group.

[00233] In another embodiment, the compounds described herein are labeled isotopically (e.g. with a radioisotope) or by another other means, including, but not limited to, the use of chromophores or fluorescent moieties, bioluminescent labels, or chemiluminescent labels.

[00234] Compounds described herein include isotopically-labeled compounds, which are identical to those recited in the various formulae and structures presented herein, but for the fact that one or more atoms are replaced by an atom having an atomic mass or mass number different from the atomic mass or mass number usually found in nature. Examples of isotopes that can be incorporated into the present compounds include isotopes of hydrogen, carbon, nitrogen, oxygen, fluorine and chlorine, such as, for example, ^{2}H, ^{3}H, ^{13}C, ^{14}C, ^{15}N, ^{18}O, ^{17}O, ^{35}S, ^{18}F, ^{36}Cl. In one aspect, isotopically-labeled compounds described herein, for example those into which radioactive isotopes such as ^{3}H and ^{14}C are incorporated, are useful in drug and/or substrate tissue distribution assays. In one aspect, substitution with isotopes such as deuterium affords certain therapeutic advantages resulting from greater metabolic stability, such as, for example, increased *in vivo* half-life or reduced dosage requirements.

[00235] In additional or further embodiments, the compounds described herein are metabolized upon administration to an organism in need to produce a metabolite that is then used to produce a desired effect, including a desired therapeutic effect.

[00236] Compounds described herein may be formed as, and/or used as, pharmaceutically acceptable salts. The type of pharmaceutical acceptable salts, include, but are not limited to: (1) acid addition salts, formed by reacting the free base form of the compound with a pharmaceutically acceptable: inorganic acid, such as, for example, hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid, metaphosphoric acid, and the like; or with an organic acid, such as, for example, acetic acid, propionic acid, hexanoic acid, cyclopentanepropionic acid, glycolic acid, pyruvic acid, lactic acid, malonic acid, succinic acid, malic acid, maleic acid, fumaric acid, trifluoroacetic acid, tartaric acid,

citric acid, benzoic acid, 3-(4-hydroxybenzoyl)benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, 1,2-ethanedisulfonic acid, 2-hydroxyethanesulfonic acid, benzenesulfonic acid, toluenesulfonic acid, 2-naphthalenesulfonic acid, 4-methylbicyclo-[2.2.2]oct-2-ene-1-carboxylic acid, glucoheptonic acid, 4,4'-methylenebis-(3-hydroxy-2-ene-1-carboxylic acid), 3-phenylpropionic acid, trimethylacetic acid, tertiary butylacetic acid, lauryl sulfuric acid, gluconic acid, glutamic acid, hydroxynaphthoic acid, salicylic acid, stearic acid, muconic acid, butyric acid, phenylacetic acid, phenylbutyric acid, valproic acid, and the like; (2) salts formed when an acidic proton present in the parent compound is replaced by a metal ion, e.g., an alkali metal ion (e.g. lithium, sodium, potassium), an alkaline earth ion (e.g. magnesium, or calcium), or an aluminum ion. In some embodiments, where the compound of Formula (I) has an acidic proton, a sodium salt of the compound of Formula (I) is formed. In some cases, compounds described herein may coordinate with an organic base to form a salt, such as, but not limited to, ethanolamine salt, diethanolamine salt, choline salt, triethanolamine salt, tromethamine salt, N-methylglucamine salt, dicyclohexylamine salt, or tris(hydroxymethyl)methylamine salt. In other cases, compounds described herein may form salts with amino acids such as, but not limited to, arginine, lysine, and the like. Acceptable inorganic bases used to form salts with compounds that include an acidic proton, include, but are not limited to, aluminum hydroxide, calcium hydroxide, potassium hydroxide, sodium carbonate, sodium hydroxide, and the like.

[00237] In one aspect, a pharmaceutically acceptable salt of a compound of Formula (I) includes a pharmaceutically acceptable salt of a compound described in Table 1, Table 2, Table 3 or Table 4.

[00238] It should be understood that a reference to a pharmaceutically acceptable salt includes the solvent addition forms or crystal forms thereof, particularly solvates or polymorphs. Solvates contain either stoichiometric or non-stoichiometric amounts of a solvent, and may be formed during the process of crystallization with pharmaceutically acceptable solvents such as water, ethanol, and the like. Hydrates are formed when the solvent is water, or alcoholates are formed when the solvent is alcohol. Solvates of compounds described herein can be conveniently prepared or formed during the processes described herein. In addition, the compounds provided herein can exist in unsolvated as well as solvated forms. In general, the solvated forms are considered equivalent to the unsolvated forms for the purposes of the compounds and methods provided herein.

[00239] Compounds described herein, such as compounds of Formula (I), may be in various forms, including but not limited to, amorphous forms, milled forms and nano-particulate forms. In addition, compounds described herein include crystalline forms, also known as polymorphs. Polymorphs include the different crystal packing arrangements of the same elemental composition of a compound. Polymorphs usually have different X-ray diffraction patterns, melting points, density, hardness, crystal shape, optical properties, stability, and solubility. Various factors such as the recrystallization solvent, rate of crystallization, and storage temperature may cause a single crystal form to dominate.

Certain Terminology

[00240] Unless otherwise stated, the following terms used in this application, including the specification and claims, have the definitions given below. It must be noted that, as used in the specification and the appended claims, the singular forms "a," "an" and "the" include plural referents unless the context clearly dictates otherwise. Unless otherwise indicated, conventional methods of mass spectroscopy, NMR, HPLC, protein chemistry, biochemistry, recombinant DNA techniques and pharmacology are employed. In this application, the use of "or" or "and" means "and/or" unless stated otherwise. Furthermore, use of the term "including" as well as other forms, such as "include", "includes," and "included," is not limiting. The section headings used herein are for organizational purposes only and are not to be construed as limiting the subject matter described.

[00241] An "alkyl" group refers to an aliphatic hydrocarbon group. The alkyl group may be a saturated alkyl group (which means that it does not contain any carbon-carbon double bonds or carbon-carbon triple bonds) or the the alkyl group may be an unsaturated alkyl group (which means that it contains at least one carbon-carbon double bonds or carbon-carbon triple bond). The alkyl moiety, whether saturated or unsaturated, may be branched or straight chain.

[00242] The "alkyl" group may have 1 to 10 carbon atoms (whenever it appears herein, a numerical range such as "1 to 10" refers to each integer in the given range; *e.g.*, "1 to 10 carbon atoms" means that the alkyl group may consist of 1 carbon atom, 2 carbon atoms, 3 carbon atoms, *etc.*, up to and including 10 carbon atoms, although the present definition also covers the occurrence of the term "alkyl" where no numerical range is designated). The alkyl group of the compounds described herein may be designated as "C_1-C_6 alkyl" or similar designations. By way of example only, "C_1-C_6 alkyl" indicates that there are one, two, three, four, five, or six carbon atoms in the alkyl chain. In one aspect the alkyl is selected from the group consisting of methyl, ethyl, propyl, iso-propyl, n-butyl, iso-butyl, sec-butyl, and t-butyl. Typical alkyl groups include, but are in no way limited to, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tertiary butyl, pentyl, neopentyl, hexyl, allyl, but-2-enyl, but-3-enyl, and the like. In one aspect, an alkyl is a C_1-C_6alkyl.

[00243] The term "alkylene" refers to a divalent alkyl radical. Any of the above mentioned monovalent alkyl groups may be an alkylene by abstraction of a second hydrogen atom from the alkyl. In one aspect, an alkelene is a C_1-C_6alkylene. In another apsect, an alkylene is a C_1-C_4alkylene. Typical alkylene groups include, but are not limited to, $-CH_2-$, $-CH(CH_3)-$, $-C(CH_3)_2-$, $-CH_2CH_2-$, $-CH_2CH(CH_3)-$, $-CH_2C(CH_3)_2-$, $-CH_2CH_2CH_2-$, $-CH_2CH_2CH_2CH_2-$, and the like.

[00244] An "alkoxy" group refers to a (alkyl)O- group, where alkyl is as defined herein.

[00245] The term "alkylamine" refers to the $-N(alkyl)_xH_y$ group, where x and y are selected from the group x=1, y=1 and x=2, y=0. In some embodiments, when x=2 and y=0, the alkyl groups taken together with the ntrogen atom to which they are attached form a cyclic ring system.

[00246] The term "aromatic" refers to a planar ring having a delocalized π-electron system containing 4n+2 π electrons, where n is an integer. Aromatic rings can be formed from five, six, seven, eight, nine, ten, or more than ten atoms. Aromatics are optionally substituted. The term "aromatic" includes

both carbocyclic aryl ("aryl", *e.g.*, phenyl) and heterocyclic aryl (or "heteroaryl" or "heteroaromatic") groups (*e.g.*, pyridine). The term includes monocyclic or fused-ring polycyclic (*i.e.*, rings which share adjacent pairs of carbon atoms) groups.

[00247] The term "carbocyclic" or "carbocycle" refers to a ring or ring system where the atoms forming the backbone of the ring are all carbon atoms. The term thus distinguishes carbocyclic from heterocyclic rings in which the ring backbone contains at least one atom which is different from carbon.

[00248] As used herein, the term "aryl" refers to an aromatic ring wherein each of the atoms forming the ring is a carbon atom. Aryl groups are optionally substituted. In one aspect, an aryl is a phenyl or a naphthalenyl. In one aspect, an aryl is a phenyl. In one aspect, an aryl is a C_6-C_{10}aryl. Depending on the structure, an aryl group can be a monoradical or a diradical (i.e., an arylene group). Examplary arylenes include, but are not limited to, phenyl-1,2-ene, phenyl-1,3-ene, and phenyl-1,4-ene.

[00249] The term "cycloalkyl" refers to a monocyclic or polycyclic aliphatic, non-aromatic radical, wherein each of the atoms forming the ring (i.e. skeletal atoms) is a carbon atom. Cycloalkyls may be saturated, or partially unsaturated. Cycloalkyls may be fused with an aromatic ring, and the point of attachment is at a carbon that is not an aromatic ring carbon atom. Cycloalkyl groups include groups having from 3 to 10 ring atoms. In some embodiments, cycloalkyl groups are selected from among cyclopropyl, cyclobutyl, cyclopentyl, cyclopentenyl, cyclohexyl, cyclohexenyl, cycloheptyl, and cyclooctyl. Cycloalkyl groups may be substituted or unsubstituted. Depending on the structure, a cycloalkyl group can be a monoradical or a diradical (i.e., an cycloalkylene group, such as, but not limited to, cyclopropan-1,1-diyl, cyclobutan-1,1-diyl, cyclopentan-1,1-diyl, cyclohexan-1,1-diyl, cyclohexan-1,4-diyl, cycloheptan-1,1-diyl, and the like). In one aspect, a cycloalkyl is a C_3-C_6cycloalkyl.

[00250] The term "halo" or, alternatively, "halogen" or "halide" means fluoro, chloro, bromo or iodo.

[00251] The term "haloalkyl" refers to an alkyl group in which one or more hydrogen atoms are replaced by one or more halide atoms. In one aspect, a haloalkyl is a C_1-C_4haloalkyl.

[00252] The term "haloalkylene" refers to an alkylene group in which one or more hydrogen atoms are replaced by one or more halide atoms. In one aspect, a haloalkylene is a C_1-C_6haloalkylene. In another aspect, a haloalkylene is a C_1-C_4haloalkylene.

[00253] The term "fluoroalkyl" refers to an alkyl in which one or more hydrogen atoms are replaced by a fluorine atom. In one aspect, a fluoralkyl is a C_1-C_4fluoroalkyl.

[00254] The term "fluoroalkylene" refers to an alkylene in which one or more hydrogen atoms are replaced by a fluorine atom. In one aspect, a fluoralkylene is a C_1-C_6fluoroalkylene. In another aspect, a fluoralkylene is a C_1-C_4fluoroalkylene.

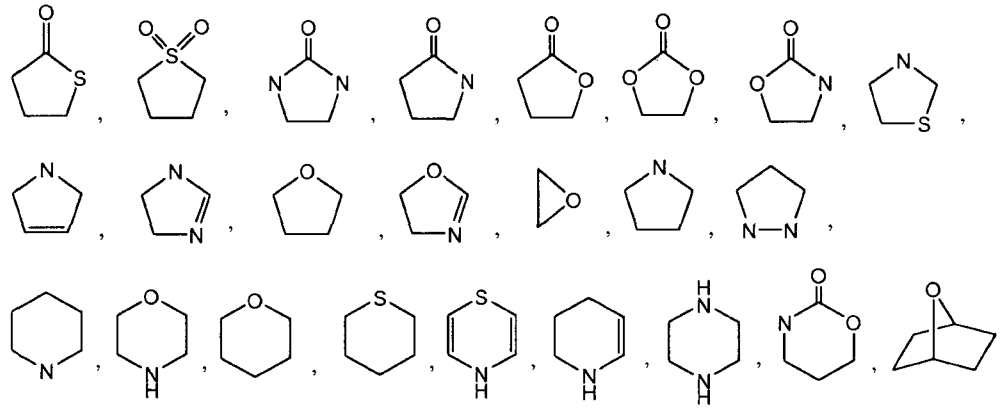
[00255] The term "heteroalkyl" refers to an alkyl group in which one or more skeletal atoms of the alkyl are selected from an atom other than carbon, *e.g.*, oxygen, nitrogen, sulfur, phosphorus or combinations thereof. In one aspect, a heteroalkyl is a C_1-C_6heteroalkyl.

[00256] The term "heterocycle" or "heterocyclic" refers to heteroaromatic rings (also known as heteroaryls) and heterocycloalkyl rings (also known as heteroalicyclic groups) containing one to four heteroatoms in the ring(s), where each heteroatom in the ring(s) is selected from O, S and N, wherein each heterocyclic group has from 4 to 10 atoms in its ring system, and with the proviso that the any ring does not contain two adjacent O or S atoms. Non-aromatic heterocyclic groups (also known as heterocycloalkyls) include groups having only 3 atoms in their ring system, but aromatic heterocyclic groups must have at least 5 atoms in their ring system. The heterocyclic groups include benzo-fused ring systems. An example of a 3-membered heterocyclic group is aziridinyl. An example of a 4-membered heterocyclic group is azetidinyl. An example of a 5-membered heterocyclic group is thiazolyl. An example of a 6-membered heterocyclic group is pyridyl, and an example of a 10-membered heterocyclic group is quinolinyl. Examples of non-aromatic heterocyclic groups are pyrrolidinyl, tetrahydrofuranyl, dihydrofuranyl, tetrahydrothienyl, oxazolidinonyl, tetrahydropyranyl, dihydropyranyl, tetrahydrothiopyranyl, piperidinyl, morpholinyl, thiomorpholinyl, thioxanyl, piperazinyl, aziridinyl, azetidinyl, oxetanyl, thietanyl, homopiperidinyl, oxepanyl, thiepanyl, oxazepinyl, diazepinyl, thiazepinyl, 1,2,3,6-tetrahydropyridinyl, pyrrolin-2-yl, pyrrolin-3-yl, indolinyl, 2H-pyranyl, 4H-pyranyl, dioxanyl, 1,3-dioxolanyl, pyrazolinyl, dithianyl, dithiolanyl, dihydropyranyl, dihydrothienyl, dihydrofuranyl, pyrazolidinyl, imidazolinyl, imidazolidinyl, 3-azabicyclo[3.1.0]hexanyl, 3-azabicyclo[4.1.0]heptanyl, 3H-indolyl and quinolizinyl. Examples of aromatic heterocyclic groups are pyridinyl, imidazolyl, pyrimidinyl, pyrazolyl, triazolyl, pyrazinyl, tetrazolyl, furyl, thienyl, isoxazolyl, thiazolyl, oxazolyl, isothiazolyl, pyrrolyl, quinolinyl, isoquinolinyl, indolyl, benzimidazolyl, benzofuranyl, cinnolinyl, indazolyl, indolizinyl, phthalazinyl, pyridazinyl, triazinyl, isoindolyl, pteridinyl, purinyl, oxadiazolyl, thiadiazolyl, furazanyl, benzofurazanyl, benzothiophenyl, benzothiazolyl, benzoxazolyl, quinazolinyl, quinoxalinyl, naphthyridinyl, and furopyridinyl. The foregoing groups may be C-attached or *N*-attached where such is possible. For instance, a group derived from pyrrole may be pyrrol-1-yl (*N*-attached) or pyrrol-3-yl (C-attached). Further, a group derived from imidazole may be imidazol-1-yl or imidazol-3-yl (both *N*-attached) or imidazol-2-yl, imidazol-4-yl or imidazol-5-yl (all C-attached). The heterocyclic groups include benzo-fused ring systems. Non-aromatic heterocycles may be substituted with one or two oxo (=O) moieties, such as pyrrolidin-2-one.

[00257] The terms "heteroaryl" or, alternatively, "heteroaromatic" refers to an aryl group that includes one or more ring heteroatoms selected from nitrogen, oxygen and sulfur. Non-limiting examples of heteroaryls include, pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, triazinyl, imidazolyl, pyrazolyl, triazolyl, tetrazolyl, furanyl, thienyl, isoxazolyl, thiazolyl, oxazolyl, isothiazolyl, pyrrolyl, oxadiazolyl, thiadiazolyl, quinolinyl, isoquinolinyl, indolyl, isoindolyl, benzimidazolyl, benzofuranyl, cinnolinyl, indazolyl, indolizinyl, phthalazinyl, pteridinyl, purinyl, oxadiazolyl, thiadiazolyl, furazanyl, benzofurazanyl, benzothiophenyl, benzothiazolyl, benzoxazolyl, quinazolinyl, quinoxalinyl, naphthyridinyl, and furopyridinyl. Monocyclic heteroaryls include pyridinyl,

imidazolyl, pyrimidinyl, pyrazolyl, triazolyl, pyrazinyl, tetrazolyl, furyl, thienyl, isoxazolyl, thiazolyl, oxazolyl, isothiazolyl, pyrrolyl, pyridazinyl, triazinyl, oxadiazolyl, thiadiazolyl, and furazanyl. In one aspect, a heteroaryl contains 0-3 N atoms. In another aspect, a heteroaryl contains 1-3 N atoms. In another aspect, a heteroaryl contains 0-3 N atoms, 0-1 O atoms, and 0-1 S atoms. In another aspect, a heteroaryl is a monocyclic or bicyclic heteroaryl. In one aspect, heteroaryl is a C_1-C_9heteroaryl. In one aspect, monocyclic heteroaryl is a C_1-C_5heteroaryl. In one aspect, monocyclic heteroaryl is a 5-membered or 6-membered heteroaryl. In one aspect, bicyclic heteroaryl is a C_6-C_9heteroaryl. Depending on the structure, a heteroaryl group can be a monoradical or a diradical (i.e., a heteroarylene group). In some embodiments, heteraryls are C-attached.

[00258] A "heterocycloalkyl" or "heteroalicyclic" group refers to a cycloalkyl group that includes at least one heteroatom selected from nitrogen, oxygen and sulfur. The radicals may be fused with an aryl or heteroaryl. Illustrative examples of heterocycloalkyl groups, also referred to as non-aromatic heterocycles, include:



and the like. In some embodiments, the heterocycloalkyl is selected from oxazolidinonyl, pyrrolidinyl, tetrahydrofuranyl, tetrahydrothienyl, tetrahydropyranyl, tetrahydrothiopyranyl, piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl, and indolinyl. The term heteroalicyclic also includes all ring forms of the carbohydrates, including but not limited to the monosaccharides, the disaccharides and the oligosaccharides. In one aspect, a heterocycloalkyl is a C_2-C_{10}heterocycloalkyl. In another aspect, a heterocycloalkyl is a C_4-C_{10}heterocycloalkyl. In one aspect, a heterocycloalkyl contains 0-2 N atoms. In another aspect, a heterocycloalkyl contains 0-2 N atoms, 0-2 O atoms or 0-1 S atoms. In some embodiments, heterocycloalkyls are C-attached. In some embodiments, heterocycloalkyls that include at least 1 N atom in the ring are N-attached.

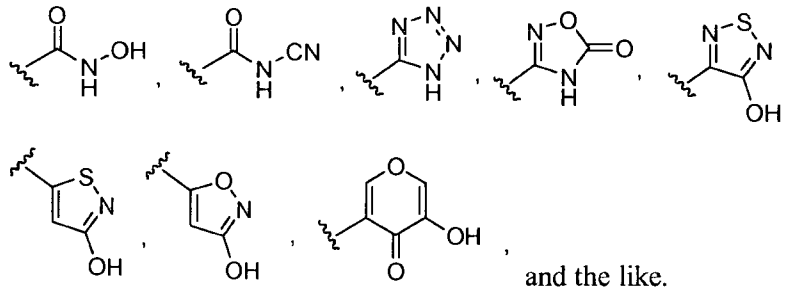
[00259] The term "bond" or "single bond" refers to a chemical bond between two atoms, or two moieties when the atoms joined by the bond are considered to be part of larger substructure. In one aspect, when a group described herein is a bond, the referenced group is absent thereby allowing a bond to be formed between the remaining identified groups.

[00260] The term "membered ring" includes any cyclic structure. The term "membered" is meant to denote the number of skeletal atoms that constitute the ring. Thus, for example, cyclohexyl, pyridinyl,

pyranyl and thiopyranyl are 6-membered rings and cyclopentyl, pyrrolyl, furanyl, and thienyl are 5-membered rings.

[00261] The term "moiety" refers to a specific segment or functional group of a molecule. Chemical moieties are often recognized chemical entities embedded in or appended to a molecule.

[00262] As used herein, "carboxylic acid bioisostere" refers to a functional group or moiety that exhibits similar physical, biological and/or chemical properties as a carboxylic acid moiety. Examples of carboxylic acid bioisosteres include, but are not limited to,



and the like.

[00263] The term "optionally substituted" or "substituted" means that the referenced group may be substituted with one or more additional group(s) individually and independently selected from alkyl, cycloalkyl, aryl, heteroaryl, heteroalicyclic, hydroxy, alkoxy, aryloxy, alkylthio, arylthio, alkylsulfoxide, arylsulfoxide, alkylsulfone, arylsulfone, cyano, halo, nitro, haloalkyl, fluoroalkyl, fluoroalkoxy, alkylamine and amino, including mono- and di-substituted amino groups, and the protected derivatives thereof. By way of example an optional substituents may be halide, -CN, $-NO_2$, or L_sR_s, wherein L_s is independently selected from a bond, -O-, -C(=O)-, -C(=O)O-, -S-, -S(=O)-, $-S(=O)_2-$, -NH-, -NHC(=O)-, -C(=O)NH-, $S(=O)_2NH-$, $-NHS(=O)_2$, -OC(=O)NH-, -NHC(=O)O-, or -(C_1-C_6 alkylene)-; and each R_s is selected from H, alkyl, fluoroalkyl, heteroalkyl, cycloalkyl, aryl, heteroaryl, or heterocycloalkyl. In some embodiments, optional substituents are selected from halogen, -CN, $-NH_2$, -OH, $-N(CH_3)_2$, alkyl, fluoroalkyl, heteroalkyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, alkoxy, aryloxy, alkylthio, arylthio, alkylsulfoxide, arylsulfoxide, alkylsulfone, and arylsulfone. In some embodiments, an optional substituent is halogen, -CN, $-NH_2$, -OH, $-NH(CH_3)$, $-N(CH_3)_2$, $-CO_2H$, $-CO_2$alkyl, $-C(=O)NH_2$, -C(=O)NHalkyl, $-C(=O)N(alkyl)_2$, $-S(=O)_2NH_2$, $-S(=O)_2NH(alkyl)$, $-S(=O)_2N(alkyl)_2$, alkyl, cycloalkyl, fluoroalkyl, heteroalkyl, alkoxy, fluoroalkoxy, -S-alkyl, or $-S(=O)_2$alkyl. In some embodiments, an optional substituent is halogen, -CN, $-NH_2$, -OH, $-NH(CH_3)$, $-N(CH_3)_2$, $-CH_3$, $-CH_2CH_3$, $-CF_3$, $-OCH_3$, $-OCH_2CH_3$, or $-OCF_3$. In some embodiments, an optional substituent is halogen, -CN, -OH, C_1-C_4alkyl, C_1-C_4alkoxy, -S-C_1-C_4alkyl, C_1-C_4fluoroalkyl, C_1-C_4fluoroalkoxy, and C_1-C_4heteroalkyl. In some embodiments, substituted groups are substituted with at least one of the preceding optional substitutents. In some embodiments, substituted groups are substituted with one or two of the preceding optional substitutents. In some embodiments, substituted groups are substituted with one of the preceding optional substitutents. In some embodiments, an optional substituent on an aliphatic carbon atom (acyclic or cyclic, saturated or unsaturated carbon atoms, excluding aromatic carbon atoms) includes oxo (=O).

[00264] In certain embodiments, the compounds presented herein possess one or more stereocenters and each center independently exists in either the R or S configuration. The compounds presented herein include all diastereomeric, enantiomeric, and epimeric forms as well as the appropriate mixtures thereof. Stereoisomers are obtained, if desired, by methods such as, stereoselective synthesis and/or the separation of stereoisomers by chiral chromatographic columns.

[00265] The methods and formulations described herein include the use of *N*-oxides (if appropriate), crystalline forms (also known as polymorphs), or pharmaceutically acceptable salts of compounds having the structure of Formula (I) as well as active metabolites of these compounds having the same type of activity. In some situations, compounds may exist as tautomers. All tautomers are included within the scope of the compounds presented herein. In specific embodiments, the compounds described herein exist in solvated forms with pharmaceutically acceptable solvents such as water, ethanol, and the like. In other embodiments, the compounds described herein exist in unsolvated form.

[00266] The term "acceptable" with respect to a formulation, composition or ingredient, as used herein, means having no persistent detrimental effect on the general health of the subject being treated.

[00267] "Pharmaceutically acceptable," as used herein, refers a material, such as a carrier or diluent, which does not abrogate the biological activity or properties of the compound, and is relatively nontoxic, i.e., the material may be administered to an individual without causing undesirable biological effects or interacting in a deleterious manner with any of the components of the composition in which it is contained.

[00268] The term "pharmaceutically acceptable salt" refers to a formulation of a compound that does not cause significant irritation to an organism to which it is administered and does not abrogate the biological activity and properties of the compound. In some embodiments, pharmaceutically acceptable salts are obtained by reacting a compound of Formula (I) with acids. Pharmaceutically acceptable salts are also obtained by reacting a compound of Formula (I) with a base to form a salt.

[00269] The term "modulate," as used herein, means to interact with a target either directly or indirectly so as to alter the activity of the target, including, by way of example only, to enhance the activity of the target, to inhibit the activity of the target, to limit the activity of the target, or to extend the activity of the target.

[00270] The term "modulator," as used herein, refers to a molecule that interacts with a target either directly or indirectly. The interactions include, but are not limited to, the interactions of an agonist, partial agonist, an inverse agonist and antagonist. In one embodiment, a modulator is an antagonist.

[00271] The term "agonist," as used herein, refers to a molecule such as a compound, a drug, an enzyme activator or a hormone modulator that binds to a specific receptor and triggers a response in the cell. An agonist mimics the action of an endogenous ligand (such as LPA, prostaglandin, hormone or neurotransmitter) that binds to the same receptor.

[00272] The term "antagonist," as used herein, refers to a molecule such as a compound, which diminishes, inhibits, or prevents the action of another molecule or the activity of a receptor site. Antagonists include, but are not limited to, competitive antagonists, non-competitive antagonists, uncompetitive antagonists, partial agonists and inverse agonists.

[00273] The term "ATX-dependent", as used herein, refers to conditions or disorders that would not occur, or would not occur to the same extent, in the absence of ATX.

[00274] The term "ATX-mediated", as used herein, refers to conditions or disorders that might occur in the absence of ATX but can occur in the presence of ATX.

[00275] The term "LPA-dependent", as used herein, refers to conditions or disorders that would not occur, or would not occur to the same extent, in the absence of LPA.

[00276] The term "LPA-mediated", as used herein, refers to conditions or disorders that might occur in the absence of LPA but can occur in the presence of LPA.

[00277] The terms "co-administration" or the like, as used herein, are meant to encompass administration of the selected therapeutic agents to a single patient, and are intended to include treatment regimens in which the agents are administered by the same or different route of administration or at the same or different time.

[00278] The terms "effective amount" or "therapeutically effective amount," as used herein, refer to a sufficient amount of an agent or a compound being administered which will relieve to some extent one or more of the symptoms of the disease or condition being treated. The result can be reduction and/or alleviation of the signs, symptoms, or causes of a disease, or any other desired alteration of a biological system. For example, an "effective amount" for therapeutic uses is the amount of the composition comprising a compound as disclosed herein required to provide a clinically significant decrease in disease symptoms. An appropriate "effective" amount in any individual case may be determined using techniques, such as a dose escalation study.

[00279] The terms "enhance" or "enhancing," as used herein, means to increase or prolong either in potency or duration a desired effect. Thus, in regard to enhancing the effect of therapeutic agents, the term "enhancing" refers to the ability to increase or prolong, either in potency or duration, the effect of other therapeutic agents on a system. An "enhancing-effective amount," as used herein, refers to an amount adequate to enhance the effect of another therapeutic agent in a desired system.

[00280] The terms "kit" and "article of manufacture" are used as synonyms.

[00281] A "metabolite" of a compound disclosed herein is a derivative of that compound that is formed when the compound is metabolized. The term "active metabolite" refers to a biologically active derivative of a compound that is formed when the compound is metabolized. The term "metabolized," as used herein, refers to the sum of the processes (including, but not limited to, hydrolysis reactions and reactions catalyzed by enzymes) by which a particular substance is changed by an organism. Thus, enzymes may produce specific structural alterations to a compound. For example, cytochrome P450 catalyzes a variety of oxidative and reductive reactions while uridine

diphosphate glucuronyltransferases catalyze the transfer of an activated glucuronic-acid molecule to aromatic alcohols, aliphatic alcohols, carboxylic acids, amines and free sulphydryl groups. In some embodiments, carboxylic acid containing compounds form taurine conjugates *in vivo*. Metabolites of the compounds disclosed herein are optionally identified either by administration of compounds to a host and analysis of tissue samples from the host, or by incubation of compounds with hepatic cells in vitro and analysis of the resulting compounds.

[00282] The term "pharmaceutical combination" as used herein, means a product that results from the mixing or combining of more than one active ingredient and includes both fixed and non-fixed combinations of the active ingredients. The term "fixed combination" means that the active ingredients, e.g. a compound of Formula (I), or a pharmaceutically acceptable salt thereof, and a co-agent, are both administered to a patient simultaneously in the form of a single entity or dosage. The term "non-fixed combination" means that the active ingredients, e.g. a compound of Formula (I), or a pharmaceutically acceptable salt thereof, and a co-agent, are administered to a patient as separate entities either simultaneously, concurrently or sequentially with no specific intervening time limits, wherein such administration provides effective levels of the two compounds in the body of the patient. The latter also applies to cocktail therapy, e.g. the administration of three or more active ingredients.

[00283] The term "subject" or "patient" encompasses mammals and non-mammals. Examples of mammals include, but are not limited to, any member of the Mammalian class: humans, non-human primates such as chimpanzees, and other apes and monkey species; farm animals such as cattle, horses, sheep, goats, swine; domestic animals such as rabbits, dogs, and cats; laboratory animals including rodents, such as rats, mice and guinea pigs, and the like. In one embodiment, the mammal is a human.

[00284] The terms "treat," "treating" or "treatment," as used herein, include alleviating, abating or ameliorating at least one symptom of a disease or condition, preventing additional symptoms, inhibiting the disease or condition, e.g., arresting the development of the disease or condition, relieving the disease or condition, causing regression of the disease or condition, relieving a condition caused by the disease or condition, or stopping the symptoms of the disease or condition either prophylactically and/or therapeutically.

Routes of Administration

[00285] Suitable routes of administration include, but are not limited to, oral, intravenous, rectal, aerosol, parenteral, ophthalmic, pulmonary, transmucosal, transdermal, vaginal, otic, nasal, and topical administration. In addition, by way of example only, parenteral delivery includes intramuscular, subcutaneous, intravenous, intramedullary injections, as well as intrathecal, direct intraventricular, intraperitoneal, intralymphatic, and intranasal injections.

[00286] In certain embodiments, a compound as described herein is administered in a local rather than systemic manner, for example, via injection of the compound directly into an organ, often in a depot

therapeutically effective amounts of compounds described herein are administered in a pharmaceutical composition to a mammal having a disease, disorder, or condition to be treated. In some embodiments, the mammal is a human. A therapeutically effective amount can vary widely depending on the severity of the disease, the age and relative health of the subject, the potency of the compound used and other factors. The compounds can be used singly or in combination with one or more therapeutic agents as components of mixtures.

[00290] The pharmaceutical formulations described herein are administered to a subject by appropriate administration routes, including but not limited to, oral, parenteral (e.g., intravenous, subcutaneous, intramuscular), intranasal, buccal, topical, rectal, or transdermal administration routes. The pharmaceutical formulations described herein include, but are not limited to, aqueous liquid dispersions, liquids, gels, syrups, elixirs, slurries, suspensions, self-emulsifying dispersions, solid solutions, liposomal dispersions, aerosols, solid oral dosage forms, powders, immediate release formulations, controlled release formulations, fast melt formulations, tablets, capsules, pills, powders, dragees, effervescent formulations, lyophilized formulations, delayed release formulations, extended release formulations, pulsatile release formulations, multiparticulate formulations, and mixed immediate and controlled release formulations.

[00291] Pharmaceutical compositions including a compound of Formula (I), or a pharmaceutically acceptable salt thereof, are manufactured in a conventional manner, such as, by way of example only, by means of conventional mixing, dissolving, granulating, dragee-making, levigating, emulsifying, encapsulating, entrapping or compression processes.

[00292] The pharmaceutical compositions will include at least one compound of Formula (I) as an active ingredient in free-acid or free-base form, or in a pharmaceutically acceptable salt form. In addition, the methods and pharmaceutical compositions described herein include the use of *N*-oxides (if appropriate), crystalline forms, amorphous phases, as well as active metabolites of these compounds having the same type of activity. In some embodiments, compounds described herein exist in unsolvated form or in solvated forms with pharmaceutically acceptable solvents such as water, ethanol, and the like. The solvated forms of the compounds presented herein are also considered to be disclosed herein.

[00293] Pharmaceutical preparations for oral use are obtained by mixing one or more solid excipient with one or more of the compounds described herein, optionally grinding the resulting mixture, and processing the mixture of granules, after adding suitable auxiliaries, if desired, to obtain tablets or dragee cores. Suitable excipients include, for example, fillers such as sugars, including lactose, sucrose, mannitol, or sorbitol; cellulose preparations such as, for example, maize starch, wheat starch, rice starch, potato starch, gelatin, gum tragacanth, methylcellulose, microcrystalline cellulose, hydroxypropylmethylcellulose, sodium carboxymethylcellulose; or others such as: polyvinylpyrrolidone (PVP or povidone) or calcium phosphate. If desired, disintegrating agents are added, such as the cross-linked croscarmellose sodium, polyvinylpyrrolidone, agar, or alginic acid or

a salt thereof such as sodium alginate. In some embodiments, dyestuffs or pigments are added to the tablets or dragee coatings for identification or to characterize different combinations of active compound doses.

[00294] Pharmaceutical preparations that are administered orally include push-fit capsules made of gelatin, as well as soft, sealed capsules made of gelatin and a plasticizer, such as glycerol or sorbitol. The push-fit capsules contain the active ingredients in admixture with filler such as lactose, binders such as starches, and/or lubricants such as talc or magnesium stearate and, optionally, stabilizers. In soft capsules, the active compounds are dissolved or suspended in suitable liquids, such as fatty oils, liquid paraffin, or liquid polyethylene glycols. In some embodiments, stabilizers are added.

[00295] All formulations for oral administration are in dosages suitable for such administration.

[00296] In one aspect, solid oral dosage forms are prepared by mixing a compound of Formula (I), or a pharmaceutically acceptable salt thereof, with one or more of the following: antioxidants, flavoring agents, and carrier materials such as binders, suspending agents, disintegration agents, filling agents, surfactants, solubilizers, stabilizers, lubricants, wetting agents, and diluents.

[00297] In some embodiments, the solid dosage forms disclosed herein are in the form of a tablet, (including a suspension tablet, a fast-melt tablet, a bite-disintegration tablet, a rapid-disintegration tablet, an effervescent tablet, or a caplet), a pill, a powder, a capsule, solid dispersion, solid solution, bioerodible dosage form, controlled release formulations, pulsatile release dosage forms, multiparticulate dosage forms, beads, pellets, granules. In other embodiments, the pharmaceutical formulation is in the form of a powder. In still other embodiments, the pharmaceutical formulation is in the form of a tablet. In other embodiments, pharmaceutical formulations of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is in the form of a capsule.

[00298] In some embodiments, solid dosage forms, e.g., tablets, effervescent tablets, and capsules, are prepared by mixing particles of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, with one or more pharmaceutical excipients to form a bulk blend composition. The bulk blend is readily subdivided into equally effective unit dosage forms, such as tablets, pills, and capsules. In some embodiments, the individual unit dosages include film coatings. These formulations are manufactured by conventional formulation techniques.

[00299] Conventional formulation techniques include, e.g., one or a combination of methods: (1) dry mixing, (2) direct compression, (3) milling, (4) dry or non-aqueous granulation, (5) wet granulation, or (6) fusion. Other methods include, e.g., spray drying, pan coating, melt granulation, granulation, fluidized bed spray drying or coating (e.g., wurster coating), tangential coating, top spraying, tableting, extruding and the like.

[00300] Suitable carriers for use in the solid dosage forms described herein include, but are not limited to, acacia, gelatin, colloidal silicon dioxide, calcium glycerophosphate, calcium lactate, maltodextrin, glycerine, magnesium silicate, sodium caseinate, soy lecithin, sodium chloride, tricalcium phosphate, dipotassium phosphate, sodium stearoyl lactylate, carrageenan, monoglyceride,

diglyceride, pregelatinized starch, hydroxypropylmethylcellulose, hydroxypropylmethylcellulose acetate stearate, sucrose, microcrystalline cellulose, lactose, mannitol and the like.

[00301] Suitable filling agents for use in the solid dosage forms described herein include, but are not limited to, lactose, calcium carbonate, calcium phosphate, dibasic calcium phosphate, calcium sulfate, microcrystalline cellulose, cellulose powder, dextrose, dextrates, dextran, starches, pregelatinized starch, hydroxypropylmethycellulose (HPMC), hydroxypropylmethycellulose phthalate, hydroxypropylmethylcellulose acetate stearate (HPMCAS), sucrose, xylitol, lactitol, mannitol, sorbitol, sodium chloride, polyethylene glycol, and the like.

[00302] Suitable disintegrants for use in the solid dosage forms described herein include, but are not limited to, natural starch such as corn starch or potato starch, a pregelatinized starch, or sodium starch glycolate, a cellulose such as methylcrystalline cellulose, methylcellulose, microcrystalline cellulose, croscarmellose, or a cross-linked cellulose, such as cross-linked sodium carboxymethylcellulose, cross-linked carboxymethylcellulose, or cross-linked croscarmellose, a cross-linked starch such as sodium starch glycolate, a cross-linked polymer such as crospovidone, a cross-linked polyvinylpyrrolidone, alginate such as alginic acid or a salt of alginic acid such as sodium alginate, a gum such as agar, guar, locust bean, Karaya, pectin, or tragacanth, sodium starch glycolate, bentonite, sodium lauryl sulfate, sodium lauryl sulfate in combination starch, and the like.

[00303] Binders impart cohesiveness to solid oral dosage form formulations: for powder filled capsule formulation, they aid in plug formation that can be filled into soft or hard shell capsules and for tablet formulation, they ensure the tablet remaining intact after compression and help assure blend uniformity prior to a compression or fill step. Materials suitable for use as binders in the solid dosage forms described herein include, but are not limited to, carboxymethylcellulose, methylcellulose, hydroxypropylmethylcellulose, hydroxypropylmethylcellulose acetate stearate, hydroxyethylcellulose, hydroxypropylcellulose, ethylcellulose, and microcrystalline cellulose, microcrystalline dextrose, amylose, magnesium aluminum silicate, polysaccharide acids, bentonites, gelatin, polyvinylpyrrolidone/vinyl acetate copolymer, crospovidone, povidone, starch, pregelatinized starch, tragacanth, dextrin, a sugar, such as sucrose, glucose, dextrose, molasses, mannitol, sorbitol, xylitol, lactose, a natural or synthetic gum such as acacia, tragacanth, ghatti gum, mucilage of isapol husks, starch, polyvinylpyrrolidone, larch arabogalactan, polyethylene glycol, waxes, sodium alginate, and the like.

[00304] Suitable lubricants or glidants for use in the solid dosage forms described herein include, but are not limited to, stearic acid, calcium hydroxide, talc, corn starch, sodium stearyl fumerate, alkali-metal and alkaline earth metal salts, such as aluminum, calcium, magnesium, zinc, stearic acid, sodium stearates, magnesium stearate, zinc stearate, waxes, Stearowet®, boric acid, sodium benzoate, sodium acetate, sodium chloride, leucine, a polyethylene glycol or a methoxypolyethylene glycol such as Carbowax™, PEG 4000, PEG 5000, PEG 6000, propylene glycol, sodium oleate, glyceryl

behenate, glyceryl palmitostearate, glyceryl benzoate, magnesium or sodium lauryl sulfate, and the like.

[00305] Suitable diluents for use in the solid dosage forms described herein include, but are not limited to, sugars (including lactose, sucrose, and dextrose), polysaccharides (including dextrates and maltodextrin), polyols (including mannitol, xylitol, and sorbitol), cyclodextrins and the like.

[00306] Suitable wetting agents for use in the solid dosage forms described herein include, for example, oleic acid, glyceryl monostearate, sorbitan monooleate, sorbitan monolaurate, triethanolamine oleate, polyoxyethylene sorbitan monooleate, polyoxyethylene sorbitan monolaurate, quaternary ammonium compounds (e.g., Polyquat 10®), sodium oleate, sodium lauryl sulfate, magnesium stearate, sodium docusate, triacetin, vitamin E TPGS and the like.

[00307] Suitable surfactants for use in the solid dosage forms described herein include, for example, sodium lauryl sulfate, sorbitan monooleate, polyoxyethylene sorbitan monooleate, polysorbates, polaxomers, bile salts, glyceryl monostearate, copolymers of ethylene oxide and propylene oxide, e.g., Pluronic® (BASF), and the like.

[00308] Suitable suspending agents for use in the solid dosage forms described here include, but are not limited to, polyvinylpyrrolidone, e.g., polyvinylpyrrolidone K12, polyvinylpyrrolidone K17, polyvinylpyrrolidone K25, or polyvinylpyrrolidone K30, polyethylene glycol, e.g., the polyethylene glycol can have a molecular weight of about 300 to about 6000, or about 3350 to about 4000, or about 7000 to about 5400, vinyl pyrrolidone/vinyl acetate copolymer (S630), sodium carboxymethylcellulose, methylcellulose, hydroxy-propylmethylcellulose, polysorbate-80, hydroxyethylcellulose, sodium alginate, gums, such as, e.g., gum tragacanth and gum acacia, guar gum, xanthans, including xanthan gum, sugars, cellulosics, such as, e.g., sodium carboxymethylcellulose, methylcellulose, sodium carboxymethylcellulose, hydroxypropylmethylcellulose, hydroxyethylcellulose, polysorbate-80, sodium alginate, polyethoxylated sorbitan monolaurate, polyethoxylated sorbitan monolaurate, povidone and the like.

[00309] It should be appreciated that there is considerable overlap between additives used in the solid dosage forms described herein. Thus, the above-listed additives should be taken as merely exemplary, and not limiting, of the types of additives that can be included in solid dosage forms of the pharmaceutical compositions described herein. The amounts of such additives can be readily determined by one skilled in the art, according to the particular properties desired.

[00310] Compressed tablets are solid dosage forms prepared by compacting the bulk blend of the formulations described above.

[00311] In various embodiments, tablets will include one or more flavoring agents.

[00312] In other embodiments, the tablets will include a film surrounding the final compressed tablet. In some embodiments, the film coating can provide a delayed release of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, from the formulation.

[00313] A capsule may be prepared, for example, by placing the bulk blend of the formulation of the compound described above, inside of a capsule. In some embodiments, the formulations (non-aqueous suspensions and solutions) are placed in a soft gelatin capsule. In other embodiments, the formulations are placed in standard gelatin capsules or non-gelatin capsules such as capsules comprising HPMC. In other embodiments, the formulation is placed in a sprinkle capsule, wherein the capsule is swallowed whole or the capsule is opened and the contents sprinkled on food prior to eating.

[00314] In various embodiments, the particles of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, and one or more excipients are dry blended and compressed into a mass, such as a tablet, having a hardness sufficient to provide a pharmaceutical composition that substantially disintegrates within less than about 30 minutes, less than about 35 minutes, less than about 40 minutes, less than about 45 minutes, less than about 50 minutes, less than about 55 minutes, or less than about 60 minutes, after oral administration, thereby releasing the formulation into the gastrointestinal fluid.

[00315] In other embodiments, a powder including a compound of Formula (I), or a pharmaceutically acceptable salt thereof, is formulated to include one or more pharmaceutical excipients and flavors. Such a powder is prepared, for example, by mixing the compound of Formula (I), or a pharmaceutically acceptable salt thereof, and optional pharmaceutical excipients to form a bulk blend composition. Additional embodiments also include a suspending agent and/or a wetting agent. This bulk blend is uniformly subdivided into unit dosage packaging or multi-dosage packaging units.

[00316] In still other embodiments, effervescent powders are also prepared. Effervescent salts have been used to disperse medicines in water for oral administration.

[00317] In some embodiments, the pharmaceutical solid oral dosage forms are formulated to provide a controlled release of the compound of Formula (I), or a pharmaceutically acceptable salt thereof. Controlled release refers to the release of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, from a dosage form in which it is incorporated according to a desired profile over an extended period of time. Controlled release profiles include, for example, sustained release, prolonged release, pulsatile release, and delayed release profiles. In contrast to immediate release compositions, controlled release compositions allow delivery of an agent to a subject over an extended period of time according to a predetermined profile. Such release rates can provide therapeutically effective levels of agent for an extended period of time and thereby provide a longer period of pharmacologic response while minimizing side effects as compared to conventional rapid release dosage forms. Such longer periods of response provide for many inherent benefits that are not achieved with the corresponding short acting, immediate release preparations.

[00318] In some embodiments, the solid dosage forms described herein are formulated as enteric coated delayed release oral dosage forms, i.e., as an oral dosage form of a pharmaceutical composition as described herein which utilizes an enteric coating to affect release in the small

intestine or large intestine. In one aspect, the enteric coated dosage form is a compressed or molded or extruded tablet/mold (coated or uncoated) containing granules, powder, pellets, beads or particles of the active ingredient and/or other composition components, which are themselves coated or uncoated. In one aspect, the enteric coated oral dosage form is in the form of a capsule containing pellets, beads or granules, which include a compound of Formula (I), or a pharmaceutically acceptable salt thereof, that are coated or uncoated.

[00319] Any coatings should be applied to a sufficient thickness such that the entire coating does not dissolve in the gastrointestinal fluids at pH below about 5, but does dissolve at pH about 5 and above. Coatings are typically selected from any of the following:

[00320] Shellac - this coating dissolves in media of pH >7; Acrylic polymers - examples of suitable acrylic polymers include methacrylic acid copolymers and ammonium methacrylate copolymers. The Eudragit series E, L, S, RL, RS and NE (Rohm Pharma) are available as solubilized in organic solvent, aqueous dispersion, or dry powders. The Eudragit series RL, NE, and RS are insoluble in the gastrointestinal tract but are permeable and are used primarily for colonic targeting. The Eudragit series E dissolve in the stomach. The Eudragit series L, L-30D and S are insoluble in stomach and dissolve in the intestine; Poly Vinyl Acetate Phthalate (PVAP) - PVAP dissolves in pH >5, and it is much less permeable to water vapor and gastric fluids.

[00321] Conventional coating techniques such as spray or pan coating are employed to apply coatings. The coating thickness must be sufficient to ensure that the oral dosage form remains intact until the desired site of topical delivery in the intestinal tract is reached.

[00322] In other embodiments, the formulations described herein are delivered using a pulsatile dosage form. A pulsatile dosage form is capable of providing one or more immediate release pulses at predetermined time points after a controlled lag time or at specific sites. Exemplary pulsatile dosage forms and methods of their manufacture are disclosed in U.S. Pat. Nos. 5,011,692, 5,017,381, 5,229,135, 5,840,329 and 5,837,284. In one embodiment, the pulsatile dosage form includes at least two groups of particles, (i.e. multiparticulate) each containing the formulation described herein. The first group of particles provides a substantially immediate dose of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, upon ingestion by a mammal. The first group of particles can be either uncoated or include a coating and/or sealant. In one aspect, the second group of particles comprises coated particles. The coating on the second group of particles provides a delay of from about 2 hours to about 7 hours following ingestion before release of the second dose. Suitable coatings for pharmaceutical compositions are described herein or known in the art.

[00323] In some embodiments, pharmaceutical formulations are provided that include particles of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, and at least one dispersing agent or suspending agent for oral administration to a subject. The formulations may be a powder and/or granules for suspension, and upon admixture with water, a substantially uniform suspension is obtained.

[00324] In one aspect, liquid formulation dosage forms for oral administration are in the form of aqueous suspensions selected from the group including, but not limited to, pharmaceutically acceptable aqueous oral dispersions, emulsions, solutions, elixirs, gels, and syrups. See, e.g., Singh *et al.*., Encyclopedia of Pharmaceutical Technology, 2nd Ed., pp. 754-757 (2002). In addition to the particles of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, the liquid dosage forms include additives, such as: (a) disintegrating agents; (b) dispersing agents; (c) wetting agents; (d) at least one preservative, (e) viscosity enhancing agents, (f) at least one sweetening agent, and (g) at least one flavoring agent. In some embodiments, the aqueous dispersions can further include a crystalline inhibitor.

[00325] Furthermore, pharmaceutical compositions optionally include one or more pH adjusting agents or buffering agents, including acids such as acetic, boric, citric, lactic, phosphoric and hydrochloric acids; bases such as sodium hydroxide, sodium phosphate, sodium borate, sodium citrate, sodium acetate, sodium lactate and tris-hydroxymethylaminomethane; and buffers such as citrate/dextrose, sodium bicarbonate and ammonium chloride. Such acids, bases and buffers are included in an amount required to maintain pH of the composition in an acceptable range.

[00326] Additionally, pharmaceutical compositions optionally include one or more salts in an amount required to bring osmolality of the composition into an acceptable range. Such salts include those having sodium, potassium or ammonium cations and chloride, citrate, ascorbate, borate, phosphate, bicarbonate, sulfate, thiosulfate or bisulfite anions; suitable salts include sodium chloride, potassium chloride, sodium thiosulfate, sodium bisulfite and ammonium sulfate.

[00327] Other pharmaceutical compositions optionally include one or more preservatives to inhibit microbial activity. Suitable preservatives include mercury-containing substances such as merfen and thiomersal; stabilized chlorine dioxide; and quaternary ammonium compounds such as benzalkonium chloride, cetyltrimethylammonium bromide and cetylpyridinium chloride.

[00328] In one embodiment, the aqueous suspensions and dispersions described herein remain in a homogenous state, as defined in The USP Pharmacists' Pharmacopeia (2005 edition, chapter 905), for at least 4 hours. In one embodiment, an aqueous suspension is re-suspended into a homogenous suspension by physical agitation lasting less than 1 minute. In still another embodiment, no agitation is necessary to maintain a homogeneous aqueous dispersion.

[00329] Examples of disintegrating agents for use in the aqueous suspensions and dispersions include, but are not limited to, a starch, e.g., a natural starch such as corn starch or potato starch, a pregelatinized starch, or sodium starch glycolate; a cellulose such as methylcrystalline cellulose, methylcellulose, croscarmellose, or a cross-linked cellulose, such as cross-linked sodium carboxymethylcellulose, cross-linked carboxymethylcellulose, or cross-linked croscarmellose; a cross-linked starch such as sodium starch glycolate; a cross-linked polymer such as crospovidone; a cross-linked polyvinylpyrrolidone; alginate such as alginic acid or a salt of alginic acid such as sodium alginate; a gum such as agar, guar, locust bean, Karaya, pectin, or tragacanth; sodium starch

glycolate; bentonite; a natural sponge; a surfactant; a resin such as a cation-exchange resin; citrus pulp; sodium lauryl sulfate; sodium lauryl sulfate in combination starch; and the like.

[00330] In some embodiments, the dispersing agents suitable for the aqueous suspensions and dispersions described herein include, for example, hydrophilic polymers, electrolytes, Tween® 60 or 80, PEG, polyvinylpyrrolidone, and the carbohydrate-based dispersing agents such as, for example, hydroxypropylcellulose and hydroxypropyl cellulose ethers, hydroxypropyl methylcellulose and hydroxypropyl methylcellulose ethers, carboxymethylcellulose sodium, methylcellulose, hydroxyethylcellulose, hydroxypropylmethyl-cellulose phthalate, hydroxypropylmethyl-cellulose acetate stearate, noncrystalline cellulose, magnesium aluminum silicate, triethanolamine, polyvinyl alcohol (PVA), polyvinylpyrrolidone/vinyl acetate copolymer, 4-(1,1,3,3-tetramethylbutyl)-phenol polymer with ethylene oxide and formaldehyde (also known as tyloxapol), poloxamers; and poloxamines. In other embodiments, the dispersing agent is selected from a group not comprising one of the following agents: hydrophilic polymers; electrolytes; Tween® 60 or 80; PEG; polyvinylpyrrolidone (PVP); hydroxypropylcellulose and hydroxypropyl cellulose ethers; hydroxypropyl methylcellulose and hydroxypropyl methylcellulose ethers; carboxymethylcellulose sodium; methylcellulose; hydroxyethylcellulose; hydroxypropylmethyl-cellulose phthalate; hydroxypropylmethyl-cellulose acetate stearate; non-crystalline cellulose; magnesium aluminum silicate; triethanolamine; polyvinyl alcohol (PVA); 4-(1,1,3,3-tetramethylbutyl)-phenol polymer with ethylene oxide and formaldehyde; poloxamers; or poloxamines.

[00331] Wetting agents suitable for the aqueous suspensions and dispersions described herein include, but are not limited to, cetyl alcohol, glycerol monostearate, polyoxyethylene sorbitan fatty acid esters (e.g., the commercially available Tweens® such as e.g., Tween 20® and Tween 80®, and polyethylene glycols, oleic acid, glyceryl monostearate, sorbitan monooleate, sorbitan monolaurate, triethanolamine oleate, polyoxyethylene sorbitan monooleate, polyoxyethylene sorbitan monolaurate, sodium oleate, sodium lauryl sulfate, sodium docusate, triacetin, vitamin E TPGS, sodium taurocholate, simethicone, phosphotidylcholine and the like

[00332] Suitable preservatives for the aqueous suspensions or dispersions described herein include, for example, potassium sorbate, parabens (e.g., methylparaben and propylparaben), benzoic acid and its salts, other esters of parahydroxybenzoic acid such as butylparaben, alcohols such as ethyl alcohol or benzyl alcohol, phenolic compounds such as phenol, or quaternary compounds such as benzalkonium chloride. Preservatives, as used herein, are incorporated into the dosage form at a concentration sufficient to inhibit microbial growth.

[00333] Suitable viscosity enhancing agents for the aqueous suspensions or dispersions described herein include, but are not limited to, methyl cellulose, xanthan gum, carboxymethyl cellulose, hydroxypropyl cellulose, hydroxypropylmethyl cellulose, Plasdon® S-630, carbomer, polyvinyl alcohol, alginates, acacia, chitosans and combinations thereof. The concentration of the viscosity enhancing agent will depend upon the agent selected and the viscosity desired.

but not limited to, gelling agents, creams and ointment bases, and the like. In some embodiments, the transdermal formulations further include a woven or non-woven backing material to enhance absorption and prevent the removal of the transdermal formulation from the skin. In other embodiments, the transdermal formulations described herein can maintain a saturated or supersaturated state to promote diffusion into the skin.

[00339] In one aspect, formulations suitable for transdermal administration of compounds described herein employ transdermal delivery devices and transdermal delivery patches and can be lipophilic emulsions or buffered, aqueous solutions, dissolved and/or dispersed in a polymer or an adhesive. In one aspect, such patches are constructed for continuous, pulsatile, or on demand delivery of pharmaceutical agents. Still further, transdermal delivery of the compounds described herein can be accomplished by means of iontophoretic patches and the like. In one aspect, transdermal patches provide controlled delivery of the compound of Formula (I), or a pharmaceutically acceptable salt thereof. In one aspect, transdermal devices are in the form of a bandage comprising a backing member, a reservoir containing the compound optionally with carriers, optionally a rate controlling barrier to deliver the compound to the skin of the host at a controlled and predetermined rate over a prolonged period of time, and means to secure the device to the skin.

[00340] In one aspect, a compound of Formula (I), or a pharmaceutically acceptable salt thereof, is formulated into a pharmaceutical composition suitable for intramuscular, subcutaneous, or intravenous injection. In one aspect, formulations suitable for intramuscular, subcutaneous, or intravenous injection include physiologically acceptable sterile aqueous or non-aqueous solutions, dispersions, suspensions or emulsions, and sterile powders for reconstitution into sterile injectable solutions or dispersions. Examples of suitable aqueous and non-aqueous carriers, diluents, solvents, or vehicles include water, ethanol, polyols (propyleneglycol, polyethylene-glycol, glycerol, cremophor and the like), suitable mixtures thereof, vegetable oils (such as olive oil) and injectable organic esters such as ethyl oleate. Proper fluidity can be maintained, for example, by the use of a coating such as lecithin, by the maintenance of the required particle size in the case of dispersions, and by the use of surfactants. In some embodiments, formulations suitable for subcutaneous injection also contain additives such as preserving, wetting, emulsifying, and dispensing agents. Prevention of the growth of microorganisms can be ensured by various antibacterial and antifungal agents, such as parabens, chlorobutanol, phenol, sorbic acid, and the like. In some cases it is desirable to include isotonic agents, such as sugars, sodium chloride, and the like. Prolonged absorption of the injectable pharmaceutical form can be brought about by the use of agents delaying absorption, such as aluminum monostearate and gelatin.

[00341] For intravenous injections, compounds described herein are formulated in aqueous solutions, preferably in physiologically compatible buffers such as Hank's solution, Ringer's solution, or physiological saline buffer. For transmucosal administration, penetrants appropriate to the barrier to be permeated are used in the formulation. Such penetrants are generally known in the art. For other

parenteral injections, appropriate formulations include aqueous or nonaqueous solutions, preferably with physiologically compatible buffers or excipients. Such excipients are known.

[00342] Parenteral injections may involve bolus injection or continuous infusion. Formulations for injection may be presented in unit dosage form, e.g., in ampoules or in multi-dose containers, with an added preservative. The pharmaceutical composition described herein may be in a form suitable for parenteral injection as a sterile suspensions, solutions or emulsions in oily or aqueous vehicles, and may contain formulatory agents such as suspending, stabilizing and/or dispersing agents. In one aspect, the active ingredient is in powder form for constitution with a suitable vehicle, e.g., sterile pyrogen-free water, before use.

[00343] In certain embodiments, delivery systems for pharmaceutical compounds may be employed, such as, for example, liposomes and emulsions. In certain embodiments, compositions provided herein can also include an mucoadhesive polymer, selected from among, for example, carboxymethylcellulose, carbomer (acrylic acid polymer), poly(methylmethacrylate), polyacrylamide, polycarbophil, acrylic acid/butyl acrylate copolymer, sodium alginate and dextran.

[00344] In some embodiments, the compounds described herein may be administered topically and can be formulated into a variety of topically administrable compositions, such as solutions, suspensions, lotions, gels, pastes, medicated sticks, balms, creams or ointments. Such pharmaceutical compounds can contain solubilizers, stabilizers, tonicity enhancing agents, buffers and preservatives.

[00345] In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is formulated in rectal compositions such as enemas, rectal gels, rectal foams, rectal aerosols, suppositories, jelly suppositories, or retention enemas, containing conventional suppository bases such as cocoa butter or other glycerides, as well as synthetic polymers such as polyvinylpyrrolidone, PEG, and the like. In suppository forms of the compositions, a low-melting wax such as, but not limited to, a mixture of fatty acid glycerides, optionally in combination with cocoa butter is first melted.

Methods of Dosing and Treatment Regimens

[00346] In one embodiment, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is used in the preparation of medicaments for the treatment of diseases or conditions that would benefit from inhibition of ATX activity. In addition, a method for treating any of the diseases or conditions described herein in a subject in need of such treatment, involves administration of pharmaceutical compositions that include at least one compound of Formula (I), or a pharmaceutically acceptable salt, active metabolite, prodrug, or pharmaceutically acceptable solvate thereof, in therapeutically effective amounts to said subject.

[00347] In certain embodiments, the compositions containing the compound(s) described herein are administered for prophylactic and/or therapeutic treatments. In certain therapeutic applications, the compositions are administered to a patient already suffering from a disease or condition, in an amount sufficient to cure or at least partially arrest at least one of the symptoms of the disease or

condition. Amounts effective for this use depend on the severity and course of the disease or condition, previous therapy, the patient's health status, weight, and response to the drugs, and the judgment of the treating physician. Therapeutically effective amounts are optionally determined by methods including, but not limited to, a dose escalation clinical trial.

[00348] In prophylactic applications, compositions containing the compounds described herein are administered to a patient susceptible to or otherwise at risk of a particular disease, disorder or condition. Such an amount is defined to be a "prophylactically effective amount or dose." In this use, the precise amounts also depend on the patient's state of health, weight, and the like. When used in a patient, effective amounts for this use will depend on the severity and course of the disease, disorder or condition, previous therapy, the patient's health status and response to the drugs, and the judgment of the treating physician. In one aspect, prophylactic treatments include admistering to a mammal, who previously experienced at least one symtom of the disease being treated and is currently in remission, a pharmaceutical composition comprising a compound of Formula (I), or a pharmaceutically acceptable salt thereof, in order to prevent a return of the symptoms of the disease or condition.

[00349] In certain embodiments wherein the patient's condition does not improve, upon the doctor's discretion the administration of the compounds are administered chronically, that is, for an extended period of time, including throughout the duration of the patient's life in order to ameliorate or otherwise control or limit the symptoms of the patient's disease or condition.

[00350] In certain embodiments the dose of drug being administered may be temporarily reduced or temporarily suspended for a certain length of time (*i.e.*, a "drug holiday"). In specific embodiments, the length of the drug holiday is between 2 days and 1 year, including by way of example only, 2 days, 3 days, 4 days, 5 days, 6 days, 7 days, 10 days, 12 days, 15 days, 20 days, 28 days, or more than 28 days. The dose reduction during a drug holiday is, by way of example only, by 10%-100%, including by way of example only 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, and 100%.

[00351] Once improvement of the patient's conditions has occurred, a maintenance dose is administered if necessary. Subsequently, in specific embodiments, the dosage or the frequency of administration, or both, is reduced, as a function of the symptoms, to a level at which the improved disease, disorder or condition is retained. In certain embodiments, however, the patient requires intermittent treatment on a long-term basis upon any recurrence of symptoms.

[00352] The amount of a given agent that corresponds to such an amount varies depending upon factors such as the particular compound, disease condition and its severity, the identity (*e.g.*, weight, sex) of the subject or host in need of treatment, but can nevertheless be determined according to the particular circumstances surrounding the case, including, *e.g.*, the specific agent being administered, the route of administration, the condition being treated, and the subject or host being treated. In general, however, doses employed for adult human treatment are typically in the range of 0.01mg-

5000 mg per day. In one aspect, doses employed for adult human treatment are from about 1mg to about 1000 mg per day. In one embodiment, the desired dose is conveniently presented in a single dose or in divided doses administered simultaneously (or over a short period of time) or at appropriate intervals, for example as two, three, four or more sub-doses per day.

[00353] In one embodiment, the daily dosages appropriate for the compound of Formula (I), or a pharmaceutically acceptable salt thereof, described herein are from about 0.01 to about 50 mg/kg per body weight. In specific embodiments, an indicated daily dosage in a large mammal, including, but not limited to, humans, is in the range from about 0.5 mg to about 1000 mg, conveniently administered in divided doses, including, but not limited to, up to four times a day. In one embodiment, the daily dosage is administered in extended release form. In certain embodiments, suitable unit dosage forms for oral administration comprise from about 1 to 500 mg active ingredient. In other embodiments, the daily dosage or the amount of active in the dosage form are lower or higher than the ranges indicated herein, based on a number of variables in regard to an individual treatment regime. In various embodiments, the daily and unit dosages are altered depending on a number of variables including, but not limited to, the activity of the compound used, the disease or condition to be treated, the mode of administration, the requirements of the individual subject, the severity of the disease or condition being treated, and the judgment of the practitioner.

[00354] Toxicity and therapeutic efficacy of such therapeutic regimens are determined by standard pharmaceutical procedures in cell cultures or experimental animals, including, but not limited to, the determination of the LD_{50} and the ED_{50}. The dose ratio between the toxic and therapeutic effects is the therapeutic index and it is expressed as the ratio between LD_{50} and ED_{50}. In certain embodiments, the data obtained from cell culture assays and animal studies are used in formulating the therapeutically effective daily dosage range and/or the therapeutically effective unit dosage amount for use in mammals, including humans. In some embodiments, the daily dosage amount of the compounds described herein lies within a range of circulating concentrations that include the ED_{50} with minimal toxicity. In certain embodiments, the daily dosage range and/or the unit dosage amount varies within this range depending upon the dosage form employed and the route of administration utilized.

Combination Treatments

[00355] In certain instances, it is appropriate to administer at least one compound of Formula (I), or a pharmaceutically acceptable salt thereof, in combination with another therapeutic agent. By way of example only, if one of the side effects experienced by a patient upon receiving one of the compounds described herein is inflammation, then it may be appropriate to administer an anti-inflammatory agent in combination with the initial therapeutic agent.

[00356] Or, in one embodiment, the therapeutic effectiveness of one of the compounds described herein is enhanced by administration of an adjuvant (*i.e.*, by itself the adjuvant may have minimal therapeutic benefit, but in combination with another therapeutic agent, the overall therapeutic benefit

to the patient is enhanced). Or, in some embodiments, the benefit experienced by a patient is increased by administering one of the compounds described herein with another therapeutic agent (which also includes a therapeutic regimen) that also has therapeutic benefit.

[00357] In one specific embodiment, a compound of Formula (I), or a pharmaceutically acceptable salt thereof, is co-administered with a second therapeutic agent, wherein the compound of Formula (I), or a pharmaceutically acceptable salt thereof, and the second therapeutic agent modulate different aspects of the disease, disorder or condition being treated, thereby providing a greater overall benefit than administration of either therapeutic agent alone.

[00358] In any case, regardless of the disease, disorder or condition being treated, the overall benefit experienced by the patient may simply be additive of the two therapeutic agents or the patient may experience a synergistic benefit.

[00359] In certain embodiments, different therapeutically-effective dosages of the compounds disclosed herein will be utilized in formulating pharmaceutical composition and/or in treatment regimens when the compounds disclosed herein are administered in combination with one or more additional agent, such as an additional therapeutically effective drug, an adjuvant or the like. Therapeutically-effective dosages of drugs and other agents for use in combination treatment regimens can be determined by means similar to those set forth hereinabove for the actives themselves. Furthermore, the methods of prevention/treatment described herein encompasses the use of metronomic dosing, i.e., providing more frequent, lower doses in order to minimize toxic side effects. In some embodiments, a combination treatment regimen encompasses treatment regimens in which administration of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, is initiated prior to, during, or after treatment with a second agent described herein, and continues until any time during treatment with the second agent or after termination of treatment with the second agent. It also includes treatments in which a compound of Formula (I), or a pharmaceutically acceptable salt thereof, and the second agent being used in combination are administered simultaneously or at different times and/or at decreasing or increasing intervals during the treatment period. Combination treatment further includes periodic treatments that start and stop at various times to assist with the clinical management of the patient.

[00360] Compositions and methods for combination therapy are provided herein. In accordance with one aspect, the pharmaceutical compositions disclosed herein are used to treat diseases or conditions that are dependent upon or mediated by ATX.

[00361] It is understood that the dosage regimen to treat, prevent, or ameliorate the condition(s) for which relief is sought, is modified in accordance with a variety of factors. These factors include the disease, disorder or condition from which the subject suffers, as well as the age, weight, sex, diet, and medical condition of the subject. Thus, in some instances, the dosage regimen actually employed varies and, in some embodiments, deviates from the dosage regimens set forth herein.

[00362] For combination therapies described herein, dosages of the co-administered compounds vary depending on the type of co-drug employed, on the specific drug employed, on the disease or condition being treated and so forth. In additional embodiments, when co-administered with one or more other therapeutic agents, the compound provided herein is administered either simultaneously with the one or more other therapeutic agents, or sequentially.

[00363] In combination therapies, the multiple therapeutic agents (one of which is one of the compounds described herein) are administered in any order or even simultaneously. If administration is simultaneous, the multiple therapeutic agents are, by way of example only, provided in a single, unified form, or in multiple forms (e.g., as a single pill or as two separate pills). In one embodiment, one of the therapeutic agents is given in multiple doses, and in another, two (or more if present) are given as multiple doses. In some embodiments of non-simultaneous administration, the timings between the multiple doses vary from more than zero weeks to less than four weeks. In addition, the combination methods, compositions and formulations are not to be limited to the use of only two agents; the use of multiple therapeutic combinations is also envisioned.

[00364] The compounds of Formula (I), or pharmaceutically acceptable salts thereof, and combination therapies are administered before, during or after the occurrence of a disease or condition, and the timing of administering the composition containing a compound varies. Thus, in one embodiment, the compounds described herein are used as a prophylactic and are administered continuously to subjects with a propensity to develop conditions or diseases in order to prevent the occurrence of the disease or condition. In another embodiment, the compounds and compositions are administered to a subject during or as soon as possible after the onset of the symptoms. In specific embodiments, a compound described herein is administered as soon as is practicable after the onset of a disease or condition is detected or suspected, and for a length of time necessary for the treatment of the disease. In some embodiments, the length required for treatment varies, and the treatment length is adjusted to suit the specific needs of each subject. For example, in specific embodiments, a compound described herein or a formulation containing the compound is administered for at least 2 weeks, about 1 month to about 5 years.

[00365] By way of example, therapies which combine a compound of Formula (I), or a pharmaceutically acceptable salt thereof, with inhibitors of LPA synthesis or LPA receptor antagonists, either acting at the same or other points in the LPA synthesis or signalling pathway, are encompassed herein for treating the diseases or conditions described herein.

Exemplary Agents for use in Combination with Compounds of Formula (I)

[00366] In another embodiment described herein, methods of treatment or prevention of conditions or diseases, such as proliferative disorders, including cancer, comprises administration to a mammal a compound of Formula (I), or a pharmaceutically acceptable salt thereof, in combination with at least one additional agent selected, by way of example only, alemtuzumab, arsenic trioxide, asparaginase (pegylated or non-), bevacizumab, cetuximab, platinum-based compounds such as cisplatin,

cladribine, daunorubicin/doxorubicin/idarubicin, irinotecan, fludarabine, 5-fluorouracil, gemtuzumab, methotrexate, Paclitaxel™, taxol, temozolomide, thioguanine, or classes of drugs including hormones (an antiestrogen, an antiandrogen, or gonadotropin releasing hormone analogues, interferons such as alpha interferon, nitrogen mustards such as busulfan or melphalan or mechlorethamine, retinoids such as tretinoin, topoisomerase inhibitors such as irinotecan or topotecan, tyrosine kinase inhibitors such as gefinitinib or imatinib, or agents to treat signs or symptoms induced by such therapy including allopurinol, filgrastim, granisetron/ondansetron/palonosetron, dronabinol.

[00367] In one aspect, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered or formulated in combination with one or more anti-cancer agents. In some embodiments, one or more of the anti-cancer agents are proapoptotic agents. Examples of anti-cancer agents include, but are not limited to, any of the following: gossypol, genasense, polyphenol E, Chlorofusin, all trans-retinoic acid (ATRA), bryostatin, tumor necrosis factor-related apoptosis-inducing ligand (TRAIL), 5-aza-2'-deoxycytidine, all trans retinoic acid, doxorubicin, vincristine, etoposide, gemcitabine, imatinib, geldanamycin, 17-N-Allylamino-17-Demethoxygeldanamycin (17-AAG), flavopiridol, LY294002, bortezomib, trastuzumab, BAY 11-7082, PKC412, or PD184352, Taxol™ (paclitaxel), and analogs of Taxol™, such as Taxotere™. Compounds that have the basic taxane skeleton as a common structure feature, have also been shown to have the ability to arrest cells in the G2-M phases due to stabilized microtubules and may be useful for treating cancer in combination with the compounds described herein.

[00368] Further examples of anti-cancer agents for use in combination with the compounds of Formula (I), or a pharmaceutically acceptable salt thereof, include inhibitors of mitogen-activated protein kinase signaling, e.g., U0126, PD98059, PD184352, PD0325901, ARRY-142886, SB239063, SP600125, BAY 43-9006, wortmannin, or LY294002; Syk inhibitors; mTOR inhibitors; and antibodies (e.g., rituxan).

[00369] Other anti-cancer agents for use in combination with the compounds of Formula (I), or a pharmaceutically acceptable salt thereof, include one or more of the following: abiraterone; abarelix; adriamycin; aactinomycin; acivicin; aclarubicin; acodazole hydrochloride; acronine; adozelesin; aldesleukin; alemtuzumab; allopurinol; alitretinoin; altretamine; ambomycin; ametantrone acetate; aminoglutethimide; aminolevulinic acid; amifostine; amsacrine; anastrozole; anthramycin; aprepitant; arsenic trioxide; asparaginase; asperlin; azacitidine; azetepa; azotomycin; batimastat; bendamustine hydrochloride; benzodepa; bevacizumab; bexarotene; bicalutamide; bisantrene hydrochloride; bisnafide dimesylate; bizelesin; bleomycin; bleomycin sulfate; bortezomib; brequinar sodium; bropirimine; busulfan; cactinomycin; calusterone; caracemide; carbetimer; carboplatin; carmustine; carubicin hydrochloride; carzelesin; capecitabine; cedefingol; cetuximab; chlorambucil; cirolemycin; cisplatin; cladribine; clofarabine; crisnatol mesylate; cyclophosphamide; cytarabine; dacarbazine; dasatinib; daunorubicin hydrochloride; dactinomycin; darbepoetin alfa; decitabine; degarelix; denileukin diftitox; dexormaplatin; dexrazoxane hydrochloride; dezaguanine; dezaguanine mesylate;

diaziquone; docetaxel; doxorubicin; doxorubicin hydrochloride; droloxifene; droloxifene citrate; dromostanolone propionate; duazomycin; edatrexate; eflornithine hydrochloride; elsamitrucin; eltrombopag olamine; enloplatin; enpromate; epipropidine; epirubicin hydrochloride; epoetin alfa; erbulozole; erlotinib hydrochloride; esorubicin hydrochloride; estramustine; estramustine phosphate sodium; etanidazole; etoposide; etoposide phosphate; etoprine; everolimus; exemestane; fadrozole hydrochloride; fazarabine; fenretinide; filgrastim; floxuridine; fludarabine phosphate; fluorouracil; flurocitabine; fosquidone; fostriecin sodium; fulvestrant; gefitinib; gemcitabine; gemcitabine hydrochloride; gemcitabine –cisplatin; gemtuzumab ozogamicin; goserelin acetate; histrelin acetate; hydroxyurea; idarubicin hydrochloride; ifosfamide; iimofosine; ibritumomab tiuxetan; idarubicin; ifosfamide; imatinib mesylate; imiquimod; interleukin Il (including recombinant interleukin II, or rlL2), interferon alfa-2a; interferon alfa-2b; interferon alfa-nl; interferon alfa-n3; interferon beta-l a; interferon gamma-l b; iproplatin; irinotecan hydrochloride; ixabepilone; lanreotide acetate; lapatinib; lenalidomide; letrozole; leuprolide acetate; leucovorin calcium; leuprolide acetate; levamisole; liposomal cytarabine; liarozole hydrochloride; lometrexol sodium; lomustine; losoxantrone hydrochloride; masoprocol; maytansine; mechlorethamine hydrochloride; megestrol acetate; melengestrol acetate; melphalan; menogaril; mercaptopurine; methotrexate; methotrexate sodium; methoxsalen; metoprine; meturedepa; mitindomide; mitocarcin; mitocromin; mitogillin; mitomalcin; mitomycin C; mitosper; mitotane; mitoxantrone hydrochloride; mycophenolic acid; nandrolone phenpropionate; nelarabine; nilotinib; nocodazoie; nofetumomab; nogalamycin; ofatumumab; oprelvekin; ormaplatin; oxaliplatin;oxisuran; paclitaxel; palifermin; palonosetron hydrochloride; pamidronate; pegfilgrastim; pemetrexed disodium; pentostatin; panitumumab; pazopanib hydrochloride; pemetrexed disodium; plerixafor; pralatrexate; pegaspargase; peliomycin; pentamustine; peplomycin sulfate; perfosfamide; pipobroman; piposulfan; piroxantrone hydrochloride; plicamycin; plomestane; porfimer sodium; porfiromycin; prednimustine; procarbazine hydrochloride; puromycin; puromycin hydrochloride; pyrazofurin; quinacrine; raloxifene hydrochloride; rasburicase; recombinant HPV bivalent vaccine; recombinant HPV quadrivalent vaccine; riboprine; rogletimide; rituximab; romidepsin; romiplostim; safingol; safingol hydrochloride; sargramostim; semustine; simtrazene; sipuleucel-T; sorafenib; sparfosate sodium; sparsomycin; spirogermanium hydrochloride; spiromustine; spiroplatin; streptonigrin; streptozocin; sulofenur; sunitinib malate; talisomycin; tamoxifen citrate; tecogalan sodium; tegafur; teloxantrone hydrochloride; temozolomide; temoporfin; temsirolimus; teniposide; teroxirone; testolactone; thalidomide;thiamiprine; thioguanine; thiotepa; tiazofurin; tirapazamine; topotecan hydrochloride; toremifene; tositumomab and I 131 Iodine tositumomab; trastuzumab; trestolone acetate; tretinoin; triciribine phosphate; trimetrexate; trimetrexate glucuronate; triptorelin; tubulozole hydrochloride; uracil mustard; uredepa; valrubicin; vapreotide; verteporfin; vinblastine; vinblastine sulfate; vincristine sulfate; vindesine; vindesine sulfate; vinepidine sulfate; vinglycinate sulfate; vinleurosine

sulfate; vinorelbine tartrate; vinrosidine sulfate; vinzolidine sulfate; vorinostat; vorozole; zeniplatin; zinostatin; zoledronic acid; and zorubicin hydrochloride.

[00370] Yet other anticancer agents for use in combination with the compound of Formula (I), or a pharmaceutically acceptable salt thereof, include alkylating agents, antimetabolites, natural products, or hormones, e.g., nitrogen mustards (e.g., mechloroethamine, cyclophosphamide, chlorambucil, etc.), alkyl sulfonates (e.g., busulfan), nitrosoureas (e.g., carmustine, lomusitne, ete.), or triazenes (decarbazine, etc.). Examples of antimetabolites include but are not limited to folic acid analog (e.g., methotrexate), or pyrimidine analogs (e.g., Cytarabine), purine analogs (e.g., mercaptopurine, thioguanine, pentostatin).

[00371] Examples of natural products for use in combination with the compound of Formula (I), or a pharmaceutically acceptable salt thereof, include but are not limited to vinca alkaloids (e.g., vinblastin, vincristine), epipodophyllotoxins (e.g., etoposide), antibiotics (e.g., daunorubicin, doxorubicin, bleomycin), enzymes (e.g., L-asparaginase), or biological response modifiers (e.g., interferon alpha).

[00372] Examples of alkylating agents for use in combination with the compound of Formula (I), or a pharmaceutically acceptable salt thereof, include, but are not limited to, nitrogen mustards (e.g., mechloroethamine, cyclophosphamide, chlorambucil, meiphalan, etc.), ethylenimine and methylmelamines (e.g., hexamethlymelamine, thiotepa), alkyl sulfonates (e.g., busulfan), nitrosoureas (e.g., carmustine, lomusitne, semustine, streptozocin, etc.), or triazenes (decarbazine, ete.). Examples of antimetabolites include, but are not limited to folic acid analog (e.g., methotrexate), or pyrimidine analogs (e.g., fluorouracil, floxouridine, Cytarabine), purine analogs (e.g., mercaptopurine, thioguanine, pentostatin.

[00373] Examples of hormones and antagonists for use in combination with the compound of Formula (I), or a pharmaceutically acceptable salt thereof, include, but are not limited to, adrenocorticosteroids (e.g., prednisone), progestins (e.g., hydroxyprogesterone caproate, megestrol acetate, medroxyprogesterone acetate), estrogens (e.g., diethlystilbestrol, ethinyl estradiol), antiestrogen (e.g., tamoxifen), androgens (e.g., testosterone propionate, fluoxymesterone), antiandrogen (e.g., flutamide), gonadotropin releasing hormone analog (e.g., leuprolide). Other agents that can be used in the methods and compositions described herein for the treatment or prevention of cancer include platinum coordination complexes (e.g., cisplatin, carboblatin), anthracenedione (e.g., mitoxantrone), substituted urea (e.g., hydroxyurea), methyl hydrazine derivative (e.g., procarbazine), adrenocortical suppressant (e.g., mitotane, aminoglutethimide).

[00374] Examples of anti-cancer agents which act by arresting cells in the G2-M phases due to stabilized microtubules include without limitation the following marketed drugs and drugs in development: Erbulozole, Dolastatin 10, Mivobulin isethionate, Vincristine, NSC-639829, Discodermolide, ABT-751, Altorhyrtins (such as Altorhyrtin A and Altorhyrtin C), Spongistatins (such as Spongistatin 1, Spongistatin 2, Spongistatin 3, Spongistatin 4, Spongistatin 5, Spongistatin 6,

Spongistatin 7, Spongistatin 8, and Spongistatin 9), Cemadotin hydrochloride, Epothilones (such as Epothilone A, Epothilone B, Epothilone C, Epothilone D, Epothilone E, Epothilone F, Epothilone B N-oxide, Epothilone A N-oxide, 16-aza-epothilone B, 21-aminoepothilone B, 21-hydroxyepothilone D, 26-fluoroepothilone, Auristatin PE, Soblidotin, Vincristine sulfate, Cryptophycin 52, Vitilevuamide, Tubulysin A, Canadensol, Centaureidin, Oncocidin A1 Fijianolide B, Laulimalide, Narcosine, Nascapine, Hemiasterlin, Vanadocene acetylacetonate, Indanocine Eleutherobins (such as Desmethyleleutherobin, Desaetyleleutherobin, Isoeleutherobin A, and Z-Eleutherobin), Caribaeoside, Caribaeolin, Halichondrin B, Diazonamide A, Taccalonolide A, Diozostatin, (-)-Phenylahistin, Myoseverin B, Resverastatin phosphate sodium.

[00375] In one aspect, a compound of Formula (I), or a pharmaceutically acceptable salt thereof, is co-administered with thrombolytic agents (e.g., alteplase anistreplase, streptokinase, urokinase, or tissue plasminogen activator), heparin, tinzaparin, warfarin, dabigatran (e.g., dabigatran etexilate), factor Xa inhibitors (e.g., fondaparinux, draparinux, rivaroxaban, DX-9065a, otamixaban, LY517717, or YM150), ticlopidine, clopidogrel, CS-747 (prasugrel, LY640315), ximelagatran, or BIBR 1048.

[00376] In some embodiments, a compound of Formula (I), or a pharmaceutically acceptable salt thereof, is used in combination with anti-emetic agents to treat nausea or emesis, which may result from the use of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, anti-cancer agent(s) and/or radiation therapy. Anti-emetic agents include, but are not limited to: neurokinin-1 receptor antagonists, 5HT3 receptor antagonists (such as ondansetron, granisetron, tropisetron, Palonosetron, and zatisetron), $GABA_B$ receptor agonists (such as baclofen), corticosteroids (such as dexamethasone, prednisone, prednisolone, or others), dopamine antagonists (such as, but not limited to, domperidone, droperidol, haloperidol, chlorpromazine, promethazine, prochlorperazine, metoclopramide), antihistamines (H1 histamine receptor antagonists, such as but not limited to, cyclizine, diphenhydramine, dimenhydrinate, meclizine, promethazine, hydroxyzine), cannabinoids (such as but not limited to, cannabis, marinol, dronabinol), and others (such as, but not limited to, trimethobenzamide; ginger, emetrol, propofol).

[00377] In some embodiments, a compound of Formula (I), or a pharmaceutically acceptable salt thereof, is used in combination with an agent useful in the treatment of anemia. Such an anemia treatment agent is, for example, a continuous eythropoiesis receptor activator (such as epoetin-α).

[00378] In some embodiments, a compound of Formula (I), or a pharmaceutically acceptable salt thereof, is used in combination with an agent useful in the treatment of neutropenia. Examples of agents useful in the treatment of neutropenia include, but are not limited to, a hematopoietic growth factor which regulates the production and function of neutrophils such as a human granulocyte colony stimulating factor, (G-CSF). Examples of a G-CSF include filgrastim.

[00379] In some embodiments, a compound of Formula (I), or a pharmaceutically acceptable salt thereof, is used in combination with radiation therapy (or radiotherapy). Radiation therapy is the treatment of cancer and other diseases with ionizing radiation. Radiation therapy can be used to treat

localized solid tumors, such as cancers of the skin, tongue, larynx, brain, breast, prostate, colon, uterus and/or cervix. It can also be used to treat leukemia and lymphoma (cancers of the blood-forming cells and lymphatic system, respectively).

[00380] A technique for delivering radiation to cancer cells is to place radioactive implants directly in a tumor or body cavity. This is called internal radiotherapy (brachytherapy, interstitial irradiation, and intracavitary irradiation are types of internal radiotherapy.) Using internal radiotherapy, the radiation dose is concentrated in a small area, and the patient stays in the hospital for a few days. Internal radiotherapy is frequently used for cancers of the tongue, uterus, prostate, colon, and cervix.

[00381] The term "radiotherapy" or "ionizing radiation" include all forms of radiation, including but not limited to α, β, and γ radiation and ultraviolet light.

Immunosuppressants

[00382] In one aspect, a compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered in combination with one or more immunosuppressants. Immunosuppressive therapy is clinically used to treat or prevent the rejection of transplanted organs and tissues (e.g. bone marrow, heart, kidney, liver); treatment of autoimmune diseases or diseases that are most likely of autoimmune origin (e.g. rheumatoid arthritis, myasthenia gravis, systemic lupus erythematosus, Crohn's disease, and ulcerative colitis); and treatment of some other non-autoimmune inflammatory diseases (e.g. long term allergic asthma control), and in the treatment of fibrotic conditions.

[00383] In some embodiments, a compound of Formula (I), or a pharmaceutically acceptable salt thereof, is adminsitered with corticosteroids. In some embodiments, a compound of Formula (I), or a pharmaceutically acceptable salt thereof, is adminsitered with an a therapeutic agent selected from among: Calcineurin inhibitors (such as, but not limited to, cyclosporin, tacrolimus); mTOR inhibitors (such as, but not limited to, sirolimus, everolimus); anti-proliferatives (such as, but not limited to, azathioprine, mycophenolic acid); corticosteroids (such as, but not limited to, prednisone, cortisone acetate, prednisolone, methylprednisolone, dexamethasone, betamethasone, triamcinolone, beclometasone, fludrocortisone acetate, deoxycorticosterone acetate, aldosterone, hydrocortisone); antibodies (such as, but not limited to, monoclonal anti-IL-2Rα receptor antibodies (basiliximab, daclizumab), polyclonal anti-T-cell antibodies (anti-thymocyte globulin (ATG), anti-lymphocyte globulin (ALG)), B-cell antagonists, rituximab, natalizumab.

[00384] Other therapeutic agents include, but are not limited to: cyclophosphamide, penicillamine, cyclosporine, nitrosoureas, cisplatin, carboplatin, oxaliplatin, methotrexate, azathioprine, mercaptopurine, pyrimidine analogues, protein synthesis inhibitors, dactinomycin, anthracyclines, mitomycin C, bleomycin, mithramycin, Atgam(R), Thymoglobuline®, OKT3®, basiliximab, daclizumab, cyclosporin, tacrolimus, sirolimus, Interferons (IFN-β, IFN-γ), opioids, TNF binding proteins (infliximab, etanercept, adalimumab, golimumab), leflunomide, gold thioglucose, gold thiomalate, aurofin, sulfasalazine, hydroxychloroquinine, minocycline, rapamicin, mycophenolic acid, mycophenolate mofetil, FTY720, as well as those listed in US 7,060,697.

[00385] In one embodiment, a compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered in combination with Cyclosporin A (CsA) or tacrolimus (FK506). In one embodiment, a compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered to a mammal in combination with an anti-inflammatory agent including, but not limited to, non-steroidal anti-inflammatory drugs (NSAIDs) and corticosteroids (glucocorticoids).

[00386] NSAIDs include, but are not limited to: aspirin, salicylic acid, gentisic acid, choline magnesium salicylate, choline salicylate, choline magnesium salicylate, choline salicylate, magnesium salicylate, sodium salicylate, diflunisal, carprofen, fenoprofen, fenoprofen calcium, flurobiprofen, ibuprofen, ketoprofen, nabutone, ketolorac, ketorolac tromethamine, naproxen, oxaprozin, diclofenac, etodolac, indomethacin, sulindac, tolmetin, meclofenamate, meclofenamate sodium, mefenamic acid, piroxicam, meloxicam, COX-2 specific inhibitors (such as, but not limited to, celecoxib, rofecoxib, valdecoxib, parecoxib, etoricoxib, lumiracoxib, CS-502, JTE-522, L-745,337 and NS398).

[00387] Corticosteroids, include, but are not limited to: betamethasone, prednisone, alclometasone, aldosterone, amcinonide, beclometasone, betamethasone, budesonide, ciclesonide, clobetasol, clobetasone, clocortolone, cloprednol, cortisone, cortivazol, deflazacort, deoxycorticosterone, desonide, desoximetasone, desoxycortone, dexamethasone, diflorasone, diflucortolone, difluprednate, fluclorolone, fludrocortisone, fludroxycortide, flumetasone, flunisolide, fluocinolone acetonide, fluocinonide, fluocortin, fluocortolone, fluorometholone, fluperolone, fluprednidene, fluticasone, formocortal, halcinonide, halometasone, hydrocortisone/cortisol, hydrocortisone aceponate, hydrocortisone buteprate, hydrocortisone butyrate, loteprednol, medrysone, meprednisone, methylprednisolone, methylprednisolone aceponate, mometasone furoate, paramethasone, prednicarbate, prednisone/prednisolone, rimexolone, tixocortol, triamcinolone, and ulobetasol.

[00388] In one embodiment, a compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered in combination with leukotriene receptor antagonists including, but are not limited to, BAY u9773 (see EP 00791576; published 27 Aug 1997), DUO-LT (Tsuji *et al*, *Org. Biomol. Chem.*, 1, 3139-3141, 2003), zafirlukast, montelukast, prankulast, and derivatives or analogs thereof.

Other Combination Therapies

[00389] In another embodiment described herein, methods for treatment or prevention of conditions or diseases described herein, such as atherosclerosis, comprises administration to a patient compounds, pharmaceutical compositions, or medicaments described herein in combination with at least one additional agent selected from, by way of example only, HMG-CoA reductase inhibitors (e.g., statins in their lactonized or dihydroxy open acid forms and pharmaceutically acceptable salts and esters thereof, including but not limited to lovastatin; simvastatin; dihydroxy open-acid simvastatin, particularly the ammonium or calcium salts thereof; pravastatin, particularly the sodium salt thereof; fluvastatin, particularly the sodium salt thereof; atorvastatin, particularly the calcium salt

thereof; nisvastatin, also referred to as NK-104; rosuvastatin); agents that have both lipid-altering effects and other pharmaceutical activities; HMG-CoA synthase inhibitors; cholesterol absorption inhibitors such as ezetimibe; cholesterol ester transfer protein (CETP) inhibitors, for example JTT-705 and CP529, 414; squalene epoxidase inhibitors; squalene synthetase inhibitors (also known as squalene synthase inhibitors); acyl-coenzyme A: cholesterol acyltransferase (ACAT) inhibitors including selective inhibitors of ACAT-1 or ACAT-2 as well as dual inhibitors of ACAT-1 and-2; microsomal triglyceride transfer protein (MTP) inhibitors; probucol; niacin; bile acid sequestrants; LDL (low density lipoprotein) receptor inducers; platelet aggregation inhibitors, for example glycoprotein IIb/IIIa fibrinogen receptor antagonists and aspirin; human peroxisome proliferator activated receptor gamma (PPARγ) agonists, including the compounds commonly referred to as glitazones, for example troglitazone, pioglitazone and rosiglitazone and including those compounds included within the structural class known as thiazolidinediones as well as those PPARγ agonists outside the thiazolidinedione structural class; PPARα agonists such as clofibrate, fenofibrate including micronized fenofibrate, and gemfibrozil ; PPAR dual α/γ agonists such as 5-[(2, 4-dioxo-5-thiazolidinyl)methyl]-2-methoxy-N-[[4-(trifluoromethyl)phenyl]methyl]-benzamide, known as KRP-297; vitamin B6 (also known as pyridoxine) and the pharmaceutically acceptable salts thereof such as the HCl salt; vitamin B12 (also known as cyanocobalamin); folic acid or a pharmaceutically acceptable salt or ester thereof such as the sodium salt and the methylglucamine salt; anti-oxidant vitamins such as vitamin C and E and beta carotene; beta-blockers; angiotensin II antagonists such as losartan; angiotensin converting enzyme inhibitors such as enalapril and captopril ; calcium channel blockers such as nifedipine and diltiazam; endothelian antagonists; agents that enhance ABC1 gene expression; FXR and LXR ligands including both inhibitors and agonists; bisphosphonate compounds such as alendronate sodium; and cyclooxygenase-2 inhibitors such as rofecoxib and celecoxib.

[00390] In another embodiment described herein, methods for treatment or prevention of conditions or diseases described herein comprises administration to a patient compounds, pharmaceutical compositions, or medicaments described herein in combination with at least one additional agent selected from COX-2 inhibitors; nitric oxide synthase inhibitors, such as N-(3-(aminomethyl)benzyl) acetamidine; Rho kinase inhibitors, such as fasudil; angiotension II type-1 receptor antagonists, including candesartan, losartan, irbesartan, eprosartan, telmisartan and valsartan; glycogen synthase kinase 3 inhibitors; sodium or calcium channel blockers, including crobenetine; p38 MAP kinase inhibitors, including SKB 239063; thromboxane AX- synthetase inhibitors, including isbogrel, ozagrel, ridogrel and dazoxiben; statins (HMG CoA reductase inhibitors), including lovastatin, simvastatin, dihydroxy open-acid simvastatin, pravastatin, fluvastatin, atorvastatin, nisvastatin, and rosuvastatin; neuroprotectants, including free radical scavengers, calcium channel blockers, excitatory amino acid antagonists, growth factors, antioxidants, such as edaravone, vitamin C, TROLOX™, citicoline and minicycline, and reactive astrocyte inhibitors, such as (2R)-2-propyloctanoic acid; beta andrenergic blockers, such as propranolol, nadolol, timolol, pindolol,

labetalol, metoprolol, atenolol, esmolol and acebutolol; NMDA receptor antagonists, including memantine; NR2B antagonists, such as traxoprodil; 5-HTlA agonists; receptor platelet fibrinogen receptor antagonists, including tirofiban and lamifiban; thrombin inhibitors; antithrombotics, such as argatroban; antihypertensive agents, such as enalapril; vasodilators, such as cyclandelate; nociceptin antagonists; DPIV antagonists; GABA 5 inverse agonists; and selective androgen receptor modulators.

[00391] In another embodiment described herein, autotaxin inhibitors described herein are coadministered with at least one additional agent selected from, by way of example only, dimethylsulfoxide, omalizumab, and pentosan polysulfate.

[00392] In yet another embodiment described herein, autotaxin inhibitors described herein are coadministered with at least one agent used in the treatment of respiratory conditions. Agents used in the treatment of respiratory conditions include, but are not limited to, bronchodilators (e.g., sympathomimetic agents and xanthine derivatives), leukotriene receptor antagonists, leukotriene formation inhibitors, leukotriene modulators, nasal decongestants, respiratory enzymes, lung surfactants, antihistamines (e.g., mepyramine (pyrilamine), antazoline, diphenhydramine, carbinoxamine, doxylamine, clemastine, dimenhydrinate, pheniramine, chlorphenamine (chlorpheniramine), dexchlorpheniramine, brompheniramine, triprolidine, cetirizine, cyclizine, chlorcyclizine, hydroxyzine, meclizine, loratadine, desloratidine, promethazine, alimemazine (trimeprazine), cyproheptadine, azatadine, ketotifen, acrivastine, astemizole, cetirizine, mizolastine, terfenadine, azelastine, levocabastine, olopatadine, levocetirizine, fexofenadine), mucolytics, corticosteroids, anticholinergics, antitussives, analgesics, expectorants, albuterol, ephedrine, epinephrine, fomoterol, metaproterenol, terbutaline, budesonide, ciclesonide, dexamethasone, flunisolide, fluticasone propionate, triamcinolone acetonide, ipratropium bromide, pseudoephedrine, theophylline, montelukast, zafirlukast, ambrisentan, bosentan, enrasentan, sitaxsentan, tezosentan, iloprost, treprostinil, pirfenidone, 5-lipoxygenase-activating protein (FLAP) inhibitors, FLAP modulators and 5-LO inhibitors.

[00393] In a specific embodiment described herein, autotaxin inhibitors described herein are coadministered with anti-inflammatory agents. In certain embodiments, autotaxin inhibitors described herein are coadministered with at least one additional agent selected from, but not limited to, epinephrine, isoproterenol, orciprenaline, bronchodilators, glucocorticoids, leukotriene modifiers, mast-cell stabilizers, xanthines, anticholinergics, β-2 agonists, FLAP inhibitors, FLAP modulators or 5-LO inhibitors. β-2 agonists include, but are not limited to, short-acting β-2 agonists (e.g., salbutamol (albuterol), levalbuterol, terbutaline, pirbuterol, procaterol, metaproterenol, fenoterol and bitolterol mesylate) and long-acting β-2 agonists (e.g., salmeterol, formoterol, bambuterol and clenbuterol). FLAP inhibitors and/or FLAP modulators include, but are not limited to, 3-[3-tert-butylsulfanyl-1-[4-(6-methoxy-pyridin-3-yl)-benzyl]-5-(pyridin-2-ylmethoxy)-1H-indol-2-yl]-2,2-dimethyl-propionic acid, 3-[3-*tert*-butylsulfanyl-1-[4-(6-ethoxy-pyridin-3-yl)-benzyl]-5-(5-methyl-

pyridin-2-ylmethoxy)-1*H*-indol-2-yl]-2,2-dimethyl-propionic acid, MK-886, MK-0591, BAY-x1005 and compounds found in US 2007/0225285, US 2007/0219206, US 2007/0173508, US 2007/0123522 and US 2007/0105866 (each of which are hereby incorporated by reference). Glucocorticoids include, but are not limited to, beclometasone, budesonide, ciclesonide, fluticasone and mometasone. Anticholinergics include, but are not limited to, ipratropium and tiotropium. Mast cell stabilizers include, but are not limited to, cromoglicate and nedocromil. Xanthines include, but are not limited to, amminophylline, theobromine and theophylline. Leukotriene antagonists include, but are not limited to, montelukast, tomelukast, pranlukast and zafirlukast. 5-LO inhibitors include, but are not limited to, zileuton, VIA-2291 (ABT761), AZ-4407 and ZD-2138 and compounds found in US 2007/0149579, WO2007/016784.

[00394] In another specific embodiment described herein, autotaxin inhibitors described herein are coadministered with at least one additional agent selected from antihistamines, leukotriene antagonists, corticosteroids and decongestants. Leukotriene antagonists include, but are not limited to, montelukast, tomelukast, pranlukast and zafirlukast.

[00395] In one aspect, autotaxin inhibitors described herein are coadministered with one or more agents used to treat used to treat asthma, including, but not limited to: combination inhalers (fluticasone and salmeterol oral inhalation (e.g. Advair)); inhaled Beta-2 agonists (albuterol inhaler; albuterol nebulizer solution; formoterol; isoproterenol oral inhalation; levalbuterol; metaproterenol inhalation; pirbuterol acetate oral inhalation; salmeterol aerosol inhalation; salmeterol powder inhalation; terbutaline inhaler); inhaled corticosteroids (beclomethasone oral inhalation; budesonide inhalation solution; budesonide inhaler; flunisolide oral inhalation; fluticasone inhalation aerosol; fluticasone powder for oral inhalation; mometasone inhalation powder; triamcinolone oral inhalation); leukotriene modifiers (montelukast; zafirlukast; zileuton); mast cell stabilizers (cromolyn inhaler; nedocromil oral inhalation); monoclonal antibodies (omalizumab); oral Beta-2 agonists (albuterol oral syrup; albuterol oral tablets; metaproterenol; terbutaline); bronchodilator (aminophylline; oxtriphylline; theophylline).

[00396] In one aspect, autotaxin inhibitors described herein are coadministered with one or more agents used to treat allergy, including, but not limited to, antihistamine and decongestant combinations (cetirizine and pseudoephedrine; desloratadine and pseudoephedrine ER; fexofenadine and pseudoephedrine; loratadine and pseudoephedrine); antihistamines (azelastine nasal spray; brompheniramine; brompheniramine oral suspension; carbinoxamine; cetirizine; chlorpheniramine; clemastine; desloratadine; dexchlorpheniramine ER; dexchlorpheniramine oral syrup; diphenhydramine oral; fexofenadine; loratadine; promethazine); decongestants (pseudoephedrine); leukotriene modifiers (montelukast; montelukast granules); nasal anticholinergics (ipratropium); nasal corticosteroids (beclomethasone nasal inhalation; budesonide nasal inhaler; flunisolide nasal inhalation; fluticasone nasal inhalation; mometasone nasal spray; triamcinolone nasal inhalation;

triamcinolone nasal spray); nasal decongestants (phenylephrine); nasal mast cell stabilizers (cromolyn nasal spray).

[00397] In one aspect, autotaxin inhibitors described herein are coadministered with one or more agents used to treat chronic obstructive pulmonary disease (COPD), including, but not limited to, anticholinergics - ipratropium bromide oral inhalation); combination Inhalers (albuterol and ipratropium (e.g. Combivent, DuoNeb); fluticasone and salmeterol oral inhalation (e.g. Advair)); corticosteroids (dexamethasone tablets; fludrocortisone acetate; hydrocortisone tablets; methylprednisolone; prednisolone liquid; prednisone oral; triamcinolone oral); inhaled Beta-2 Agonists (albuterol inhaler; albuterol nebulizer solution; formoterol; isoproterenol oral inhalation; levalbuterol; metaproterenol inhalation; pirbuterol acetate oral inhalation; salmeterol aerosol inhalation; salmeterol powder inhalation; terbutaline inhaler); inhaled Corticosteroids (beclomethasone oral inhalation; budesonide inhalation solution; budesonide inhaler; flunisolide oral inhalation; fluticasone inhalation aerosol; fluticasone powder for oral inhalation; triamcinolone oral inhalation); mukolytics (guaifenesin); oral Beta-2 agonists (albuterol oral syrup; albuterol oral tablets; metaproterenol; terbutaline); bronchodilator (aminophylline; oxtriphylline; theophylline).

Kits/Articles of Manufacture

[00398] For use in the therapeutic applications described herein, kits and articles of manufacture are also described herein. Such kits can comprise a carrier, package, or container that is compartmentalized to receive one or more containers such as vials, tubes, and the like, each of the container(s) comprising one of the separate elements to be used in a method described herein. Suitable containers include, for example, bottles, vials, syringes, and test tubes. The containers are formed from any acceptable material including, e.g., glass or plastic.

[00399] For example, the container(s) can comprise one or more compounds described herein, optionally in a composition or in combination with another agent as disclosed herein. The container(s) optionally have a sterile access port (for example the container can be an intravenous solution bag or a vial having a stopper pierceable by a hypodermic injection needle). Such kits optionally comprising a compound with an identifying description or label or instructions relating to its use in the methods described herein.

[00400] A kit will typically comprise one or more additional containers, each with one or more of various materials (such as reagents, optionally in concentrated form, and/or devices) desirable from a commercial and user standpoint for use of a compound described herein. Non-limiting examples of such materials include, but not limited to, buffers, diluents, filters, needles, syringes; carrier, package, container, vial and/or tube labels listing contents and/or instructions for use, and package inserts with instructions for use. A set of instructions will also typically be included.

[00401] A label can be on or associated with the container. A label can be on a container when letters, numbers or other characters forming the label are attached, molded or etched into the container itself; a label can be associated with a container when it is present within a receptacle or carrier that also

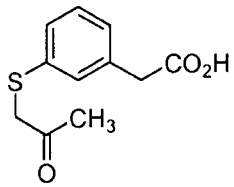
holds the container, e.g., as a package insert. A label can be used to indicate that the contents are to be used for a specific therapeutic application. The label can also indicate directions for use of the contents, such as in the methods described herein.

EXAMPLES

[00402] These examples are provided for illustrative purposes only and not to limit the scope of the claims provided herein.

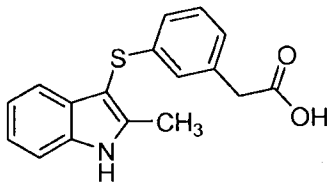
Synthesis of Compounds

Example 1: Synthesis of [3-(2-Methyl-1*H*-indol-3-ylsulfanyl)-phenyl]-acetic acid (Compound 1-1)



Step 1: [3-(2-Oxo-propylsulfanyl)-phenyl]-acetic acid

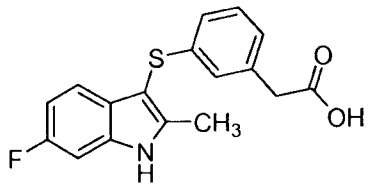
[00403] 3-Mercaptophenylacetic acid (3.0 g, 17.9 mmol) and chloroacetone (1.5 mL, 18.8 mmol) were combined in THF (100 mL) then a solution of *N,N*-diisopropylethylamine (10.9 mL, 62.7 mmol) in THF (100 mL) was added by addition funnel over the course of 20 minutes at room temperature. After 2 hours H_2O (100 mL) was added and the reaction mixture was worked up to give the title compound as a solid.



Step 2: [3-(2-Methyl-1*H*-indol-3-ylsulfanyl)-phenyl]-acetic acid

[00404] [3-(2-Oxo-propylsulfanyl)-phenyl]-acetic acid (0.200 g, 1.12 mmol) was dissolved in *t*-BuOH (5 mL) then phenylhydrazine (121 µL, 1.232 mmol) was added followed by HCl (1.232 mL, 1.0M in ether). The reaction was heated to 70 °C for 1 hour then cooled and submitted to aqueous workup to afford the title compound.

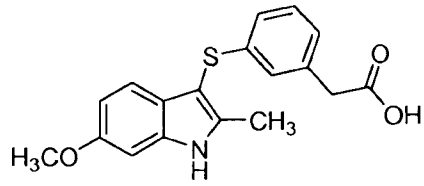
Example 2: Synthesis of [3-(6-Fluoro-2-methyl-1*H*-indol-3-ylsulfanyl)-phenyl]-acetic acid (Compound 1-2)



Step 1: [3-(6-Fluoro-2-methyl-1*H*-indol-3-ylsulfanyl)-phenyl]-acetic acid

[00405] [3-(2-Oxo-propylsulfanyl)-phenyl]-acetic acid (0.500 g, 2.2 mmol) and 3-fluorophenylhydrazine hydrochloride (0.400 g, 2.45 mmol) were dissolved in *t*-BuOH (10 mL). The reaction was stirred at 70 °C for 1.5 hours then submitted to aqueous workup. Purification by preparatory HPLC (10-100% ACN in H_2O) afforded a 5:3 mixture of separable regioisomers of which the title compound was the major component.

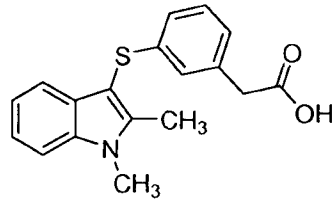
Example 3: Synthesis of [3-(6-Methoxy-2-methyl-1*H*-indol-3-ylsulfanyl)-phenyl]-acetic acid (Compound 1-3)



Step 1: [3-(6-Methoxy-2-methyl-1*H*-indol-3-ylsulfanyl)-phenyl]-acetic acid

[00406] Prepared according to the procedure described in Example 2, Step 1, using the following starting materials: [3-(2-oxo-propylsulfanyl)-phenyl]-acetic acid and 3-methoxyphenylhydrazine hydrochloride.

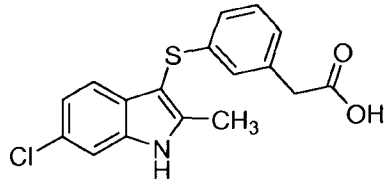
Example 4: Synthesis of [3-(1,2-Dimethyl-1*H*-indol-3-ylsulfanyl)-phenyl]-acetic acid (Compound 1-4)



Step 1: [3-(1,2-Dimethyl-1*H*-indol-3-ylsulfanyl)-phenyl]-acetic acid

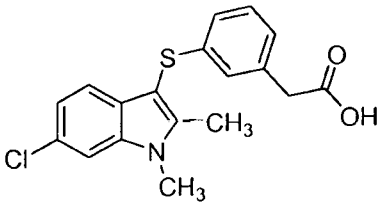
[00407] [3-(2-Methyl-1*H*-indol-3-ylsulfanyl)-phenyl]-acetic acid (0.050 g, 0.17 mmol) was dissolved in DMF:THF (1:1, 4 mL) and cooled to 0 °C. Lithium bis(trimethylsilyl)amide solution (0.370 mL, 0.37 mmol, 1.0M in hexanes) was added. After 5 minutes iodomethane (11 µL, 0.18 mmol) was added and the reaction was allowed to warm to room temperature. The reaction was stirred for an additional 5 minutes then submitted to aqueous workup. Purification by preparatory HPLC (10-100% ACN in H_2O) provided the title compound.

Example 5: Synthesis of [3-(6-Chloro-1,2-dimethyl-1*H*-indol-3-ylsulfanyl)-phenyl]-acetic acid (Compound 1-5)



Step 1: [3-(6-Chloro-2-methyl-1*H*-indol-3-ylsulfanyl)-phenyl]-acetic acid

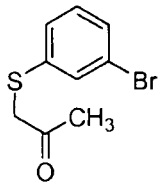
[00408] Prepared according to the procedure described in Example 2, Step 1, using the following starting materials: [3-(2-oxo-propylsulfanyl)-phenyl]-acetic acid and 3-chlorophenylhydrazine hydrochloride.



Step 2: [3-(6-Chloro-1,2-dimethyl-1*H*-indol-3-ylsulfanyl)-phenyl]-acetic acid

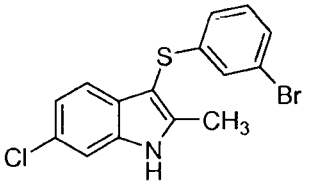
[00409] [3-(6-Chloro-2-methyl-1*H*-indol-3-ylsulfanyl)-phenyl]-acetic acid (0.062 g, 0.19 mmol) was dissolved in DMF (3 mL) and cooled to -10 °C and then sodium bis(trimethyl)amide solution (0.420 mL, 0.42 mmol, 1.0M solution) was added. The reaction was stirred for 1 hour then iodomethane (13 µL, 0.21 mmol) was added in one portion. Standard aqueous workup and purification by preparatory HPLC provided the title compound.

Example 6: Synthesis of 3-(6-Chloro-1,2-dimethyl-1*H*-indol-3-ylsulfanyl)-benzoic acid (Compound 1-6)



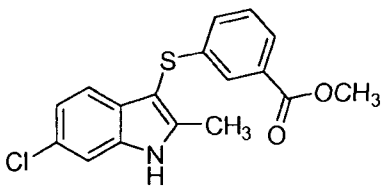
Step 1: 1-(3-Bromo-phenylsulfanyl)-propan-2-one

[00410] 3-Bromothiophenol (2.89 g, 15.29 mmol) and chloroacetone (1.278 mL, 16.06 mmol) were mixed in THF (80 mL) and cooled to 0 °C. *N,N*-Diisopropylethylamine (6.65 mL, 38.23 mmol) was added and the reaction was stirred at 0 °C for five minutes then allowed to warm to room temperature and stirred overnight. The reaction was then extracted with EtOAc and H_2O and the organic portion was concentrated to afford the title compound.



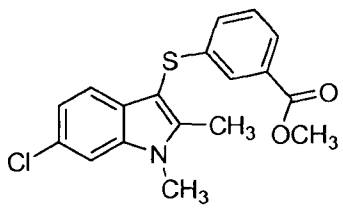
Step 2: 3-(3-Bromo-phenylsulfanyl)-6-chloro-2-methyl-1*H*-indole

[00411] 1-(3-Bromo-phenylsulfanyl)-propan-2-one (1.5 g, 6.12 mmol) and 3-chlorophenylhydrazine hydrochloride (1.21 g, 6.73 mmol) were combined in *t*-BuOH (50 mL) and the reaction was heated to 80 °C and stirred overnight. After cooling the reaction was worked-up using standard procedures to afford a crude mixture of two regioisomers which was then purified using silica gel chromatography (0-30% EtOAc in hexanes) to give the title compound.



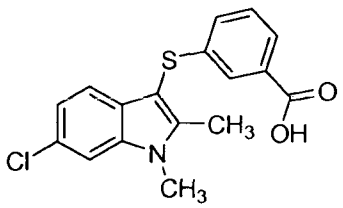
Step 3: 3-(6-Chloro-2-methyl-1*H*-indol-3-ylsulfanyl)-benzoic acid methyl ester

[00412] 3-(3-Bromo-phenylsulfanyl)-6-chloro-2-methyl-1*H*-indole (4.764 g, 13.5 mmol) was combined with triethylamine (4.7 mL, 33.75 mmol) in DMF:MeOH (1:1, 150 mL) and N_2 (g) was bubbled through the mixture for 30 minutes. (1,1'-Bis(diphenylphosphino)ferrocene)-dichloropalladium(II) (0.988 g, 1.35 mmol) was added to the reaction then CO (g) at atmospheric pressure was bubbled in for 30 seconds. The reaction was then heated under an atmosphere of CO at 80 °C for 4 hours followed by standard workup. The crude material was purified by silica gel chromatography (0-30% EtOAc in hexanes) to afford the title compound.



Step 4: 3-(6-Chloro-1,2-dimethyl-1*H*-indol-3-ylsulfanyl)-benzoic acid methyl ester

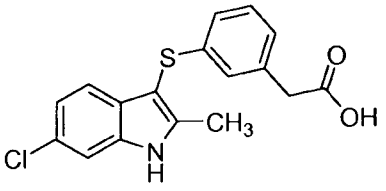
[00413] 3-(6-Chloro-2-methyl-1*H*-indol-3-ylsulfanyl)-benzoic acid methyl ester (0.0752 g, 0.23 mmol) was dissolved in DMF:THF (1:1, 4 mL) and cooled to -78 °C. Lithium bis(trimethylsilyl)amide solution (0.500 mL, 0.5 mmol, 1.0M in hexanes) was added. After 1 hour, iodomethane (11 µL, 0.18 mmol) was added and the reaction was allowed to warm to room temperature over 30 minutes then submitted to aqueous workup. Purification by silica gel chromatography (0-100% EtOAc in hexanes) provided the title compound.



Step 5: 3-(6-Chloro-1,2-dimethyl-1*H*-indol-3-ylsulfanyl)-benzoic acid

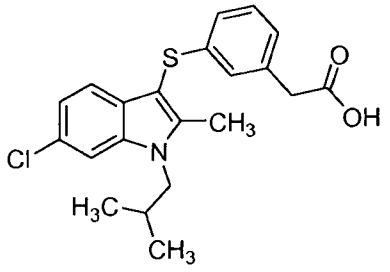
[00414] 3-(6-Chloro-1,2-dimethyl-1*H*-indol-3-ylsulfanyl)-benzoic acid methyl ester (0.079 g, 0.23 mmol) was dissolved in MeOH:THF (1:1, 5 mL) and LiOH (2.30 mL, 1M aq., 2.3 mmol) was added. The reaction was stirred at room temperature overnight then submitted to aqueous workup procedure. Purification by preparatory HPLC (10-100% ACN in H_2O) to yield the title compound.

Example 7: Synthesis of [3-(6-Chloro-1-isobutyl-2-methyl-1*H*-indol-3-ylsulfanyl)-phenyl]-acetic acid (Compound 1-7)



Step 1: [3-(6-Chloro-2-methyl-1*H*-indol-3-ylsulfanyl)-phenyl]-acetic acid

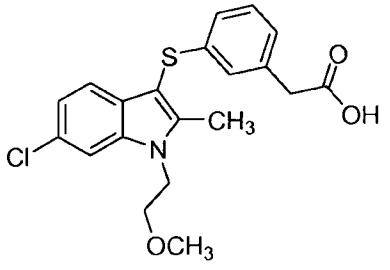
[00415] Prepared according to the procedure described in Example 2, Step 1, using the following starting materials: [3-(2-oxo-propylsulfanyl)-phenyl]-acetic acid and 3-chlorophenylhydrazine hydrochloride.



Step 2: [3-(6-Chloro-1-isobutyl-2-methyl-1*H*-indol-3-ylsulfanyl)-phenyl]-acetic acid

[00416] Prepared according to the procedure described in Example 4, Step 1, using the following starting materials: [3-(6-chloro-2-methyl-1*H*-indol-3-ylsulfanyl)-phenyl]-acetic acid and 1-bromo-2-methylpropane.

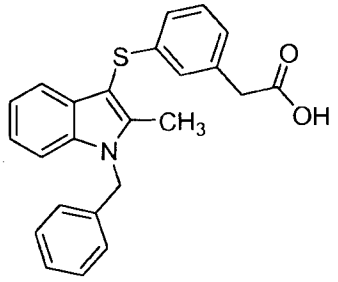
Example 8: Synthesis of {3-[6-Chloro-1-(2-methoxy-ethyl)-2-methyl-1*H*-indol-3-ylsulfanyl]-phenyl}-acetic acid (Compound 1-8)



Step 1: {3-[6-Chloro-1-(2-methoxy-ethyl)-2-methyl-1*H*-indol-3-ylsulfanyl]-phenyl}-acetic acid

[00417] Prepared according to the procedure described in Example 4, Step 1, using the following starting materials: [3-(6-chloro-2-methyl-1*H*-indol-3-ylsulfanyl)-phenyl]-acetic acid and 2-bromethyl methyl ether.

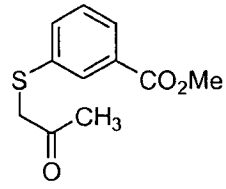
Example 9: Synthesis of [3-(1-Benzyl-2-methyl-1*H*-indol-3-ylsulfanyl)-phenyl]-acetic acid (Compound 1-9)



Step 1: 3-(1-Benzyl-2-methyl-1*H*-indol-3-ylsulfanyl)-phenyl]-acetic acid

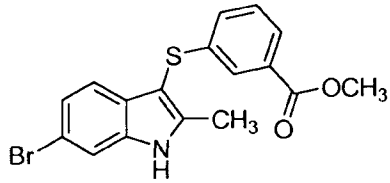
[00418] Prepared according to the procedure described in Example 4, Step 1, using the following starting materials: [3-(2-methyl-1*H*-indol-3-ylsulfanyl)-phenyl]-acetic acid and benzyl bromide.

Example 10: Synthesis of 3-(1-Benzyl-6-bromo-2-methyl-1*H*-indol-3-ylsulfanyl)-benzoic acid (Compound 1-10)



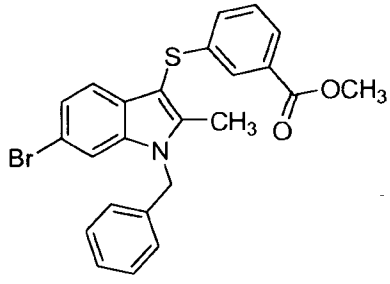
Step 1: 3-(2-Oxo-propylsulfanyl)-benzoic acid methyl ester

[00419] 1-(3-Bromo-phenylsulfanyl)-propan-2-one (4.0 g, 16.3 mmol) was dissolved in MeOH:DMF (1:1, 100 mL) and N_2 (g) was bubbled through the solution for 5 minutes. Triethylamine (5.7 mL, 40.8 mmol) and (1,1'-bis(diphenylphosphino)ferrocene)-dichloropalladium(II) (0.600 g, 0.82 mmol) were added then CO (g) was bubbled into the reaction mixture for five minutes. The reaction was kept under CO atmosphere and heated to 80 °C overnight. The reaction was worked up then filtered through a plug of silica gel (1:1 EtOAc: hexanes) and concentrated to give the title compound.



Step 2: 3-(6-Bromo-2-methyl-1*H*-indol-3-ylsulfanyl)-benzoic acid methyl ester

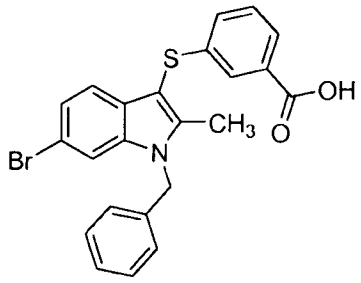
[00420] 3-(2-Oxo-propylsulfanyl)-benzoic acid methyl ester (3.65 g, 16.29 mmol) and 3-bromophenylhydrazine hydrochloride (4.01 g, 17.92 mmol) were mixed together in *t*-BuOH (100 mL) and heated to reflux for 1 hour. After cooling the reaction was concentrated then submitted to standard workup procedure and the crude mixture was purified by silica gel chromatography (0-30% EtOAc in hexanes) to afford a separable 5:4 mixture of regioisomers wherein the title compound was the major product.



Step 3: 3-(1-Benzyl-6-bromo-2-methyl-1*H*-indol-3-ylsulfanyl)-benzoic acid methyl ester

[00421] 3-(6-Bromo-2-methyl-1*H*-indol-3-ylsulfanyl)-benzoic acid methyl ester (1.13 g, 3.0 mmol) was dissolved in DMF and cooled to 0 °C then sodium hydride (60% dispersion in mineral oil, 0.156 g, 3.9 mmol) was added. After 5 minutes benzyl bromide (0.500 mL, 4.2 mmol) was added and the

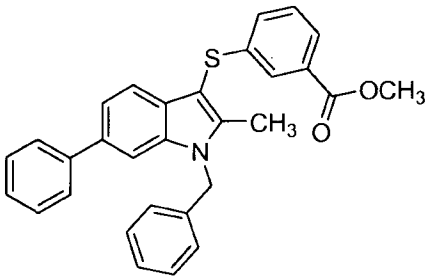
reaction was allowed to warm to room temperature. After 1 hour the reaction was re-cooled to 0 °C then quenched with aqueous HCl (5 mL, 1N). After extraction the crude product was purified by silica gel chromatography (0-30% EtOAc in hexanes) to afford the title compound.



Step 4: 3-(1-Benzyl-6-bromo-2-methyl-1*H*-indol-3-ylsulfanyl)-benzoic acid

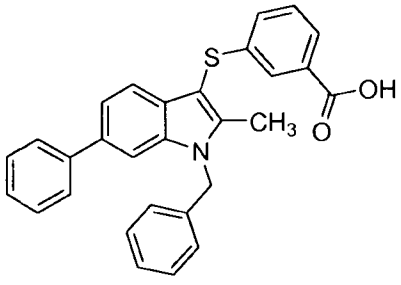
[00422] 3-(1-Benzyl-6-bromo-2-methyl-1*H*-indol-3-ylsulfanyl)-benzoic acid methyl ester (0.040 g, 0.086 mmol) was dissolved in THF:MeOH (1:1) then LiOH (1M aq.) was added and the reaction stirred at room temperature overnight. Acid-base extraction afforded the title compound.

Example 11: Synthesis of 3-(1-Benzyl-2-methyl-6-phenyl-1*H*-indol-3-ylsulfanyl)-benzoic acid (Compound 1-11)



Step 1: 3-(1-Benzyl-2-methyl-6-phenyl-1*H*-indol-3-ylsulfanyl)-benzoic acid methyl ester

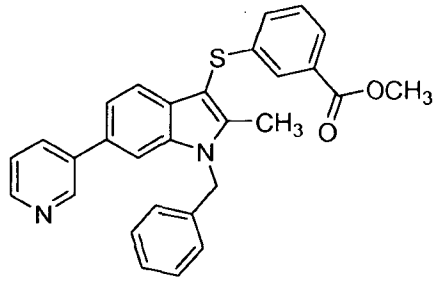
[00423] 3-(1-Benzyl-6-bromo-2-methyl-1*H*-indol-3-ylsulfanyl)-benzoic acid methyl ester (0.080 g, 0.17 mmol), phenylboronic acid (0.042 g, 0.34 mmol), $NaHCO_3$ (0.073 g, 0.85 mmol) and bis(triphenylphosphine)palladium(II) dichloride (0.012 g, 0.02 mmol) were suspended in DME:H_2O (1:1, 3 mL) and the reaction vessel was purged with N_2 (g). The reaction was heated to 90 °C and after two hours the mixture was submitted to aqueous workup then purified by silica gel chromatography (0-30% EtOAc in hexanes) to give the title compound.



Step 2: 3-(1-Benzyl-2-methyl-6-phenyl-1*H*-indol-3-ylsulfanyl)-benzoic acid

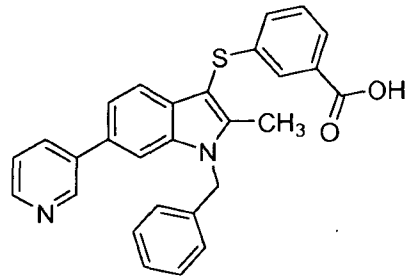
[00424] Prepared according to the procedure described in Example 10, Step 4, using the following starting material: 3-(1-benzyl-2-methyl-6-phenyl-1*H*-indol-3-ylsulfanyl)-benzoic acid methyl ester.

Example 12: Synthesis of 3-(1-Benzyl-2-methyl-6-pyridin-3-yl-1*H*-indol-3-ylsulfanyl)-benzoic acid (Compound 1-12)



Step 1: 3-(1-Benzyl-2-methyl-6-pyridin-3-yl-1*H*-indol-3-ylsulfanyl)-benzoic acid methyl ester

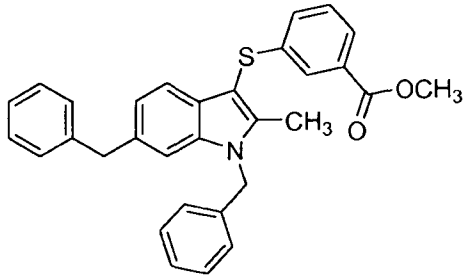
[00425] Prepared according to the procedure described in Example 11, Step 1, using the following starting materials: 3-(1-benzyl-6-bromo-2-methyl-1*H*-indol-3-ylsulfanyl)-benzoic acid methyl ester and 3-pyridineboronic acid.



Step 2: 3-(1-Benzyl-2-methyl-6-pyridin-3-yl-1*H*-indol-3-ylsulfanyl)-benzoic acid

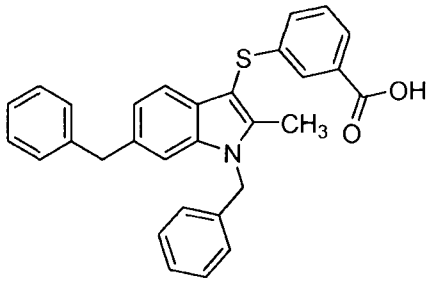
[00426] Prepared according to the procedure described in Example 10, Step 4, using the following starting material: 3-(1-benzyl-2-methyl-6-pyridin-3-yl-1*H*-indol-3-ylsulfanyl)-benzoic acid methyl ester.

Example 13: Synthesis of 3-(1,6-Dibenzyl-2-methyl-1*H*-indol-3-ylsulfanyl)-benzoic acid (Compound 1-13)



Step 1: 3-(1,6-Dibenzyl-2-methyl-1*H*-indol-3-ylsulfanyl)-benzoic acid methyl ester

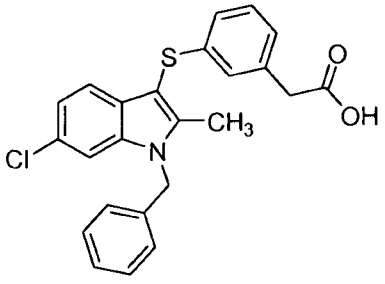
[00427] Prepared according to the procedure described in Example 11, Step 1, using the following starting materials: 3-(1-benzyl-6-bromo-2-methyl-1*H*-indol-3-ylsulfanyl)-benzoic acid methyl ester and benzylboronic acid pinacol ester.



Step 2: 3-(1,6-Dibenzyl-2-methyl-1*H*-indol-3-ylsulfanyl)-benzoic acid

[00428] Prepared according to the procedure described in Example 10, Step 4, using the following starting material: 3-(1,6-dibenzyl-2-methyl-1*H*-indol-3-ylsulfanyl)-benzoic acid methyl ester.

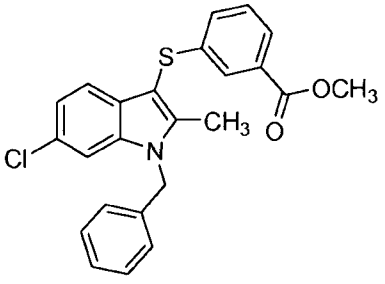
Example 14: Synthesis of [3-(1-Benzyl-6-chloro-2-methyl-1*H*-indol-3-ylsulfanyl)-phenyl]-acetic acid (Compound 1-14)



Step 1: [3-(1-Benzyl-6-chloro-2-methyl-1*H*-indol-3-ylsulfanyl)-phenyl]-acetic acid

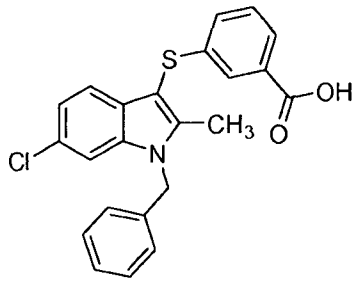
[00429] Prepared according to the procedure described in Example 4, Step 1, using the following starting materials: [3-(6-chloro-2-methyl-1*H*-indol-3-ylsulfanyl)-phenyl]-acetic acid and benzyl bromide.

Example 15: Synthesis of 3-(1-Benzyl-6-chloro-2-methyl-1*H*-indol-3-ylsulfanyl)-benzoic acid (Compound 1-15)



Step 1: 3-(1-Benzyl-6-chloro-2-methyl-1*H*-indol-3-ylsulfanyl)-benzoic acid methyl ester

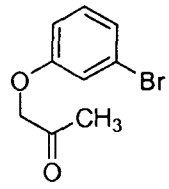
[00430] Prepared according to the procedure described in Example 4, Step 1, using the following starting materials: 3-(6-chloro-2-methyl-1H-indol-3-ylsulfanyl)-benzoic acid methyl ester and benzyl bromide.



Step 2: 3-(1-Benzyl-6-chloro-2-methyl-1*H*-indol-3-ylsulfanyl)-benzoic acid

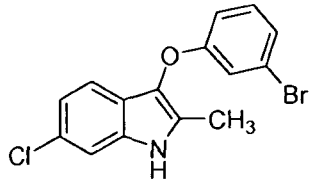
[00431] Prepared according to the procedure described in Example 10, Step 4, using the following starting material: 3-(1-benzyl-6-chloro-2-methyl-1*H*-indol-3-ylsulfanyl)-benzoic acid methyl ester.

Example 16: Synthesis of [3-(1-Benzyl-6-chloro-2-methyl-1*H*-indol-3-yloxy)-phenyl]-acetic acid (Compound 1-16)



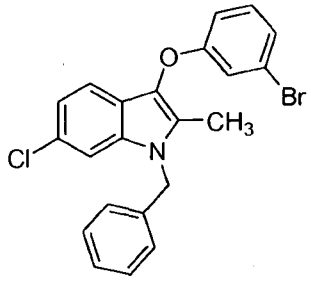
Step 1: 1-(3-Bromo-phenoxy)-propan-2-one

[00432] 3-Bromophenol (6.27 g, 36 mmol) and cesium carbonate (20. g, 61.2 mmol) were dissolved in DMF (50 mL) and stirred for 15 minutes at room temperature. Chloroacetone (4.3 mL, 54 mmol) was added and the reaction stirred for 1 hour and was submitted to aqueous workup. Purification by silica gel chromatography (0-50% EtOAc in hexanes) afforded the title compound.



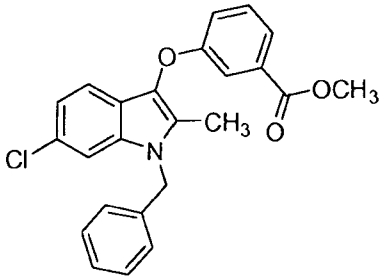
Step 2: 3-(3-Bromo-phenoxy)-6-chloro-2-methyl-1*H*-indole

[00433] 1-(3-Bromo-phenoxy)-propan-2-one (5.95 g, 26 mmol) and 3-chlorophenylhydrazine hydrochloride (4.65 g, 26 mmol) were combined in ACN (100 mL) and the reaction was heated to reflux for 1 hour. After cooling the reaction was worked-up using standard procedures then purified using silica gel chromatography to give a 3:4 mixture of separable regioisomers of which the minor component was the title compound.



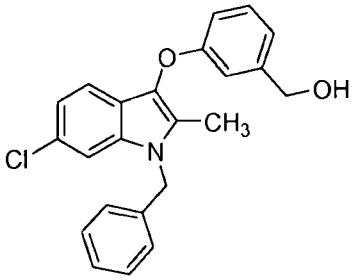
Step 3: 1-Benzyl-3-(3-bromo-phenoxy)-6-chloro-2-methyl-1*H*-indole

[00434] Prepared according to the procedure described in Example 4, Step 1, using the following starting materials: 3-(3-bromo-phenoxy)-6-chloro-2-methyl-1*H*-indole and benzyl bromide.



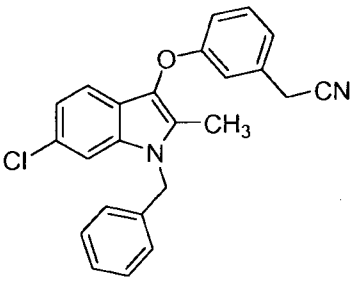
Step 4: 3-(1-Benzyl-6-chloro-2-methyl-1*H*-indol-3-yloxy)-benzoic acid methyl ester

[00435] Prepared according to the procedure described in Example 6, Step 3, using the following starting material: 1-benzyl-3-(3-bromo-phenoxy)-6-chloro-2-methyl-1*H*-indole.



Step 5: [3-(1-Benzyl-6-chloro-2-methyl-1*H*-indol-3-yloxy)-phenyl]-methanol

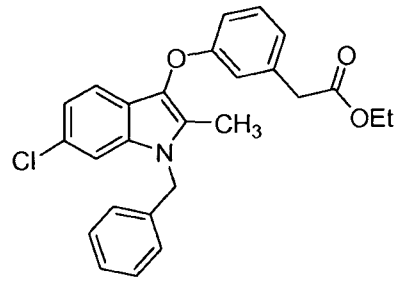
[00436] 3-(1-Benzyl-6-chloro-2-methyl-1*H*-indol-3-yloxy)-benzoic acid methyl ester (0.100 g, 0.25 mmol) was dissolved in THF (3 mL) and the solution was cooled to 0 °C. Diisobutylaluminum hydride (0.750 mL, 1.0M in hexanes, 0.75 mmol) was added dropwise and the reaction was stirred for 20 minutes then an additional amount of diisobutylaluminum hydride (0.100 mL, 1.0M in hexanes, 0.10 mmol) was added. The reaction was allowed to stir for 20 minutes then quenched with aq. HCl (2 mL, 1M). The reaction was submitted to a standard workup procedure to give the title compound.



Step 6: [3-(1-Benzyl-6-chloro-2-methyl-1*H*-indol-3-yloxy)-phenyl]-acetonitrile

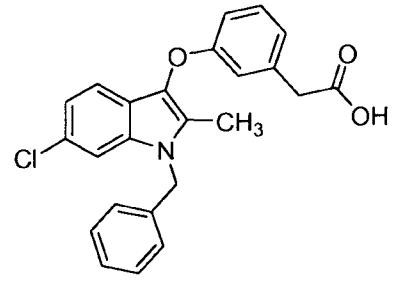
[00437] [3-(1-Benzyl-6-chloro-2-methyl-1*H*-indol-3-yloxy)-phenyl]-methanol (0.092 g, 0.243 mmol) and *N,N*-diisopropylethylamine (3 µL, 0.486 mmol) were dissolved in DCM at 0 °C. Methanesulfonyl chloride (28 µL, 0.365 mmol) was added and the reaction stirred for 5 minutes then sodium cyanide (0.024 g, 0.486 mmol) and DMF (2 mL) were added. The reaction was then

concentrated under vacuum and DMF (2 mL) was added. The reaction was heated to 60 °C for 20 minutes then submitted to aqueous workup to give the title compound.



Step 7: [3-(1-Benzyl-6-chloro-2-methyl-1*H*-indol-3-yloxy)-phenyl]-acetic acid ethyl ester

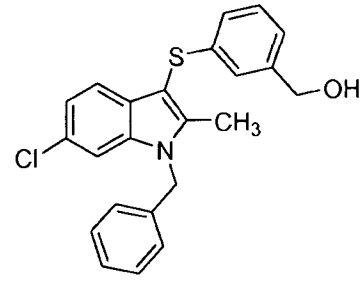
[00438] [3-(1-Benzyl-6-chloro-2-methyl-1*H*-indol-3-yloxy)-phenyl]-acetonitrile (0.065 g, 0.168 mmol) was dissolved in EtOH (3 mL) then acetyl chloride (0.240 mL, 3.36 mmol) was added and the reaction was heated to reflux for 3 days. After cooling the reaction was submitted to aqueous workup and silica gel chromatography to afford the title compound.



Step 8: [3-(1-Benzyl-6-chloro-2-methyl-1*H*-indol-3-yloxy)-phenyl]-acetic acid

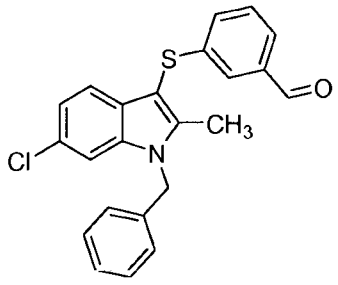
[00439] Prepared according to the procedure described in Example 10, Step 4, using the following starting material: [3-(1-benzyl-6-chloro-2-methyl-1*H*-indol-3-yloxy)-phenyl]-acetic acid ethyl ester.

Example 17: Synthesis of 3-[3-(1-Benzyl-6-chloro-2-methyl-1*H*-indol-3-ylsulfanyl)-phenyl]-propionic acid (Compound 1-17)



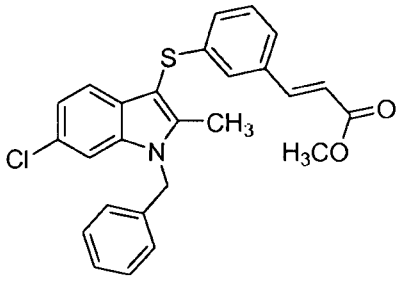
Step 1: [3-(1-Benzyl-6-chloro-2-methyl-1*H*-indol-3-ylsulfanyl)-phenyl]-methanol

[00440] 3-(1-Benzyl-6-chloro-2-methyl-1*H*-indol-3-ylsulfanyl)-benzoic acid methyl ester (1.08 g, 2.6 mmol) was dissolved in THF (20 mL) and the solution was cooled to -78 °C. Diisobutylaluminum hydride (6.5 mL, 1.0M in THF, 6.5 mmol) was added dropwise and the reaction was stirred for 30 minutes then an additional amount of diisobutylaluminum hydride (6.5 mL, 1.0M in THF, 6.5 mmol) was added. The reaction was allowed to warm to 0 °C then quenched with H_2O and HCl (aq.). The reaction was submitted to a standard workup procedure to give the title compound.



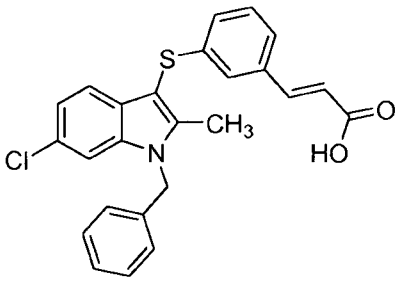
Step 2: 3-(1-Benzyl-6-chloro-2-methyl-1*H*-indol-3-ylsulfanyl)-benzaldehyde

[00441] [3-(1-Benzyl-6-chloro-2-methyl-1*H*-indol-3-ylsulfanyl)-phenyl]-methanol (0.750 g, 1.9 mmol) was dissolved in DCM:ACN (9:1, 20 mL) then 4-methylmorpholine *N*-oxide (0.334 g, 2.85 mmol) and tetrapropylammonium perruthenate (0.067 g, 0.19 mmol) were added. After 30 minutes the reaction mixture was concentrated and loaded directly onto a silica gel column. Silica gel chromatography (0-30% EtOAc in hexanes) provided the title compound.



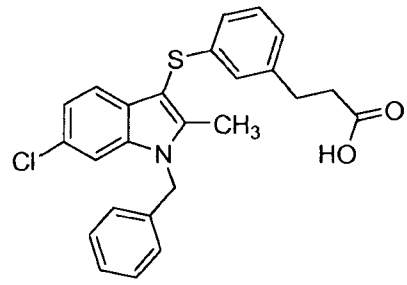
Step 3: (E)-3-[3-(1-Benzyl-6-chloro-2-methyl-1*H*-indol-3-ylsulfanyl)-phenyl]-acrylic acid methyl ester

[00442] Trimethylphosphonoacetate (248 μL, 1.72 mmol) was dissolved in THF (10 mL) and the reaction was cooled to 0 °C then sodium hydride (60% dispersion in mineral oil, 0.042 g, 1.77 mmol) was added and the reaction stirred for 10 minutes. 3-(1-Benzyl-6-chloro-2-methyl-1*H*-indol-3-ylsulfanyl)-benzaldehyde (0.225 g, 0.57 mmol) as a THF solution was added and the reaction was allowed to warm to room temperature. After 30 minutes, the reaction was diluted with EtOAc then quenched with aq. HCl (5 mL, 1M). Standard workup procedure afforded the title compound.



Step 4: (E)-3-[3-(1-Benzyl-6-chloro-2-methyl-1*H*-indol-3-ylsulfanyl)-phenyl]-acrylic acid

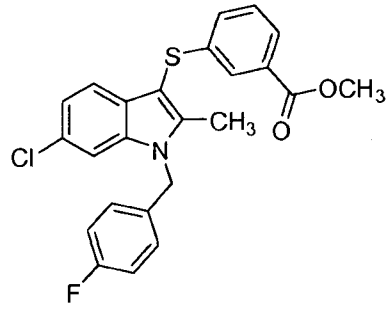
[00443] Prepared according to the procedure described in Example 10, Step 4, using the following starting material: (E)-3-[3-(1-benzyl-6-chloro-2-methyl-1*H*-indol-3-ylsulfanyl)-phenyl]-acrylic acid methyl ester.



Step 5: 3-[3-(1-Benzyl-6-chloro-2-methyl-1*H*-indol-3-ylsulfanyl)-phenyl]-propionic acid

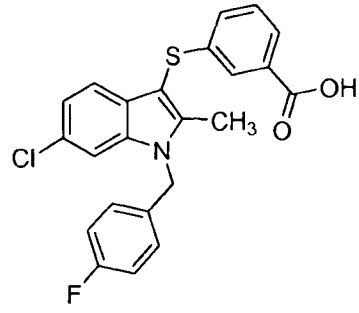
[00444] (E)-3-[3-(1-Benzyl-6-chloro-2-methyl-1*H*-indol-3-ylsulfanyl)-phenyl]-acrylic acid (0.2912 g, 0.67 mmol) was dissolved in EtOAc:MeOH (7:3, 10 mL) then palladium on carbon (0.214 g, 10% by weight, wet 50% H_2O) was added and H_2 (g) was bubbled through the mixture for 5 minutes. The reaction was stirred overnight under H_2 atmosphere and then the palladium on carbon was filtered off. Standard workup procedure followed by preparatory HPLC (10-100% ACN in H_2O) provided the title compound.

Example 18: Synthesis of 3-[6-Chloro-1-(4-fluoro-benzyl)-2-methyl-1*H*-indol-3-ylsulfanyl]-benzoic acid (Compound 1-18)



Step 1: 3-[6-Chloro-1-(4-fluoro-benzyl)-2-methyl-1*H*-indol-3-ylsulfanyl]-benzoic acid methyl ester

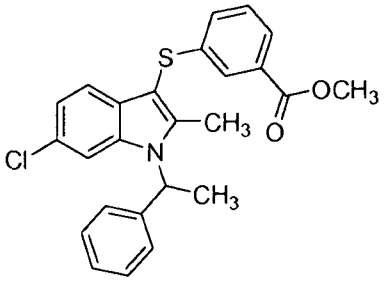
[00445] Prepared according to the procedure described in Example 4, Step 1, using the following starting materials: 3-(6-chloro-2-methyl-1*H*-indol-3-ylsulfanyl)-benzoic acid methyl ester and 4-fluorobenzyl bromide.



Step 2: 3-[6-Chloro-1-(4-fluoro-benzyl)-2-methyl-1*H*-indol-3-ylsulfanyl]-benzoic acid

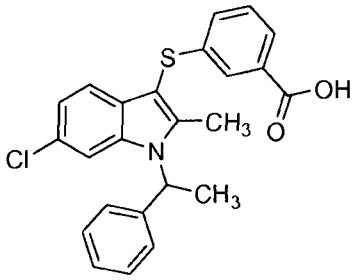
[00446] Prepared according to the procedure described in Example 10, Step 4, using the following starting material: (E)-3-[3-(1-benzyl-6-chloro-2-methyl-1*H*-indol-3-ylsulfanyl)-phenyl]-acrylic acid methyl ester.

Example 19: Synthesis of 3-[6-Chloro-2-methyl-1-(1-phenyl-ethyl)-1*H*-indol-3-ylsulfanyl]-benzoic acid (Compound 1-19)



Step 1: 3-[6-Chloro-2-methyl-1-(1-phenyl-ethyl)-1*H*-indol-3-ylsulfanyl]-benzoic acid methyl ester

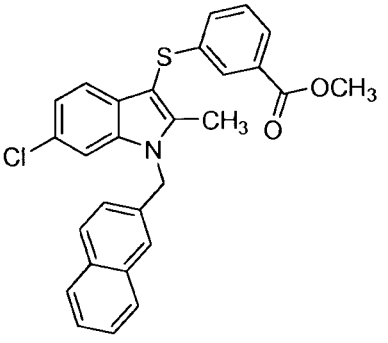
[00447] 3-(6-chloro-2-methyl-1*H*-indol-3-ylsulfanyl)-benzoic acid methyl ester (0.100 g, 0.30 mmol) was dissolved in DMF (3 mL) then sodium hydride (60% dispersion in mineral oil, 0.015 g, 0.36 mmol) was added followed by (1-bromoethyl)benzene (0.045 mL, 0.33 mmol). After 1 hour, the reaction was quenched with HCl (1N), followed by standard workup. Silica gel chromatography yielded the title compound.



Step 2: 3-[6-Chloro-2-methyl-1-(1-phenyl-ethyl)-1*H*-indol-3-ylsulfanyl]-benzoic acid

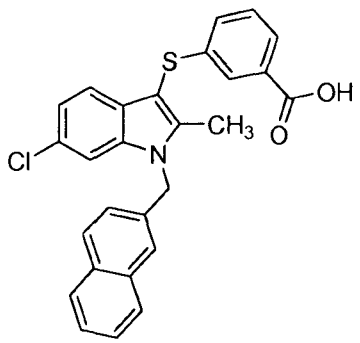
[00448] Prepared according to the procedure described in Example 10, Step 4, using the following starting material: 3-[6-chloro-2-methyl-1-(1-phenyl-ethyl)-1*H*-indol-3-ylsulfanyl]-benzoic acid methyl ester.

Example 20: Synthesis of 3-(6-Chloro-2-methyl-1-naphthalen-2-ylmethyl-1*H*-indol-3-ylsulfanyl)-benzoic acid (Compound 1-20)



Step 1: 3-(6-Chloro-2-methyl-1-naphthalen-2-ylmethyl-1*H*-indol-3-ylsulfanyl)-benzoic acid methyl ester

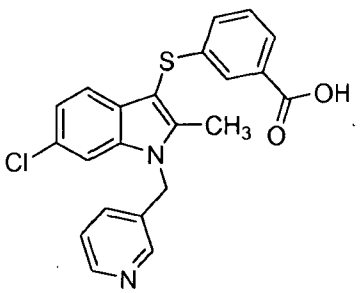
[00449] Prepared according to the procedure described in Example 4, Step 1, using the following starting materials: 3-(6-chloro-2-methyl-1*H*-indol-3-ylsulfanyl)-benzoic acid methyl ester and 2-(bromomethyl)naphthalene.



Step 2: 3-(6-Chloro-2-methyl-1-naphthalen-2-ylmethyl-1*H*-indol-3-ylsulfanyl)-benzoic acid

[00450] Prepared according to the procedure described in Example 10, Step 4, using the following starting material: 3-(6-chloro-2-methyl-1-naphthalen-2-ylmethyl-1*H*-indol-3-ylsulfanyl)-benzoic acid methyl ester.

Example 21: Synthesis of 3-(6-Chloro-2-methyl-1-pyridin-3-ylmethyl-1*H*-indol-3-ylsulfanyl)-benzoic acid (Compound 1-21)



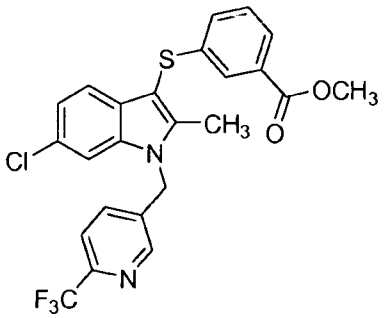
Step 1: 3-(6-Chloro-2-methyl-1-pyridin-3-ylmethyl-1*H*-indol-3-ylsulfanyl)-benzoic acid

[00451] 3-(6-chloro-2-methyl-1*H*-indol-3-ylsulfanyl)-benzoic acid methyl ester (0.050 g, 0.15 mmol) was dissolved in DMF:THF (1:1, 4 mL) and the reaction was cooled to 0 °C. Lithium bis(trimethylsilyl)amide (0.375 mL, 1.0M solution in hexanes, 0.375 mmol) was added and the reaction stirred for 5 minutes before 3-(bromomethyl)pyridine hydrobromide (0.057 g, 0.225 mmol) was added. The ice bath was removed and after 5 minutes an additional portion of 3-(bromomethyl)pyridine hydrobromide (0.075 mmol) and a small amount of tetrabutylammonium iodide was added. The reaction was heated to 50 °C and after 30 minutes an additional portion of 3-(bromomethyl)pyridine hydrobromide (0.075 mmol) was added. The reaction stirred overnight and was then submitted to standard aqueous workup procedures.

[00452] The recovered crude material, along with an additional portion of the starting material, 3-(6-chloro-2-methyl-1*H*-indol-3-ylsulfanyl)-benzoic acid methyl ester (0.075 g, 0.23 mmol), were dissolved in DMF:THF (1:1, 4 mL) and the reaction was cooled to 0 °C. Sodium hydride (60% dispersion in mineral oil, 0.95 mmol) was added and after five minutes 3-(bromomethyl)pyridine hydrobromide (0.57 mmol) was added and the ice bath was removed. After 10 minutes, LCMS of the

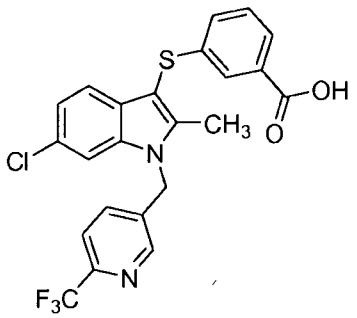
reaction mixture indicated that the starting material was consumed and that the product was also hydrolyzed to from the methyl ester to the free acid in situ. Standard aqueous workup and purification by preparatory HPLC (10-100% ACN in H_2O) afforded the title compound.

Example 22 – Synthesis of 3-[6-Chloro-2-methyl-1-(6-trifluoromethyl-pyridin-3-ylmethyl)-1*H*-indol-3-ylsulfanyl]-benzoic acid (Compound 1-22)



Step 1: 3-[6-Chloro-2-methyl-1-(6-trifluoromethyl-pyridin-3-ylmethyl)-1*H*-indol-3-ylsulfanyl]-benzoic acid methyl ester

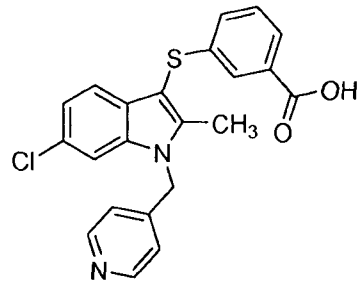
[00453] 3-(6-Chloro-2-methyl-1*H*-indol-3-ylsulfanyl)-benzoic acid methyl ester (0.050 g, 0.15 mmol) was dissolved in DMF:THF (1:1, 4 mL) and cooled to 0 °C. Lithium bis(trimethylsilyl)amide solution (0.375 mL, 0.375 mmol, 1.0M in hexanes) was added. 3-(Chloromethyl)-6-(trifluoromethyl)pyridine (0.044 g, 0.225 mmol) was added and the reaction was allowed to warm to room temperature. After 20 minutes the reaction was heated to 50 °C for 1 hour and then submitted to aqueous workup to provide the title compound.



Step 2: 3-[6-Chloro-2-methyl-1-(6-trifluoromethyl-pyridin-3-ylmethyl)-1*H*-indol-3-ylsulfanyl]-benzoic acid

[00454] Prepared according to the procedure described in Example 6, Step 5, using the following starting material: 3-[6-chloro-2-methyl-1-(6-trifluoromethyl-pyridin-3-ylmethyl)-1*H*-indol-3-ylsulfanyl]-benzoic acid methyl ester.

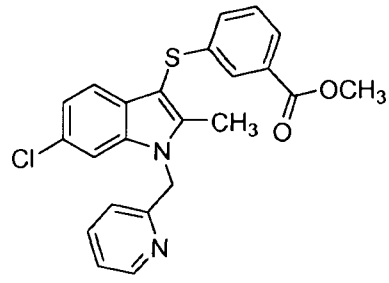
Example 23: Synthesis of 3-(6-Chloro-2-methyl-1-pyridin-4-ylmethyl-1*H*-indol-3-ylsulfanyl)-benzoic acid (Compound 1-23)



Step 1: 3-(6-Chloro-2-methyl-1-pyridin-4-ylmethyl-1*H*-indol-3-ylsulfanyl)-benzoic acid

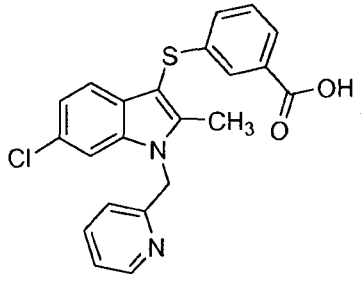
[00455] 3-(6-Chloro-2-methyl-1*H*-indol-3-ylsulfanyl)-benzoic acid methyl ester (0.050 g, 0.15 mmol) was dissolved in DMF (4 mL), cooled to °C, and sodium hydride (60% dispersion in mineral oil, 0.015 g, 0.375 mmol) was added. After 15 minutes, 4-(bromomethyl)pyridine hydrobromide (0.057 g, 0.225 mmol) was added and the reaction stirred at room temperature for 70 minutes. The reaction was then heated to 50 °C for 2 hours then submitted to standard aqueous workup. Preparatory HPLC (10-100% ACN in H_2O) afforded the title compound as a minor component.

Example 24: Synthesis of 3-(6-Chloro-2-methyl-1-pyridin-2-ylmethyl-1*H*-indol-3-ylsulfanyl)-benzoic acid (Compound 1-24)



Step 1: 3-(6-Chloro-2-methyl-1-pyridin-2-ylmethyl-1*H*-indol-3-ylsulfanyl)-benzoic acid methyl ester

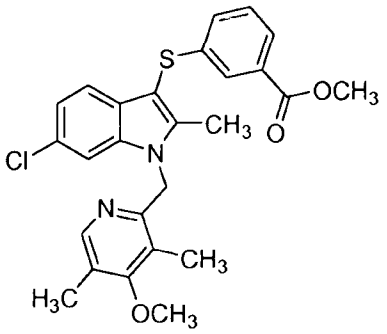
[00456] 3-(6-Chloro-2-methyl-1*H*-indol-3-ylsulfanyl)-benzoic acid methyl ester (0.050 g, 0.15 mmol) and 2-(bromomethyl)pyridine hydrobromide (0.049 g, 0.175 mmol) were dissolved in DMF:THF (1:1, 4 mL) and the mixture was cooled to 0 °C. Cesium carbonate (0.122 g, 0.373 mmol) was added and the reaction was warmed to 90 °C for 30 minutes. The reaction as submitted to aqueous workup and silica gel chromatography (0-100% EtOAc in hexanes) to give the title compound.



Step 2: 3-(6-Chloro-2-methyl-1-pyridin-2-ylmethyl-1*H*-indol-3-ylsulfanyl)-benzoic acid

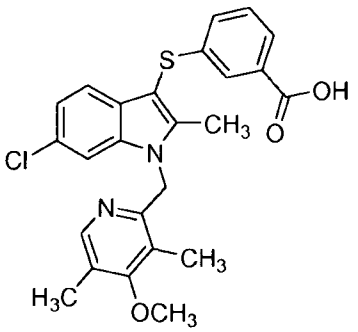
[00457] Prepared according to the procedure described in Example 6, Step 5, using the following starting material: 3-(6-chloro-2-methyl-1-pyridin-2-ylmethyl-1*H*-indol-3-ylsulfanyl)-benzoic acid methyl ester.

Example 25: Synthesis of 3-[6-Chloro-1-(4-methoxy-3,5-dimethyl-pyridin-2-ylmethyl)-2-methyl-1*H*-indol-3-ylsulfanyl]-benzoic acid (Compound 1-25)



Step 1: 3-[6-Chloro-1-(4-methoxy-3,5-dimethyl-pyridin-2-ylmethyl)-2-methyl-1*H*-indol-3-ylsulfanyl]-benzoic acid methyl ester

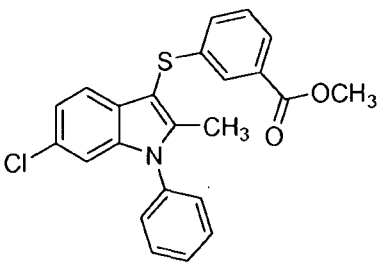
[00458] Prepared according to the procedure described in Example 24, Step 1, using the following starting materials: 3-(6-chloro-2-methyl-1*H*-indol-3-ylsulfanyl)-benzoic acid methyl ester and 2-chloromethyl-4-methoxy-3,5-dimethyl-pyridine hydrochloride.



Step 2: Synthesis of 3-[6-Chloro-1-(4-methoxy-3,5-dimethyl-pyridin-2-ylmethyl)-2-methyl-1*H*-indol-3-ylsulfanyl]-benzoic acid

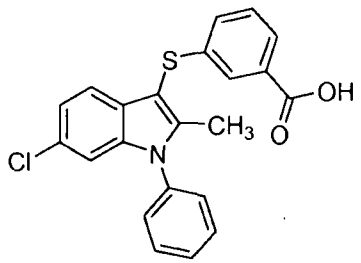
[00459] Prepared according to the procedure described in Example 6, Step 5, using the following starting material: 3-[6-chloro-1-(4-methoxy-3,5-dimethyl-pyridin-2-ylmethyl)-2-methyl-1*H*-indol-3-ylsulfanyl]-benzoic acid methyl ester.

Example 26: Synthesis of 3-(6-Chloro-2-methyl-1-phenyl-1*H*-indol-3-ylsulfanyl)-benzoic acid (Compound 1-26)



Step 1: 3-(6-Chloro-2-methyl-1-phenyl-1*H*-indol-3-ylsulfanyl)-benzoic acid methyl ester

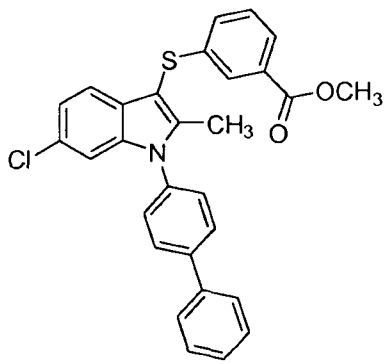
[00460] 3-(6-Chloro-2-methyl-1*H*-indol-3-ylsulfanyl)-benzoic acid methyl ester (0.252 g, 0.759 mmol), (±)-trans-1,2-diaminocyclohexane (18 μL, 0.15 mmol), iodobenzene (103 μL, 0.911 mmol), K_3PO_4 (0.402 g, 1.89 mmol) and copper(I) iodide (0.0072 g, 0.04 mmol) were dissolved in toluene (0.750 mL) and the reaction vessel was purged with N_2 (g) for 1 minute. The reaction was heated to 120 °C and stirred overnight. Standard workup procedure followed by silica gel chromatography (0-20% EtOAc in hexanes) afforded the title compound.



Step 2: 3-(6-Chloro-2-methyl-1-phenyl-1*H*-indol-3-ylsulfanyl)-benzoic acid

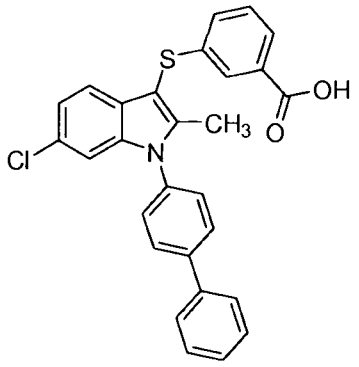
[00461] Prepared according to the procedure described in Example 10, Step 4, using the following starting material: 3-(6-chloro-2-methyl-1-phenyl-1*H*-indol-3-ylsulfanyl)-benzoic acid methyl ester.

Example 27: Synthesis of 3-(1-Biphenyl-4-yl-6-chloro-2-methyl-1*H*-indol-3-ylsulfanyl)-benzoic acid (Compound 1-27)



Step 1: 3-(1-Biphenyl-4-yl-6-chloro-2-methyl-1*H*-indol-3-ylsulfanyl)-benzoic acid methyl ester

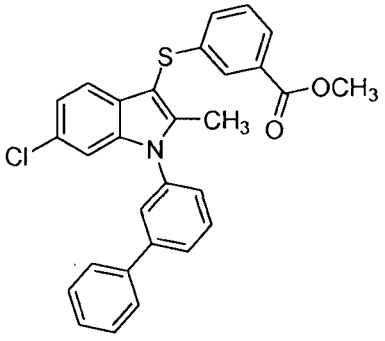
[00462] 3-(6-Chloro-2-methyl-1*H*-indol-3-ylsulfanyl)-benzoic acid methyl ester (0.100 g, 0.3 mmol) was combined with CuO (0.0024 g, 0.03 mmol), potassium carbonate (0.041 g, 0.3 mmol) and 4-bromobiphenyl (0.0699 g, 0.3 mmol) in DMF (150 μL) and the reaction was heated to 170 °C overnight. After cooling the reaction was submitted to standard aqueous workup to give the title compound as a crude mixture that was taken directly to the next step without purification.



Step 2: 3-(1-Biphenyl-4-yl-6-chloro-2-methyl-1*H*-indol-3-ylsulfanyl)-benzoic acid

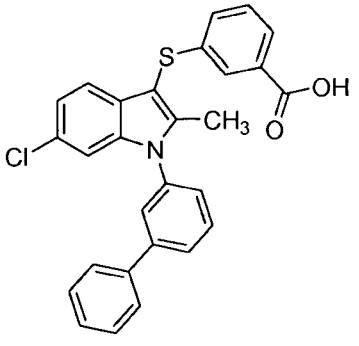
[00463] Prepared according to the procedure described in Example 6, Step 5, using the following starting material: 3-(1-biphenyl-4-yl-6-chloro-2-methyl-1*H*-indol-3-ylsulfanyl)-benzoic acid methyl ester.

Example 28: Synthesis of 3-(1-Biphenyl-3-yl-6-chloro-2-methyl-1*H*-indol-3-ylsulfanyl)-benzoic acid (Compound 1-28)



Step 1: 3-(1-Biphenyl-3-yl-6-chloro-2-methyl-1*H*-indol-3-ylsulfanyl)-benzoic acid methyl ester

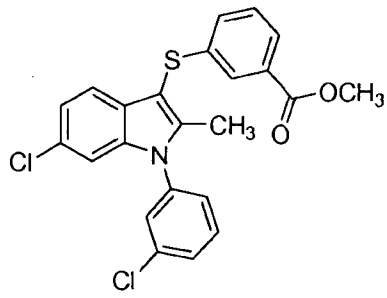
[00464] Prepared according to the procedure described in Example 27, Step 1, using the following starting materials: 3-(6-chloro-2-methyl-1*H*-indol-3-ylsulfanyl)-benzoic acid methyl ester and 3-bromobiphenyl.



Step 2: 3-(1-Biphenyl-3-yl-6-chloro-2-methyl-1*H*-indol-3-ylsulfanyl)-benzoic acid

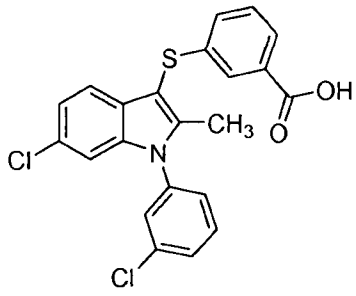
[00465] Prepared according to the procedure described in Example 6, Step 5, using the following starting material: 3-(1-biphenyl-3-yl-6-chloro-2-methyl-1*H*-indol-3-ylsulfanyl)-benzoic acid methyl ester.

Example 29: Synthesis of 3-[6-Chloro-1-(3-chloro-phenyl)-2-methyl-1*H*-indol-3-ylsulfanyl]-benzoic acid (Compound 1-29)



Step 1: 3-[6-Chloro-1-(3-chloro-phenyl)-2-methyl-1*H*-indol-3-ylsulfanyl]-benzoic acid methyl ester

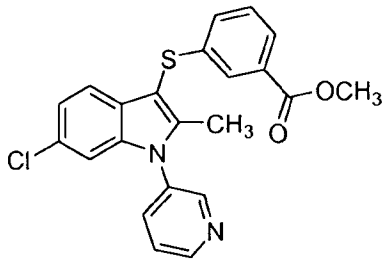
[00466] Prepared according to the procedure described in Example 27, Step 1, using the following starting materials: 3-(6-chloro-2-methyl-1*H*-indol-3-ylsulfanyl)-benzoic acid methyl ester and 1-bromo-3-chlorobenzene.



Step 2: 3-[6-Chloro-1-(3-chloro-phenyl)-2-methyl-1*H*-indol-3-ylsulfanyl]-benzoic acid

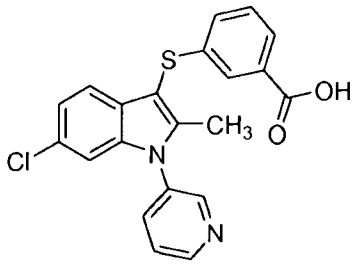
[00467] Prepared according to the procedure described in Example 6, Step 5, using the following starting material: 3-[6-chloro-1-(3-chloro-phenyl)-2-methyl-1*H*-indol-3-ylsulfanyl]-benzoic acid methyl ester.

Example 30: Synthesis of 3-(6-Chloro-2-methyl-1-pyridin-3-yl-1*H*-indol-3-ylsulfanyl)-benzoic acid (Compound 1-30)



Step 1: 3-(6-Chloro-2-methyl-1-pyridin-3-yl-1*H*-indol-3-ylsulfanyl)-benzoic acid methyl ester

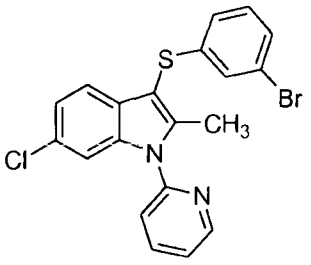
[00468] Prepared according to the procedure described in Example 26, Step 1, using the following starting materials: 3-(6-chloro-2-methyl-1*H*-indol-3-ylsulfanyl)-benzoic acid methyl ester and 3-bromopyridine.



Step 2: 3-(6-Chloro-2-methyl-1-pyridin-3-yl-1*H*-indol-3-ylsulfanyl)-benzoic acid

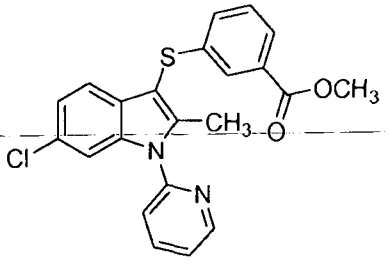
[00469] Prepared according to the procedure described in Example 10, Step 4, using the following starting material: 3-(6-chloro-2-methyl-1-pyridin-3-yl-1*H*-indol-3-ylsulfanyl)-benzoic acid methyl ester.

Example 31: Synthesis of 3-(6-Chloro-2-methyl-1-pyridin-2-yl-1*H*-indol-3-ylsulfanyl)-benzoic acid (Compound 1-31)



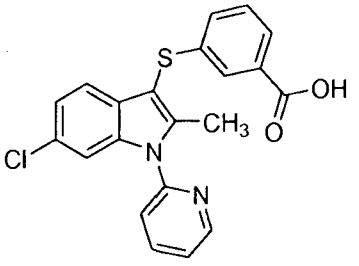
Step 1: 3-(3-Bromo-phenylsulfanyl)-6-chloro-2-methyl-1-pyridin-2-yl-1*H*-indole

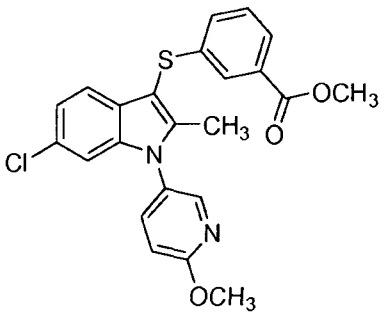
[00470] 3-(3-Bromo-phenylsulfanyl)-6-chloro-2-methyl-1*H*-indole (0.500 g, 1.4 mmol) along with K_2CO_3 (0.488 g, 3.5 mmol) and 2-fluoropyridine (87 μL, 2.1 mmol) were dissolved in DMF (2 mL) and reacted in a microwave at 200 °C for 20 minutes. The reaction was returned to the microwave at 200 °C for an additional 10 minutes. Standard workup followed by silica gel chromatography (0-100% EtOAc in hexanes) afforded the title compound.



Step 2: 3-(6-Chloro-2-methyl-1-pyridin-2-yl-1*H*-indol-3-ylsulfanyl)-benzoic acid methyl ester

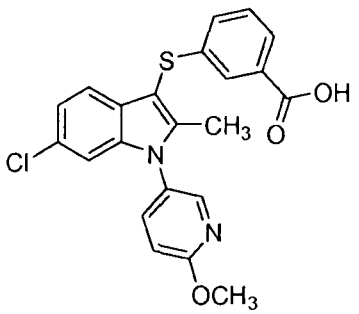
[00471] Prepared according to the procedure described in Example 6, Step 3, using the following starting material: 3-(3-bromo-phenylsulfanyl)-6-chloro-2-methyl-1-pyridin-2-yl-1*H*-indole.





Step 1: 3-[6-Chloro-1-(6-methoxy-pyridin-3-yl)-2-methyl-1*H*-indol-3-ylsulfanyl]-benzoic acid methyl ester

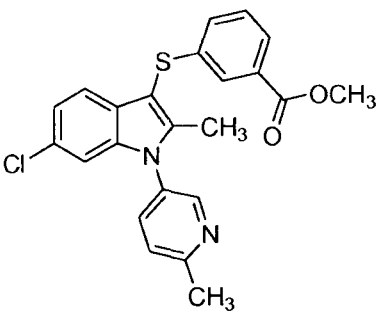
[00475] Prepared according to the procedure described in Example 27, Step 1, using the following starting materials: 3-(6-chloro-2-methyl-1*H*-indol-3-ylsulfanyl)-benzoic acid methyl ester and 5-bromo-2-methoxypyridine.



Step 2: 3-[6-Chloro-1-(6-methoxy-pyridin-3-yl)-2-methyl-1*H*-indol-3-ylsulfanyl]-benzoic acid

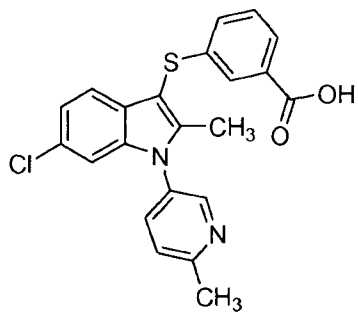
[00476] Prepared according to the procedure described in Example 6, Step 5, using the following starting material: 3-[6-chloro-1-(6-methoxy-pyridin-3-yl)-2-methyl-1*H*-indol-3-ylsulfanyl]-benzoic acid methyl ester.

Example 34: Synthesis of 3-[6-Chloro-2-methyl-1-(6-methyl-pyridin-3-yl)-1*H*-indol-3-ylsulfanyl]-benzoic acid (Compound 1-34)



Step 1: 3-[6-Chloro-2-methyl-1-(6-methyl-pyridin-3-yl)-1*H*-indol-3-ylsulfanyl]-benzoic acid methyl ester

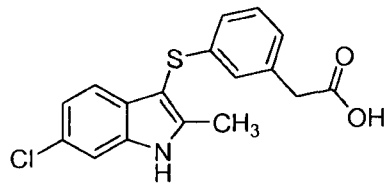
[00477] Prepared according to the procedure described in Example 27, Step 1, using the following starting materials: 3-(6-chloro-2-methyl-1*H*-indol-3-ylsulfanyl)-benzoic acid methyl ester and 5-bromo-2-methylpyridine.



Step 2: 3-[6-Chloro-2-methyl-1-(6-methyl-pyridin-3-yl)-1*H*-indol-3-ylsulfanyl]-benzoic acid

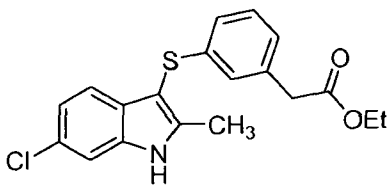
[00478] Prepared according to the procedure described in Example 6, Step 5, using the following starting material: 3-[6-chloro-2-methyl-1-(6-methyl-pyridin-3-yl)-1*H*-indol-3-ylsulfanyl]-benzoic acid methyl ester.

Example 35: Synthesis of [3-(6-Chloro-2-methyl-1-pyridin-3-yl-1*H*-indol-3-ylsulfanyl)-phenyl]-acetic acid (Compound 1-35)



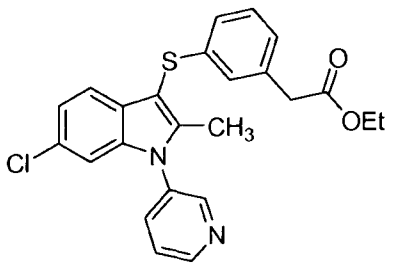
Step 1: [3-(6-Chloro-2-methyl-1*H*-indol-3-ylsulfanyl)-phenyl]-acetic acid

[00479] [3-(2-Oxo-propylsulfanyl)-phenyl]-acetic acid (3.69 g, 16.5 mmol) was dissolved in *t*-BuOH (100 mL) then 3-chlorophenylhydrazine hydrochloride (3.25 g, 18.15 mmol) was added. The reaction was heated to 70 °C for 2 hour then cooled and submitted to aqueous workup to afford a mixture of regioisomers which included the title compound. The crude material was brought forward to the next step without further purification.



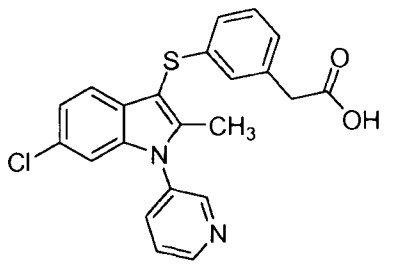
Step 2: [3-(6-Chloro-2-methyl-1*H*-indol-3-ylsulfanyl)-phenyl]-acetic acid ethyl ester

[00480] [3-(6-Chloro-2-methyl-1*H*-indol-3-ylsulfanyl)-phenyl]-acetic acid (from the previous step) was dissolved in EtOH (100 mL), conc. H_2SO_4 (2 mL) was added, and the reaction was stirred at room temperature for 2 hours. The reaction was submitted to standard workup procedures then purified via silica gel chromatography to afford the title compound.



Step 3: [3-(6-Chloro-2-methyl-1-pyridin-3-yl-1*H*-indol-3-ylsulfanyl)-phenyl]-acetic acid ethyl ester

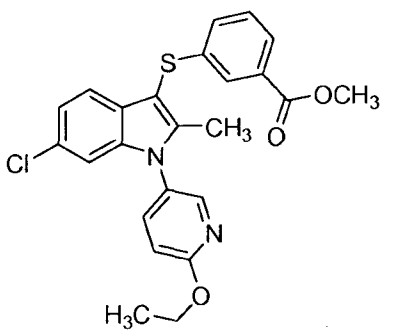
[00481] Prepared according to the procedure described in Example 27, Step 1, using the following starting materials: [3-(6-chloro-2-methyl-1*H*-indol-3-ylsulfanyl)-phenyl]-acetic acid ethyl ester and 3-bromopyridine.



Step 4: [3-(6-Chloro-2-methyl-1-pyridin-3-yl-1*H*-indol-3-ylsulfanyl)-phenyl]-acetic acid

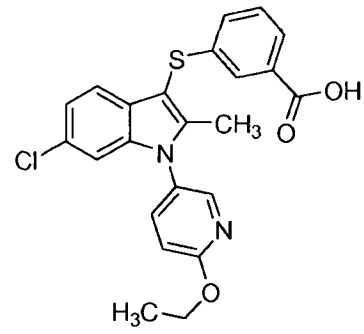
[00482] Prepared according to the procedure described in Example 10, Step 4, using the following starting material: [3-(6-chloro-2-methyl-1-pyridin-3-yl-1*H*-indol-3-ylsulfanyl)-phenyl]-acetic acid ethyl ester.

Example 36: Synthesis of 3-[6-Chloro-1-(6-ethoxy-pyridin-3-yl)-2-methyl-1*H*-indol-3-ylsulfanyl]-benzoic acid (Compound 1-36)



Step 1: 3-[6-Chloro-1-(6-ethoxy-pyridin-3-yl)-2-methyl-1*H*-indol-3-ylsulfanyl]-benzoic acid methyl ester

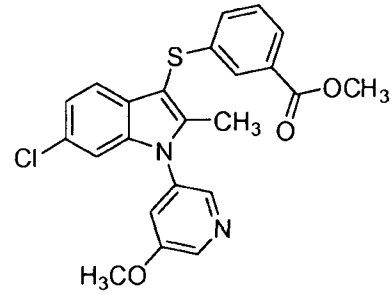
[00483] Prepared according to the procedure described in Example 27, Step 1, using the following starting materials: 3-(6-chloro-2-methyl-1*H*-indol-3-ylsulfanyl)-benzoic acid methyl ester and 5-bromo-2-ethoxypyridine.



Step 2: 3-[6-Chloro-1-(6-ethoxy-pyridin-3-yl)-2-methyl-1*H*-indol-3-ylsulfanyl]-benzoic acid

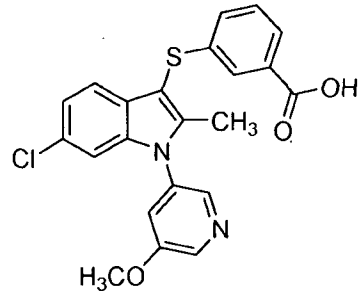
[00484] Prepared according to the procedure described in Example 6, Step 5, using the following starting material: 3-[6-chloro-1-(6-ethoxy-pyridin-3-yl)-2-methyl-1*H*-indol-3-ylsulfanyl]-benzoic acid methyl ester.

Example 37: Synthesis of 3-[6-Chloro-1-(5-methoxy-pyridin-3-yl)-2-methyl-1*H*-indol-3-ylsulfanyl]-benzoic acid (Compound 1-37)



Step 1: 3-[6-Chloro-1-(5-methoxy-pyridin-3-yl)-2-methyl-1*H*-indol-3-ylsulfanyl]-benzoic acid methyl ester

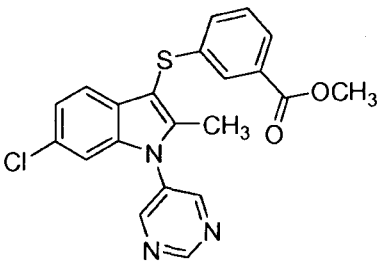
[00485] Prepared according to the procedure described in Example 27, Step 1, using the following starting materials: 3-(6-chloro-2-methyl-1*H*-indol-3-ylsulfanyl)-benzoic acid methyl ester and 3-bromo-5-methoxypyridine.



Step 2: 3-[6-Chloro-1-(5-methoxy-pyridin-3-yl)-2-methyl-1*H*-indol-3-ylsulfanyl]-benzoic acid

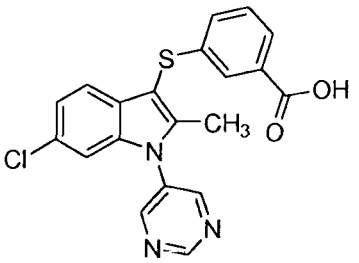
[00486] Prepared according to the procedure described in Example 6, Step 5, using the following starting material: 3-[6-chloro-1-(5-methoxy-pyridin-3-yl)-2-methyl-1*H*-indol-3-ylsulfanyl]-benzoic acid methyl ester.

Example 38: Synthesis of 3-(6-Chloro-2-methyl-1-pyrimidin-5-yl-1*H*-indol-3-ylsulfanyl)-benzoic acid (Compound 1-38)



Step 1: 3-(6-Chloro-2-methyl-1-pyrimidin-5-yl-1*H*-indol-3-ylsulfanyl)-benzoic acid methyl ester

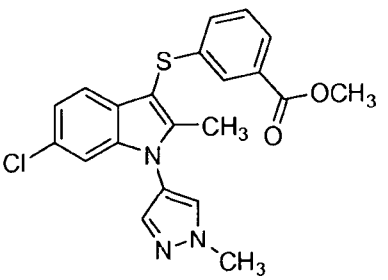
[00487] Prepared according to the procedure described in Example 27, Step 1, using the following starting materials: 3-(6-chloro-2-methyl-1*H*-indol-3-ylsulfanyl)-benzoic acid methyl ester and 5-bromopyrimidine.



Step 2: 3-(6-Chloro-2-methyl-1-pyrimidin-5-yl-1*H*-indol-3-ylsulfanyl)-benzoic acid

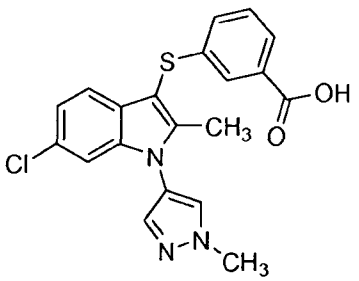
[00488] Prepared according to the procedure described in Example 6, Step 5, using the following starting material: 3-(6-chloro-2-methyl-1-pyrimidin-5-yl-1*H*-indol-3-ylsulfanyl)-benzoic acid methyl ester.

Example 39: Synthesis of 3-[6-Chloro-2-methyl-1-(1-methyl-1*H*-pyrazol-4-yl)-1*H*-indol-3-ylsulfanyl]-benzoic acid (Compound 1-39)



Step 1: 3-[6-Chloro-2-methyl-1-(1-methyl-1*H*-pyrazol-4-yl)-1*H*-indol-3-ylsulfanyl]-benzoic acid methyl ester

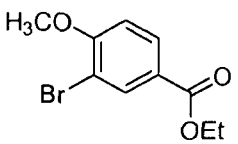
[00489] Prepared according to the procedure described in Example 27, Step 1, using the following starting materials: 3-(6-chloro-2-methyl-1*H*-indol-3-ylsulfanyl)-benzoic acid methyl ester and 4-bromo-1-methylpyrazole.



Step 2: 3 Synthesis of 3-[6-Chloro-2-methyl-1-(1-methyl-1*H*-pyrazol-4-yl)-1*H*-indol-3-ylsulfanyl]-benzoic acid

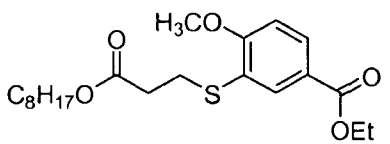
[00490] Prepared according to the procedure described in Example 6, Step 5, using the following starting material: 3-[6-chloro-2-methyl-1-(1-methyl-1*H*-pyrazol-4-yl)-1*H*-indol-3-ylsulfanyl]-benzoic acid methyl ester.

Example 40: Synthesis of 3-(6-Chloro-2-methyl-1-pyridin-3-yl-1*H*-indol-3-ylsulfanyl)-4-methoxy-benzoic acid (Compound 1-40)



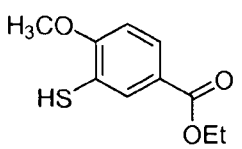
Step 1: 3-Bromo-4-methoxy-benzoic acid ethyl ester

[00491] 3-Bromo-4-methoxy-benzoic acid (2.5 g, 11.6 mmol) was dissolved in EtOH (20 mL) and conc. H_2SO_4 (1 mL) was added. The reaction was heated to reflux overnight then submitted to standard aqueous workup. The residue was purified by silica gel chromatography (0-50% EtOAc in hexanes) to yield the title compound.



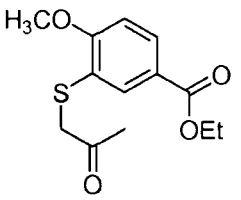
Step 2: 4-Methoxy-3-(2-octyloxycarbonyl-ethylsulfanyl)-benzoic acid ethyl ester

[00492] 3-Bromo-4-methoxy-benzoic acid ethyl ester (1.61 g, 6.62 mmol) and isooctyl-3-mercaptopropionate (1.73 g, 7.95 mmol) were dissolved in dioxane (26 mL) and the mixture was sparged with N_2 (g) for 10 minutes. Diisopropylethyl amine (2.31 mL, 13.25 mmol), Xanthphos (0.1917 g, 0.33 mmol) and tris(dibenzylideneacetone)dipalladium(0) (0.1517 g, 0.166 mmol) were added and the mixture was sparged with N_2 (g) for 5 minutes. The reaction was then heated to 90 °C for 2 hours after which time it was filtered to remove solid impurities. The mixture was concentrated and the residue was purified on silica gel (0-40% EtOAc in hexanes) to give the title compound.



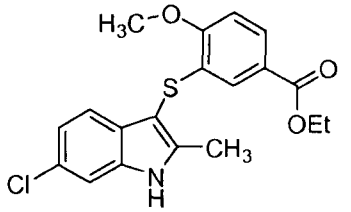
Step 3: 3-Mercapto-4-methoxy-benzoic acid ethyl ester

[00493] 4-Methoxy-3-(2-octyloxycarbonyl-ethylsulfanyl)-benzoic acid ethyl ester (2.93 g, 7.40 mmol) was dissolved in THF and the mixture was chilled to -78 °C. N_2 (g) was bubbled through the reaction mixture and potassium *tert*-butoxide (8.88 mL, 1.0M in THF, 8.88 mmol) was added via syringe over 2 minutes. The reaction was stirred at -78 °C for 1 hour then slowly allowed to warm to 10 °C for 2 hours. The reaction was then quenched with 1N aq. HCl (30 mL) and submitted to standard aqueous workup. The residue was purified by silica gel chromatography (0-10% EtOAc in hexanes:MeOH (98:2)) to afford the title compound.



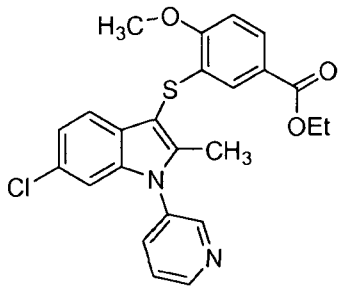
Step 4: 4-Methoxy-3-(2-oxo-propylsulfanyl)-benzoic acid ethyl ester

[00494] 3-Mercapto-4-methoxy-benzoic acid ethyl ester (1.29 g, 6.08 mmol) and triethylamine (2.12 mL, 15.19 mmol) were dissolved in THF (20 mL) at 0 °C. Chloroacetone (0.58 mL, 7.29 mmol) was then added and the reaction stirred at room temperature for 30 minutes. It was then allowed to slowly warm to room temperature and stirred an additional 30 minutes. Standard aqueous workup followed by silica gel chromatography (0-70% EtOAc in hexanes) gave the title compound.



Step 5: 3-(6-Chloro-2-methyl-1*H*-indol-3-ylsulfanyl)-4-methoxy-benzoic acid ethyl ester

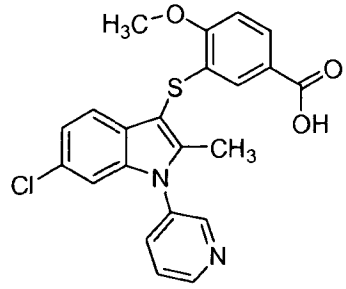
[00495] Prepared according to the procedure described in Example 10, Step 2, using the following starting materials: 4-methoxy-3-(2-oxo-propylsulfanyl)-benzoic acid ethyl ester and 3-chlorophenylhydrazine hydrochloride.



Step 6: 3-(6-Chloro-2-methyl-1-pyridin-3-yl-1*H*-indol-3-ylsulfanyl)-4-methoxy-benzoic acid ethyl ester

[00496] 3-(6-Chloro-2-methyl-1*H*-indol-3-ylsulfanyl)-4-methoxy-benzoic acid ethyl ester (0.175 g, 0.466 mmol) was combined with CuO (3.71 mg, 0.046 mmol), potassium carbonate (0.0805 g, 0.582 mmol) and 3-bromopyridine (0.229 mL, 2.33 mmol) in DMF (250 µL) and the reaction was heated to

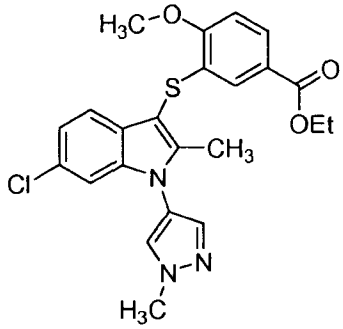
170 °C overnight. After cooling the reaction was submitted to standard aqueous workup and the residue was purified by silica gel chromatography (0-100% (EtOAc:MeOH 98:2) in hexanes) to give the title compound.



Step 7: 3-(6-Chloro-2-methyl-1-pyridin-3-yl-1*H*-indol-3-ylsulfanyl)-4-methoxy-benzoic acid

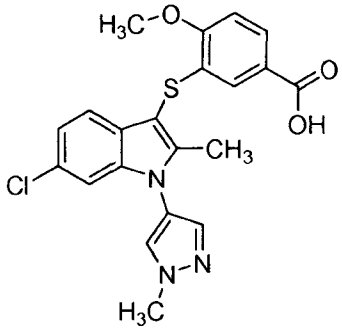
[00497] Prepared according to the procedure described in Example 10, Step 4, using the following starting material: 3-(6-chloro-2-methyl-1-pyridin-3-yl-1*H*-indol-3-ylsulfanyl)-4-methoxy-benzoic acid ethyl ester.

Example 41: Synthesis of 3-[6-Chloro-2-methyl-1-(1-methyl-1*H*-pyrazol-4-yl)-1*H*-indol-3-ylsulfanyl]-4-methoxy-benzoic acid (Compound 1-41)



Step 1: 3-[6-Chloro-2-methyl-1-(1-methyl-1*H*-pyrazol-4-yl)-1*H*-indol-3-ylsulfanyl]-4-methoxy-benzoic acid ethyl ester

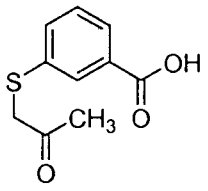
[00498] Prepared according to the procedure described in Example 40, Step 6, using the following starting materials: 3-(6-chloro-2-methyl-1*H*-indol-3-ylsulfanyl)-4-methoxy-benzoic acid ethyl ester and 4-bromo-1-methylpyrazole.



Step 2: 3-[6-Chloro-2-methyl-1-(1-methyl-1*H*-pyrazol-4-yl)-1*H*-indol-3-ylsulfanyl]-4-methoxy-benzoic acid

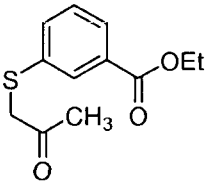
[00499] Prepared according to the procedure described in Example 10, Step 4, using the following starting material: 3-[6-chloro-2-methyl-1-(1-methyl-1*H*-pyrazol-4-yl)-1*H*-indol-3-ylsulfanyl]-4-methoxy-benzoic acid ethyl ester.

Example 42: Synthesis of 3-(6-Chloro-1-isothiazol-4-yl-2-methyl-1*H*-indol-3-ylsulfanyl)-benzoic acid (Compound 1-42)



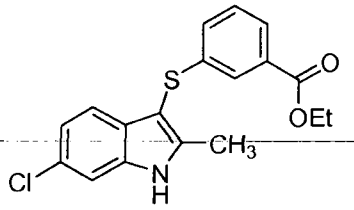
Step 1: 3-(2-Oxo-propylsulfanyl)-benzoic acid

[00500] 3-Mercapto-benzoic acid (5.0 g, 32.3 mmol) and triethylamine (11.3 mL, 81.1 mmol) were dissolved in THF at 0 °C. Chloroacetone (2.7 mL, 33.9 mmol) was then added and the reaction was allowed to slowly warm to room temperature as it stirred overnight. Standard aqueous workup afforded the title compound which was brought forward to the next step without further purification.



Step 2: 3-(2-Oxo-propylsulfanyl)-benzoic acid ethyl ester

[00501] 3-(2-Oxo-propylsulfanyl)-benzoic acid from the previous reaction was dissolved in ethanol and a catalytic amount of conc. H_2SO_4 was added. The reaction was monitored by analytical TLC and when it was complete the reaction was concentrated to dryness and the resulting residue was purified via silica gel chromatography to give the title compound.

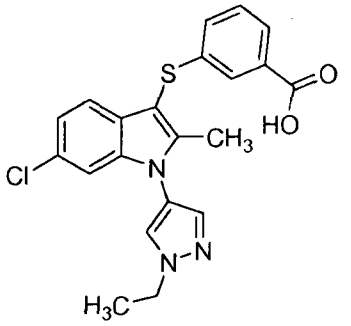


Step 3: 3-(6-Chloro-2-methyl-1*H*-indol-3-ylsulfanyl)-benzoic acid ethyl ester

[00502] Prepared according to the procedure described in Example 10, Step 2, using the following starting materials: 3-(2-oxo-propylsulfanyl)-benzoic acid ethyl ester and 3-chlorophenylhydrazine hydrochloride.

Step 1: 3-[6-Chloro-1-(1-ethyl-1*H*-pyrazol-4-yl)-2-methyl-1*H*-indol-3-ylsulfanyl]-benzoic acid ethyl ester

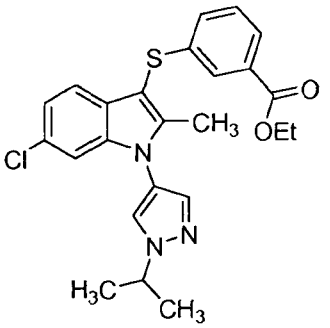
[00505] Prepared according to the procedure described in Example 42, Step 4, using the following starting materials: 3-(6-chloro-2-methyl-1*H*-indol-3-ylsulfanyl)-benzoic acid ethyl ester and 4-bromo-1-ethylpyrazole.



Step 2: 3-[6-Chloro-1-(1-ethyl-1*H*-pyrazol-4-yl)-2-methyl-1*H*-indol-3-ylsulfanyl]-benzoic acid

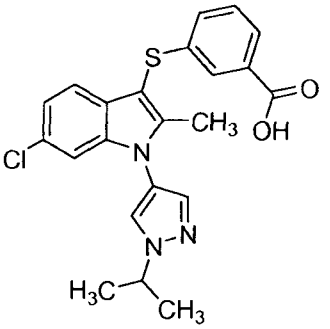
[00506] Prepared according to the procedure described in Example 42, Step 5, using the following starting material: 3-[6-chloro-1-(1-ethyl-1*H*-pyrazol-4-yl)-2-methyl-1*H*-indol-3-ylsulfanyl]-benzoic acid ethyl ester.

Example 44: Synthesis of 3-[6-Chloro-1-(1-isopropyl-1*H*-pyrazol-4-yl)-2-methyl-1*H*-indol-3-ylsulfanyl]-benzoic acid (Compound 1-44)



Step 1: 3-[6-Chloro-1-(1-isopropyl-1*H*-pyrazol-4-yl)-2-methyl-1*H*-indol-3-ylsulfanyl]-benzoic acid ethyl ester

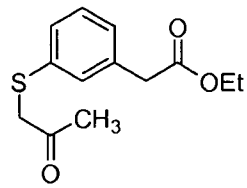
[00507] Prepared according to the procedure described in Example 42, Step 4, using the following starting materials: 3-(6-chloro-2-methyl-1*H*-indol-3-ylsulfanyl)-benzoic acid ethyl ester and 4-bromo-1-isopropylpyrazole.



Step 2: Synthesis of 3-[6-Chloro-1-(1-isopropyl-1*H*-pyrazol-4-yl)-2-methyl-1*H*-indol-3-ylsulfanyl]-benzoic acid

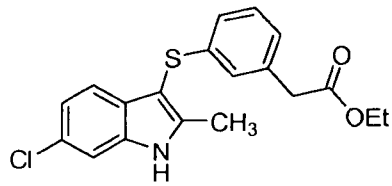
[00508] Prepared according to the procedure described in Example 42, Step 5, using the following starting material: 3-[6-chloro-1-(1-isopropyl-1*H*-pyrazol-4-yl)-2-methyl-1*H*-indol-3-ylsulfanyl]-benzoic acid ethyl ester.

Example 45: Synthesis of {3-[6-Chloro-2-methyl-1-(1-methyl-1*H*-pyrazol-4-yl)-1*H*-indol-3-ylsulfanyl]-phenyl}-acetic acid (Compound 1-45)



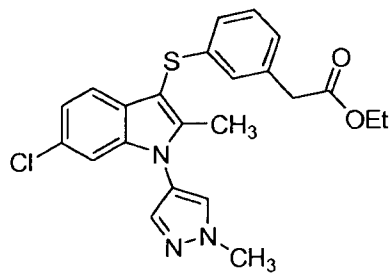
Step 1: [3-(2-Oxo-propylsulfanyl)-phenyl]-acetic acid ethyl ester

[00509] Prepared according to the procedure described in Example 42, Step 1, using the following starting materials: (3-mercapto-phenyl)-acetic acid ethyl ester and chloroacetone.



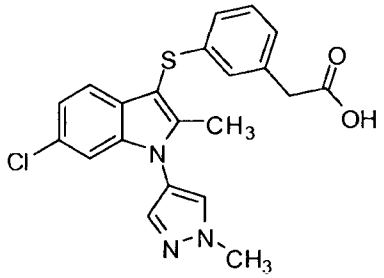
Step 2: [3-(6-Chloro-2-methyl-1*H*-indol-3-ylsulfanyl)-phenyl]-acetic acid ethyl ester

[00510] Prepared according to the procedure described in Example 10, Step 2, using the following starting materials: [3-(2-oxo-propylsulfanyl)-phenyl]-acetic acid ethyl ester and 3-chlorophenylhydrazine hydrochloride.



Step 3: {3-[6-Chloro-2-methyl-1-(1-methyl-1*H*-pyrazol-4-yl)-1*H*-indol-3-ylsulfanyl]-phenyl}-acetic acid ethyl ester

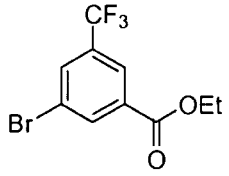
[00511] Prepared according to the procedure described in Example 42, Step 4, using the following starting materials: [3-(6-chloro-2-methyl-1*H*-indol-3-ylsulfanyl)-phenyl]-acetic acid ethyl ester and 4-bromo-1-methylpyrazole.



Step 4: {3-[6-Chloro-2-methyl-1-(1-methyl-1*H*-pyrazol-4-yl)-1*H*-indol-3-ylsulfanyl]-phenyl}-acetic acid

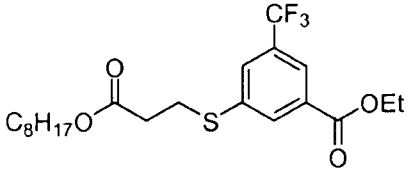
[00512] Prepared according to the procedure described in Example 42, Step 5, using the following starting material: {3-[6-chloro-2-methyl-1-(1-methyl-1*H*-pyrazol-4-yl)-1*H*-indol-3-ylsulfanyl]-phenyl}-acetic acid ethyl ester.

Example 46: Synthesis of 3-(6-Chloro-2-methyl-1-pyridin-3-yl-1*H*-indol-3-ylsulfanyl)-5-trifluoromethyl-benzoic acid (Compound 1-46)



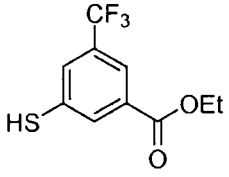
Step 1: 3-Bromo-5-trifluoromethyl-benzoic acid ethyl ester

[00513] Prepared according to the procedure described in Example 40, Step 1, using the following starting material: 3-bromo-5-trifluoromethyl-benzoic acid.



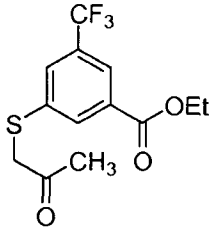
Step 2: 3-(2-Octyloxycarbonyl-ethylsulfanyl)-5-trifluoromethyl-benzoic acid ethyl ester

[00514] Prepared according to the procedure described in Example 40, Step 2, using the following starting material: 3-bromo-5-trifluoromethyl-benzoic acid ethyl ester.



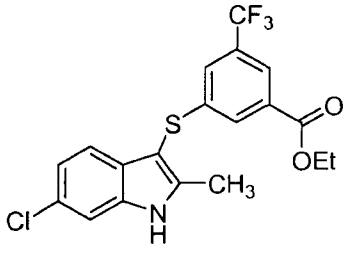
Step 3: 3-Mercapto-5-trifluoromethyl-benzoic acid ethyl ester

[00515] Prepared according to the procedure described in Example 40, Step 3, using the following starting material: 3-(2-octyloxycarbonyl-ethylsulfanyl)-5-trifluoromethyl-benzoic acid ethyl ester.



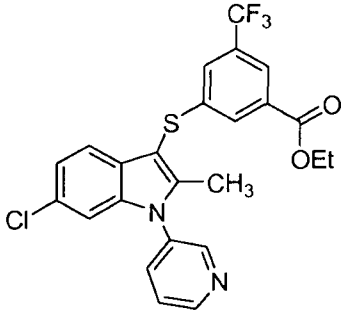
Step 4: 3-(2-Oxo-propylsulfanyl)-5-trifluoromethyl-benzoic acid ethyl ester

[00516] Prepared according to the procedure described in Example 40, Step 4, using the following starting materials: 3-mercapto-5-trifluoromethyl-benzoic acid ethyl ester and chloroacetone.



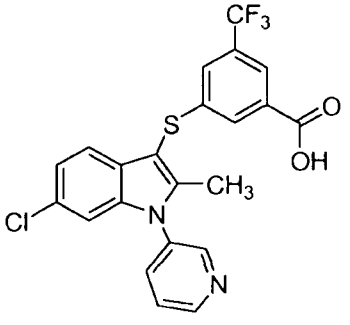
Step 5: 3-(6-Chloro-2-methyl-1*H*-indol-3-ylsulfanyl)-5-trifluoromethyl-benzoic acid ethyl ester

[00517] Prepared according to the procedure described in Example 10, Step 2, using the following starting materials: 3-(2-oxo-propylsulfanyl)-5-trifluoromethyl-benzoic acid ethyl ester and 3-chlorophenylhydrazine hydrochloride.



Step 6: 3-(6-Chloro-2-methyl-1-pyridin-3-yl-1*H*-indol-3-ylsulfanyl)-5-trifluoromethyl-benzoic acid ethyl ester

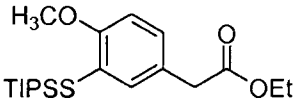
[00518] Prepared according to the procedure described in Example 42, Step 4, using the following starting materials: 3-(6-chloro-2-methyl-1*H*-indol-3-ylsulfanyl)-5-trifluoromethyl-benzoic acid ethyl ester and 3-bromopyridine.



Step 7: 3-(6-Chloro-2-methyl-1-pyridin-3-yl-1*H*-indol-3-ylsulfanyl)-5-trifluoromethyl-benzoic acid

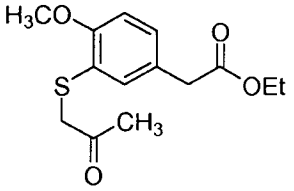
[00519] Prepared according to the procedure described in Example 6, Step 5, using the following starting material: 3-(6-chloro-2-methyl-1-pyridin-3-yl-1*H*-indol-3-ylsulfanyl)-5-trifluoromethyl-benzoic acid ethyl ester.

Example 47: Synthesis of {3-[6-Chloro-2-methyl-1-(1-methyl-1*H*-pyrazol-4-yl)-1*H*-indol-3-ylsulfanyl]-4-methoxy-phenyl}-acetic acid (Compound 1-47)



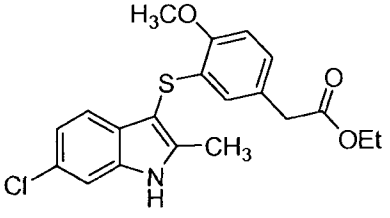
Step 1: (4-Methoxy-3-triisopropylsilanylsulfanyl-phenyl)-acetic acid ethyl ester

[00520] Triisopropylsilanethiol (6.7 mL, 31.2 mmol) was dissolved in THF (75 mL) at 0 °C and sodium hydride (1.25 g, 60% dispersion in mineral oil, 31.3 mmol) was added, then the solution was allowed to warm to room temperature. Meanwhile, (3-bromo-4-methoxy-phenyl)-acetic acid ethyl ester (6.38 g, 23.4 mmol) was dissolved in THF (75 mL) and sparged with N_2 (g). The first solution was added to the second and tetrakis(triphenylphosphine)palladium(0) (1.3 g, 1.1 mmol) was also added. The reaction was heated to reflux overnight then treated to standard aqueous workup. The residue was purified by silica gel chromatography (0-10% EtOAc in hexanes) to give the title compound.



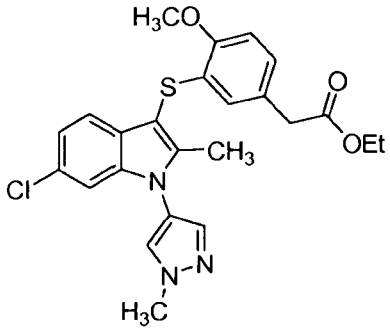
Step 2: [4-Methoxy-3-(2-oxo-propylsulfanyl)-phenyl]-acetic acid ethyl ester

[00521] (4-Methoxy-3-triisopropylsilanylsulfanyl-phenyl)-acetic acid ethyl ester (2.5 g, 6.53 mmol) was dissolved in THF (40 mL) and cooled to 0 °C. Tetrabutylammonium fluoride (6.6 mL, 1.0M in THF, 6.6 mmol) was added and the reaction stirred for 15 minutes, after which time analytical TLC indicated complete reaction. Chloroacetone (0.520 mL, 6.53 mmol) was then added and the reaction was allowed to warm to room temperature. When analytical TLC indicated the reaction was complete, it was submitted to standard workup procedures then purified via silica gel chromatography to yield the title compound.



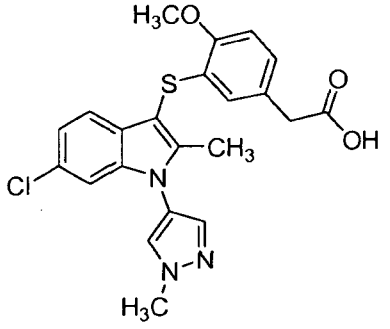
Step 3: [3-(6-Chloro-2-methyl-1*H*-indol-3-ylsulfanyl)-4-methoxy-phenyl]-acetic acid ethyl ester

[00522] Prepared according to the procedure described in Example 10, Step 2, using the following starting materials: [4-methoxy-3-(2-oxo-propylsulfanyl)-phenyl]-acetic acid ethyl ester and 3-chlorophenylhydrazine hydrochloride.



Step 4: {3-[6-Chloro-2-methyl-1-(1-methyl-1*H*-pyrazol-4-yl)-1*H*-indol-3-ylsulfanyl]-4-methoxy-phenyl}-acetic acid ethyl ester

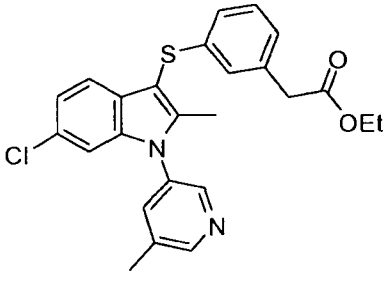
[00523] Prepared according to the procedure described in Example 42, Step 4, using the following starting materials: [3-(6-chloro-2-methyl-1*H*-indol-3-ylsulfanyl)-4-methoxy-phenyl]-acetic acid ethyl ester and 4-bromo-1-methylpyrazole.



Step 5: {3-[6-Chloro-2-methyl-1-(1-methyl-1*H*-pyrazol-4-yl)-1*H*-indol-3-ylsulfanyl]-4-methoxy-phenyl}-acetic acid

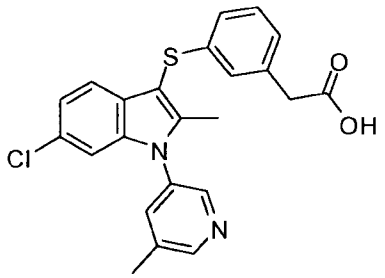
[00524] Prepared according to the procedure described in Example 42, Step 5, using the following starting material: {3-[6-chloro-2-methyl-1-(1-methyl-1*H*-pyrazol-4-yl)-1*H*-indol-3-ylsulfanyl]-4-methoxy-phenyl}-acetic acid ethyl ester.

Example 48: Synthesis of {3-[6-Chloro-2-methyl-1-(5-methyl-pyridin-3-yl)-1*H*-indol-3-ylsulfanyl]-phenyl}-acetic acid (Compound 1-48)



Step 1: {3-[6-Chloro-2-methyl-1-(5-methyl-pyridin-3-yl)-1*H*-indol-3-ylsulfanyl]-phenyl}-acetic acid ethyl ester

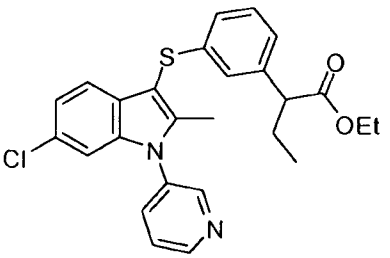
[00525] Prepared according to the procedure described in Example 42, Step 4, using the following starting materials: [3-(6-chloro-2-methyl-1*H*-indol-3-ylsulfanyl)-phenyl]-acetic acid ethyl ester and 3-bromo-5-methylpyridine.



Step 2: {3-[6-Chloro-2-methyl-1-(5-methyl-pyridin-3-yl)-1*H*-indol-3-ylsulfanyl]-phenyl}-acetic acid

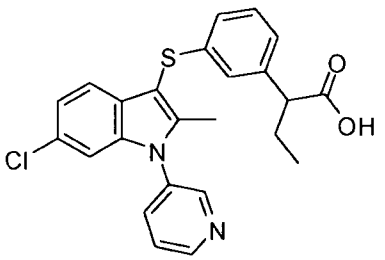
[00526] Prepared according to the procedure described in Example 42, Step 5, using the following starting material: {3-[6-Chloro-2-methyl-1-(5-methyl-pyridin-3-yl)-1*H*-indol-3-ylsulfanyl]-phenyl}-acetic acid ethyl ester.

Example 49: Synthesis of 2-[3-(6-Chloro-2-methyl-1-pyridin-3-yl-1*H*-indol-3-ylsulfanyl)-phenyl]-butyric acid (Compound 1-49)



Step 1: 2-[3-(6-Chloro-2-methyl-1-pyridin-3-yl-1*H*-indol-3-ylsulfanyl)-phenyl]-butyric acid ethyl ester

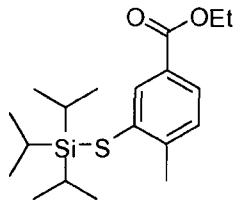
[00527] Prepared according to the procedure described in Example 108, step 1, using the following starting materials: [3-(6-Chloro-2-methyl-1-pyridin-3-yl-1*H*-indol-3-ylsulfanyl)-phenyl]-acetic acid ethyl ester and iodoethane.



Step 2: 2-[3-(6-Chloro-2-methyl-1-pyridin-3-yl-1*H*-indol-3-ylsulfanyl)-phenyl]-butyric acid

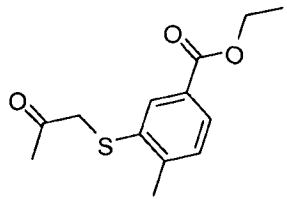
[00528] Prepared according to the procedure described in Example 42, Step 5, using the following starting material: 2-[3-(6-Chloro-2-methyl-1-pyridin-3-yl-1*H*-indol-3-ylsulfanyl)-phenyl]-butyric acid ethyl ester

Example 50: Synthesis of 3-[6-Chloro-2-methyl-1-(1-methyl-1*H*-pyrazol-4-yl)-1*H*-indol-3-ylsulfanyl]-4-methyl-benzoic acid (Compound 1-50)



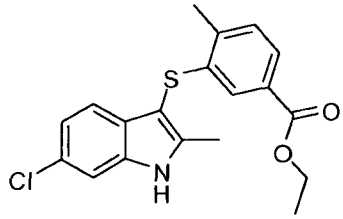
Step 1: 4-Methyl-3-triisopropylsilanylsulfanyl-benzoic acid ethyl ester

[00529] To a 0°C stirred solution of triisopropylsilanethiol (14.28 mmol, 3.07 mL) in THF was added sodium hydride (14.28 mmol, 0.57 g of a 60 wt % dispersion in mineral oil). After 30 min, the mixture was added to a solution of ethyl 3-bromo-4-methylbenzoate (10.99 mmol, 2.67 g) at room temperature, followed by tetrakis(triphenylphosphine)palladium(0) (0.55 mmol, 0.64 g). The resulting mixture was warmed to reflux and stirred for 18 hours, then cooled to room temperature and subjected to standard aqueous workup to afford the title compound which was used crude in the next step.



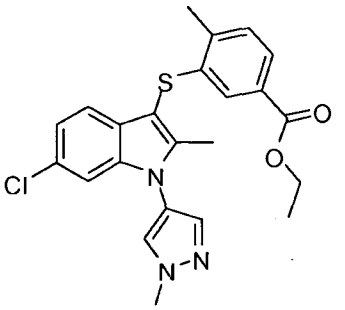
Step 2: 4-Methyl-3-(2-oxo-propylsulfanyl)-benzoic acid ethyl ester

[00530] To a stirred solution of 4-Methyl-3-triisopropylsilanylsulfanyl-benzoic acid ethyl ester (crude from step 1) in THF (50 mL) at 0°C was added TBAF (13.9 mmol, 13.9 mL of a 1.0 M solution in THF). After 25 minutes, triethylamine (34.7 mmol, 4.74 mL) was added, followed by chloroacetone (16.7 mmol, 1.33 mL). The reaction was stirred for an additional 5 minutes, then subjected to standard aqueous workup. The crude material was purified by silica gel chromatography (0-50% EtOAc in hexanes) to afford the title compound.



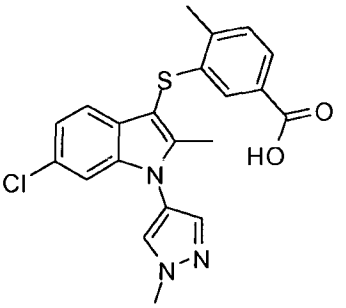
Step 3: 3-(6-Chloro-2-methyl-1*H*-indol-3-ylsulfanyl)-4-methyl-benzoic acid ethyl ester

[00531] Prepared according to the procedure described in Example 2, Step 1, using the following starting materials: 4-Methyl-3-(2-oxo-propylsulfanyl)-benzoic acid ethyl ester and 3-chlorophenylhydrazine hydrochloride.



Step 4: 3-[6-Chloro-2-methyl-1-(1-methyl-1*H*-pyrazol-4-yl)-1*H*-indol-3-ylsulfanyl]-4-methyl-benzoic acid ethyl ester

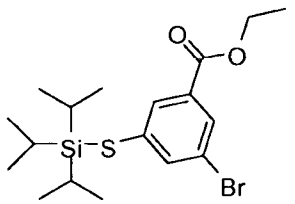
[00532] Prepared according to the procedure described in Example 42, Step 4, using the following starting materials: 3-(6-Chloro-2-methyl-1*H*-indol-3-ylsulfanyl)-4-methyl-benzoic acid ethyl ester and 4-bromo-1-methylpyrazole.



Step 5: 3-[6-Chloro-2-methyl-1-(1-methyl-1*H*-pyrazol-4-yl)-1*H*-indol-3-ylsulfanyl]-4-methyl-benzoic acid

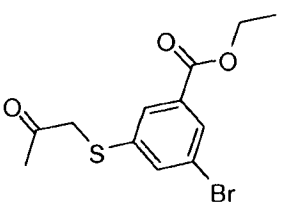
[00533] Prepared according to the procedure described in Example 42, Step 5, using the following starting material: 3-[6-Chloro-2-methyl-1-(1-methyl-1*H*-pyrazol-4-yl)-1*H*-indol-3-ylsulfanyl]-4-methyl-benzoic acid ethyl ester.

Example 51: Synthesis of 3-Bromo-5-[6-chloro-1-(1-ethyl-1*H*-pyrazol-4-yl)-2-methyl-1*H*-indol-3-ylsulfanyl]-benzoic acid (Compound 1-51)



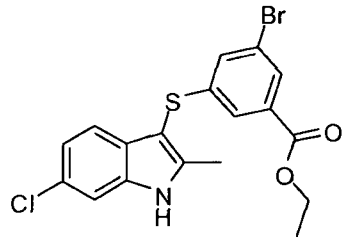
Step 1: 3-Bromo-5-triisopropylsilanylsulfanyl-benzoic acid ethyl ester

[00534] Prepared according to the procedure described in Example 50, Step 1, using the following starting material: 3-Bromo-5-iodo-benzoic acid ethyl ester.



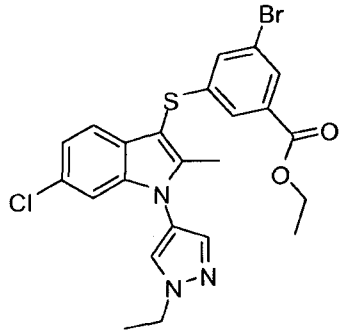
Step 2: 3-Bromo-5-(2-oxo-propylsulfanyl)-benzoic acid ethyl ester

[00535] Prepared according to the procedure described in Example 50, Step 2, using the following starting material: 3-Bromo-5-triisopropylsilanylsulfanyl-benzoic acid ethyl ester.



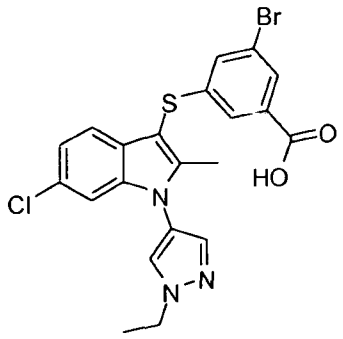
Step 3: 3-Bromo-5-(6-chloro-2-methyl-1*H*-indol-3-ylsulfanyl)-benzoic acid ethyl ester

[00536] Prepared according to the procedure described in Example 2, Step 1, using the following starting materials: 3-Bromo-5-(2-oxo-propylsulfanyl)-benzoic acid ethyl ester and 3-chlorophenylhydrazine hydrochloride.



Step 4: 3-Bromo-5-[6-chloro-1-(1-ethyl-1*H*-pyrazol-4-yl)-2-methyl-1*H*-indol-3-ylsulfanyl]-benzoic acid ethyl ester

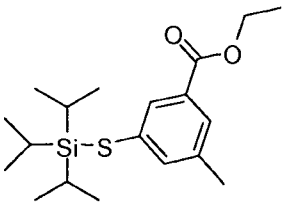
[00537] Prepared according to the procedure described in Example 42, Step 4, using the following starting materials: 3-Bromo-5-(6-chloro-2-methyl-1*H*-indol-3-ylsulfanyl)-benzoic acid ethyl ester and 4-bromo-1-ethylpyrazole.



Step 5: 3-Bromo-5-[6-chloro-1-(1-ethyl-1*H*-pyrazol-4-yl)-2-methyl-1*H*-indol-3-ylsulfanyl]-benzoic acid

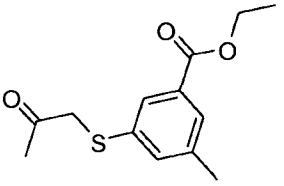
[00538] Prepared according to the procedure described in Example 42, Step 5, using the following starting material: 3-Bromo-5-[6-chloro-1-(1-ethyl-1*H*-pyrazol-4-yl)-2-methyl-1*H*-indol-3-ylsulfanyl]-benzoic acid ethyl ester.

Example 52: Synthesis of 3-[6-Chloro-1-(1-ethyl-1*H*-pyrazol-4-yl)-2-methyl-1*H*-indol-3-ylsulfanyl]-5-methyl-benzoic acid (Compound 1-52)



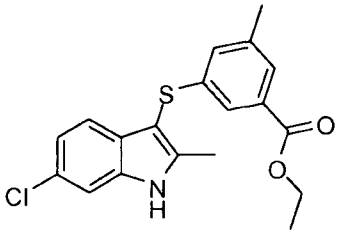
Step 1: 3-Methyl-5-triisopropylsilanylsulfanyl-benzoic acid ethyl ester

[00539] Prepared according to the procedure described in Example 50, Step 1, using the following starting material: 3-Bromo-5-methyl-benzoic acid ethyl ester.



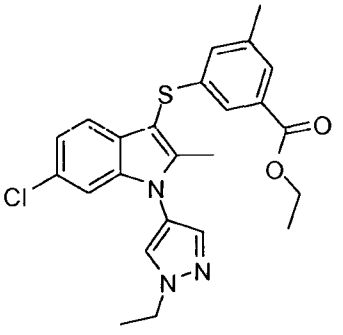
Step 2: 3-Methyl-5-(2-oxo-propylsulfanyl)-benzoic acid ethyl ester

[00540] Prepared according to the procedure described in Example 50, Step 2, using the following starting material: 3-Methyl-5-triisopropylsilanylsulfanyl-benzoic acid ethyl ester.



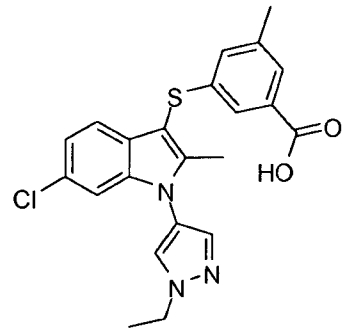
Step 3: 3-(6-Chloro-2-methyl-1*H*-indol-3-ylsulfanyl)-5-methyl-benzoic acid ethyl ester

[00541] Prepared according to the procedure described in Example 2, Step 1, using the following starting materials: 3-Methyl-5-(2-oxo-propylsulfanyl)-benzoic acid ethyl ester and 3-chlorophenylhydrazine hydrochloride.



Step 4: 3-[6-Chloro-1-(1-ethyl-1*H*-pyrazol-4-yl)-2-methyl-1*H*-indol-3-ylsulfanyl]-5-methyl-benzoic acid ethyl ester

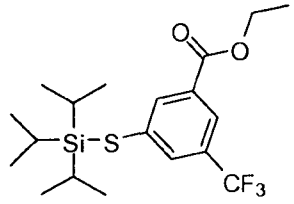
[00542] Prepared according to the procedure described in Example 42, Step 4, using the following starting materials: 3-(6-Chloro-2-methyl-1*H*-indol-3-ylsulfanyl)-5-methyl-benzoic acid ethyl ester and 4-bromo-1-ethylpyrazole.



Step 5: 3-[6-Chloro-1-(1-ethyl-1*H*-pyrazol-4-yl)-2-methyl-1*H*-indol-3-ylsulfanyl]-5-methyl-benzoic acid

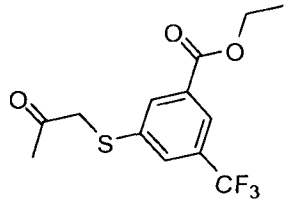
[00543] Prepared according to the procedure described in Example 42, Step 5, using the following starting material: 3-[6-Chloro-1-(1-ethyl-1*H*-pyrazol-4-yl)-2-methyl-1*H*-indol-3-ylsulfanyl]-5-methyl-benzoic acid ethyl ester.

Example 53: Synthesis of 3-[6-Chloro-2-methyl-1-(1-methyl-1*H*-pyrazol-4-yl)-1*H*-indol-3-ylsulfanyl]-5-trifluoromethyl-benzoic acid (Compound 1-53)



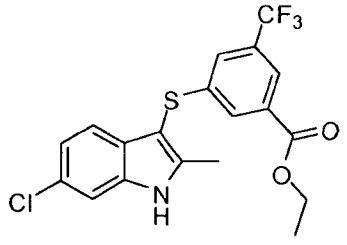
Step 1: 3-Trifluoromethyl-5-triisopropylsilanylsulfanyl-benzoic acid ethyl ester

[00544] Prepared according to the procedure described in Example 50, Step 1, using the following starting material: 3-Bromo-5-trifluoromethyl-benzoic acid ethyl ester.



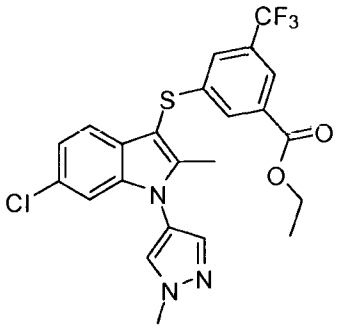
Step 2: 3-Trifluoromethyl-5-(2-oxo-propylsulfanyl)-benzoic acid ethyl ester

[00545] Prepared according to the procedure described in Example 50, Step 2, using the following starting material: 3-Trifluoromethyl-5-triisopropylsilanylsulfanyl-benzoic acid ethyl ester.



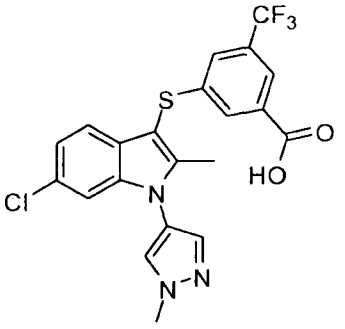
Step 3: 3-(6-Chloro-2-methyl-1*H*-indol-3-ylsulfanyl)-5-trifluoromethyl-benzoic acid ethyl ester

[00546] Prepared according to the procedure described in Example 2, Step 1, using the following starting materials: 3-trifluoromethyl-5-(2-oxo-propylsulfanyl)-benzoic acid ethyl ester and 3-chlorophenylhydrazine hydrochloride.



Step 4: 3-[6-Chloro-1-(1-methyl-1*H*-pyrazol-4-yl)-2-methyl-1*H*-indol-3-ylsulfanyl]-5-trifluoromethyl-benzoic acid ethyl ester

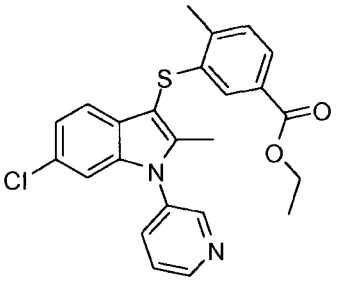
[00547] Prepared according to the procedure described in Example 42, Step 4, using the following starting materials: 3-(6-Chloro-2-methyl-1*H*-indol-3-ylsulfanyl)-5-trifluoromethyl-benzoic acid ethyl ester and 4-bromo-1-methylpyrazole.



Step 5: 3-[6-Chloro-1-(1-methyl-1*H*-pyrazol-4-yl)-2-methyl-1*H*-indol-3-ylsulfanyl]-5-trifluoromethyl-benzoic acid

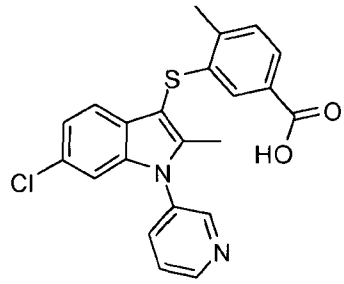
[00548] Prepared according to the procedure described in Example 42, Step 5, using the following starting material: 3-[6-Chloro-1-(1-methyl-1*H*-pyrazol-4-yl)-2-methyl-1*H*-indol-3-ylsulfanyl]-5-trifluoromethyl-benzoic acid ethyl ester.

Example 54: Synthesis of 3-(6-Chloro-2-methyl-1-pyridin-3-yl-1*H*-indol-3-ylsulfanyl)-4-methyl-benzoic acid (Compound 1-54)



Step 1: 3-(6-Chloro-2-methyl-1-pyridin-3-yl-1*H*-indol-3-ylsulfanyl)-4-methyl-benzoic acid ethyl ester

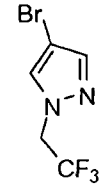
[00549] Prepared according to the procedure described in Example 42, Step 4, using the following starting materials: 3-(6-Chloro-2-methyl-1*H*-indol-3-ylsulfanyl)-4-methyl-benzoic acid ethyl ester and 3-bromopyridine.



Step 2: 3-(6-Chloro-2-methyl-1-pyridin-3-yl-1*H*-indol-3-ylsulfanyl)-4-methyl-benzoic acid

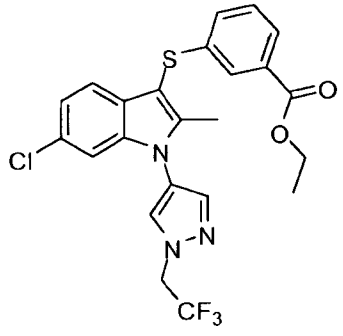
[00550] Prepared according to the procedure described in Example 42, Step 5, using the following starting material 3-(6-Chloro-2-methyl-1-pyridin-3-yl-1*H*-indol-3-ylsulfanyl)-4-methyl-benzoic acid ethyl ester.

Example 55: Synthesis of 3-{6-Chloro-2-methyl-1-[1-(2,2,2-trifluoro-ethyl)-1*H*-pyrazol-4-yl]-1*H*-indol-3-ylsulfanyl}-benzoic acid (Compound 1-55)



Step 1: 4-Bromo-1-(2,2,2-trifluoro-ethyl)-1*H*-pyrazole

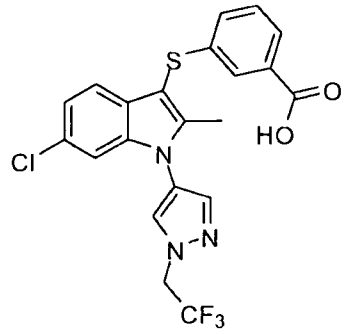
[00551] 4-Bromo-1-H-pyrazole (9.4 mmol, 1.38 g), 1,1,1-trifluoro-2-iodo-ethane (28.2 mmol, 2.75 mL), and cesium carbonate (14.1 mmol, 4.58 g) were combined in DMF (10 mL) and stirred at room temperature for overnight. The resulting mixture was subjected to standard aqueous workup to afford the title compound which was used crude in the next step.



Step 2: 3-{6-Chloro-2-methyl-1-[1-(2,2,2-trifluoro-ethyl)-1*H*-pyrazol-4-yl]-1*H*-indol-3-ylsulfanyl}-benzoic acid ethyl ester

[00552] To a mixture of 3-(6-Chloro-2-methyl-1*H*-indol-3-ylsulfanyl)-benzoic acid ethyl ester (1.3 mmol, 0.45 g) in toluene (10 mL) was added 4-bromo-1-(2,2,2-trifluoro-ethyl)-1*H*-pyrazole (2.6 mmol, 0.60 g), copper(I) iodide (0.13 mmol, 0.025 g), potassium phosphate tribasic (3.25 mmol, 0.69 g), and *N*,*N*'-dimethyl-ethane-1,2-diamine (0.52 mmol, 0.056 mL). The reaction was capped tightly

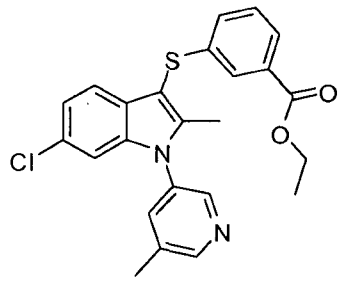
and stirred at 120°C for overnight. The resulting mixture was cooled to room temperature, and subjected to standard aqueous workup. The crude residue was purified by preparative RP-HPLC to afford the title compound.



Step 3: 3-{6-Chloro-2-methyl-1-[1-(2,2,2-trifluoro-ethyl)-1*H*-pyrazol-4-yl]-1*H*-indol-3-ylsulfanyl}-benzoic acid

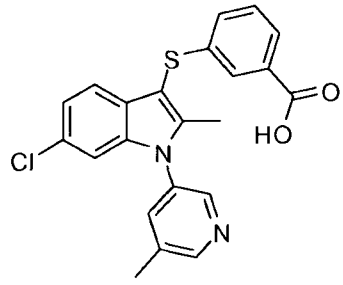
[00553] Prepared according to the procedure described in Example 42, Step 5, using the following starting material: 3-{6-Chloro-2-methyl-1-[1-(2,2,2-trifluoro-ethyl)-1*H*-pyrazol-4-yl]-1*H*-indol-3-ylsulfanyl}-benzoic acid ethyl ester.

Example 56: Synthesis of 3-[6-Chloro-2-methyl-1-(5-methyl-pyridin-3-yl)-1*H*-indol-3-ylsulfanyl]-benzoic acid (Compound 1-56)



Step 1: 3-[6-Chloro-2-methyl-1-(5-methyl-pyridin-3-yl)-1*H*-indol-3-ylsulfanyl]-benzoic acid ethyl ester

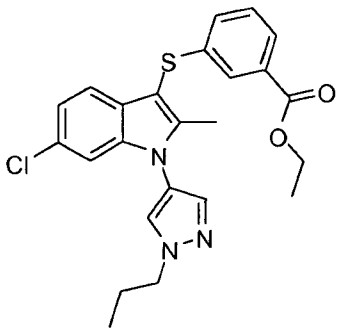
[00554] Prepared according to the procedure described in Example 42, Step 4, using the following starting materials: 3-(6-Chloro-2-methyl-1*H*-indol-3-ylsulfanyl)-4-methyl-benzoic acid ethyl ester and 3-bromo-5-methyl-pyridine



Step 2: 3-[6-Chloro-2-methyl-1-(5-methyl-pyridin-3-yl)-1*H*-indol-3-ylsulfanyl]-benzoic acid

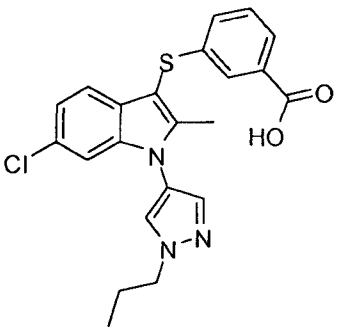
[00555] Prepared according to the procedure described in Example 42, Step 5, using the following starting material: 3-[6-Chloro-2-methyl-1-(5-methyl-pyridin-3-yl)-1*H*-indol-3-ylsulfanyl]-benzoic acid ethyl ester.

Example 57: Synthesis of 3-[6-Chloro-2-methyl-1-(1-propyl-1*H*-pyrazol-4-yl)-1*H*-indol-3-ylsulfanyl]-benzoic acid (Compound 1-57)



Step 1: 3-[6-Chloro-2-methyl-1-(1-propyl-1*H*-pyrazol-4-yl)-1*H*-indol-3-ylsulfanyl]-benzoic acid ethyl ester

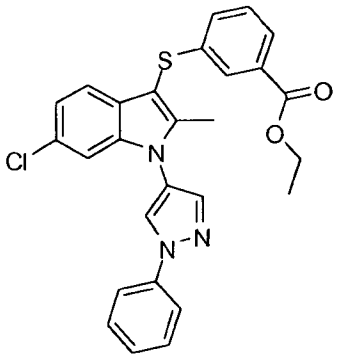
[00556] Prepared according to the procedure described in Example 55, Step 2 using the the following starting materials: 3-(6-chloro-2-methyl-1*H*-indol-3-ylsulfanyl)-benzoic acid ethyl ester and 4-bromo-1-propylpyrazole.



Step 2: 3-[6-Chloro-2-methyl-1-(1-propyl-1*H*-pyrazol-4-yl)-1*H*-indol-3-ylsulfanyl]-benzoic acid

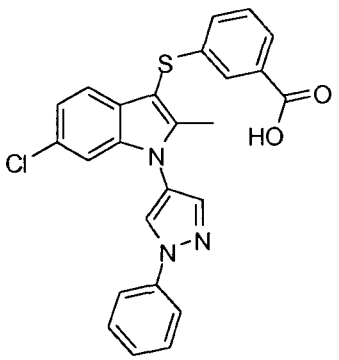
[00557] Prepared according to the procedure described in Example 42, Step 5, using the following starting material: 3-[6-Chloro-2-methyl-1-(1-propyl-1*H*-pyrazol-4-yl)-1*H*-indol-3-ylsulfanyl]-benzoic acid ethyl ester.

Example 58: Synthesis of 3-[6-Chloro-2-methyl-1-(1-phenyl-1*H*-pyrazol-4-yl)-1*H*-indol-3-ylsulfanyl]-benzoic acid (Compound 1-58)



Step 1: 3-[6-Chloro-2-methyl-1-(1-phenyl-1*H*-pyrazol-4-yl)-1*H*-indol-3-ylsulfanyl]-benzoic acid ethyl ester

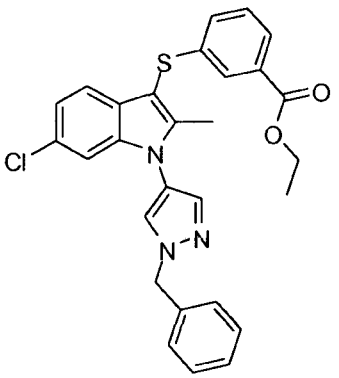
[00558] Prepared according to the procedure described in Example 55, Step 2 using the the following starting materials: 3-(6-chloro-2-methyl-1*H*-indol-3-ylsulfanyl)-benzoic acid ethyl ester and 4-bromo-1-phenylpyrazole.



Step 2: 3-[6-Chloro-2-methyl-1-(1-phenyl-1*H*-pyrazol-4-yl)-1*H*-indol-3-ylsulfanyl]-benzoic acid

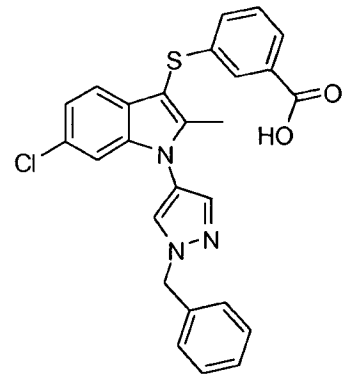
[00559] Prepared according to the procedure described in Example 42, Step 5, using the following starting material: 3-[6-Chloro-2-methyl-1-(1-phenyl-1*H*-pyrazol-4-yl)-1*H*-indol-3-ylsulfanyl]-benzoic acid ethyl ester.

Example 59: Synthesis of 3-[1-(1-Benzyl-1*H*-pyrazol-4-yl)-6-chloro-2-methyl-1*H*-indol-3-ylsulfanyl]-benzoic acid (Compound 1-59)



Step 1: 3-[1-(1-Benzyl-1*H*-pyrazol-4-yl)-6-chloro-2-methyl-1*H*-indol-3-ylsulfanyl]-benzoic acid ethyl ester

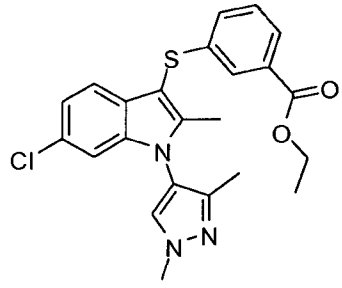
[00560] Prepared according to the procedure described in Example 55, Step 2 using the the following starting materials: 3-(6-chloro-2-methyl-1*H*-indol-3-ylsulfanyl)-benzoic acid ethyl ester and 4-bromo-1-benzylpyrazole.



Step 2: 33-[1-(1-Benzyl-1*H*-pyrazol-4-yl)-6-chloro-2-methyl-1*H*-indol-3-ylsulfanyl]-benzoic acid

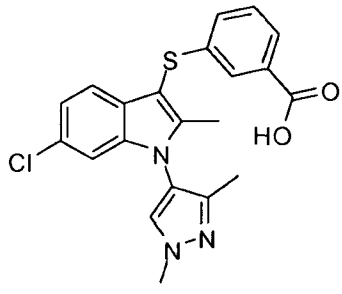
[00561] Prepared according to the procedure described in Example 42, Step 5, using the following starting material: 3-[1-(1-Benzyl-1*H*-pyrazol-4-yl)-6-chloro-2-methyl-1*H*-indol-3-ylsulfanyl]-benzoic acid ethyl ester.

Example 60: Synthesis of 3-[6-Chloro-1-(1,3-dimethyl-1*H*-pyrazol-4-yl)-2-methyl-1*H*-indol-3-ylsulfanyl]-benzoic acid (Compound 1-60)



Step 1: 3-[6-Chloro-1-(1,3-dimethyl-1*H*-pyrazol-4-yl)-2-methyl-1*H*-indol-3-ylsulfanyl]-benzoic acid ethyl ester

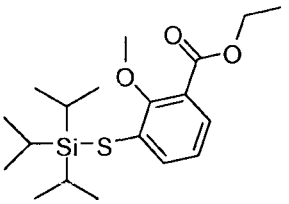
[00562] Prepared according to the procedure described in Example 55, Step 2 using the the following starting materials: 3-(6-chloro-2-methyl-1*H*-indol-3-ylsulfanyl)-benzoic acid ethyl ester and 4-Bromo-1,3-dimethyl-1*H*-pyrazole.



Step 2: 3-[6-Chloro-1-(1,3-dimethyl-1*H*-pyrazol-4-yl)-2-methyl-1*H*-indol-3-ylsulfanyl]-benzoic acid

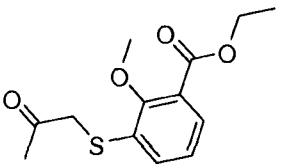
[00563] Prepared according to the procedure described in Example 42, Step 5, using the following starting material: 3-[6-Chloro-1-(1,3-dimethyl-1*H*-pyrazol-4-yl)-2-methyl-1*H*-indol-3-ylsulfanyl]-benzoic acid ethyl ester.

Example 61: Synthesis of 3-[6-Chloro-2-methyl-1-(1-methyl-1*H*-pyrazol-4-yl)-1*H*-indol-3-ylsulfanyl]-2-methoxy-benzoic acid (Compound 1-61)



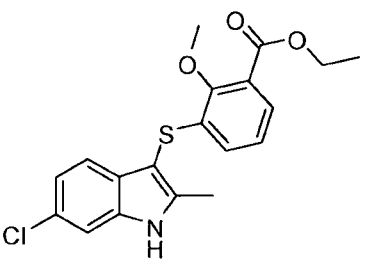
Step 1: 2-Methoxy-3-triisopropylsilanylsulfanyl-benzoic acid ethyl ester

[00564] Prepared according to the procedure described in Example 50, Step 1, using the following starting material: 2-methoxy-3-bromo-benzoic acid ethyl ester.



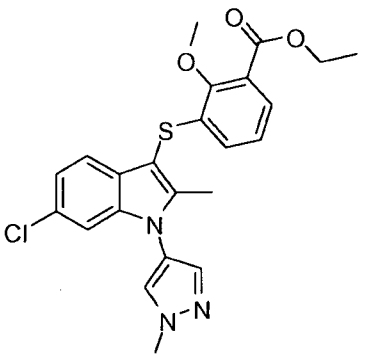
Step 2: 2-Methoxy-3-(2-oxo-propylsulfanyl)-benzoic acid ethyl ester

[00565] Prepared according to the procedure described in Example 50, Step 2, using the following starting material: 2-methoxy-3-triisopropylsilanylsulfanyl-benzoic acid ethyl ester.



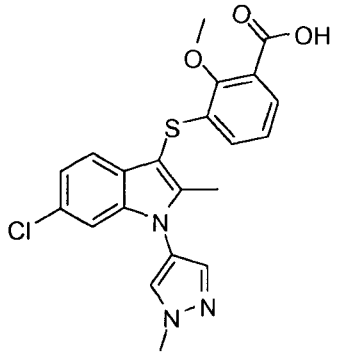
Step 3: 3-(6-Chloro-2-methyl-1*H*-indol-3-ylsulfanyl)-2-methoxy-benzoic acid ethyl ester

[00566] Prepared according to the procedure described in Example 2, Step 1, using the following starting materials: 2-Methoxy-3-(2-oxo-propylsulfanyl)-benzoic acid ethyl ester and 3-chlorophenylhydrazine hydrochloride.



Step 4: 3-[6-Chloro-2-methyl-1-(1-methyl-1*H*-pyrazol-4-yl)-1*H*-indol-3-ylsulfanyl]-2-methoxy-benzoic acid ethyl ester

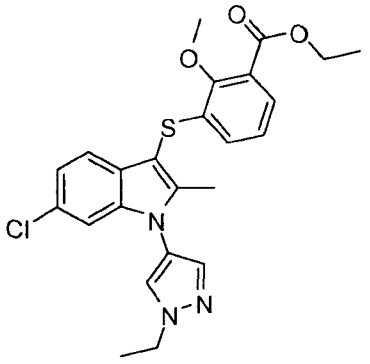
[00567] Prepared according to the procedure described in Example 42, Step 4, using the following starting materials: 3-(6-chloro-2-methyl-1*H*-indol-3-ylsulfanyl)-2-methoxy-benzoic acid ethyl ester and 4-bromo-1-methylpyrazole.



Step 5: 3-[6-Chloro-2-methyl-1-(1-methyl-1*H*-pyrazol-4-yl)-1*H*-indol-3-ylsulfanyl]-2-methoxy-benzoic acid

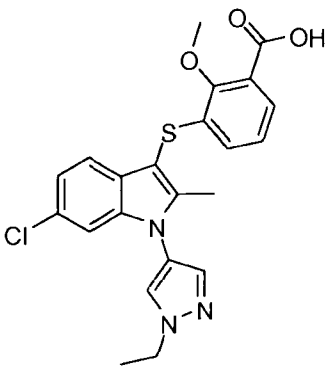
[00568] Prepared according to the procedure described in Example 42, Step 5, using the following starting material: 3-[6-Chloro-2-methyl-1-(1-methyl-1*H*-pyrazol-4-yl)-1*H*-indol-3-ylsulfanyl]-2-methoxy-benzoic acid ethyl ester.

Example 62: Synthesis of 3-[6-Chloro-2-methyl-1-(1-ethyl-1*H*-pyrazol-4-yl)-1*H*-indol-3-ylsulfanyl]-2-methoxy-benzoic acid (Compound 1-62)



Step 1: 3-[6-Chloro-2-methyl-1-(1-ethyl-1*H*-pyrazol-4-yl)-1*H*-indol-3-ylsulfanyl]-2-methoxy-benzoic acid ethyl ester

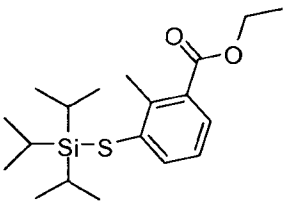
[00569] Prepared according to the procedure described in Example 42, Step 4, using the following starting materials: 3-(6-chloro-2-methyl-1*H*-indol-3-ylsulfanyl)-2-methoxy-benzoic acid ethyl ester and 4-bromo-1-ethylpyrazole.



Step 2: 3-[6-Chloro-2-methyl-1-(1-ethyl-1*H*-pyrazol-4-yl)-1*H*-indol-3-ylsulfanyl]-2-methoxy-benzoic acid

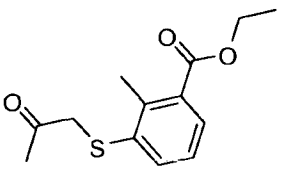
[00570] Prepared according to the procedure described in Example 42, Step 5, using the following starting material: 3-[6-Chloro-2-ethyl-1-(1-ethyl-1*H*-pyrazol-4-yl)-1*H*-indol-3-ylsulfanyl]-2-methoxy-benzoic acid ethyl ester.

Example 63: Synthesis of 3-[6-Chloro-2-methyl-1-(1-methyl-1*H*-pyrazol-4-yl)-1*H*-indol-3-ylsulfanyl]-2-methyl-benzoic acid (Compound 1-63)



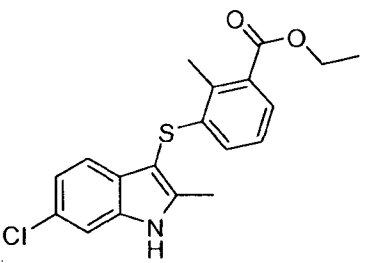
Step 1: 2-Methyl-3-triisopropylsilanylsulfanyl-benzoic acid ethyl ester

[00571] Prepared according to the procedure described in Example 50, Step 1, using the following starting material: 2-methyl-3-bromo-benzoic acid ethyl ester.



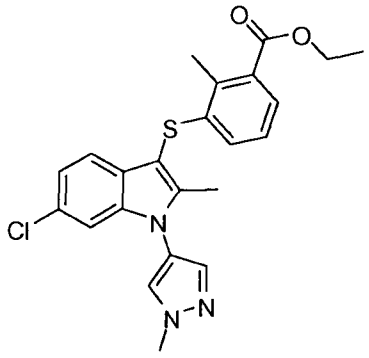
Step 2: 2-Methyl-3-(2-oxo-propylsulfanyl)-benzoic acid ethyl ester

[00572] Prepared according to the procedure described in Example 50, Step 2, using the following starting material: 2-methyl-3-triisopropylsilanylsulfanyl-benzoic acid ethyl ester.



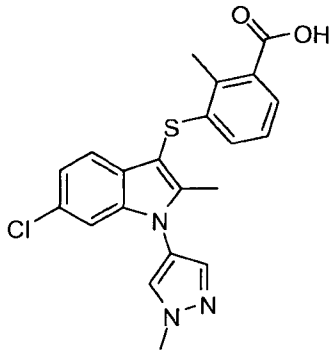
Step 3: 3-(6-Chloro-2-methyl-1*H*-indol-3-ylsulfanyl)-2-methyl-benzoic acid ethyl ester

[00573] Prepared according to the procedure described in Example 2, Step 1, using the following starting materials: 2-Methyl-3-(2-oxo-propylsulfanyl)-benzoic acid ethyl ester and 3-chlorophenylhydrazine hydrochloride.



Step 4: 3-[6-Chloro-2-methyl-1-(1-methyl-1*H*-pyrazol-4-yl)-1*H*-indol-3-ylsulfanyl]-2-methyl-benzoic acid ethyl ester

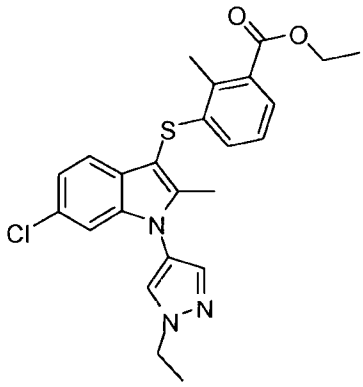
[00574] Prepared according to the procedure described in Example 42, Step 4, using the following starting materials: 3-(6-chloro-2-methyl-1*H*-indol-3-ylsulfanyl)-2-methyl-benzoic acid ethyl ester and 4-bromo-1-methylpyrazole.



Step 5: 3-[6-Chloro-2-methyl-1-(1-methyl-1*H*-pyrazol-4-yl)-1*H*-indol-3-ylsulfanyl]-2-methyl-benzoic acid

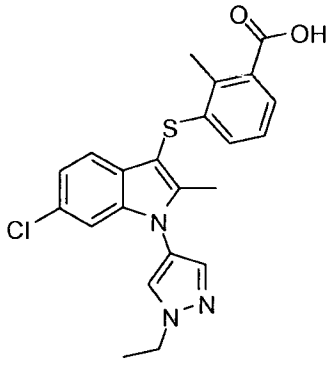
[00575] Prepared according to the procedure described in Example 42, Step 5, using the following starting material: 3-[6-Chloro-2-methyl-1-(1-methyl-1*H*-pyrazol-4-yl)-1*H*-indol-3-ylsulfanyl]-2-methyl-benzoic acid ethyl ester.

Example 64: Synthesis of 3-[6-Chloro-2-methyl-1-(1-ethyl-1*H*-pyrazol-4-yl)-1*H*-indol-3-ylsulfanyl]-2-methyl-benzoic acid (Compound 1-64)



Step 1: 3-[6-Chloro-2-methyl-1-(1-ethyl-1*H*-pyrazol-4-yl)-1*H*-indol-3-ylsulfanyl]-2-methyl-benzoic acid ethyl ester

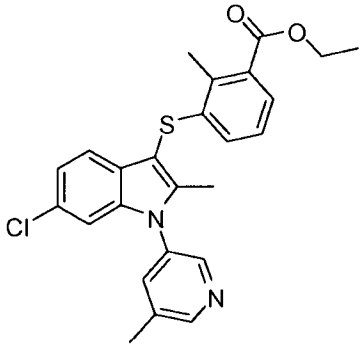
[00576] Prepared according to the procedure described in Example 42, Step 4, using the following starting materials: 3-(6-chloro-2-methyl-1*H*-indol-3-ylsulfanyl)-2-methyl-benzoic acid ethyl ester and 4-bromo-1-ethylpyrazole.



Step 2: 3-[6-Chloro-2-methyl-1-(1-ethyl-1*H*-pyrazol-4-yl)-1*H*-indol-3-ylsulfanyl]-2-methyl-benzoic acid

[00577] Prepared according to the procedure described in Example 42, Step 5, using the following starting material: 3-[6-Chloro-2-methyl-1-(1-ethyl-1*H*-pyrazol-4-yl)-1*H*-indol-3-ylsulfanyl]-2-methyl-benzoic acid ethyl ester.

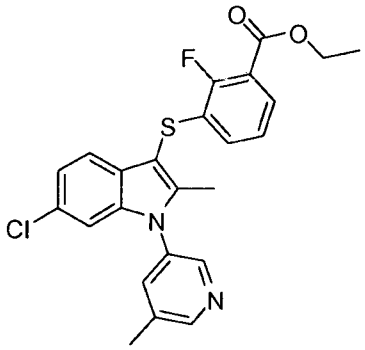
Example 65: Synthesis of 3-[6-Chloro-2-methyl-1-(5-methyl-pyridin-3-yl)-1*H*-indol-3-ylsulfanyl]-2-methyl-benzoic acid (Compound 1-65)



Step 1: 3-[6-Chloro-2-methyl-1-(5-methyl-pyridin-3-yl)-1*H*-indol-3-ylsulfanyl]-2-methyl-benzoic acid ethyl ester

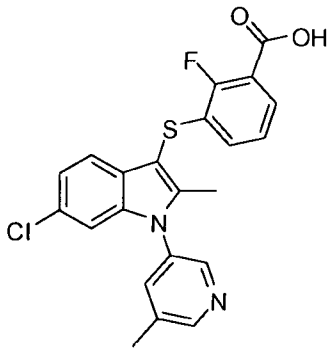
Step 3: 3-(6-Chloro-2-methyl-1*H*-indol-3-ylsulfanyl)-2-fluoro-benzoic acid ethyl ester

[00582] Prepared according to the procedure described in Example 2, Step 1, using the following starting materials: 2-fluoro-3-(2-oxo-propylsulfanyl)-benzoic acid ethyl ester and 3-chlorophenylhydrazine hydrochloride.



Step 4: 3-[6-Chloro-2-methyl-1-(5-methyl-pyridin-3-yl)-1*H*-indol-3-ylsulfanyl]-2-fluoro-benzoic acid ethyl ester

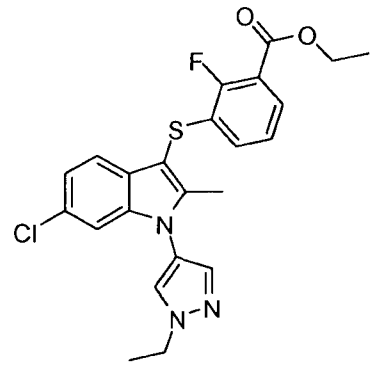
[00583] Prepared according to the procedure described in Example 42, Step 4, using the following starting materials: 3-(6-chloro-2-methyl-1*H*-indol-3-ylsulfanyl)-2-fluoro-benzoic acid ethyl ester and 3-bromo-5-methylpyridine.



Step 5: 3-[6-Chloro-2-methyl-1-(5-methyl-pyridin-3-yl)-1*H*-indol-3-ylsulfanyl]-2-fluoro-benzoic acid

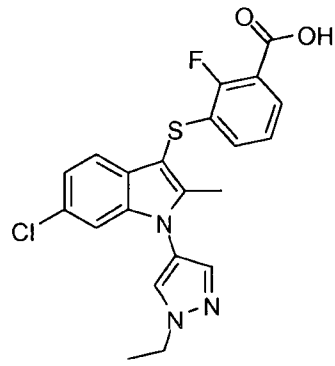
[00584] Prepared according to the procedure described in Example 42, Step 5, using the following starting material: 3-[6-Chloro-2-methyl-1-(5-methyl-pyridin-3-yl)-1*H*-indol-3-ylsulfanyl]-2-methyl-benzoic acid ethyl ester.

Example 67: Synthesis of 3-[6-Chloro-2-methyl-1-(1-ethyl-1*H*-pyrazol-4-yl)-1*H*-indol-3-ylsulfanyl]-2-fluoro-benzoic acid (Compound 1-67)



Step 1: 3-[6-Chloro-2-methyl-1-(1-ethyl-1*H*-pyrazol-4-yl)-1*H*-indol-3-ylsulfanyl]-2-fluoro-benzoic acid ethyl ester

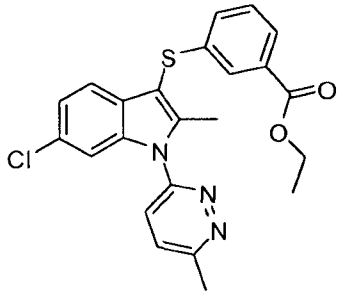
[00585] Prepared according to the procedure described in Example 42, Step 4, using the following starting materials: 3-(6-chloro-2-methyl-1*H*-indol-3-ylsulfanyl)-2-fluoro-benzoic acid ethyl ester and 4-bromo-1-ethylpyrazole.



Step2: 3-[6-Chloro-2-methyl-1-(1-ethyl-1*H*-pyrazol-4-yl)-1*H*-indol-3-ylsulfanyl]-2-fluoro-benzoic acid

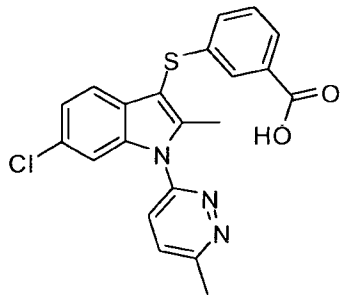
[00586] Prepared according to the procedure described in Example 42, Step 5, using the following starting material: 3-[6-Chloro-2-methyl-1-(1-ethyl-1*H*-pyrazol-4-yl)-1*H*-indol-3-ylsulfanyl]-2-methyl-benzoic acid ethyl ester.

Example 68: Synthesis of 3-[6-Chloro-2-methyl-1-(6-methyl-pyridazin-3-yl)-1*H*-indol-3-ylsulfanyl]-benzoic acid (Compound 1-68)



Step 1: 3-[6-Chloro-2-methyl-1-(6-methyl-pyridazin-3-yl)-1*H*-indol-3-ylsulfanyl]-benzoic acid ethyl ester

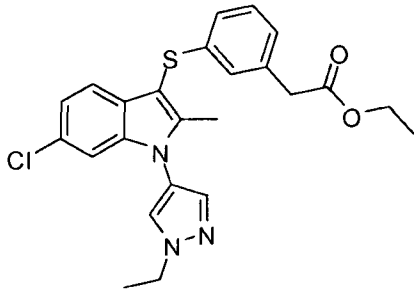
[00587] Prepared according to the procedure described in Example 55, Step 2 using the the following starting materials: 3-(6-chloro-2-methyl-1*H*-indol-3-ylsulfanyl)-benzoic acid ethyl ester and 3-chloro-6-methyl-pyridazine.



Step 2: 3-[6-Chloro-2-methyl-1-(6-methyl-pyridazin-3-yl)-1*H*-indol-3-ylsulfanyl]-benzoic acid

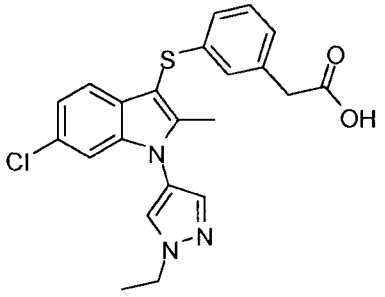
[00588] Prepared according to the procedure described in Example 42, Step 5, using the following starting material: 3-[6-Chloro-2-methyl-1-(6-methyl-pyridazin-3-yl)-1*H*-indol-3-ylsulfanyl]-benzoic acid ethyl ester.

Example 69: Synthesis of {3-[6-Chloro-1-(1-ethyl-1*H*-pyrazol-4-yl)-2-methyl-1*H*-indol-3-ylsulfanyl]-phenyl}-acetic acid (Compound 1-69)



Step 1: {3-[6-Chloro-1-(1-ethyl-1*H*-pyrazol-4-yl)-2-methyl-1*H*-indol-3-ylsulfanyl]-phenyl}-acetic acid ethyl ester

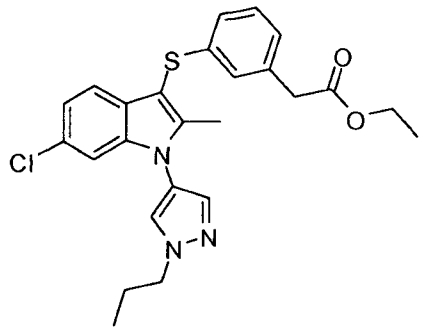
[00589] Prepared according to the procedure described in Example 42, Step 4, using the following starting materials: [3-(6-chloro-2-methyl-1*H*-indol-3-ylsulfanyl)-phenyl]-acetic acid ethyl ester and 4-bromo-1-ethylpyrazole.



Step 2: {3-[6-Chloro-1-(1-ethyl-1*H*-pyrazol-4-yl)-2-methyl-1*H*-indol-3-ylsulfanyl]-phenyl}-acetic acid

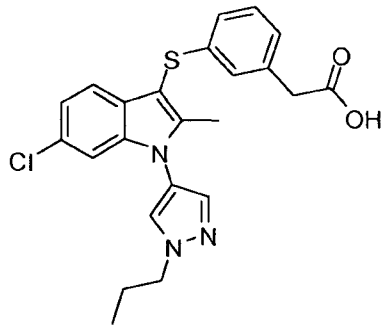
[00590] Prepared according to the procedure described in Example 42, Step 5, using the following starting material: {3-[6-Chloro-1-(1-ethyl-1*H*-pyrazol-4-yl)-2-methyl-1*H*-indol-3-ylsulfanyl]-phenyl}-acetic acid ethyl ester.

Example 70: Synthesis of {3-[6-Chloro-1-(1-propyl-1*H*-pyrazol-4-yl)-2-methyl-1*H*-indol-3-ylsulfanyl]-phenyl}-acetic acid (Compound 1-70)



Step 1: {3-[6-Chloro-1-(1-propyl-1*H*-pyrazol-4-yl)-2-methyl-1*H*-indol-3-ylsulfanyl]-phenyl}-acetic acid ethyl ester

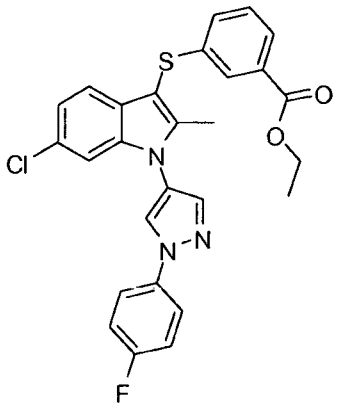
[00591] Prepared according to the procedure described in Example 42, Step 4, using the following starting materials: [3-(6-chloro-2-methyl-1*H*-indol-3-ylsulfanyl)-phenyl]-acetic acid ethyl ester and 4-bromo-1-propylpyrazole.



Step 2: {3-[6-Chloro-1-(1-propyl-1*H*-pyrazol-4-yl)-2-methyl-1*H*-indol-3-ylsulfanyl]-phenyl}-acetic acid

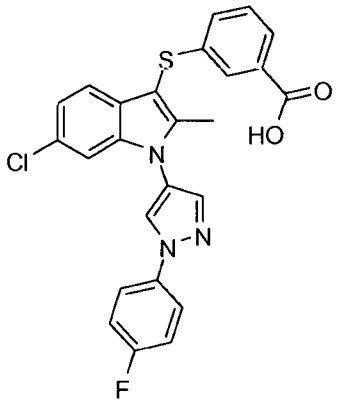
[00592] Prepared according to the procedure described in Example 42, Step 5, using the following starting material: {3-[6-Chloro-1-(1-propyl-1*H*-pyrazol-4-yl)-2-methyl-1*H*-indol-3-ylsulfanyl]-phenyl}-acetic acid ethyl ester.

Example 71: Synthesis of 3-{6-Chloro-1-[1-(4-fluoro-phenyl)-1*H*-pyrazol-4-yl]-2-methyl-1*H*-indol-3-ylsulfanyl}-benzoic acid (Compound 1-71)



Step 1: 3-{6-Chloro-1-[1-(4-fluoro-phenyl)-1*H*-pyrazol-4-yl]-2-methyl-1*H*-indol-3-ylsulfanyl}-benzoic acid ethyl ester

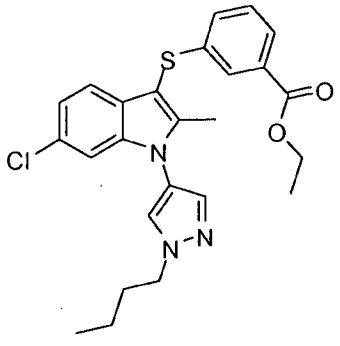
[00593] Prepared according to the procedure described in Example 55, Step 2 using the the following starting materials: 3-(6-chloro-2-methyl-1*H*-indol-3-ylsulfanyl)-benzoic acid ethyl ester and 4-Bromo-1-(4-fluoro-phenyl)-1*H*-pyrazole.



Step 2: 3-{6-Chloro-1-[1-(4-fluoro-phenyl)-1*H*-pyrazol-4-yl]-2-methyl-1*H*-indol-3-ylsulfanyl}-benzoic acid

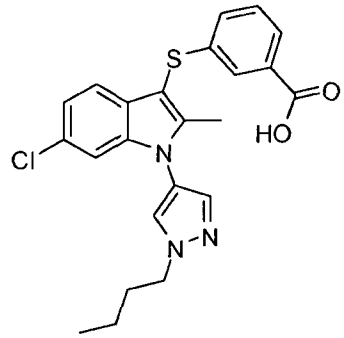
[00594] Prepared according to the procedure described in Example 42, Step 5, using the following starting material: 3-{6-Chloro-1-[1-(4-fluoro-phenyl)-1*H*-pyrazol-4-yl]-2-methyl-1*H*-indol-3-ylsulfanyl}-benzoic acid ethyl ester.

Example 72: Synthesis of 3-[1-(1-Butyl-1*H*-pyrazol-4-yl)-6-chloro-2-methyl-1*H*-indol-3-ylsulfanyl]-benzoic acid (Compound 1-72)



Step 1: 3-[1-(1-Butyl-1*H*-pyrazol-4-yl)-6-chloro-2-methyl-1*H*-indol-3-ylsulfanyl]-benzoic acid ethyl ester

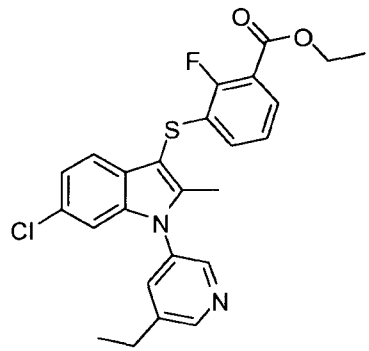
[00595] Prepared according to the procedure described in Example 55, Step 2 using the the following starting materials: 3-(6-chloro-2-methyl-1*H*-indol-3-ylsulfanyl)-benzoic acid ethyl ester and 4-Bromo-1-butyl-1*H*-pyrazole



Step 2: 3-[1-(1-Butyl-1*H*-pyrazol-4-yl)-6-chloro-2-methyl-1*H*-indol-3-ylsulfanyl]-benzoic acid

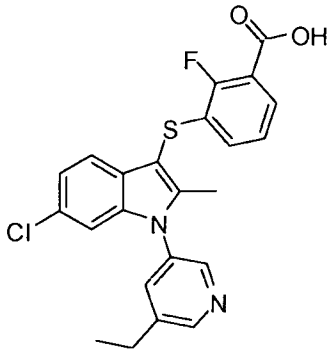
[00596] Prepared according to the procedure described in Example 42, Step 5, using the following starting material: 3-[1-(1-Butyl-1*H*-pyrazol-4-yl)-6-chloro-2-methyl-1*H*-indol-3-ylsulfanyl]-benzoic acid ethyl ester.

Example 73: Synthesis of 3-[6-Chloro-1-(5-ethyl-pyridin-3-yl)-2-methyl-1*H*-indol-3-ylsulfanyl]-2-fluoro-benzoic acid (Compound 1-73)



Step 1: 3-[6-Chloro-1-(5-ethyl-pyridin-3-yl)-2-methyl-1*H*-indol-3-ylsulfanyl]-2-fluoro-benzoic acid ethyl ester

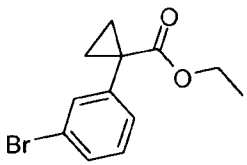
[00597] Prepared according to the procedure described in Example 42, Step 4, using the following starting materials: 3-(6-chloro-2-methyl-1*H*-indol-3-ylsulfanyl)-2-fluoro-benzoic acid ethyl ester and 3-bromo-5-ethylpyridine.



Step 2: 3-[6-Chloro-2-methyl-1-(5-ethyl-pyridin-3-yl)-1*H*-indol-3-ylsulfanyl]-2-fluoro-benzoic acid

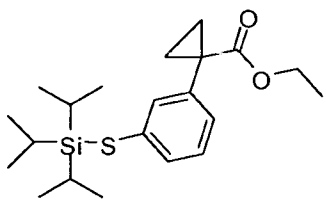
[00598] Prepared according to the procedure described in Example 42, Step 5, using the following starting material: 3-[6-Chloro-1-(5-ethyl-pyridin-3-yl)-2-methyl-1*H*-indol-3-ylsulfanyl]-2-fluoro-benzoic acid ethyl ester.

Example 74: Synthesis of 1-{3-[6-Chloro-1-(1-ethyl-1*H*-pyrazol-4-yl)-2-methyl-1*H*-indol-3-ylsulfanyl]-phenyl}-cyclopropanecarboxylic acid (Compound 1-74)



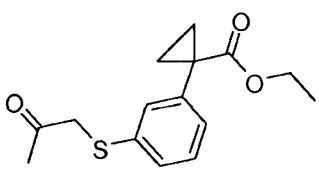
Step 1: 1-(3-Bromo-phenyl)-cyclopropanecarboxylic acid ethyl ester

[00599] To a stirred solution of 1-(3-bromophenyl)-cyclopropanecarboxyllic acid (3.0 g, 12.45 mmol) in absolute EtOH (100 mL) at room temperature was added concentrated H_2SO_4 (10 mL) and the mixture was warmed to reflux. After 4 hrs, the reaction was cooled to room temperature, evaporated under reduced pressure, diluted with DCM (500 mL) and stirred over solid K_2CO_3. After 1 hr, the resulting mixture was filtered and concentrated to dryness to afford the title compound.



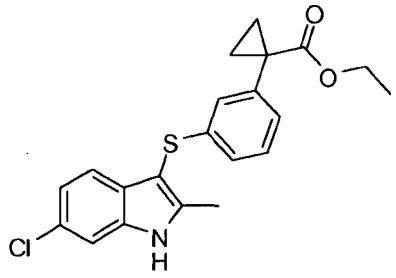
Step 2: 1-(3-Triisopropylsilanylsulfanyl-phenyl)-cyclopropanecarboxylic acid ethyl ester

[00600] Prepared according to the procedure described in Example 50, Step 1, using the following starting material: 1-(3-Bromo-phenyl)-cyclopropanecarboxylic acid ethyl ester.



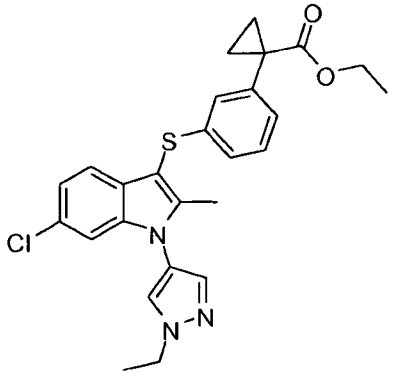
Step 3: 1-[3-(2-Oxo-propylsulfanyl)-phenyl]-cyclopropanecarboxylic acid ethyl ester

[00601] Prepared according to the procedure described in Example 50, Step 2, using the following starting material: 1-(3-Triisopropylsilanylsulfanyl-phenyl)-cyclopropanecarboxylic acid ethyl ester.



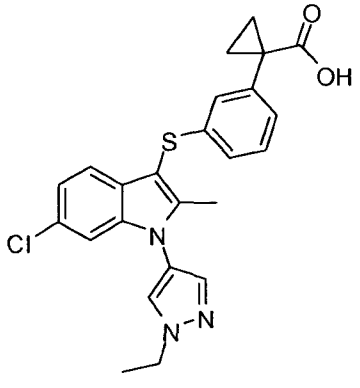
Step 4: 1-[3-(6-Chloro-2-methyl-1*H*-indol-3-ylsulfanyl)-phenyl]-cyclopropanecarboxylic acid ethyl ester

[00602] Prepared according to the procedure described in Example 2, Step 1, using the following starting materials: 1-[3-(2-oxo-propylsulfanyl)-phenyl]-cyclopropanecarboxylic acid ethyl ester and 3-chlorophenylhydrazine hydrochloride.



Step 5: 1-{3-[6-Chloro-1-(1-ethyl-1*H*-pyrazol-4-yl)-2-methyl-1*H*-indol-3-ylsulfanyl]-phenyl}-cyclopropanecarboxylic acid ethyl ester

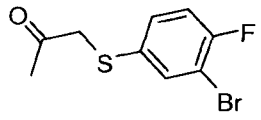
[00603] Prepared according to the procedure described in Example 42, Step 4, using the following starting materials: 1-[3-(6-Chloro-2-methyl-1*H*-indol-3-ylsulfanyl)-phenyl]-cyclopropanecarboxylic acid ethyl ester and 4-bromo-1-ethylpyrazole.



Step 6: 1-{3-[6-Chloro-1-(1-ethyl-1*H*-pyrazol-4-yl)-2-methyl-1*H*-indol-3-ylsulfanyl]-phenyl}-cyclopropanecarboxylic acid

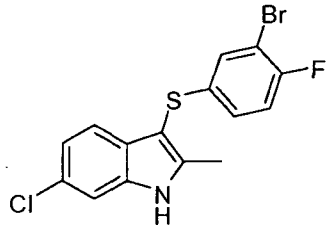
[00607] Prepared according to the procedure described in Example 42, Step 5, using the following starting material: 3-[1-(1-Ethyl-1*H*-pyrazol-4-yl)-6-methanesulfonyl-2-methyl-1*H*-indol-3-ylsulfanyl]-benzoic acid methyl ester.

Example 76: Synthesis of 5-[6-chloro-1-(1-ethyl-1*H*-pyrazol-4-yl)-2-methyl-1*H*-indol-3-ylsulfanyl]-2-fluoro-benzoic acid (Compound 1-76)



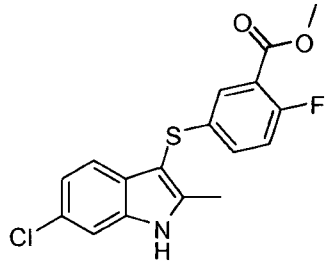
Step 1: 1-(3-Bromo-4-fluoro-phenylsulfanyl)-propan-2-one

[00608] Prepared according to the procedure described in Example 6, Step 1, using the following starting material: 3-bromo-4-fluoro-thiophenol.



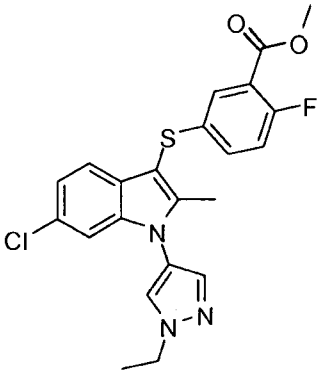
Step 2: 3-(3-Bromo-4-fluoro-phenylsulfanyl)-6-chloro-2-methyl-1*H*-indole

[00609] Prepared according to the procedure described in Example 2, Step 1, using the following starting materials: 1-(3-Bromo-4-fluoro-phenylsulfanyl)-propan-2-one and 3-chlorophenylhydrazine hydrochloride.



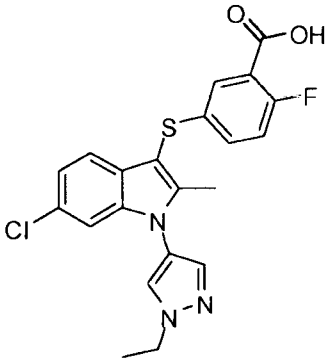
Step 3: 5-(6-Chloro-2-methyl-1*H*-indol-3-ylsulfanyl)-2-fluoro-benzoic acid methyl ester

[00610] To a stirred, degassed solution of 3-(3-Bromo-4-fluoro-phenylsulfanyl)-6-chloro-2-methyl-1*H*-indole (1.48 mmol, 0.55 g) and TEA (3.7 mmol, 0.52 mL) in DMF (14 mL) and MeOH (7 mL) at room temperature was added [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (0.148 mmol, 0.11 g). The mixture was then bubbled for 5 min with carbon monoxide gas, then fitted with a balloon containing carbon monoxide through a needle inlet. The reaction was warmed to 80°C and stirred overnight. The resulting mixture was cooled to room temperature, and subjected to standard aqueous workup. The crude residue was purified by silica gel chromatography (10-100% EtOAc in hexanes) to afford the title compound.



Step 4: 5-[6-Chloro-1-(1-ethyl-1*H*-pyrazol-4-yl)-2-methyl-1*H*-indol-3-ylsulfanyl]-2-fluoro-benzoic acid methyl ester

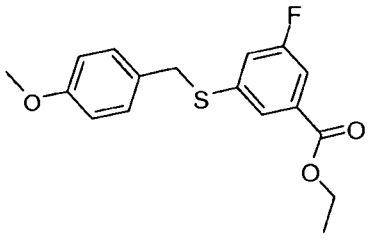
[00611] Prepared according to the procedure described in Example 55, Step 2 using the the following starting materials: 5-(6-Chloro-2-methyl-1*H*-indol-3-ylsulfanyl)-2-fluoro-benzoic acid methyl ester and 4-bromo-1-ethyl-1*H*-pyrazole.



Step 5: 5-[6-Chloro-1-(1-ethyl-1*H*-pyrazol-4-yl)-2-methyl-1*H*-indol-3-ylsulfanyl]-2-fluoro-benzoic acid

[00612] Prepared according to the procedure described in Example 42, Step 5, using the following starting material: 5-[6-Chloro-1-(1-ethyl-1*H*-pyrazol-4-yl)-2-methyl-1*H*-indol-3-ylsulfanyl]-2-fluoro-benzoic acid methyl ester.

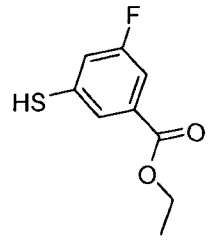
Example 77: Synthesis of 3-[6-Chloro-1-(1-ethyl-1*H*-pyrazol-4-yl)-2-methyl-1*H*-indol-3-ylsulfanyl]-5-fluoro-benzoic acid (Compound 1-129)



Step 1: 3-Fluoro-5-(4-methoxy-benzylsulfanyl)-benzoic acid ethyl ester

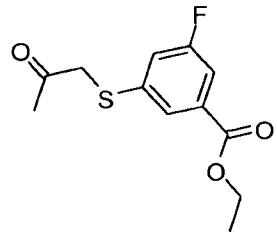
[00613] To a room temperature, degassed solution of 3-Bromo-5-fluoro-benzoic acid ethyl ester (4.0 g, 16.2 mmol) in dioxane (100 mL) was added 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene (0.48 g, 0.82 mmol), 4-methoxy-benzylmercaptan (2.26 mL, 16.2 mmol), DIEA (5.6 mL, 32.4 mmol), and tris(dibenzylideneacetone)dipalladium(0) (0.37 g, 0.41 mmol). The resulting mixture

was warmed to 90°C and stirred for 2 hrs, then cooled to room temperature. The mixture was subjected to standard aqueous workup, and the crude residue was filtered through a pad of silica gel to afford the title compound.



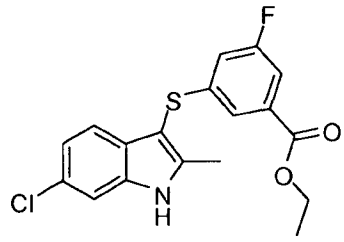
Step 2: 3-Fluoro-5-mercapto-benzoic acid ethyl ester

[00614] 3-Fluoro-5-(4-methoxy-benzylsulfanyl)-benzoic acid ethyl ester (7.24 g, 22.5 mmol)was stirred in TFA (10 mL) at 70°C for overnight. The resulting mixture was cooled to room temperature and subjected to standard aqueous workup. The crude residue was purified on silica gel (0-30% EtOAc in hexanes) to afford the title compound.



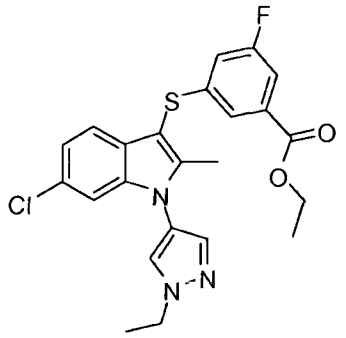
Step 3: 3-Fluoro-5-(2-oxo-propylsulfanyl)-benzoic acid ethyl ester

[00615] Prepared according to the procedure described in Example 6, Step 1, using the following starting material: 3-Fluoro-5-mercapto-benzoic acid ethyl ester.



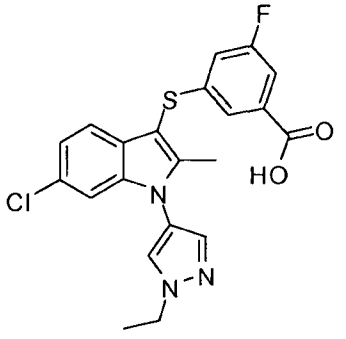
Step 4: 3-(6-Chloro-2-methyl-1*H*-indol-3-ylsulfanyl)-5-fluoro-benzoic acid ethyl ester

[00616] Prepared according to the procedure described in Example 2, Step 1, using the following starting materials: 3-fluoro-5-(2-oxo-propylsulfanyl)-benzoic acid ethyl ester and 3-chlorophenylhydrazine hydrochloride.



Step 5: 3-[6-Chloro-1-(1-ethyl-1*H*-pyrazol-4-yl)-2-methyl-1*H*-indol-3-ylsulfanyl]-5-fluoro-benzoic acid ethyl ester

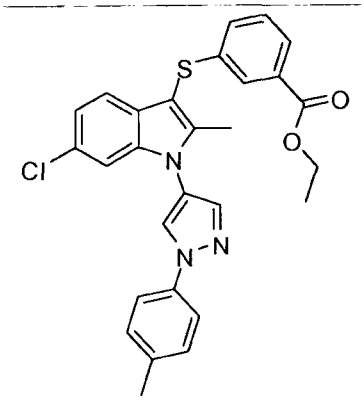
[00617] Prepared according to the procedure described in Example 55, Step 2 using the the following starting materials: 3-(6-Chloro-2-methyl-1*H*-indol-3-ylsulfanyl)-5-fluoro-benzoic acid ethyl ester and 4-bromo-1-ethyl-1*H*-pyrazole.



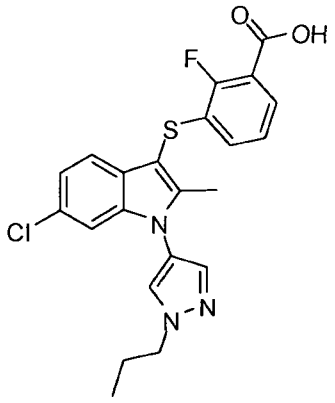
Step 6: 3-[6-Chloro-1-(1-ethyl-1*H*-pyrazol-4-yl)-2-methyl-1*H*-indol-3-ylsulfanyl]-5-fluoro-benzoic acid

[00618] Prepared according to the procedure described in Example 42, Step 5, using the following starting material: 3-[6-Chloro-1-(1-ethyl-1*H*-pyrazol-4-yl)-2-methyl-1*H*-indol-3-ylsulfanyl]-5-fluoro-benzoic acid ethyl ester.

Example 78: Synthesis of 3-[6-Chloro-2-methyl-1-(1-*p*-tolyl-1*H*-pyrazol-4-yl)-1*H*-indol-3-ylsulfanyl]-benzoic acid (Compound 1-130)



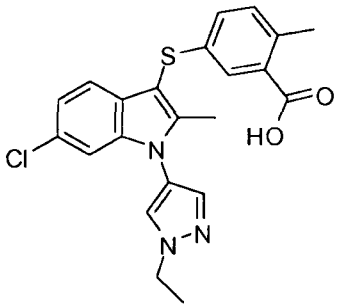
Step 1: 3-[6-Chloro-2-methyl-1-(1-*p*-tolyl-1*H*-pyrazol-4-yl)-1*H*-indol-3-ylsulfanyl]-benzoic acid ethyl ester



Step 2: 3-[6-Chloro-2-methyl-1-(1-propyl-1*H*-pyrazol-4-yl)-1*H*-indol-3-ylsulfanyl]-2-fluoro-benzoic acid

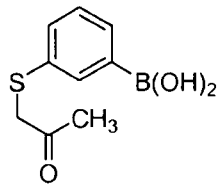
[00622] Prepared according to the procedure described in Example 42, Step 5, using the following starting material: 3-[6-Chloro-2-methyl-1-(1-propyl-1*H*-pyrazol-4-yl)-1*H*-indol-3-ylsulfanyl]-2-fluoro-benzoic acid ethyl ester.

Example 80: Synthesis of 5-[6-Chloro-1-(1-ethyl-1*H*-pyrazol-4-yl)-2-methyl-1*H*-indol-3-ylsulfanyl]-2-methyl-benzoic acid (Compound 1-132)



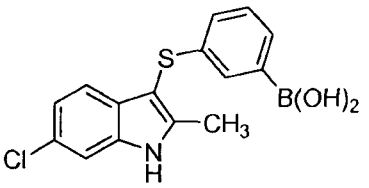
[00623] Prepared according to the procedures described in Example 77, substituting 3-bromo-5-methyl-benzoic acid ethyl ester for 3-Bromo-5-fluoro-benzoic acid ethyl ester in step 1 of that sequence.

Example 81: Synthesis of 3-(6-Chloro-2-methyl-1*H*-indol-3-ylsulfanyl)-phenylboronic acid (Compound 2-1)



Step 1: 3-(2-Oxo-propylsulfanyl)-phenylboronic acid

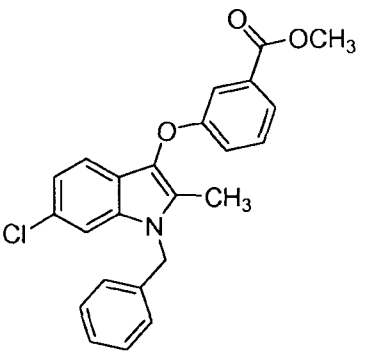
[00624] Prepared according to the procedure described in Example 1, Step 1, using the following starting materials: 3-mercaptophenylboronic acid and chloroacetone.



Step 2: 3-(6-Chloro-2-methyl-1*H*-indol-3-ylsulfanyl)-phenylboronic acid

[00625] Prepared according to the procedure described in Example 2, Step 1, using the following starting materials: [3-(2-oxo-propylsulfanyl)-phenyl]-acetic acid and 3-chlorophenylhydrazine hydrochloride.

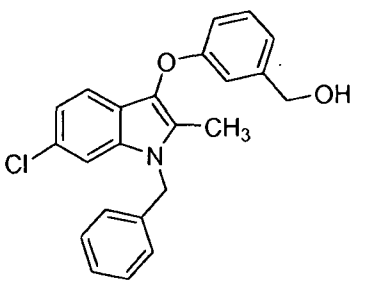
Example 82: Synthesis of 3-(1-Benzyl-6-chloro-2-methyl-1*H*-indol-3-yloxy)-benzoic acid methyl ester (Compound 2-3)



Step 1: 3-(1-Benzyl-6-chloro-2-methyl-1*H*-indol-3-yloxy)-benzoic acid methyl ester

[00626] Prepared according to the procedure described in Example 16, Step 4.

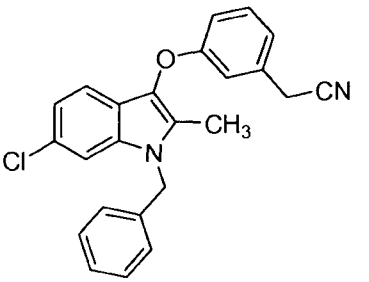
Example 83: Synthesis of [3-(1-Benzyl-6-chloro-2-methyl-1*H*-indol-3-yloxy)-phenyl]-methanol (Compound 2-4)



Step 1: [3-(1-Benzyl-6-chloro-2-methyl-1*H*-indol-3-yloxy)-phenyl]-methanol

[00627] Prepared according to the procedure described in Example 16, Step 5.

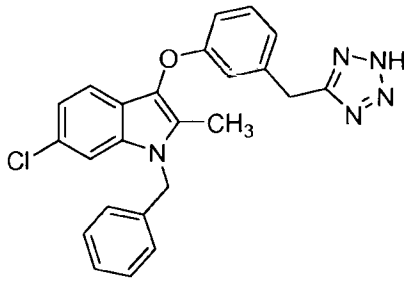
Example 84: Synthesis of [3-(1-Benzyl-6-chloro-2-methyl-1*H*-indol-3-yloxy)-phenyl]-acetonitrile (Compound 2-5)



Step 1: [3-(1-Benzyl-6-chloro-2-methyl-1*H*-indol-3-yloxy)-phenyl]-acetonitrile

[00628] Prepared according to the procedure described in Example 16, Step 6.

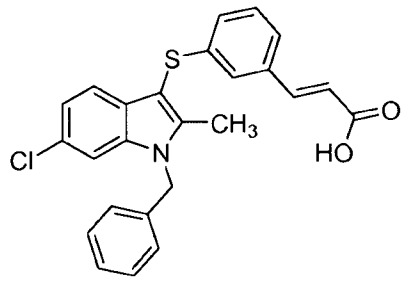
Example 85: Synthesis of 1-Benzyl-6-chloro-2-methyl-3-[3-(2*H*-tetrazol-5-ylmethyl)-phenoxy]-1*H*-indole (Compound 2-6)



Step 1: 1-Benzyl-6-chloro-2-methyl-3-[3-(2*H*-tetrazol-5-ylmethyl)-phenoxy]-1*H*-indole

[00629] [3-(1-Benzyl-6-chloro-2-methyl-1*H*-indol-3-yloxy)-phenyl]-acetonitrile (0.030 g, 0.078 mmol) was dissolved in toluene (1 mL) along with azidotrimethylsilane (44 µL, 0.33 mmol) and dibutyltin(IV) oxide (0.002 g, 0.008 mmol). The reaction was heated to 90 °C for 2 days then concentrated. The crude material was dissolved in DMSO and purified via preparatory HPLC to give the title compound.

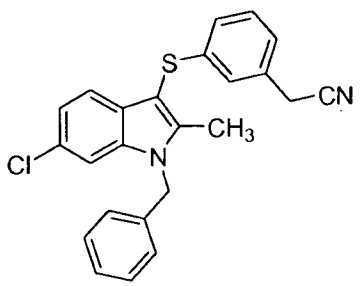
Example 86: Synthesis of (E)-3-[3-(1-Benzyl-6-chloro-2-methyl-1*H*-indol-3-ylsulfanyl)-phenyl]-acrylic acid (Compound 2-7)



Step 1: (E)-3-[3-(1-Benzyl-6-chloro-2-methyl-1*H*-indol-3-ylsulfanyl)-phenyl]-acrylic acid

[00630] Prepared according to the procedure described in Example 17, Step 4.

Example 87: Synthesis of 1-Benzyl-6-chloro-2-methyl-3-[3-(2*H*-tetrazol-5-ylmethyl)-phenylsulfanyl]-1*H*-indole (Compound 2-8)

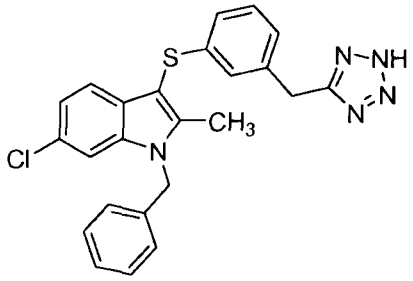


Step 1: [3-(1-Benzyl-6-chloro-2-methyl-1*H*-indol-3-ylsulfanyl)-phenyl]-acetonitrile

[00631] [3-(1-Benzyl-6-chloro-2-methyl-1*H*-indol-3-ylsulfanyl)-phenyl]-methanol (0.250 g, 0.63 mmol) was dissolved in DCM (10 mL) and cooled to 0 °C. *N,N*-Diisopropylethyl amine (0.274 mL,

1.575 mmol) was added followed by methanesulfonyl chloride (0.073 mL, 0.95 mmol). After 30 minutes the reaction was evaporated to dryness then added DMF (10 mL) and sodium cyanide (0.0617 g, 1.26 mmol) were added and the reaction was heated to 60 °C for 30 minutes. The reaction was submitted to aqueous workup and all solvents were removed.

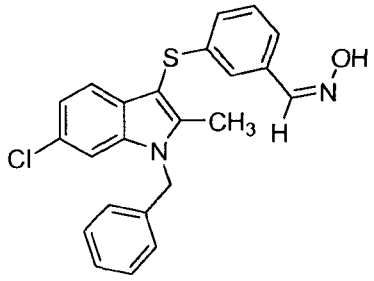
[00632] The crude material was dissolved in DMF (10 mL) and sodium cyanide (0.617 g, 1.26 mmol) was added along with tetrabutylammonium iodide (0.012 g, 0.032 mmol) and the reaction was heated to 90 °C. After two hours the reaction was submitted to standard aqueous workup procedure to afford the title compound.



Step 2: 1-Benzyl-6-chloro-2-methyl-3-[3-(2*H*-tetrazol-5-ylmethyl)-phenylsulfanyl]-1*H*-indole

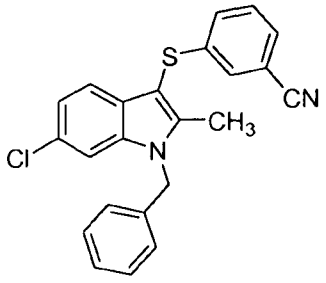
[00633] Prepared according to the procedure described in Example 85, Step 1 using the following starting material: [3-(1-benzyl-6-chloro-2-methyl-1*H*-indol-3-ylsulfanyl)-phenyl]-acetonitrile.

Example 88: Synthesis of 1-Benzyl-6-chloro-2-methyl-3-[3-(2*H*-tetrazol-5-yl)-phenylsulfanyl]-1*H*-indole (Compound 2-9)



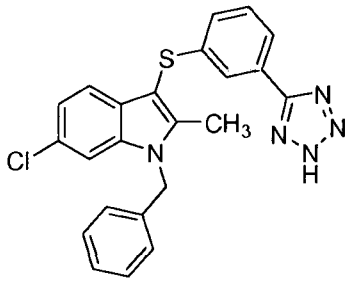
Step 1: 3-(1-Benzyl-6-chloro-2-methyl-1*H*-indol-3-ylsulfanyl)-benzaldehyde oxime

[00634] 3-(1-Benzyl-6-chloro-2-methyl-1*H*-indol-3-ylsulfanyl)-benzaldehyde (0.225 g, 0.57 mmol) was dissolved in pyridine (10 mL) and then hydroxylamine hydrochloride (0.235 g, 3.42 mmol). The reaction stirred at room temperature for 45 minutes and was submitted to an aqueous workup to provide the title compound, which was taken to the next step without further purification.



Step 2: 3-(1-Benzyl-6-chloro-2-methyl-1*H*-indol-3-ylsulfanyl)-benzonitrile

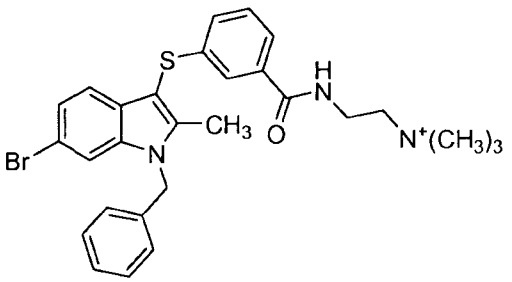
[00635] 3-(1-Benzyl-6-chloro-2-methyl-1*H*-indol-3-ylsulfanyl)-benzaldehyde oxime from the previous step was dissolved in acetic anhydride (0.500 mL) and the reaction was heated to 135 °C overnight. The reaction mixture was diluted with EtOAc then concentrated and purified by silica gel chromatography (0-50% EtOAc in hexanes) to give the title compound.



Step 3: 1-Benzyl-6-chloro-2-methyl-3-[3-(2*H*-tetrazol-5-yl)-phenylsulfanyl]-1*H*-indole

[00636] Prepared according to the procedure described in Example 85, Step 1 using the following starting material: 3-(1-benzyl-6-chloro-2-methyl-1*H*-indol-3-ylsulfanyl)-benzonitrile.

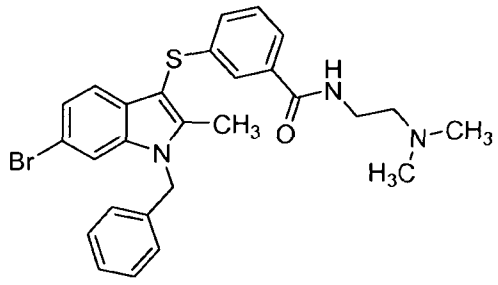
Example 89: Synthesis of {2-[3-(1-Benzyl-6-bromo-2-methyl-1*H*-indol-3-ylsulfanyl)-benzoylamino]-ethyl}-trimethyl-ammonium (Compound 2-10)



Step 1: {2-[3-(1-Benzyl-6-bromo-2-methyl-1*H*-indol-3-ylsulfanyl)-benzoylamino]-ethyl}-trimethyl-ammonium

[00637] 3-(1-Benzyl-6-bromo-2-methyl-1*H*-indol-3-ylsulfanyl)-benzoic acid (0.100 g, 0.22 mmol) and (2-aminoethyl)trimethylammonium chloride hydrochloride (0.058 g, 0.33 mmol) were dissolved in DMF (2 mL). *N*-(3-Dimethylaminopropyl)-*N'*-ethylcarbodiimide hydrochloride (0.051 g, 0.264 mmol), 1-hydroxybenzotriazole (0.039 g, 0.29 mmol) and *N,N*-diisopropylethylamine (0.115 mL, 0.66 mmol) were added and the reaction stirred at room temperature. After 2 hours the reaction was diluted with DMSO (2 mL) and filtered through a syringe filter then purified by preparatory HPLC to afford the title compounds as the trifluoroacetate salt.

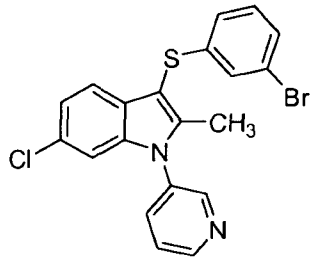
Example 90: Synthesis of 3-(1-Benzyl-6-bromo-2-methyl-1*H*-indol-3-ylsulfanyl)-*N*-(2-dimethylamino-ethyl)-benzamide (Compound 2-11)



Step 1: 3-(1-Benzyl-6-bromo-2-methyl-1*H*-indol-3-ylsulfanyl)-*N*-(2-dimethylamino-ethyl)-benzamide

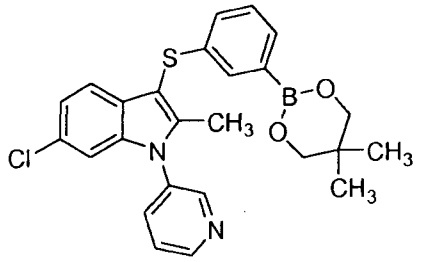
[00638] Prepared according to the procedure described in Example 89, Step 1 using the following starting materials: 3-(1-benzyl-6-bromo-2-methyl-1*H*-indol-3-ylsulfanyl)-benzoic acid and *N,N*-dimethylethylenediamine.

Example 91: Synthesis of 3-(6-Chloro-2-methyl-1-pyridin-3-yl-1*H*-indol-3-ylsulfanyl)-phenylboronic acid (Compound 2-12)



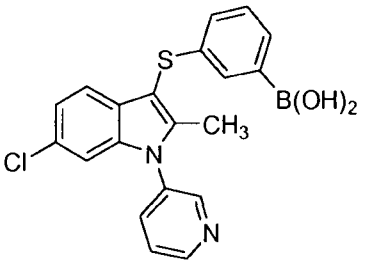
Step 1: 3-(3-Bromo-phenylsulfanyl)-6-chloro-2-methyl-1-pyridin-3-yl-1*H*-indole

[00639] Prepared according to the procedure described in Example 27, Step 1, using the following starting materials: 3-(3-bromo-phenylsulfanyl)-6-chloro-2-methyl-1*H*-indole and 3-bromopyridine.



Step 2: 3-(6-Chloro-2-methyl-1-pyridin-3-yl-1*H*-indol-3-ylsulfanyl)-phenylboronic acid neopentyl glycolate ester

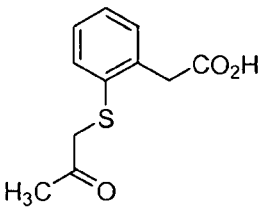
[00640] 3-(3-Bromo-phenylsulfanyl)-6-chloro-2-methyl-1-pyridin-3-yl-1*H*-indole (1.05 g, 2.44 mmol), bis(neopentyl glycolato)diboron (0.607 g, 2.69 mmol) and potassium acetate (0.8784 g, 9.76 mmol) were suspended in dioxane (50 mL) and N_2 (g) was bubbled through the mixture for 20 minutes. (1,1'-Bis(diphenylphosphino)ferrocene)-dichloropalladium(II) (0.178 g, 0.244 mmol) was added and the reaction was heated to 100 °C for 1 hour. The reaction mixture was submitted to standard aqueous workup procedures then purified by silica gel chromatography (0-100% EtOAc in hexanes) to give the title compound.



Step 3: 3-(6-Chloro-2-methyl-1-pyridin-3-yl-1*H*-indol-3-ylsulfanyl)-phenylboronic acid

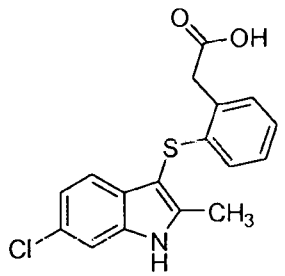
[00641] 3-(6-Chloro-2-methyl-1-pyridin-3-yl-1*H*-indol-3-ylsulfanyl)-phenylboronic acid pinacol ester (0.400 g, 0.86 mmol) was dissolved in THF:MeOH (1:1, 10 mL) and sodium hydroxide (2.5 mL of 1.0M aqueous solution, 2.5 mmol) was added. The reaction was stirred at room temperature overnight then submitted to aqueous workup and purified by preparatory HPLC (30-100% ACN in H_2O) to afford the title compound.

Example 92: Synthesis of [2-(6-Chloro-2-methyl-1*H*-indol-3-ylsulfanyl)-phenyl]-acetic acid (Compound 3-1)



Step 1: [2-(2-Oxo-propylsulfanyl)-phenyl]-acetic acid

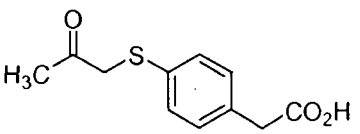
[00642] Prepared according to the procedure described in Example 1, Step 1, using the following starting materials: 2-mercaptophenylacetic acid and chloroacetone.



Step 2: [2-(6-Chloro-2-methyl-1*H*-indol-3-ylsulfanyl)-phenyl]-acetic acid

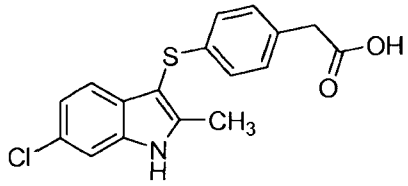
[00643] Prepared according to the procedure described in Example 2, Step 1, using the following starting materials: [2-(2-oxo-propylsulfanyl)-phenyl]-acetic acid and 3-chlorophenylhydrazine hydrochloride.

Example 93: Synthesis of [4-(6-Chloro-2-methyl-1*H*-indol-3-ylsulfanyl)-phenyl]-acetic acid (Compound 3-2)



Step 1: [4-(2-Oxo-propylsulfanyl)-phenyl]-acetic acid

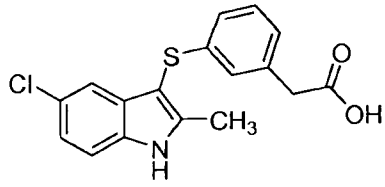
[00644] Prepared according to the procedure described in Example 1, Step 1, using the following starting materials: 4-mercaptophenylacetic acid and chloroacetone.



Step 2: [4-(6-Chloro-2-methyl-1*H*-indol-3-ylsulfanyl)-phenyl]-acetic acid

[00645] Prepared according to the procedure described in Example 2, Step 1, using the following starting materials: [4-(2-oxo-propylsulfanyl)-phenyl]-acetic acid and 3-chlorophenylhydrazine hydrochloride.

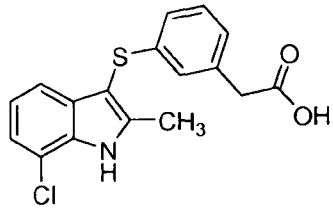
Example 94: Synthesis of [3-(5-Chloro-2-methyl-1*H*-indol-3-ylsulfanyl)-phenyl]-acetic acid (Compound 3-3)



Step 1: [3-(5-Chloro-2-methyl-1*H*-indol-3-ylsulfanyl)-phenyl]-acetic acid

[00646] Prepared according to the procedure described in Example 2, Step 1, using the following starting materials: [3-(2-oxo-propylsulfanyl)-phenyl]-acetic acid and 4-chlorophenylhydrazine hydrochloride.

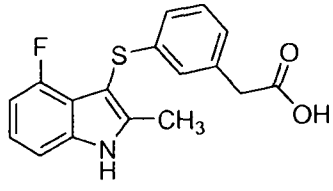
Example 95: Synthesis of [3-(7-Chloro-2-methyl-1*H*-indol-3-ylsulfanyl)-phenyl]-acetic acid (Compound 3-4)



Step 1: [3-(7-Chloro-2-methyl-1*H*-indol-3-ylsulfanyl)-phenyl]-acetic acid

[00647] Prepared according to the procedure described in Example 2, Step 1, using the following starting materials: [3-(2-oxo-propylsulfanyl)-phenyl]-acetic acid and 2-chlorophenylhydrazine hydrochloride.

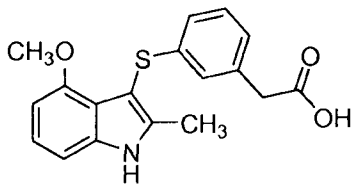
Example 96: Synthesis of [3-(4-Fluoro-2-methyl-1*H*-indol-3-ylsulfanyl)-phenyl]-acetic acid (Compound 3-5)



Step 1: [3-(4-Fluoro-2-methyl-1*H*-indol-3-ylsulfanyl)-phenyl]-acetic acid

[00648] Prepared according to the procedure described in Example 2, Step 1, using the following starting materials: [3-(2-oxo-propylsulfanyl)-phenyl]-acetic acid and 3-fluorophenylhydrazine hydrochloride.

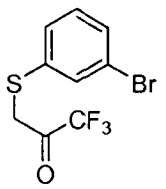
Example 97: Synthesis of [3-(4-Methoxy-2-methyl-1*H*-indol-3-ylsulfanyl)-phenyl]-acetic acid (Compound 3-6)



Step 1: [3-(4-Methoxy-2-methyl-1*H*-indol-3-ylsulfanyl)-phenyl]-acetic acid

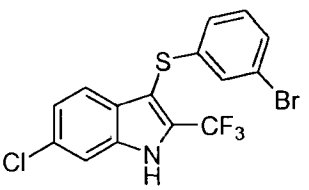
[00649] Prepared according to the procedure described in Example 2, Step 1, using the following starting materials: [3-(2-oxo-propylsulfanyl)-phenyl]-acetic acid and 3-methoxyphenylhydrazine hydrochloride.

Example 98: Synthesis of 3-(6-Chloro-2-trifluoromethyl-1*H*-indol-3-ylsulfanyl)-benzoic acid (Compound 3-7)



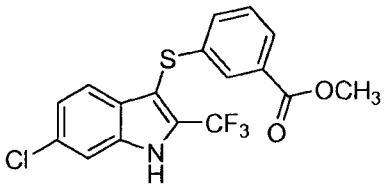
Step 1: 3-(3-Bromo-phenylsulfanyl)-1,1,1-trifluoro-propan-2-one

[00650] Prepared according to the procedure described in Example 6, Step 1, using the following starting materials: 3-bromothiophenol and 3-chloro-1,1,1-trifluoropropane-2-one.



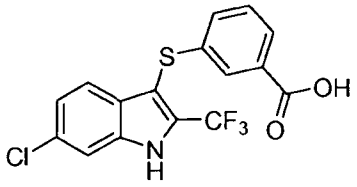
Step 2: 3-(3-Bromo-phenylsulfanyl)-6-chloro-2-trifluoromethyl-1*H*-indole

[00651] 3-(3-Bromo-phenylsulfanyl)-1,1,1-trifluoro-propan-2-one (5.0 g, 16.8 mmol) and 3-chlorophenylhyrdazine hydrochloride (3.0 g, 16.8 mmol) were dissolved in *t*-BuOH (200 mL). The reaction was stirred at 70 °C overnight then submitted to aqueous workup. The crude mixture was then diluted with toluene and *p*-toluensulfonic acid (3.0 g, 15.8 mmol) was added. The reaction was heated to reflux for 2 hours then submitted to standard aqueous workup and purified by silica gel chromatography (0-20% EtOAc in hexanes) to give a separable 4:3 mixture of regioisomers of which the title compound was the major component.



Step 3: 3-(6-Chloro-2-trifluoromethyl-1*H*-indol-3-ylsulfanyl)-benzoic acid methyl ester

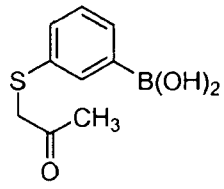
[00652] Prepared according to the procedure described in Example 6, Step 3, using the following starting material: 3-(3-bromo-phenylsulfanyl)-6-chloro-2-trifluoromethyl-1*H*-indole.



Step 4: 3-(6-Chloro-2-trifluoromethyl-1*H*-indol-3-ylsulfanyl)-benzoic acid

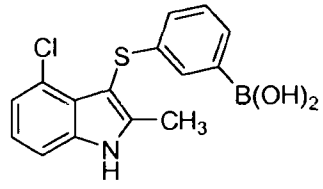
[00653] Prepared according to the procedure described in Example 10, Step 4, using the following starting material: 3-(6-chloro-2-trifluoromethyl-1*H*-indol-3-ylsulfanyl)-benzoic acid methyl ester.

Example 99: Synthesis of 3-(4-Chloro-2-methyl-1*H*-indol-3-ylsulfanyl)-phenylboronic acid (Compound 3-9)



Step 1: 3-(2-Oxo-propylsulfanyl)-phenylboronic acid

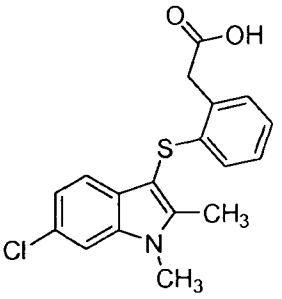
[00654] Prepared according to the procedure described in Example 1, Step 1, using the following starting materials: 3-mercaptophenylboronic acid and chloroacetone.



Step 2: 3-(4-Chloro-2-methyl-1*H*-indol-3-ylsulfanyl)-phenylboronic acid

[00655] Prepared according to the procedure described in Example 2, Step 1, using the following starting materials: 3-(4-chloro-2-methyl-1*H*-indol-3-ylsulfanyl)-phenylboronic acid and 3-chlorophenylhydrazine hydrochloride.

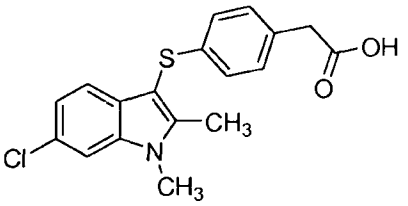
Example 100: Synthesis of [2-(6-Chloro-1,2-dimethyl-1*H*-indol-3-ylsulfanyl)-phenyl]-acetic acid (Compound 3-10)



Step 1: [2-(6-Chloro-1,2-dimethyl-1*H*-indol-3-ylsulfanyl)-phenyl]-acetic acid

[00656] Prepared according to the procedure described in Example 5, Step 2, using the following starting materials: [2-(6-chloro-2-methyl-1*H*-indol-3-ylsulfanyl)-phenyl]-acetic acid and iodomethane.

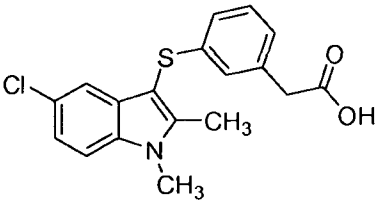
Example 101: Synthesis of [4-(6-Chloro-1,2-dimethyl-1*H*-indol-3-ylsulfanyl)-phenyl]-acetic acid (Compound 3-11)



Step 1: [4-(6-Chloro-1,2-dimethyl-1*H*-indol-3-ylsulfanyl)-phenyl]-acetic acid

[00657] Prepared according to the procedure described in Example 5, Step 2, using the following starting materials: [4-(6-chloro-2-methyl-1*H*-indol-3-ylsulfanyl)-phenyl]-acetic acid and iodomethane.

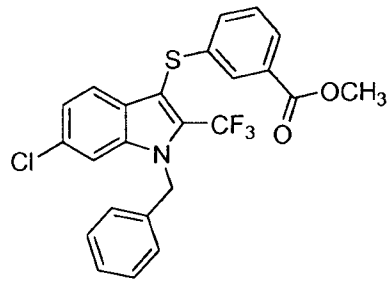
Example 102: Synthesis of [3-(5-Chloro-1,2-dimethyl-1*H*-indol-3-ylsulfanyl)-phenyl]-acetic acid (Compound 3-12)



Step 1: [3-(5-Chloro-1,2-dimethyl-1*H*-indol-3-ylsulfanyl)-phenyl]-acetic acid

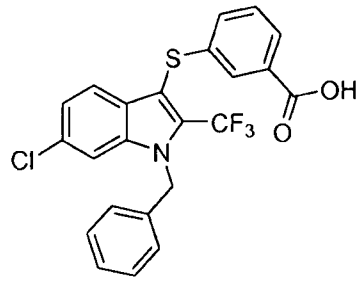
[00658] Prepared according to the procedure described in Example 5, Step 2, using the following starting materials: [3-(5-chloro-2-methyl-1*H*-indol-3-ylsulfanyl)-phenyl]-acetic acid and iodomethane

Example 103: Synthesis of 3-(1-Benzyl-6-chloro-2-trifluoromethyl-1*H*-indol-3-ylsulfanyl)-benzoic acid (Compound 3-13)



Step 1: 3-(1-Benzyl-6-chloro-2-trifluoromethyl-1*H*-indol-3-ylsulfanyl)-benzoic acid methyl ester

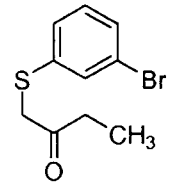
[00659] Prepared according to the procedure described in Example 10, Step 3, using the following starting materials: 3-(6-chloro-2-trifluoromethyl-1*H*-indol-3-ylsulfanyl)-benzoic acid methyl ester and benzyl bromide.



Step 2: 3-(1-Benzyl-6-chloro-2-trifluoromethyl-1*H*-indol-3-ylsulfanyl)-benzoic acid

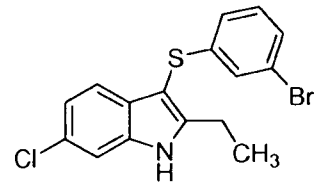
[00660] Prepared according to the procedure described in Example 6, Step 5, using the following starting material: 3-(1-benzyl-6-chloro-2-trifluoromethyl-1*H*-indol-3-ylsulfanyl)-benzoic acid methyl ester.

Example 104: Synthesis of 3-(1-Benzyl-6-chloro-2-ethyl-1*H*-indol-3-ylsulfanyl)-benzoic acid (Compound 3-15)



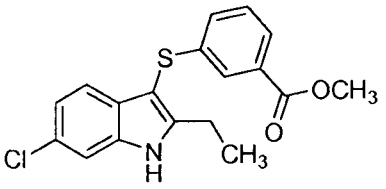
Step 1: 1-(3-Bromo-phenylsulfanyl)-butan-2-one

[00661] Prepared according to the procedure described in Example 1, Step 1, using the following starting materials: 3-bromothiophenol and 1-chloro-butan-2-one.



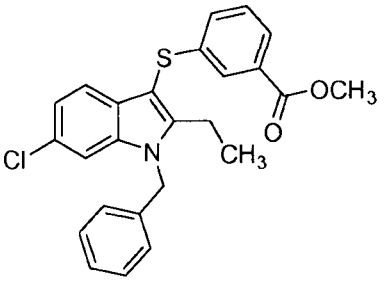
Step 2: 3-(3-Bromo-phenylsulfanyl)-6-chloro-2-ethyl-1*H*-indole

[00662] Prepared according to the procedure described in Example 2, Step 1, using the following starting materials: 1-(3-bromo-phenylsulfanyl)-butan-2-one and 3-chlorophenylhydrazine hydrochloride.



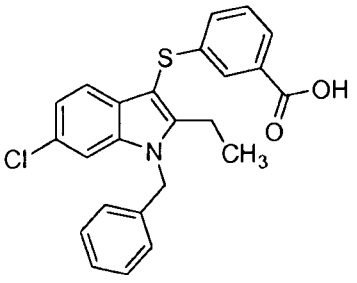
Step 3: 3-(6-Chloro-2-ethyl-1*H*-indol-3-ylsulfanyl)-benzoic acid methyl ester

[00663] Prepared according to the procedure described in Example 6, Step 3, using the following starting material: 3-(3-bromo-phenylsulfanyl)-6-chloro-2-ethyl-1*H*-indole.



Step 4: 3-(1-Benzyl-6-chloro-2-ethyl-1*H*-indol-3-ylsulfanyl)-benzoic acid methyl ester

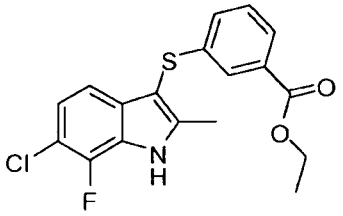
[00664] Prepared according to the procedure described in Example 10, Step 3, using the following starting materials: 3-(6-chloro-2-ethyl-1*H*-indol-3-ylsulfanyl)-benzoic acid methyl ester and benzyl bromide.



Step 5: 3-(1-Benzyl-6-chloro-2-ethyl-1*H*-indol-3-ylsulfanyl)-benzoic acid

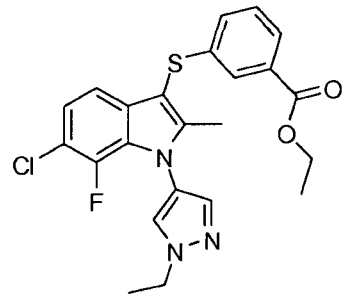
[00665] Prepared according to the procedure described in Example 6, Step 5, using the following starting material: 3-(1-benzyl-6-chloro-2-ethyl-1*H*-indol-3-ylsulfanyl)-benzoic acid methyl ester.

Example 105: Synthesis of 3-[6-Chloro-1-(1-ethyl-1*H*-pyrazol-4-yl)-7-fluoro-2-methyl-1*H*-indol-3-ylsulfanyl]-benzoic acid (Compound 3-16)



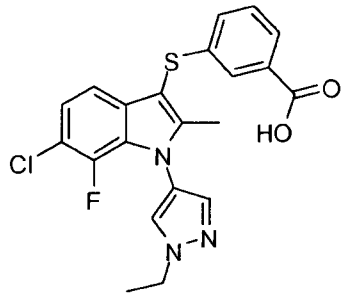
Step 1: 3-(6-Chloro-7-fluoro-2-methyl-1*H*-indol-3-ylsulfanyl)-benzoic acid ethyl ester

[00666] Prepared according to the procedure described in Example 2, step 1, using the following starting materials: 3-(2-Oxo-propylsulfanyl)-benzoic acid ethyl ester and (3-Chloro-2-fluoro-phenyl)-hydrazine hydrochloride.



Step 2: 3-[6-Chloro-1-(1-ethyl-1*H*-pyrazol-4-yl)-7-fluoro-2-methyl-1*H*-indol-3-ylsulfanyl]-benzoic acid ethyl ester

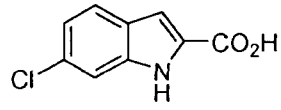
[00667] Prepared according to the procedure described in Example 55, Step 2 using the the following starting materials: 3-(6-chloro-7-fluoro-2-methyl-1*H*-indol-3-ylsulfanyl)-benzoic acid ethyl ester and 4-bromo-1-ethyl-1*H*-pyrazole.



Step 3: 3-[6-Chloro-1-(1-ethyl-1*H*-pyrazol-4-yl)-7-fluoro-2-methyl-1*H*-indol-3-ylsulfanyl]-benzoic acid

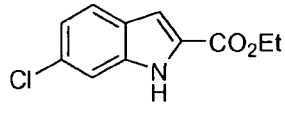
[00668] Prepared according to the procedure described in Example 42, Step 5, using the following starting material: 3-[6-Chloro-1-(1-ethyl-1*H*-pyrazol-4-yl)-7-fluoro-2-methyl-1*H*-indol-3-ylsulfanyl]-benzoic acid ethyl ester.

Example 106: Synthesis of 3-(1-Benzyl-6-chloro-1*H*-indol-3-ylsulfanyl)-benzoic acid (Compound 3-17)



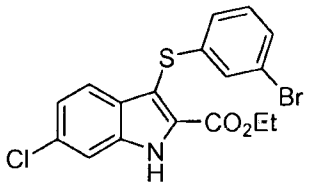
Step 1: 6-Chloro-1*H*-indole-2-carboxylic acid

[00669] 5-Chloro-2-iodoaniline (5.8 g, 23 mmol) and pyruvic acid (8 mL, 115 mmol) were dissolved in DMF (100 mL). DABCO (12.8 g, 115 mmol) was added and N_2 (g) was bubbled through solution for 20 minutes, then palladium acetate (1.03 g, 4.6 mmol) was added. The reaction was heated to 110 °C for 1 hour then submitted to aqueous workup and purified by silica gel chromatography (0-100% EtOAc in hexanes) to yield the title compound.



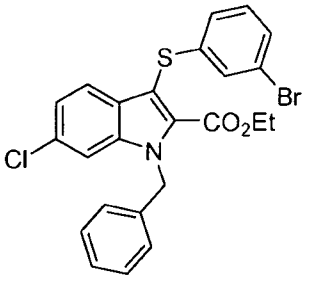
Step 2: 6-Chloro-1*H*-indole-2-carboxylic acid ethyl ester

[00670] 6-Chloro-1*H*-indole-2-carboxylic acid (2.59 g, 13.4 mmol) was dissolved in EtOH (75 mL) and conc. H_2SO_4 (1 mL) was added. The reaction was heated to 120 °C overnight then submitted to aqueous workup to give the title compound.



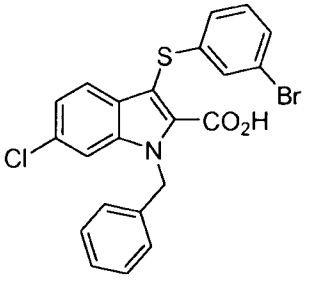
Step 3: 3-(3-Bromo-phenylsulfanyl)-6-chloro-1*H*-indole-2-carboxylic acid ethyl ester

[00671] *N*-Chlorosuccinimide (1.59 g, 12 mmol) was dissolved in DCM (100 mL) and the solution was cooled to -78 °C. 3-Bromothiophenol (1.24 mL, 12 mmol) was added dropwise and the reaction stirred for 30 minutes. Then, 6-chloro-1*H*-indole-2-carboxylic acid ethyl ester (2.2 g, 10 mmol) as a solution in DCM was added in 3 portions and the reaction was allowed to slowly warm to room temperature and continued stirring overnight. The reaction mixture was concentrated then purified by silica gel chromatography (0-30% EtOAc in hexanes) to afford the title compound.



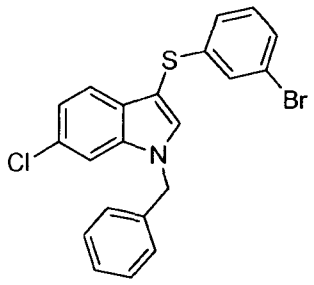
Step 4: 1-Benzyl-3-(3-bromo-phenylsulfanyl)-6-chloro-1*H*-indole-2-carboxylic acid ethyl ester

[00672] Prepared according to the procedure described in Example 4, Step 1, using the following starting materials: 3-(3-bromo-phenylsulfanyl)-6-chloro-1*H*-indole-2-carboxylic acid ethyl ester and benzyl bromide.



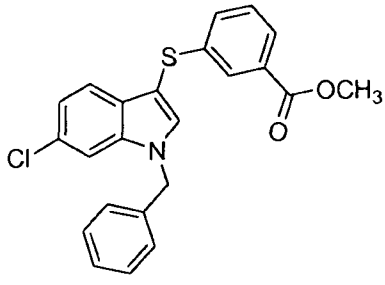
Step 5: 1-Benzyl-3-(3-bromo-phenylsulfanyl)-6-chloro-1*H*-indole-2-carboxylic acid

[00673] 1-Benzyl-3-(3-bromo-phenylsulfanyl)-6-chloro-1*H*-indole-2-carboxylic acid ethyl ester (0.520 g, 1.04 mmol) was dissolved in MeOH:THF (1:1, 10 mL) and LiOH (5 mL, 1.0M aq., 5 mmol) was added. The reaction was heated to 50 °C for 1 hour then removed from heat and submitted to aqueous workup to give the title compound which was carried to the next step without further purification.



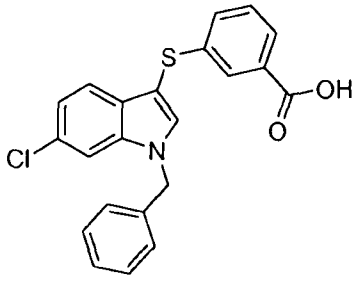
Step 6: 1-Benzyl-3-(3-bromo-phenylsulfanyl)-6-chloro-1*H*-indole

[00674] 1-Benzyl-3-(3-bromo-phenylsulfanyl)-6-chloro-1*H*-indole-2-carboxylic acid (from the previous step) was dissolved in quinoline (5 mL) then copper (0.120 g, 2 mmol) was added and the reaction was placed in the microwave for 10 minutes at 150 °C, and this heating was repeated 3 additional times. The reaction was submitted to standard workup procedures then purified by silica gel chromatography (0-20% EtOAc in hexanes) to provide the title compound.



Step 7: 3-(1-Benzyl-6-chloro-1*H*-indol-3-ylsulfanyl)-benzoic acid methyl ester

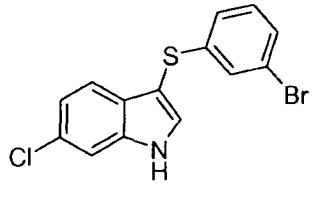
[00675] Prepared according to the procedure described in Example 6, Step 3, using the following starting material: 1-benzyl-3-(3-bromo-phenylsulfanyl)-6-chloro-1*H*-indole.



Step 8: 3-(1-Benzyl-6-chloro-1*H*-indol-3-ylsulfanyl)-benzoic acid

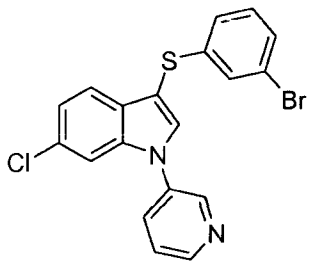
[00676] Prepared according to the procedure described in Example 10, Step 4, using the following starting material: 3-(1-benzyl-6-chloro-1*H*-indol-3-ylsulfanyl)-benzoic acid methyl ester.

Example 107: Synthesis of 3-(6-Chloro-1-pyridin-3-yl-1*H*-indol-3-ylsulfanyl)-benzoic acid (Compound 3-19)



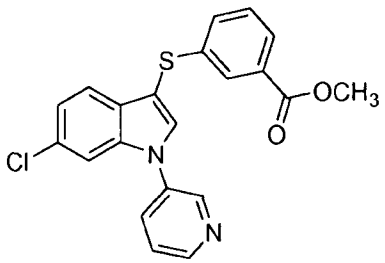
Step 1: 3-(3-Bromo-phenylsulfanyl)-6-chloro-1*H*-indole

[00677] *N*-chlorosuccinimide (1.93 g, 14.5 mmol) was dissolved in DCM (120 mL) and cooled to -78 °C. 3-Bromothiophenol was added and the reaction was warmed to 0 °C. After 1 hour, a solution of 6-chloroindole (2.0 g, 13.2 mmol) in DCM (20 mL) was added via canula. The reaction was stirred at 0 °C for 3 hours after which time it was submitted to aqueous workup and purification by silica gel chromatography (0-50% EtOAc in hexanes) to give the title compound.



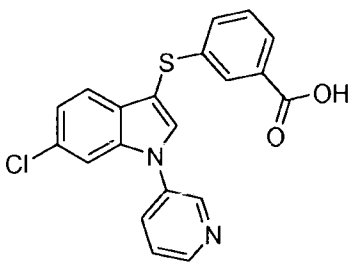
Step 2: 3-(3-Bromo-phenylsulfanyl)-6-chloro-1-pyridin-3-yl-1*H*-indole

[00678] Prepared according to the procedure described in Example 27, Step 1, using the following starting materials: 3-(3-bromo-phenylsulfanyl)-6-chloro-1*H*-indole and 3-bromopyridine.



Step 3: 3-(6-Chloro-1-pyridin-3-yl-1*H*-indol-3-ylsulfanyl)-benzoic acid methyl ester

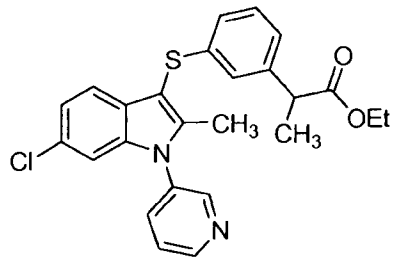
[00679] Prepared according to the procedure described in Example 6, Step 3, using the following starting material: 3-(3-bromo-phenylsulfanyl)-6-chloro-1-pyridin-3-yl-1*H*-indole.



Step 4: 3-(6-Chloro-1-pyridin-3-yl-1*H*-indol-3-ylsulfanyl)-benzoic acid

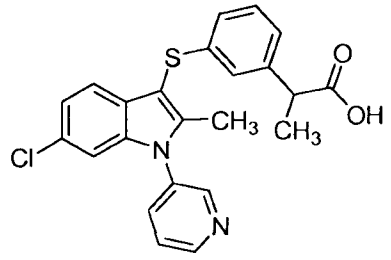
[00680] Prepared according to the procedure described in Example 6, Step 5, using the following starting material: 3-(6-chloro-1-pyridin-3-yl-1*H*-indol-3-ylsulfanyl)-benzoic acid methyl ester.

Example 108: Synthesis of 2-[3-(6-Chloro-2-methyl-1-pyridin-3-yl-1*H*-indol-3-ylsulfanyl)-phenyl]-propionic acid (Compound 3-20)



Step 1: 2-[3-(6-Chloro-2-methyl-1-pyridin-3-yl-1*H*-indol-3-ylsulfanyl)-phenyl]-propionic acid ethyl ester

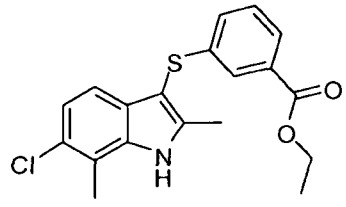
[00681] A solution of lithium diisopropylamide (10.7 mmol) in THF (10 mL), freshly prepared at -78 °C, was added to a solution of ([3-(6-Chloro-2-methyl-1-pyridin-3-yl-1*H*-indol-3-ylsulfanyl)-phenyl]-acetic acid ethyl ester (0.256 g, 0.586 mmol) in THF (5 mL) at -78 °C. The reaction was stirred at -78 °C for 2 hours then iodomethane (0.044 mL, 0.71 mmol) was added and the reaction was allowed to warm to 0 °C. After stirring at 0 °C for 30 minutes the reaction was submitted to standard aqueous workup then purified by silica gel chromatography (0-30% EtOAc in hexanes) to yield the title compound.



Step 2: 2-[3-(6-Chloro-2-methyl-1-pyridin-3-yl-1*H*-indol-3-ylsulfanyl)-phenyl]-propionic acid

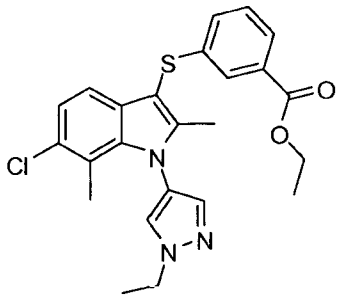
[00682] Prepared according to the procedure described in Example 10, Step 4, using the following starting material: 2-[3-(6-chloro-2-methyl-1-pyridin-3-yl-1*H*-indol-3-ylsulfanyl)-phenyl]-propionic acid ethyl ester.

Example 109: Synthesis of 3-[6-Chloro-1-(1-ethyl-1*H*-pyrazol-4-yl)-2,7-dimethyl-1*H*-indol-3-ylsulfanyl]-benzoic acid (Compound 3-21)



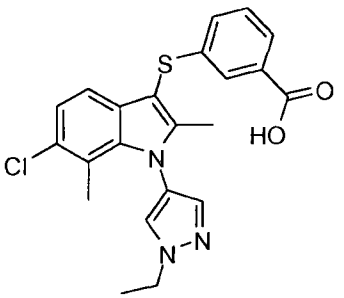
Step 1: 3-(6-Chloro-2,7-dimethyl-1*H*-indol-3-ylsulfanyl)-benzoic acid ethyl ester

[00683] Prepared according to the procedure described in Example 2, step 1, using the following starting materials: 3-(2-Oxo-propylsulfanyl)-benzoic acid ethyl ester and (3-Chloro-2-methyl-phenyl)-hydrazine hydrochloride.



Step 2: 3-[6-Chloro-1-(1-ethyl-1*H*-pyrazol-4-yl)-2,7-dimethyl-1*H*-indol-3-ylsulfanyl]-benzoic acid ethyl ester

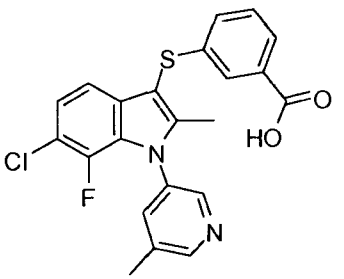
[00684] Prepared according to the procedure described in Example 55, Step 2 using the the following starting materials: 3-(6-Chloro-2,7-dimethyl-1*H*-indol-3-ylsulfanyl)-benzoic acid ethyl ester and 4-bromo-1-ethyl-1*H*-pyrazole.



Step 3: 3-[6-Chloro-1-(1-ethyl-1*H*-pyrazol-4-yl)-2,7-dimethyl-1*H*-indol-3-ylsulfanyl]-benzoic acid

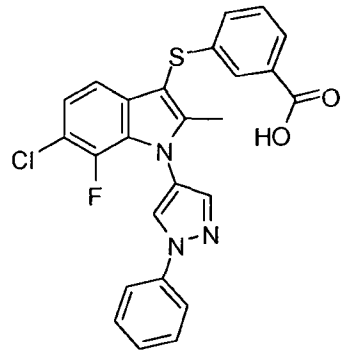
[00685] Prepared according to the procedure described in Example 42, Step 5, using the following starting material: 3-[6-Chloro-1-(1-ethyl-1*H*-pyrazol-4-yl)-2,7-dimethyl-1*H*-indol-3-ylsulfanyl]-benzoic acid ethyl ester.

Example 110: Synthesis of 3-[6-Chloro-7-fluoro-2-methyl-1-(5-methyl-pyridin-3-yl)-1*H*-indol-3-ylsulfanyl]-benzoic acid (Compound 3-22)



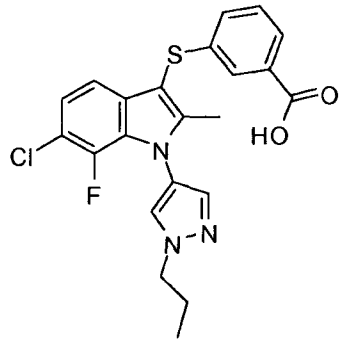
[00686] Prepared according to the procedure described for Example 105 by substituting 3-bromo-5-methyl-pyridine for 4-bromo-1-ethyl-1*H*-pyrazole in step 2 of that sequence.

Example 111: Synthesis of 3-[6-Chloro-7-fluoro-2-methyl-1-(1-phenyl-1*H*-pyrazol-4-yl)-1*H*-indol-3-ylsulfanyl]-benzoic acid (Compound 3-23)



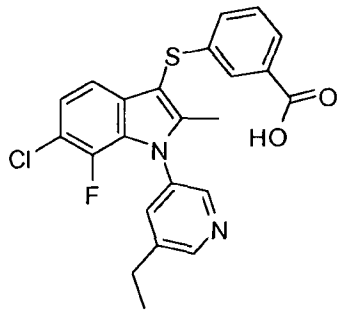
[00687] Prepared according to the procedure described for Example 105 by substituting 4-bromo-1-phenylpyrazole for 4-bromo-1-ethyl-1*H*-pyrazole in step 2 of that sequence.

Example 112: Synthesis of 3-[6-Chloro-7-fluoro-2-methyl-1-(1-propyl-1*H*-pyrazol-4-yl)-1*H*-indol-3-ylsulfanyl]-benzoic acid (Compound 3-24)



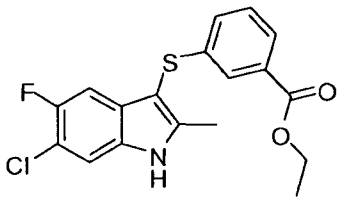
[00688] Prepared according to the procedure described for Example 105 by substituting 4-bromo-1-propylpyrazole for 4-bromo-1-ethyl-1*H*-pyrazole in step 2 of that sequence.

Example 113: Synthesis of 3-[6-Chloro-1-(5-ethyl-pyridin-3-yl)-7-fluoro-2-methyl-1*H*-indol-3-ylsulfanyl]-benzoic acid (Compound 3-25)



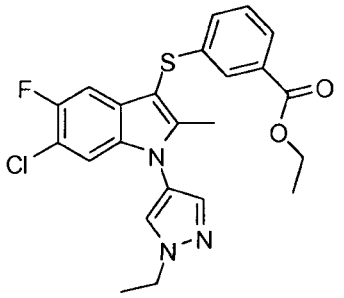
[00689] Prepared according to the procedure described for Example 105 by substituting 3-bromo-5-ethyl-pyridine for 4-bromo-1-ethyl-1*H*-pyrazole in step 2 of that sequence.

Example 114: Synthesis of 3-[6-Chloro-1-(1-ethyl-1*H*-pyrazol-4-yl)-5-fluoro-2-methyl-1*H*-indol-3-ylsulfanyl]-benzoic acid (Compound 3-26)



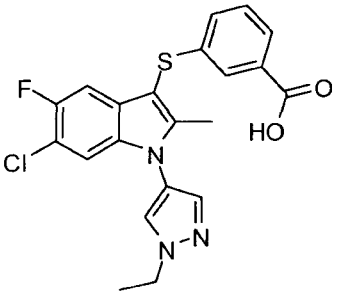
Step 1: 3-(6-Chloro-5-fluoro-2-methyl-1*H*-indol-3-ylsulfanyl)-benzoic acid ethyl ester

[00690] Prepared according to the procedure described in Example 2, step 1, using the following starting materials: 3-(2-Oxo-propylsulfanyl)-benzoic acid ethyl ester and (3-Chloro-4-fluoro-phenyl)-hydrazine.



Step 2: 3-[6-Chloro-1-(1-ethyl-1*H*-pyrazol-4-yl)-5-fluoro-2-methyl-1*H*-indol-3-ylsulfanyl]-benzoic acid ethyl ester

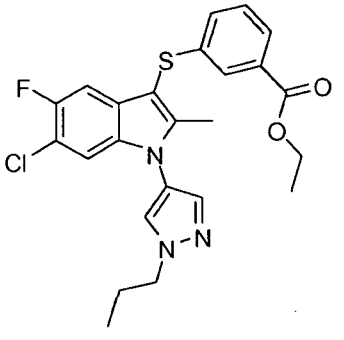
[00691] Prepared according to the procedure described in Example 55, Step 2 using the the following starting materials: 3-(6-Chloro-5-fluoro-2-methyl-1*H*-indol-3-ylsulfanyl)-benzoic acid ethyl ester and 4-bromo-1-ethyl-1*H*-pyrazole.



Step 3: 3-[6-Chloro-1-(1-ethyl-1*H*-pyrazol-4-yl)-5-fluoro-2-methyl-1*H*-indol-3-ylsulfanyl]-benzoic acid

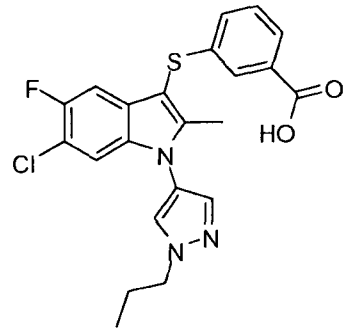
[00692] Prepared according to the procedure described in Example 42, Step 5, using the following starting material: 3-[6-Chloro-1-(1-ethyl-1*H*-pyrazol-4-yl)-5-fluoro-2-methyl-1*H*-indol-3-ylsulfanyl]-benzoic acid ethyl ester.

Example 115: Synthesis of 3-[6-Chloro-5-fluoro-2-methyl-1-(1-propyl-1*H*-pyrazol-4-yl)-1*H*-indol-3-ylsulfanyl]-benzoic acid (Compound 3-27)



Step 1: 3-[6-Chloro-5-fluoro-2-methyl-1-(1-propyl-1*H*-pyrazol-4-yl)-1*H*-indol-3-ylsulfanyl]-benzoic acid ethyl ester

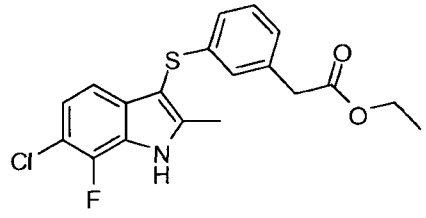
[00693] Prepared according to the procedure described in Example 55, Step 2 using the the following starting materials: 3-(6-Chloro-5-fluoro-2-methyl-1*H*-indol-3-ylsulfanyl)-benzoic acid ethyl ester and 4-bromo-1-propyl-1*H*-pyrazole.



Step 2: 3-[6-Chloro-5-fluoro-2-methyl-1-(1-propyl-1*H*-pyrazol-4-yl)-1*H*-indol-3-ylsulfanyl]-benzoic acid

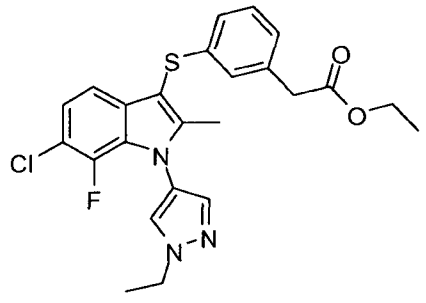
[00694] Prepared according to the procedure described in Example 42, Step 5, using the following starting material: 3-[6-Chloro-5-fluoro-2-methyl-1-(1-propyl-1*H*-pyrazol-4-yl)-1*H*-indol-3-ylsulfanyl]-benzoic acid ethyl ester.

Example 116: {3-[6-Chloro-1-(1-ethyl-1*H*-pyrazol-4-yl)-7-fluoro-2-methyl-1*H*-indol-3-ylsulfanyl]-phenyl}-acetic acid (Compound 3-28)



Step 1: [3-(6-Chloro-7-fluoro-2-methyl-1*H*-indol-3-ylsulfanyl)-phenyl]-acetic acid ethyl ester

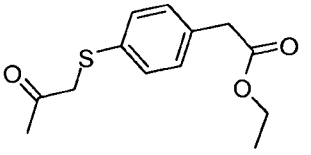
[00695] Prepared according to the procedure described in Example 2, step 1, using the following starting materials: [3-(2-oxo-propylsulfanyl)-phenyl]-acetic acid ethyl ester and (3-Chloro-2-fluoro-phenyl)-hydrazine hydrochloride.



Step 2: {3-[6-Chloro-1-(1-ethyl-1*H*-pyrazol-4-yl)-7-fluoro-2-methyl-1*H*-indol-3-ylsulfanyl]-phenyl}-acetic acid ethyl ester

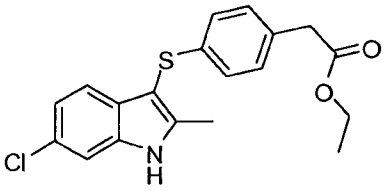
[00696] Prepared according to the procedure described in Example 55, Step 2 using the the following starting materials: [3-(6-Chloro-7-fluoro-2-methyl-1*H*-indol-3-ylsulfanyl)-phenyl]-acetic acid ethyl ester and 4-bromo-1-ethyl-1*H*-pyrazole.

[00699] To a stirred solution of (4-mercapto-phenyl)-acetic acid (5.0 g, 29.8 mmol) in absolute EtOH (100 mL) at room temperature was added concentrated H_2SO_4 (10 mL) and the mixture was warmed to reflux. After 4 hrs, the reaction was cooled to room temperature, evaporated under reduced pressure, diluted with DCM (500 mL) and stirred over solid K_2CO_3. After 1 hr, the resulting mixture was filtered and concentrated to dryness to afford the title compound.



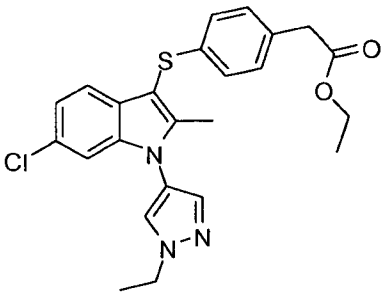
Step 2: [4-(2-Oxo-propylsulfanyl)-phenyl]-acetic acid ethyl ester

[00700] Prepared according to the procedure described in Example 6, Step 1, using the following starting material: (4-mercapto-phenyl)-acetic acid ethyl ester.



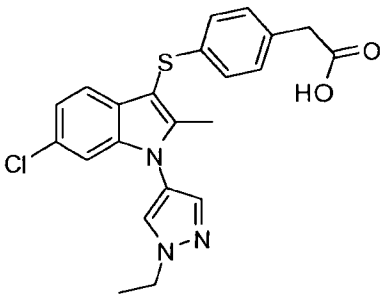
[00701] Step 3: [4-(6-Chloro-2-methyl-1*H*-indol-3-ylsulfanyl)-phenyl]-acetic acid ethyl ester

[00702] Prepared according to the procedure described in Example 2, Step 1, using the following starting materials: [4-(2-Oxo-propylsulfanyl)-phenyl]-acetic acid ethyl ester and 3-chlorophenylhydrazine hydrochloride.



Step 4: {4-[6-Chloro-1-(1-ethyl-1*H*-pyrazol-4-yl)-2-methyl-1*H*-indol-3-ylsulfanyl]-phenyl}-acetic acid ethyl ester

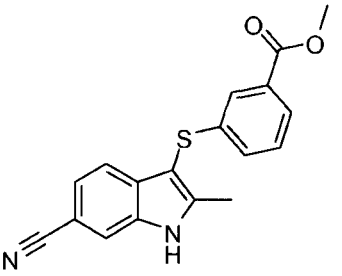
[00703] Prepared according to the procedure described in Example 55, Step 2 using the the following starting materials: [4-(6-Chloro-2-methyl-1*H*-indol-3-ylsulfanyl)-phenyl]-acetic acid ethyl ester and 4-bromo-1-ethyl-1*H*-pyrazole.



Step 5: {4-[6-Chloro-1-(1-ethyl-1*H*-pyrazol-4-yl)-2-methyl-1*H*-indol-3-ylsulfanyl]-phenyl}-acetic acid

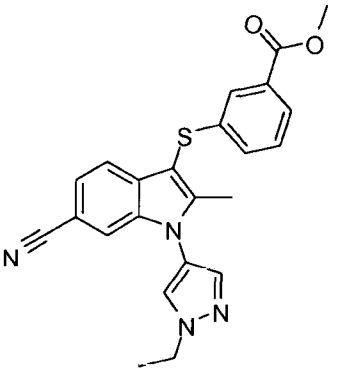
[00704] Prepared according to the procedure described in Example 42, Step 5, using the following starting material: {4-[6-Chloro-1-(1-ethyl-1*H*-pyrazol-4-yl)-2-methyl-1*H*-indol-3-ylsulfanyl]-phenyl}-acetic acid ethyl ester.

Example 119: Synthesis of 3-[6-Cyano-1-(1-ethyl-1*H*-pyrazol-4-yl)-2-methyl-1*H*-indol-3-ylsulfanyl]-benzoic acid (Compound 3-31)



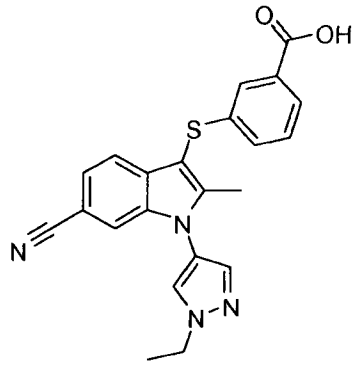
Step 1: 3-(6-Cyano-2-methyl-1*H*-indol-3-ylsulfanyl)-benzoic acid methyl ester

[00705] 3-(6-Bromo-2-methyl-1*H*-indol-3-ylsulfanyl)-benzoic acid methyl ester (0.19 g, 0.5 mmol) and copper(I) cyanide (0.090 g, 1.0 mmol) were combined in DMSO (10 mL) in a sealed reaction vessel and stirred at 130°C for overnight. The resulting mixture was cooled to room temperature, and subjected to standard aqueous workup. The crude residue was purified by silica gel chromatography (10-100% EtOAc in hexanes) to afford the title compound.



Step 2: 3-[6-cyano-1-(1-ethyl-1*H*-pyrazol-4-yl)-2-methyl-1*H*-indol-3-ylsulfanyl]-benzoic acid methyl ester

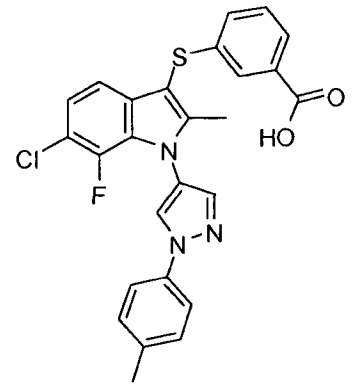
[00706] Prepared according to the procedure described in Example 55, Step 2 using the the following starting materials: 3-(6-cyano-2-methyl-1*H*-indol-3-ylsulfanyl)-benzoic acid methyl ester and 4-bromo-1-ethyl-1*H*-pyrazole.



Step 3: 3-[6-Cyano-1-(1-ethyl-1*H*-pyrazol-4-yl)-2-methyl-1*H*-indol-3-ylsulfanyl]-benzoic acid

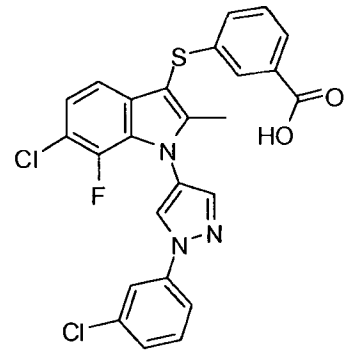
[00707] Prepared according to the procedure described in Example 42, Step 5, using the following starting material: 3-[6-cyano-1-(1-ethyl-1*H*-pyrazol-4-yl)-2-methyl-1*H*-indol-3-ylsulfanyl]-benzoic acid methyl ester.

Example 120: Synthesis of 3-[6-Chloro-7-fluoro-2-methyl-1-(1-*p*-tolyl-1*H*-pyrazol-4-yl)-1*H*-indol-3-ylsulfanyl]-benzoic acid (Compound 3-32)



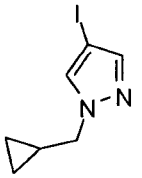
[00708] Prepared according to the procedure described for Example 105 by substituting 4-bromo-1-*p*-tolyl-1*H*-pyrazole for 4-bromo-1-ethyl-1*H*-pyrazole in step 2 of that sequence.

Example 121: Synthesis of 3-{6-Chloro-1-[1-(3-chloro-phenyl)-1*H*-pyrazol-4-yl]-7-fluoro-2-methyl-1*H*-indol-3-ylsulfanyl}-benzoic acid (Compound 3-33)



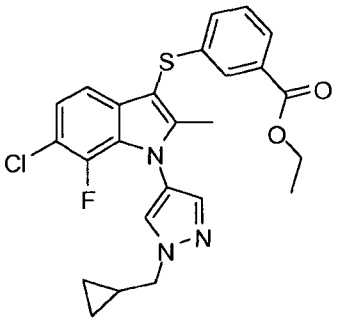
[00709] Prepared according to the procedure described for Example 105 by substituting 4-Bromo-1-(3-chloro-phenyl)-1*H*-pyrazole for 4-bromo-1-ethyl-1*H*-pyrazole in step 2 of that sequence.

Example 122: Synthesis of 3-[6-Chloro-1-(1-cyclopropylmethyl-1*H*-pyrazol-4-yl)-7-fluoro-2-methyl-1*H*-indol-3-ylsulfanyl]-benzoic acid (Compound 3-34)



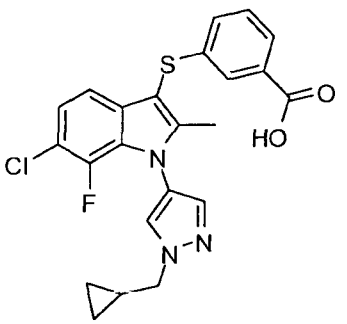
Step 1: 1-Cyclopropylmethyl-4-iodo-1*H*-pyrazole

[00710] 4-Iodo-1*H*-pyrazole (0.50 g, 2.5 mmol), bromomethyl cyclopropane (0.75 mL, 7.5 mmol), and cesium carbonate (1.20 g, 3.75 mmol) were combined in DMF (10 mL) and stirred at room temperature for overnight. The mixture was subjected to standard aqueous workup, and the crude residue was purified on silica gel (0-20% EtOAc in hexanes) to afford the title compound.



Step 2: 3-[6-Chloro-1-(1-cyclopropylmethyl-1*H*-pyrazol-4-yl)-7-fluoro-2-methyl-1*H*-indol-3-ylsulfanyl]-benzoic acid ethyl ester

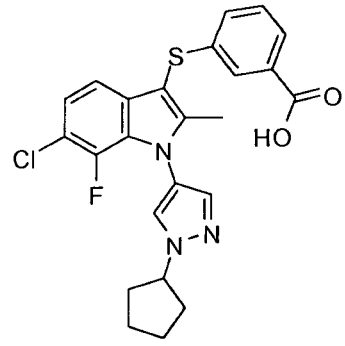
[00711] Prepared according to the procedure described in Example 55, Step 2 using the the following starting materials: 3-(6-chloro-7-fluoro-2-methyl-1*H*-indol-3-ylsulfanyl)-benzoic acid ethyl ester and 1-cyclopropylmethyl-4-iodo-1*H*-pyrazole.



Step 3: 3-[6-Chloro-1-(1-cyclopropylmethyl-1*H*-pyrazol-4-yl)-7-fluoro-2-methyl-1*H*-indol-3-ylsulfanyl]-benzoic acid

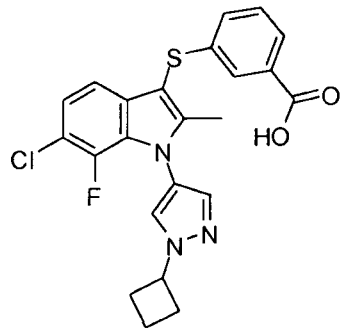
[00712] Prepared according to the procedure described in Example 42, Step 5, using the following starting material: 3-[6-Chloro-1-(1-cyclopropylmethyl-1*H*-pyrazol-4-yl)-7-fluoro-2-methyl-1*H*-indol-3-ylsulfanyl]-benzoic acid ethyl ester.

Example 123: Synthesis of 3-[6-Chloro-1-(1-cyclopentyl-1*H*-pyrazol-4-yl)-7-fluoro-2-methyl-1*H*-indol-3-ylsulfanyl]-benzoic acid (Compound 3-35)



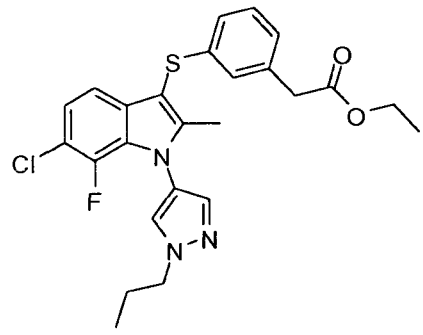
[00713] Prepared according to the procedures described in the synthesis of Example 122 by substituting bromocyclopentane for bromomethyl cyclopropane in Step 1 of that sequence.

Example 124: Synthesis 3-[6-Chloro-1-(1-cyclobutyl-1*H*-pyrazol-4-yl)-7-fluoro-2-methyl-1*H*-indol-3-ylsulfanyl]-benzoic acid (Compound 3-36)



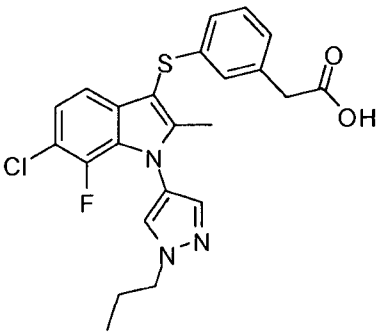
[00714] Prepared according to the procedures described in the synthesis of Example 122 by substituting bromocyclobutane for bromomethyl cyclopropane in Step 1 of that sequence.

Example 125: Synthesis of {3-[6-chloro-7-fluoro-2-methyl-1-(1-propyl-1*H*-pyrazol-4-yl)-1*H*-indol-3-ylsulfanyl]-phenyl}-acetic acid (Compound 3-37)



Step 1: {3-[6-chloro-7-fluoro-2-methyl-1-(1-propyl-1*H*-pyrazol-4-yl)-1*H*-indol-3-ylsulfanyl]-phenyl}-acetic acid ethyl ester

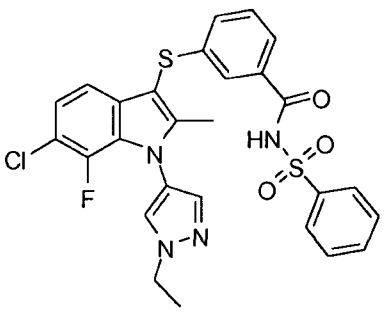
[00715] Prepared according to the procedure described in Example 55, Step 2 using the the following starting materials: [3-(6-Chloro-7-fluoro-2-methyl-1*H*-indol-3-ylsulfanyl)-phenyl]-acetic acid ethyl ester and 4-bromo-1-propyl-1*H*-pyrazole.



Step 2: {3-[6-chloro-7-fluoro-2-methyl-1-(1-propyl-1*H*-pyrazol-4-yl)-1*H*-indol-3-ylsulfanyl]-phenyl}-acetic acid

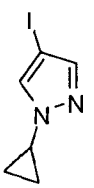
[00716] Prepared according to the procedure described in Example 42, Step 5, using the following starting material: {3-[6-chloro-7-fluoro-2-methyl-1-(1-propyl-1*H*-pyrazol-4-yl)-1*H*-indol-3-ylsulfanyl]-phenyl}-acetic acid ethyl ester.

Example 126: *N*-{3-[6-Chloro-1-(1-ethyl-1*H*-pyrazol-4-yl)-7-fluoro-2-methyl-1*H*-indol-3-ylsulfanyl]-benzoyl}-benzenesulfonamide (Compound 3-42)



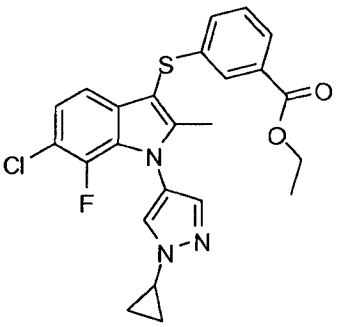
[00717] Prepared according to the procedure described in the synthesis of Example 117 by substituting benzenesulfonamide for methanesulfonamide in Step 1 of that sequence.

Example 127: Synthesis of 3-[6-Chloro-1-(1-cyclopropyl-1*H*-pyrazol-4-yl)-7-fluoro-2-methyl-1*H*-indol-3-ylsulfanyl]-benzoic acid (Compound 3-47)



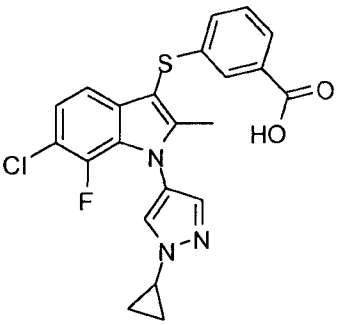
Step 1: 1-Cyclopropyl-4-iodo-1*H*-pyrazole

[00718] To a stirred solution of 4-Iodo-1*H*-pyrazole (2.0 g, 10.3 mmol) in DMF (100 mL) at room temperature was added sodium hydride (0.45 g of a 60% wt/wt dispersion in mineral oil, 11.3 mmol). After 15 minutes, bromocyclopropane (2.5 mL, 30.9 mmol), and tetra-*n*-butyl ammonium iodide (0.020 g) were added, and the reaction mixture was warmed to 140°C for overnight. The mixture was subjected to standard aqueous workup, and the crude residue was purified on silica gel (0-20% EtOAc in hexanes) to afford the title compound.



Step 2: 3-[6-Chloro-1-(1-cyclopropyl-1*H*-pyrazol-4-yl)-7-fluoro-2-methyl-1*H*-indol-3-ylsulfanyl]-benzoic acid ethyl ester

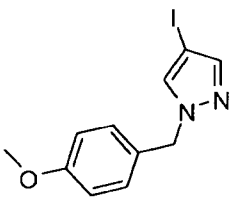
[00719] Prepared according to the procedure described in Example 55, Step 2 using the the following starting materials: 3-(6-chloro-7-fluoro-2-methyl-1*H*-indol-3-ylsulfanyl)-benzoic acid ethyl ester and 1-cyclopropyl-4-iodo-1*H*-pyrazole.



Step 3: 3-[6-Chloro-1-(1-cyclopropyl-1*H*-pyrazol-4-yl)-7-fluoro-2-methyl-1*H*-indol-3-ylsulfanyl]-benzoic acid

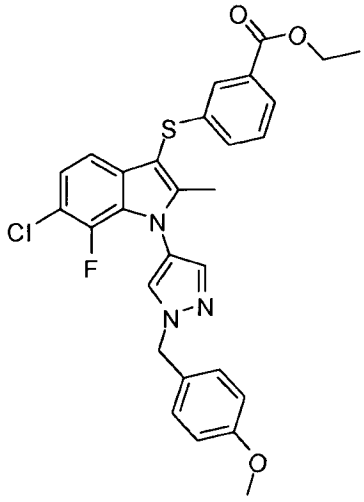
[00720] Prepared according to the procedure described in Example 42, Step 5, using the following starting material: 3-[6-Chloro-1-(1-cyclopropyl-1*H*-pyrazol-4-yl)-7-fluoro-2-methyl-1*H*-indol-3-ylsulfanyl]-benzoic acid ethyl ester.

Example 128: 3-{6-Chloro-7-fluoro-1-[1-(4-methoxy-benzyl)-1*H*-pyrazol-4-yl]-2-methyl-1*H*-indol-3-ylsulfanyl}-benzoic acid (Compound 3-48)



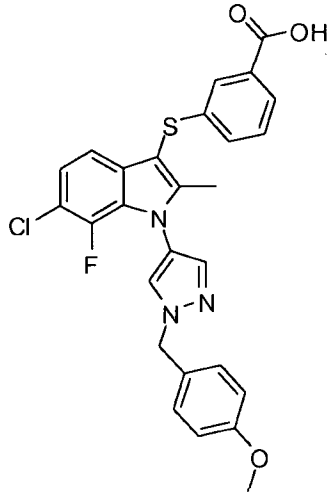
Step 1: 4-Iodo-1-(4-methoxy-benzyl)-1*H*-pyrazole

[00721] 4-Iodo-1*H*-pyrazole (2.0 g, 10.3 mmol), 4-methoxy-benzyl bromide (3.0 mL, 20.6 mmol), and cesium carbonate (5.0 g, 15.5 mmol) were combined in DMF (20 mL) and stirred at room temperature for 30 minutes. The mixture was subjected to standard aqueous workup, and the crude residue was purified on silica gel (0-20% EtOAc in hexanes) to afford the title compound.



Step 2: 3-{6-Chloro-7-fluoro-1-[1-(4-methoxy-benzyl)-1*H*-pyrazol-4-yl]-2-methyl-1*H*-indol-3-ylsulfanyl}-benzoic acid ethyl ester

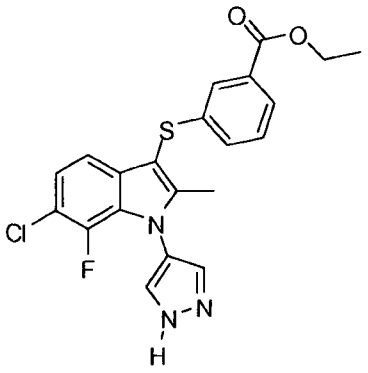
[00722] Prepared according to the procedure described in Example 55, Step 2 using the the following starting materials: 3-(6-chloro-7-fluoro-2-methyl-1*H*-indol-3-ylsulfanyl)-benzoic acid ethyl ester and 4-iodo-1-(4-methoxy-benzyl)-1*H*-pyrazole.



Step 3: 3-{6-Chloro-7-fluoro-1-[1-(4-methoxy-benzyl)-1*H*-pyrazol-4-yl]-2-methyl-1*H*-indol-3-ylsulfanyl}-benzoic acid

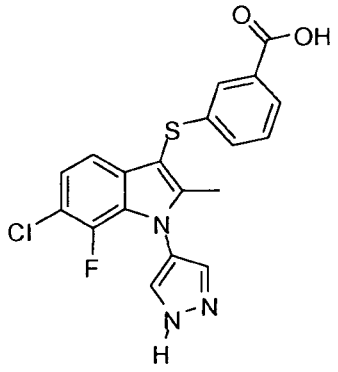
[00723] Prepared according to the procedure described in Example 42, Step 5, using the following starting material: 3-{6-Chloro-7-fluoro-1-[1-(4-methoxy-benzyl)-1*H*-pyrazol-4-yl]-2-methyl-1*H*-indol-3-ylsulfanyl}-benzoic acid ethyl ester.

Example 129: Synthesis of 3-[6-Chloro-7-fluoro-2-methyl-1-(1*H*-pyrazol-4-yl)-1*H*-indol-3-ylsulfanyl]-benzoic acid (Compound 3-49)



Step 1: 3-[6-Chloro-7-fluoro-2-methyl-1-(1*H*-pyrazol-4-yl)-1*H*-indol-3-ylsulfanyl]-benzoic acid ethyl ester

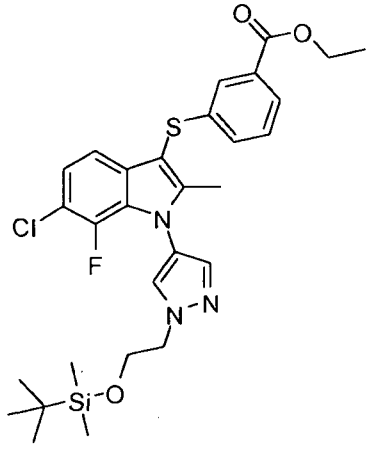
[00724] 3-{6-Chloro-7-fluoro-1-[1-(4-methoxy-benzyl)-1*H*-pyrazol-4-yl]-2-methyl-1*H*-indol-3-ylsulfanyl}-benzoic acid ethyl ester (0.10 g, 0.18 mmol) was stirred in neat TFA (4 mL) for 18 hrs. The mixture was then subjected to standard aqueous workup and used crude in the next step.



Step 2: 3-[6-Chloro-7-fluoro-2-methyl-1-(1*H*-pyrazol-4-yl)-1*H*-indol-3-ylsulfanyl]-benzoic acid

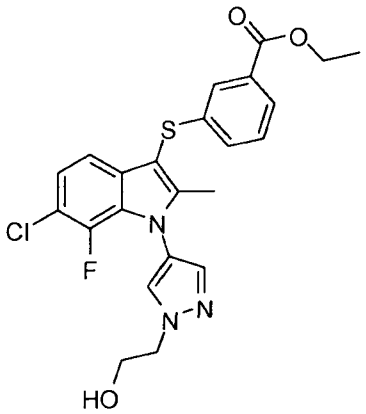
[00725] Prepared according to the procedure described in Example 42, Step 5, using the following starting material: 3-[6-Chloro-7-fluoro-2-methyl-1-(1*H*-pyrazol-4-yl)-1*H*-indol-3-ylsulfanyl]-benzoic acid ethyl ester.

Example 130: Synthesis of 3-{6-Chloro-7-fluoro-1-[1-(2-hydroxy-ethyl)-1*H*-pyrazol-4-yl]-2-methyl-1*H*-indol-3-ylsulfanyl}-benzoic acid (Compound 3-50)



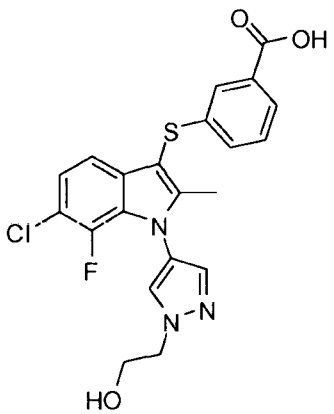
Step 1: 3-(1-{1-[2-(*tert*-Butyl-dimethyl-silanyloxy)-ethyl]-1*H*-pyrazol-4-yl}-6-chloro-7-fluoro-2-methyl-1*H*-indol-3-ylsulfanyl)-benzoic acid ethyl ester

[00726] Prepared according to the procedure described in Example 55, Step 2 using the the following starting materials: 3-(6-chloro-7-fluoro-2-methyl-1*H*-indol-3-ylsulfanyl)-benzoic acid ethyl ester and 4-Bromo-1-[2-(*tert*-butyl-dimethyl-silanyloxy)-ethyl]-1*H*-pyrazole.



Step 2: 3-{6-Chloro-7-fluoro-1-[1-(2-hydroxy-ethyl)-1*H*-pyrazol-4-yl]-2-methyl-1*H*-indol-3-ylsulfanyl}-benzoic acid ethyl ester

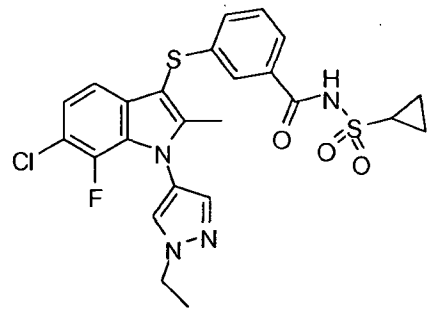
[00727] To a stirred solution of 3-(1-{1-[2-(*tert*-Butyl-dimethyl-silanyloxy)-ethyl]-1*H*-pyrazol-4-yl}-6-chloro-7-fluoro-2-methyl-1*H*-indol-3-ylsulfanyl)-benzoic acid ethyl ester (0.125 g, 0.21 mmol) in THF (2 mL) at room temperature was added TBAF (0.30 mL of a 1.0 M solution in THF, 0.30 mmol). The mixture was stirred for and additional 5 minutes, then subjected to standard aqueous workup to afford the title compound.



Step 3: 3-{6-Chloro-7-fluoro-1-[1-(2-hydroxy-ethyl)-1*H*-pyrazol-4-yl]-2-methyl-1*H*-indol-3-ylsulfanyl}-benzoic acid

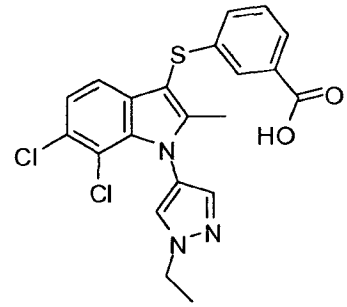
[00728] Prepared according to the procedure described in Example 42, Step 5, using the following starting material: 3-{6-chloro-7-fluoro-1-[1-(2-hydroxy-ethyl)-1*H*-pyrazol-4-yl]-2-methyl-1*H*-indol-3-ylsulfanyl}-benzoic acid ethyl ester.

Example 131: Synthesis of cyclopropanesulfonic acid 3-[6-chloro-1-(1-ethyl-1*H*-pyrazol-4-yl)-7-fluoro-2-methyl-1*H*-indol-3-ylsulfanyl]-benzoylamide (Compound 3-51)



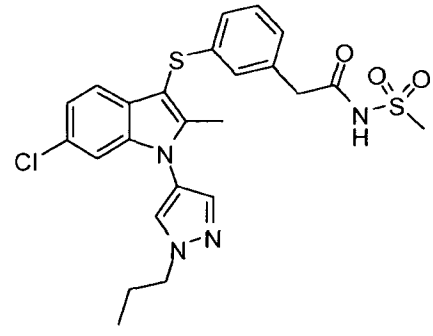
[00729] Prepared according to the procedure described in the synthesis of Example 117 by substituting cyclopropanesulfonamide for methanesulfonamide in Step 1 of that sequence.

Example 132: Synthesis of 3-[6,7-Dichloro-1-(1-ethyl-1*H*-pyrazol-4-yl)-2-methyl-1*H*-indol-3-ylsulfanyl]-benzoic acid (Compound 3-52)



[00730] Prepared according to the procedures described in the synthesis of Example 105 by substituting (2,3-dichloro-phenyl)-hydrazine hydrochloride for (3-chloro-2-fluoro-phenyl)-hydrazine hydrochloride in Step 1 of that sequence.

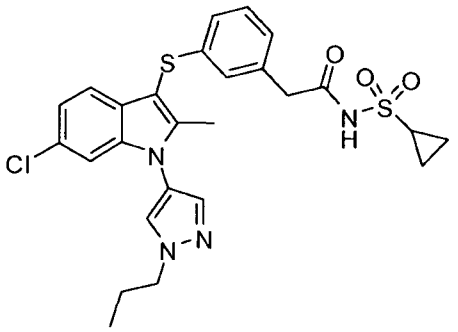
Example 133: Synthesis of *N*-(2-{3-[6-Chloro-2-methyl-1-(1-propyl-1*H*-pyrazol-4-yl)-1*H*-indol-3-ylsulfanyl]-phenyl}-acetyl)-methanesulfonamide (Compound 3-53)



Step 1: *N*-(2-{3-[6-Chloro-2-methyl-1-(1-propyl-1*H*-pyrazol-4-yl)-1*H*-indol-3-ylsulfanyl]-phenyl}-acetyl)-methanesulfonamide

[00731] Prepared according to the procedure described in the synthesis of Example 117 using the following starting materials: {3-[6-Chloro-1-(1-propyl-1*H*-pyrazol-4-yl)-2-methyl-1*H*-indol-3-ylsulfanyl]-phenyl}-acetic acid and methanesulfonamide.

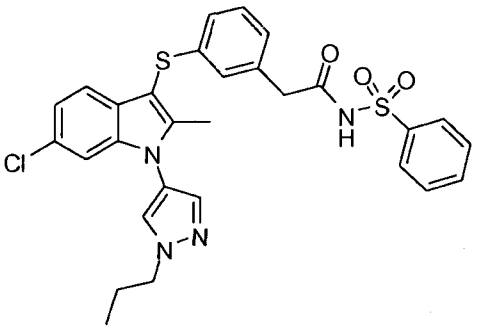
Example 134: Synthesis of cyclopropanesulfonic acid (2-{3-[6-chloro-2-methyl-1-(1-propyl-1*H*-pyrazol-4-yl)-1*H*-indol-3-ylsulfanyl]-phenyl}-acetyl)-amide (Compound 3-54)



Step 1: cyclopropanesulfonic acid (2-{3-[6-chloro-2-methyl-1-(1-propyl-1*H*-pyrazol-4-yl)-1*H*-indol-3-ylsulfanyl]-phenyl}-acetyl)-amide

[00732] Prepared according to the procedure described in the synthesis of Example 117 using the following starting materials: {3-[6-Chloro-1-(1-propyl-1*H*-pyrazol-4-yl)-2-methyl-1*H*-indol-3-ylsulfanyl]-phenyl}-acetic acid and cyclopropanesulfonamide.

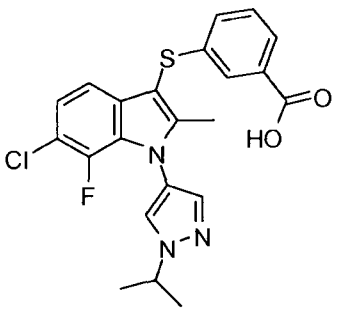
Example 135: Synthesis of *N*-(2-{3-[6-Chloro-2-methyl-1-(1-propyl-1*H*-pyrazol-4-yl)-1*H*-indol-3-ylsulfanyl]-phenyl}-acetyl)-benzenesulfonamide (Compound 3-55)



Step 1: *N*-(2-{3-[6-Chloro-2-methyl-1-(1-propyl-1*H*-pyrazol-4-yl)-1*H*-indol-3-ylsulfanyl]-phenyl}-acetyl)-benzenesulfonamide

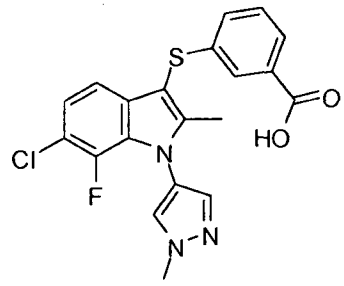
[00733] Prepared according to the procedure described in the synthesis of Example 117 using the following starting materials: {3-[6-Chloro-1-(1-propyl-1*H*-pyrazol-4-yl)-2-methyl-1*H*-indol-3-ylsulfanyl]-phenyl}-acetic acid and benzenesulfonamide.

Example 136: Synthesis of 3-[6-Chloro-7-fluoro-1-(1-isopropyl-1*H*-pyrazol-4-yl)-2-methyl-1*H*-indol-3-ylsulfanyl]-benzoic acid (Compound 3-56)



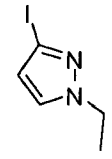
[00734] Prepared according to the procedure described for Example 105 by substituting 4-bromo-1-isopropyl-1*H*-pyrazole for 4-bromo-1-ethyl-1*H*-pyrazole in step 2 of that sequence.

Example 137: Synthesis of 3-[6-Chloro-7-fluoro-2-methyl-1-(1-methyl-1*H*-pyrazol-4-yl)-1*H*-indol-3-ylsulfanyl]-benzoic acid (Compound 3-57)



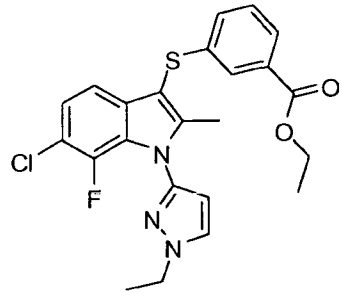
[00735] Prepared according to the procedure described for Example 105 by substituting 4-bromo-1-methyl-1*H*-pyrazole for 4-bromo-1-ethyl-1*H*-pyrazole in step 2 of that sequence.

Example 138: Synthesis of 3-[6-Chloro-1-(1-ethyl-1*H*-pyrazol-3-yl)-7-fluoro-2-methyl-1*H*-indol-3-ylsulfanyl]-benzoic acid (Compound 3-58)



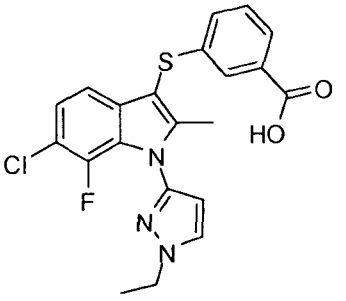
Step 1: 1-Ethyl-3-iodo-1*H*-pyrazole

[00736] 3-Iodo-1*H*-pyrazole (0.50 g, 2.5 mmol) and iodoethane (2.1 mL, 26 mmol) were stirred at 0°C in DMF. Sodium hydride (0.112 g of a 60% wt/wt dispersion in mineral oil, 2.8 mmol) was then added, and the cold bath was removed. After 15 minutes, the mixture was subjected to standard aqueous workup, and the crude residue was purified on silica gel (0-30% EtOAc in hexanes) to afford the title compound as the major of 2 possible alkylation products.



Step 2: 3-[6-Chloro-1-(1-ethyl-1*H*-pyrazol-3-yl)-7-fluoro-2-methyl-1*H*-indol-3-ylsulfanyl]-benzoic acid ethyl ester

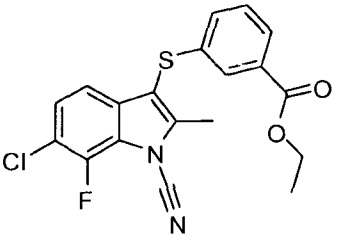
[00737] Prepared according to the procedure described in Example 55, Step 2 using the the following starting materials: 3-(6-chloro-7-fluoro-2-methyl-1*H*-indol-3-ylsulfanyl)-benzoic acid ethyl ester and 1-ethyl-3-iodo-1*H*-pyrazole.



Step 3: 3-[6-Chloro-1-(1-ethyl-1*H*-pyrazol-3-yl)-7-fluoro-2-methyl-1*H*-indol-3-ylsulfanyl]-benzoic acid

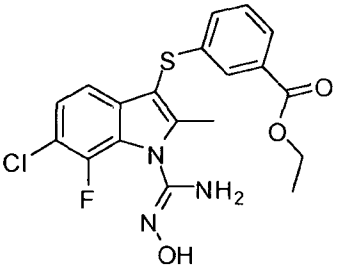
[00738] Prepared according to the procedure described in Example 42, Step 5, using the following starting material: 3-[6-Chloro-1-(1-ethyl-1*H*-pyrazol-3-yl)-7-fluoro-2-methyl-1*H*-indol-3-ylsulfanyl]-benzoic acid ethyl ester.

Example 139: Synthesis of 3-[6-Chloro-7-fluoro-2-methyl-1-(5-propyl-1,2,4-oxadiazol-3-yl)-1*H*-indol-3-ylsulfanyl]-benzoic acid (Compound 3-59)



Step 1: 3-(6-Chloro-1-cyano-7-fluoro-2-methyl-1*H*-indol-3-ylsulfanyl)-benzoic acid ethyl ester

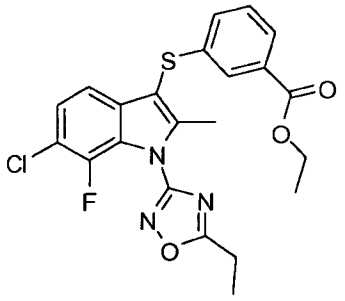
[00739] To a stirred solution of 3-(6-chloro-7-fluoro-2-methyl-1*H*-indol-3-ylsulfanyl)-benzoic acid ethyl ester (0.50 g, 1.37 mmol) in THF (10 mL) at RT was added sodium bis(trimethylsilyl)amide (0.76 mL of a 2.0M solution in THF, 1.51 mmol). After 30 minutes, tosyl cyanide (0.279 g, 1.54 mmol) was added, and the reaction was stirred for 2hrs, then subjected to standard aqueous workup. The crude residue was purified on silica gel (0-30% EtOAc in hexanes) to afford the title compound.



Step 2: 3-[6-Chloro-7-fluoro-1-(*N*-hydroxycarbamimidoyl)-2-methyl-1*H*-indol-3-ylsulfanyl]-benzoic acid ethyl ester

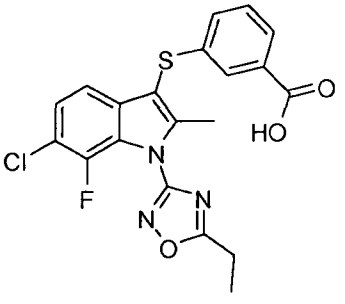
[00740] 3-(6-Chloro-1-cyano-7-fluoro-2-methyl-1*H*-indol-3-ylsulfanyl)-benzoic acid ethyl ester (0.45 g, 1.15 mmol), hydroxylamine hydrochloride (0.40 g, 5.79 mmol), and potassium carbonate (0.80 g, 5.79 mmol) were combined in absolute EtOH (4 mL) and stirred at reflux for overnight. The heterogeneous mixture was then filtered, and the solids were washed with hot absolute EtOH (2X10

mL). The resulting filtrate was concentrated to dryness under reduced pressure to afford the title compound.



Step 3: 3-[6-Chloro-1-(5-ethyl-1,2,4-oxadiazol-3-yl)-7-fluoro-2-methyl-1*H*-indol-3-ylsulfanyl]-benzoic acid ethyl ester

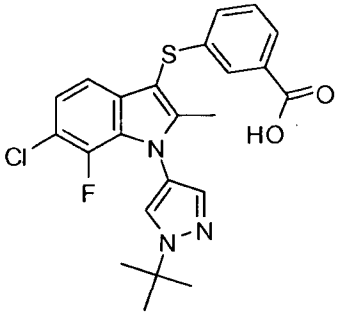
[00741] Propionyl chloride (0.042 mL, 0.48 mmol) was added to a solution of 3-[6-Chloro-7-fluoro-1-(*N*-hydroxycarbamimidoyl)-2-methyl-1*H*-indol-3-ylsulfanyl]-benzoic acid ethyl ester (0.12 g, 0.24 mmol) in pyridine (2 mL) at room temperature. The resulting mixture was heated to 80°C and stirred for overnight, then cooled to room temeperature and subjected to standard aqueous workup. The crude residue was purified on silica gel (0-60% EtOAc in hexanes) to afford the title compound.



[00742] Step 4: 3-[6-Chloro-1-(5-ethyl-1,2,4-oxadiazol-3-yl)-7-fluoro-2-methyl-1*H*-indol-3-ylsulfanyl]-benzoic acid

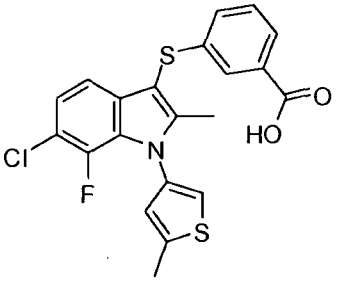
[00743] Prepared according to the procedure described in Example 42, Step 5, using the following starting material: 3-[6-Chloro-1-(5-ethyl-1,2,4-oxadiazol-3-yl)-7-fluoro-2-methyl-1*H*-indol-3-ylsulfanyl]-benzoic acid ethyl ester.

Example 140: Synthesis of 3-[1-(1-*tert*-Butyl-1*H*-pyrazol-4-yl)-6-chloro-7-fluoro-2-methyl-1*H*-indol-3-ylsulfanyl]-benzoic acid (Compound 3-60)



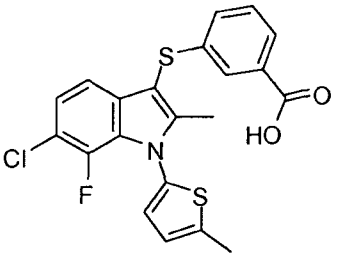
[00744] Prepared according to the procedure described for Example 105 by substituting 4-bromo-1-*tert*-butyl-1*H*-pyrazole for 4-bromo-1-ethyl-1*H*-pyrazole in step 2 of that sequence.

Example 141: Synthesis of 3-[6-Chloro-7-fluoro-2-methyl-1-(5-methyl-thiophen-3-yl)-1*H*-indol-3-ylsulfanyl]-benzoic acid (Compound 3-61)



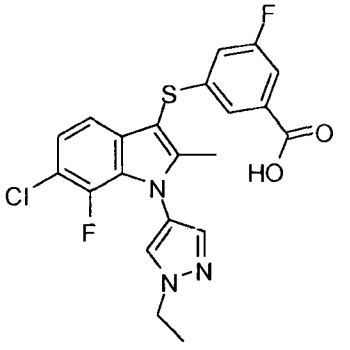
[00745] Prepared according to the procedure described for Example 105 by substituting 4-bromo-2-methyl-thiophene for 4-bromo-1-ethyl-1*H*-pyrazole in step 2 of that sequence.

Example 142: Synthesis of 3-[6-Chloro-7-fluoro-2-methyl-1-(5-methyl-thiophen-2-yl)-1*H*-indol-3-ylsulfanyl]-benzoic acid (Compound 3-62)



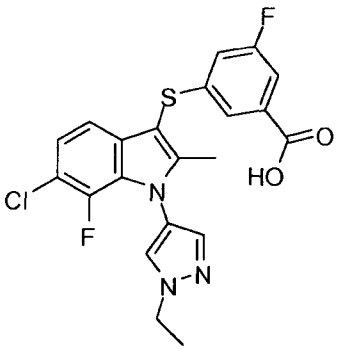
[00746] Prepared according to the procedure described for Example 105 by substituting 2-iodo-5-methyl-thiophene for 4-bromo-1-ethyl-1*H*-pyrazole in step 2 of that sequence.

Example 143: Synthesis of 5-[6-Chloro-1-(1-ethyl-1*H*-pyrazol-4-yl)-7-fluoro-2-methyl-1*H*-indol-3-ylsulfanyl]-2-fluoro-benzoic acid (Compound 4-1)



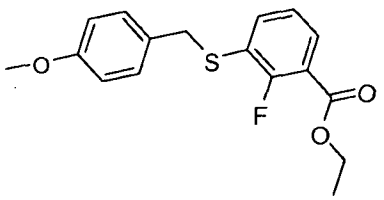
[00747] Prepared according to the procedures described for Example 76 by substituting (3-chloro-2-fluoro-phenyl)-hydrazine hydrochloride for (3-chloro-phenyl)-hydrazine hydrochloride in Step 2 of that sequence.

Example 144: Synthesis of 3-[6-Chloro-1-(1-ethyl-1*H*-pyrazol-4-yl)-7-fluoro-2-methyl-1*H*-indol-3-ylsulfanyl]-5-fluoro-benzoic acid (Compound 4-2)



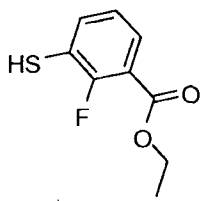
[00748] Prepared according to the procedures described for Example 77 by substituting (3-chloro-2-fluoro-phenyl)-hydrazine hydrochloride for (3-chloro-phenyl)-hydrazine hydrochloride in Step 4 of that sequence.

Example 145: Synthesis of 3-[6-Chloro-1-(1-ethyl-1*H*-pyrazol-4-yl)-7-fluoro-2-methyl-1*H*-indol-3-ylsulfanyl]-2-fluoro-benzoic acid (Compound 4-3)



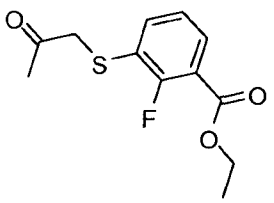
Step 1: 2-Fluoro-3-(4-methoxy-benzylsulfanyl)-benzoic acid ethyl ester

[00749] Prepared according to the procedure described for Example 77, Step 1 using the following starting material: 3-Bromo-2-fluoro-benzoic acid ethyl ester



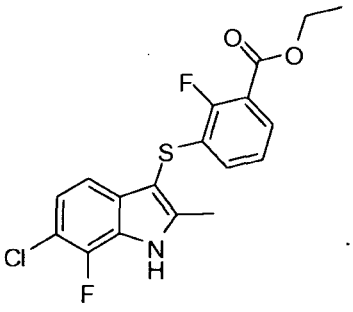
Step 2: 2-fluoro-3-mercapto-benzoic acid ethyl ester

[00750] Prepared according to the procedure described for Example 77, Step 2 using the following starting material: 2-fluoro-3-(4-methoxy-benzylsulfanyl)-benzoic acid ethyl ester.



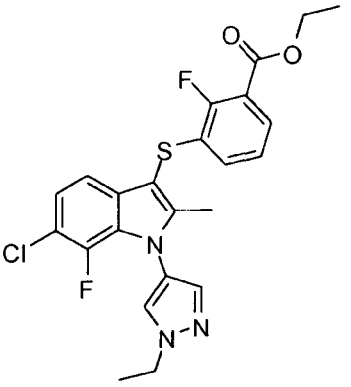
Step 3: 2-Fluoro-3-(2-oxo-propylsulfanyl)-benzoic acid ethyl ester

[00751] Prepared according to the procedure described in Example 77, Step 3, using the following starting material: 2-fluoro-3-mercapto-benzoic acid ethyl ester.



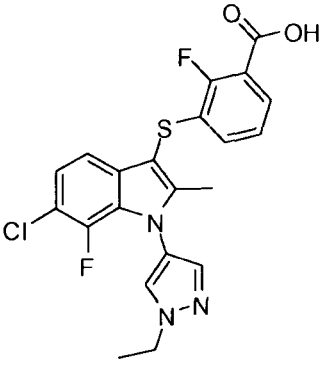
Step 4: 3-(6-Chloro-7-fluoro-2-methyl-1*H*-indol-3-ylsulfanyl)-2-fluoro-benzoic acid ethyl ester

[00752] Prepared according to the procedure described in Example 2, Step 1, using the following starting materials: 2-Fluoro-3-(2-oxo-propylsulfanyl)-benzoic acid ethyl ester and (3-chloro-2-fluoro-phenyl) hydrazine hydrochloride



Step 5: 3-[6-Chloro-1-(1-ethyl-1*H*-pyrazol-4-yl)-2-methyl-1*H*-indol-3-ylsulfanyl]-2-fluoro-benzoic acid ethyl ester

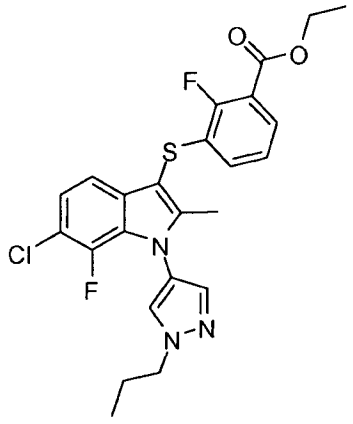
[00753] Prepared according to the procedure described in Example 55, Step 2 using the the following starting materials: 3-(6-chloro-7-fluoro-2-methyl-1*H*-indol-3-ylsulfanyl)-2-fluoro-benzoic acid ethyl ester and 4-bromo-1-ethyl-1*H*-pyrazole.



Step 6: 3-[6-Chloro-1-(1-ethyl-1*H*-pyrazol-4-yl)-2-methyl-1*H*-indol-3-ylsulfanyl]-2-fluoro-benzoic acid

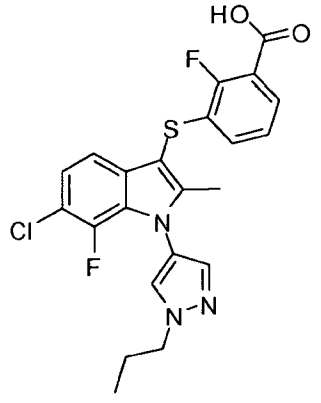
[00754] Prepared according to the procedure described in Example 42, Step 5, using the following starting material: 3-[6-Chloro-1-(1-ethyl-1*H*-pyrazol-4-yl)-2-methyl-1*H*-indol-3-ylsulfanyl]-2-fluoro-benzoic acid ethyl ester.

Example 146: 3-[6-Chloro-7-fluoro-2-methyl-1-(1-propyl-1*H*-pyrazol-4-yl)-1*H*-indol-3-ylsulfanyl]-2-fluoro-benzoic acid (Compound 4-4)



Step 5: 3-[6-Chloro-7-fluoro-2-methyl-1-(1-propyl-1*H*-pyrazol-4-yl)-1*H*-indol-3-ylsulfanyl]-2-fluoro-benzoic acid ethyl ester

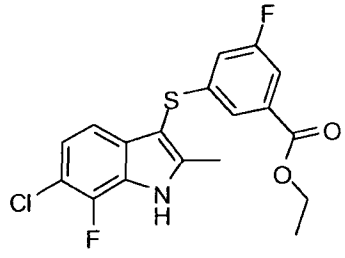
[00755] Prepared according to the procedure described in Example 55, Step 2 using the the following starting materials: 3-(6-chloro-7-fluoro-2-methyl-1*H*-indol-3-ylsulfanyl)-2-fluoro-benzoic acid ethyl ester and 4-iodo-1-propyl-1*H*-pyrazole.



Step 6: 3-[6-Chloro-7-fluoro-2-methyl-1-(1-propyl-1*H*-pyrazol-4-yl)-1*H*-indol-3-ylsulfanyl]-2-fluoro-benzoic acid

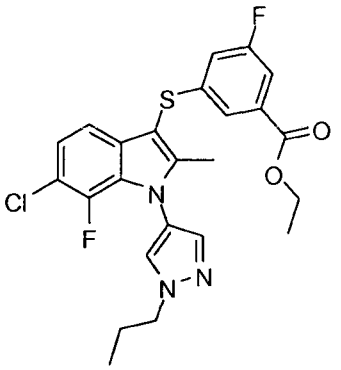
[00756] Prepared according to the procedure described in Example 42, Step 5, using the following starting material: 3-[6-Chloro-7-fluoro-2-methyl-1-(1-propyl-1*H*-pyrazol-4-yl)-1*H*-indol-3-ylsulfanyl]-2-fluoro-benzoic acid ethyl ester.

Example 147: Synthesis of 3-[6-Chloro-7-fluoro-2-methyl-1-(1-propyl-1*H*-pyrazol-4-yl)-1*H*-indol-3-ylsulfanyl]-5-fluoro-benzoic acid (Compound 4-5)



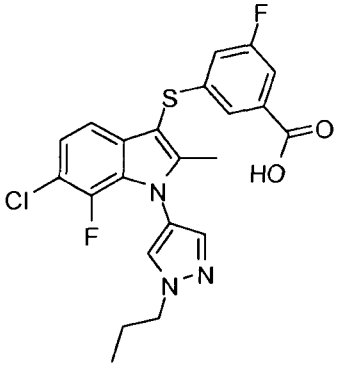
Step 1: 3-(6-Chloro-7-fluoro-2-methyl-1*H*-indol-3-ylsulfanyl)-5-fluoro-benzoic acid ethyl ester

[00757] Prepared according to the procedure described in Example 2, Step 1, using the following starting materials: 3-fluoro-5-(2-oxo-propylsulfanyl)-benzoic acid ethyl ester and (3-chloro-2-fluoro-phenyl) hydrazine hydrochloride



Step 2: 3-[6-Chloro-7-fluoro-2-methyl-1-(1-propyl-1*H*-pyrazol-4-yl)-1*H*-indol-3-ylsulfanyl]-5-fluoro-benzoic acid ethyl ester

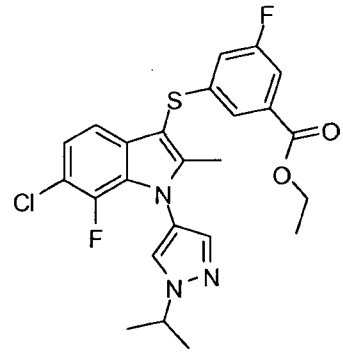
[00758] Prepared according to the procedure described in Example 55, Step 2 using the the following starting materials: 3-(6-Chloro-7-fluoro-2-methyl-1*H*-indol-3-ylsulfanyl)-5-fluoro-benzoic acid ethyl ester and 4-bromo-1-propyl-1*H*-pyrazole.



Step 3: 3-[6-Chloro-7-fluoro-2-methyl-1-(1-propyl-1*H*-pyrazol-4-yl)-1*H*-indol-3-ylsulfanyl]-5-fluoro-benzoic acid

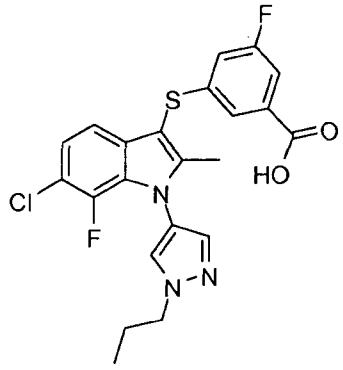
[00759] Prepared according to the procedure described in Example 42, Step 5, using the following starting material: 3-[6-Chloro-7-fluoro-2-methyl-1-(1-propyl-1*H*-pyrazol-4-yl)-1*H*-indol-3-ylsulfanyl]-5-fluoro-benzoic acid ethyl ester.

Example 148: Synthesis of 3-[6-Chloro-7-fluoro-1-(1-isopropyl-1*H*-pyrazol-4-yl)-2-methyl-1*H*-indol-3-ylsulfanyl]-5-fluoro-benzoic acid (Compound 4-6)



Step 1: 3-[6-Chloro-7-fluoro-1-(1-isopropyl-1*H*-pyrazol-4-yl)-2-methyl-1*H*-indol-3-ylsulfanyl]-5-fluoro-benzoic acid ethyl ester

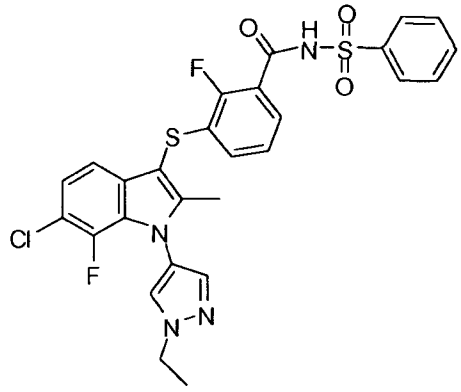
[00760] Prepared according to the procedure described in Example 55, Step 2 using the the following starting materials: 3-(6-Chloro-7-fluoro-2-methyl-1*H*-indol-3-ylsulfanyl)-5-fluoro-benzoic acid ethyl ester and 4-bromo-1-isopropyl-1*H*-pyrazole.



Step 2: 3-[6-Chloro-7-fluoro-1-(1-isopropyl-1*H*-pyrazol-4-yl)-2-methyl-1*H*-indol-3-ylsulfanyl]-5-fluoro-benzoic acid

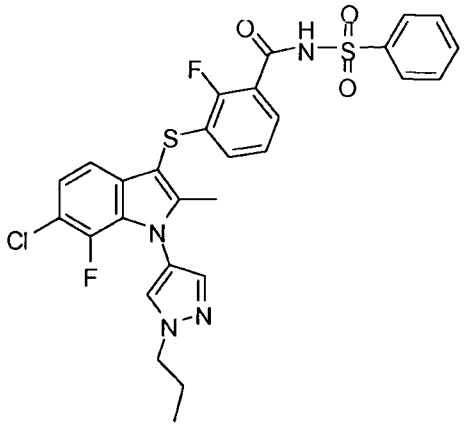
[00761] Prepared according to the procedure described in Example 42, Step 5, using the following starting material: 3-[6-Chloro-7-fluoro-1-(1-isopropyl-1*H*-pyrazol-4-yl)-2-methyl-1*H*-indol-3-ylsulfanyl]-5-fluoro-benzoic acid ethyl ester.

Example 149: Synthesis of *N*-{3-[6-Chloro-1-(1-ethyl-1*H*-pyrazol-4-yl)-7-fluoro-2-methyl-1*H*-indol-3-ylsulfanyl]-2-fluoro-benzoyl}-benzenesulfonamide (Compound 4-7)



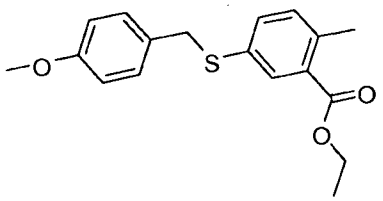
[00762] Prepared according to the procedure described in the synthesis of Example 117 using the following starting materials: 3-[6-Chloro-1-(1-ethyl-1*H*-pyrazol-4-yl)-2-methyl-1*H*-indol-3-ylsulfanyl]-2-fluoro-benzoic acid and benzenesulfonamide.

Example 150: Synthesis of *N*-{3-[6-Chloro-1-(1-propyl-1*H*-pyrazol-4-yl)-7-fluoro-2-methyl-1*H*-indol-3-ylsulfanyl]-2-fluoro-benzoyl}-benzenesulfonamide (Compound 4-8)



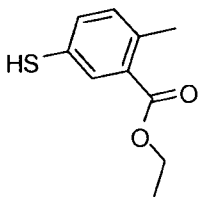
[00763] Prepared according to the procedure described in the synthesis of Example 117 using the following starting materials: 3-[6-Chloro-1-(1-propyl-1*H*-pyrazol-4-yl)-2-methyl-1*H*-indol-3-ylsulfanyl]-2-fluoro-benzoic acid and benzenesulfonamide.

Example 151: 5-[6-Chloro-1-(1-ethyl-1*H*-pyrazol-4-yl)-7-fluoro-2-methyl-1*H*-indol-3-ylsulfanyl]-2-methyl-benzoic acid (Compound 4-9)



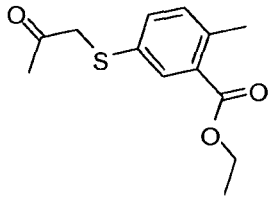
Step 1: 5-(4-Methoxy-benzylsulfanyl)-2-methyl-benzoic acid ethyl ester

[00764] Prepared according to the procedure described for Example 77, Step 1 using the following starting material: 5-Bromo-2-methyl-benzoic acid ethyl ester.



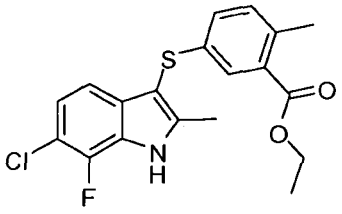
Step 2: 5-Mercapto-2-methyl-benzoic acid ethyl ester

[00765] Prepared according to the procedure described for Example 77, Step 2 using the following starting material: 5-(4-Methoxy-benzylsulfanyl)-2-methyl-benzoic acid ethyl ester.



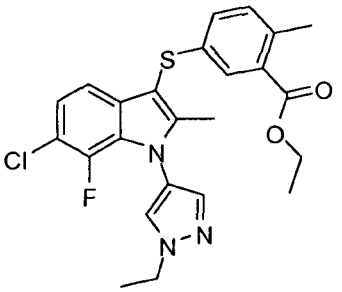
Step 3: 2-Methyl-5-(2-oxo-propylsulfanyl)-benzoic acid ethyl ester

[00766] Prepared according to the procedure described in Example 77, Step 3, using the following starting material: 5-Mercapto-2-methyl-benzoic acid ethyl ester.



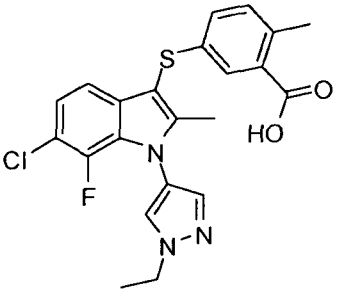
Step 4: 5-(6-Chloro-7-fluoro-2-methyl-1*H*-indol-3-ylsulfanyl)-2-methyl-benzoic acid ethyl ester

[00767] Prepared according to the procedure described in Example 2, Step 1, using the following starting materials: 2-Methyl-5-(2-oxo-propylsulfanyl)-benzoic acid ethyl ester and (3-chloro-2-fluoro-phenyl) hydrazine hydrochloride.



Step 5: 5-[6-Chloro-1-(1-ethyl-1*H*-pyrazol-4-yl)-7-fluoro-2-methyl-1*H*-indol-3-ylsulfanyl]-2-methyl-benzoic acid ethyl ester

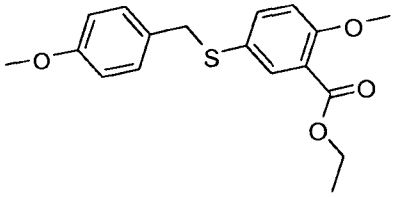
[00768] Prepared according to the procedure described in Example 55, Step 2 using the the following starting materials: 5-(6-Chloro-7-fluoro-2-methyl-1*H*-indol-3-ylsulfanyl)-2-methyl-benzoic acid ethyl ester and 4-bromo-1-ethyl-1*H*-pyrazole.



Step 6: 5-[6-Chloro-1-(1-ethyl-1*H*-pyrazol-4-yl)-7-fluoro-2-methyl-1*H*-indol-3-ylsulfanyl]-2-methyl-benzoic acid

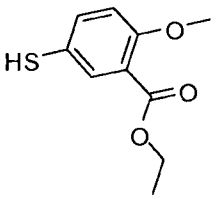
[00769] Prepared according to the procedure described in Example 42, Step 5, using the following starting material: 5-[6-Chloro-1-(1-ethyl-1*H*-pyrazol-4-yl)-7-fluoro-2-methyl-1*H*-indol-3-ylsulfanyl]-2-methyl-benzoic acid ethyl ester.

Example 152: Synthesis of 5-[6-Chloro-7-fluoro-2-methyl-1-(1-propyl-1*H*-pyrazol-4-yl)-1*H*-indol-3-ylsulfanyl]-2-methoxy-benzoic acid (Compound 4-10)



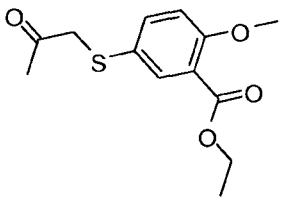
Step 1: 5-(4-Methoxy-benzylsulfanyl)-2-methoxy-benzoic acid ethyl ester

[00770] Prepared according to the procedure described for Example 77, Step 1 using the following starting material: 5-Bromo-2-methoxy-benzoic acid ethyl ester.



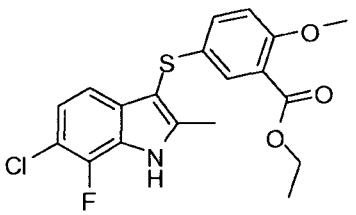
Step 2: 5-Mercapto-2-methoxy-benzoic acid ethyl ester

[00771] Prepared according to the procedure described for Example 77, Step 2 using the following starting material: 5-(4-Methoxy-benzylsulfanyl)-2-methoxy-benzoic acid ethyl ester.



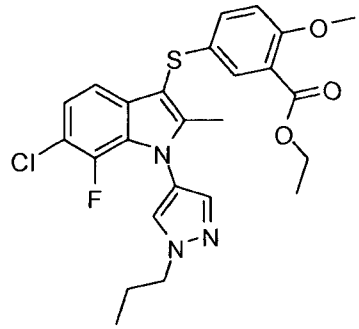
Step 3: 2-Methoxy-5-(2-oxo-propylsulfanyl)-benzoic acid ethyl ester

[00772] Prepared according to the procedure described in Example 77, Step 3, using the following starting material: 5-Mercapto-2-methoxy-benzoic acid ethyl ester.



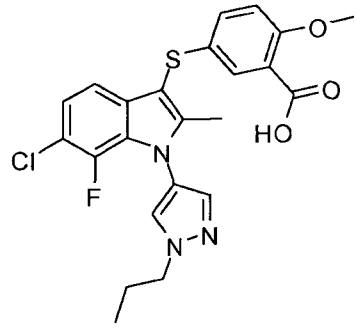
Step 4: 5-(6-Chloro-7-fluoro-2-methyl-1*H*-indol-3-ylsulfanyl)-2-methoxy-benzoic acid ethyl ester

[00773] Prepared according to the procedure described in Example 2, Step 1, using the following starting materials: 2-Methoxy-5-(2-oxo-propylsulfanyl)-benzoic acid ethyl ester and (3-chloro-2-fluoro-phenyl) hydrazine hydrochloride.



Step 5: 5-[6-Chloro-1-(1-propyl-1*H*-pyrazol-4-yl)-7-fluoro-2-methyl-1*H*-indol-3-ylsulfanyl]-2-methoxy-benzoic acid ethyl ester

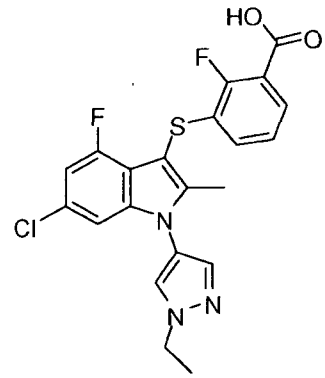
[00774] Prepared according to the procedure described in Example 55, Step 2 using the the following starting materials: 5-(6-Chloro-7-fluoro-2-methyl-1*H*-indol-3-ylsulfanyl)-2-methoxy-benzoic acid ethyl ester and 4-bromo-1-propyl-1*H*-pyrazole.



Step 6: 5-[6-Chloro-1-(1-propyl-1*H*-pyrazol-4-yl)-7-fluoro-2-methyl-1*H*-indol-3-ylsulfanyl]-2-methoxy-benzoic acid

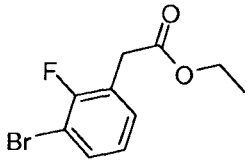
[00775] Prepared according to the procedure described in Example 42, Step 5, using the following starting material: 5-[6-Chloro-1-(1-propyl-1*H*-pyrazol-4-yl)-7-fluoro-2-methyl-1*H*-indol-3-ylsulfanyl]-2-methoxy-benzoic acid ethyl ester.

Example 153: Synthesis of 3-[6-Chloro-1-(1-ethyl-1*H*-pyrazol-4-yl)-4-fluoro-2-methyl-1*H*-indol-3-ylsulfanyl]-2-fluoro-benzoic acid (Compound 4-11)



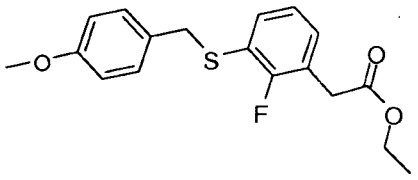
[00776] Prepared according to the procedures described in Example 145 by substituting (3-Chloro-5-fluoro-phenyl)-hydrazine hydrochloride for (3-Chloro-2-fluoro-phenyl)-hydrazine hydrochloride in Step 4 of that sequence.

Example 154: Synthesis of {3-[6-Chloro-7-fluoro-2-methyl-1-(1-propyl-1*H*-pyrazol-4-yl)-1*H*-indol-3-ylsulfanyl]-2-fluoro-phenyl}-acetic acid (Compound 4-12)



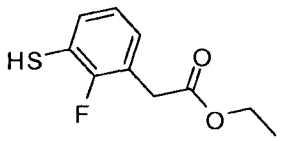
Step 1: (3-Bromo-2-fluoro-phenyl)-acetic acid ethyl ester

[00777] To a stirred solution of 3-bromo-2-fluorophenylacetonitrile (2.5 g, 11.7 mmol) in absolute EtOH (25 mL) at room temperature was added concentrated H_2SO_4 (4 mL) and the mixture was warmed to reflux. After 48 hrs, the reaction was cooled to room temperature, evaporated under reduced pressure, diluted with EtOAc (100 mL) and partitioned with saturated aqueous sodium bicarbonate(50 mL). The organic layer was dried over magnesium sulfate, filtered and concentrated to dryness to afford the title compound.



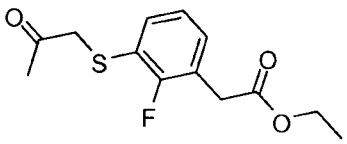
Step 2: [2-Fluoro-3-(4-methoxy-benzylsulfanyl)-phenyl]-acetic acid ethyl ester

[00778] Prepared according to the procedure described for Example 77, Step 1 using the following starting material: (3-Bromo-2-fluoro-phenyl)-acetic acid ethyl ester.



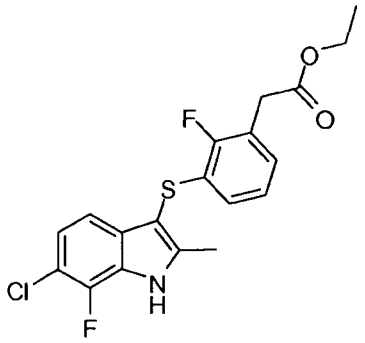
Step 3: (2-Fluoro-3-mercapto-phenyl)-acetic acid ethyl ester

[00779] Prepared according to the procedure described for Example 77, Step 2 using the following starting material: [2-Fluoro-3-(4-methoxy-benzylsulfanyl)-phenyl]-acetic acid ethyl ester.



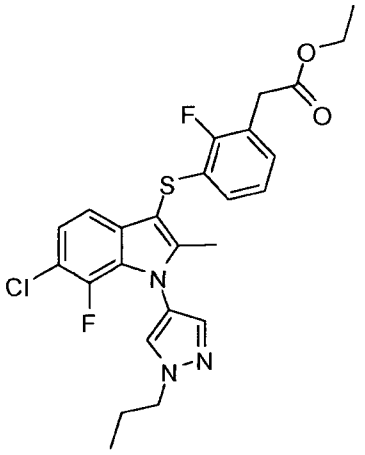
Step 4: [2-Fluoro-3-(2-oxo-propylsulfanyl)-phenyl]-acetic acid ethyl ester

[00780] Prepared according to the procedure described in Example 77, Step 3, using the following starting material: (2-Fluoro-3-mercapto-phenyl)-acetic acid ethyl ester.



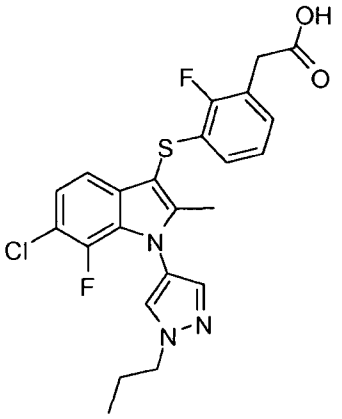
Step 5: [3-(6-Chloro-7-fluoro-2-methyl-1*H*-indol-3-ylsulfanyl)-2-fluoro-phenyl]-acetic acid ethyl ester

[00781] Prepared according to the procedure described in Example 2, Step 1, using the following starting materials: [2-Fluoro-3-(2-oxo-propylsulfanyl)-phenyl]-acetic acid ethyl ester and (3-chloro-2-fluoro-phenyl) hydrazine hydrochloride.



Step 6: {3-[6-Chloro-7-fluoro-2-methyl-1-(1-propyl-1*H*-pyrazol-4-yl)-1*H*-indol-3-ylsulfanyl]-2-fluoro-phenyl}-acetic acid ethyl ester

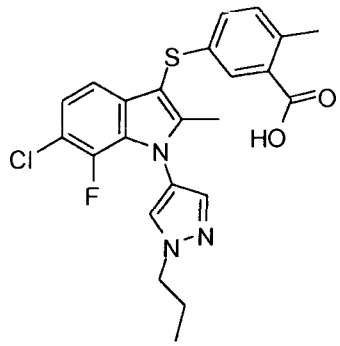
[00782] Prepared according to the procedure described in Example 55, Step 2 using the the following starting materials: [3-(6-Chloro-7-fluoro-2-methyl-1*H*-indol-3-ylsulfanyl)-2-fluoro-phenyl]-acetic acid ethyl ester and 4-iodo-1-propyl-1*H*-pyrazole.



Step 7: {3-[6-Chloro-7-fluoro-2-methyl-1-(1-propyl-1*H*-pyrazol-4-yl)-1*H*-indol-3-ylsulfanyl]-2-fluoro-phenyl}-acetic acid

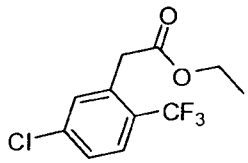
[00783] Prepared according to the procedure described in Example 42, Step 5, using the following starting material: {3-[6-Chloro-7-fluoro-2-methyl-1-(1-propyl-1*H*-pyrazol-4-yl)-1*H*-indol-3-ylsulfanyl]-2-fluoro-phenyl}-acetic acid ethyl ester.

Example 155: 5-[6-Chloro-1-(1-propyl-1*H*-pyrazol-4-yl)-7-fluoro-2-methyl-1*H*-indol-3-ylsulfanyl]-2-methyl-benzoic acid (Compound 4-13)



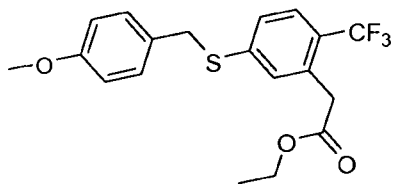
[00784] Prepared according to the procedures described in Example 151 by substituting 4-bromo-1-propyl-1*H*-pyrazole for 4-bromo-1-ethyl-1*H*-pyrazole in Step 5 of that sequence.

Example 156: Synthesis of {5-[6-Chloro-7-fluoro-2-methyl-1-(1-propyl-1*H*-pyrazol-4-yl)-1*H*-indol-3-ylsulfanyl]-2-trifluoromethyl-phenyl}-acetic acid (Compound 4-14)



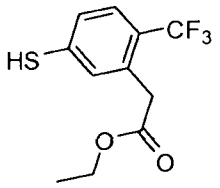
Step 1: (5-Chloro-2-trifluoromethyl-phenyl)-acetic acid ethyl ester

[00785] To a stirred solution of (5-Chloro-2-trifluoromethyl-phenyl)-acetic acid (10.0 g, 47.2 mmol) in absolute EtOH (300 mL) at room temperature was added concentrated H_2SO_4 (4 mL) and the mixture was warmed to reflux. After 4 hrs, the reaction was cooled to room temperature, evaporated under reduced pressure, diluted with DCM (500 mL) and stirred over solid K_2CO_3. After 1 hr, the resulting mixture was filtered and concentrated to dryness to afford the title compound.



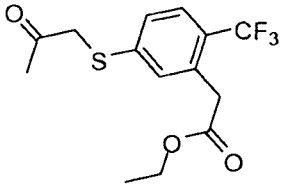
Step 2: [5-(4-Methoxy-benzylsulfanyl)-2-trifluoromethyl-phenyl]-acetic acid ethyl ester

[00786] Prepared according to the procedure described for Example 77, Step 1 using the following starting material: (5-Chloro-2-trifluoromethyl-phenyl)-acetic acid ethyl ester.



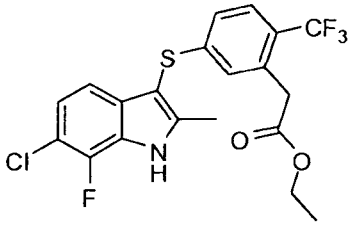
Step 3: (5-Mercapto-2-trifluoromethyl-phenyl)-acetic acid ethyl ester

[00787] Prepared according to the procedure described for Example 77, Step 2 using the following starting material: [5-(4-Methoxy-benzylsulfanyl)-2-trifluoromethyl-phenyl]-acetic acid ethyl ester.



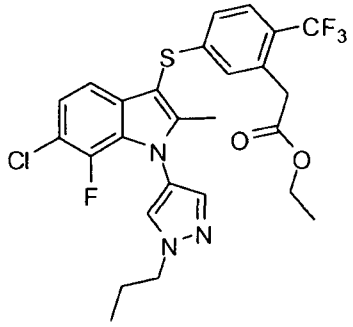
Step 4: [5-(2-Oxo-propylsulfanyl)-2-trifluoromethyl-phenyl]-acetic acid ethyl ester

[00788] Prepared according to the procedure described in Example 77, Step 3, using the following starting material: (5-Mercapto-2-trifluoromethyl-phenyl)-acetic acid ethyl ester.



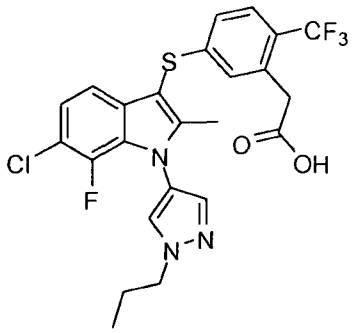
Step 5: [5-(6-Chloro-7-fluoro-2-methyl-1*H*-indol-3-ylsulfanyl)-2-trifluoromethyl-phenyl]-acetic acid ethyl ester

[00789] Prepared according to the procedure described in Example 2, Step 1, using the following starting materials: [5-(2-Oxo-propylsulfanyl)-2-trifluoromethyl-phenyl]-acetic acid ethyl ester and (3-chloro-2-fluoro-phenyl) hydrazine hydrochloride.



Step 6: {5-[6-Chloro-7-fluoro-2-methyl-1-(1-propyl-1*H*-pyrazol-4-yl)-1*H*-indol-3-ylsulfanyl]-2-trifluoromethyl-phenyl}-acetic acid ethyl ester

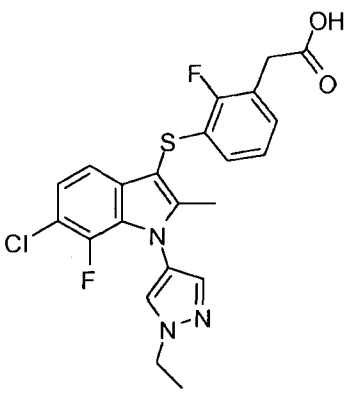
[00790] Prepared according to the procedure described in Example 55, Step 2 using the the following starting materials: [5-(6-Chloro-7-fluoro-2-methyl-1*H*-indol-3-ylsulfanyl)-2-trifluoromethyl-phenyl]-acetic acid ethyl ester and 4-iodo-1-propyl-1*H*-pyrazole.



Step 7: {5-[6-Chloro-7-fluoro-2-methyl-1-(1-propyl-1*H*-pyrazol-4-yl)-1*H*-indol-3-ylsulfanyl]-2-trifluoromethyl-phenyl}-acetic acid

[00791] Prepared according to the procedure described in Example 42, Step 5, using the following starting material: {5-[6-Chloro-7-fluoro-2-methyl-1-(1-propyl-1*H*-pyrazol-4-yl)-1*H*-indol-3-ylsulfanyl]-2-trifluoromethyl-phenyl}-acetic acid ethyl ester.

Example 157: Synthesis of {3-[6-Chloro-1-(1-ethyl-1*H*-pyrazol-4-yl)-7-fluoro-2-methyl-1*H*-indol-3-ylsulfanyl]-2-fluoro-phenyl}-acetic acid (Compound 4-15)



[00792] Prepared according to the procedures described in Example 154 by substituting 4-bromo-1-ethyl-1*H*-pyrazole for 4-iodo-1-propyl-1*H*-pyrazole in Step 5 of that sequence.

Example 158: Native Autotaxin Choline Release assay.

[00793] Inhibition of autotaxin (ATX) activity is assayed in conditioned medium from the human melanoma cell line, MDA-MB-435S, which endogenously expresses autotaxin. ATX activity is determined by measuring the amount of choline realeased from the substrate, lyosphophatidylcholine (LPC). MDA-MB-435S cells (American Type Tissue Culture Cat# HTB-129) are grown to confluence in DMEM containing 10% fetal bovine serum (FBS) and sodium pyruvate. After reaching confluency, the cells are washed twice with phosphate-buffered saline (PBS) then cultured for 48 hours in phenol-red free, serum-free DMEM containing sodium pyruvate. The conditioned medium is then removed, centrifuged at 1200 rpm and concentrated 20-fold using Centriprep-30 filter devices (Millipore Cat# 4322). To assay for autotaxin inhibition, 20 µl of the concentrated conditioned media is incubated with 2.5 µl test compound in DMSO and 72.5 µl lyso-PLD buffer (100 mM Tris pH 9, 500 mM NaCl, 5 mM $MgCl_2$, 30 µM $CoCl_2$, 0.05% Triton X-100 ± 0.2% fatty-acid-free human serum albumin) (fatty-acid-free human serum albumin is from SeraCare Diagnostics Cat# HS-455-80

or Sigma Cat #A3782) for 15 minutes at 37°C. Following the 15 min incubation, 5 μl of 3 mM LPC (14:0; Avanti Polar Lipids Cat# 855575C) diluted in lyso-PLD buffer is added for a final concentration of 150 μM and the incubation continued for 90 minutes at 37°C. 100 μl of a color mix which contains 4.5 mM 4-aminoantipyrine, 2.7 mM N-ethyl-N-(2-hydroxy-3-sulfopropyl)-m-toluidine, 21 units/ml horseradish peroxidase and 3 units/ml choline oxidase in 50 mM Tris, pH 8, 4.5 mM $MgCl_2$ is added and the incubation continued at 37°C for 10 minutes before reading the absorbance at 555 nm. The concentration of released choline in the sample is determined from a choline standard curve and is equal to the concentration of LPA produced.

[00794] Illustrative biological activity of representative compounds described herein is presented in the following table:

Cmpd No	MDA-MB-435S Assay IC_{50}
1-1	C
1-2	C
1-3	C
1-4	C
1-5	C
1-6	C
1-7	C
1-8	B
1-9	C
1-10	B
1-11	C
1-12	C
1-13	C
1-14	C
1-15	B
1-16	C
1-17	C
1-18	C
1-19	C
1-20	C
1-21	A
1-22	C
1-23	A
1-24	B
1-25	A
1-26	A
1-27	B
1-28	B
1-29	A
1-30	A
1-31	B
1-32	B
1-33	A
1-34	A
1-35	A
1-36	A
1-37	A

Cmpd No	MDA-MB-435S Assay IC_{50}
1-38	A
1-39	A
1-40	C
1-41	C
1-42	A
1-43	A
1-44	A
1-45	A
1-46	C
1-47	C
1-48	A
1-49	A
1-50	C
1-51	C
1-52	C
1-53	C
1-54	C
1-55	A
1-56	A
1-57	A
1-58	A
1-59	A
1-60	A
1-61	A
1-62	A
1-63	A
1-64	A
1-65	A
1-66	A
1-67	A
1-68	B
1-69	A
1-70	A
1-71	A
1-72	A
1-73	A
1-74	A
1-75	C
1-76	A
1-130	A
1-129	A
1-131	A
1-132	A
2-1	C
2-3	C
2-4	C
2-5	C
2-6	C
2-7	C
2-8	C
2-9	C
2-10	C

Cmpd No	MDA-MB-435S Assay IC_{50}
2-11	C
2-12	C
3-1	C
3-2	C
3-3	C
3-4	C
3-5	C
3-6	C
3-7	C
3-9	C
3-10	C
3-11	C
3-12	C
3-13	C
3-15	C
3-16	A
3-17	B
3-19	B
3-20	A
3-21	A
3-22	A
3-23	A
3-24	A
3-25	A
3-26	A
3-27	A
3-28	A
3-29	A
3-30	A
3-31	A
3-32	A
3-33	A
3-34	A
3-35	A
3-36	A
3-37	A
3-47	A
3-48	A
3-49	A
3-50	A
3-51	A
3-52	A
3-42	A
3-53	A
3-54	A
3-55	A
3-56	A
3-57	A
3-58	B
3-59	C
3-60	A
3-61	A

Cmpd No	MDA-MB-435S Assay IC_{50}
3-62	B
4-1	A
4-2	A
4-3	A
4-4	A
4-5	A
4-6	A
4-7	A
4-8	A
4-9	A
4-10	A
4-11	A
4-12	A
4-13	A
4-14	A
4-15	A

A < 0.3 μM; B = 0.3 to 1.0 μM; C >1.0 μM

Example 159: Human Serum Autotaxin Assay.

[00795] Inhibition of autotaxin activity is assayed in human serum by measuring the amount of choline released from the substrate, lysophosphatidylcholine (LPC). Human serum (Delipidated/Opticlear Serum Cat #1121-00; Biocell Laboratories Inc) is dialyzed for 18-24 hours at 4°C in 0.9% saline in Slide-A-Lyzer G2 dialysis cassettes (2 KD MWCO; Pierce Biotechnology Cat# 87720) with three changes of the dialysis buffer. To assay for autotaxin inhibition, 20 μl of the dialyzed human serum is incubated with 2 μl test compound in DMSO and 73 μl lyso-PLD buffer (100 mM Tris pH 9, 500 mM NaCl, 5 mM $MgCl_2$, 30 μM $CoCl_2$, 0.05% Triton X-100) for 15 minutes at 37°C. After the 15 min incubation, 5 μl of 6 mM LPC (14:0; Avanti Polar Lipids Cat# 855575C) diluted in lyso-PLD buffer is added for a final concentration of 300 μM and the incubation continued for 4 hours at 37°C. 100 μl of a color mix which contains 4.5 mM 4-aminoantipyrine, 2.7 mM N-ethyl-N-(2-hydroxy-3-sulfopropyl)-m-toluidine, 21 units/ml Horseradish peroxidase and 3 units/ml choline oxidase in 50 mM Tris, pH 8, 4.5 mM $MgCl_2$ is added and the incubation continued for 15 minutes at room temperature before reading the absorbance at 555 nm. The concentration of released choline in the sample is determined from a choline standard curve and is equal to the concentration of LPA produced.

Example 160: Human Whole Blood Autotaxin Assay.

[00796] Inhibition of autotaxin activity in human whole blood is assayed by measuring the concentration of 20:4 LPA in plasma after a prolonged incubation at 37°C. Briefly, blood is drawn from consenting human volunteers into heparin vacutainer tubes and 150-300 μl aliquots added to test compound in DMSO or DMSO alone (vehicle). Several of the vehicle tubes are centrifuged immediately at 800 x g for 10 minutes at 4°C and the plasma removed for processing to determine the baseline concentration of LPA. The remaining blood samples containing vehicle or test compound are incubated at 37°C for 4 hours before centrifuging at 800 x g for 10 minutes at 4°C to obtain

plasma. Plasma is processed for LCMS as follows: plasma is removed and 3 volumes of an organic solution (50/50/1 of methanol/acetonitrile/acetic acid containing 125 ng/ml 17:0 LPA) are added and the mixture incubated at -20°C for at least one hour before centrifuging at 4000 x g for 30 minutes at 4°C. ≥ 100 µl of the supernatant is transferred to a 96-well plate and diluted with 2-3 volumes of an organic solution (66:34:0.1 of methanol/water/triethylamine) for analysis of 20:4 LPA concentrations by LCMS. LPA 20:4 and the internal standard (LPA 17:0) were analyzed on a quadrupole mass spectrometer (ABI Sciex 4000QTrap) in the negative ion mode (ESI) by multiple reaction monitoring (MRM). The mobile phases contained 10 mM ammonium acetate in water with 0.05% formic acid (solvent A) and 10mM ammonium acetate in 50% acetonitrile/50% methanol with 0.05% formic acid (solvent B). The flow rate was maintained at 1 mL/min and the total run time was 4 min. Analytes were separated using a linear gradient as follows:

1. mobile phase was held for 1 min at 5% B,
2. B was increased from 5% to 95% over then next 0.2 min,
3. B was held constant for 2.3 min at 95%, and
4. B was returned to the initial gradient conditions.

Example 161: Mouse air pouch assay

[00797] A mouse air pouch assay was utilized to determine efficacy of autotaxin inhibitors in reducing carrageenan-induced LPA biosynthesis. An air pouch was formed in female CD-1 mice (weighing 20 - 30 grams) by instilling 5 ml of 0.2 µm filtered air into the subcutaneous space in the scapular region. Three days later, 3 ml of air was instilled into the pouch. One to seven days following pouch initiation test compounds were administered by oral gavage in a dose volume of 10 ml/kg. At the appropriate time after compound administration mice were injected with carrageenan (1 ml of 1% in sterile saline) into their air pouch. One to four hours following carrageenan challenge mice were placed into an enclosed Plexiglas chamber and exposed to CO_2 for a period of 1-2 minutes or until breathing ceased. They were then removed and blood was taken via a cardiac puncture. Cervical dislocation was performed to ensure mice would not recover from the CO_2. A 1 ml bolus of bolus of ice cold phosphate buffered saline solution was instilled into the air pouch using a 1ml syringe. After 20 seconds of gentle massaging the pouch was opened and the fluid removed. An aliquot was mixed with equal parts ice cold quenching reagent (MeCH/ACN/water/TEA, 116/50/34/0.1) and centrifuged at 10,000 X g for 10 minutes at 4°C. LPA concentrations in the supernatant were determined by LCMS. A separate aliquot was taken, centrifuged (800 x g, 10 min) and assayed for choline content using a TOOS method. Plasma prepared from blood was assayed for drug concentrations by LCMS. Drug concentrations to achieve 50% inhibition of carrageenan-induced pouch LPA could be calculated by nonlinear regression (Graphpad Prism) of % inhibition versus log drug concentration.

Example 162: Collagen Induced Arthritis (CIA)

[00798] Collagen-induced arthritis (CIA) is a preclinical animal inflammation model of rheumatoid arthritis (RA) that can be used to evaluate the therapeutic effects of autotaxin inhibitors in reducing inflammation and pain (Bourgoin and Zhao, *Current Opinions in Investigational Drugs*, 2010, 11(5):515-526). The model is performed in mice or rats by immunization with heterologous type II collagen in adjuvant. Susceptibility to collagen-induced rheumatoid arthritis is strongly associated with major histocompatibility complex class II genes, and the development of rheumatoid arthritis is accompanied by a robust T-cell and B-cell inflammation response to type II collagen. The chief pathological features of collagen-induced arthritis include a proliferative synovitis with infiltration of polymorphonuclear and mononuclear cells, pannus formation, cartilage degradation, erosion of bone, and fibrosis. As in human rheumatoid arthritis, pro-inflammatory cytokines, such as tumor necrosis factor alpha (TNF-a), interleukin-1b (IL-1b) and IL-6 are increased in collagen-induced arthritis.

[00799] Disease activity is assessed by measuring inflammation swelling in the affected joints (paw volume or thickness) over time. Treatments can be assessed in either prophylactic or therapeutic testing paradigms. Additional measure of disease activity may include evaluation of serum IL-1b, IL-6, C-reactive protein (CRP) or serum amyloid A (SAA), and erythrocyte sedimentation rate. Bone lesion scoring may be conducted by preclinical Positron Emission Tomography (preclinical PET).

Example 163: Rat Model of Neuropathic Pain

[00800] A rat model of neuropathic pain involving a partial sciatic nerve ligation is used to test efficacy of compounds disclosed herein in reducing pain. The rat model is adapted from Kim *et al.* *Exp Brain Res* (1997) 113:200-206. Briefly, male Sprague-Dawley rats weighing 150-200 g are used and neuropathic surgery is done on all rats under gaseous anesthesia with a mixture of halothane (2% for induction and 0.8% for maintenance) and a 1:1 flow ratio of N_2O and O_2. The rats recover sufficiently from the surgical procedures to resume normal activity within 30 min after termination of the gaseous anesthesia. Briefly, the left sciatic nerve is exposed at the upper-thigh level. The dorsal third to half of the sciatic nerve is tightly ligated with an 8-0 silk suture at a site just distal to the point at which the posterior biceps-semitendinosus nerve branches off.

[00801] Four behavioral tests representing two different components of neuropathic pain are performed: evoked pain (mechanical and cold allodynia) and ongoing pain (spontaneous pain and coldstress exacerbated ongoing pain). Unless otherwise specified, behavioral tests are conducted for all rats at 1 day prior to surgery, 1, 3, 5 and 7 days postoperatively (PO), and periodically thereafter. Test compound is administered (orally or injection) postoperatively. Comparison of the behavioral test results obtained for rats administered test compound and control rats provides an assessment of the therapeutic effects of test compound.

Example 164: Lung Metastases Model

[00802] An experimental lung metastasis model is used to test efficacy of compounds in reducing the number of metastases of injected B16-F10 mouse melanoma cells to the lung. The model is adapted from Kolber *et al.*, *J. of National Cancer Institute*, vol 87, no. 4, 1995, 304-309. Briefly, female

C57BL/6J mice, female (BALB/cByJ x C57BL/6J)F_1, mice (hereafter referred to as CByB6F_1/J), athymic nude female and male CByB6F_1/J mice (nu/nu), and control littermates (nu/nu) are used at ages 7-18 weeks, when they weighed between 18 and 28 g. A single-cell suspension of B16F10 cells, harvested in log phase by brief exposure to 0.05% trypsin-0.53 mM EDTA, is suspended in complete MEM. Cells (approx. 5-10 x 10^4) in 0.2 mL of Hanks' balanced salt solution are injected intravenously into the lateral tail vein of the mice. Treatment with test compound, endotoxin at less than 0.25 endotoxin units/mg, or the buffer control (10 *mM* sodium acetate/150 mM NaCl [pH 5.0]) is administered either intravenously or subcutaneously. Six mice per group are included in each experiment, unless otherwise noted. After 21 days, the mice are killed, and lungs are removed. Lungs are fixed in 10% buffered formalin overnight and weighed, and the tumor colonies at the surface are enumerated with the aid of a dissecting microscope. Studies are typically conducted as unblinded experiments. The injection schedule systematically alternates between animals in the control group and animals in the experimental groups to minimize variances that might be attributed to the duration of the injection protocol.

Example 165: Mouse carbon tetrachloride (CCl_4)-induced liver fibrosis model

[00803] Female C57BL/6 mice (Harlan, 20-25g) housed 4/cage are given free access to food and water and allowed to acclimate for at least 7 days prior to test initiation. After the habituation phase, mice receive CCl_4 (1.0 ml/kg body weight) diluted in corn oil vehicle (100 µL volume) via i.p. injection twice a week for 8 weeks. (Higazi, A. A. *et al.*, *Clin Exp Immunol.* 2008 Apr;152(1):163-73. Epub 2008 Feb 14.). Control mice receive an equivalent volume of corn oil vehicle only. Test compound or vehicle is delivered po, ip or sc daily. At the end of the study (8 weeks after first i.p. injection of CCl_4), mice are sacrificed using inhaled isoflurane and blood is drawn via cardiac puncture for subsequent analysis of ALT/AST levels. The liver is harvested, and one half of the liver is frozen at -80°C and the other half is fixed in 10% neutral buffered formalin for histological assessment of liver fibrosis using light microscopy (10x magnification). Liver tissue homogenates are analyzed for collagen levels using Sircol (Biocolor Ltd, UK). Fixed Liver tissue is stained using hematoxylin and eosin (H&E) and trichrome and liver fibrosis is determined by quantitative, computer-assisted densitometry of collagen in liver tissue sections using light microscopy. Plasma and liver tissue lysates are also analyzed for concentrations of inflammatory, pro-fibrotic and tissue injury biomarkers including transforming growth factor β1, hyaluronic acid, tissue inhibitor of metalloproteinase-1, matrix matelloproteinase-7, connective tissue growth factor and lactate dehydrogenase activity, using commercially available ELISA. The resulting data are plotted using Graphpad prism and statistical differences between groups determined.

Example 166: Parenteral Composition

[00804] To prepare a parenteral pharmaceutical composition suitable for administration by injection (subcutaneous, intravenous, and the like), 100 mg of a compound of Formula (I) or a water-soluble

salt of a compound of Formula (I) is dissolved in DMSO and then mixed with 10 mL of 0.9% sterile saline. The mixture is incorporated into a dosage unit form suitable for administration by injection

[00805] In another embodiment, the following ingredients are mixed to form an injectable formulation: 1.2 g of a compound of Formulas (I), or a pharmaceutically acceptable salt thereof, 2.0 mL of sodium acetate buffer solution (0.4 M), HCl (1 N) or NaOH (1 M) (q.s. to suitable pH), water (distilled, sterile) (q.s.to 20 mL). All of the above ingredients, except water, are combined and stirred and if necessary, with slight heating if necessary. A sufficient quantity of water is then added.

Example 167: Oral Composition

[00806] To prepare a pharmaceutical composition for oral delivery, 100 mg of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, is mixed with 750 mg of starch. The mixture is incorporated into an oral dosage unit for, such as a hard gelatin capsule, which is suitable for oral administration.

Example 168: Sublingual (Hard Lozenge) Composition

[00807] To prepare a pharmaceutical composition for buccal delivery, such as a hard lozenge, mix 100 mg of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, with 420 mg of powdered sugar mixed, with 1.6 mL of light corn syrup, 2.4 mL distilled water, and 0.42 mL mint extract. The mixture is gently blended and poured into a mold to form a lozenge suitable for buccal administration.

Example 169: Fast-Disintegrating Sublingual Tablet

[00808] A fast-disintegrating sublingual tablet is prepared by mixing 48.5% by weigh of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, 44.5% by weight of microcrystalline cellulose (KG-802), 5% by weight of low-substituted hydroxypropyl cellulose (50 μm), and 2% by weight of magnesium stearate. Tablets are prepared by direct compression (*AAPS PharmSciTech.* 2006;7(2):E41). The total weight of the compressed tablets is maintained at 150 mg. The formulation is prepared by mixing the amount of compound of Formula (I), or a pharmaceutically acceptable salt thereof, with the total quantity of microcrystalline cellulose (MCC) and two-thirds of the quantity of low-substituted hydroxypropyl cellulose (L-HPC) by using a three dimensional manual mixer (Inversina®, Bioengineering AG, Switzerland) for 4.5 minutes. All of the magnesium stearate (MS) and the remaining one-third of the quantity of L-HPC are added 30 seconds before the end of mixing.

Example 170: Inhalation Composition

[00809] To prepare a pharmaceutical composition for inhalation delivery, 20 mg of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, is mixed with 50 mg of anhydrous citric acid and 100 mL of 0.9% sodium chloride solution. The mixture is incorporated into an inhalation delivery unit, such as a nebulizer, which is suitable for inhalation administration.

[00810] In another embodiment, a compound of Formula (I), or a pharmaceutically acceptable salt thereof, (500 mg) is suspended in sterile water (100 mL), Span 85 (1 g) is added followed by addition of dextrose (5.5 g) and ascorbic acid (10 mg). Benzalkonium chloride (3 mL of a 1:750 aqueous

solution) is added and the pH is adjusted to 7 with phosphate buffer. The suspension is packaged in sterile nebulizers.

Example 171: Rectal Gel Composition

[00811] To prepare a pharmaceutical composition for rectal delivery, 100 mg of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, is mixed with 2.5 g of methylcelluose (1500 mPa), 100 mg of methylparapen, 5 g of glycerin and 100 mL of purified water. The resulting gel mixture is then incorporated into rectal delivery units, such as syringes, which are suitable for rectal administration.

Example 172: Topical Gel Composition

[00812] To prepare a pharmaceutical topical gel composition, 100 mg of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, is mixed with 1.75 g of hydroxypropyl celluose, 10 mL of propylene glycol, 10 mL of isopropyl myristate and 100 mL of purified alcohol USP. The resulting gel mixture is then incorporated into containers, such as tubes, which are suitable for topicl administration.

Example 173: Ophthalmic Solution Composition

[00813] To prepare a pharmaceutical opthalmic solution composition, 100 mg of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, is mixed with 0.9 g of NaCl in 100 mL of purified water and filterd using a 0.2 micron filter. The resulting isotonic solution is then incorporated into ophthalmic delivery units, such as eye drop containers, which are suitable for ophthalmic administration.

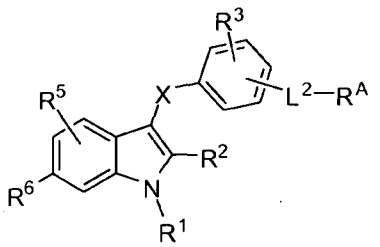
Example 174: Nasal spray solution

[00814] To prepare a pharmaceutical nasal spray solution, 10 g of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, is mixed with 30 mL of a 0.05M phosphate buffer solution (pH 4.4). The solution is placed in a nasal administrator designed to deliver 100 μl of spray for each application.

[00815] The examples and embodiments described herein are for illustrative purposes only and various modifications or changes suggested to persons skilled in the art are to be included within the spirit and purview of this application and scope of the appended claims.

WHAT IS CLAIMED IS:

1. A compound of Formula (I), or a pharmaceutically acceptable salt thereof:



Formula (I)

wherein,

R^1 is H, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6fluoroalkyl, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted C_3-C_6cycloalkyl, substituted or unsubstituted phenyl, substituted or unsubstituted monocyclic heteroaryl, or $-L^1$-R^4;

L^1 is substituted or unsubstituted C_1-C_6alkylene, substituted or unsubstituted phenylene, or substituted or unsubstituted monocyclic heteroarylene;

R^4 is substituted or unsubstituted C_3-C_6cycloalkyl, substituted or unsubstituted phenyl, substituted or unsubstituted benzyl, substituted or unsubstituted naphthyl, or substituted or unsubstituted monocyclic heteroaryl;

R^2 is H, C_1-C_4alkyl or C_1-C_4fluoroalkyl;

X is -O-, -S-, -S(O)-, $-S(O)_2-$, $-CH_2-$, $-CH_2CH_2-$, $-OCH_2-$, $-CH_2O-$, $-SCH_2-$, $-CH_2S-$, -C(=O)-, $-C(=O)CH_2-$, or $-CH_2C(=O)-$;

L^2 is absent, C_1-C_6alkylene or C_3-C_6cycloalkylene;

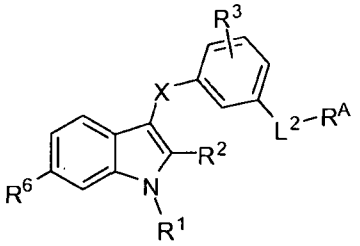
R^A is $-CO_2H$, $-CO_2(C_1$-C_6alkyl), -OH, -CN, $-B(OH)_2$, $-C(=O)NHSO_2R^9$, $-C(=O)N(R^{10})_2$, $-C(=O)NHCH_2CH_2N(CH_3)_2$, $-C(=O)NHCH_2CH_2N(CH_3)_3$, -C(=O)NH-OH, -C(=O)NH-CN, $-SO_2NHC(=O)R^9$, -CN, tetrazolyl or carboxylic acid bioisostere;

R^3 and R^5 are each independently H, halogen, -CN, -OH, C_1-C_4alkyl, C_1-C_4alkoxy, -S-C_1-C_4alkyl, C_1-C_4fluoroalkyl, C_1-C_4fluoroalkoxy, and C_1-C_4heteroalkyl;

R^6 is H, halogen, -CN, $-NO_2$, -OH, $-OR^9$, $-SR^9$, $-S(=O)R^9$, $-S(=O)_2R^9$, $-S(=O)_2N(R^{10})_2$, $-NR^{10}S(=O)_2R^9$, $-C(=O)R^9$, $-OC(=O)R^9$, $-CO_2R^{10}$, $-OCO_2R^9$, $-N(R^{10})_2$, $-C(=O)N(R^{10})_2$, $-OC(=O)N(R^{10})_2$, $-NHC(=O)R^9$, $-NHC(=O)OR^9$, C_1-C_4alkyl, C_1-C_4alkoxy, -S-C_1-C_4alkyl, $-S(O)_2$-C_1-C_4alkyl, C_1-C_4fluoroalkyl, C_1-C_4fluoroalkoxy, C_1-C_4heteroalkyl, C_3-C_6cycloalkyl, substituted or unsubstituted phenyl, substituted or unsubstituted monocyclic heteroaryl;

R^9 is C_1-C_6alkyl, C_3-C_6cycloalkyl, a substituted or unsubstituted phenyl, or a substituted or unsubstituted monocyclic heteroaryl;

7. The compound of any one of claims 1-5, or a pharmaceutically acceptable salt thereof, wherein the compound of Formula (I) has the structure of Formula (II):



Formula (II).

8. The compound of claim 6, or a pharmaceutically acceptable salt thereof, wherein:

R^A is $-CO_2H$, $-CO_2(C_1\text{-}C_6alkyl)$, $-B(OH)_2$, or tetrazolyl;

X is -S-.

9. The compound of claim 8, or a pharmaceutically acceptable salt thereof, wherein:

R^2 is $-CH_3$, $-CH_2CH_3$, or $-CF_3$;

L^2 is absent, $-CH_2-$, or $-CH_2CH_2-$;

R^A is $-CO_2H$ or $-CO_2(C_1\text{-}C_6alkyl)$.

10. The compound of any one of claims 1-9, or a pharmaceutically acceptable salt thereof, wherein:

R^1 is $C_1\text{-}C_6$alkyl, $C_1\text{-}C_6$heteroalkyl, $C_3\text{-}C_6$cycloalkyl, substituted or unsubstituted phenyl, substituted or unsubstituted monocyclic heteroaryl, or $-L^1\text{-}R^4$;

L^1 is $-CH_2-$, substituted or unsubstituted phenylene, or substituted or unsubstituted monocyclic heteroarylene;

R^4 is $C_3\text{-}C_6$cycloalkyl, substituted or unsubstituted phenyl, substituted or unsubstituted naphthyl, substituted or unsubstituted monocyclic heteroaryl.

11. The compound of any one of claims 1-9, or a pharmaceutically acceptable salt thereof, wherein:

R^1 is substituted or unsubstituted phenyl, substituted or unsubstituted monocyclic heteroaryl, or $-L^1\text{-}R^4$;

L^1 is substituted or unsubstituted phenylene, or substituted or unsubstituted monocyclic heteroarylene;

R^4 is substituted or unsubstituted phenyl, substituted or unsubstituted benzyl, substituted or unsubstituted naphthyl, substituted or unsubstituted monocyclic heteroaryl.

12. The compound of any one of claims 1-9, or a pharmaceutically acceptable salt thereof, wherein:

R^1 is substituted or unsubstituted phenyl, substituted or unsubstituted monocyclic heteroaryl.

13. The compound of claim 12, or a pharmaceutically acceptable salt thereof, wherein:

R^1 is a substituted or unsubstituted phenyl, substituted or unsubstituted furanyl, substituted or unsubstituted pyrrolyl, substituted or unsubstituted oxazolyl, substituted or unsubstituted

thiazolyl, substituted or unsubstituted imidazolyl, substituted or unsubstituted pyrazolyl, substituted or unsubstituted triazolyl, substituted or unsubstituted tetrazolyl, substituted or unsubstituted isoxazolyl, substituted or unsubstituted isothiazolyl, substituted or unsubstituted oxadiazolyl, substituted or unsubstituted thiadiazolyl, substituted or unsubstituted pyridinyl, substituted or unsubstituted pyrimidinyl, substituted or unsubstituted pyrazinyl, substituted or unsubstituted pyridazinyl, or substituted or unsubstituted triazinyl.

14. The compound claim 13, or a pharmaceutically acceptable salt thereof, wherein:

R^1 is a substituted or unsubstituted phenyl.

15. The compound of any one of claims 1-9, or a pharmaceutically acceptable salt thereof, wherein:

R^1 is a substituted or unsubstituted monocyclic 5-membered heteroaryl.

16. The compound of claim 15, or a pharmaceutically acceptable salt thereof, wherein:

R^1 is a substituted or unsubstituted pyrrolyl, substituted or unsubstituted oxazolyl, substituted or unsubstituted thiazolyl, substituted or unsubstituted imidazolyl, substituted or unsubstituted pyrazolyl, substituted or unsubstituted triazolyl, substituted or unsubstituted isoxazolyl, substituted or unsubstituted isothiazolyl, substituted or unsubstituted oxadiazolyl, or substituted or unsubstituted thiadiazolyl.

17. The compound of any one of claims 1-8, or a pharmaceutically acceptable salt thereof, wherein:

R^1 is a substituted or unsubstituted monocyclic 6-membered heteroaryl.

18. The compound of claim 17, or a pharmaceutically acceptable salt thereof, wherein:

R^1 is a substituted or unsubstituted pyridinyl, substituted or unsubstituted pyrimidinyl, substituted or unsubstituted pyrazinyl, or substituted or unsubstituted pyridazinyl.

19. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein:

R^1 is a substituted or unsubstituted monocyclic heteroaryl;

R^2 is H or C_1-C_4alkyl;

X is -O-, -S-, -S(O)-, or -$S(O)_2$-;

L^2 is absent, C_1-C_6alkylene or C_3-C_6cycloalkylene;

R^A is $-CO_2H$;

R^3 and R^5 are each independently H, halogen, -CN, -OH, C_1-C_4alkyl, C_1-C_4alkoxy, -S-C_1-C_4alkyl, C_1-C_4fluoroalkyl, and C_1-C_4fluoroalkoxy;

R^6 is halogen, -CN, -OH, C_1-C_4alkyl, C_1-C_4alkoxy, -S-C_1-C_4alkyl, C_1-C_4fluoroalkyl, C_1-C_4fluoroalkoxy, or C_1-C_4heteroalkyl.

20. The compound of claim 6, or a pharmaceutically acceptable salt thereof, wherein:

R^1 is a substituted or unsubstituted monocyclic heteroaryl;

R^2 is C_1-C_4alkyl;

X is -S-;

L^2 is absent, or C_1-C_4alkylene;

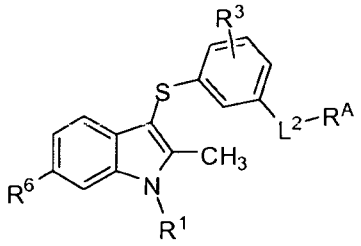
R^A is $-CO_2H$;

R^3 is H, halogen, C_1-C_4alkyl, C_1-C_4alkoxy, or C_1-C_4fluoroalkyl;

R^5 is H, or halogen;

R^6 is halogen.

21. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein the compound of Formula (I) has the structure of Formula (III):



Formula (III)

wherein,

R^1 is a substituted or unsubstituted phenyl or a substituted or unsubstituted monocyclic heteroaryl;

L^2 is absent, $-CH_2-$, or $-CH_2CH_2-$;

R^A is $-CO_2H$ or $-CO_2(C_1$-C_6alkyl);

R^3 is H, halogen, -CN, -OH, C_1-C_4alkyl, C_1-C_4alkoxy, -S-C_1-C_4alkyl, C_1-C_4fluoroalkyl, C_1-C_4fluoroalkoxy, or C_1-C_4heteroalkyl;

R^6 is H, halogen, -CN, -OH, C_1-C_4alkyl, C_1-C_4alkoxy, -S-C_1-C_4alkyl, C_1-C_4fluoroalkyl, or C_1-C_4fluoroalkoxy;

each substituted group is substituted with 1 or more groups independently selected from halogen, -CN, -OH, C_1-C_4alkyl, C_1-C_4alkoxy, -S-C_1-C_4alkyl, C_1-C_4fluoroalkyl, C_1-C_4fluoroalkoxy, and C_1-C_4heteroalkyl.

22. The compound of claim 19, or a pharmaceutically acceptable salt thereof, wherein:

R^1 is a substituted or unsubstituted monocyclic 5-membered heteroaryl or a substituted or unsubstituted monocyclic 6-membered heteroaryl;

L^2 is absent or $-CH_2-$;

R^A is $-CO_2H$;

R^6 is F, Cl, Br, I, -CN, -OH, $-CH_3$, $-OCH_3$, $-OCH_2CH_3$, $-CF_3$, $-OCF_3$, or -S-CH_3.

23. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein the compound of Formula (I) has the structure of Formula (IV):

26. The compound of any one of claims 25, or a pharmaceutically acceptable salt thereof, wherein:

R^1 is a substituted or unsubstituted pyrazolyl; each substituted group is substituted with C_1-C_4alkyl;

R^3 is H, F, Cl, $-CH_3$, $-OCH_3$, $-CF_3$, $-OCF_3$, or -S-CH_3;

R^5 is H, F, or Cl;

R^6 is Cl.

27. A compound that is:

[3-(2-Methyl-1*H*-indol-3-ylsulfanyl)-phenyl]-acetic acid (Compound 1-1); [3-(6-Fluoro-2-methyl-1*H*-indol-3-ylsulfanyl)-phenyl]-acetic acid (Compound 1-2); [3-(6-Methoxy-2-methyl-1*H*-indol-3-ylsulfanyl)-phenyl]-acetic acid (Compound 1-3); [3-(1,2-Dimethyl-1*H*-indol-3-ylsulfanyl)-phenyl]-acetic acid (Compound 1-4); [3-(6-Chloro-1,2-dimethyl-1*H*-indol-3-ylsulfanyl)-phenyl]-acetic acid (Compound 1-5); 3-(6-Chloro-1,2-dimethyl-1*H*-indol-3-ylsulfanyl)-benzoic acid (Compound 1-6); [3-(6-Chloro-1-isobutyl-2-methyl-1*H*-indol-3-ylsulfanyl)-phenyl]-acetic acid (Compound 1-7); {3-[6-Chloro-1-(2-methoxy-ethyl)-2-methyl-1*H*-indol-3-ylsulfanyl]-phenyl}-acetic acid (Compound 1-8); [3-(1-Benzyl-2-methyl-1*H*-indol-3-ylsulfanyl)-phenyl]-acetic acid (Compound 1-9); 3-(1-Benzyl-6-bromo-2-methyl-1*H*-indol-3-ylsulfanyl)-benzoic acid (Compound 1-10); 3-(1-Benzyl-2-methyl-6-phenyl-1*H*-indol-3-ylsulfanyl)-benzoic acid (Compound 1-11); 3-(1-Benzyl-2-methyl-6-pyridin-3-yl-1*H*-indol-3-ylsulfanyl)-benzoic acid (Compound 1-12); 3-(1,6-Dibenzyl-2-methyl-1*H*-indol-3-ylsulfanyl)-benzoic acid (Compound 1-13); [3-(1-Benzyl-6-chloro-2-methyl-1*H*-indol-3-ylsulfanyl)-phenyl]-acetic acid (Compound 1-14); 3-(1-Benzyl-6-chloro-2-methyl-1*H*-indol-3-ylsulfanyl)-benzoic acid (Compound 1-15); [3-(1-Benzyl-6-chloro-2-methyl-1*H*-indol-3-yloxy)-phenyl]-acetic acid (Compound 1-16); 3-[3-(1-Benzyl-6-chloro-2-methyl-1*H*-indol-3-ylsulfanyl)-phenyl]-propionic acid (Compound 1-17); 3-[6-Chloro-1-(4-fluoro-benzyl)-2-methyl-1*H*-indol-3-ylsulfanyl]-benzoic acid (Compound 1-18); 3-[6-Chloro-2-methyl-1-(1-phenyl-ethyl)-1*H*-indol-3-ylsulfanyl]-benzoic acid (Compound 1-19); 3-(6-Chloro-2-methyl-1-naphthalen-2-ylmethyl-1*H*-indol-3-ylsulfanyl)-benzoic acid (Compound 1-20); 3-(6-Chloro-2-methyl-1-pyridin-3-ylmethyl-1*H*-indol-3-ylsulfanyl)-benzoic acid (Compound 1-21); 3-[6-Chloro-2-methyl-1-(6-trifluoromethyl-pyridin-3-ylmethyl)-1*H*-indol-3-ylsulfanyl]-benzoic acid (Compound 1-22); 3-(6-Chloro-2-methyl-1-pyridin-4-ylmethyl-1*H*-indol-3-ylsulfanyl)-benzoic acid (Compound 1-23); 3-(6-Chloro-2-methyl-1-pyridin-2-ylmethyl-1*H*-indol-3-ylsulfanyl)-benzoic acid (Compound 1-24); 3-[6-Chloro-1-(4-methoxy-3,5-dimethyl-pyridin-2-ylmethyl)-2-methyl-1*H*-indol-3-ylsulfanyl]-benzoic acid (Compound 1-25); 3-(6-Chloro-2-methyl-1-phenyl-1*H*-indol-3-ylsulfanyl)-benzoic acid (Compound 1-26); 3-(1-Biphenyl-4-yl-6-chloro-2-methyl-1*H*-indol-3-ylsulfanyl)-benzoic acid (Compound 1-27); 3-(1-Biphenyl-3-yl-6-chloro-2-methyl-1*H*-indol-3-ylsulfanyl)-benzoic acid (Compound 1-28);

3-[6-Chloro-1-(3-chloro-phenyl)-2-methyl-1*H*-indol-3-ylsulfanyl]-benzoic acid (Compound 1-29); 3-(6-Chloro-2-methyl-1-pyridin-3-yl-1*H*-indol-3-ylsulfanyl)-benzoic acid (Compound 1-30); 3-(6-Chloro-2-methyl-1-pyridin-2-yl-1*H*-indol-3-ylsulfanyl)-benzoic acid (Compound 1-31); 3-[6-Chloro-2-methyl-1-(6-trifluoromethyl-pyridin-3-yl)-1*H*-indol-3-ylsulfanyl]-benzoic acid (Compound 1-32); 3-[6-Chloro-1-(6-methoxy-pyridin-3-yl)-2-methyl-1*H*-indol-3-ylsulfanyl]-benzoic acid (Compound 1-33); 3-[6-Chloro-2-methyl-1-(6-methyl-pyridin-3-yl)-1*H*-indol-3-ylsulfanyl]-benzoic acid (Compound 1-34); [3-(6-Chloro-2-methyl-1-pyridin-3-yl-1*H*-indol-3-ylsulfanyl)-phenyl]-acetic acid (Compound 1-35); 3-[6-Chloro-1-(6-ethoxy-pyridin-3-yl)-2-methyl-1*H*-indol-3-ylsulfanyl]-benzoic acid (Compound 1-36); 3-[6-Chloro-1-(5-methoxy-pyridin-3-yl)-2-methyl-1*H*-indol-3-ylsulfanyl]-benzoic acid (Compound 1-37); 3-(6-Chloro-2-methyl-1-pyrimidin-5-yl-1*H*-indol-3-ylsulfanyl)-benzoic acid (Compound 1-38); 3-[6-Chloro-2-methyl-1-(1-methyl-1*H*-pyrazol-4-yl)-1*H*-indol-3-ylsulfanyl]-benzoic acid (Compound 1-39); 3-(6-Chloro-2-methyl-1-pyridin-3-yl-1*H*-indol-3-ylsulfanyl)-4-methoxy-benzoic acid (Compound 1-40); 3-[6-Chloro-2-methyl-1-(1-methyl-1*H*-pyrazol-4-yl)-1*H*-indol-3-ylsulfanyl]-4-methoxy-benzoic acid (Compound 1-41); 3-(6-Chloro-1-isothiazol-4-yl-2-methyl-1*H*-indol-3-ylsulfanyl)-benzoic acid (Compound 1-42); 3-[6-Chloro-1-(1-ethyl-1*H*-pyrazol-4-yl)-2-methyl-1*H*-indol-3-ylsulfanyl]-benzoic acid (Compound 1-43); 3-[6-Chloro-1-(1-isopropyl-1*H*-pyrazol-4-yl)-2-methyl-1*H*-indol-3-ylsulfanyl]-benzoic acid (Compound 1-44); {3-[6-Chloro-2-methyl-1-(1-methyl-1*H*-pyrazol-4-yl)-1*H*-indol-3-ylsulfanyl]-phenyl}-acetic acid (Compound 1-45); 3-(6-Chloro-2-methyl-1-pyridin-3-yl-1*H*-indol-3-ylsulfanyl)-5-trifluoromethyl-benzoic acid (Compound 1-46); {3-[6-Chloro-2-methyl-1-(1-methyl-1*H*-pyrazol-4-yl)-1*H*-indol-3-ylsulfanyl]-4-methoxy-phenyl}-acetic acid (Compound 1-47); {3-[6-Chloro-2-methyl-1-(5-methyl-pyridin-3-yl)-1*H*-indol-3-ylsulfanyl]-phenyl}-acetic acid (Compound 1-48); 2-[3-(6-Chloro-2-methyl-1-pyridin-3-yl-1*H*-indol-3-ylsulfanyl)-phenyl]-butyric acid (Compound 1-49); 3-[6-Chloro-2-methyl-1-(1-methyl-1*H*-pyrazol-4-yl)-1*H*-indol-3-ylsulfanyl]-4-methyl-benzoic acid (Compound 1-50); 3-Bromo-5-[6-chloro-1-(1-ethyl-1*H*-pyrazol-4-yl)-2-methyl-1*H*-indol-3-ylsulfanyl]-benzoic acid (Compound 1-51); 3-[6-Chloro-1-(1-ethyl-1*H*-pyrazol-4-yl)-2-methyl-1*H*-indol-3-ylsulfanyl]-5-methyl-benzoic acid (Compound 1-52); 3-[6-Chloro-2-methyl-1-(1-methyl-1*H*-pyrazol-4-yl)-1*H*-indol-3-ylsulfanyl]-5-trifluoromethyl-benzoic acid (Compound 1-53); 3-(6-Chloro-2-methyl-1-pyridin-3-yl-1*H*-indol-3-ylsulfanyl)-4-methyl-benzoic acid (Compound 1-54); 3-{6-Chloro-2-methyl-1-[1-(2,2,2-trifluoro-ethyl)-1*H*-pyrazol-4-yl]-1*H*-indol-3-ylsulfanyl}-benzoic acid (Compound 1-55); 3-[6-Chloro-2-methyl-1-(5-methyl-pyridin-3-yl)-1*H*-indol-3-ylsulfanyl]-benzoic acid (Compound 1-56); 3-[6-Chloro-2-methyl-1-(1-propyl-1*H*-pyrazol-4-yl)-1*H*-indol-3-ylsulfanyl]-benzoic acid (Compound 1-57); 3-[6-Chloro-2-methyl-1-(1-phenyl-1*H*-pyrazol-4-yl)-1*H*-indol-3-ylsulfanyl]-benzoic acid (Compound 1-58); 3-[1-(1-Benzyl-1*H*-pyrazol-4-yl)-6-chloro-2-methyl-1*H*-indol-3-ylsulfanyl]-benzoic acid (Compound 1-59); 3-

methyl-1*H*-indol-3-ylsulfanyl)-*N*-(2-dimethylamino-ethyl)-benzamide (Compound 2-11); 3-(6-Chloro-2-methyl-1-pyridin-3-yl-1*H*-indol-3-ylsulfanyl)-phenylboronic acid (Compound 2-12); [2-(6-Chloro-2-methyl-1*H*-indol-3-ylsulfanyl)-phenyl]-acetic acid (Compound 3-1); [4-(6-Chloro-2-methyl-1*H*-indol-3-ylsulfanyl)-phenyl]-acetic acid (Compound 3-2); [3-(5-Chloro-2-methyl-1*H*-indol-3-ylsulfanyl)-phenyl]-acetic acid (Compound 3-3); [3-(7-Chloro-2-methyl-1*H*-indol-3-ylsulfanyl)-phenyl]-acetic acid (Compound 3-4); [3-(4-Fluoro-2-methyl-1*H*-indol-3-ylsulfanyl)-phenyl]-acetic acid (Compound 3-5); [3-(4-Methoxy-2-methyl-1*H*-indol-3-ylsulfanyl)-phenyl]-acetic acid (Compound 3-6); 3-(6-Chloro-2-trifluoromethyl-1*H*-indol-3-ylsulfanyl)-benzoic acid (Compound 3-7); 3-(4-Chloro-2-methyl-1*H*-indol-3-ylsulfanyl)-phenylboronic acid (Compound 3-9); [2-(6-Chloro-1,2-dimethyl-1*H*-indol-3-ylsulfanyl)-phenyl]-acetic acid (Compound 3-10); [4-(6-Chloro-1,2-dimethyl-1*H*-indol-3-ylsulfanyl)-phenyl]-acetic acid (Compound 3-11); [3-(5-Chloro-1,2-dimethyl-1*H*-indol-3-ylsulfanyl)-phenyl]-acetic acid (Compound 3-12); 3-(1-Benzyl-6-chloro-2-trifluoromethyl-1*H*-indol-3-ylsulfanyl)-benzoic acid (Compound 3-13); 3-(1-Benzyl-6-chloro-2-ethyl-1*H*-indol-3-ylsulfanyl)-benzoic acid (Compound 3-15); 3-[6-Chloro-1-(1-ethyl-1*H*-pyrazol-4-yl)-7-fluoro-2-methyl-1*H*-indol-3-ylsulfanyl]-benzoic acid (Compound 3-16); 3-(1-Benzyl-6-chloro-1*H*-indol-3-ylsulfanyl)-benzoic acid (Compound 3-17); 3-(6-Chloro-1-pyridin-3-yl-1*H*-indol-3-ylsulfanyl)-benzoic acid (Compound 3-19); 2-[3-(6-Chloro-2-methyl-1-pyridin-3-yl-1*H*-indol-3-ylsulfanyl)-phenyl]-propionic acid (Compound 3-20); 3-[6-Chloro-1-(1-ethyl-1*H*-pyrazol-4-yl)-2,7-dimethyl-1*H*-indol-3-ylsulfanyl]-benzoic acid (Compound 3-21); 3-[6-Chloro-7-fluoro-2-methyl-1-(5-methyl-pyridin-3-yl)-1*H*-indol-3-ylsulfanyl]-benzoic acid (Compound 3-22); 3-[6-Chloro-7-fluoro-2-methyl-1-(1-phenyl-1*H*-pyrazol-4-yl)-1*H*-indol-3-ylsulfanyl]-benzoic acid (Compound 3-23); 3-[6-Chloro-7-fluoro-2-methyl-1-(1-propyl-1*H*-pyrazol-4-yl)-1*H*-indol-3-ylsulfanyl]-benzoic acid (Compound 3-24); 3-[6-Chloro-1-(5-ethyl-pyridin-3-yl)-7-fluoro-2-methyl-1*H*-indol-3-ylsulfanyl]-benzoic acid (Compound 3-25); 3-[6-Chloro-1-(1-ethyl-1*H*-pyrazol-4-yl)-5-fluoro-2-methyl-1*H*-indol-3-ylsulfanyl]-benzoic acid (Compound 3-26); 3-[6-Chloro-5-fluoro-2-methyl-1-(1-propyl-1*H*-pyrazol-4-yl)-1*H*-indol-3-ylsulfanyl]-benzoic acid (Compound 3-27); {3-[6-Chloro-1-(1-ethyl-1*H*-pyrazol-4-yl)-7-fluoro-2-methyl-1*H*-indol-3-ylsulfanyl]-phenyl}-acetic acid (Compound 3-28); *N*-{3-[6-Chloro-1-(1-ethyl-1*H*-pyrazol-4-yl)-7-fluoro-2-methyl-1*H*-indol-3-ylsulfanyl]-benzoyl}-methanesulfonamide (Compound 3-29); {4-[6-Chloro-1-(1-ethyl-1*H*-pyrazol-4-yl)-2-methyl-1*H*-indol-3-ylsulfanyl]-phenyl}-acetic acid (Compound 3-30); 3-[6-Cyano-1-(1-ethyl-1*H*-pyrazol-4-yl)-2-methyl-1*H*-indol-3-ylsulfanyl]-benzoic acid (Compound 3-31); 3-[6-Chloro-7-fluoro-2-methyl-1-(1-*p*-tolyl-1*H*-pyrazol-4-yl)-1*H*-indol-3-ylsulfanyl]-benzoic acid (Compound 3-32); 3-{6-Chloro-1-[1-(3-chloro-phenyl)-1*H*-pyrazol-4-yl]-7-fluoro-2-methyl-1*H*-indol-3-ylsulfanyl}-benzoic acid (Compound 3-33); 3-[6-Chloro-1-(1-cyclopropylmethyl-1*H*-pyrazol-4-yl)-7-fluoro-2-methyl-

INTERLOCUTORY APPLICATION

IN

THE PATENT OFFICE, AT MUMBAI

IN THE OFFICE OF CONTROLLER GENERAL PF PATENTS DESIGNS AND TRADEMARKS

IN

Patent application No. 202221034803

IN THE MATTER OF:

Maharaja Krishnakumarsinhji Bhavnagar
University, Gaurishankar Lake Road,
Bhavnagar, 364 002 ...Applicant

Versus

Mr. T. Iyer, 124, Anaikkuraipatty,
Madurai, Tamil Nadu ...Opponent

Cause Title: - Interlocutory Application

An application for a temporary injunction under Order XXXIX Rule 1 of the Civil Procedure Code, 1908

The applicant above-named states as follows:

1. That, the Plaintiff has filed the instant Interlocutory Application against the defendant of restoration of first pre grant notice u/r 55(3) received on January 30, 2023 by a first Hearing Officer Soumen Ghosh, Deputy Controller of Patents & Designs, Kolkata

2. That, the Plaintiff is a researcher working in the field of Pharmaceutical sciences and particularly the domain of "ANTIMALARIAL AGENTS".

3. That, the Plaintiff has again received a revised pre-grant notice u/r 55(3) is issued by a Second Hearing Officer Dr. Amarandra Samal, Deputy Controller of Patents & Designs on March 24, 2023 without cancelling the earlier one.

4. That, the Plaintiff is in possession of two notices u/s 55(3) which is in contradiction to the prevailing Patent act and Rules.

5. That, the Plaintiff is compelled to attend hearing notice issued by the Second Hearing Officer, without any observation from the Patent Office who is the custodian of Patent applications filed in India, as to why the First Hearing officer has been changed without ant notice to the Plaintiff.

6. That the Plaintiff, vide impugned Interlocutory Petition, wants to know the Allotment – Re-allottment policy of the Intellectual Property (IP) Applications in the Patent Office and the reasons as to why the First Hearing officer has been recused from the present proceedings without any intimation to the Plaintiff.

7. That the Plaintiff, is aware of the fact that both the first and second Hearing Officers are presently serving in the Patent Office.

8. That the Plaintiff, has noticed that applicant has filed the reply statement to the pre-grant notice on the same date (March 24, 2023) when the pre-grant notice u/r 55(3) is issued by the second Hearing Officer.

9. That the Plaintiff, with reference to aforesaid declared facts and procedural faults by reallottment of the impugned patent application to a second hearing officer, with any notice / declaration / observation to Plaintiff is extremely prejudicial and may cause injury to plaintiff.

10. That the applicant's title to the IP is in dispute, and there is also a threat of wrongful practice from the applicant, the plaintiff will have to sue for declaration of title and the consequential relief of injunction.

11. That, Irreparable damages would be caused which may lead to wrongfully grant of the IP application to great losses to public. Reinstating

the first hearing officer would cause no harm to the applicant and if not will only add to the misery of the Plaintiff.

DECLARATION

The applicant above named hereby solemnly declare that nothing material has been concealed or suppressed and all the documents are available at the Patent Office Records.

Verified at Chennai dated at 10th day of June 2023.

Iyer.T.

T Iyer

Appellant

each R^B is independently H, halogen, -CN, $-NO_2$, -OH, $-OR^9$, $-SR^9$, $-S(=O)R^9$, $-S(=O)_2R^9$, $-S(=O)_2N(R^{10})_2$, $-NR^{10}S(=O)_2R^9$, $-C(=O)R^9$, $-OC(=O)R^9$, $-CO_2R^{10}$, $-OCO_2R^9$, $-N(R^{10})_2$, $-C(=O)N(R^{10})_2$, $-OC(=O)N(R^{10})_2$, $-NHC(=O)R^9$, $-NHC(=O)OR^9$, C_1-C_6alkyl, C_1-C_6fluoroalkyl, C_1-C_6deuteroalkyl, C_1-C_6heteroalkyl, substituted or unsubstituted C_3-C_{10}cycloalkyl, substituted or unsubstituted C_2-C_{10}heterocycloalkyl, substituted or unsubstituted phenyl, C_1-C_4alkylene-(substituted or unsubstituted phenyl), substituted unsubstituted monocyclic heteroaryl, C_1-C_4alkylene-(substituted or unsubstituted monocyclic heteroaryl), a substituted or unsubstituted bicyclic heteroaryl, or C_1-C_4alkylene-(substituted or unsubstituted bicyclic heteroaryl);

n is 0, 1, or 2;

R^9 is C_1-C_6alkyl, C_1-C_6fluoroalkyl, C_1-C_6deuteroalkyl, C_3-C_6cycloalkyl, a substituted or unsubstituted phenyl,a substituted or unsubstituted monocyclic heteroaryl, or a substituted or unsubstituted bicyclic heteroaryl;

each R^{10} is independently selected from H, C_1-C_6alkyl, C_1-C_6fluoroalkyl, C_1-C_6deuteroalkyl, C_3-C_6cycloalkyl, a substituted or unsubstituted phenyl, or a substituted or unsubstituted monocyclic heteroaryl; or

two R^{10} groups attached to the same N atom are taken together with the N atom to which they are attached to form a substituted or unsubstituted heterocycle.

[0007] For any and all of the embodiments, substituents are selected from among a subset of the listed alternatives. For example, in some embodiments, X is -O-, -S-, -S(=O)-, or $-S(=O)_2$-. In other embodiments, X is -O- or -S-. In other embodiments, X is -S-, -S(=O)-, or $-S(=O)_2$-. In some embodiments, X is -S-.

[0008] In some embodiments, R^1 is -F, -Cl, -Br, -CN, vinyl, cyclopropyl, cyclobutyl, $-NH_2$, $-NH(CH_3)$, $-N(CH_3)_2$, $-O-CH_3$, or $-S-CH_3$.

[0009] In some embodiments, R^1 is vinyl, cyclopropyl, or cyclobutyl.

[0010] In some embodiments, R^1 is cyclopropyl, or cyclobutyl.

[0011] In some embodiments, R^1 is -F, -Cl, or -Br.

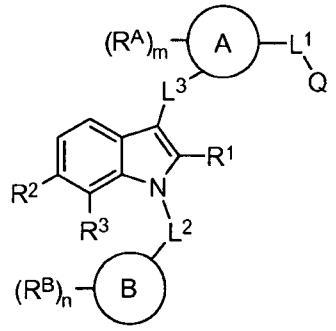
[0012] In some embodiments, L^2 is absent, or C_1-C_4alkylene; L^3 is –S-, S(=O), or $S(=O)_2$.

[0013] In some embodiments, L^2 is absent, $-CH_2$-, $-CH_2CH_2$-, $-CH_2CH_2CH_2$-, or $-CH(CH_3)$-.

[0014] In some embodiments, L^1 is absent, $-CH_2$-, $-CH_2CH_2$-, $-CH_2CH_2CH_2$-, $-CH(CH_3)$-, $-CH(CH_2CH_3)$-, $-C(CH_3)_2$- ,$-C(CH_2CH_3)_2$- , cyclopropyl-1,1-diyl, cyclobutyl-1,1-diyl, cyclopentyl-1,1-diyl or cyclohexyl-1,1-diyl; Q is $–CO_2H$, $–CO_2(C_1$-C_6alkyl), $–C(=O)NHSO_2R^9$ or tetrazolyl.

[0015] In some embodiments, L^1 is absent or $-CH_2-$; Q is $-CO_2H$, or $-CO_2(C_1-C_6alkyl)$.

[0016] In some embodiments, the compound of Formula (I) has the following structure of Formula (II):



Formula (II)

or a pharmaceutically acceptable salt, or solvate thereof.

[0017] In some embodiments, Ring A is phenyl, naphthyl, monocyclic heteroaryl containing 1-4 N atoms and 0 or 1 O or S atoms, monocyclic heteroaryl containing 0-4 N atoms and 1 O or S atoms, bicyclic heteroaryl containing 1-4 N atoms and 0 or 1 O or S atoms, or bicyclic heteroaryl containing 0-4 N atoms and 1 O or S atoms; Ring B is phenyl, naphthyl, monocyclic heteroaryl containing 1-4 N atoms and 0 or 1 O or S atoms, monocyclic heteroaryl containing 0-4 N atoms and 1 O or S atoms, bicyclic heteroaryl containing 1-4 N atoms and 0 or 1 O or S atoms, or bicyclic heteroaryl containing 0-4 N atoms and 1 O or S atoms.

[0018] In some embodiments, Ring A is phenyl, naphthyl, furanyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, pyrazolyl, triazolyl, tetrazolyl, isoxazolyl, isothiazolyl, oxadiazolyl, thiadiazolyl, pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, triazinyl, quinolinyl, isoquinolinyl, quinazolinyl, quinoxalinyl, naphthyridinyl, indolyl, indazolyl, benzoxazolyl, benzisoxazolyl, benzofuranyl, benzothienyl, benzothiazolyl, benzimidazolyl, purinyl, cinnolinyl, phthalazinyl, pteridinyl, pyridopyrimidinyl, pyrazolopyrimidinyl, or azaindolyl.

[0019] In some embodiments, Ring A is phenyl or naphthyl.

[0020] In some embodiments, Ring A is furanyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, pyrazolyl, triazolyl, tetrazolyl, isoxazolyl, isothiazolyl, oxadiazolyl, thiadiazolyl, pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, or triazinyl.

[0021] In some embodiments, Ring A is pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, or triazinyl.

[0022] In some embodiments, Ring A is furanyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, pyrazolyl, triazolyl, tetrazolyl, isoxazolyl, isothiazolyl, oxadiazolyl, or thiadiazolyl.

R^2 is H, halogen, -CN, -NO_2, -OH, -OR^9, -SR^9, -$S(=O)R^9$, -$S(=O)_2R^9$, -$S(=O)_2N(R^{10})_2$, C_1-C_4alkyl, C_1-C_4fluoroalkyl, C_1-C_4deuteroalkyl, or C_3-C_6cycloalkyl;

R^3 is H, halogen, -CN, -OH, C_1-C_4alkyl, C_1-C_4fluoroalkyl, C_1-C_4deuteroalkyl, C_1-C_4alkoxy, or C_1-C_4fluoroalkoxy;

W is CH, CF or N;

each R^A is H, halogen, -CN, -NO_2, -OH, -OR^9, -SR^9, -$S(=O)R^9$, -$S(=O)_2R^9$, -$S(=O)_2N(R^{10})_2$, C_1-C_6alkyl, or C_1-C_6fluoroalkyl;

L^1 is absent, C_1-C_6alkylene, or C_3-C_6cycloalkylene;

Q is –CO_2H, –CO_2(C_1-C_6alkyl), -OH, -CN, -$B(OH)_2$, –$C(=O)NHSO_2R^9$, –$C(=O)N(R^{10})_2$, -$SO_2NHC(=O)R^9$, -CN, tetrazolyl, -$OP(=O)(OH)_2$, -$P(=O)(OH)_2$ or carboxylic acid bioisostere;

Ring B is a monocyclic heteroaryl;

each R^B is independently H, halogen, -CN, -NO_2, -OH, -OR^9, -SR^9, -$S(=O)R^9$, -$S(=O)_2R^9$, -$S(=O)_2N(R^{10})_2$, C_1-C_6alkyl, C_1-C_6fluoroalkyl, C_1-C_6deuteroalkyl, C_1-C_6heteroalkyl, substituted or unsubstituted C_3-C_{10}cycloalkyl, substituted or unsubstituted C_2-C_{10}heterocycloalkyl, substituted or unsubstituted phenyl, C_1-C_4alkylene-(substituted or unsubstituted phenyl), substituted unsubstituted monocyclic heteroaryl, C_1-C_4alkylene-(substituted or unsubstituted monocyclic heteroaryl), a substituted or unsubstituted bicyclic heteroaryl, or C_1-C_4alkylene-(substituted or unsubstituted bicyclic heteroaryl);

n is 0, 1, or 2;

R^9 is C_1-C_6alkyl, C_1-C_6fluoroalkyl, C_1-C_6deuteroalkyl, C_3-C_6cycloalkyl, a substituted or unsubstituted phenyl, a substituted or unsubstituted monocyclic heteroaryl, or a substituted or unsubstituted bicyclic heteroaryl;

each R^{10} is independently H, C_1-C_6alkyl, C_1-C_6fluoroalkyl, C_1-C_6deuteroalkyl, C_3-C_6cycloalkyl, a substituted or unsubstituted phenyl, or a substituted or unsubstituted monocyclic heteroaryl; or

two R^{10} groups attached to the same N atom are taken together with the N atom to which they are attached to form a substituted or unsubstituted heterocycle.

[0030] In some embodiments, R^1 is -Cl, -Br, -CN, or cyclopropyl. In some embodiments, R^1 is cyclopropyl. In some embodiments, R^1 is -Cl.

[0031] In some embodiments, L^1 is absent, -CH_2-, -CH_2CH_2-, -$CH_2CH_2CH_2$-, -$CH(CH_3)$-, -$CH(CH_2CH_3)$-, -$C(CH_3)_2$- ,-$C(CH_2CH_3)_2$- , cyclopropyl-1,1-diyl, cyclobutyl-1,1-diyl,

cyclopentyl-1,1-diyl or cyclohexyl-1,1-diyl; and Q is $-CO_2H$, $-CO_2(C_1\text{-}C_6alkyl)$, $-C(=O)NHSO_2R^9$ or tetrazolyl.

[0032] In some embodiments, L^1 is absent, $-CH_2-$, $-CH(CH_3)-$, $-C(CH_3)_2-$, or cyclopropyl-1,1-diyl; and Q is $-CO_2H$, or $-CO_2(C_1\text{-}C_6alkyl)$.

[0033] In some embodiments, L^1 is absent or $-CH_2-$; and Q is $-CO_2H$, or $-CO_2(C_1\text{-}C_6alkyl)$.

[0034] In some embodiments, Ring B is monocyclic heteroaryl containing 1-4 N atoms and 0 or 1 O or S atoms, or monocyclic heteroaryl containing 0-4 N atoms and 1 O or S atoms.

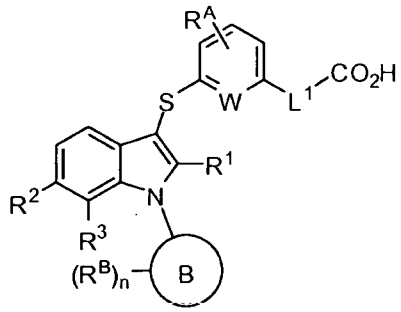
[0035] In some embodiments, Ring B is furanyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, pyrazolyl, triazolyl, tetrazolyl, isoxazolyl, isothiazolyl, oxadiazolyl, thiadiazolyl, pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, or triazinyl.

[0036] In some embodiments, each R^A is H, halogen, -CN, -OH, $-OR^9$, $-SR^9$, $C_1\text{-}C_6$alkyl, or $C_1\text{-}C_6$fluoroalkyl.

[0037] In some embodiments, L^1 is absent, $-CH_2-$, $-CH(CH_3)-$, $-C(CH_3)_2-$, or cyclopropyl-1,1-diyl; and Q is $-CO_2H$.

[0038] In some embodiments, L^1 is absent; and Q is $-CO_2H$.

[0039] In some embodiments, the compound or Formula (III) has the following structure:



or a pharmaceutically acceptable salt, or solvate thereof.

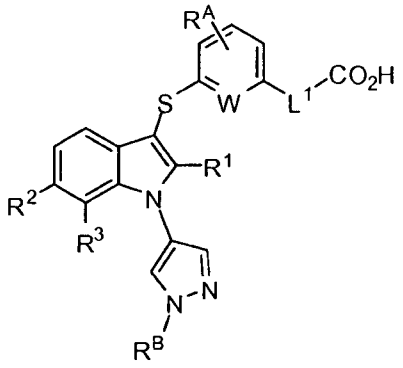
[0040] In some embodiments, R^2 is H, F, Cl, Br, I, -CN, -OH, $-CH_3$, $-CF_3$, $-CD_3$, $-OCH_3$, $-OCH_2CH_3$, $-OCF_3$, or $-OCH_2CF_3$; R^3 is H, F, Cl, Br, I, -CN, -OH, $-CH_3$, $-CF_3$, $-CD_3$, $-OCH_3$, $-OCH_2CH_3$, $-OCF_3$, or $-OCH_2CF_3$.

[0041] In some embodiments, R^2 is Cl; R^3 is H, F, or Cl.

[0042] In some embodiments, Ring B is furanyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, pyrazolyl, triazolyl, tetrazolyl, isoxazolyl, isothiazolyl, oxadiazolyl, thiadiazolyl, pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, or triazinyl.

[0043] In some embodiments, Ring B is pyrazolyl.

[0044] In some embodiments, the compound of Forumla (III) has the following structure:



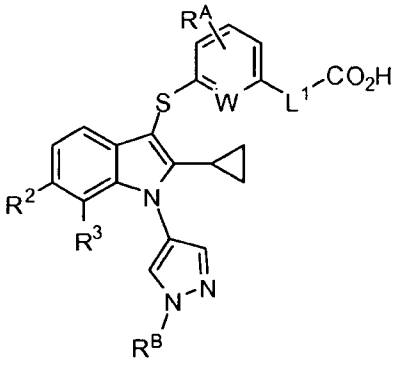
or a pharmaceutically acceptable salt, or solvate thereof.

[0045] In some embodiments, R^A is H, halogen, -CN, -OH, $-OR^9$, $-SR^9$, C_1-C_6alkyl, or C_1-C_6fluoroalkyl;

[0046] R^B is H, C_1-C_6alkyl, C_1-C_6fluoroalkyl, or C_1-C_6deuteroalkyl; R^1 is -Cl, -Br, -CN, or cyclopropyl; R^2 is H, halogen, -CN, -OH, C_1-C_4alkyl, C_1-C_4fluoroalkyl, C_1-C_4deuteroalkyl, C_1-C_4alkoxy, or C_1-C_4fluoroalkoxy; and R^3 is H, halogen, -CN, -OH, C_1-C_4alkyl, C_1-C_4fluoroalkyl, C_1-C_4deuteroalkyl, C_1-C_4alkoxy, or C_1-C_4fluoroalkoxy.

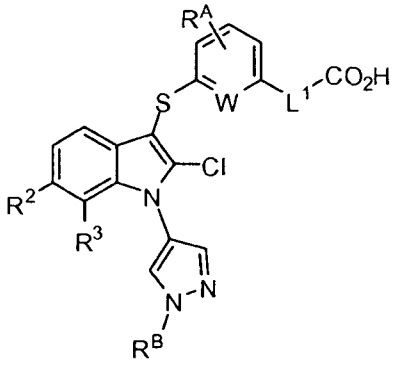
[0047] In some embodiments, R^1 is -Cl, or -Br. In some embodiments, R^1 is cyclopropyl.

[0048] In some embodiments, the compound of Formula (III) has the following structure:



or a pharmaceutically acceptable salt, or solvate thereof.

[0049] In some embodiments, the compound of Formula (III) has the following structure:



or a pharmaceutically acceptable salt, or solvate thereof.

[0050] In some embodiments, R^A is H, F, Cl, Br, I, -CN, -OH, $-OCH_3$, $-OCH_2CH_3$, $-OCF_3$, $-OCH_2CF_3$, $-CH_3$, $-CH_2CH_3$, $-CF_3$, or $-CD_3$.

[0051] In some embodiments, R^B is C_1-C_6alkyl.

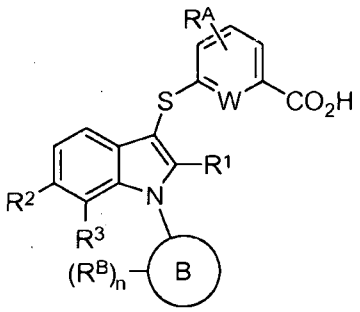
[0052] In some embodiments, R^2 is H, F, Cl, Br, I, -CN, -OH, $-CH_3$, $-CF_3$, $-CD_3$, $-OCH_3$, $-OCH_2CH_3$, $-OCF_3$, or $-OCH_2CF_3$; R^3 is H, F, Cl, Br, I, -CN, -OH, $-CH_3$, $-CF_3$, $-CD_3$, $-OCH_3$, $-OCH_2CH_3$, $-OCF_3$, or $-OCH_2CF_3$.

[0053] In some embodiments, R^2 is Cl; R^3 is H, F, or Cl.

[0054] In some embodiments, L^1 is absent, $-CH_2-$, $-CH(CH_3)-$, $-C(CH_3)_2-$, or cyclopropyl-1,1-diyl.

[0055] In some embodiments, L^1 is absent.

[0056] In some embodiments, the compound of Formula (I), Formula (II), or Formula (III) has the following structure of Formula (IV):



wherein,

W is CH, CF or N;

or a pharmaceutically acceptable salt, or solvate thereof.

[0057] In some embodiments, R^2 is H, halogen, -CN, -OH, C_1-C_4alkyl, C_1-C_4fluoroalkyl, C_1-C_4deuteroalkyl, C_1-C_4alkoxy, C_1-C_4fluoroalkoxy, or C_1-C_4hydroxyalkyl.

[0058] In some embodiments, R^2 is H, F, Cl, Br, I, -CN, -OH, $-CH_3$, $-CF_3$, $-CD_3$, $-OCH_3$, $-OCH_2CH_3$, $-OCF_3$, $-OCH_2CF_3$, or $-CH_2OH$.

[0059] In some embodiments, R^2 is Cl.

[0060] In some embodiments, R^3 is H, halogen, -CN, -OH, C_1-C_4alkyl, C_1-C_4fluoroalkyl, C_1-C_4deuteroalkyl, C_1-C_4alkoxy, C_1-C_4fluoroalkoxy, or C_1-C_4hydroxyalkyl.

[0061] In some embodiments, R^3 is H, F, Cl, Br, I, -CN, -OH, $-CH_3$, $-CF_3$, $-CD_3$, $-OCH_3$, $-OCH_2CH_3$, $-OCF_3$, $-OCH_2CF_3$, or $-CH_2OH$.

[0062] In some embodiments, R^3 is H, F, or Cl.

[0063] In some embodiments, Ring B is phenyl, naphthyl, furanyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, pyrazolyl, triazolyl, tetrazolyl, isoxazolyl, isothiazolyl, oxadiazolyl,

thiadiazolyl, pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, triazinyl, quinolinyl, isoquinolinyl, quinazolinyl, quinoxalinyl, naphthyridinyl, indolyl, indazolyl, benzoxazolyl, benzisoxazolyl, benzofuranyl, benzothienyl, benzothiazolyl, benzimidazolyl, purinyl, cinnolinyl, phthalazinyl, pteridinyl, pyridopyrimidinyl, pyrazolopyrimidinyl, or azaindolyl.

[0064] In some embodiments, Ring B is phenyl or naphthyl.

[0065] In some embodiments, Ring B is furanyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, pyrazolyl, triazolyl, tetrazolyl, isoxazolyl, isothiazolyl, oxadiazolyl, thiadiazolyl, pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, or triazinyl.

[0066] In some embodiments, Ring B is furanyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, pyrazolyl, triazolyl, tetrazolyl, isoxazolyl, isothiazolyl, oxadiazolyl, or thiadiazolyl.

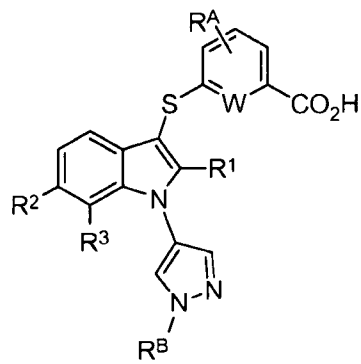
[0067] In some embodiments, Ring B is pyrazolyl.

[0068] In some embodiments, Ring B is pyrazolyl; and each R^B is independently H, C_1-C_6alkyl, C_1-C_6fluoroalkyl, or C_1-C_6deuteroalkyl; n is 1.

[0069] In some embodiments, Ring B is pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, or triazinyl.

[0070] In some embodiments, Ring B is quinolinyl, isoquinolinyl, quinazolinyl, quinoxalinyl, naphthyridinyl, indolyl, indazolyl, benzoxazolyl, benzisoxazolyl, benzofuranyl, benzothienyl, benzothiazolyl, benzimidazolyl, purinyl, cinnolinyl, phthalazinyl, pteridinyl, pyridopyrimidinyl, pyrazolopyrimidinyl, or azaindolyl.

[0071] In some embodiments, the compound of Formula (I) has the following structure of Formula (V):



Formula (V)

wherein,

W is CH, CF or N;

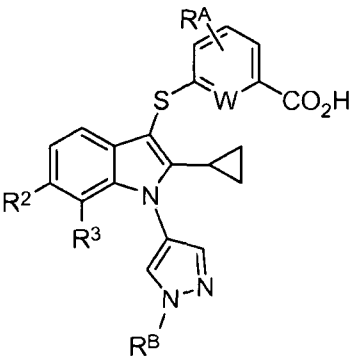
or a pharmaceutically acceptable salt, or solvate thereof.

[0072] In some embodiments, R^A is H, halogen, -CN, -OH, -OR^9, -SR^9, C_1-C_6alkyl, C_1-C_6fluoroalkyl, C_1-C_6deuteroalkyl, C_1-C_6heteroalkyl; R^B is H, C_1-C_6alkyl, C_1-C_6fluoroalkyl, or

C_1-C_6deuteroalkyl; R^1 is -F, -Cl, -Br, -CN, C_3-C_6cyloalkyl, -NH_2, or -O-C_1-C_4 alkyl; R^2 is H, halogen, -CN, -OH, C_1-C_4alkyl, C_1-C_4fluoroalkyl, C_1-C_4deuteroalkyl, C_1-C_4alkoxy, C_1-C_4fluoroalkoxy, or C_1-C_4hydroxyalkyl; R^3 is H, halogen, -CN, -OH, C_1-C_4alkyl, C_1-C_4fluoroalkyl, C_1-C_4deuteroalkyl, C_1-C_4alkoxy, C_1-C_4fluoroalkoxy, or C_1-C_4hydroxyalkyl.

[0073] In some embodiments, R^1 is -F, -Cl, -Br, -CN, cyclopropyl, -NH_2, or -O-CH_3. In some embodiments, R^1 is -F, -Cl, or -Br. In some embodiments, R^1 is C_3-C_6cyloalkyl. In some embodiments, R^1 is cyclopropyl.

[0074] In some embodiments, the compound of Formula (I) or Formula (V) has the following structure of Formula (VI):



Formula (VI)

wherein,

W is CH, CF or N;

or a pharmaceutically acceptable salt, or solvate thereof.

[0075] In some embodiments, R^A is H, F, Cl, Br, I, -CN, -OH, -OCH_3, -OCH_2CH_3, -OCF_3, -OCH_2CF_3, -CH_3, -CH_2CH_3, -CF_3, or -CD_3. In some embodiments, R^A is H.

[0076] In some embodiments, R^B is C_1-C_6alkyl. In some embodiments, R^B is -CH_3, -CH_2CH_3, or -$CH_2CH_2CH_3$, or -$CH(CH_3)_2$.

[0077] In some embodiments, R^2 is H, F, Cl, Br, I, -CN, -OH, –CH_3, –CF_3, –CD_3, –OCH_3, –OCH_2CH_3, –OCF_3, –OCH_2CF_3, or –CH_2OH. In some embodiments, R^2 is Cl.

[0078] In some embodiments, R^3 is H, F, Cl, Br, I, -CN, -OH, –CH_3, –CF_3, –CD_3, –OCH_3, –OCH_2CH_3, –OCF_3, –OCH_2CF_3, or –CH_2OH. In some embodiments, R^3 is H, F, or Cl.

[0079] In some embodiments, a compound of Formula (I), or a pharmaceutically acceptable salt, or solvate there, is:

3-((2,6-dichloro-1-(1-propyl-1H-pyrazol-4-yl)-1H-indol-3-yl)thio)benzoic acid (Compound no. 1-1);

3-((6-chloro-2-cyano-1-(1-propyl-1H-pyrazol-4-yl)-1H-indol-3-yl)thio)benzoic acid (Compound no. 1-3);

3-((6-chloro-2-cyclopropyl-1-(1-propyl-1H-pyrazol-4-yl)-1H-indol-3-yl)thio)benzoic acid (Compound no. 1-4);

3-((2,6-dichloro-7-fluoro-1-(1-propyl-1H-pyrazol-4-yl)-1H-indol-3-yl)thio)benzoic acid (Compound no. 1-7);

3-((2-bromo-6-chloro-1-(1-propyl-1*H*-pyrazol-4-yl)-1*H*-indol-3-yl)thio) benzoic acid (Compound no. 1-2);

3-((6-chloro-2-cyclopropyl-7-fluoro-1-(1-propyl-1H-pyrazol-4-yl)-1H-indol-3-yl)thio)benzoic acid (Compound no. 1-10);

3-((6-chloro-2-cyclopropyl-7-fluoro-1-(1-propyl-1H-pyrazol-4-yl)-1H-indol-3-yl)thio)-2-fluorobenzoic acid (Compound no. 1-16);

3-((2,6-dichloro-7-fluoro-1-(1-propyl-1H-pyrazol-4-yl)-1H-indol-3-yl)thio)-2-fluorobenzoic acid (Compound no. 1-13);

3-((6-Chloro-2-cyclopropyl-1-(1-ethyl-1H-pyrazol-4-yl)-7-fluoro-1H-indol-3-yl)thio)-2-fluorobenzoic acid (Compound no. 1-34);

6-((6-chloro-2-cyclopropyl-1-(1-ethyl-1H-pyrazol-4-yl)-7-fluoro-1H-indol-3-yl)thio)picolinic acid (Compound no. 1-92);

3-((6-chloro-2-cyclopropyl-7-fluoro-1-(1*H*-pyrazol-4-yl)-1*H*-indol-3-yl)thio)-2-fluorobenzoic acid (Compound no. 1-119);

3-((6-chloro-2-cyclopropyl-7-fluoro-1-(1-(2-hydroxyethyl)-1*H*-pyrazol-4-yl)-1*H*-indol-3-yl)thio)-2-fluorobenzoic acid (Compound no. 1-120);

3-((1-(1-(2-(carbamoyloxy)ethyl)-1*H*-pyrazol-4-yl)-6-chloro-2-cyclopropyl-7-fluoro-1*H*-indol-3-yl)thio)-2-fluorobenzoic acid (Compound no. 1-121);

3-((1-(1-(2-aminoethyl)-1*H*-pyrazol-4-yl)-6-chloro-2-cyclopropyl-7-fluoro-1*H*-indol-3-yl)thio)-2-fluorobenzoic acid (Compound no. 1-122);

3-((6-chloro-2-cyclopropyl-7-fluoro-1-(1-(2-ureidoethyl)-1H-pyrazol-4-yl)-1H-indol-3-yl)thio)-2-fluorobenzoic acid (Compound no. 1-123);

3-((1-(1-(3-carboxypropyl)-1H-pyrazol-4-yl)-6-chloro-2-cyclopropyl-7-fluoro-1H-indol-3-yl)thio)-2-fluorobenzoic acid (Compound no. 1-124);

3-((1-(1-(4-amino-4-oxobutyl)-1*H*-pyrazol-4-yl)-6-chloro-2-cyclopropyl-7-fluoro-1*H*-indol-3-yl)thio)-2-fluorobenzoic acid (Compound no. 1-125);

3-((2,6-dichloro-7-fluoro-1-(1-methyl-1*H*-pyrazol-4-yl)-1*H*-indol-3-yl)thio)-2-fluorobenzoic acid (Compound no. 1-49);

3-((6-chloro-2-cyclopropyl-7-fluoro-1-(1-(2,2,2-trifluoroethyl)-1*H*-pyrazol-4-yl)-1*H*-indol-3-yl)thio)-2-fluorobenzoic acid (Compound no. 1-126);

3-((6-chloro-2-cyclopropyl-1-(1-(ethyl-d_5)-1*H*-pyrazol-4-yl)-7-fluoro-1*H*-indol-3-yl)thio)-2-fluorobenzoic acid (Compound no. 1-127);

3-((2,6-dichloro-1-(1-ethyl-1H-pyrazol-4-yl)-7-fluoro-1H-indol-3-yl)thio)-2-fluorobenzoic acid (Compound no. 1-31);

3-((2,6-dichloro-7-fluoro-1-(pyridin-3-yl)-1*H*-indol-3-yl)thio)-2-fluorobenzoic acid (Compound no. 2-1);

3-((2-bromo-6-chloro-7-fluoro-1-(pyridin-3-yl)-1*H*-indol-3-yl)thio)-2-fluorobenzoic acid (Compound no. 2-2);

3-((6-chloro-2-cyclopropyl-7-fluoro-1-(pyridin-3-yl)-1*H*-indol-3-yl)thio)-2-fluorobenzoic acid (Compound no. 2-3);

3-((1-(1-(6-aminoethyl)-1*H*-pyrazol-4-yl)-6-chloro-2-cyclopropyl-7-fluoro-1*H*-indol-3-yl)thio)-2-fluorobenzoic acid (Compound no. 1-128);

3-((6-chloro-2-cyclopropyl-7-fluoro-1-(1-(hex-5-yn-1-yl)-1H-pyrazol-4-yl)-1H-indol-3-yl)thio)-2-fluorobenzoic acid (Compound no. 1-129);

3-((1-(1-(3-hydroxy-2,2-dimethylpropyl)-1*H*-pyrazol-4-yl)-6-chloro-2-cyclopropyl-7-fluoro-1*H*-indol-3-yl)thio)-2-fluorobenzoic acid (Compound no. 1-130); or

3-((6-chloro-2-cyclopropyl-1-(1-(6-(3-(3',6'-dihydroxy-3-oxo-3H-spiro[isobenzofuran-1,9'-xanthen]-5-yl)ureido)hexyl)-1H-pyrazol-4-yl)-7-fluoro-1H-indol-3-yl)thio)-2-fluorobenzoic acid (Compound 1-131).

[0080] Any combination of the groups described above for the various variables is contemplated herein. Throughout the specification, groups and substituents thereof are chosen by one skilled in the field to provide stable moieties and compounds.

[0081] In one aspect, described herein is a pharmaceutical composition comprising a compound described herein, or a pharmaceutically acceptable salt, or solvate thereof, and at least one pharmaceutically acceptable excipient. In some embodiments, the pharmaceutical composition is formulated for administration to a mammal by intravenous administration, subcutaneous administration, oral administration, inhalation, nasal administration, dermal administration, or ophthalmic administration. In some embodiments, the pharmaceutical composition is in the form of a tablet, a pill, a capsule, a liquid, a suspension, a gel, a dispersion, a solution, an emulsion, an ointment, or a lotion.

[0082] In one aspect, described herein is a method of treating or preventing any one of the diseases or conditions described herein comprising administering a therapeutically effective amount of a compound described herein, or a pharmaceutically acceptable salt, or solvate thereof, to a mammal in need thereof.

agent in addition to the administration of a compound described herein, or a pharmaceutically acceptable salt thereof. In various embodiments, each agent is administered in any order, including simultaneously.

[0089] In any of the embodiments disclosed herein, the mammal is a human.

[0090] In some embodiments, compounds provided herein are administered to a human.

[0091] In some embodiments, compounds provided herein are orally administered.

[0092] Articles of manufacture, which include packaging material, a compound described herein, or a pharmaceutically acceptable salt thereof, within the packaging material, and a label that indicates that the compound or composition, or pharmaceutically acceptable salt, tautomers, pharmaceutically acceptable N-oxide, pharmaceutically active metabolite, pharmaceutically acceptable prodrug, or pharmaceutically acceptable solvate thereof, is used for inhibiting the activity of autotaxin, or for the treatment, prevention or amelioration of one or more symptoms of a disease or condition that would benefit from inhibition of the activity of autotaxin, are provided.

[0093] Other objects, features and advantages of the compounds, methods and compositions described herein will become apparent from the following detailed description. It should be understood, however, that the detailed description and the specific examples, while indicating specific embodiments, are given by way of illustration only, since various changes and modifications within the spirit and scope of the instant disclosure will become apparent to those skilled in the art from this detailed description.

DETAILED DESCRIPTION OF THE INVENTION

Autotaxin and LPA

[0094] Autotaxin (ATX, NPP2, or E-NPP2), an approximately 120 kDa glycoprotein, is a secreted nucleotide pyrophosphatase/phosphodiesterase (NPP) with lysophospholipase D activity that converts extracellular lysophosphatidylcholine (LPC) and other lysophospholipids to lysophosphatidic acid (LPA). ATX is considered to be responsible for the majority of circulating LPA production.

[0095] LPA acts through sets of specific G protein-coupled receptors (GPCRs), such as LPA1, LPA2, LPA3, LPA4, LPA5, LPA6, LPA7, LPA8, in an autocrine and paracrine fashion to produce a variety of biological responses. For example, lysophospholipids, such as lysophosphatidic acid (LPA), are known to affect such biological functions as cellular proliferation, differentiation, survival, migration, adhesion, invasion, and morphogenesis. In

addition, LPA is known to play a role in such processes as platelet activation, smooth muscle contraction, actin stress fiber formation, and cell migration.

[0096] ATX and LPA have been detected in various biological fluids such as serum, plasma, cerebrospinal fluid, seminal fluid, urine, and saliva, both in animals and humans, suggesting that they are potential biomarkers to predict certain diseases. For example, serum ATX concentration and activity is elevated in patients with chronic liver diseases and in pregnant women. In addition, ATX concentration has been found to be lower in postoperative cancer patients as a result of postoperative damage or poor nutritional state. In addition, ATX is known to be essential for normal development. For example, ATX-deficient mice die at embryonic day 9.5 with profound vascular defects in both the yolk sac and the embryo. Furthermore, at embryonic day 8.5 ATX-deficient embryos were found to have malformed allantois, neural tube defects, and asymmetric headfolds.

Cancer

[0097] ATX has been demonstrated to increase cell motility, neovascularization, proliferation and aggressiveness of tumors. It is upregulated in numerous tumor lineages, such as breast, renal, liver, glioblastoma, ovarian and prostate cancer.

[0098] In some embodiments, disclosed herein are methods of treating cancer with a compound disclosed herein.

[0099] ATX is a prometastatic enzyme initially isolated from the conditioned medium of human melanoma cells. In addition, ATX overexpression is frequently observed in malignant tumor tissues such as breast cancer, renal cancer, Hodgkin lymphoma, hepatocellular carcinoma, pancreatic cancer and glioblastoma. LPA also contributes to tumorigenesis by increasing motility and invasiveness of cells.

[00100] The term "cancer" as used herein, refers to an abnormal growth of cells that tend to proliferate in an uncontrolled way and, in some cases, to metastasize (spread). Types of cancer include, but are not limited to, solid tumors (such as those of the bladder, bowel, brain, breast, endometrium, heart, kidney, lung, liver, uterus, lymphatic tissue (lymphoma), ovary, pancreas or other endocrine organ (thyroid), prostate, skin (melanoma or basal cell cancer) or hematological tumors (such as the leukemias and lymphomas) at any stage of the disease with or without metastases.

Fibrosis

[00101] In some embodiments, disclosed herein are methods of treating fibrosis with a compound disclosed herein.

[00102] "Fibrosis," as used herein, refers to the accumulation of extracellular matrix constituents that occurs following trauma, inflammation, tissue repair, immunological reactions, cellular hyperplasia, and neoplasia.

[00103] In some embodiments, disclosed herein is a method of reducing fibrosis in a tissue comprising contacting a fibrotic cell or tissue with a compound disclosed herein, in an amount sufficient to decrease or inhibit the fibrosis. In some embodiments, the fibrosis includes a fibrotic condition.

[00104] In some embodiments, reducing fibrosis, or treatment of a fibrotic condition, includes reducing or inhibiting one or more of: formation or deposition of extracellular matrix proteins; the number of pro-fibrotic cell types (e.g., fibroblast or immune cell numbers); cellular collagen or hydroxyproline content within a fibrotic lesion; expression or activity of a fibrogenic protein; or reducing fibrosis associated with an inflammatory response.

[00105] In some embodiments, the fibrotic condition is primary fibrosis. In some embodiments, the fibrotic condition is idiopathic. In some embodiments, the fibrotic condition is associated with (e.g., is secondary to) a disease; a toxin; an insult (e.g., an environmental hazard); a medical treatment, or a combination thereof.

[00106] In some embodiments, the fibrotic condition is a fibrotic condition of the lung (pulmonary fibrosis), a fibrotic condition of the liver (renal fibrosis), a fibrotic condition of the heart or vasculature (cardiac fibrosis), a fibrotic condition of the kidney (renal fibrosis), a fibrotic condition of the skin, a fibrotic condition of the gastrointestinal tract, or a combination thereof.

[00107] In some embodiments, the fibrotic condition is a fibrotic condition of the lung. In some embodiments, the fibrotic condition of the lung is chosen from one or more of: pulmonary fibrosis, idiopathic pulmonary fibrosis (IPF), usual interstitial pneumonitis (UIP), interstitial lung disease, cryptogenic fibrosing alveolitis (CFA), bronchiolitis obliterans, or bronchiectasis. In some embodiments, the fibrotic condition of the lung treated with the methods of the invention is associated with (e.g., secondary to) a cancer treatment.

[00108] In some embodiments, the fibrotic condition is a fibrotic condition of the liver.

[00109] In some embodiments, the fibrotic condition is a fibrotic condition of the heart.

[00110] In some embodiments, the fibrotic condition is a fibrotic condition of the kidney.

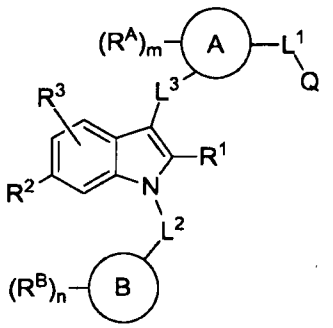
[00111] In some embodiments, the fibrotic condition is a fibrotic condition of the skin.

[00112] In some embodiments, the fibrotic condition is a fibrotic condition of the gastrointestinal tract.

Compounds

[00113] Compounds described herein, including pharmaceutically acceptable salts, prodrugs, active metabolites and pharmaceutically acceptable solvates thereof, are autotaxin inhibitors.

[00114] In one aspect, described herein is a compound of Formula (I), or a pharmaceutically acceptable salt, or solvate thereof:



Formula (I)

wherein,

R^1 is -F, -Cl, -Br, -CN, vinyl, C_3-C_6cyloalkyl, $-NH_2$, $-NH(C_1$-C_4 alkyl), $-N(C_1$-C_4 alkyl$)_2$, -O-C_1-C_4 alkyl, or -S-C_1-C_4 alkyl;

R^2 is H, halogen, -CN, $-NO_2$, -OH, $-OR^9$, $-SR^9$, $-S(=O)R^9$, $-S(=O)_2R^9$, $-S(=O)_2N(R^{10})_2$, $-NR^{10}S(=O)_2R^9$, $-C(=O)R^9$, $-OC(=O)R^9$, $-CO_2R^{10}$, $-OCO_2R^9$, $-N(R^{10})_2$, $-C(=O)N(R^{10})_2$, $-OC(=O)N(R^{10})_2$, $-NHC(=O)R^9$, $-NHC(=O)OR^9$, C_1-C_4alkyl, C_1-C_4fluoroalkyl, C_1-C_4deuteroalkyl, C_1-C_4hydroxyalkyl, C_1-C_4heteroalkyl, C_3-C_6cycloalkyl, substituted or unsubstituted phenyl, or substituted or unsubstituted monocyclic heteroaryl;

Ring A is a monocyclic aryl, bicyclic aryl, monocyclic heterocycloalkyl, monocyclic heteroaryl or bicyclic heteroaryl;

each R^A is H, halogen, -CN, $-NO_2$, -OH, $-OR^9$, $-SR^9$, $-S(=O)R^9$, $-S(=O)_2R^9$, $-S(=O)_2N(R^{10})_2$, $-NR^{10}S(=O)_2R^9$, $-C(=O)R^9$, $-OC(=O)R^9$, $-CO_2R^{10}$, $-OCO_2R^9$, $-N(R^{10})_2$, $-C(=O)N(R^{10})_2$, $-OC(=O)N(R^{10})_2$, $-NHC(=O)R^9$, $-NHC(=O)OR^9$, C_1-C_6alkyl, C_1-C_6fluoroalkyl, C_1-C_6deuteroalkyl, C_1-C_6heteroalkyl, substituted or unsubstituted C_3-C_{10}cycloalkyl, substituted or unsubstituted C_2-C_{10}heterocycloalkyl, substituted or unsubstituted phenyl, or substituted or unsubstituted monocyclic heteroaryl;

m is 0, 1, or 2;

L^1 is absent, C_1-C_6alkylene, C_1-C_6fluoroalkylene, or C_3-C_6cycloalkylene;

Q is $-CO_2H$, $-CO_2(C_1$-C_6alkyl), -OH, -CN, $-B(OH)_2$, $-C(=O)NHSO_2R^9$, $-C(=O)N(R^{10})_2$, $-SO_2NHC(=O)R^9$, -CN, tetrazolyl, $-OP(=O)(OH)_2$, $-P(=O)(OH)_2$ or carboxylic acid bioisostere;

L^2 is absent, C_1-C_4alkylene, or C_3-C_7cycloalkylene;

L^3 is –S-, S(=O), $S(=O)_2$, or -O-;

Ring B is a monocyclic aryl, bicyclic aryl, monocyclic heteroaryl or bicyclic heteroaryl;

each R^B is independently H, halogen, -CN, $-NO_2$, -OH, $-OR^9$, $-SR^9$, $-S(=O)R^9$, $-S(=O)_2R^9$, $-S(=O)_2N(R^{10})_2$, $-NR^{10}S(=O)_2R^9$, $-C(=O)R^9$, $-OC(=O)R^9$, $-CO_2R^{10}$, $-OCO_2R^9$, $-N(R^{10})_2$, $-C(=O)N(R^{10})_2$, $-OC(=O)N(R^{10})_2$, $-NHC(=O)R^9$, $-NHC(=O)OR^9$, C_1-C_6alkyl, C_1-C_6fluoroalkyl, C_1-C_6deuteroalkyl, C_1-C_6heteroalkyl, substituted or unsubstituted C_3-C_{10}cycloalkyl, substituted or unsubstituted C_2-C_{10}heterocycloalkyl, substituted or unsubstituted phenyl, C_1-C_4alkylene-(substituted or unsubstituted phenyl), substituted unsubstituted monocyclic heteroaryl, C_1-C_4alkylene-(substituted or unsubstituted monocyclic heteroaryl), a substituted or unsubstituted bicyclic heteroaryl, or C_1-C_4alkylene-(substituted or unsubstituted bicyclic heteroaryl);

n is 0, 1, or 2;

R^9 is C_1-C_6alkyl, C_1-C_6fluoroalkyl, C_1-C_6deuteroalkyl, C_3-C_6cycloalkyl, a substituted or unsubstituted phenyl,a substituted or unsubstituted monocyclic heteroaryl, or a substituted or unsubstituted bicyclic heteroaryl;

each R^{10} is independently selected from H, C_1-C_6alkyl, C_1-C_6fluoroalkyl, C_1-C_6deuteroalkyl, C_3-C_6cycloalkyl, a substituted or unsubstituted phenyl, or a substituted or unsubstituted monocyclic heteroaryl; or

two R^{10} groups attached to the same N atom are taken together with the N atom to which they are attached to form a substituted or unsubstituted heterocycle.

[00115] For any and all of the embodiments, substituents are selected from among a subset of the listed alternatives. For example, in some embodiments, X is -O-, -S-, -S(=O)-, or $-S(=O)_2$-. In other embodiments, X is -O- or -S-. In other embodiments, X is -S-, -S(=O)-, or $-S(=O)_2$-. In some embodiments, X is -S-.

[00116] In some embodiments, R^1 is -F, -Cl, -Br, -CN, vinyl, cyclopropyl, cyclobutyl, $-NH_2$, $-NH(CH_3)$, $-N(CH_3)_2$, $-O-CH_3$, or $-S-CH_3$.

[00117] In some embodiments, R^1 is vinyl, cyclopropyl, or cyclobutyl.

[00118] In some embodiments, R^1 is cyclopropyl, or cyclobutyl.

[00119] In some embodiments, R^1 is -F, -Cl, or -Br.

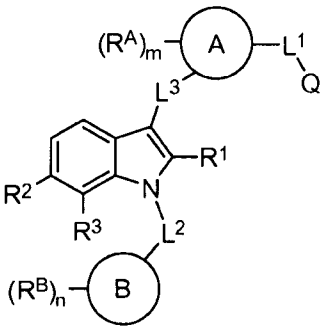
[00120] In some embodiments, L^2 is absent, or C_1-C_4alkylene; L^3 is –S-, S(=O), or $S(=O)_2$.

[00121] In some embodiments, L^2 is absent, $-CH_2-$, $-CH_2CH_2-$, $-CH_2CH_2CH_2-$, or $-CH(CH_3)-$.

[00122] In some embodiments, L^1 is absent, $-CH_2-$, $-CH_2CH_2-$, $-CH_2CH_2CH_2-$, $-CH(CH_3)-$, $-CH(CH_2CH_3)-$, $-C(CH_3)_2-$,$-C(CH_2CH_3)_2-$, cyclopropyl-1,1-diyl, cyclobutyl-1,1-diyl, cyclopentyl-1,1-diyl or cyclohexyl-1,1-diyl; Q is $–CO_2H$, $–CO_2(C_1$-C_6alkyl), $–C(=O)NHSO_2R^9$ or tetrazolyl.

[00123] In some embodiments, L^1 is absent or $-CH_2-$; Q is $–CO_2H$, or $–CO_2(C_1$-C_6alkyl).

[00124] In some embodiments, the compound of Formula (I) has the following structure of Formula (II):



Formula (II)

or a pharmaceutically acceptable salt, or solvate thereof.

[00125] In some embodiments, Ring A is phenyl, naphthyl, monocyclic heteroaryl containing 1-4 N atoms and 0 or 1 O or S atoms, monocyclic heteroaryl containing 0-4 N atoms and 1 O or S atoms, bicyclic heteroaryl containing 1-4 N atoms and 0 or 1 O or S atoms, or bicyclic heteroaryl containing 0-4 N atoms and 1 O or S atoms; Ring B is phenyl, naphthyl, monocyclic heteroaryl containing 1-4 N atoms and 0 or 1 O or S atoms, monocyclic heteroaryl containing 0-4 N atoms and 1 O or S atoms, bicyclic heteroaryl containing 1-4 N atoms and 0 or 1 O or S atoms, or bicyclic heteroaryl containing 0-4 N atoms and 1 O or S atoms.

[00126] In some embodiments, Ring A is phenyl, naphthyl, furanyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, pyrazolyl, triazolyl, tetrazolyl, isoxazolyl, isothiazolyl, oxadiazolyl, thiadiazolyl, pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, triazinyl, quinolinyl, isoquinolinyl, quinazolinyl, quinoxalinyl, naphthyridinyl, indolyl, indazolyl, benzoxazolyl, benzisoxazolyl, benzofuranyl, benzothienyl, benzothiazolyl, benzimidazolyl, purinyl, cinnolinyl, phthalazinyl, pteridinyl, pyridopyrimidinyl, pyrazolopyrimidinyl, or azaindolyl.

[00127] In some embodiments, Ring A is phenyl or naphthyl.

[00128] In some embodiments, Ring A is furanyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, pyrazolyl, triazolyl, tetrazolyl, isoxazolyl, isothiazolyl, oxadiazolyl, thiadiazolyl, pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, or triazinyl.

[00129] In some embodiments, Ring A is pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, or triazinyl.

[00130] In some embodiments, Ring A is furanyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, pyrazolyl, triazolyl, tetrazolyl, isoxazolyl, isothiazolyl, oxadiazolyl, or thiadiazolyl.

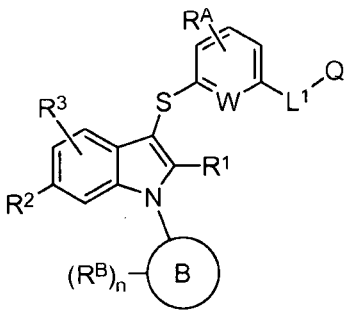
[00131] In some embodiments, Ring A is quinolinyl, isoquinolinyl, quinazolinyl, quinoxalinyl, naphthyridinyl, indolyl, indazolyl, benzoxazolyl, benzisoxazolyl, benzofuranyl, benzothienyl, benzothiazolyl, benzimidazolyl, purinyl, cinnolinyl, phthalazinyl, pteridinyl, pyridopyrimidinyl, pyrazolopyrimidinyl, or azaindolyl.

[00132] In some embodiments, each R^A is H, halogen, -CN, -OH, $-OR^9$, $-SR^9$, C_1-C_6alkyl, C_1-C_6fluoroalkyl, C_1-C_6deuteroalkyl, C_1-C_6heteroalkyl.

[00133] In some embodiments, L^3 is –S-.

[00134] In some embodiments, L^2 is absent.

[00135] In some embodiments, the compound of Formula (I) or Formula (II) has the following structure of Formula (III):



Formula (III)

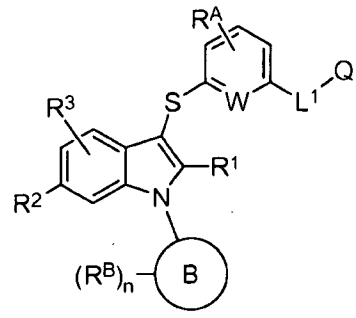
wherein,

W is CH, CF or N;

or a pharmaceutically acceptable salt, or solvate thereof.

[00136] In some embodiments, L^1 is absent; and Q is $–CO_2H$.

[00137] In some embodiments, described herein is a compound of Formula (III), or a pharmaceutically acceptable salt, or solvate thereof:



Formula (III)

wherein,

R^1 is -Cl, -Br, -CN, or C_3-C_6cyloalkyl;

R^2 is H, halogen, -CN, -NO_2, -OH, -OR^9, -SR^9, -S(=O)R^9, -$S(=O)_2R^9$, -$S(=O)_2N(R^{10})_2$, C_1-C_4alkyl, C_1-C_4fluoroalkyl, C_1-C_4deuteroalkyl, or C_3-C_6cycloalkyl;

R^3 is H, halogen, -CN, -OH, C_1-C_4alkyl, C_1-C_4fluoroalkyl, C_1-C_4deuteroalkyl, C_1-C_4alkoxy, or C_1-C_4fluoroalkoxy;

W is CH, CF or N;

each R^A is H, halogen, -CN, -NO_2, -OH, -OR^9, -SR^9, -S(=O)R^9, -$S(=O)_2R^9$, -$S(=O)_2N(R^{10})_2$, C_1-C_6alkyl, or C_1-C_6fluoroalkyl;

L^1 is absent, C_1-C_6alkylene, or C_3-C_6cycloalkylene;

Q is –CO_2H, –CO_2(C_1-C_6alkyl), -OH, -CN, -$B(OH)_2$, –C(=O)NHSO_2R^9, –C(=O)$N(R^{10})_2$, -$SO_2NHC(=O)R^9$, -CN, tetrazolyl, -OP(=O)$(OH)_2$, -P(=O)$(OH)_2$ or carboxylic acid bioisostere;

Ring B is a monocyclic heteroaryl;

each R^B is independently H, halogen, -CN, -NO_2, -OH, -OR^9, -SR^9, -S(=O)R^9, -$S(=O)_2R^9$, -$S(=O)_2N(R^{10})_2$, C_1-C_6alkyl, C_1-C_6fluoroalkyl, C_1-C_6deuteroalkyl, C_1-C_6heteroalkyl, substituted or unsubstituted C_3-C_{10}cycloalkyl, substituted or unsubstituted C_2-C_{10}heterocycloalkyl, substituted or unsubstituted phenyl, C_1-C_4alkylene-(substituted or unsubstituted phenyl), substituted unsubstituted monocyclic heteroaryl, C_1-C_4alkylene-(substituted or unsubstituted monocyclic heteroaryl), a substituted or unsubstituted bicyclic heteroaryl, or C_1-C_4alkylene-(substituted or unsubstituted bicyclic heteroaryl);

n is 0, 1, or 2;

R^9 is C_1-C_6alkyl, C_1-C_6fluoroalkyl, C_1-C_6deuteroalkyl, C_3-C_6cycloalkyl, a substituted or unsubstituted phenyl, a substituted or unsubstituted monocyclic heteroaryl, or a substituted or unsubstituted bicyclic heteroaryl;

each R^{10} is independently H, C_1-C_6alkyl, C_1-C_6fluoroalkyl, C_1-C_6deuteroalkyl, C_3-C_6cycloalkyl, a substituted or unsubstituted phenyl, or a substituted or unsubstituted monocyclic heteroaryl; or

two R^{10} groups attached to the same N atom are taken together with the N atom to which they are attached to form a substituted or unsubstituted heterocycle.

[00138] In some embodiments, R^1 is -Cl, -Br, -CN, or cyclopropyl. In some embodiments, R^1 is cyclopropyl. In some embodiments, R^1 is -Cl.

[00139] In some embodiments, L^1 is absent, $-CH_2-$, $-CH_2CH_2-$, $-CH_2CH_2CH_2-$, $-CH(CH_3)-$, $-CH(CH_2CH_3)-$, $-C(CH_3)_2-$,$-C(CH_2CH_3)_2-$, cyclopropyl-1,1-diyl, cyclobutyl-1,1-diyl, cyclopentyl-1,1-diyl or cyclohexyl-1,1-diyl; and Q is $-CO_2H$, $-CO_2(C_1$-C_6alkyl), $-C(=O)NHSO_2R^9$ or tetrazolyl.

[00140] In some embodiments, L^1 is absent, $-CH_2-$, $-CH(CH_3)-$, $-C(CH_3)_2-$, or cyclopropyl-1,1-diyl; and Q is $-CO_2H$, or $-CO_2(C_1$-C_6alkyl).

[00141] In some embodiments, L^1 is absent, $-CH_2-$, $-CH_2CH_2-$, $-CH_2CH_2CH_2-$, $-CH(CH_3)-$, $-CH(CH_2CH_3)-$, $-C(CH_3)_2-$, or $-C(CH_2CH_3)_2-$. In some embodiments, L^1 is absent, $-CH_2-$, $-CH(CH_3)-$, $-CH(CH_2CH_3)-$, $-C(CH_3)_2-$, or $-C(CH_2CH_3)_2-$. In some embodiments, L^1 is absent, $-CH_2-$, $-CH(CH_3)-$, or $-C(CH_3)_2-$. In some embodiments, L^1 is absent, or $-CH_2-$.

[00142] In some embodiments, L^1 is $-CH_2-$, $-CH_2CH_2-$, $-CH_2CH_2CH_2-$, $-CH(CH_3)-$, $-CH(CH_2CH_3)-$, $-C(CH_3)_2-$, or $-C(CH_2CH_3)_2-$. In some embodiments, L^1 is $-CH_2-$, $-CH(CH_3)-$, $-CH(CH_2CH_3)-$, $-C(CH_3)_2-$, or $-C(CH_2CH_3)_2-$. In some embodiments, L^1 is $-CH_2-$, $-CH(CH_3)-$, or $-C(CH_3)_2-$. In some embodiments, L^1 is $-CH_2-$.

[00143] In some embodiments, L^1 is absent or $-CH_2-$; and Q is $-CO_2H$, or $-CO_2(C_1$-C_6alkyl).

[00144] In some embodiments, Ring B is monocyclic heteroaryl containing 1-4 N atoms and 0 or 1 O or S atoms, or monocyclic heteroaryl containing 0-4 N atoms and 1 O or S atoms.

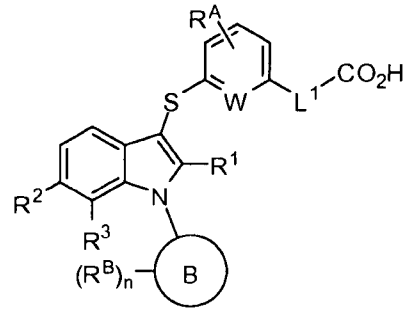
[00145] In some embodiments, Ring B is furanyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, pyrazolyl, triazolyl, tetrazolyl, isoxazolyl, isothiazolyl, oxadiazolyl, thiadiazolyl, pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, or triazinyl.

[00146] In some embodiments, each R^A is H, halogen, -CN, -OH, $-OR^9$, $-SR^9$, C_1-C_6alkyl, or C_1-C_6fluoroalkyl.

[00147] In some embodiments, L^1 is absent, $-CH_2-$, $-CH(CH_3)-$, $-C(CH_3)_2-$, or cyclopropyl-1,1-diyl; and Q is $-CO_2H$.

[00148] In some embodiments, L^1 is absent; and Q is $-CO_2H$.

[00149] In some embodiments, the compound or Formula (III) has the following structure:



or a pharmaceutically acceptable salt, or solvate thereof.

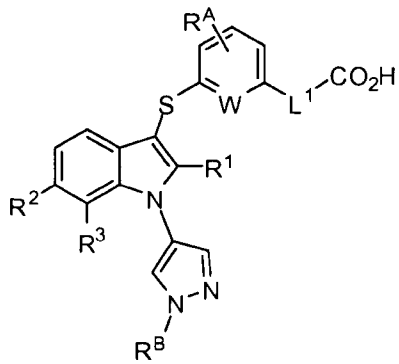
[00150] In some embodiments, R^2 is H, F, Cl, Br, I, -CN, -OH, $-CH_3$, $-CF_3$, $-CD_3$, $-OCH_3$, $-OCH_2CH_3$, $-OCF_3$, or $-OCH_2CF_3$; R^3 is H, F, Cl, Br, I, -CN, -OH, $-CH_3$, $-CF_3$, $-CD_3$, $-OCH_3$, $-OCH_2CH_3$, $-OCF_3$, or $-OCH_2CF_3$.

[00151] In some embodiments, R^2 is Cl; R^3 is H, F, or Cl.

[00152] In some embodiments, Ring B is furanyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, pyrazolyl, triazolyl, tetrazolyl, isoxazolyl, isothiazolyl, oxadiazolyl, thiadiazolyl, pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, or triazinyl.

[00153] In some embodiments, Ring B is pyrazolyl.

[00154] In some embodiments, the compound of Forumla (III) has the following structure:



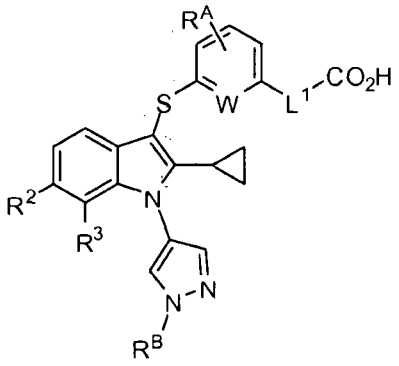
or a pharmaceutically acceptable salt, or solvate thereof.

[00155] In some embodiments, R^A is H, halogen, -CN, -OH, $-OR^9$, $-SR^9$, C_1-C_6alkyl, or C_1-C_6fluoroalkyl;

[00156] R^B is H, C_1-C_6alkyl, C_1-C_6fluoroalkyl, or C_1-C_6deuteroalkyl; R^1 is -Cl, -Br, -CN, or cyclopropyl; R^2 is H, halogen, -CN, -OH, C_1-C_4alkyl, C_1-C_4fluoroalkyl, C_1-C_4deuteroalkyl, C_1-C_4alkoxy, or C_1-C_4fluoroalkoxy; and R^3 is H, halogen, -CN, -OH, C_1-C_4alkyl, C_1-C_4fluoroalkyl, C_1-C_4deuteroalkyl, C_1-C_4alkoxy, or C_1-C_4fluoroalkoxy.

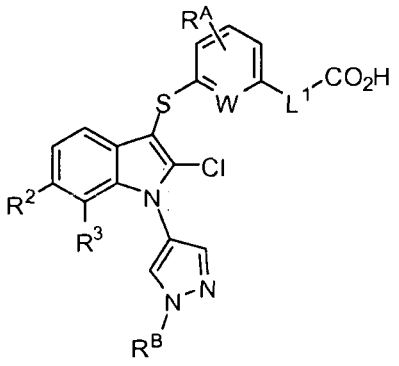
[00157] In some embodiments, R^1 is -Cl, or -Br. In some embodiments, R^1 is cyclopropyl.

[00158] In some embodiments, the compound of Formula (III) has the following structure:



or a pharmaceutically acceptable salt, or solvate thereof.

[00159] In some embodiments, the compound of Formula (III) has the following structure:



or a pharmaceutically acceptable salt, or solvate thereof.

[00160] In some embodiments, R^A is H, F, Cl, Br, I, -CN, -OH, $-OCH_3$, $-OCH_2CH_3$, $-OCF_3$, $-OCH_2CF_3$, $-CH_3$, $-CH_2CH_3$, $-CF_3$, or $-CD_3$.

[00161] In some embodiments, R^B is C_1-C_6alkyl.

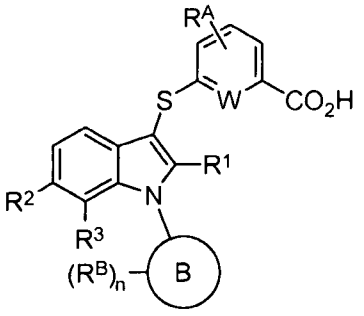
[00162] In some embodiments, R^2 is H, F, Cl, Br, I, -CN, -OH, $-CH_3$, $-CF_3$, $-CD_3$, $-OCH_3$, $-OCH_2CH_3$, $-OCF_3$, or $-OCH_2CF_3$; R^3 is H, F, Cl, Br, I, -CN, -OH, $-CH_3$, $-CF_3$, $-CD_3$, $-OCH_3$, $-OCH_2CH_3$, $-OCF_3$, or $-OCH_2CF_3$.

[00163] In some embodiments, R^2 is Cl; R^3 is H, F, or Cl.

[00164] In some embodiments, L^1 is absent, $-CH_2-$, $-CH(CH_3)-$, $-C(CH_3)_2-$, or cyclopropyl-1,1-diyl.

[00165] In some embodiments, L^1 is absent.

[00166] In some embodiments, the compound of Formula (I), Formula (II), or Formula (III) has the following structure of Formula (IV):



wherein,

W is CH, CF or N;

or a pharmaceutically acceptable salt, or solvate thereof.

[00167] In some embodiments, R^2 is H, halogen, -CN, -OH, C_1-C_4alkyl, C_1-C_4fluoroalkyl, C_1-C_4deuteroalkyl, C_1-C_4alkoxy, C_1-C_4fluoroalkoxy, or C_1-C_4hydroxyalkyl.

[00168] In some embodiments, R^2 is H, F, Cl, Br, I, -CN, -OH, $-CH_3$, $-CF_3$, $-CD_3$, $-OCH_3$, $-OCH_2CH_3$, $-OCF_3$, $-OCH_2CF_3$, or $-CH_2OH$.

[00169] In some embodiments, R^2 is Cl.

[00170] In some embodiments, R^3 is H, halogen, -CN, -OH, C_1-C_4alkyl, C_1-C_4fluoroalkyl, C_1-C_4deuteroalkyl, C_1-C_4alkoxy, C_1-C_4fluoroalkoxy, or C_1-C_4hydroxyalkyl.

[00171] In some embodiments, R^3 is H, F, Cl, Br, I, -CN, -OH, $-CH_3$, $-CF_3$, $-CD_3$, $-OCH_3$, $-OCH_2CH_3$, $-OCF_3$, $-OCH_2CF_3$, or $-CH_2OH$.

[00172] In some embodiments, R^3 is H, F, or Cl.

[00173] In some embodiments, Ring B is phenyl, naphthyl, furanyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, pyrazolyl, triazolyl, tetrazolyl, isoxazolyl, isothiazolyl, oxadiazolyl, thiadiazolyl, pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, triazinyl, quinolinyl, isoquinolinyl, quinazolinyl, quinoxalinyl, naphthyridinyl, indolyl, indazolyl, benzoxazolyl, benzisoxazolyl, benzofuranyl, benzothienyl, benzothiazolyl, benzimidazolyl, purinyl, cinnolinyl, phthalazinyl, pteridinyl, pyridopyrimidinyl, pyrazolopyrimidinyl, or azaindolyl.

[00174] In some embodiments, Ring B is phenyl or naphthyl.

[00175] In some embodiments, Ring B is furanyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, pyrazolyl, triazolyl, tetrazolyl, isoxazolyl, isothiazolyl, oxadiazolyl, thiadiazolyl, pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, or triazinyl.

[00176] In some embodiments, Ring B is furanyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, pyrazolyl, triazolyl, tetrazolyl, isoxazolyl, isothiazolyl, oxadiazolyl, or thiadiazolyl.

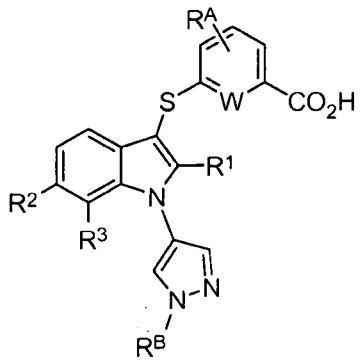
[00177] In some embodiments, Ring B is pyrazolyl.

[00178] In some embodiments, Ring B is pyrazolyl; and each R^B is independently H, C_1-C_6alkyl, C_1-C_6fluoroalkyl, or C_1-C_6deuteroalkyl; n is 1.

[00179] In some embodiments, Ring B is pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, or triazinyl.

[00180] In some embodiments, Ring B is quinolinyl, isoquinolinyl, quinazolinyl, quinoxalinyl, naphthyridinyl, indolyl, indazolyl, benzoxazolyl, benzisoxazolyl, benzofuranyl, benzothienyl, benzothiazolyl, benzimidazolyl, purinyl, cinnolinyl, phthalazinyl, pteridinyl, pyridopyrimidinyl, pyrazolopyrimidinyl, or azaindolyl.

[00181] In some embodiments, the compound of Formula (I) has the following structure of Formula (V):



Formula (V)

wherein,

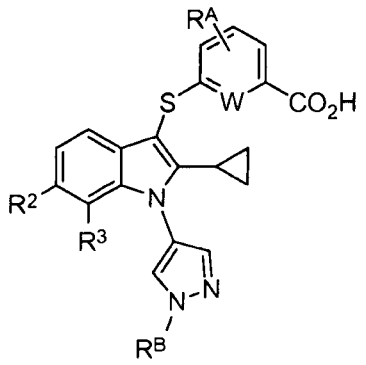
W is CH, CF or N;

or a pharmaceutically acceptable salt, or solvate thereof.

[00182] In some embodiments, R^A is H, halogen, -CN, -OH, -OR^9, -SR^9, C_1-C_6alkyl, C_1-C_6fluoroalkyl, C_1-C_6deuteroalkyl, C_1-C_6heteroalkyl; R^B is H, C_1-C_6alkyl, C_1-C_6fluoroalkyl, or C_1-C_6deuteroalkyl; R^1 is -F, -Cl, -Br, -CN, C_3-C_6cyloalkyl, -NH_2, or -O-C_1-C_4 alkyl; R^2 is H, halogen, -CN, -OH, C_1-C_4alkyl, C_1-C_4fluoroalkyl, C_1-C_4deuteroalkyl, C_1-C_4alkoxy, C_1-C_4fluoroalkoxy, or C_1-C_4hydroxyalkyl; R^3 is H, halogen, -CN, -OH, C_1-C_4alkyl, C_1-C_4fluoroalkyl, C_1-C_4deuteroalkyl, C_1-C_4alkoxy, C_1-C_4fluoroalkoxy, or C_1-C_4hydroxyalkyl.

[00183] In some embodiments, R^1 is -F, -Cl, -Br, -CN, cyclopropyl, -NH_2, or -O-CH_3. In some embodiments, R^1 is -F, -Cl, or -Br. In some embodiments, R^1 is -Cl. In some embodiments, R^1 is C_3-C_6cyloalkyl. In some embodiments, R^1 is cyclopropyl.

[00184] In some embodiments, the compound of Formula (I) or Formula (V) has the following structure of Formula (VI):



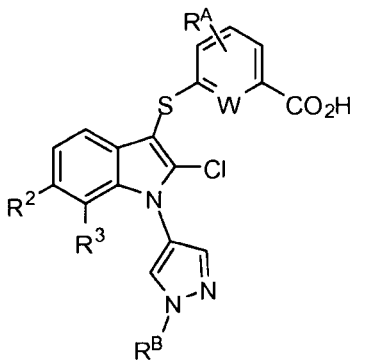
Formula (VI)

wherein,

W is CH, CF or N;

or a pharmaceutically acceptable salt, or solvate thereof.

[00185] In some embodiments, the compound of Formula (I) or Formula (V) has the following structure of Formula (VII):



Formula (VII)

wherein,

W is CH, CF or N;

or a pharmaceutically acceptable salt, or solvate thereof.

[00186] In some embodiments, R^A is H, F, Cl, Br, I, -CN, -OH, -OCH_3, -OCH_2CH_3, -OCF_3, -OCH_2CF_3, -CH_3, -CH_2CH_3, -CF_3, or -CD_3. In some embodiments, R^A is H.

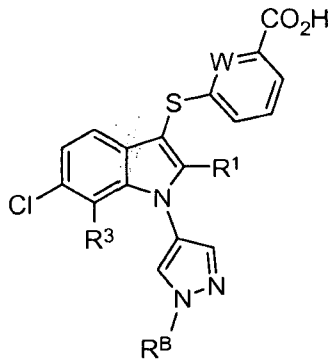
[00187] In some embodiments, R^B is C_1-C_6alkyl. In some embodiments, R^B is -CH_3, -CH_2CH_3, or -$CH_2CH_2CH_3$, or -$CH(CH_3)_2$.

[00188] In some embodiments, R^2 is H, F, Cl, Br, I, -CN, -OH, –CH_3, –CF_3, –CD_3, –OCH_3, –OCH_2CH_3, –OCF_3, –OCH_2CF_3, or –CH_2OH. In some embodiments, R^2 is Cl.

[00189] In some embodiments, R^3 is H, F, Cl, Br, I, -CN, -OH, –CH_3, –CF_3, –CD_3, –OCH_3, –OCH_2CH_3, –OCF_3, –OCH_2CF_3, or –CH_2OH. In some embodiments, R^3 is H, F, or Cl.

[00190] In some embodiments, W is CH, CF or N. In some embodiments, W is CH. In some embodiments, W is CH or CF. In some embodiments, W is CF. In some embodiments, W is N.

[00191] In some embodiments, the compound of Formula (I) has the following structure:



wherein,

W is CH, CF or N;

or a pharmaceutically acceptable salt, or solvate thereof.

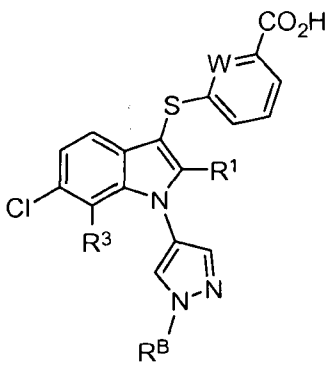
[00192] In some embodiments, R^1 is -Cl or cyclopropyl. In some embodiments, R^1 is -Cl. In some embodiments, R^1 is cyclopropyl.

[00193] In some embodiments, R^1 is as described in Tables 1 and 2. In some embodiments, R^3 is as described in Tables 1 and 2. In some embodiments, R^B is as described in Tables 1 and 2. In some embodiments, R^1, R^3 and R^B are as described in Tables 1 and 2. In some embodiments, L^1 is as described in Table 2.

[00194] Any combination of the groups described above for the various variables is contemplated herein. Throughout the specification, groups and substituents thereof are chosen by one skilled in the field to provide stable moieties and compounds.

[00195] Exemplary compounds include the following compounds:

Table 1:



Compound no.	R^B	R^1	W	R^3
1-1	1-propyl	-Cl	CH	H

Compound no.	R^B	R^1	W	R^3
1-2	1-propyl	-Br	CH	H
1-3	1-propyl	-CN	CH	H
1-4	1-propyl	c-C_3H_5	CH	H
1-5	1-propyl	-NH_2	CH	H
1-6	1-propyl	-OMe	CH	H
1-7	1-propyl	-Cl	CH	F
1-8	1-propyl	-Br	CH	F
1-9	1-propyl	-CN	CH	F
1-10	1-propyl	c-C_3H_5	CH	F
1-11	1-propyl	-NH_2	CH	F
1-12	1-propyl	-OMe	CH	F
1-13	1-propyl	-Cl	CF	F
1-14	1-propyl	-Br	CF	F
1-15	1-propyl	-CN	CF	F
1-16	1-propyl	c-C_3H_5	CF	F
1-17	1-propyl	-NH_2	CF	F
1-18	1-propyl	-OMe	CF	F
1-19	ethyl	-Cl	CH	H
1-20	ethyl	-Br	CH	H
1-21	ethyl	-CN	CH	H
1-22	ethyl	c-C_3H_5	CH	H
1-23	ethyl	-NH_2	CH	H
1-24	ethyl	-OMe	CH	H
1-25	ethyl	-Cl	CH	F
1-26	ethyl	-Br	CH	F
1-27	ethyl	-CN	CH	F
1-28	ethyl	c-C_3H_5	CH	F
1-29	ethyl	-NH_2	CH	F
1-30	ethyl	-OMe	CH	F
1-31	ethyl	-Cl	CF	F
1-32	ethyl	-Br	CF	F
1-33	ethyl	-CN	CF	F
1-34	ethyl	c-C_3H_5	CF	F
1-35	ethyl	-NH_2	CF	F
1-36	ethyl	-OMe	CF	F
1-37	methyl	-Cl	CH	H
1-38	methyl	-Br	CH	H
1-39	methyl	-CN	CH	H
1-40	methyl	c-C_3H_5	CH	H
1-41	methyl	-NH_2	CH	H
1-42	methyl	-OMe	CH	H
1-43	methyl	-Cl	CH	F
1-44	methyl	-Br	CH	F
1-45	methyl	-CN	CH	F
1-46	methyl	c-C_3H_5	CH	F
1-47	methyl	-NH_2	CH	F
1-48	methyl	-OMe	CH	F

Compound no.	R^B	R^1	W	R^3
1-49	methyl	-Cl	CF	F
1-50	methyl	-Br	CF	F
1-51	methyl	-CN	CF	F
1-52	methyl	c-C_3H_5	CF	F
1-53	methyl	-NH_2	CF	F
1-54	2-propyl	-Cl	CH	H
1-55	2-propyl	-Br	CH	H
1-56	2-propyl	-CN	CH	H
1-57	2-propyl	c-C_3H_5	CH	H
1-58	2-propyl	-NH_2	CH	H
1-59	2-propyl	-OMe	CH	H
1-60	2-propyl	-Cl	CH	F
1-61	2-propyl	-Br	CH	F
1-62	2-propyl	-CN	CH	F
1-63	2-propyl	c-C_3H_5	CH	F
1-64	2-propyl	-NH_2	CH	F
1-65	2-propyl	-OMe	CH	F
1-66	2-propyl	-Cl	CF	F
1-67	2-propyl	-Br	CF	F
1-68	2-propyl	-CN	CF	F
1-69	2-propyl	c-C_3H_5	CF	F
1-70	2-propyl	-NH_2	CF	F
1-71	1-propyl	-Cl	N	H
1-72	1-propyl	-Br	N	H
1-73	1-propyl	-CN	N	H
1-74	1-propyl	c-C_3H_5	N	H
1-75	1-propyl	-NH_2	N	H
1-76	1-propyl	-OMe	N	H
1-77	1-propyl	-Cl	N	F
1-78	1-propyl	-Br	N	F
1-79	1-propyl	-CN	N	F
1-80	1-propyl	c-C_3H_5	N	F
1-81	1-propyl	-NH_2	N	F
1-82	1-propyl	-OMe	N	F
1-83	ethyl	-Cl	N	H
1-84	ethyl	-Br	N	H
1-85	ethyl	-CN	N	H
1-86	ethyl	c-C_3H_5	N	H
1-87	ethyl	-NH_2	N	H
1-88	ethyl	-OMe	N	H
1-89	ethyl	-Cl	N	F
1-90	ethyl	-Br	N	F
1-91	ethyl	-CN	N	F
1-92	ethyl	c-C_3H_5	N	F
1-93	ethyl	-NH_2	N	F
1-94	ethyl	-OMe	N	F
1-95	methyl	-Cl	N	H

Compound no.	R^B	R^1	W	R^3
1-96	methyl	-Br	N	H
1-97	methyl	-CN	N	H
1-98	methyl	c-C_3H_5	N	H
1-99	methyl	-NH_2	N	H
1-100	methyl	-OMe	N	H
1-101	methyl	-Cl	N	F
1-102	methyl	-Br	N	F
1-103	methyl	-CN	N	F
1-104	methyl	c-C_3H_5	N	F
1-105	methyl	-NH_2	N	F
1-106	methyl	-OMe	N	F
1-107	2-propyl	-Cl	N	H
1-108	2-propyl	-Br	N	H
1-109	2-propyl	-CN	N	H
1-110	2-propyl	c-C_3H_5	N	H
1-111	2-propyl	-NH_2	N	H
1-112	2-propyl	-OMe	N	H
1-113	2-propyl	-Cl	N	F
1-114	2-propyl	-Br	N	F
1-115	2-propyl	-CN	N	F
1-116	2-propyl	c-C_3H_5	N	F
1-117	2-propyl	-NH_2	N	F
1-118	2-propyl	-OMe	N	F
1-119	H	c-C_3H_5	CF	F
1-120	-CH_2CH_2OH	c-C_3H_5	CF	F
1-121	-$CH_2CH_2OC(O)NH_2$	c-C_3H_5	CF	F
1-122	-$CH_2CH_2NH_2$	c-C_3H_5	CF	F
1-123	-$CH_2CH_2NHC(O)NH_2$	c-C_3H_5	CF	F
1-124	-$CH_2CH_2CH_2CO_2H$	c-C_3H_5	CF	F
1-125	-$CH_2CH_2CH_2CONH_2$	c-C_3H_5	CF	F
1-126	-CH_2CF_3	c-C_3H_5	CF	F
1-127	-CD_2CD_3	c-C_3H_5	CF	F
1-128	-$(CH_2)_6NH_2$	c-C_3H_5	CF	F
1-129	-$(CH_2)_4CCH$	c-C_3H_5	CF	F
1-130	-$CH_2C(CH_3)_2CH_2OH$	c-C_3H_5	CF	F
1-131	-$(CH_2)_6NHC(O)N$- fluorescein	c-C_3H_5	CF	F
1-132	-$CH_2CH_2CH_2C(O)NHCH_3$	c-C_3H_5	CF	F
1-133	-$CH_2CH_2CH_2C(O)NH(CH_3)_2$	c-C_3H_5	CF	F
1-134	-$CH_2CH_2C(CH_3)_2C(O)NH_2$	c-C_3H_5	CF	F
1-135	-$CH_2CH_2CH_2C(O)NH_2$	c-C_3H_5	N	F
1-136	-$CH_2CH_2CH_2C(O)NHCH_3$	c-C_3H_5	N	F
1-137	-$CH_2CH_2CH_2C(O)NH(CH_3)_2$	c-C_3H_5	N	F
1-138	-$CH_2CH_2C(CH_3)_2C(O)NH_2$	c-C_3H_5	N	F

[00196] Compounds in Table 1 are named:

3-((2,6-dichloro-1-(1-propyl-1H-pyrazol-4-yl)-1H-indol-3-yl)thio)benzoic acid (compound no. 1-1);

3-((2-bromo-6-chloro-1-(1-propyl-1H-pyrazol-4-yl)-1H-indol-3-yl)thio)benzoic acid (compound no. 1-2);

3-((6-chloro-2-cyano-1-(1-propyl-1H-pyrazol-4-yl)-1H-indol-3-yl)thio)benzoic acid (compound no. 1-3);

3-((6-chloro-2-cyclopropyl-1-(1-propyl-1H-pyrazol-4-yl)-1H-indol-3-yl)thio)benzoic acid (compound no. 1-4);

3-((2-amino-6-chloro-1-(1-propyl-1H-pyrazol-4-yl)-1H-indol-3-yl)thio)benzoic acid (compound no. 1-5);

3-((6-chloro-2-methoxy-1-(1-propyl-1H-pyrazol-4-yl)-1H-indol-3-yl)thio)benzoic acid (compound no. 1-6);

3-((2,6-dichloro-7-fluoro-1-(1-propyl-1H-pyrazol-4-yl)-1H-indol-3-yl)thio)benzoic acid (compound no. 1-7);

3-((2-bromo-6-chloro-7-fluoro-1-(1-propyl-1H-pyrazol-4-yl)-1H-indol-3-yl)thio)benzoic acid (compound no. 1-8);

3-((6-chloro-2-cyano-7-fluoro-1-(1-propyl-1H-pyrazol-4-yl)-1H-indol-3-yl)thio)benzoic acid (compound no. 1-9);

3-((6-chloro-2-cyclopropyl-7-fluoro-1-(1-propyl-1H-pyrazol-4-yl)-1H-indol-3-yl)thio)benzoic acid (compound no. 1-10);

3-((2-amino-6-chloro-7-fluoro-1-(1-propyl-1H-pyrazol-4-yl)-1H-indol-3-yl)thio)benzoic acid (compound no. 1-11);

3-((6-chloro-7-fluoro-2-methoxy-1-(1-propyl-1H-pyrazol-4-yl)-1H-indol-3-yl)thio)benzoic acid (compound no. 1-12);

3-((2,6-dichloro-7-fluoro-1-(1-propyl-1H-pyrazol-4-yl)-1H-indol-3-yl)thio)-2-fluorobenzoic acid (compound no. 1-13);

3-((2-bromo-6-chloro-7-fluoro-1-(1-propyl-1H-pyrazol-4-yl)-1H-indol-3-yl)thio)-2-fluorobenzoic acid (compound no. 1-14);

3-((6-chloro-2-cyano-7-fluoro-1-(1-propyl-1H-pyrazol-4-yl)-1H-indol-3-yl)thio)-2-fluorobenzoic acid (compound no. 1-15);

3-((6-chloro-2-cyclopropyl-7-fluoro-1-(1-propyl-1H-pyrazol-4-yl)-1H-indol-3-yl)thio)-2-fluorobenzoic acid (compound no. 1-16);

3-((2-amino-6-chloro-7-fluoro-1-(1-propyl-1H-pyrazol-4-yl)-1H-indol-3-yl)thio)-2-fluorobenzoic acid (compound no. 1-17);

3-((6-chloro-7-fluoro-2-methoxy-1-(1-propyl-1H-pyrazol-4-yl)-1H-indol-3-yl)thio)-2-fluorobenzoic acid (compound no. 1-18);

3-((2,6-dichloro-1-(1-ethyl-1H-pyrazol-4-yl)-1H-indol-3-yl)thio)benzoic acid (compound no. 1-19);

3-((2-bromo-6-chloro-1-(1-ethyl-1H-pyrazol-4-yl)-1H-indol-3-yl)thio)benzoic acid (compound no. 1-20);

3-((6-chloro-2-cyano-1-(1-ethyl-1H-pyrazol-4-yl)-1H-indol-3-yl)thio)benzoic acid (compound no. 1-21);

3-((6-chloro-2-cyclopropyl-1-(1-ethyl-1H-pyrazol-4-yl)-1H-indol-3-yl)thio)benzoic acid (compound no. 1-22);

3-((2-amino-6-chloro-1-(1-ethyl-1H-pyrazol-4-yl)-1H-indol-3-yl)thio)benzoic acid (compound no. 1-23);

3-((6-chloro-2-methoxy-1-(1-ethyl-1H-pyrazol-4-yl)-1H-indol-3-yl)thio)benzoic acid (compound no. 1-24);

3-((2,6-dichloro-1-(1-ethyl-1H-pyrazol-4-yl)-7-fluoro-1H-indol-3-yl)thio)benzoic acid (compound no. 1-25);

3-((2-bromo-6-chloro-1-(1-ethyl-1H-pyrazol-4-yl)-7-fluoro-1H-indol-3-yl)thio)benzoic acid (compound no. 1-26);

3-((6-chloro-2-cyano-1-(1-ethyl-1H-pyrazol-4-yl)-7-fluoro-1H-indol-3-yl)thio)benzoic acid (compound no. 1-27);

3-((6-chloro-2-cyclopropyl-1-(1-ethyl-1H-pyrazol-4-yl)-7-fluoro-1H-indol-3-yl)thio)benzoic acid (compound no. 1-28);

3-((2-amino-6-chloro-1-(1-ethyl-1H-pyrazol-4-yl)-7-fluoro-1H-indol-3-yl)thio)benzoic acid (compound no. 1-29);

3-((6-chloro-1-(1-ethyl-1H-pyrazol-4-yl)-7-fluoro-2-methoxy-1H-indol-3-yl)thio)benzoic acid (compound no. 1-30);

3-((2,6-dichloro-1-(1-ethyl-1H-pyrazol-4-yl)-7-fluoro-1H-indol-3-yl)thio)-2-fluorobenzoic acid (compound no. 1-31);

3-((2-bromo-6-chloro-1-(1-ethyl-1H-pyrazol-4-yl)-7-fluoro-1H-indol-3-yl)thio)-2-fluorobenzoic acid (compound no. 1-32);

3-((6-chloro-2-cyano-1-(1-ethyl-1H-pyrazol-4-yl)-7-fluoro-1H-indol-3-yl)thio)-2-fluorobenzoic acid (compound no. 1-33);

3-((6-chloro-2-cyclopropyl-1-(1-ethyl-1H-pyrazol-4-yl)-7-fluoro-1H-indol-3-yl)thio)-2-fluorobenzoic acid (compound no. 1-34);

3-((2-amino-6-chloro-1-(1-ethyl-1H-pyrazol-4-yl)-7-fluoro-1H-indol-3-yl)thio)-2-fluorobenzoic acid (compound no. 1-35);

3-((6-chloro-2-methoxy-1-(1-ethyl-1H-pyrazol-4-yl)-7-fluoro-1H-indol-3-yl)thio)-2-fluorobenzoic acid (compound no. 1-36);

3-((2,6-dichloro-1-(1-methyl-1H-pyrazol-4-yl)-1H-indol-3-yl)thio)benzoic acid (compound no. 1-37);

3-((2-bromo-6-chloro-1-(1-methyl-1H-pyrazol-4-yl)-1H-indol-3-yl)thio)benzoic acid (compound no. 1-38);

3-((6-chloro-2-cyano-1-(1-methyl-1H-pyrazol-4-yl)-1H-indol-3-yl)thio)benzoic acid (compound no. 1-39);

3-((6-chloro-2-cyclopropyl-1-(1-methyl-1H-pyrazol-4-yl)-1H-indol-3-yl)thio)benzoic acid (compound no. 1-40);

3-((2-amino-6-chloro-1-(1-methyl-1H-pyrazol-4-yl)-1H-indol-3-yl)thio)benzoic acid (compound no. 1-41);

3-((6-chloro-2-methoxy-1-(1-methyl-1H-pyrazol-4-yl)-1H-indol-3-yl)thio)benzoic acid (compound no. 1-42);

3-((2,6-dichloro-7-fluoro-1-(1-methyl-1H-pyrazol-4-yl)-1H-indol-3-yl)thio)benzoic acid (compound no. 1-43);

3-((2-bromo-6-chloro-7-fluoro-1-(1-methyl-1H-pyrazol-4-yl)-1H-indol-3-yl)thio)benzoic acid (compound no. 1-44);

3-((6-chloro-2-cyano-7-fluoro-1-(1-methyl-1H-pyrazol-4-yl)-1H-indol-3-yl)thio)benzoic acid (compound no. 1-45);

3-((6-chloro-2-cyclopropyl-7-fluoro-1-(1-methyl-1H-pyrazol-4-yl)-1H-indol-3-yl)thio)benzoic acid (compound no. 1-46);

3-((2-amino-6-chloro-7-fluoro-1-(1-methyl-1H-pyrazol-4-yl)-1H-indol-3-yl)thio)benzoic acid (compound no. 1-47);

3-((6-chloro-7-fluoro-1-(1-methyl-1H-pyrazol-4-yl)-2-methoxy-1H-indol-3-yl)thio)benzoic acid (compound no. 1-48);

3-((2,6-dichloro-7-fluoro-1-(1-methyl-1H-pyrazol-4-yl)-1H-indol-3-yl)thio)-2-fluorobenzoic acid (compound no. 1-49);

3-((2-bromo-6-chloro-7-fluoro-1-(1-methyl-1H-pyrazol-4-yl)-1H-indol-3-yl)thio)-2-fluorobenzoic acid (compound no. 1-50);

3-((6-chloro-2-cyano-7-fluoro-1-(1-methyl-1H-pyrazol-4-yl)-1H-indol-3-yl)thio)-2-fluorobenzoic acid (compound no. 1-51);

3-((6-chloro-2-cyclopropyl-7-fluoro-1-(1-methyl-1H-pyrazol-4-yl)-1H-indol-3-yl)thio)-2-fluorobenzoic acid (compound no. 1-52);

3-((2-amino-6-chloro-7-fluoro-1-(1-methyl-1H-pyrazol-4-yl)-1H-indol-3-yl)thio)-2-fluorobenzoic acid (compound no. 1-53);

3-((2,6-dichloro-1-(1-isopropyl-1H-pyrazol-4-yl)-1H-indol-3-yl)thio)benzoic acid (compound no. 1-54);

3-((2-bromo-6-chloro-1-(1-isopropyl-1H-pyrazol-4-yl)-1H-indol-3-yl)thio)benzoic acid (compound no. 1-55);

3-((6-chloro-2-cyano-1-(1-isopropyl-1H-pyrazol-4-yl)-1H-indol-3-yl)thio)benzoic acid (compound no. 1-56);

3-((6-chloro-2-cyclopropyl-1-(1-isopropyl-1H-pyrazol-4-yl)-1H-indol-3-yl)thio)benzoic acid (compound no. 1-57);

3-((2-amino-6-chloro-1-(1-isopropyl-1H-pyrazol-4-yl)-1H-indol-3-yl)thio)benzoic acid (compound no. 1-58);

3-((6-chloro-2-methoxy-1-(1-isopropyl-1H-pyrazol-4-yl)-1H-indol-3-yl)thio)benzoic acid (compound no. 1-59);

3-((2,6-dichloro-7-fluoro-1-(1-isopropyl-1H-pyrazol-4-yl)-1H-indol-3-yl)thio)benzoic acid (compound no. 1-60);

3-((2-bromo-6-chloro-7-fluoro-1-(1-isopropyl-1H-pyrazol-4-yl)-1H-indol-3-yl)thio)benzoic acid (compound no. 1-61);

3-((6-chloro-2-cyano-7-fluoro-1-(1-isopropyl-1H-pyrazol-4-yl)-1H-indol-3-yl)thio)benzoic acid (compound no. 1-62);

3-((6-chloro-2-cyclopropyl-7-fluoro-1-(1-isopropyl-1H-pyrazol-4-yl)-1H-indol-3-yl)thio)benzoic acid (compound no. 1-63);

3-((2-amino-6-chloro-7-fluoro-1-(1-isopropyl-1H-pyrazol-4-yl)-1H-indol-3-yl)thio)benzoic acid (compound no. 1-64);

3-((6-chloro-7-fluoro-1-(1-isopropyl-1H-pyrazol-4-yl)-2-methoxy-1H-indol-3-yl)thio)benzoic acid (compound no. 1-65);

3-((2,6-dichloro-7-fluoro-1-(1-isopropyl-1H-pyrazol-4-yl)-1H-indol-3-yl)thio)-2-fluorobenzoic acid (compound no. 1-66);

3-((2-bromo-6-chloro-7-fluoro-1-(1-isopropyl-1H-pyrazol-4-yl)-1H-indol-3-yl)thio)-2-fluorobenzoic acid (compound no. 1-67);

3-((6-chloro-2-cyano-7-fluoro-1-(1-isopropyl-1H-pyrazol-4-yl)-1H-indol-3-yl)thio)-2-fluorobenzoic acid (compound no. 1-68);

3-((6-chloro-2-cyclopropyl-7-fluoro-1-(1-isopropyl-1H-pyrazol-4-yl)-1H-indol-3-yl)thio)-2-fluorobenzoic acid (compound no. 1-69);

3-((2-amino-6-chloro-7-fluoro-1-(1-isopropyl-1H-pyrazol-4-yl)-1H-indol-3-yl)thio)-2-fluorobenzoic acid (compound no. 1-70);

6-((2,6-dichloro-1-(1-propyl-1H-pyrazol-4-yl)-1H-indol-3-yl)thio)picolinic acid (compound no. 1-71);

6-((2-bromo-6-chloro-1-(1-propyl-1H-pyrazol-4-yl)-1H-indol-3-yl)thio)picolinic acid (compound no. 1-72);

6-((6-chloro-2-cyano-1-(1-propyl-1H-pyrazol-4-yl)-1H-indol-3-yl)thio)picolinic acid (compound no. 1-73);

6-((6-chloro-2-cyclopropyl-1-(1-propyl-1H-pyrazol-4-yl)-1H-indol-3-yl)thio)picolinic acid (compound no. 1-74);

6-((2-amino-6-chloro-1-(1-propyl-1H-pyrazol-4-yl)-1H-indol-3-yl)thio)picolinic acid (compound no. 1-75);

6-((6-chloro-2-methoxy-1-(1-propyl-1H-pyrazol-4-yl)-1H-indol-3-yl)thio)picolinic acid (compound no. 1-76);

6-((2,6-dichloro-7-fluoro-1-(1-propyl-1H-pyrazol-4-yl)-1H-indol-3-yl)thio)picolinic acid (compound no. 1-77);

6-((2-bromo-6-chloro-7-fluoro-1-(1-propyl-1H-pyrazol-4-yl)-1H-indol-3-yl)thio)picolinic acid (compound no. 1-78);

6-((6-chloro-2-cyano-7-fluoro-1-(1-propyl-1H-pyrazol-4-yl)-1H-indol-3-yl)thio)picolinic acid (compound no. 1-79);

6-((6-chloro-2-cyclopropyl-7-fluoro-1-(1-propyl-1H-pyrazol-4-yl)-1H-indol-3-yl)thio)picolinic acid (compound no. 1-80);

6-((2-amino-6-chloro-7-fluoro-1-(1-propyl-1H-pyrazol-4-yl)-1H-indol-3-yl)thio)picolinic acid (compound no. 1-81);

6-((6-chloro-7-fluoro-2-methoxy-1-(1-propyl-1H-pyrazol-4-yl)-1H-indol-3-yl)thio)picolinic acid (compound no. 1-82);

6-((2,6-dichloro-1-(1-ethyl-1H-pyrazol-4-yl)-1H-indol-3-yl)thio)picolinic acid (compound no. 1-83);

6-((2-bromo-6-chloro-1-(1-ethyl-1H-pyrazol-4-yl)-1H-indol-3-yl)thio)picolinic acid (compound no. 1-84);

6-((6-chloro-2-cyano-1-(1-ethyl-1H-pyrazol-4-yl)-1H-indol-3-yl)thio)picolinic acid (compound no. 1-85);

6-((6-chloro-2-cyclopropyl-1-(1-ethyl-1H-pyrazol-4-yl)-1H-indol-3-yl)thio)picolinic acid (compound no. 1-86);

6-((2-amino-6-chloro-1-(1-ethyl-1H-pyrazol-4-yl)-1H-indol-3-yl)thio)picolinic acid (compound no. 1-87);

6-((6-chloro-1-(1-ethyl-1H-pyrazol-4-yl)-2-methoxy-1H-indol-3-yl)thio)picolinic acid (compound no. 1-88);

6-((2,6-dichloro-1-(1-ethyl-1H-pyrazol-4-yl)-7-fluoro-1H-indol-3-yl)thio)picolinic acid (compound no. 1-89);

6-((2-bromo-6-chloro-1-(1-ethyl-1H-pyrazol-4-yl)-7-fluoro-1H-indol-3-yl)thio)picolinic acid (compound no. 1-90);

6-((6-chloro-2-cyano-1-(1-ethyl-1H-pyrazol-4-yl)-7-fluoro-1H-indol-3-yl)thio)picolinic acid (compound no. 1-91);

6-((6-chloro-2-cyclopropyl-1-(1-ethyl-1H-pyrazol-4-yl)-7-fluoro-1H-indol-3-yl)thio)picolinic acid (compound no. 1-92);

6-((2-amino-6-chloro-1-(1-ethyl-1H-pyrazol-4-yl)-7-fluoro-1H-indol-3-yl)thio)picolinic acid (compound no. 1-93);

6-((6-chloro-1-(1-ethyl-1H-pyrazol-4-yl)-7-fluoro-2-methoxy-1H-indol-3-yl)thio)picolinic acid (compound no. 1-94);

6-((2,6-dichloro-1-(1-methyl-1H-pyrazol-4-yl)-1H-indol-3-yl)thio)picolinic acid (compound no. 1-95);

6-((2-bromo-6-chloro-1-(1-methyl-1H-pyrazol-4-yl)-1H-indol-3-yl)thio)picolinic acid (compound no. 1-96);

6-((6-chloro-2-cyano-1-(1-methyl-1H-pyrazol-4-yl)-1H-indol-3-yl)thio)picolinic acid (compound no. 1-97);

6-((6-chloro-2-cyclopropyl-1-(1-methyl-1H-pyrazol-4-yl)-1H-indol-3-yl)thio)picolinic acid (compound no. 1-98);

6-((2-amino-6-chloro-1-(1-methyl-1H-pyrazol-4-yl)-1H-indol-3-yl)thio)picolinic acid (compound no. 1-99);

6-((6-chloro-2-methoxy-1-(1-methyl-1H-pyrazol-4-yl)-1H-indol-3-yl)thio)picolinic acid (compound no. 1-100);

6-((2,6-dichloro-7-fluoro-1-(1-methyl-1H-pyrazol-4-yl)-1H-indol-3-yl)thio)picolinic acid (compound no. 1-101);

6-((2-bromo-6-chloro-7-fluoro-1-(1-methyl-1H-pyrazol-4-yl)-1H-indol-3-yl)thio)picolinic acid (compound no. 1-102);

6-((6-chloro-2-cyano-7-fluoro-1-(1-methyl-1H-pyrazol-4-yl)-1H-indol-3-yl)thio)picolinic acid (compound no. 1-103);

6-((6-chloro-2-cyclopropyl-7-fluoro-1-(1-methyl-1H-pyrazol-4-yl)-1H-indol-3-yl)thio)picolinic acid (compound no. 1-104);

6-((2-amino-6-chloro-7-fluoro-1-(1-methyl-1H-pyrazol-4-yl)-1H-indol-3-yl)thio)picolinic acid (compound no. 1-105);

6-((6-chloro-7-fluoro-2-methoxy-1-(1-methyl-1H-pyrazol-4-yl)-1H-indol-3-yl)thio)picolinic acid (compound no. 1-106);

6-((2,6-dichloro-1-(1-isopropyl-1H-pyrazol-4-yl)-1H-indol-3-yl)thio)picolinic acid (compound no. 1-107);

6-((2-bromo-6-chloro-1-(1-isopropyl-1H-pyrazol-4-yl)-1H-indol-3-yl)thio)picolinic acid (compound no. 1-108);

6-((6-chloro-2-cyano-1-(1-isopropyl-1H-pyrazol-4-yl)-1H-indol-3-yl)thio)picolinic acid (compound no. 1-109);

6-((6-chloro-2-cyclopropyl-1-(1-isopropyl-1H-pyrazol-4-yl)-1H-indol-3-yl)thio)picolinic acid (compound no. 1-110;

6-((2-amino-6-chloro-1-(1-isopropyl-1H-pyrazol-4-yl)-1H-indol-3-yl)thio)picolinic acid (compound no. 1-111);

6-((6-chloro-1-(1-isopropyl-1H-pyrazol-4-yl)-2-methoxy-1H-indol-3-yl)thio)picolinic acid (compound no. 1-112);

6-((2,6-dichloro-7-fluoro-1-(1-isopropyl-1H-pyrazol-4-yl)-1H-indol-3-yl)thio)picolinic acid (compound no. 1-113);

6-((2-bromo-6-chloro-7-fluoro-1-(1-isopropyl-1H-pyrazol-4-yl)-1H-indol-3-yl)thio)picolinic acid (compound no. 1-114);

6-((6-chloro-2-cyano-7-fluoro-1-(1-isopropyl-1H-pyrazol-4-yl)-1H-indol-3-yl)thio)picolinic acid (compound no. 1-115);

6-((6-chloro-2-cyclopropyl-7-fluoro-1-(1-isopropyl-1H-pyrazol-4-yl)-1H-indol-3-yl)thio)picolinic acid (compound no. 1-116);

6-((2-amino-6-chloro-7-fluoro-1-(1-isopropyl-1H-pyrazol-4-yl)-1H-indol-3-yl)thio)picolinic acid (compound no. 1-117);

6-((6-chloro-7-fluoro-1-(1-isopropyl-1H-pyrazol-4-yl)-2-methoxy-1H-indol-3-yl)thio)picolinic acid (compound no. 1-118);

3-((6-chloro-2-cyclopropyl-7-fluoro-1-(1H-pyrazol-4-yl)-1H-indol-3-yl)thio)-2-fluorobenzoic acid (compound no. 1-119);

3-((6-chloro-2-cyclopropyl-7-fluoro-1-(1-(2-hydroxyethyl)-1H-pyrazol-4-yl)-1H-indol-3-yl)thio)-2-fluorobenzoic acid (compound no. 1-120);

3-(1-(1-(2-(carbamoyloxy)ethyl)-1H-pyrazol-4-yl)-(6-chloro-2-cyclopropyl-7-fluoro-1H-indol-3-yl)thio)-2-fluorobenzoic acid (compound no. 1-121);

3-(1-(1-(2-aminoethyl)-1H-pyrazol-4-yl)-(6-chloro-2-cyclopropyl-7-fluoro-1H-indol-3-yl)thio)-2-fluorobenzoic acid (compound no. 1-122);

3-((6-chloro-2-cyclopropyl-7-fluoro-1-(1-(2-ureidoethyl)-1H-pyrazol-4-yl)-1H-indol-3-yl)thio)-2-fluorobenzoic acid (compound no. 1-123);

3-(1-(1-(3-carboxypropyl)-1H-pyrazol-4-yl)-(6-chloro-2-cyclopropyl-7-fluoro-1H-indol-3-yl)thio)-2-fluorobenzoic acid (compound no. 1-124);

3-(1-(1-(4-amino-4-oxobutyl)-1H-pyrazol-4-yl)-(6-chloro-2-cyclopropyl-7-fluoro-1H-indol-3-yl)thio)-2-fluorobenzoic acid (compound no. 1-125);

3-((6-chloro-2-cyclopropyl-7-fluoro-1-(1-(2,2,2-trifluoroethyl)-1H-pyrazol-4-yl)-1H-indol-3-yl)thio)-2-fluorobenzoic acid (compound no. 1-126);

3-((6-chloro-2-cyclopropyl-1-(1-($^{2}H_5$)ethyl-1H-pyrazol-4-yl)-7-fluoro-1H-indol-3-yl)thio)-2-fluorobenzoic acid; (compound no. 1-127);

3-(1-(1-(6-aminohexyl)-1H-pyrazol-4-yl)-(6-chloro-2-cyclopropyl-7-fluoro-1H-indol-3-yl)thio)-2-fluorobenzoic acid (compound no. 1-128);

3-((6-chloro-2-cyclopropyl-7-fluoro-1-(1-(hex-5-ynyl)-1H-pyrazol-4-yl)-1H-indol-3-yl)thio)-2-fluorobenzoic acid (compound no. 1-129);

3-((6-chloro-2-cyclopropyl-7-fluoro-1-(1-(3-hydroxy-2,2-dimethylpropyl)-1H-pyrazol-4-yl)-1H-indol-3-yl)thio)-2-fluorobenzoic acid (compound no. 1-130);

3-((6-chloro-2-cyclopropyl-1-(1-(6-(3-(3',6'-dihydroxy-3-oxo-3H-spiro[isobenzofuran-1,9'-xanthen]-5-yl)ureido)hexyl)-1H-pyrazol-4-yl)-7-fluoro-1H-indol-3-yl)thio)-2-fluorobenzoic acid (compound no. 1-131);

3-((6-chloro-2-cyclopropyl-7-fluoro-1-(1-(4-(methylamino)-4-oxobutyl)-1H-pyrazol-4-yl)-1H-indol-3-yl)thio)-2-fluorobenzoic acid (compound no. 1-132);

3-(6-chloro-2-cyclopropyl-1-(1-(4-(dimethylamino)-4-oxobutyl)-1H-pyrazol-4-yl)-7-fluoro-1H-indol-3-ylthio)-2-fluorobenzoic acid (compound no. 1-133);

3-(1-(1-(4-amino-3,3-dimethyl-4-oxobutyl)-1H-pyrazol-4-yl)-6-chloro-2-cyclopropyl-7-fluoro-1H-indol-3-ylthio)-2-fluorobenzoic acid (compound no. 1-134);

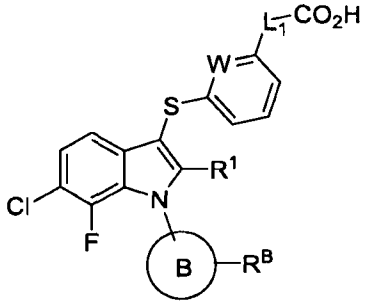
6-(1-(1-(4-amino-4-oxobutyl)-1H-pyrazol-4-yl)-(6-chloro-2-cyclopropyl-7-fluoro-1H-indol-3-yl)thio)picolinic acid (compound no. 1-135);

6-((6-chloro-2-cyclopropyl-7-fluoro-1-(1-(4-(methylamino)-4-oxobutyl)-1H-pyrazol-4-yl)-1H-indol-3-yl)thio)picolinic acid (compound no. 1-136);

6-((6-chloro-2-cyclopropyl-1-(1-(4-(dimethylamino)-4-oxobutyl)-1H-pyrazol-4-yl)-7-fluoro-1H-indol-3-yl)thio)picolinic acid (compound no. 1-137);

6-(1-(1-(4-amino-3,3-dimethyl-4-oxobutyl)-1H-pyrazol-4-yl)-(6-chloro-2-cyclopropyl-7-fluoro-1H-indol-3-yl)thio)picolinic acid (compound no. 1-138).

Table 2:



Compound no.	B—R^B	R^1	W	L^1
2-1	pyridin-3-yl	-Cl	CF	absent
2-2	pyridin-3-yl	-Br	CF	absent
2-3	pyridin-3-yl	c-C_3H_5	CF	absent
2-4	pyridin-3-yl	-CN	CF	absent
2-5	1-ethyl-1H-pyrazol-4-yl	-Cl	CF	CH_2
2-6	1-ethyl-1H-pyrazol-4-yl	-Br	CF	CH_2
2-7	1-ethyl-1H-pyrazol-4-yl	c-C_3H_5	CF	CH_2
2-8	1-ethyl-1H-pyrazol-4-yl	-CN	CF	CH_2
2-9	1-ethyl-1H-pyrazol-4-yl	-Cl	CF	$C(CH_3)_2$
2-10	1-ethyl-1H-pyrazol-4-yl	-Br	CF	$C(CH_3)_2$
2-11	1-ethyl-1H-pyrazol-4-yl	c-C_3H_5	CF	$C(CH_3)_2$
2-12	1-ethyl-1H-pyrazol-4-yl	-CN	CF	$C(CH_3)_2$
2-13	1-ethyl-1H-pyrazol-4-yl	-Cl	CF	$C(CH_2CH_2)_2$
2-14	1-ethyl-1H-pyrazol-4-yl	-Br	CF	$C(CH_2CH_2)_2$
2-15	1-ethyl-1H-pyrazol-4-yl	c-C_3H_5	CF	$C(CH_2CH_2)_2$
2-16	1-ethyl-1H-pyrazol-4-yl	-CN	CF	$C(CH_2CH_2)_2$
2-17	1-propyl-1H-pyrazol-4-yl	-Cl	CF	CH_2
2-18	1-propyl-1H-pyrazol-4-yl	-Br	CF	CH_2
2-19	1-propyl-1H-pyrazol-4-yl	c-C_3H_5	CF	CH_2
2-20	1-propyl-1H-pyrazol-4-yl	-CN	CF	CH_2
2-21	1-propyl-1H-pyrazol-4-yl	-Cl	CF	$C(CH_3)_2$
2-22	1-propyl-1H-pyrazol-4-yl	-Br	CF	$C(CH_3)_2$
2-23	1-propyl-1H-pyrazol-4-yl	c-C_3H_5	CF	$C(CH_3)_2$
2-24	1-propyl-1H-pyrazol-4-yl	-CN	CF	$C(CH_3)_2$

Compound no.	B—R^B	R^1	W	L^1
2-25	1-propyl-1H-pyrazol-4-yl	-Cl	CF	$C(CH_2CH_2)_2$
2-26	1-propyl-1H-pyrazol-4-yl	-Br	CF	$C(CH_2CH_2)_2$
2-27	1-propyl-1H-pyrazol-4-yl	c-C_3H_5	CF	$C(CH_2CH_2)_2$
2-28	1-propyl-1H-pyrazol-4-yl	-CN	CF	$C(CH_2CH_2)_2$
2-29	1-ethyl-1H-pyrazol-4-yl	-Cl	N	CH_2
2-30	1-ethyl-1H-pyrazol-4-yl	-Cl	N	$C(CH_3)_2$
2-31	1-ethyl-1H-pyrazol-4-yl	-Cl	N	$C(CH_2CH_2)_2$
2-32	1-propyl-1H-pyrazol-4-yl	-Cl	N	CH_2
2-33	1-propyl-1H-pyrazol-4-yl	-Cl	N	$C(CH_3)_2$
2-34	1-propyl-1H-pyrazol-4-yl	-Cl	N	$C(CH_2CH_2)_2$

[00197] Compounds in Table 2 are named:

3-((2,6-dichloro-7-fluoro-1-(pyridin-3-yl)-1H-indol-3-yl)thio)-2-fluorobenzoic acid (compound no. 2-1);

3-((2-bromo-6-chloro-7-fluoro-1-(pyridin-3-yl)-1H-indol-3-yl)thio)-2-fluorobenzoic acid (compound no. 2-2);

3-((6-chloro-2-cyclopropyl-7-fluoro-1-(pyridin-3-yl)-1H-indol-3-yl)thio)-2-fluorobenzoic acid (compound no. 2-3);

3-((6-chloro-2-cyano-7-fluoro-1-(pyridin-3-yl)-1H-indol-3-yl)thio)-2-fluorobenzoic acid (compound no. 2-4);

2-(3-((2,6-dichloro-1-(1-ethyl-1H-pyrazol-4-yl)-7-fluoro-1H-indol-3-yl)thio)-2-fluorophenyl)acetic acid (compound no. 2-5);

2-(3-((2-bromo-6-chloro-1-(1-ethyl-1H-pyrazol-4-yl)-7-fluoro-1H-indol-3-yl)thio)-2-fluorophenyl)acetic acid (compound no. 2-6);

2-(3-((6-chloro-2-cyclopropyl-1-(1-ethyl-1H-pyrazol-4-yl)-7-fluoro-1H-indol-3-yl)thio)-2-fluorophenyl)acetic acid (compound no. 2-7);

2-(3-((6-chloro-2-cyano-1-(1-ethyl-1H-pyrazol-4-yl)-7-fluoro-1H-indol-3-yl)thio)-2-fluorophenyl)acetic acid (compound no. 2-8);

2-(3-((2,6-dichloro-1-(1-ethyl-1H-pyrazol-4-yl)-7-fluoro-1H-indol-3-yl)thio)-2-fluorophenyl)-2-methylpropanoic acid (compound no. 2-9);

2-(3-((2-bromo-6-chloro-1-(1-ethyl-1H-pyrazol-4-yl)-7-fluoro-1H-indol-3-yl)thio)-2-fluorophenyl)-2-methylpropanoic acid (compound no. 2-10);

2-(3-((6-chloro-2-cyclopropyl-1-(1-ethyl-1H-pyrazol-4-yl)-7-fluoro-1H-indol-3-yl)thio)-2-fluorophenyl)-2-methylpropanoic acid (compound no. 2-11);

2-(3-((6-chloro-2-cyano-1-(1-ethyl-1H-pyrazol-4-yl)-7-fluoro-1H-indol-3-yl)thio)-2-fluorophenyl)-2-methylpropanoic acid (compound no. 2-12)

1-(3-((2,6-dichloro-1-(1-ethyl-1H-pyrazol-4-yl)-7-fluoro-1H-indol-3-yl)thio)-2-fluorophenyl)cyclopropanecarboxylic acid (compound no. 2-13);

1-(3-((2-bromo-6-chloro-1-(1-ethyl-1H-pyrazol-4-yl)-7-fluoro-1H-indol-3-yl)thio)-2-fluorophenyl) cyclopropanecarboxylic acid (compound no. 2-14);

1-(3-((6-chloro-2-cyclopropyl-1-(1-ethyl-1H-pyrazol-4-yl)-7-fluoro-1H-indol-3-yl)thio)-2-fluorophenyl)cyclopropanecarboxylic acid (compound no. 2-15);

1-(3-((6-chloro-2-cyano-1-(1-ethyl-1H-pyrazol-4-yl)-7-fluoro-1H-indol-3-yl)thio)-2-fluorophenyl) cyclopropanecarboxylic acid (compound no. 2-16);

2-(3-((2,6-dichloro-1-(1-propyl-1H-pyrazol-4-yl)-7-fluoro-1H-indol-3-yl)thio)-2-fluorophenyl)acetic acid (compound no. 2-17);

2-(3-((2-bromo-6-chloro-1-(1-propyl-1H-pyrazol-4-yl)-7-fluoro-1H-indol-3-yl)thio)-2-fluorophenyl)acetic acid (compound no. 2-18);

2-(3-((6-chloro-2-cyclopropyl-1-(1-propyl-1H-pyrazol-4-yl)-7-fluoro-1H-indol-3-yl)thio)-2-fluorophenyl)acetic acid (compound no. 2-19);

2-(3-((6-chloro-2-cyano-1-(1-propyl-1H-pyrazol-4-yl)-7-fluoro-1H-indol-3-yl)thio)-2-fluorophenyl)acetic acid (compound no. 2-20);

2-(3-((2,6-dichloro-1-(1-propyl-1H-pyrazol-4-yl)-7-fluoro-1H-indol-3-yl)thio)-2-fluorophenyl)-2-methylpropanoic acid (compound no. 2-21);

2-(3-((2-bromo-6-chloro-1-(1-propyl-1H-pyrazol-4-yl)-7-fluoro-1H-indol-3-yl)thio)-2-fluorophenyl)-2-methylpropanoic acid (compound no. 2-22);

2-(3-((6-chloro-2-cyclopropyl-1-(1-propyl-1H-pyrazol-4-yl)-7-fluoro-1H-indol-3-yl)thio)-2-fluorophenyl)-2-methylpropanoic acid (compound no. 2-23);

2-(3-((6-chloro-2-cyano-1-(1-propyl-1H-pyrazol-4-yl)-7-fluoro-1H-indol-3-yl)thio)-2-fluorophenyl)-2-methylpropanoic acid (compound no. 2-24)

1-(3-((2,6-dichloro-1-(1-propyl-1H-pyrazol-4-yl)-7-fluoro-1H-indol-3-yl)thio)-2-fluorophenyl)cyclopropanecarboxylic acid (compound no. 2-25);

1-(3-((2-bromo-6-chloro-1-(1-propyl-1H-pyrazol-4-yl)-7-fluoro-1H-indol-3-yl)thio)-2-fluorophenyl) cyclopropanecarboxylic acid (compound no. 2-26);

1-(3-((6-chloro-2-cyclopropyl-1-(1-propyl-1H-pyrazol-4-yl)-7-fluoro-1H-indol-3-yl)thio)-2-fluorophenyl)cyclopropanecarboxylic acid (compound no. 2-27);

1-(3-((6-chloro-2-cyano-1-(1-propyl-1H-pyrazol-4-yl)-7-fluoro-1H-indol-3-yl)thio)-2-fluorophenyl) cyclopropanecarboxylic acid (compound no. 2-28);

2-(6-((2,6-dichloro-1-(1-ethyl-1H-pyrazol-4-yl)-7-fluoro-1H-indol-3-yl)thio)pyridine-2-yl)acetic acid (compound no. 2-29);

2-(6-((2,6-dichloro-1-(1-ethyl-1H-pyrazol-4-yl)-7-fluoro-1H-indol-3-yl)thio)pyridine-2-yl)-2-methylpropanoic acid (compound no. 2-30);

1-(6-((2,6-dichloro-1-(1-ethyl-1H-pyrazol-4-yl)-7-fluoro-1H-indol-3-yl)thio)pyridine-2-yl)cyclopropanecarboxylic acid (compound no. 2-31);

2-(6-((2,6-dichloro-1-(1-propyl-1H-pyrazol-4-yl)-7-fluoro-1H-indol-3-yl)thio)pyridine-2-yl)acetic acid (compound no. 2-32);

2-(6-((2,6-dichloro-1-(1-propyl-1H-pyrazol-4-yl)-7-fluoro-1H-indol-3-yl)thio)pyridine-2-yl)-2-methylpropanoic acid (compound no. 2-33);

1-(6-((2,6-dichloro-1-(1-propyl-1H-pyrazol-4-yl)-7-fluoro-1H-indol-3-yl)thio)pyridine-2-yl)cyclopropanecarboxylic acid (compound no. 2-34).

[00198] In one aspect, compounds described herein are in the form of pharmaceutically acceptable salts. As well, active metabolites of these compounds having the same type of activity are included in the scope of the present disclosure. In addition, the compounds described herein can exist in unsolvated as well as solvated forms with pharmaceutically acceptable solvents such as water, ethanol, and the like. The solvated forms of the compounds presented herein are also considered to be disclosed herein.

[00199] "Pharmaceutically acceptable," as used herein, refers a material, such as a carrier or diluent, which does not abrogate the biological activity or properties of the compound, and is relatively nontoxic, i.e., the material is administered to an individual without causing undesirable biological effects or interacting in a deleterious manner with any of the components of the composition in which it is contained.

[00200] The term "pharmaceutically acceptable salt" refers to a form of a therapeutically active agent that consists of a cationic form of the therapeutically active agent in combination with a suitable anion, or in alternative embodiments, an anionic form of the therapeutically active agent in combination with a suitable cation. Handbook of Pharmaceutical Salts: Properties, Selection and Use. International Union of Pure and Applied Chemistry, Wiley-VCH 2002. S.M. Berge, L.D. Bighley, D.C. Monkhouse, J. Pharm. Sci. 1977, 66, 1-19. P. H. Stahl and C. G. Wermuth, editors, *Handbook of Pharmaceutical Salts: Properties, Selection and Use*, Weinheim/Zürich:Wiley-VCH/VHCA, 2002. Pharmaceutical salts typically are more soluble and more rapidly soluble in stomach and intestinal juices than non-ionic species and so are useful in solid dosage forms. Furthermore, because their solubility often is a function of pH, selective dissolution in one or another part of the digestive tract is possible and this capability can be

manipulated as one aspect of delayed and sustained release behaviours. Also, because the salt-forming molecule can be in equilibrium with a neutral form, passage through biological membranes can be adjusted.

[00201] In some embodiments, pharmaceutically acceptable salts are obtained by reacting a compound described herein with an acid. In some embodiments, the compound described herein (i.e. free base form) is basic and is reacted with an organic acid or an inorganic acid. Inorganic acids include, but are not limited to, hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid, nitric acid, and metaphosphoric acid. Organic acids include, but are not limited to, 1-hydroxy-2-naphthoic acid; 2,2-dichloroacetic acid; 2-hydroxyethanesulfonic acid; 2-oxoglutaric acid; 4-acetamidobenzoic acid; 4-aminosalicylic acid; acetic acid; adipic acid; ascorbic acid (L); aspartic acid (L); benzenesulfonic acid; benzoic acid; camphoric acid (+); camphor-10-sulfonic acid (+); capric acid (decanoic acid); caproic acid (hexanoic acid); caprylic acid (octanoic acid); carbonic acid; cinnamic acid; citric acid; cyclamic acid; dodecylsulfuric acid; ethane-1,2-disulfonic acid; ethanesulfonic acid; formic acid; fumaric acid; galactaric acid; gentisic acid; glucoheptonic acid (D); gluconic acid (D); glucuronic acid (D); glutamic acid; glutaric acid; glycerophosphoric acid; glycolic acid; hippuric acid; isobutyric acid; lactic acid (DL); lactobionic acid; lauric acid; maleic acid; malic acid (- L); malonic acid; mandelic acid (DL); methanesulfonic acid; naphthalene-1,5-disulfonic acid; naphthalene-2-sulfonic acid; nicotinic acid; oleic acid; oxalic acid; palmitic acid; pamoic acid; phosphoric acid; proprionic acid; pyroglutamic acid (- L); salicylic acid; sebacic acid; stearic acid; succinic acid; sulfuric acid; tartaric acid (+ L); thiocyanic acid; toluenesulfonic acid (*p*); and undecylenic acid.

[00202] In some embodiments, a compound described herein is prepared as a chloride salt, sulfate salt, bromide salt, mesylate salt, maleate salt, citrate salt or phosphate salt. In some embodiments, a compound described herein is prepared as a hydrochloride salt.

[00203] In some embodiments, pharmaceutically acceptable salts are obtained by reacting a compound described herein with a base. In some embodiments, the compound described herein is acidic and is reacted with a base. In such situations, an acidic proton of the compound described herein is replaced by a metal ion, e.g., lithium, sodium, potassium, magnesium, calcium, or an aluminum ion. In some cases, compounds described herein coordinate with an organic base, such as, but not limited to, ethanolamine, diethanolamine, triethanolamine, tromethamine, meglumine, N-methylglucamine, dicyclohexylamine, tris(hydroxymethyl)methylamine. In other cases, compounds described herein form salts with amino acids such as, but not limited to, arginine, lysine, and the like. Acceptable inorganic bases used to form salts with compounds that include an acidic proton, include, but are not limited to,

aluminum hydroxide, calcium hydroxide, potassium hydroxide, sodium carbonate, potassium carbonate, sodium hydroxide, lithium hydroxide, and the like. In some embodiments, the compounds provided herein are prepared as a sodium salt, calcium salt, potassium salt, magnesium salt, meglumine salt, N-methylglucamine salt or ammonium salt. In some embodiments, the compounds provided herein are prepared as a sodium salt.

[00204] It should be understood that a reference to a pharmaceutically acceptable salt includes the solvent addition forms. In some embodiments, solvates contain either stoichiometric or non-stoichiometric amounts of a solvent, and are formed during the process of crystallization with pharmaceutically acceptable solvents such as water, ethanol, and the like. Hydrates are formed when the solvent is water, or alcoholates are formed when the solvent is alcohol. Solvates of compounds described herein are conveniently prepared or formed during the processes described herein. In addition, the compounds provided herein optionally exist in unsolvated as well as solvated forms.

[00205] The methods and formulations described herein include the use of *N*-oxides (if appropriate), crystalline forms (also known as polymorphs), or pharmaceutically acceptable salts of compounds described herein, as well as active metabolites of these compounds having the same type of activity.

[00206] In some embodiments, sites on the organic radicals (e.g. alkyl groups, aromatic rings) of compounds described herein are susceptible to various metabolic reactions. Incorporation of appropriate substituents on the organic radicals will reduce, minimize or eliminate this metabolic pathway. In specific embodiments, the appropriate substituent to decrease or eliminate the susceptibility of the aromatic ring to metabolic reactions is, by way of example only, a halogen, deuterium, an alkyl group, a haloalkyl group, or a deuteroalkyl group.

[00207] In another embodiment, the compounds described herein are labeled isotopically (e.g. with a radioisotope) or by another other means, including, but not limited to, the use of chromophores or fluorescent moieties, bioluminescent labels, or chemiluminescent labels.

[00208] Compounds described herein include isotopically-labeled compounds, which are identical to those recited in the various formulae and structures presented herein, but for the fact that one or more atoms are replaced by an atom having an atomic mass or mass number different from the atomic mass or mass number usually found in nature. Examples of isotopes that can be incorporated into the present compounds include isotopes of hydrogen, carbon, nitrogen, oxygen, fluorine and chlorine, such as, for example, ^{2}H, ^{3}H, ^{13}C, ^{14}C, ^{15}N, ^{18}O, ^{17}O, ^{35}S, ^{18}F, ^{36}Cl. In one aspect, isotopically-labeled compounds described herein, for example those into which radioactive isotopes such as ^{3}H and ^{14}C are incorporated, are useful in drug and/or substrate

tissue distribution assays. In one aspect, substitution with isotopes such as deuterium affords certain therapeutic advantages resulting from greater metabolic stability, such as, for example, increased *in vivo* half-life or reduced dosage requirements.

[00209] In some embodiments, the compounds described herein possess one or more stereocenters and each stereocenter exists independently in either the R or S configuration. The compounds presented herein include all diastereomeric, enantiomeric, atropisomers, and epimeric forms as well as the appropriate mixtures thereof. The compounds and methods provided herein include all cis, trans, syn, anti, entgegen (E), and zusammen (Z) isomers as well as the appropriate mixtures thereof.

[00210] Individual stereoisomers are obtained, if desired, by methods such as, stereoselective synthesis and/or the separation of stereoisomers by chiral chromatographic columns. In certain embodiments, compounds described herein are prepared as their individual stereoisomers by reacting a racemic mixture of the compound with an optically active resolving agent to form a pair of diastereoisomeric compounds/salts, separating the diastereomers and recovering the optically pure enantiomers. In some embodiments, resolution of enantiomers is carried out using covalent diastereomeric derivatives of the compounds described herein. In another embodiment, diastereomers are separated by separation/resolution techniques based upon differences in solubility. In other embodiments, separation of steroisomers is performed by chromatography or by the forming diastereomeric salts and separation by recrystallization, or chromatography, or any combination thereof. Jean Jacques, Andre Collet, Samuel H. Wilen, "Enantiomers, Racemates and Resolutions", John Wiley And Sons, Inc., 1981. In some embodiments, stereoisomers are obtained by stereoselective synthesis.

[00211] In some embodiments, compounds described herein are prepared as prodrugs. A "prodrug" refers to an agent that is converted into the parent drug *in vivo*. Prodrugs are often useful because, in some situations, they are easier to administer than the parent drug. They are, for instance, bioavailable by oral administration whereas the parent is not. Further or alternatively, the prodrug also has improved solubility in pharmaceutical compositions over the parent drug. In some embodiments, the design of a prodrug increases the effective water solubility. An example, without limitation, of a prodrug is a compound described herein, which is administered as an ester (the "prodrug") but then is metabolically hydrolyzed to provide the active entity. A further example of a prodrug is a short peptide (polyaminoacid) bonded to an acid group where the peptide is metabolized to reveal the active moiety. In certain embodiments, upon *in vivo* administration, a prodrug is chemically converted to the biologically, pharmaceutically or therapeutically active form of the compound. In certain embodiments, a

prodrug is enzymatically metabolized by one or more steps or processes to the biologically, pharmaceutically or therapeutically active form of the compound.

[00212] Prodrugs of the compounds described herein include, but are not limited to, esters, ethers, carbonates, thiocarbonates, N-acyl derivatives, N-acyloxyalkyl derivatives, quaternary derivatives of tertiary amines, N-Mannich bases, Schiff bases, amino acid conjugates, phosphate esters, and sulfonate esters. See for example Design of Prodrugs, Bundgaard, A. Ed., Elseview, 1985 and Method in Enzymology, Widder, K. *et al.*, Ed.; Academic, 1985, vol. 42, p. 309-396; Bundgaard, H. "Design and Application of Prodrugs" in A Textbook of Drug Design and Development, Krosgaard-Larsen and H. Bundgaard, Ed., 1991, Chapter 5, p. 113-191; and Bundgaard, H., Advanced Drug Delivery Review, 1992, 8, 1-38, each of which is incorporated herein by reference. In some embodiments, a hydroxyl group in the compounds disclosed herein is used to form a prodrug, wherein the hydroxyl group is incorporated into an acyloxyalkyl ester, alkoxycarbonyloxyalkyl ester, alkyl ester, aryl ester, phosphate ester, sugar ester, ether, and the like. In some embodiments, a hydroxyl group in the compounds disclosed herein is a prodrug wherein the hydroxyl is then metabolized in vivo to provide a carboxylic acid group. In some embodiments, a carboxyl group is used to provide an ester or amide (i.e. the prodrug), which is then metabolized in vivo to provide a carboxylic acid group. In some embodiments, compounds described herein are prepared as alkyl ester prodrugs.

[00213] Prodrug forms of the herein described compounds, wherein the prodrug is metabolized *in vivo* to produce a compound described herein as set forth herein are included within the scope of the claims. In some cases, some of the herein-described compounds is a prodrug for another derivative or active compound.

[00214] In additional or further embodiments, the compounds described herein are metabolized upon administration to an organism in need to produce a metabolite that is then used to produce a desired effect, including a desired therapeutic effect.

[00215] A "metabolite" of a compound disclosed herein is a derivative of that compound that is formed when the compound is metabolized. The term "active metabolite" refers to a biologically active derivative of a compound that is formed when the compound is metabolized. The term "metabolized," as used herein, refers to the sum of the processes (including, but not limited to, hydrolysis reactions and reactions catalyzed by enzymes) by which a particular substance is changed by an organism. Thus, enzymes may produce specific structural alterations to a compound. For example, cytochrome P450 catalyzes a variety of oxidative and reductive reactions while uridine diphosphate glucuronyltransferases catalyze the transfer of an activated glucuronic-acid molecule to aromatic alcohols, aliphatic alcohols, carboxylic acids, amines and

free sulphydryl groups. Metabolites of the compounds disclosed herein are optionally identified either by administration of compounds to a host and analysis of tissue samples from the host, or by incubation of compounds with hepatic cells in vitro and analysis of the resulting compounds.

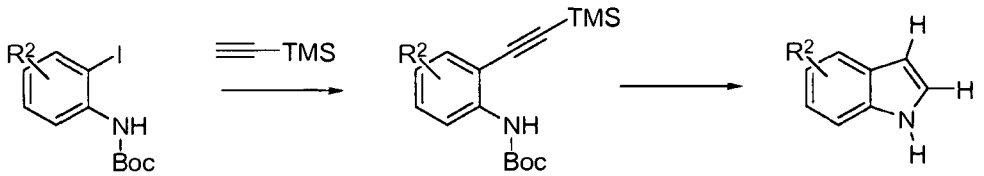
Synthesis of Compounds

[00216] Compounds described herein are synthesized using standard synthetic techniques or using methods known in the art in combination with methods described herein.

[00217] Indoles are readily prepared by chemical synthesis using standard methodologies as described in the review "Practical methodologies for the synthesis of indoles" Humphrey and Kuethe, *Chem. Rev.*, **2006**, *106*, 2875-2911. Compounds are prepared using standard organic chemistry techniques such as those described in, for example, March's Advanced Organic Chemistry, 6th Edition, John Wiley and Sons, Inc. Alternative reaction conditions for the synthetic transformations described herein may be employed such as variation of solvent, reaction temperature, reaction time, as well as different chemical reagents and other reaction conditions. The starting materials are available from commercial sources or are readily prepared. Many functionalized indole and 2-oxindole compounds are commercially available.

[00218] In some embodiments, the preparation of indole compounds begins with the sequence of steps shown in Scheme 1.

Scheme I

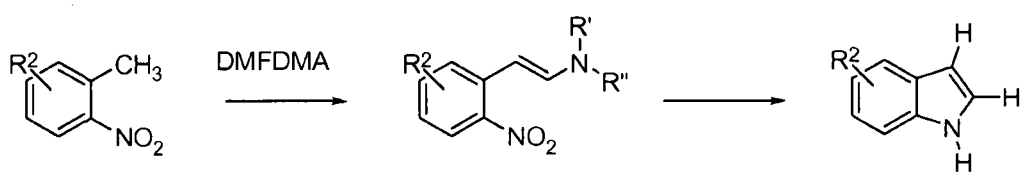


I-1 I-2 I-3

[00219] In some embodiments, Boc-protected 2-iodoanilines (**I-1**) are treated with TMS-acetylene using Sonogashira cross-coupling conditions to generate the alkyne **I-2** which, upon treatment with base then cyclizes to give indoles of general structure **I-3**.

[00220] In other embodiments, the preparation of indole compounds begins with the sequence of steps shown in Scheme II.

Scheme II

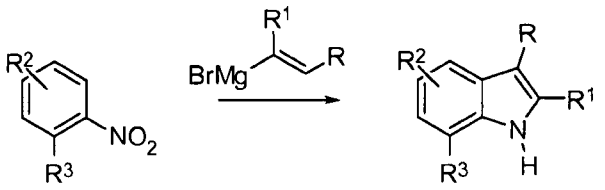


II-1 II-2 II-3

[00221] The Leimgruber-Batcho indole synthesis is described in Scheme II. Substituted *O*-nitrotoluene **II-1** can be reacted with dimethylformamide dimethyl acetal (DMFDMA) to provide the vinyl intermediate **II-2**. Reductive cyclization usinig, for example, nickel boride and hydrazine then yields the indole of general structure **II-3**.

[00222] In other embodiments, the preparation of indole compounds begins with the sequence of steps shown in Scheme III.

Scheme III

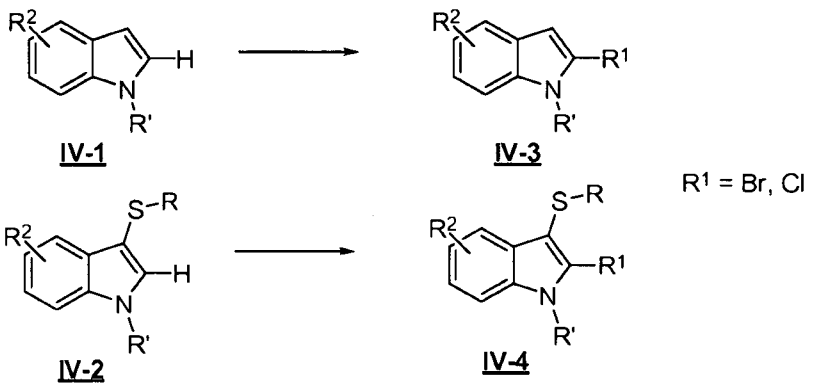


III-1 III-2

[00223] The Bartoli indole synthesis is shown in Scheme III and requires an ortho-substituted nitrobenzene (**III-1**). Treatment of **III-1** with a vinyl magnesium Grignard reagent results in an indole of general structure **III-2**.

[00224] In some embodiments, 2-H Indoles are functionalized as shown in Scheme IV.

Scheme IV



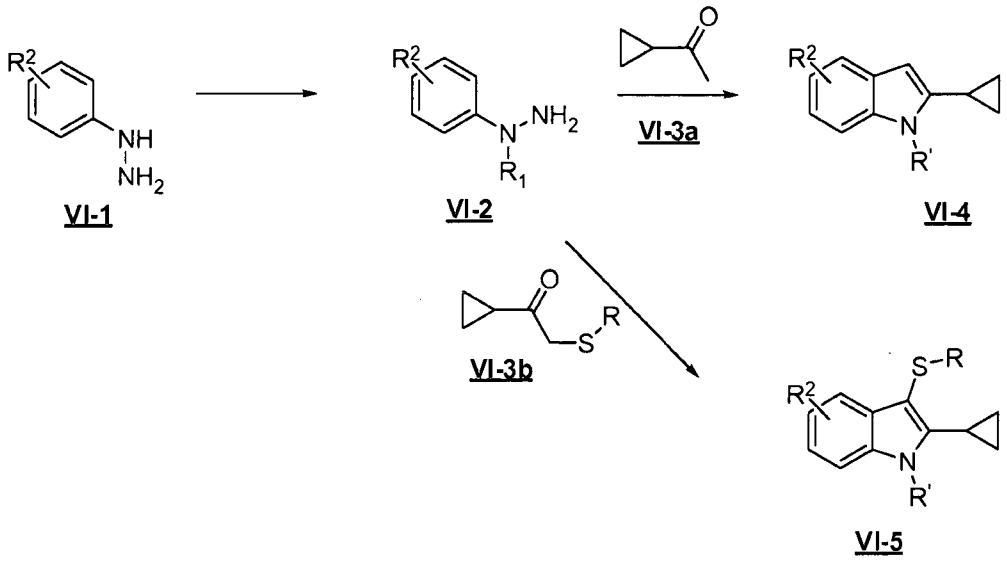
IV-1 IV-3

IV-2 IV-4

[00225] In some embodiments, treatment of 2-H Indoles of general structure **IV-1** or **IV-2** with NCS or NBS in an inert solvent affords 2-chloro or bromo indoles of general structure **IV-3** or **IV-4**.

[00226] In yet other embodiments, 2-oxindoles are used to preare compounds described herein as shown in Scheme V.

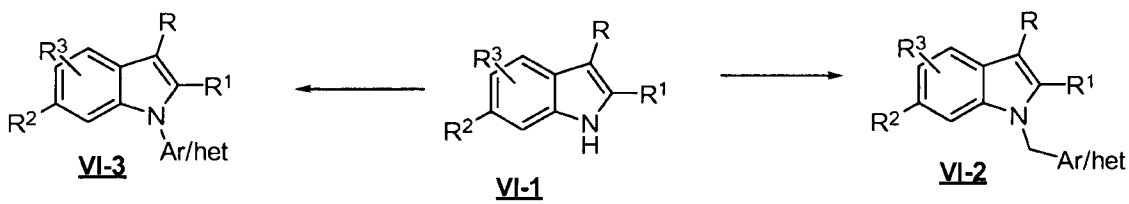
Scheme VI



[00229] In some embodiments, the Fisher indole reaction using the hydrazine **VI-1** or **VI-2** and the cyclopropylketone **VI-3a** is used to prepare 2-cyclopropyl indoles of general structure **VI-4** (Scheme VI). In some embodiments, the 3-thio substituted 2-cyclopropyl indole **VI-5** is prepared using the cyclopropylketone **VI-3b**.

[00230] N-H Indoles of general structure **VII-1** may be further modified as shown in Scheme VII.

Scheme VII



[00231] Treatment with a base such as NaH followed by alkylation with an electrophile (for example $BrCH_2CONR'R''$ or $BrCH_2CH_2CO_2tBu$ or $ClCH_2Aryl$) can then form compounds of general structure **VII-2**. Subsequent chemical modifications can then be made to the indole N-substituent using standard chemical transformations. Direct arylation or heteroarylation may be achieved using Ullman-type conditions to generate **VII-3**.

[00232] In some embodiments, compounds described herein are synthesized as outlined in the Examples.

Certain Terminology

[00233] Unless otherwise stated, the following terms used in this application have the definitions given below. The use of the term "including" as well as other forms, such as

"include", "includes," and "included," is not limiting. The section headings used herein are for organizational purposes only and are not to be construed as limiting the subject matter described.

[00234] As used herein, C_1-C_x includes C_1-C_2, C_1-C_3 . . . C_1-C_x. By way of example only, a group designated as "C_1-C_4" indicates that there are one to four carbon atoms in the moiety, i.e. groups containing 1 carbon atom, 2 carbon atoms, 3 carbon atoms or 4 carbon atoms. Thus, by way of example only, "C_1-C_4 alkyl" indicates that there are one to four carbon atoms in the alkyl group, *i.e.*, the alkyl group is selected from among methyl, ethyl, propyl, *iso*-propyl, *n*-butyl, *iso*-butyl, *sec*-butyl, and *t*-butyl.

[00235] An "alkyl" group refers to an aliphatic hydrocarbon group. The alkyl group is branched or straight chain. In some embodiments, the "alkyl" group has 1 to 10 carbon atoms, i.e. a C_1-C_{10}alkyl. Whenever it appears herein, a numerical range such as "1 to 10" refers to each integer in the given range; *e.g.*, "1 to 10 carbon atoms" means that the alkyl group consist of 1 carbon atom, 2 carbon atoms, 3 carbon atoms, *etc.*, up to and including 10 carbon atoms, although the present definition also covers the occurrence of the term "alkyl" where no numerical range is designated. In some embodiments, an alkyl is a C_1-C_6alkyl. In one aspect the alkyl is methyl, ethyl, propyl, iso-propyl, n-butyl, iso-butyl, sec-butyl, or t-butyl. Typical alkyl groups include, but arc in no way limited to, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tertiary butyl, pentyl, neopentyl, or hexyl.

[00236] An "alkylene" group refers refers to a divalent alkyl radical. Any of the above mentioned monovalent alkyl groups may be an alkylene by abstraction of a second hydrogen atom from the alkyl. In some embodiments, an alkelene is a C_1-C_6alkylene. In other embodiments, an alkylene is a C_1-C_4alkylene. Typical alkylene groups include, but are not limited to, $-CH_2-$, $-CH(CH_3)-$, $-C(CH_3)_2-$, $-CH_2CH_2-$, $-CH_2CH(CH_3)-$, $-CH_2C(CH_3)_2-$, $-CH_2CH_2CH_2-$, $-CH_2CH_2CH_2CH_2-$, and the like.

[00237] "Deuteroalkyl" refers to an alkyl group where 1 or more hydrogen atoms of an alkyl are replaced with deuterium.

[00238] The term "alkenyl" refers to a type of alkyl group in which at least one carbon-carbon double bond is present. In one embodiment, an alkenyl group has the formula $-C(R)=CR_2$, wherein R refers to the remaining portions of the alkenyl group, which may be the same or different. In some embodiments, R is H or an alkyl. Non-limiting examples of an alkenyl group include $-CH=CH_2$, $-C(CH_3)=CH_2$, $-CH=CHCH_3$, $-C(CH_3)=CHCH_3$, and $-CH_2CH=CH_2$.

[00239] The term "alkynyl" refers to a type of alkyl group in which at least one carbon-carbon triple bond is present. In one embodiment, an alkenyl group has the formula -C≡C-R, wherein R refers to the remaining portions of the alkynyl group. In some embodiments, R is H or an alkyl.

Non-limiting examples of an alkynyl group include -C≡CH, -C≡CCH$_3$ -C≡CCH$_2$CH$_3$, -CH$_2$C≡CH.

[00240] An "alkoxy" group refers to a (alkyl)O- group, where alkyl is as defined herein.

[00241] The term "alkylamine" refers to the –N(alkyl)$_x$H$_y$ group, where x is 0 and y is 2, or where x is 1 and y is 1, or where x is 2 and y is 0.

[00242] The term "aromatic" refers to a planar ring having a delocalized π-electron system containing 4n+2 π electrons, where n is an integer. The term "aromatic" includes both carbocyclic aryl ("aryl", *e.g.*, phenyl) and heterocyclic aryl (or "heteroaryl" or "heteroaromatic") groups (*e.g.*, pyridine). The term includes monocyclic or fused-ring polycyclic (*i.e.*, rings which share adjacent pairs of carbon atoms) groups.

[00243] The term "carbocyclic" or "carbocycle" refers to a ring or ring system where the atoms forming the backbone of the ring are all carbon atoms. The term thus distinguishes carbocyclic from "heterocyclic" rings or "heterocycles" in which the ring backbone contains at least one atom which is different from carbon. In some embodiments, at least one of the two rings of a bicyclic carbocycle is aromatic. In some embodiments, both rings of a bicyclic carbocycle are aromatic.

[00244] As used herein, the term "aryl" refers to an aromatic ring wherein each of the atoms forming the ring is a carbon atom. In one aspect, aryl is phenyl or a naphthyl. In some embodiments, an aryl is a phenyl. In some embodiments, an aryl is a C$_6$-C$_{10}$aryl. Depending on the structure, an aryl group is a monoradical or a diradical (i.e., an arylene group).

[00245] The term "cycloalkyl" refers to a monocyclic or polycyclic aliphatic, non-aromatic radical, wherein each of the atoms forming the ring (i.e. skeletal atoms) is a carbon atom. . In some embodiments, cycloalkyls are spirocyclic or bridged compounds. In some embodiments, cycloalkyls are optionally fused with an aromatic ring, and the point of attachment is at a carbon that is not an aromatic ring carbon atom. Cycloalkyl groups include groups having from 3 to 10 ring atoms. In some embodiments, cycloalkyl groups are selected from among cyclopropyl, cyclobutyl, cyclopentyl, cyclopentenyl, cyclohexyl, cyclohexenyl, cycloheptyl, cyclooctyl, spiro[2.2]pentyl, norbornyl and bicycle[1.1.1]pentyl. In some embodiments, a cycloalkyl is a C$_3$-C$_6$cycloalkyl.

[00246] The term "halo" or, alternatively, "halogen" or "halide" means fluoro, chloro, bromo or iodo. In some embodiments, halo is fluoro, chloro, or bromo.

[00247] The term "fluoroalkyl" refers to an alkyl in which one or more hydrogen atoms are replaced by a fluorine atom. In one aspect, a fluoralkyl is a C$_1$-C$_6$fluoroalkyl.

[00248] The term "heteroalkyl" refers to an alkyl group in which one or more skeletal atoms of the alkyl are selected from an atom other than carbon, *e.g.*, oxygen, nitrogen (e.g. –NH-, -N(alkyl)-, sulfur, or combinations thereof. A heteroalkyl is attached to the rest of the molecule at a carbon atom of the heteroalkyl. In one aspect, a heteroalkyl is a C_1-C_6heteroalkyl.

[00249] The term "heterocycle" or "heterocyclic" refers to heteroaromatic rings (also known as heteroaryls) and heterocycloalkyl rings (also known as heteroalicyclic groups) containing one to four heteroatoms in the ring(s), where each heteroatom in the ring(s) is selected from O, S and N, wherein each heterocyclic group has from 3 to 10 atoms in its ring system, and with the proviso that any ring does not contain two adjacent O or S atoms. Non-aromatic heterocyclic groups (also known as heterocycloalkyls) include rings having 3 to 10 atoms in its ring system and aromatic heterocyclic groups include rings having 5 to 10 atoms in its ring system. The heterocyclic groups include benzo-fused ring systems. Examples of non-aromatic heterocyclic groups are pyrrolidinyl, tetrahydrofuranyl, dihydrofuranyl, tetrahydrothienyl, oxazolidinonyl, tetrahydropyranyl, dihydropyranyl, tetrahydrothiopyranyl, piperidinyl, morpholinyl, thiomorpholinyl, thioxanyl, piperazinyl, aziridinyl, azetidinyl, oxetanyl, thietanyl, homopiperidinyl, oxepanyl, thiepanyl, oxazepinyl, diazepinyl, thiazepinyl, 1,2,3,6-tetrahydropyridinyl, pyrrolin-2-yl, pyrrolin-3-yl, indolinyl, 2H-pyranyl, 4H-pyranyl, dioxanyl, 1,3-dioxolanyl, pyrazolinyl, dithianyl, dithiolanyl, dihydropyranyl, dihydrothienyl, dihydrofuranyl, pyrazolidinyl, imidazolinyl, imidazolidinyl, 3-azabicyclo[3.1.0]hexanyl, 3-azabicyclo[4.1.0]heptanyl, 3H-indolyl, indolin-2-onyl, isoindolin-1-onyl, isoindoline-1,3-dionyl, 3,4-dihydroisoquinolin-1(2H)-onyl, 3,4-dihydroquinolin-2(1H)-onyl, isoindoline-1,3-dithionyl, benzo[d]oxazol-2(3H)-onyl, 1H-benzo[d]imidazol-2(3H)-onyl, benzo[d]thiazol-2(3H)-onyl, and quinolizinyl. Examples of aromatic heterocyclic groups are pyridinyl, imidazolyl, pyrimidinyl, pyrazolyl, triazolyl, pyrazinyl, tetrazolyl, furyl, thienyl, isoxazolyl, thiazolyl, oxazolyl, isothiazolyl, pyrrolyl, quinolinyl, isoquinolinyl, indolyl, benzimidazolyl, benzofuranyl, cinnolinyl, indazolyl, indolizinyl, phthalazinyl, pyridazinyl, triazinyl, isoindolyl, pteridinyl, purinyl, oxadiazolyl, thiadiazolyl, furazanyl, benzofurazanyl, benzothiophenyl, benzothiazolyl, benzoxazolyl, quinazolinyl, quinoxalinyl, naphthyridinyl, and furopyridinyl. The foregoing groups are either C-attached (or C-linked) or *N*-attached where such is possible. For instance, a group derived from pyrrole includes both pyrrol-1-yl (*N*-attached) or pyrrol-3-yl (C-attached). Further, a group derived from imidazole includes imidazol-1-yl or imidazol-3-yl (both *N*-attached) or imidazol-2-yl, imidazol-4-yl or imidazol-5-yl (all C-attached). The heterocyclic groups include benzo-fused ring systems. Non-aromatic heterocycles are optionally substituted with one or two oxo (=O) moieties, such as pyrrolidin-2-one. In some embodiments, at least one

[00253] The term "moiety" refers to a specific segment or functional group of a molecule. Chemical moieties are often recognized chemical entities embedded in or appended to a molecule.

[00254] The term "optionally substituted" or "substituted" means that the referenced group is optionally substituted with one or more additional group(s) individually and independently selected from halogen, -CN, $-NH_2$, -NH(alkyl), $-N(alkyl)_2$, -OH, $-CO_2H$, $-CO_2$alkyl, $-C(=O)NH_2$, -C(=O)NH(alkyl), $-C(=O)N(alkyl)_2$, $-S(=O)_2NH_2$, -S(=O)$_2$NH(alkyl), $-S(=O)_2N(alkyl)_2$, alkyl, cycloalkyl, fluoroalkyl, heteroalkyl, alkoxy, fluoroalkoxy, heterocycloalkyl, aryl, heteroaryl, aryloxy, alkylthio, arylthio, alkylsulfoxide, arylsulfoxide, alkylsulfone, and arylsulfone. In some other embodiments, optional substituents are independently selected from halogen, -CN, $-NH_2$, $-NH(CH_3)$, $-N(CH_3)_2$, -OH, $-CO_2H$, $-CO_2(C_1$-C_4alkyl), $-C(=O)NH_2$, $-C(=O)NH(C_1$-C_4alkyl), $-C(=O)N(C_1$-C_4alkyl)$_2$, $-S(=O)_2NH_2$, $-S(=O)_2NH(C_1$-C_4alkyl), $-S(=O)_2N(C_1$-C_4alkyl)$_2$, C_1-C_4alkyl, C_3-C_6cycloalkyl, C_1-C_4fluoroalkyl, C_1-C_4heteroalkyl, C_1-C_4alkoxy, C_1-C_4fluoroalkoxy, $-SC_1$-C_4alkyl, $-S(=O)C_1$-C_4alkyl, and $-S(=O)_2C_1$-C_4alkyl. In some embodiments, optional substituents are independently selected from halogen, -CN, $-NH_2$, -OH, $-NH(CH_3)$, $-N(CH_3)_2$, $-CH_3$, $-CH_2CH_3$, $-CF_3$, $-OCH_3$, and $-OCF_3$. In some embodiments, substituted groups are substituted with one or two of the preceding groups. In some embodiments, an optional substituent on an aliphatic carbon atom (acyclic or cyclic) includes oxo (=O).

[00255] The term "acceptable" with respect to a formulation, composition or ingredient, as used herein, means having no persistent detrimental effect on the general health of the subject being treated.

[00256] The term "modulate" as used herein, means to interact with a target either directly or indirectly so as to alter the activity of the target, including, by way of example only, to enhance the activity of the target, to inhibit the activity of the target, to limit the activity of the target, or to extend the activity of the target.

[00257] The term "modulator" as used herein, refers to a molecule that interacts with a target either directly or indirectly. The interactions include, but are not limited to, the interactions of an agonist, partial agonist, an inverse agonist, antagonist, degrader, or combinations thereof. In some embodiments, a modulator is an antagonist. In some embodiments, a modulator is a degrader.

[00258] The terms "administer," "administering", "administration," and the like, as used herein, refer to the methods that may be used to enable delivery of compounds or compositions to the desired site of biological action. These methods include, but are not limited to oral routes, intraduodenal routes, parenteral injection (including intravenous, subcutaneous, intraperitoneal,

intramuscular, intravascular or infusion), topical and rectal administration. Those of skill in the art are familiar with administration techniques that can be employed with the compounds and methods described herein. In some embodiments, the compounds and compositions described herein are administered orally.

[00259] The terms "co-administration" or the like, as used herein, are meant to encompass administration of the selected therapeutic agents to a single patient, and are intended to include treatment regimens in which the agents are administered by the same or different route of administration or at the same or different time.

[00260] The terms "effective amount" or "therapeutically effective amount," as used herein, refer to a sufficient amount of an agent or a compound being administered, which will relieve to some extent one or more of the symptoms of the disease or condition being treated. The result includes reduction and/or alleviation of the signs, symptoms, or causes of a disease, or any other desired alteration of a biological system. For example, an "effective amount" for therapeutic uses is the amount of the composition comprising a compound as disclosed herein required to provide a clinically significant decrease in disease symptoms. An appropriate "effective" amount in any individual case is optionally determined using techniques, such as a dose escalation study.

[00261] The terms "enhance" or "enhancing," as used herein, means to increase or prolong either in potency or duration a desired effect. Thus, in regard to enhancing the effect of therapeutic agents, the term "enhancing" refers to the ability to increase or prolong, either in potency or duration, the effect of other therapeutic agents on a system. An "enhancing-effective amount," as used herein, refers to an amount adequate to enhance the effect of another therapeutic agent in a desired system.

[00262] The term "pharmaceutical combination" as used herein, means a product that results from the mixing or combining of more than one active ingredient and includes both fixed and non-fixed combinations of the active ingredients. The term "fixed combination" means that the active ingredients, e.g. a compound described herein, or a pharmaceutically acceptable salt thereof, and a co-agent, are both administered to a patient simultaneously in the form of a single entity or dosage. The term "non-fixed combination" means that the active ingredients, e.g. a compound described herein, or a pharmaceutically acceptable salt thereof, and a co-agent, are administered to a patient as separate entities either simultaneously, concurrently or sequentially with no specific intervening time limits, wherein such administration provides effective levels of the two compounds in the body of the patient. The latter also applies to cocktail therapy, e.g. the administration of three or more active ingredients.

[00263] The terms "kit" and "article of manufacture" are used as synonyms.

[00264] The term "subject" or "patient" encompasses mammals. Examples of mammals include, but are not limited to, any member of the Mammalian class: humans, non-human primates such as chimpanzees, and other apes and monkey species; farm animals such as cattle, horses, sheep, goats, swine; domestic animals such as rabbits, dogs, and cats; laboratory animals including rodents, such as rats, mice and guinea pigs, and the like. In one aspect, the mammal is a human.

[00265] The terms "treat," "treating" or "treatment," as used herein, include alleviating, abating or ameliorating at least one symptom of a disease or condition, preventing additional symptoms, inhibiting the disease or condition, e.g., arresting the development of the disease or condition, relieving the disease or condition, causing regression of the disease or condition, relieving a condition caused by the disease or condition, or stopping the symptoms of the disease or condition either prophylactically and/or therapeutically.

Pharmaceutical compositions

[00266] In some embodiments, the compounds described herein are formulated into pharmaceutical compositions. Pharmaceutical compositions are formulated in a conventional manner using one or more pharmaceutically acceptable inactive ingredients that facilitate processing of the active compounds into preparations that are used pharmaceutically. Proper formulation is dependent upon the route of administration chosen. A summary of pharmaceutical compositions described herein is found, for example, in Remington: The Science and Practice of Pharmacy, Nineteenth Ed (Easton, Pa.: Mack Publishing Company, 1995); Hoover, John E., Remington's Pharmaceutical Sciences, Mack Publishing Co., Easton, Pennsylvania 1975; Liberman, H.A. and Lachman, L., Eds., Pharmaceutical Dosage Forms, Marcel Decker, New York, N.Y., 1980; and Pharmaceutical Dosage Forms and Drug Delivery Systems, Seventh Ed. (Lippincott Williams & Wilkins1999), herein incorporated by reference for such disclosure.

[00267] In some embodiments, the compounds described herein are administered either alone or in combination with pharmaceutically acceptable carriers, excipients or diluents, in a pharmaceutical composition. Administration of the compounds and compositions described herein can be effected by any method that enables delivery of the compounds to the site of action. These methods include, though are not limited to delivery via enteral routes (including oral, gastric or duodenal feeding tube, rectal suppository and rectal enema), parenteral routes (injection or infusion, including intraarterial, intracardiac, intradermal, intraduodenal, intramedullary, intramuscular, intraosseous, intraperitoneal, intrathecal, intravascular, intravenous, intravitreal, epidural and subcutaneous), inhalational, transdermal, transmucosal, sublingual, buccal and topical (including epicutaneous, dermal, enema, eye drops, ear drops, intranasal, vaginal) administration, although the most suitable route may depend upon for

example the condition and disorder of the recipient. By way of example only, compounds described herein can be administered locally to the area in need of treatment, by for example, local infusion during surgery, topical application such as creams or ointments, injection, catheter, or implant. The administration can also be by direct injection at the site of a diseased tissue or organ.

[00268] In some embodiments, pharmaceutical compositions suitable for oral administration are presented as discrete units such as capsules, cachets or tablets each containing a predetermined amount of the active ingredient; as a powder or granules; as a solution or a suspension in an aqueous liquid or a non-aqueous liquid; or as an oil-in-water liquid emulsion or a water-in-oil liquid emulsion. In some embodiments, the active ingredient is presented as a bolus, electuary or paste.

[00269] Pharmaceutical compositions which can be used orally include tablets, push-fit capsules made of gelatin, as well as soft, sealed capsules made of gelatin and a plasticizer, such as glycerol or sorbitol. Tablets may be made by compression or molding, optionally with one or more accessory ingredients. Compressed tablets may be prepared by compressing in a suitable machine the active ingredient in a free-flowing form such as a powder or granules, optionally mixed with binders, inert diluents, or lubricating, surface active or dispersing agents. Molded tablets may be made by molding in a suitable machine a mixture of the powdered compound moistened with an inert liquid diluent. In some embodiments, the tablets are coated or scored and are formulated so as to provide slow or controlled release of the active ingredient therein. All formulations for oral administration should be in dosages suitable for such administration. The push-fit capsules can contain the active ingredients in admixture with filler such as lactose, binders such as starches, and/or lubricants such as talc or magnesium stearate and, optionally, stabilizers. In soft capsules, the active compounds may be dissolved or suspended in suitable liquids, such as fatty oils, liquid paraffin, or liquid polyethylene glycols. In some embodiments, stabilizers are added. Dragee cores are provided with suitable coatings. For this purpose, concentrated sugar solutions may be used, which may optionally contain gum arabic, talc, polyvinyl pyrrolidone, carbopol gel, polyethylene glycol, and/or titanium dioxide, lacquer solutions, and suitable organic solvents or solvent mixtures. Dyestuffs or pigments may be added to the tablets or Dragee coatings for identification or to characterize different combinations of active compound doses.

[00270] In some embodiments, pharmaceutical compositions are formulated for parenteral administration by injection, e.g., by bolus injection or continuous infusion. Formulations for injection may be presented in unit dosage form, e.g., in ampoules or in multi-dose containers,

with an added preservative. The compositions may take such forms as suspensions, solutions or emulsions in oily or aqueous vehicles, and may contain formulatory agents such as suspending, stabilizing and/or dispersing agents. The compositions may be presented in unit-dose or multi-dose containers, for example sealed ampoules and vials, and may be stored in powder form or in a freeze-dried (lyophilized) condition requiring only the addition of the sterile liquid carrier, for example, saline or sterile pyrogen-free water, immediately prior to use. Extemporaneous injection solutions and suspensions may be prepared from sterile powders, granules and tablets of the kind previously described.

[00271] Pharmaceutical compositions for parenteral administration include aqueous and non-aqueous (oily) sterile injection solutions of the active compounds which may contain antioxidants, buffers, bacteriostats and solutes which render the formulation isotonic with the blood of the intended recipient; and aqueous and non-aqueous sterile suspensions which may include suspending agents and thickening agents. Suitable lipophilic solvents or vehicles include fatty oils such as sesame oil, or synthetic fatty acid esters, such as ethyl oleate or triglycerides, or liposomes. Aqueous injection suspensions may contain substances which increase the viscosity of the suspension, such as sodium carboxymethyl cellulose, sorbitol, or dextran. Optionally, the suspension may also contain suitable stabilizers or agents which increase the solubility of the compounds to allow for the preparation of highly concentrated solutions.

[00272] Pharmaceutical compositions may also be formulated as a depot preparation. Such long acting formulations may be administered by implantation (for example subcutaneously or intramuscularly) or by intramuscular injection. Thus, for example, the compounds may be formulated with suitable polymeric or hydrophobic materials (for example, as an emulsion in an acceptable oil) or ion exchange resins, or as sparingly soluble derivatives, for example, as a sparingly soluble salt.

[00273] For buccal or sublingual administration, the compositions may take the form of tablets, lozenges, pastilles, or gels formulated in conventional manner. Such compositions may comprise the active ingredient in a flavored basis such as sucrose and acacia or tragacanth.

[00274] Pharmaceutical compositions may also be formulated in rectal compositions such as suppositories or retention enemas, e.g., containing conventional suppository bases such as cocoa butter, polyethylene glycol, or other glycerides.

[00275] Pharmaceutical compositions may be administered topically, that is by non-systemic administration. This includes the application of a compound of the present invention externally to the epidermis or the buccal cavity and the instillation of such a compound into the ear, eye and

nose, such that the compound does not significantly enter the blood stream. In contrast, systemic administration refers to oral, intravenous, intraperitoneal and intramuscular administration.

[00276] Pharmaceutical compositions suitable for topical administration include liquid or semi-liquid preparations suitable for penetration through the skin to the site of inflammation such as gels, liniments, lotions, creams, ointments or pastes, and drops suitable for administration to the eye, ear or nose. The active ingredient may comprise, for topical administration, from 0.001% to 10% w/w, for instance from 1% to 2% by weight of the formulation.

[00277] Pharmaceutical compositions for administration by inhalation are conveniently delivered from an insufflator, nebulizer pressurized packs or other convenient means of delivering an aerosol spray. Pressurized packs may comprise a suitable propellant such as dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, carbon dioxide or other suitable gas. In the case of a pressurized aerosol, the dosage unit may be determined by providing a valve to deliver a metered amount. Alternatively, for administration by inhalation or insufflation, pharmaceutical preparations may take the form of a dry powder composition, for example a powder mix of the compound and a suitable powder base such as lactose or starch. The powder composition may be presented in unit dosage form, in for example, capsules, cartridges, gelatin or blister packs from which the powder may be administered with the aid of an inhalator or insufflator.

[00278] It should be understood that in addition to the ingredients particularly mentioned above, the compounds and compositions described herein may include other agents conventional in the art having regard to the type of formulation in question, for example those suitable for oral administration may include flavoring agents.

Methods of Dosing and Treatment Regimens

[00279] In one embodiment, the compounds described herein, or a pharmaceutically acceptable salt thereof, are used in the preparation of medicaments for the treatment of diseases or conditions in a mammal that would benefit from inhibition or reduction of autotaxin activity. Methods for treating any of the diseases or conditions described herein in a mammal in need of such treatment, involves administration of pharmaceutical compositions that include at least one compound described herein or a pharmaceutically acceptable salt, active metabolite, prodrug, or pharmaceutically acceptable solvate thereof, in therapeutically effective amounts to said mammal.

[00280] In certain embodiments, the compositions containing the compound(s) described herein are administered for prophylactic and/or therapeutic treatments. In certain therapeutic applications, the compositions are administered to a patient already suffering from a disease or

condition, in an amount sufficient to cure or at least partially arrest at least one of the symptoms of the disease or condition. Amounts effective for this use depend on the severity and course of the disease or condition, previous therapy, the patient's health status, weight, and response to the drugs, and the judgment of the treating physician. Therapeutically effective amounts are optionally determined by methods including, but not limited to, a dose escalation and/or dose ranging clinical trial.

[00281] In prophylactic applications, compositions containing the compounds described herein are administered to a patient susceptible to or otherwise at risk of a particular disease, disorder or condition. Such an amount is defined to be a "prophylactically effective amount or dose." In this use, the precise amounts also depend on the patient's state of health, weight, and the like. When used in patients, effective amounts for this use will depend on the severity and course of the disease, disorder or condition, previous therapy, the patient's health status and response to the drugs, and the judgment of the treating physician. In one aspect, prophylactic treatments include administering to a mammal, who previously experienced at least one symptom of the disease being treated and is currently in remission, a pharmaceutical composition comprising a compound described herein, or a pharmaceutically acceptable salt thereof, in order to prevent a return of the symptoms of the disease or condition.

[00282] In certain embodiments wherein the patient's condition does not improve, upon the doctor's discretion the administration of the compounds are administered chronically, that is, for an extended period of time, including throughout the duration of the patient's life in order to ameliorate or otherwise control or limit the symptoms of the patient's disease or condition.

[00283] In certain embodiments wherein a patient's status does improve, the dose of drug being administered is temporarily reduced or temporarily suspended for a certain length of time (*i.e.*, a "drug holiday"). In specific embodiments, the length of the drug holiday is between 2 days and 1 year, including by way of example only, 2 days, 3 days, 4 days, 5 days, 6 days, 7 days, 10 days, 12 days, 15 days, 20 days, 28 days, or more than 28 days. The dose reduction during a drug holiday is, by way of example only, by 10%-100%, including by way of example only 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, and 100%.

[00284] Once improvement of the patient's conditions has occurred, a maintenance dose is administered if necessary. Subsequently, in specific embodiments, the dosage or the frequency of administration, or both, is reduced, as a function of the symptoms, to a level at which the improved disease, disorder or condition is retained. In certain embodiments, however, the patient requires intermittent treatment on a long-term basis upon any recurrence of symptoms.

[00285] The amount of a given agent that corresponds to such an amount varies depending upon factors such as the particular compound, disease condition and its severity, the identity (*e.g.*, weight, sex) of the subject or host in need of treatment, but nevertheless is determined according to the particular circumstances surrounding the case, including, *e.g.*, the specific agent being administered, the route of administration, the condition being treated, and the subject or host being treated.

[00286] In general, however, doses employed for adult human treatment are typically in the range of 0.01 mg-5000 mg per day. In one aspect, doses employed for adult human treatment are from about 1 mg to about 1000 mg per day. In one embodiment, the desired dose is conveniently presented in a single dose or in divided doses administered simultaneously or at appropriate intervals, for example as two, three, four or more sub-doses per day.

[00287] In one embodiment, the daily dosages appropriate for the compound described herein, or a pharmaceutically acceptable salt thereof, are from about 0.01 to about 50 mg/kg per body weight. In some embodiments, the daily dosage or the amount of active in the dosage form are lower or higher than the ranges indicated herein, based on a number of variables in regard to an individual treatment regime. In various embodiments, the daily and unit dosages are altered depending on a number of variables including, but not limited to, the activity of the compound used, the disease or condition to be treated, the mode of administration, the requirements of the individual subject, the severity of the disease or condition being treated, and the judgment of the practitioner.

[00288] Toxicity and therapeutic efficacy of such therapeutic regimens are determined by standard pharmaceutical procedures in cell cultures or experimental animals, including, but not limited to, the determination of the LD_{50} and the ED_{50}. The dose ratio between the toxic and therapeutic effects is the therapeutic index and it is expressed as the ratio between LD_{50} and ED_{50}. In certain embodiments, the data obtained from cell culture assays and animal studies are used in formulating the therapeutically effective daily dosage range and/or the therapeutically effective unit dosage amount for use in mammals, including humans. In some embodiments, the daily dosage amount of the compounds described herein lies within a range of circulating concentrations that include the ED_{50} with minimal toxicity. In certain embodiments, the daily dosage range and/or the unit dosage amount varies within this range depending upon the dosage form employed and the route of administration utilized.

[00289] In some embodiments, liver toxicity can be assessed in suitable in vivo assays. In some embodiments, liver toxicity is assessed by monitoring any increases in the levels of liver markers ALT, AST, AlkP and bilirubin. For example, in a suitable dog liver toxicity study, Compound (1-

34) exhibited undesired elevated liver markers whereas Compound (1-13) did not exhibit the same effects. In some embodiments, no increases in liver markers ALT, AST, AlkP and bilirubin were observed for Compound (1-13) when dosed at 100mpk for 5 days.

[00290] In any of the aforementioned aspects are further embodiments in which the effective amount of the compound described herein, or a pharmaceutically acceptable salt thereof, is: (a) systemically administered to the mammal; and/or (b) administered orally to the mammal; and/or (c) intravenously administered to the mammal; and/or (d) administered by injection to the mammal; and/or (e) administered topically to the mammal; and/or (f) administered non-systemically or locally to the mammal.

[00291] In any of the aforementioned aspects are further embodiments comprising single administrations of the effective amount of the compound, including further embodiments in which (i) the compound is administered once a day; or (ii) the compound is administered to the mammal multiple times over the span of one day.

[00292] In any of the aforementioned aspects are further embodiments comprising multiple administrations of the effective amount of the compound, including further embodiments in which (i) the compound is administered continuously or intermittently: as in a single dose; (ii) the time between multiple administrations is every 6 hours; (iii) the compound is administered to the mammal every 8 hours; (iv) the compound is administered to the mammal every 12 hours; (v) the compound is administered to the mammal every 24 hours. In further or alternative embodiments, the method comprises a drug holiday, wherein the administration of the compound is temporarily suspended or the dose of the compound being administered is temporarily reduced; at the end of the drug holiday, dosing of the compound is resumed. In one embodiment, the length of the drug holiday varies from 2 days to 1 year.

[00293] In certain instances, it is appropriate to administer at least one compound described herein, or a pharmaceutically acceptable salt thereof, in combination with one or more other therapeutic agents. In certain embodiments, the pharmaceutical composition further comprises one or more anti-cancer agents.

[00294] In one embodiment, the therapeutic effectiveness of one of the compounds described herein is enhanced by administration of an adjuvant (*i.e.*, by itself the adjuvant has minimal therapeutic benefit, but in combination with another therapeutic agent, the overall therapeutic benefit to the patient is enhanced). Or, in some embodiments, the benefit experienced by a patient is increased by administering one of the compounds described herein with another agent (which also includes a therapeutic regimen) that also has therapeutic benefit.

[00295] In one specific embodiment, a compound described herein, or a pharmaceutically acceptable salt thereof, is co-administered with a second therapeutic agent, wherein the compound described herein, or a pharmaceutically acceptable salt thereof, and the second therapeutic agent modulate different aspects of the disease, disorder or condition being treated, thereby providing a greater overall benefit than administration of either therapeutic agent alone.

[00296] In any case, regardless of the disease, disorder or condition being treated, the overall benefit experienced by the patient is simply be additive of the two therapeutic agents or the patient experiences a synergistic benefit.

[00297] In certain embodiments, different therapeutically-effective dosages of the compounds disclosed herein will be utilized in formulating pharmaceutical composition and/or in treatment regimens when the compounds disclosed herein are administered in combination with one or more additional agent, such as an additional therapeutically effective drug, an adjuvant or the like. Therapeutically-effective dosages of drugs and other agents for use in combination treatment regimens is optionally determined by means similar to those set forth hereinabove for the actives themselves. Furthermore, the methods of prevention/treatment described herein encompasses the use of metronomic dosing, i.e., providing more frequent, lower doses in order to minimize toxic side effects. In some embodiments, a combination treatment regimen encompasses treatment regimens in which administration of a compound described herein, or a pharmaceutically acceptable salt thereof, is initiated prior to, during, or after treatment with a second agent described herein, and continues until any time during treatment with the second agent or after termination of treatment with the second agent. It also includes treatments in which a compound described herein, or a pharmaceutically acceptable salt thereof, and the second agent being used in combination are administered simultaneously or at different times and/or at decreasing or increasing intervals during the treatment period. Combination treatment further includes periodic treatments that start and stop at various times to assist with the clinical management of the patient.

[00298] It is understood that the dosage regimen to treat, prevent, or ameliorate the condition(s) for which relief is sought, is modified in accordance with a variety of factors (e.g. the disease, disorder or condition from which the subject suffers; the age, weight, sex, diet, and medical condition of the subject). Thus, in some instances, the dosage regimen actually employed varies and, in some embodiments, deviates from the dosage regimens set forth herein.

[00299] For combination therapies described herein, dosages of the co-administered compounds vary depending on the type of co-drug employed, on the specific drug employed, on the disease or condition being treated and so forth. In additional embodiments, when co-administered with

one or more other therapeutic agents, the compound provided herein is administered either simultaneously with the one or more other therapeutic agents, or sequentially.

[00300] In combination therapies, the multiple therapeutic agents (one of which is one of the compounds described herein) are administered in any order or even simultaneously. If administration is simultaneous, the multiple therapeutic agents are, by way of example only, provided in a single, unified form, or in multiple forms (e.g., as a single pill or as two separate pills).

[00301] The compounds described herein, or a pharmaceutically acceptable salt thereof, as well as combination therapies, are administered before, during or after the occurrence of a disease or condition, and the timing of administering the composition containing a compound varies. Thus, in one embodiment, the compounds described herein are used as a prophylactic and are administered continuously to subjects with a propensity to develop conditions or diseases in order to prevent the occurrence of the disease or condition. In another embodiment, the compounds and compositions are administered to a subject during or as soon as possible after the onset of the symptoms. In specific embodiments, a compound described herein is administered as soon as is practicable after the onset of a disease or condition is detected or suspected, and for a length of time necessary for the treatment of the disease. In some embodiments, the length required for treatment varies, and the treatment length is adjusted to suit the specific needs of each subject. For example, in specific embodiments, a compound described herein or a formulation containing the compound is administered for at least 2 weeks, about 1 month to about 5 years.

[00302] In some embodiments, a compound described herein, or a pharmaceutically acceptable salt thereof, is administered in combination with chemotherapy, hormone blocking therapy, radiation therapy, monoclonal antibodies, or combinations thereof.

[00303] Chemotherapy includes the use of anti-cancer agents.

EXAMPLES

[00304] The following examples are provided for illustrative purposes only and not to limit the scope of the claims provided herein.

Synthesis of ethyl 2-fluoro-3-mercaptobenzoate (Intermediate A):

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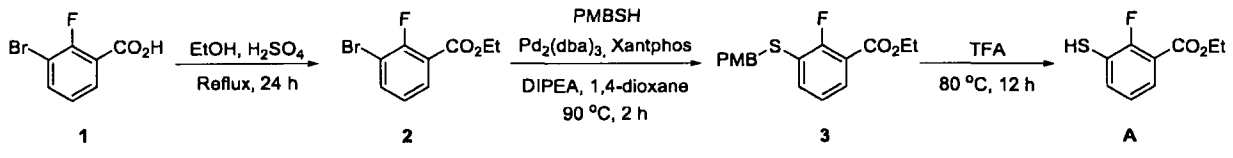


1 2 3 A

Step 1: Synthesis of ethyl 3-bromo-2-fluorobenzoate (2):

[00305] To a stirred solution of 3-bromo-2-fluorobenzoic acid **1** (25.0 g, 114.15 mmol) in ethanol (400 mL) was added conc. H_2SO_4 (3 mL) at RT and stirred at reflux temperature for 24 h. The reaction was monitored by LC-MS; after completion of the reaction, the reaction mixture was concentrated to obtain the residue. The residue was diluted with EtOAc (500 mL), washed with water (300 mL), brine (300 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to afford compound **2** (26.0 g, 92%) as a light yellow liquid. **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.88-7.84 (m, 1H), 7.72-7.69 (m, 1H), 7.08-7.04 (m, 1H), 4.39 (q, J = 7.2 Hz, 2H), 1.39 (t, J = 7.2 Hz, 3H).

Step 2: Synthesis of ethyl 2-fluoro-3-((4-methoxybenzyl)thio)benzoate (3):

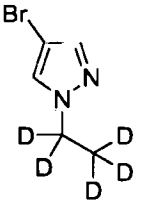
[00306] 1,4-dioxane (250 mL) was degassed by purging with N_2 gas for 30 min and to this, were added a solution of compound **2** (13.2 g, 53.4 mmol) in 1,4-dioxane (50 mL; *degassed*), (4-methoxyphenyl)methanethiol (PMBSH) (8.2 g, 53.4 mmol), xantphos (1.54 g, 2.66 mmol), diisopropyl ethyl amine (19.6 mL, 106.8 mmol) and $Pd_2(dba)_3$ (1.22 g, 1.33 mmol) at RT. The reaction mixture was heated to 90 °C and stirred for 2 h. The reaction was monitored by TLC; after completion of the reaction, the reaction mixture was diluted with hexane (450 mL) and stirred at RT for 15 min. The resultant solution was filtered through celite and washed with hexane (100 mL). The filtrate was washed water (250 mL) dried over Na_2SO_4, filtered and concentrated under reduced pressure to obtain the crude. This was purified by silica gel column chromatography using 3-4% EtOAc/Hexanes to afford compound **3** (15 g, 88%) as pale yellow solid. **^{1}H NMR (500 MHz, $CDCl_3$):** δ 7.78-7.74 (m, 1H), 7.43-7.39 (m, 1H), 7.19 (d, J = 8.0 Hz, 2H), 7.07-7.04 (m, 1H), 6.80 (d, J = 8.0 Hz, 2H), 4.41 (q, J = 7.2 Hz, 2H), 4.08 (s, 2H), 3.78 (s, 3H), 1.41 (t, J = 7.2 Hz, 3H). **LC-MS (ESI):** 89.7%; *m/z* 318.9 (M - H^+); (column: X Select CSH C-18, 50 × 3.0 mm, 3.5 µm); RT 4.22 min; 5 mM NH_4OAc: ACN; 0.8 mL/min).

Step 3: Synthesis of ethyl 2-fluoro-3-mercaptobenzoate (A):

[00307] A stirred solution of compound **3** (30.0 g, 93.75 mmol) in TFA (54.5 mL) was heated to 80 °C and stirred for 12 h under inert atmosphere. The reaction was monitored by TLC; after completion of the reaction, the volatiles were removed under reduced pressure. The residue was dissolved in ice-cold water (100 mL), basified with solid sodium bicarbonate and extracted with EtOAc (2 x 200 mL). The combined organic extracts were dried over Na_2SO_4, filtered and concentrated under reduced pressure to obtain the crude. This was purified by silica gel column chromatography using 3% EtOAc/Hexanes to afford compound **A** (11.7 g, 62%) as a pale brown syrup. **^{1}H NMR (500 MHz, $CDCl_3$):** δ 7.70-7.66 (m, 1H), 7.48-7.44 (m, 1H), 7.08-7.04 (m, 1H), 4.20 (q, J = 7.5 Hz, 2H), 3.67 (s, 1H), 1.40 (t, J = 7.5 Hz, 3H); **LC-MS (ESI):** 91.8%; *m/z* 199.0

δ 8.15 (s, 1H), 7.63 (s, 1H), 5.38 (s, 2H), 3.52 (t, J = 8.5 Hz, 2H), 0.82 (t, J = 7.5 Hz, 2H), 0.04 (s, 9H).

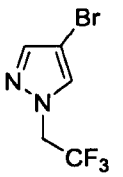
Synthesis of 4-bromo-1-(ethyl-d_5)-1*H*-pyrazole (Intermediate E):



E

[00311] Following the procedure for Intermediate **B** but using ethyl iodide-d_5 in place of iodopropane, Intermediate **E** was prepared as a colorless oil. **^{1}H NMR (500 MHz, $CDCl_3$):** δ 7.44 (s, 1H), 7.40 (s, 1H).

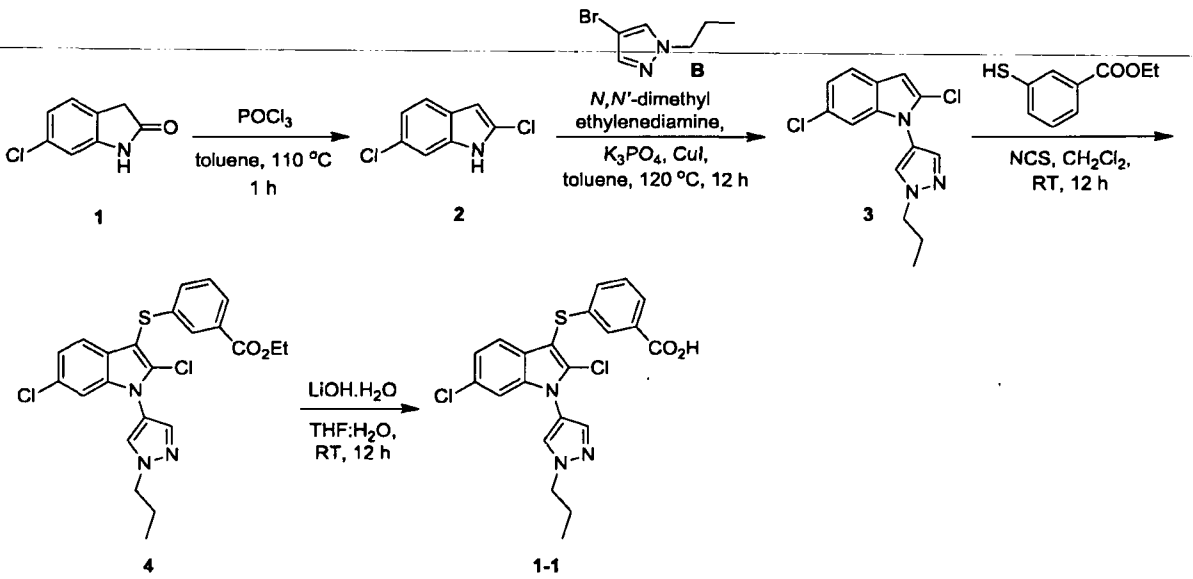
Synthesis of 4-bromo-1-(2,2,2-trifluoroethyl)-1*H*-pyrazole (Intermediate F):



F

[00312] Following the procedure for Intermediate **B** but using 1,1,1-trifluoro-2-iodoethane in place of iodopropane and Cs_2CO_3 /DMF in place of NaH/THF, Intermediate **F** was prepared as a colorless oil. **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.55 (s, 1H), 7.54 (s, 1H), 4.67 (q, 2H).

Example 1: Synthesis of 3-((2,6-dichloro-1-(1-propyl-1H-pyrazol-4-yl)-1H-indol-3-yl)thio)benzoic acid (Compound 1-1)



Step 1: Synthesis of 2,6-dichloro-1*H*-indole (2):

[00313] To a stirred solution of 6-chloroindolin-2-one **1** (500 mg, 2.99 mmol) in toluene (25 mL) under inert atmosphere were added *N,N*-dimethylaniline (362 mg, 2.99 mmol) and $POCl_3$ (918 g, 5.98 mmol) at RT; heated to 110 °C and stirred for 1 h. The reaction was monitored by TLC; after completion of the reaction, the reaction mixture was quenched with 10% aq. $NaHCO_3$ solution (30 mL) and extracted with EtOAc (2 x 30 mL). The combined organic extracts were dried over Na_2SO_4, filtered and concentrated under reduced pressure to obtain the crude. This was purified by silica gel column chromatography using 5% EtOAc/ Hexanes to afford compound **2** (350 mg, 63%) as an off-white solid. **^{1}H NMR (400 MHz, $CDCl_3$):** δ 8.09 (br s, 1H), 7.41 (d, J = 8.4 Hz, 1H), 7.28 (s, 1H), 7.09 (d, J = 8.4 Hz, 1H), 6.39 (s, 1H); **MS (ESI):** *m/z* 184 (M - H^+)

Step 2: Synthesis of 2,6-dichloro-1-(1-propyl-1*H*-pyrazol-4-yl)-1*H*-indole (3):

[00314] To a stirred solution of compound **2** (350 mg, 1.89 mmol) in toluene (10 mL) under inert atmosphere were added 4-bromo-1-propyl-1*H*-pyrazole (Intermediate **B**; 422 mg, 2.27 mmol), potassium phosphate (1 g, 4.72 mmol), *N,N'*-dimethylethylene diamine (66.7 mg, 0.75 mmol) and CuI (36 mg, 0.18 mmol) at RT; heated to 120 °C and stirred for 12 h in a sealed tube. The reaction was monitored by TLC; after completion of the reaction, the volatiles were removed under reduced pressure to obtain the crude. This was purified by silica gel column chromatography using 5-7% EtOAc/Hexanes to afford compound **3** (200 mg, 36%) as colorless oil. **^{1}H NMR (500 MHz, $CDCl_3$):** δ 7.63 (s, 1H), 7.59 (s, 1H), 7.44 (d, J = 9.0 Hz, 1H), 7.14 (s, 1H), 7.11 (d, J = 9.0 Hz, 1H), 6.55 (s, 1H), 4.18 (t, J = 7.0 Hz, 2H), 2.02-1.97 (m, 2H), 0.98 (t, J = 7.5 Hz, 3H); **LC-MS (ESI):** 59.4%; *m/z* 294.2 (M + H^+); (column: X Select C-18, 50 × 3.0 mm, 3.5 µm); RT 4.66 min; 5 mM NH_4OAc: ACN; 0.8 mL/min).

Step 3: Synthesis of ethyl 3-((2,6-dichloro-1-(1-propyl-1*H*-pyrazol-4-yl)-1*H*-indol-3-yl)thio) benzoate (4):

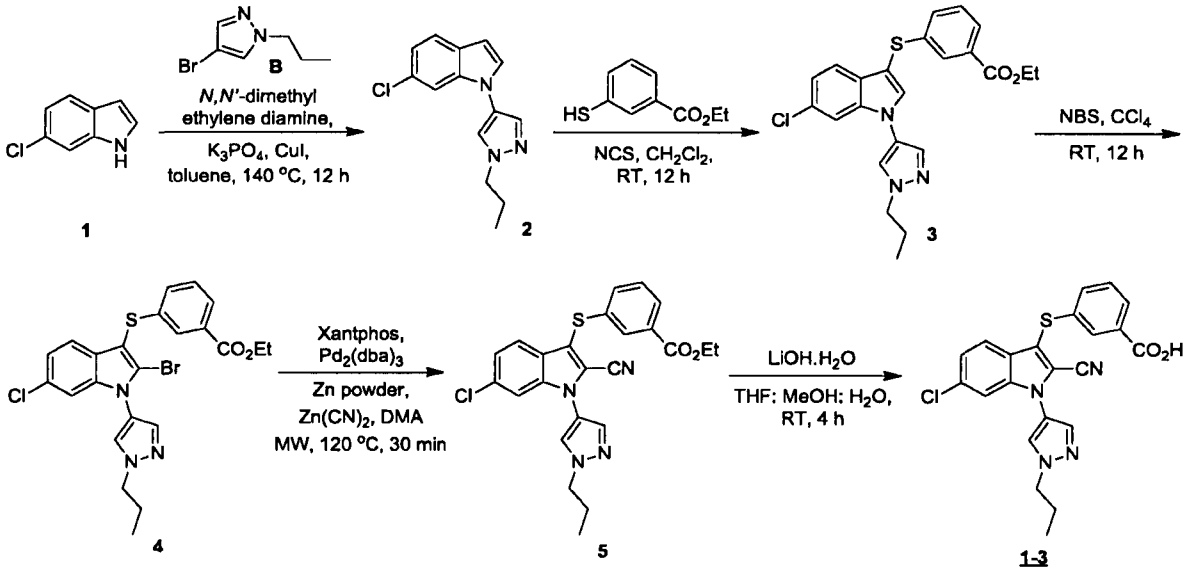
[00315] To a stirred solution of ethyl 3-mercaptobenzoate (124.9 mg, 0.68 mmol) in CH_2Cl_2 (20 mL) under inert atmosphere was added NCS (109 mg, 0.81 mmol) at 0 °C; warmed to RT and stirred for 1 h. To this, compound **3** (200 mg, 0.68 mmol) was added at 0 °C; warmed to RT and stirred for 12 h. The reaction was monitored by TLC; after completion of the reaction, the reaction mixture was diluted with water (25 mL) and extracted with CH_2Cl_2 (3 x 25 mL). The combined organic extracts were dried over Na_2SO_4, filtered and concentrated under reduced pressure to obtain the crude. This was purified by preparative HPLC to afford compound **4** (15 mg, 5%) as colorless oil. **^{1}H NMR (500 MHz, $CDCl_3$):** δ 7.90 (s, 1H), 7.79-7.77 (m, 1H), 7.69 (s, 1H), 7.66 (s, 1H), 7.48 (d, J = 9.0 Hz, 1H), 7.26-7.22 (m, 3H), 7.16 (d, J = 9.0 Hz, 1H), 4.32

(q, J = 7.5 Hz, 2H), 4.20 (t, J = 7.0 Hz, 2H), 2.02-1.98 (m, 2H), 1.37-1.34 (t, J = 7.5 Hz, 3H), 1.01 (t, J = 7.0 Hz, 3H); **LC-MS (ESI):** 92.7%; *m/z* 475.8 ($M + H^+$); (column: X Select C-18, 50 × 3.0 mm, 3.5 µm); RT 5.03 min; 5 mM NH_4OAc: ACN; 0.8 mL/min).

Step 4: Synthesis of 3-((2,6-dichloro-1-(1-propyl-1*H*-pyrazol-4-yl)-1*H*-indol-3-yl)thio) benzoic acid:

[00316] To a stirred solution of compound **4** (15 mg, 0.031 mmol) in THF:H_2O (1:1, 5 mL) under inert atmosphere was added $LiOH.H_2O$ (5.3 mg, 0.12 mmol) at 0 °C; warmed to RT and stirred for 12 h. The reaction was monitored by TLC; after completion of the reaction, the volatiles were removed under reduced pressure. The residue was diluted with water (20 mL), acidified with citric acid and extracted with CH_2Cl_2 (2 x 20 mL). The combined organic extracts were dried over Na_2SO_4, filtered and concentrated under reduced pressure to afford the title compound **1-1** (10 mg, 71%) as an off-white solid. **^{1}H NMR (400 MHz, CD_3OD):** δ 8.12 (s, 1H), 7.78-7.75 (m, 3H), 7.49 (d, J = 8.4 Hz, 1H), 7.32-7.31 (m, 2H), 7.22-7.18 (m, 2H), 4.24 (t, J = 7.2 Hz, 2H), 2.02-1.93 (m, 2H), 0.98 (t, J = 7.2 Hz, 3H); **MS (ESI):** *m/z* 446.3 (M^+); **HPLC:** 98.8%; (column: Acquity BEH C-18 (50 x 2.1 mm, 1.7 µ); RT 2.94 min; ACN: 0.025% TFA (aq); 0.5 mL/min.

Example 2: Synthesis of 3-((6-chloro-2-cyano-1-(1-propyl-1H-pyrazol-4-yl)-1H-indol-3-yl)thio)benzoic acid (Compound 1-3)



Step 1: Synthesis of 6-chloro-1-(1-propyl-1*H*-pyrazol-4-yl)-1*H*-indole (2):

[00317] To a stirred solution of 6-chloro-1*H*-indole **1** (1.0 g, 6.62 mmol) in toluene (25 mL) under inert atmosphere were added *N,N'*-dimethylethylene diamine (233 mg, 2.64 mmol), potassium phosphate (3.50 g, 16.55 mmol) and 4-bromo-1-propyl-1*H*-pyrazole (Intermediate **B**;

1.23 g, 6.62 mmol) at RT and then degassed under argon for 15 min. To this, CuI (126 mg, 0.66 mmol) was added and sealed the tube. The reaction mixture was heated to 140 °C and stirred for 12 h. The reaction was monitored by TLC; after completion of the reaction, the reaction mixture was filtered and the filtrate was concentrated under reduced pressure to obtain the crude. This was purified by silica gel column chromatography using 10-15% EtOAc/Hexanes to afford compound **2** (1.5 g, 88%) as yellow oil. **^{1}H NMR (500 MHz, $CDCl_3$):** δ 7.68 (s, 1H), 7.62 (s, 1H), 7.55 (d, J = 10.0 Hz, 1H), 7.35 (s, 1H), 7.17 (d, J = 3.5 Hz, 1H), 7.11 (d, J = 10.0 Hz, 1H), 6.59 (d, J = 3.5 Hz, 1H), 4.17 (t, J = 7.5 Hz, 2H), 2.00-1.96 (m, 2H), 1.00 (t, J = 7.5 Hz, 3H); **LC-MS (ESI):** 93.3%; *m/z* 260.2 ($M + H^+$); (column: X Select CSH C-18, 50 × 3.0 mm, 3.5 µm); RT 4.04 min; 5 mM NH_4OAc: ACN; 0.8 mL/min).

Step 2: Synthesis of ethyl 3-((6-chloro-1-(1-propyl-1*H*-pyrazol-4-yl)-1*H*-indol-3-yl)thio) benzoate (3):

[00318] To a stirred solution of ethyl 3-mercaptobenzoate (372 mg, 2.03 mmol) in CH_2Cl_2 (20 mL) under inert atmosphere was added NCS (271 mg, 2.03 mmol) at 0 °C; warmed to RT and stirred for 45 min. To this, compound **2** (500 mg, 1.93 mmol) was added at 0 °C; warmed to RT and stirred for 12 h. The reaction was monitored by TLC; after completion of the reaction, the reaction mixture was diluted with water (40 mL) and extracted with CH_2Cl_2 (3 x 20 mL). The combined organic extracts were dried over Na_2SO_4, filtered and concentrated under reduced pressure to obtain the crude. This was purified by silica gel column chromatography using 10-15% EtOAc/Hexanes to afford compound **3** (700 mg, 83%) as a yellow oil. **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.89 (s, 1H), 7.76-7.74 (m, 1H), 7.72 (s, 1H), 7.68 (s, 1H), 7.49-7.47 (m, 2H), 7.40 (s, 1H), 7.24-7.23 (m, 2H), 7.15 (d, J = 8.4 Hz, 1H), 4.32 (q, J = 7.2 Hz, 2H), 4.18 (t, J = 7.2 Hz, 2H), 2.01-1.96 (m, 2H), 1.34 (t, J = 7.2 Hz, 3H), 1.00 (t, J = 7.2 Hz, 3H); **LC-MS (ESI):** 72.2%; *m/z* 440.4 ($M + H^+$); (column: X Select CSH C-18, 50 × 3.0 mm, 3.5 µm); RT 4.87 min; 5 mM NH_4OAc: ACN; 0.8 mL/min).

Step 3: Synthesis of ethyl 3-((2-bromo-6-chloro-1-(1-propyl-1*H*-pyrazol-4-yl)-1*H*-indol-3-yl)thio) benzoate (4):

[00319] To a stirred solution of compound **3** (100 mg, 0.22 mmol) in CCl_4 (10 mL) was added NBS (44.85 mg, 0.25 mmol) at RT under inert atmosphere and stirred for 12 h. The reaction was monitored by TLC; after completion of the reaction, the reaction mixture was diluted with water (20 mL) and extracted with CH_2Cl_2 (3 x 20 mL). The combined organic extracts were dried over sodium sulphate, filtered and concentrated under reduced pressure to obtain the crude. This was purified by silica gel column chromatography using 10-15% EtOAc/Hexanes to afford compound **4** (55 mg, 47%) as an off-white solid. **^{1}H NMR (500 MHz, $CDCl_3$):** δ 7.90 (s, 1H), 7.78-7.77 (m,

1H), 7.68 (s, 1H), 7.66 (s, 1H), 7.49 (d, J = 8.5 Hz, 1H), 7.25-7.24 (m, 2H), 7.20 (s, 1H), 7.14 (d, J = 8.5 Hz, 1H), 4.35 (q, J = 7.0 Hz, 2H), 4.20 (t, J = 7.5 Hz, 2H), 2.03-1.98 (m, 2H), 1.35 (t, J = 7.0 Hz, 3H), 1.01 (t, J = 7.5 Hz, 3H); **LC-MS (ESI):** 93.3%; *m/z* 520.8 (M^+ + 2); (column: X Select CSH C-18, 50 × 3.0 mm, 3.5 µm); RT 5.02 min; 5 mM NH_4OAc: ACN; 0.8 mL/min).

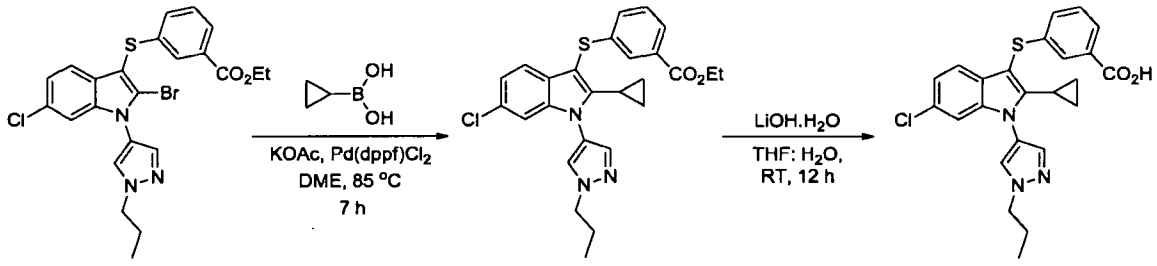
Step 4: Synthesis of ethyl 3-((6-chloro-2-cyano-1-(1-propyl-1*H*-pyrazol-4-yl)-1*H*-indol-3-yl) thio) benzoate (5):

[00320] To a stirred solution of compound **4** (200 mg, 0.38 mmol) in DMA (20 mL) under inert atmosphere were added zinc powder (5.02 mg, 0.07 mmol), $ZnCN_2$ (67.8 mg, 0.58 mmol), xantphos (89.5 mg, 0.15 mmol), $Pd_2(dba)_3$ (70.85 mg, 0.07 mmol) at RT; heated to 120 °C under microwave for 30 min. The reaction was monitored by TLC; after completion of the reaction, the reaction mixture was diluted with water (20 mL) and extracted with CH_2Cl_2 (3 x 20 mL). The combined organic extracts were dried over Na_2SO_4, filtered and concentrated under reduced pressure to obtain the crude. This was purified by silica gel column chromatography using 10-15% EtOAc/ Hexanes to afford compound **5** (60 mg, 33%) as an off-white solid. **^{1}H NMR (500 MHz, $CDCl_3$):** δ 7.99 (s, 1H), 7.87 (d, J = 7.5 Hz, 1H), 7.78 (s, 2H), 7.54 (d, J = 8.5 Hz, 1H), 7.42-7.27 (m, 3H), 7.24-7.22 (m, 1H), 4.36 (*q*, J = 7.0 Hz, 2H), 4.21 (t, J = 7.5 Hz, 2H), 2.02-1.98 (m, 2H), 1.36 (t, J = 7.0 Hz, 3H), 1.01 (t, J = 7.5 Hz, 3H); **LC-MS (ESI):** 92.5%; *m/z* 465 (M + H^+); (column: X Select CSH C-18, 50 × 3.0 mm, 3.5 µm); RT 4.92 min; 5 mM NH_4OAc: ACN; 0.8 mL/min).

Step 5: Synthesis of 3-((6-chloro-2-cyano-1-(1-propyl-1*H*-pyrazol-4-yl)-1*H*-indol-3-yl) thio) benzoic acid:

[00321] To a stirred solution of compound **5** (60 mg, 0.12 mmol) in THF:MeOH:H_2O (3:1:1, 5 mL) under inert atmosphere was added $LiOH.H_2O$ (16.3 mg, 0.38 mmol) at 0 °C; warmed to RT and stirred for 4 h. The reaction was monitored by TLC; after completion of the reaction, the volatiles were removed under reduced pressure. The residue was diluted with water (15 mL), acidified with citric acid to pH ~ 2.0. The obtained solid was filtered and dried under reduced pressure to afford the title compound **1-3** (20 mg, 35%) as an off-white solid. **^{1}H NMR (400 MHz, CD_3OD):** δ 8.23 (s, 1H), 7.88 (s, 1H), 7.87 (s, 1H), 7.82 (d, J = 8.0 Hz, 1H), 7.57 (d, J = 8.4 Hz, 1H), 7.43 (d, J = 8.4 Hz, 1H), 7.38-7.32 (m, 2H), 7.27 (d, J = 8.4 Hz, 1H), 4.25 (t, J = 7.2 Hz, 2H), 2.02-1.93 (m, 2H), 0.98 (t, J = 7.2 Hz, 3H); **LC-MS (ESI):** 96.4%; *m/z* 435.4 (M - H^+); (column: X Select CSH C-18, 50 × 3.0 mm, 3.5 µm); RT 3.19 min; 5 mM NH_4OAc: ACN; 0.8 mL/min); **HPLC:** 94.6%; (column: Acquity BEH C-18 (50 x 2.1 mm, 1.7 µ); RT 2.78 min; ACN: 0.025% TFA (aq); 0.5 mL/min.

Example 3: Synthesis of 3-((6-chloro-2-cyclopropyl-1-(1-propyl-1H-pyrazol-4-yl)-1H-indol-3-yl)thio)benzoic acid (Compound 1-4)



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Step 1: Synthesis of ethyl 3-((6-chloro-2-cyclopropyl-1-(1-propyl-1*H*-pyrazol-4-yl)-1*H*-indol-3-yl)thio)benzoate (2):

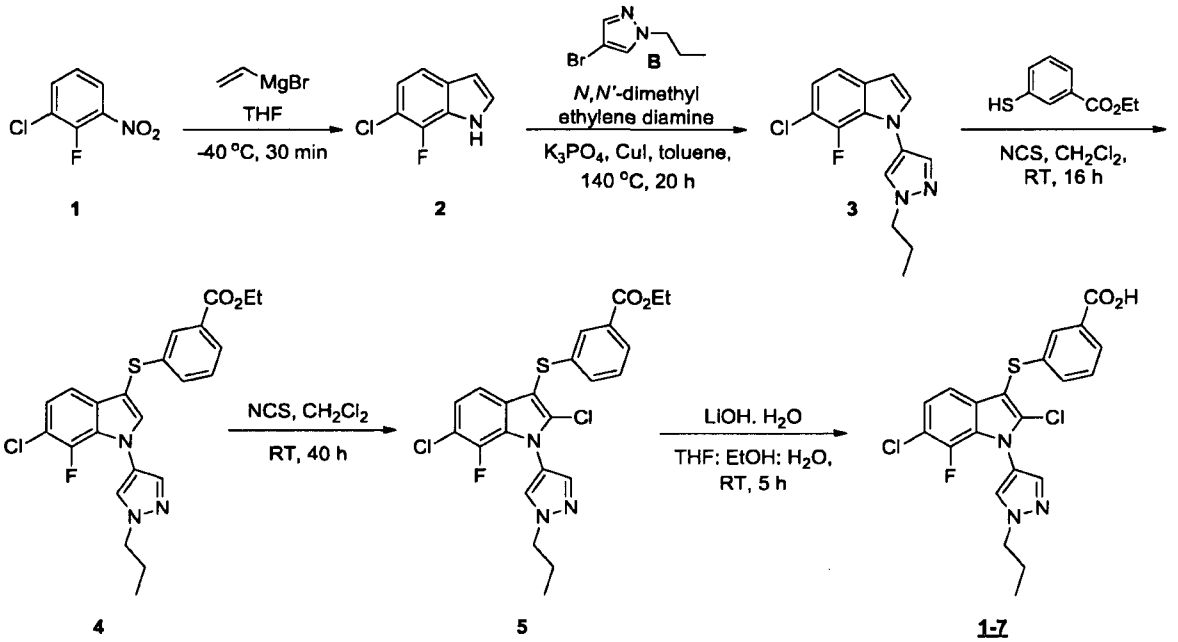
[00322] To a stirred solution of ethyl 3-((2-bromo-6-chloro-1-(1-propyl-1*H*-pyrazol-4-yl)-1*H*-indol-3-yl)thio)benzoate **1** (Example 2, Step 3; 100 mg, 0.19 mmol) in DME (20 mL) under inert atmosphere were added cyclopropyl boronic acid (16.6 mg, 0.19 mmol), KOAc (56.8 mg, 0.58 mmol) at RT and degassed for 15 min. To this, was added $Pd(dppf)Cl_2$ (28.3 mg, 0.038 mmol), heated to 85 °C and stirred for 7 h. The reaction was monitored by TLC; after completion of the reaction, the reaction mixture was diluted with water (20 mL) and extracted with CH_2Cl_2 (3 x 20 mL). The combined organic extracts were dried over Na_2SO_4, filtered and concentrated under reduced pressure to obtain the crude. The crude was purified by silica gel column chromatography using 8-10% EtOAc/Hexanes to afford 43 mg of compound **2** with 51% purity. The impure material was further purified by preparative HPLC to afford pure compound **2** (25 mg, 27%) as a colorless oil. **^{1}H NMR (500 MHz, $CDCl_3$):** δ 7.83 (s, 1H), 7.74 (d, J = 7.5 Hz, 1H), 7.69 (s, 1H), 7.65 (s, 1H), 7.41 (d, J = 8.5 Hz, 1H), 7.26-7.22 (m, 2H), 7.14-7.08 (m, 2H), 4.34 (q, J = 7.5 Hz, 2H), 4.21 (t, J = 7.0 Hz, 2H), 2.03-1.98 (m, 2H), 1.76-1.75 (m, 1H), 1.05-1.01 (m, 2H), 1.36 (t, J = 7.5 Hz, 3H), 1.00 (t, J = 7.0 Hz, 3H), 0.87-0.84 (m, 2H); **LC-MS (ESI):** 89.7%; *m/z* 480.5 ($M+H^+$); (column: X Select CSH C-18, 50 × 3.0 mm, 3.5 µm); RT 4.83 min; 5 mM NH_4OAc: ACN; 0.8 mL/min).

Step 2: Synthesis of 3-((6-chloro-2-cyclopropyl-1-(1-propyl-1*H*-pyrazol-4-yl)-1*H*-indol-3-yl)thio)benzoic acid:

[00323] To a stirred solution of compound **2** (25 mg, 0.05 mmol) in THF:H_2O (1:1, 5 mL) under inert atmosphere was added $LiOH.H_2O$ (6.5 mg, 0.15 mmol) at 0 °C; warmed to RT and stirred for 12 h. The reaction was monitored by TLC; after completion of the reaction, the volatiles were removed under reduced pressure. The residue was diluted with water (15 mL), acidified with citric acid and extracted with EtOAc (2 x 20 mL). The combined organic extracts were dried over Na_2SO_4, filtered and concentrated under reduced pressure to obtain the crude. The crude was

triturated with *n*-pentane (2 x 5 mL) to afford the title compound **1-4** (10 mg, 43%) as an off-white solid. **^{1}H NMR (400 MHz, CD_3OD):** δ 8.07 (s, 1H), 7.76 (s, 1H), 7.71 (d, J = 7.6 Hz, 1H), 7.68 (s, 1H), 7.38 (d, J = 8.0 Hz, 1H), 7.31-7.28 (m, 1H), 7.21-7.18 (m, 1H), 7.09-7.05 (m, 2H), 4.24 (t, J = 7.2 Hz, 2H), 2.02-1.97 (m, 2H), 1.86-1.82 (m, 1H), 1.01-0.97 (m, 5H), 0.85-0.82 (m, 2H); **MS (ESI):** *m/z* 452.3 ($M + H^+$); **HPLC:** 86.9%; (column: Acquity BEH C-18 (50 x 2.1 mm, 1.7 µ); RT 3.00 min; ACN: 0.025% TFA (aq); 0.5 mL/min.

Example 4: Synthesis of 3-((2,6-dichloro-7-fluoro-1-(1-propyl-1H-pyrazol-4-yl)-1H-indol-3-yl)thio)benzoic acid (Compound 1-7)



Step 1: Synthesis of 6-chloro-7-fluoro-1*H*-indole (2):

[00324] To a stirred solution of 1-chloro-2-fluoro-3-nitrobenzene **1** (10.0 g, 56.98 mmol) in THF (100 mL) under inert atmosphere was added vinyl magnesium bromide (1*M* in THF solution; 170 mL, 170.94 mmol) at RT, cooled to -40 °C and stirred for 30 min. The reaction was monitored by TLC; after completion of the reaction, the reaction mixture was quenched with saturated NH_4Cl solution (50 mL), extracted with EtOAc (2 x 50 mL). The combined organic extracts were washed with NH_4Cl solution (40 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to obtain the crude. This was purified by silica gel column chromatography using 2% EtOAc/ Hexanes to afford compound **2** (1.1 g, 11.4%) as a brown oil. **^{1}H NMR (500 MHz, $CDCl_3$):** δ 8.36 (br s, 1H), 7.31 (d, J = 8.0 Hz, 1H), 7.25-7.22 (m, 1H), 7.08-7.05 (m, 1H), 6.56-6.54 (m, 1H).

Step 2: Synthesis of 6-chloro-7-fluoro-1-(1-propyl-1*H*-pyrazol-4-yl)-1*H*-indole (3):

[00325] To a stirred solution of compound **2** (1.1 g, 6.48 mmol) in toluene (15 mL) under inert atmosphere were added *N,N'*-dimethyl ethylene diamine (229 mg, 2.60 mmol), potassium phosphate (3.44 g, 16.27 mmol), 4-bromo-1-propyl-1*H*-pyrazole (Intermediate **B**; 1.21 g, 6.50 mmol), CuI (124 mg, 0.65 mmol) at RT, degassed under argon for 15 min; heated to 140 °C and stirred for 20 h in sealed tube. The reaction was monitored by TLC; after completion of the reaction, the reaction mixture was diluted with EtOAc (30 mL), filtered and the filtrate was concentrated under reduced pressure to obtain the crude. This was purified by silica gel column chromatography using 8-10% EtOAc/ Hexanes to afford compound **3** (1.3 g, 72%) as brown liquid. **^{1}H NMR (500 MHz, $CDCl_3$):** δ 7.64 (s, 1H), 7.60 (s, 1H), 7.31 (d, J = 7.5 Hz, 1H), 7.12-7.07 (m, 2H), 6.60 (s, 1H), 4.13 (t, J = 7.0 Hz, 2H), 1.99-1.91 (m, 2H), 0.97 (t, J = 8.0 Hz, 3H); **LC-MS (ESI):** 93.5%; *m/z* 278.2 (M + H^+); (column: X Select CSH C-18, 50 × 3.0 mm, 3.5 µm); RT 4.08 min; 5 mM NH_4OAc: ACN; 0.8 mL/min).

Step 3: Synthesis of ethyl 3-((6-chloro-7-fluoro-1-(1-propyl-1H-pyrazol-4-yl)-1H-indol-3-yl) thio)benzoate (4):

[00326] To a stirred solution of ethyl 3-mercaptobenzoate (66 mg, 0.36 mmol) in CH_2Cl_2 (5 mL) under inert atmosphere was added NCS (48.2 mg, 0.36 mmol) at RT and stirred for 50 min. To this, compound **3** (100 mg, 0.36 mmol) was added at RT and stirred for 16 h. The reaction was monitored by TLC; after completion of the reaction, the reaction mixture was diluted with water (25 mL) and extracted with CH_2Cl_2 (2 x 20 mL). The combined organic extracts were washed with brine (20 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to obtain the crude. This was purified by silica gel column chromatography using 9% EtOAc/Hexanes to afford compound **4** (100 mg, 61%) as a colorless syrup. **^{1}H NMR (500 MHz, $CDCl_3$):** δ 7.88 (s, 1H), 7.77-7.76 (m, 1H), 7.69 (s, 1H), 7.67 (s, 1H), 7.43 (s, 1H), 7.27-7.24 (m, 3H), 7.15-7.12 (m, 1H), 4.33 (q, J = 7.5 Hz, 2H), 4.15 (t, J = 7.0 Hz, 2H), 1.98-1.94 (m, 2H), 1.35 (t, J = 7.5 Hz, 3H), 0.98 (t, J = 7.0 Hz, 3H); **LC-MS:** 94.6%; *m/z* 458.4 (M + H^+); (column: X Select CSH C-18, 50 × 3.0 mm, 3.5 µm); RT 4.91 min; 5 mM NH_4OAc: ACN; 0.8 mL/min).

Step 4: Synthesis of ethyl 3-((2,6-dichloro-7-fluoro-1-(1-propyl-1H-pyrazol-4-yl)-1H-indol-3-yl)thio)benzoate (5):

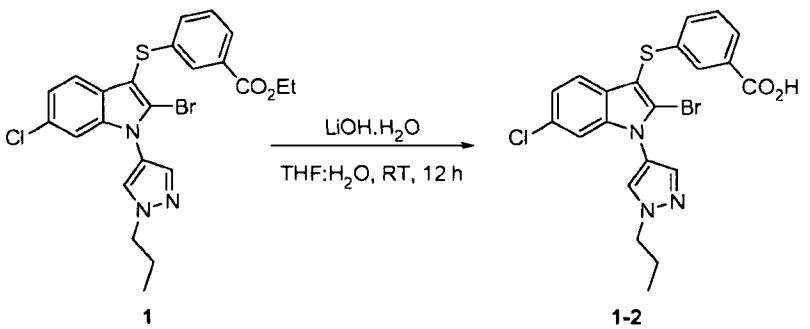
[00327] To a stirred solution of compound **4** (150 mg, 0.32 mmol) in CH_2Cl_2 (3 mL) under inert atmosphere was added NCS (87 mg, 0.65 mmol) at RT. After 16 h stirring, NCS (87 mg, 0.65 mmol) was added again at RT and stirred for additional 24 h. The reaction was monitored by TLC; after completion of the reaction, the reaction mixture was diluted with water (15 mL) and extracted with CH_2Cl_2 (2 x 20 mL). The combined organic extracts were washed with water (15

mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to obtain the crude. This was purified by silica gel column chromatography using 7% EtOAc/ *n*-Hexane to afford compound **5** (100 mg, 62%) as a brown solid. **^{1}H NMR (500 MHz, $CDCl_3$):** δ 7.89 (s, 1H), 7.80-7.79 (m, 1H), 7.67 (s, 1H), 7.65 (s, 1H), 7.28-7.26 (m, 3H), 7.17-7.14 (m, 1H), 4.33 (q, J = 7.5 Hz, 2H), 4.18 (t, J = 7.5 Hz, 2H), 2.00-1.95 (m, 2H), 1.36 (t, J = 7.5 Hz, 3H), 0.98 (t, J = 7.5 Hz, 3H); **LC-MS (ESI):** 97.6%; *m/z* 492.4 ($M + H^+$); (column: X Select CSH C-18, 50 × 3.0 mm, 3.5 µm); RT 5.07 min; 5 mM NH_4OAc: ACN; 0.8 mL/min).

Step 5: Synthesis of 3-((2,6-dichloro-7-fluoro-1-(1-propyl-1*H*-pyrazol-4-yl)-1*H*-indol-3-yl)thio)benzoic acid:

[00328] To a stirred solution of compound **5** (100 mg, 0.20 mmol) in THF:EtOH:H_2O (3:1:1, 5 mL) under inert atmosphere was added $LiOH.H_2O$ (25.6 mg, 0.61 mmol) at RT and stirred for 5 h. The reaction was monitored by TLC; after completion of the reaction, the volatiles were removed under reduced pressure. The residue was diluted with water (10 mL), washed with Et_2O (2 x 10 mL). The aqueous layer was acidified with 1*N* HCl and extracted with CH_2Cl_2 (2 x 20 mL). The combined organic extracts were washed with water (15 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to obtain the crude. The crude was triturated with *n*-pentane (2 x 5 mL) to afford the title compound **1-7** (60 mg, 64%) as an off-white solid. **^{1}H NMR (400 MHz, DMSO-d_6):** δ 12.90 (br s, 1H), 8.31 (s, 1H), 7.82 (s, 1H), 7.72-7.70 (m, 2H), 7.37-7.28 (m, 4H), 4.16 (t, J = 6.8 Hz, 2H), 1.87-1.82 (m, 2H), 0.85 (t, J = 7.6 Hz, 3H); **MS (ESI):** *m/z* 464.2 ($M + H^+$); **HPLC:** 99.1%; (column: Acquity BEH C-18 (50 x 2.1 mm, 1.7 µ); RT 2.94 min; ACN: 0.025% TFA (aq); 0.5 mL/min.

Example 5: Synthesis of 3-((2-bromo-6-chloro-1-(1-propyl-1*H*-pyrazol-4-yl)-1*H*-indol-3-yl)thio) benzoic acid (Compound 1-2)

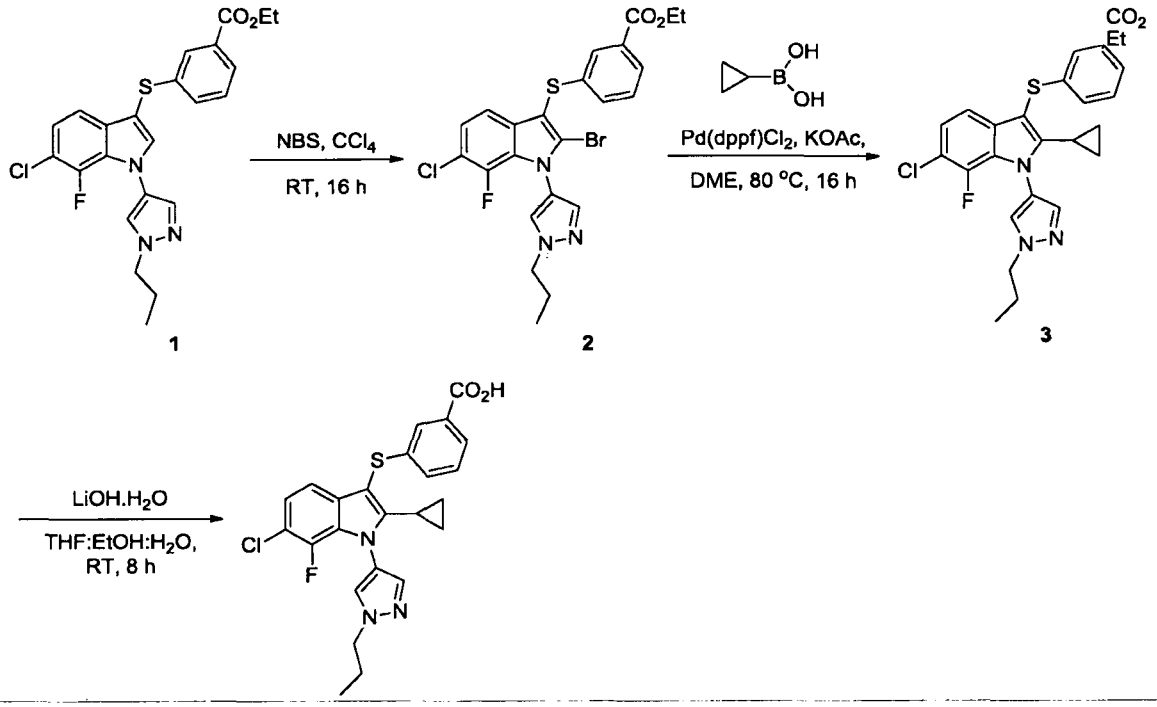


1 1-2

[00329] To a stirred solution of ethyl 3-((2-bromo-6-chloro-1-(1-propyl-1*H*-pyrazol-4-yl)-1*H*-indol-3-yl)thio)benzoate **1** (Example 2, Step 3; 70 mg, 0.13 mmol) in THF:H_2O (1:1, 10 mL) under inert atmosphere was added $LiOH.H_2O$ (17 mg, 0.40 mmol) at 0 °C; warmed to RT and stirred for 12 h. The reaction was monitored by TLC; after completion of the reaction, the

volatiles were removed under reduced pressure. The residue was diluted with water (15 mL), acidified with citric acid to pH ~ 2.0. The obtained solid was filtered and dried under reduced pressure to afford the title compound **1-2** (50 mg, 76%) as an off-white solid. **^{1}H NMR (400 MHz, CD_3OD):** δ 8.10 (s, 1H), 7.77-7.75 (m, 3H), 7.49 (d, J = 8.4 Hz, 1H), 7.32-7.30 (m, 2H), 7.20-7.16 (m, 2H), 4.24 (t, J = 7.2 Hz, 2H), 2.02-1.93 (m, 2H), 0.98 (t, J = 7.2 Hz, 3H); **LC-MS (ESI):** 90.8%; *m/z* 488.8 ($M - H^+$); (column: X Select CSH C-18, 50 × 3.0 mm, 3.5 µm); RT 3.35 min; 5 mM NH_4OAc: ACN; 0.8 mL/min); **HPLC:** 96.4%; (column: Acquity BEH C-18 (50 x 2.1 mm, 1.7 µ); RT 2.96 min; ACN: 0.025% TFA (aq); 0.5 mL/min.

Example 6: Synthesis of 3-((6-chloro-2-cyclopropyl-7-fluoro-1-(1-propyl-1H-pyrazol-4-yl)-1H-indol-3-yl)thio)benzoic acid (Compound 1-10)



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Step 1: Synthesis of ethyl 3-((2-bromo-6-chloro-7-fluoro-1-(1-propyl-1*H*-pyrazol-4-yl)-1*H*-indol-3-yl)thio)benzoate (2):

[00330] To a stirred solution of ethyl 3-((6-chloro-7-fluoro-1-(1-propyl-1*H*-pyrazol-4-yl)-1*H*-indol-3-yl)thio)benzoate **1** (Example 4, Step 3; 500 mg, 1.09 mmol) in CCl_4 (10 mL) under inert atmosphere was added NBS (391 mg, 2.18 mmol) at RT and stirred for 16 h. The reaction was monitored by TLC; after completion of the reaction, the reaction mixture was diluted with water (30 mL) and extracted with CH_2Cl_2 (2 x 30 mL). The combined organic extracts were washed with water (30 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to obtain the crude. This was purified by silica gel column chromatography using 10% EtOAc/

Hexanes to afford compound **2** (360 mg, 62%) as an off-white solid. **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.89 (br s, 1H), 7.80-7.78 (m, 1H), 7.67 (s, 1H), 7.65 (s, 1H), 7.29-7.27 (m, 2H), 7.24-7.23 (m, 1H), 7.16-7.13 (m, 1H), 4.34 (q, J = 7.2 Hz, 2H), 4.19 (t, J = 6.8 Hz, 2H), 2.01-1.95 (m, 2H), 1.36 (t, J = 6.8 Hz, 3H), 0.98 (t, J = 7.2 Hz, 3H); **LC-MS (ESI):** 97.6%; *m/z* 536.8 (M + H^+); (column: X Select CSH C-18, 50 × 3.0 mm, 3.5 µm); RT 5.03 min; 5 mM NH_4OAc: ACN; 0.8 mL/min).

Step 2: Synthesis of ethyl 3-((6-chloro-2-cyclopropyl-7-fluoro-1-(1-propyl-1*H*-pyrazol-4-yl)-1*H*-indol-3-yl)thio)benzoate (3):

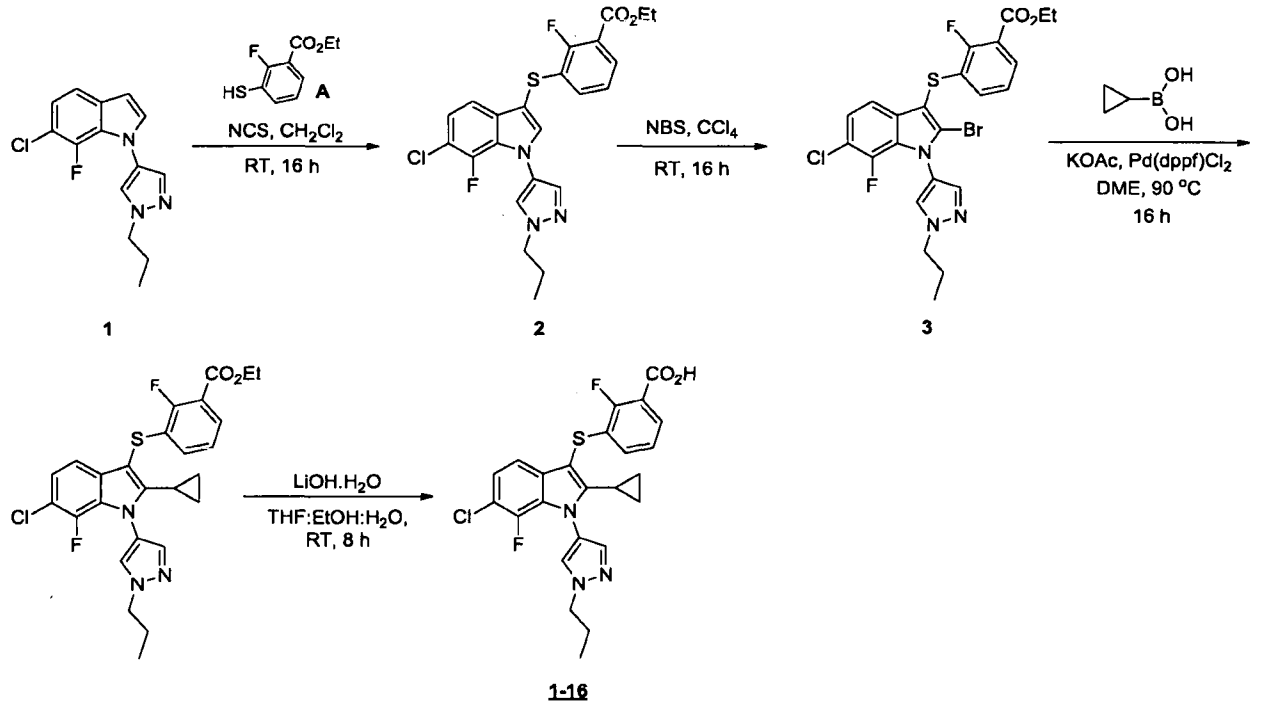
[00331] To a stirred solution of compound **2** (360 mg, 0.67 mmol) in DME (5 mL) under inert atmosphere were added KOAc (197 mg, 2.01 mmol), $Pd(dppf)Cl_2$ (98 mg, 0.13 mmol), cyclopropylboronic acid (57.8 mg, 0.67 mmol) at RT and degassed under Ar for 20 min; heated to 80 °C and stirred for 16 h. The reaction was monitored by TLC; after completion of the reaction, the reaction mixture was diluted with EtOAc (40 mL), filtered through celite. The filtrate was washed with water (25 mL), brine (25 mL), dried over Na_2SO_4 and concentrated under reduced pressure to obtain the crude. This was purified by silica gel column chromatography and then preparative HPLC to afford pure compound **3** (50 mg, 15%) as a white solid. **^{1}H NMR (500 MHz, $CDCl_3$):** δ 7.79 (s, 1H), 7.74 (d, J = 7.5 Hz, 1H), 7.67 (s, 1H), 7.63 (s, 1H), 7.25-7.18 (m, 2H), 7.12 (d, J = 8.0 Hz, 1H), 7.06-7.05 (m, 1H), 4.33 (q, J = 7.5 Hz, 2H), 4.18 (t, J = 7.5 Hz, 2H), 2.00-1.95 (m, 2H), 1.70-1.69 (m, 1H), 1.36 (t, J = 7.5 Hz, 3H), 1.07-1.05 (m, 2H), 0.99-0.97 (t, J = 7.5 Hz, 3H), 0.87-0.84 (m, 2H); **LC-MS (ESI):** 99.7%; *m/z* 498.5 (M + H^+); (column: X Select CSH C-18, 50 × 3.0 mm, 3.5 µm); RT 5.11 min; 5 mM NH_4OAc: ACN; 0.8 mL/min).

Step 3: Synthesis of 3-((6-chloro-2-cyclopropyl-7-fluoro-1-(1-propyl-1*H*-pyrazol-4-yl)-1*H*-indol-3-yl)thio)benzoic acid:

[00332] To a stirred solution of compound **3** (50 mg, 0.10 mmol) in THF:EtOH:H_2O (3:1:1, 5 mL) under inert atmosphere was added $LiOH.H_2O$ (12.6 mg, 0.30 mmol) at RT and stirred for 8 h. The reaction was monitored by TLC; after completion of the reaction, the volatiles were removed under reduced pressure. The residue was diluted with water (20 mL), acidified with 1*N* HCl to pH~2 and extracted with CH_2Cl_2 (2 x 20 mL). The combined organic extracts were dried over Na_2SO_4, filtered and concentrated under reduced pressure to obtain the crude. The crude was triturated with *n*-pentane (2 x 5 mL) and dried under reduced pressure to afford the title compound **1-10** (25 mg, 53%) as an off-white solid. **^{1}H NMR (400 MHz, DMSO-d_6):** δ 12.90 (br s, 1H), 8.26 (s, 1H), 7.79 (s, 1H), 7.66 (d, J = 7.6 Hz, 1H), 7.61 (s, 1H), 7.34 (t, J = 7.6 Hz, 1H), 7.19-7.16 (m, 3H), 4.15 (t, J = 6.8 Hz, 2H), 1.87-1.78 (m, 3H), 0.95-0.92 (m, 2H), 0.87-0.80

(m, 5H); **MS (ESI):** *m/z* 470.7 (M + H^+); **HPLC:** 97.8%; (column: Acquity BEH C-18 (50 x 2.1 mm, 1.7 μ); RT 3.00 min; ACN: 0.025% TFA (aq); 0.5 mL/min.

Example 7: Synthesis of 3-((6-chloro-2-cyclopropyl-7-fluoro-1-(1-propyl-1H-pyrazol-4-yl)-1H-indol-3-yl)thio)-2-fluorobenzoic acid (Compound 1-16)



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Step 1: Synthesis of ethyl 3-((6-chloro-7-fluoro-1-(1-propyl-1H-pyrazol-4-yl)-1H-indol-3-yl)thio)-2-fluorobenzoate (2):

[00333] To a stirred solution of ethyl 2-fluoro-3-mercaptobenzoate (Intermediate **A**; 108 mg, 0.54 mmol) in CH_2Cl_2 (3 mL) under inert atmosphere was added NCS (72 mg, 0.54 mmol) at RT and stirred for 1 h. To this, compound **1** (Example 4, Step 2; 150 mg, 0.54 mmol) was added and stirred for 16 h. The reaction was monitored by TLC; after completion of the reaction, the reaction mixture was diluted with water (25 mL) and extracted with CH_2Cl_2 (2 x 25 mL). The combined organic extracts were washed with brine (20 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to obtain the crude. This was purified by silica gel column chromatography using 10% EtOAc/Hexanes to afford compound **2** (130 mg, 50%) as an off-white solid. **^{1}H NMR (500 MHz, $CDCl_3$):** δ 7.69 (s, 1H), 7.67-7.64 (m, 2H), 7.44 (s, 1H), 7.29-7.27 (m, 1H), 7.17-7.14 (m, 1H), 7.01-6.94 (m, 2H), 4.40 (q, J = 7.5 Hz, 2H), 4.15 (t, J = 8.0 Hz, 2H), 1.98-1.94 (m, 2H), 1.40 (t, J = 7.5 Hz, 3H), 0.98 (t, J = 8.0 Hz, 3H); **LC-MS (ESI):** 97.6%; *m/z* 476.7 (M + H^+); (column: X Select CSH C-18, 50 × 3.0 mm, 3.5 μm); RT 4.84 min; 5 mM NH_4OAc: ACN; 0.8 mL/min).

Step 2: Synthesis of ethyl 3-((2-bromo-6-chloro-7-fluoro-1-(1-propyl-1*H*-pyrazol-4-yl)-1*H*-indol-3-yl)thio)-2-fluorobenzoate (3):

[00334] To a stirred solution of compound **2** (200 mg, 0.42 mmol) in CCl_4 (3 mL) under inert atmosphere was added NBS (150 mg, 0.84 mmol) at RT and stirred for 16 h. The reaction was monitored by TLC and LC-MS; after completion of the reaction, the reaction mixture was diluted with water (20 mL) and extracted with CH_2Cl_2 (2 x 20 mL). The combined organic extracts were washed with brine (15 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to obtain the crude. This was purified by silica gel column chromatography using 10-15% EtOAc/Hexanes to afford compound **3** (100 mg, 43%) as an off-white solid. **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.71-7.67 (m, 1H), 7.66 (s, 1H), 7.64 (s, 1H), 7.31 (d, J = 8.8 Hz, 1H), 7.18-7.15 (m, 1H), 7.00-6.96 (m, 2H), 4.40 (q, J = 7.2 Hz, 2H), 4.18 (t, J = 7.2 Hz, 2H), 2.02-1.93 (m, 2H), 1.40 (t, J = 7.2 Hz, 3H), 0.97 (t, J = 7.2 Hz, 3H); **LC-MS (ESI):** 98.1%; *m/z* 556.2 (M^+ + 2); (column: X Select CSH C-18, 50 × 3.0 mm, 3.5 µm); RT 4.94 min; 5 mM NH_4OAc: ACN; 0.8 mL/min).

Step 3: Synthesis of ethyl 3-((6-chloro-2-cyclopropyl-7-fluoro-1-(1-propyl-1*H*-pyrazol-4-yl)-1*H*-indol-3-yl)thio)-2-fluorobenzoate (4):

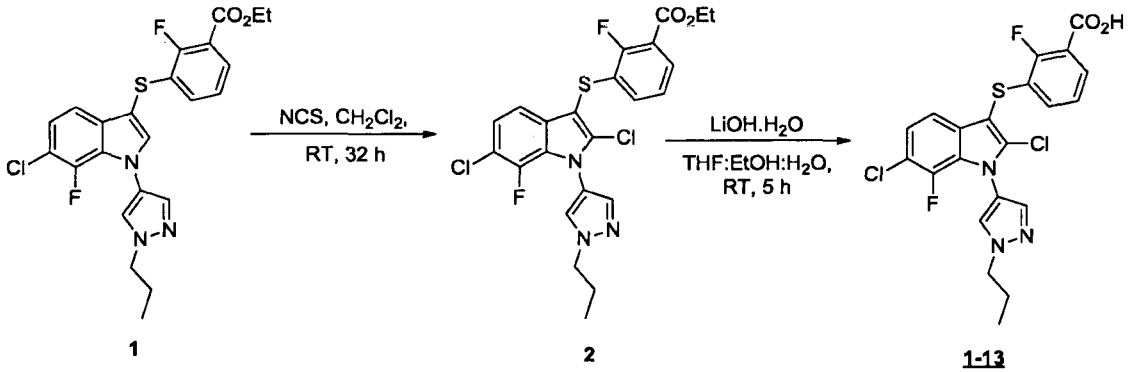
[00335] To a stirred solution of compound **3** (260 mg, 0.47 mmol) in DME (5 mL) under inert atmosphere were added cyclopropylboronic acid (40.4 mg, 0.47 mmol), $Pd(dppf)_2Cl_2$ (69 mg, 0.09 mmol), KOAc (138 mg, 1.41 mmol) at RT; heated to 90 °C and stirred for 16 h. The reaction was monitored by TLC; after completion of the reaction, the reaction mixture was diluted with water (20 mL) and extracted with EtOAc (2 x 25 mL). The combined organic extracts were washed with brine (20 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to obtain the crude. This was purified by silica gel column chromatography using 7-9% EtOAc/Hexanes to afford 70 mg of compound **4** which was further purified by preparative HPLC to afford pure compound **4** (20 mg, 9%) as a yellow syrup. **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.67 (s, 1H), 7.64-7.60 (m, 2H), 7.18 (d, J = 8.8 Hz, 1H), 7.10-7.06 (m, 1H), 6.95-6.91 (m, 1H), 6.79-6.75 (m, 1H), 4.41 (q, J = 7.2 Hz, 2H), 4.18 (t, J = 7.2 Hz, 2H), 2.00-1.93 (m, 2H), 1.74-1.67 (m, 1H), 1.41 (t, J = 7.2 Hz, 3H), 1.08-1.06 (m, 2H), 0.99 (t, J = 7.2 Hz, 3H), 0.87-0.84 (m, 2H); **LC-MS (ESI):** 99.9%; *m/z* 516.5 ($M + H^+$); (column: X Select CSH C-18, 50 × 3.0 mm, 3.5 µm); RT 5.00 min; 5 mM NH_4OAc: ACN; 0.8 mL/min).

Step 4: Synthesis of 3-((6-chloro-2-cyclopropyl-7-fluoro-1-(1-propyl-1*H*-pyrazol-4-yl)-1*H*-indol-3-yl)thio)-2-fluorobenzoic acid:

[00336] To a stirred solution of compound **4** (30 mg, 0.058 mmol) in THF:EtOH:H_2O (3:1:1, 2.5 mL) under inert atmosphere was added $LiOH.H_2O$ (7.3 mg, 0.17 mmol) at RT and stirred for

8 h. The reaction was monitored by TLC; after completion of the reaction, the volatiles were removed under reduced pressure. The residue was diluted with water (10 mL), washed with Et_2O (2 x 10 mL). The aqueous layer was acidified with 1*N* HCl solution and extracted with CH_2Cl_2 (2 x 15 mL). The combined organic extracts were washed with brine (15 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to obtain the crude. This was triturated with *n*-pentane (5 mL) to afford the title compound **1-16** (25 mg, 89%) as an off-white solid. **^{1}H NMR (400 MHz, DMSO-d_6):** δ 8.25 (s, 1H), 7.80 (s, 1H), 7.18-7.14 (m, 3H), 6.81 (t, J = 7.6 Hz, 1H), 6.42 (t, J = 7.6 Hz, 1H), 4.15 (t, J = 6.8 Hz, 2H), 1.87-1.76 (m, 3H), 0.95-0.93 (m, 2H), 0.86-0.80 (m, 5H); **MS (ESI):** *m/z* 488.4 (M +H$^+$); **HPLC:** 99.7%; (column: Acquity BEH C-18 (50 x 2.1 mm, 1.7 µ); RT 2.88 min; ACN: 0.025% TFA (aq); 0.5 mL/min.

Example 8: Synthesis of 3-((2,6-dichloro-7-fluoro-1-(1-propyl-1H-pyrazol-4-yl)-1H-indol-3-yl)thio)-2-fluorobenzoic acid (Compound 1-13)



1 2 1-13

Step 1: Synthesis of ethyl 3-((2,6-dichloro-7-fluoro-1-(1-propyl-1*H*-pyrazol-4-yl)-1*H*-indol-3-yl)thio)-2-fluorobenzoate (2):

[00337] To a stirred solution of ethyl 3-((6-chloro-7-fluoro-1-(1-propyl-1*H*-pyrazol-4-yl)-1*H*-indol-3-yl)thio)-2-fluorobenzoate **1** (Example 7, Step 1; 100 mg, 0.21 mmol) in CH_2Cl_2 (3 mL) was added NCS (33.7 mg, 0.25 mmol) at RT under inert atmosphere. After 8 h stirring, additional NCS (33.7 mg, 0.25 mmol) was added at RT and stirred again for 24 h. The reaction was monitored by TLC; after completion of the reaction, the reaction mixture was diluted with water (20 mL) and extracted with CH_2Cl_2 (2 x 20 mL). The combined organic extracts were washed with brine (15 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to obtain the crude. This was purified by silica gel column chromatography using 9-11% EtOAc/Hexanes to afford compound **2** (50 mg, 47%) as an off-white solid. **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.71-7.67 (m, 1H), 7.66 (s, 1H), 7.64 (s, 1H), 7.30 (d, J = 8.8 Hz, 1H), 7.18 (dd, J = 8.4, 6.0 Hz, 1H), 7.04-6.97 (m, 2H), 4.40 (q, J = 7.2 Hz, 2H), 4.18 (t, J = 7.2 Hz, 2H), 2.04-1.93 (m, 2H), 1.40 (t, J = 7.2 Hz, 3H), 0.97 (t, J = 7.2 Hz, 3H); **LC-MS (ESI):** 98.8%; *m/z* 510.4 (M+

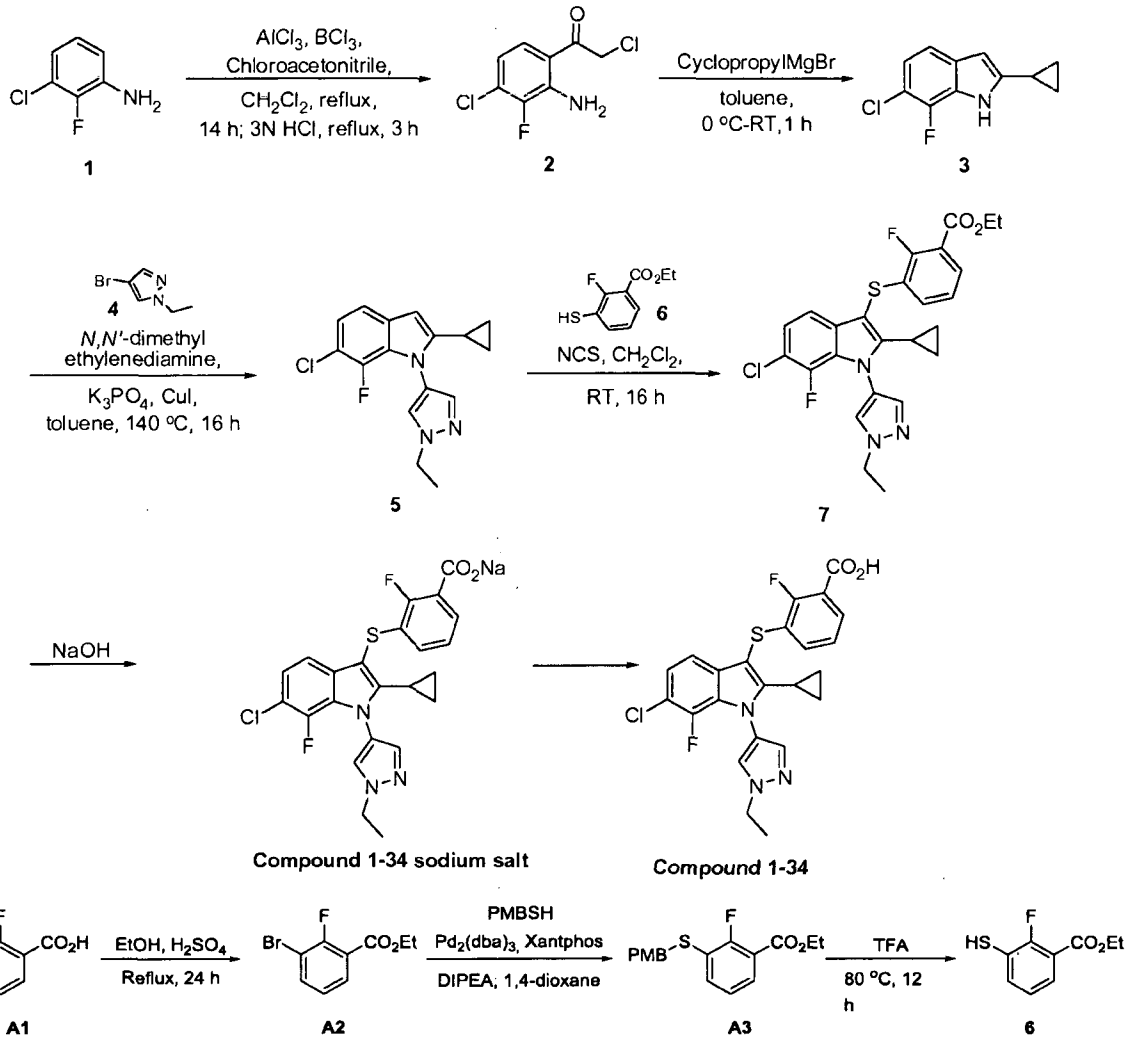
H^+); (column: X Select CSH C-18, 50 × 3.0 mm, 3.5 μm); RT 4.94 min; 5 mM NH_4OAc: ACN; 0.8 mL/min).

Step 2: Synthesis of 3-((2,6-dichloro-7-fluoro-1-(1-propyl-1*H*-pyrazol-4-yl)-1*H*-indol-3-yl)thio)-2-fluorobenzoic acid:

[00338] To a stirred solution of compound **2** (50 mg, 0.09 mmol) in THF:EtOH:H_2O (3:1:1, 5 mL) under inert atmosphere was added $LiOH.H_2O$ (12.3 mg, 0.29 mmol) at RT and stirred for 5 h. The reaction was monitored by TLC; after completion of the reaction, the volatiles were removed under reduced pressure. The residue was diluted with water (10 mL), acidified with 1*N* HCl and extracted with CH_2Cl_2 (2 x 10 mL). The combined organic extracts were washed with brine (10 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to obtain the crude. This was triturated with n-pentane (2 x 5 mL) to afford the title compound **1-13** (15 mg, 34%) as an off-white solid. **^{1}H NMR (400 MHz, DMSO-d_6):** δ 13.24 (br s, 1H), 8.29 (s, 1H), 7.83 (s, 1H), 7.64-7.60 (m, 1H), 7.36-7.34 (m, 2H), 7.15-7.05 (m, 2H), 4.16 (t, J = 7.2 Hz, 2H), 1.89-1.80 (m, 2H), 0.85 (t, J = 7.2 Hz, 3H); **MS (ESI):** 480.1 (M - H^+); **HPLC:** 97.0%; (column: Acquity BEH C-18 (50 x 2.1 mm, 1.7 μ); RT 2.86 min; ACN: 0.025% TFA (aq); 0.5 mL/min.

Example 9: Synthesis of 3-((6-Chloro-2-cyclopropyl-1-(1-ethyl-1H-pyrazol-4-yl)-7-fluoro-1H-indol-3-yl)thio)-2-fluorobenzoic acid (Compound 1-34):

Route 1



Step 1: Synthesis of 1-(2-amino-4-chloro-3-fluorophenyl)-2-chloroethan-1-one (2):

[00339] To a stirred solution of $AlCl_3$ (10.0 g, 75.01 mmol) and BCl_3 (1M in n-hexane) (74 mL, 75.01 mmol) in CH_2Cl_2 (80 mL) was added 3-chloro-2-fluoroaniline **1** (9.0 g, 6.18 mmol) followed by a solution of chloroacetonitrile (11.6 g, 153.64 mmol) in CH_2Cl_2 (20 mL) at 0 °C under inert atmosphere. The reaction mixture was allowed to stir at RT for 30 minutes; heated to reflux temperature and maintained for additional 14 h. The reaction mixture was then cooled to 0 °C, added aqueous 3N HCl solution (100 mL) and raised the temperature to reflux and stirred for 3 h. After completion of the reaction by TLC, the reaction mixture was cooled RT, diluted with water (50 mL) and extracted with CH_2Cl_2 (2 x 150 mL). The combined organic extracts were dried over Na_2SO_4, filtered and concentrated under reduced pressure to obtain the crude. The crude was purified by triturating with n-pentane to afford compound **2** (4.5 g, 33%) as an off-

white solid. **^{1}H NMR (500 MHz, DMSO-d_6):** δ 7.61 (d, J = 9.0 Hz, 1H), 7.35 (br s, 2H), 6.72 (d, J = 9.0 Hz, 1H), 5.06 (s, 2H).

Step 2: Synthesis of 6-chloro-2-cyclopropyl-7-fluoro-1H-indole (3):

[00340] To a stirred solution of compound **2** (4.5 g, 20.3 mmol) in toluene (50 mL) was added cyclopropyl magnesium bromide (0.5 M in THF; 102.0 mL, 50.9 mmol) at 0 °C under inert atmosphere. The reaction mixture was stirred at 0 °C for 15 min and then warmed to RT and stirring was continued for additional 1 h. After completion of the reaction by TLC, the reaction mixture was quenched with saturated ammonium chloride solution (10 mL) and extracted with EtOAc (3 x 75 mL). The combined organic extracts were dried over Na_2SO_4, filtered and concentrated under reduced pressure to obtain the crude. The crude was purified (silica gel chromatography; 1% EtOAc/Hexanes) to afford compound **3** (2.7 g, 63%) as an off-white solid. **^{1}H NMR (500 MHz, DMSO-d_6):** δ 11.55 (s, 1H), 7.18 (d, J = 8.5 Hz, 1H), 6.97 (dd, J = 8.5, 6.5 Hz, 1H), 6.16 (s, 1H), 2.03-1.99 (m, 1H), 0.99-0.96 (m, 2H), 0.83-0.80 (m, 2H); **LC-MS (ESI):** 91.6%; m/z 208.1 (M - H^+); (column: X Select CSH C-18, 50 × 3.0 mm, 3.5 µm); RT 4.32 min; 5 mM NH_4OAc: ACN; 0.8 mL/min).

Step 3: Synthesis of 4-bromo-1-ethyl-1H-pyrazole (4):

[00341] To a stirred solution of NaH (34.0 g, 0.85 mol; 60% in mineral oil) in THF (400 mL) was added a solution of 4-bromo-1H-pyrazole (50 g, 0.34 mol) in THF (100 mL) at 0 °C under inert atmosphere. The reaction mixture was warmed to RT and maintained at same temperature for 1 h. The reaction mixture was cooled again to 0 °C and added EtI (63.67 g, 0.408 mol) slowly for 5 min. The resultant solution was allowed to warm to RT and then stirred for 16 h. After completion of the reaction (monitored by TLC), the reaction mixture was quenched with ice-cold water (100 mL) and extracted with EtOAc (3 x 250 mL). The combined organic extracts were dried over Na_2SO_4, filtered and concentrated under reduced pressure to obtain the crude. The crude was purified (silica gel chromatography; 4-6% EtOAc/Hexanes) to afford compound **4** (43 g, 72%) as a pale yellow liquid. **^{1}H NMR (500 MHz, $CDCl_3$):** δ 7.45 (s, 1H), 7.41 (s, 1H), 4.15 (q, J = 7.5 Hz, 2H), 1.47 (t, J = 7.5 Hz, 3H); **MS (ESI):** m/z 175.0 (M + H^+).

Step 4: Synthesis of 6-chloro-2-cyclopropyl-1-(1-ethyl-1H-pyrazol-4-yl)-7-fluoro-1H-indole (5):

[00342] To a solution of compound **3** (4.3 g, 20.5 mmol) in toluene (50 mL) were added 4-bromo-1-ethyl-1H-pyrazole **4** (4.0 g, 22.8 mmol), potassium phosphate (11.0 g, 51.2 mmol), N,N'-dimethylethylenediamine (722 mg, 8.2 mmol) and Cu(I)I (390 mg, 2.0 mmol) at RT under inert atmosphere. The reaction solution was purged with argon for 15 min and then sealed the tube. The reaction mixture was heated to 140 °C and stirred for 16 h. After completion of the reaction

by TLC, the reaction mixture was cooed to RT, diluted with EtOAc (50 mL) and filtered. The filtrate was washed with water (40 mL), brine (40 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to obtain the crude. The crude was purified (silica gel chromatography; 9% EtOAc/Hexanes) to afford compound **5** (3.9 g, 63%) as a pale brown solid. **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.64 (s, 1H), 7.60 (s, 1H), 7.16 (d, J = 8.4 Hz, 1II), 7.01 (dd, J = 8.4, 6.4 Hz, 1H), 6.12 (s, 1H), 4.25 (q, J = 7.2 Hz, 2H), 1.69-1.62 (m, 1H), 1.56 (t, J = 7.2 Hz, 3H), 0.92-0.87 (m, 2H), 0.76-0.72 (m, 2H); **LC-MS (ESI):** 98.6%; m/z 304.3 ($M + H^+$); (column: X Select C-18, 50 × 3.0 mm, 3.5 μm); RT 4.23 min; 5 mM NH_4OAc: ACN; 0.8 mL/min).

Step 5: Synthesis of ethyl 3-bromo-2-fluorobenzoate (A2):

[00343] To a stirred solution of 3-bromo-2-fluorobenzoic acid **A1** (25.0 g, 114.15 mmol) in ethanol (400 mL) was added conc. H_2SO_4 (3 mL) at RT and stirred at reflux temperature for 24 h. The reaction was monitored by LC-MS; after completion of the reaction, the reaction mixture was concentrated to obtain the residue. The residue was diluted with EtOAc (500 mL), washed with water (300 mL), brine (300 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to afford compound **A2** (26.0 g, 92%) as a light yellow liquid. **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.88-7.84 (m, 1H), 7.72-7.69 (m, 1H), 7.08-7.04 (m, 1H), 4.39 (q, J = 7.2 Hz, 2H), 1.39 (t, J = 7.2 Hz, 3H).

Step 6: Synthesis of ethyl 2-fluoro-3-((4-methoxybenzyl)thio)benzoate (A3):

[00344] 1,4-dioxane (250 mL) was degassed by purging with N_2 gas for 30 min and to this, were added a solution of compound **A2** (13.2 g, 53.4 mmol) in 1,4-dioxane (50 mL; degassed), (4-methoxyphenyl)methanethiol (PMBSH) (8.2 g, 53.4 mmol), xantphos (1.54 g, 2.66 mmol), diisopropyl ethyl amine (19.6 mL, 106.8 mmol) and $Pd_2(dba)_3$ (1.22 g, 1.33 mmol) at RT. The reaction mixture was heated to 90 °C and stirred for 2 h. The reaction was monitored by TLC; after completion of the reaction, the reaction mixture was diluted with hexane (450 mL) and stirred at RT for 15 min. The resultant solution was filtered through celite and washed with hexane (100 mL). The filtrate was washed water (250 mL) dried over Na_2SO_4, filtered and concentrated under reduced pressure to obtain the crude. The crude was purified through silica gel column chromatography using 3-4% EtOAc/Hexanes to afford compound **A3** (15 g, 88%) as pale yellow solid. **^{1}H NMR (500 MHz, $CDCl_3$):** δ 7.78-7.74 (m, 1H), 7.43-7.39 (m, 1H), 7.19 (d, J = 8.0 Hz, 2H), 7.07-7.04 (m, 1H), 6.80 (d, J = 8.0 Hz, 2H), 4.41 (q, J = 7.2 Hz, 2H), 4.08 (s, 2H), 3.78 (s, 3H), 1.41 (t, J = 7.2 Hz, 3H). **LC-MS (ESI):** 89.7%; m/z 318.9 ($M - H^+$); (column: X Select CSH C-18, 50 × 3.0 mm, 3.5 μm); RT 4.22 min; 5 mM NH_4OAc: ACN; 0.8 mL/min).

Step 7: Synthesis of ethyl 2-fluoro-3-mercaptobenzoate (6):

[00345] A stirred solution of compound **A3** (30.0 g, 93.75 mmol) in TFA (54.5 mL) was heated to 80 °C and stirred for 12 h under inert atmosphere. The reaction was monitored by TLC; after completion of the reaction, the volatiles were removed under reduced pressure. The residue was dissolved in ice-cold water (100 mL), basified with solid sodium bicarbonate and extracted with EtOAc (2 x 200 mL). The combined organic extracts were dried over Na_2SO_4, filtered and concentrated under reduced pressure to obtain the crude. The crude was purified through silica gel column chromatography using 3% EtOAc/Hexanes to afford compound **6** (11.7 g, 62%) as a pale brown syrup. **^{1}H NMR (500 MHz, $CDCl_3$):** δ 7.70-7.66 (m, 1H), 7.48-7.44 (m, 1H), 7.08-7.04 (m, 1H), 4.20 (q, J = 7.5 Hz, 2H), 3.67 (s, 1H), 1.40 (t, J = 7.5 Hz, 3H); **LC-MS (ESI):** 91.8%; m/z 199.0 (M - H^+); (column: X Select CSH C-18, 50 × 3.0 mm, 3.5 μm); RT 2.60 min; 5 mM NH_4OAc: ACN; 0.8 mL/min).

Step 8: Synthesis of ethyl 3-((6-chloro-2-cyclopropyl-1-(1-ethyl-1H-pyrazol-4-yl)-7-fluoro-1H-indol-3-yl)thio)-2-fluorobenzoate (7):

[00346] To a stirred solution of ethyl 2-fluoro-3-mercaptobenzoate **6** (2.8 g, 14.0 mmol) in CH_2Cl_2 (30 mL) under inert atmosphere was added NCS (1.9 g, 14.0 mmol) at RT and allowed to stir for 2 h. To this, compound **5** (3.9 g, 12.8 mmol) in CH_2Cl_2 (10 mL) was added at RT and stirred for 16 h. After completion of the reaction by TLC, the reaction mixture was diluted with water (100 mL) and extracted with CH_2Cl_2 (2 x 80 mL). The combined organic extracts were washed with water (2 x 200 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to obtain the crude. The crude was purified by triturating with n-pentane (2 X 50 mL) to afford 7 (5.2 g, 81%) as a pale yellow solid. **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.66-7.7.60 (m, 3H), 7.18 (d, J = 8.4 Hz, 1H), 7.08 (dd, J = 8.4, 6.5 Hz, 1H), 6.93 (t, J = 8.4 Hz, 1H), 6.79-6.75 (m, 1H), 4.40 (q, J = 7.2 Hz, 2H), 4.26 (q, J = 7.6 Hz, 2H), 1.74-1.68 (m, 1H), 1.56 (t, J = 7.2 Hz, 3H), 1.41 (t, J = 7.6 Hz, 3H), 1.08-1.04 (m, 2H), 0.89-0.84 (m, 2H); **MS (ESI):** m/z 502.5 (M + H^+); **HPLC:** 97.5%; (column: Acquity BEH C-18 (50 x 2.1 mm, 1.7 μ); RT 3.44 min; ACN: 0.025% TFA (aq); 0.5 mL/min.

Step 9: Synthesis of 3-((6-chloro-2-cyclopropyl-1-(1-ethyl-1H-pyrazol-4-yl)-7-fluoro-1H-indol-3-yl)thio)-2-fluorobenzoic acid sodium salt (Compound 1-34 sodium salt):

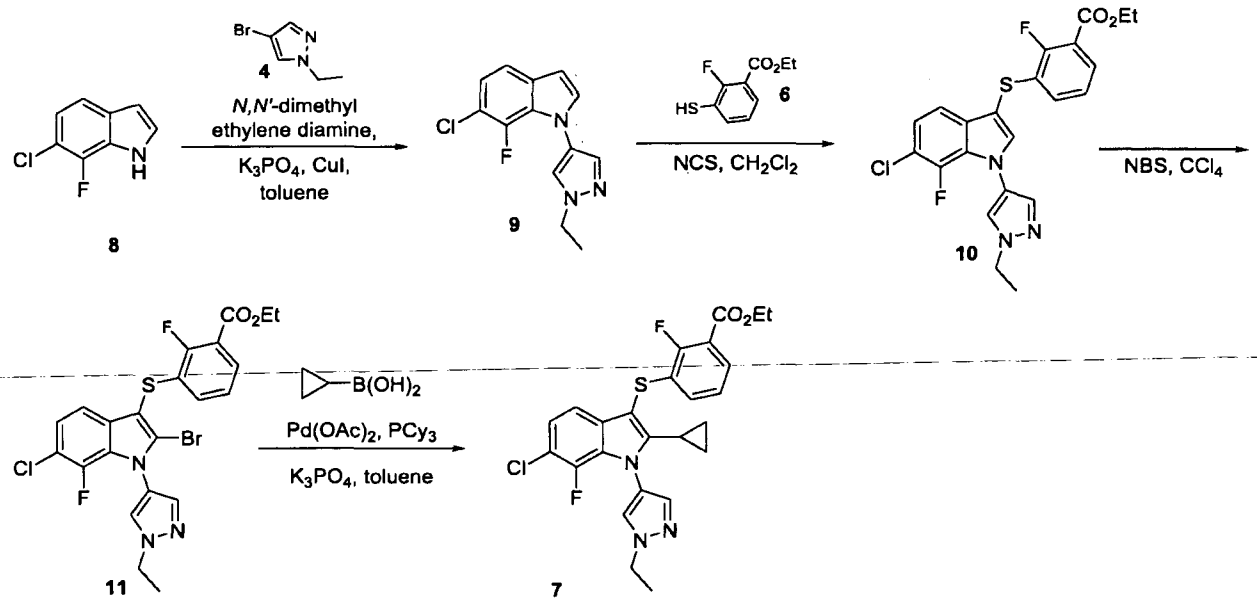
[00347] 1.0 M NaOH (10.25 mL, 10.2 mmol) was added to a solution of compound **7** (5.14 g, 10.2 mmol) in THF/MeOH (3 : 1)(56 mL). The mixture was heated at 65 °C for 1.5 h. Additional 1.0 M NaOH (0.23 mL, 0.2 mmol) was added to the reaction and heated at 65 °C for 0.5 h. The mixture was concentrated under reduced pressure to afford the crude acid sodium salt (5.12 g, 100 %) as a pale pink solid. The crude solid (600 mg) in THF/EtOH (4 : 1) (6 mL) and a

few drops of water. The mixture filtered and concentrated under reduced pressure and precipitants formed. The solids filtered off and washed with THF/EtOH (9 : 1) to afford 3-((6-chloro-2-cyclopropyl-1-(1-ethyl-1H-pyrazol-4-yl)-7-fluoro-1H-indol-3-yl)thio)-2-fluorobenzoic acid sodium salt (**Compound 1-34 sodium salt**; 449 mg) as an off white solid. **^{1}H NMR (300 MHz, DMSO-d_6):** δ 8.26 (s, 1H), 7.79 (m, 1H), 7.18-7.13 (m, 3H), 6.81 (t, 1H), 6.43-6.38 (m, 1H), 4.21 (q, 2H), 1.84-1.72 (m, 1H), 1.42 (t, 3H), 0.96-0.93 (m, 2H), 0.84-0.80 (m, 2H); **LC-MS:** 474 (M^+).

Step 9: 3-((6-Chloro-2-cyclopropyl-1-(1-ethyl-1H-pyrazol-4-yl)-7-fluoro-1H-indol-3-yl)thio)-2-fluorobenzoic acid (Compound 1-34):

[00348] To Compound 1-34 sodium salt (50 mg, 0.10 mmol) suspended in CH_2Cl_2 (1 mL) and water (1 mL) was added saturated citric acid until pH 3. The suspension stirred until clear solution. The organic layer was separated, washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure to obtain the crude material to afford compound B as a white solid (33 mg, 70%) **^{1}H NMR (300 MHz, DMSO-d_6):** δ 13.39 (s, 1H), 8.24 (s, 1H), 7.79 (s, 1H), 7.57 (t, 1H), 7.22-7.06 (m, 3H), 6.80 (t, 1H), 4.21 (q, 2H), 1.84-1.72 (m, 1H), 1.42 (t, 3H), 0.96-0.88 (m, 2H), 0.86-0.80 (m, 2H); **LC-MS:** 474 (M^+).

Alternative route to intermediate 7:



Step 1: Synthesis of 6-chloro-1-(1-ethyl-1H-pyrazol-4-yl)-7-fluoro-1H-indole (9):

[00349] To a stirred solution of 6-chloro-7-fluoro-1H-indole **8** (400 mg, 2.36 mmol) in toluene (10 mL) were added 4-bromo-1-ethyl-1H-pyrazole **4** (Step 3 above; 414 mg, 2.36 mmol), potassium phosphate (1.25 g, 5.91 mmol), N,N'-dimethylethylenediamine (84 mg, 0.95 mmol)

and Cu(I)I (45 mg, 0.24 mmol) at RT under inert atmosphere. The resulted solution was purged with argon and sealed the tube. The reaction mixture was then heated to 140 °C for 16 h. After completion of the reaction (monitored by TLC), the reaction mixture was cooled to RT, diluted with hexane (10 mL) and filtered through a short pad of celite. The filtrate was washed with water (2x10 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to obtain the crude. The crude was purified (silica gel chromatography; 8-10% EtOAc/Hexanes) to afford compound **9** (224 mg, 36%) as a light brown thick liquid. **^{1}H NMR (500 MHz, $CDCl_3$):** δ 7.64 (s, 1H), 7.61 (s, 1H), 7.31 (d, J = 8.0 Hz, 1H), 7.12-7.07 (m, 2H), 6.60-6.59 (m, 1H), 4.22 (q, J = 7.5 Hz, 2H), 1.55 (t, J = 7.5 Hz, 3H); **LC-MS (ESI):** 94.7%; m/z 264.1 ($M + H^+$); (column: X Select C-18, 50 × 3.0 mm, 3.5 μm); RT 3.87 min; 5 mM NH_4OAc: ACN; 0.8 mL/min).

Step 2: Synthesis of ethyl 3-((6-chloro-1-(1-ethyl-1H-pyrazol-4-yl)-7-fluoro-1H-indol-3-yl)thio)-2-fluorobenzoate (10):

[00350] To a stirred solution of ethyl 2-fluoro-3-mercaptobenzoate **6** (Step 7 above; 212 mg, 1.06 mmol) in CH_2Cl_2 (4 mL) under inert atmosphere was added NCS (156 mg, 1.16 mmol) at 0 °C and allowed to stir at RT for 1 h. The reaction mixture was cooled to 0 °C and compound **3** (280 mg, 1.06 mmol) in CH_2Cl_2 (1 mL) was added slowly and stirred at RT for 16 h. After completion of the reaction by TLC, the reaction mixture was diluted with CH_2Cl_2 (15 mL) and washed with water (2 x 20 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to obtain the crude. The crude was purified (silica gel chromatography; 8-10% EtOAc/Hexanes) to afford compound **10** (300 mg, 61%) as a pale brown solid. **^{1}H NMR (500 MHz, $CDCl_3$):** δ 7.69-7.64 (m, 3H), 7.44 (s, 1H), 7.27 (t, J = 8.0 Hz, 1H), 7.16 (dd, J = 8.5, 6.0 Hz, 1H), 7.01-6.94 (m, 2H), 4.39 (q, J = 7.5 Hz, 2H), 4.24 (q, J = 7.0 Hz, 2H), 1.57 (t, J = 7.0 Hz, 3H), 1.40 (t, J = 7.5 Hz, 3H); **LC-MS (ESI):** 98.6%; m/z 462.3 ($M + H^+$); (column: X Select C-18, 50 × 3.0 mm, 3.5 μm); RT 4.70 min; 5 mM NH_4OAc: ACN; 0.8 mL/min).

Step 3: Synthesis of ethyl 3-((2-bromo-6-chloro-1-(1-ethyl-1H-pyrazol-4-yl)-7-fluoro-1H-indol-3-yl)thio)-2-fluorobenzoate (11):

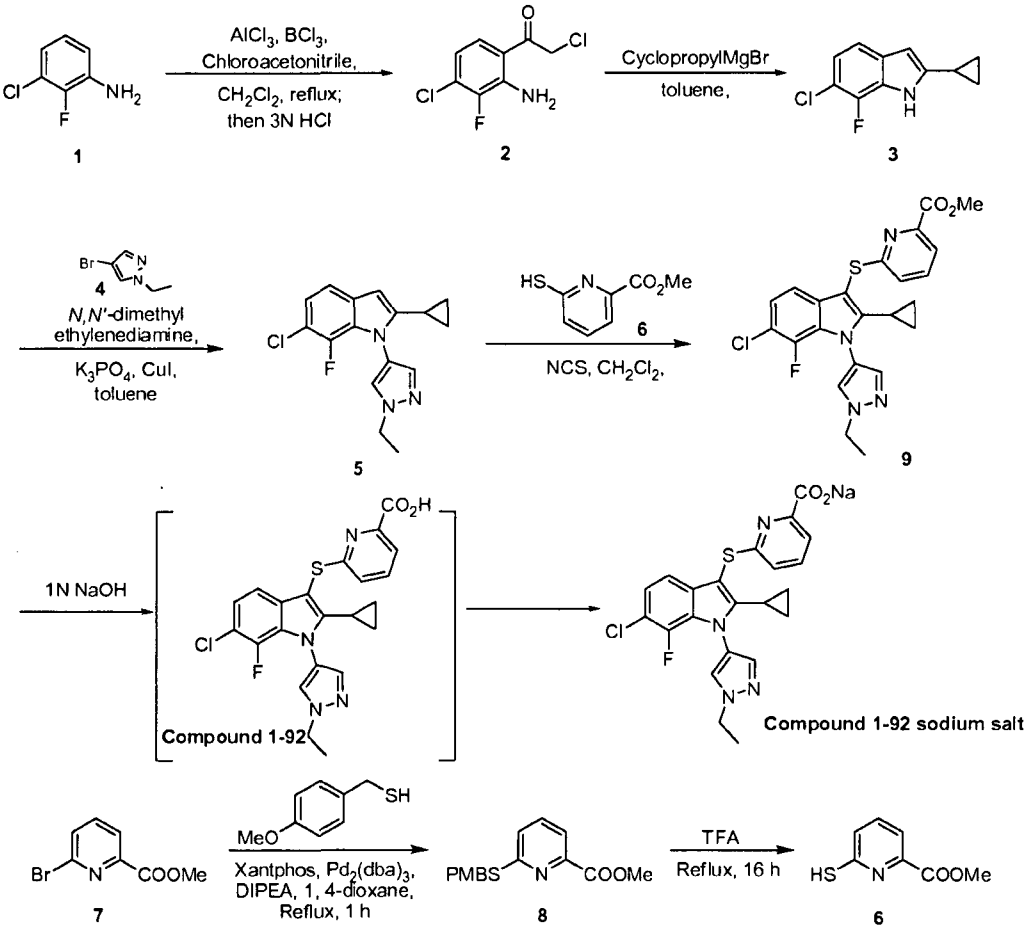
[00351] To a stirred solution of compound **10** (200 mg, 0.43 mmol) in CCl_4 (10 mL) under inert atmosphere was added NBS (178 mg, 0.99 mmol) at RT and stirred for 16 h. After completion of the reaction by TLC, the reaction mixture was diluted with water (10 mL) and extracted with CH_2Cl_2 (2 x 20 mL). The combined organic extracts were washed with brine (10 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to obtain the crude. The crude was purified (silica gel chromatography; 5-7% EtOAc/Hexanes) to afford compound **11** (180 mg, 77%) as an off-white solid. **^{1}H NMR (500 MHz, $CDCl_3$):** δ 7.70-7.67 (m, 1H), 7.65 (s, 2H), 7.30 (d, J = 8.0 Hz, 1H), 7.17 (dd, J = 8.5, 6.0 Hz, 1H), 7.00-6.98 (m, 2H), 4.40 (q, J = 7.5 Hz, 2H),

4.27 (q, J = 7.5 Hz, 2H), 1.58 (t, J = 7.5 Hz, 3H), 1.40 (t, J = 7.5 Hz, 3H); **LC-MS (ESI):** 99.5%; m/z 542.4 ($M^+ + 2$); (column: X Select CSH C-18, 50 × 3.0 mm, 3.5 µm); RT 4.80 min; 5 mM NH_4OAc: ACN; 0.8 mL/min).

Step 4: Synthesis of ethyl 3-((6-chloro-2-cyclopropyl-1-(1-ethyl-1H-pyrazol-4-yl)-7-fluoro-1H-indol-3-yl)thio)-2-fluorobenzoate (7):

[00352] A solution of compound **11** (150 mg, 0.27 mmol) in toluene (10 mL) under inert atmosphere was purged with argon at RT for 10 min. To this, cyclopropylboronic acid (48 mg, 0.55 mmol), tricyclohexyl phosphine (16 mg, 0.05 mmol), $Pd(OAc)_2$ (6 mg, 0.02 mmol) and potassium phosphate (202 mg, 0.01 mmol) were added at RT under argon. The resultant solution was purged again with argon at RT for 5 min. The reaction mixture was then heated to reflux temperature and stirred for 3 h. The reaction was monitored by TLC & LC-MS; after completion of the reaction, the reaction was cooled to RT, diluted with EtOAc (20 mL) and filtered. The filtrate was washed with water (2 x 10 mL) and brine (10 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to obtain the crude. This was purified (silica gel chromatography; 6% EtOAc/Hexanes) to afford 7 as a pale yellow solid. **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.66-7.7.60 (m, 3H), 7.18 (d, J = 8.4 Hz, 1H), 7.08 (dd, J = 8.4, 6.5 Hz, 1H), 6.93 (t, J = 8.4 Hz, 1H), 6.79-6.75 (m, 1H), 4.40 (q, J = 7.2 Hz, 2H), 4.26 (q, J = 7.6 Hz, 2H), 1.74-1.68 (m, 1H), 1.56 (t, J = 7.2 Hz, 3H), 1.41 (t, J = 7.6 Hz, 3H), 1.08-1.04 (m, 2H), 0.89-0.84 (m, 2H); **LC-MS (ESI):** 92.9%; m/z 502.5 (M^+); (column: X Select CSH C-18, 50 × 3.0 mm, 3.5 µm); RT 4.85 min; 5 mM NH_4OAc: ACN; 0.8 mL/min); **HPLC:** 93.1%; (column: Acquity BEH C-18 (50 x 2.1 mm, 1.7 µ); RT 3.44 min; ACN: 0.025% TFA (aq); 0.5 mL/min.

Example 10: Synthesis of 6-((6-chloro-2-cyclopropyl-1-(1-ethyl-1H-pyrazol-4-yl)-7-fluoro-1H-indol-3-yl)thio)picolinic acid (Compound 1-92)



Step 1: Synthesis of 1-(2-amino-4-chloro-3-fluorophenyl)-2-chloroethan-1-one (2):

[00353] To a stirred solution of $AlCl_3$ (10.0 g, 75.01 mmol) and BCl_3 (1M in n-hexane) (74 mL, 75.01 mmol) in CH_2Cl_2 (80 mL) was added 3-chloro-2-fluoroaniline **1** (9.0 g, 6.18 mmol) followed by a solution of chloroacetonitrile (11.6 g, 153.64 mmol) in CH_2Cl_2 (20 mL) at 0 °C under inert atmosphere. The reaction mixture was allowed to stir at RT for 30 minutes; heated to reflux temperature and maintained for additional 14 h. The reaction mixture was then cooled to 0 °C, added aqueous 3N HCl solution (100 mL) and raised the temperature to reflux and stirred for 3 h. After completion of the reaction (TLC), the reaction mixture was cooled RT, diluted with water (50 mL) and extracted with CH_2Cl_2 (2 x 150 mL). The combined organic extracts were dried over Na_2SO_4, filtered and concentrated under reduced pressure to obtain the crude. The crude was purified by triturating with n-pentane to afford compound **2** (4.5 g, 33%) as an off-white solid. **^{1}H NMR (500 MHz, DMSO-d_6):** δ 7.61 (d, J = 9.0 Hz, 1H), 7.35 (br s, 2H), 6.72 (d, J = 9.0 Hz, 1H), 5.06 (s, 2H).

Step 2: Synthesis of 6-chloro-2-cyclopropyl-7-fluoro-1H-indole (3):

[00354] To a stirred solution of compound **2** (4.5 g, 20.3 mmol) in toluene (50 mL) was added cyclopropyl magnesium bromide (0.5 M in THF; 102.0 mL, 50.9 mmol) at 0 °C under inert atmosphere. The reaction mixture was stirred at 0 °C for 15 min and then warmed to RT and stirring was continued for additional 1 h. After completion of the reaction (TLC), the reaction mixture was quenched with sat. NH_4Cl solution (10 mL) and extracted with EtOAc (3 x 75 mL). The combined organic extracts were dried over Na_2SO_4, filtered and concentrated under reduced pressure to obtain the crude. The crude was purified (silica gel column chromatography; 1% EtOAc/Hexanes to afford compound **3** (2.7 g, 63%) as an off-white solid. **^{1}H NMR (500 MHz, DMSO-d_6):** δ 11.55 (s, 1H), 7.18 (d, J = 8.5 Hz, 1H), 6.97 (dd, J = 8.5, 6.5 Hz, 1H), 6.16 (s, 1H), 2.03-1.99 (m, 1H), 0.99-0.96 (m, 2H), 0.83-0.80 (m, 2H); **LC-MS (ESI):** 91.6%; m/z 208.1 ($M - H^+$); (column: X Select CSH C-18, 50 × 3.0 mm, 3.5 µm); RT 4.32 min; 5 mM NH_4OAc: ACN; 0.8 mL/min).

Step 3: Synthesis of 6-chloro-2-cyclopropyl-1-(1-ethyl-1H-pyrazol-4-yl)-7-fluoro-1H-indole (5):

[00355] To a solution of compound **3** (4.3 g, 20.5 mmol) in toluene (50 mL) were added 4-bromo-1-ethyl-1H-pyrazole **4** (Example 2, Step 3; 4.0 g, 22.8 mmol), potassium phosphate (11.0 g, 51.2 mmol), N,N'-dimethylethylenediamine (722 mg, 8.2 mmol) and Cu(I)I (390 mg, 2.0 mmol) at RT under inert atmosphere. The reaction solution was purged with argon for 15 min and then sealed the tube. The reaction mixture was heated to 140 °C and stirred for 16 h. After completion of the reaction (TLC), the reaction mixture was cooled to RT, diluted with EtOAc (50 mL) and filtered. The filtrate was washed with water (40 mL), brine (40 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to obtain the crude. The crude was purified (silica gel column chromatography; 9% EtOAc/Hexanes) to afford compound **5** (3.9 g, 63%) as a pale brown solid. **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.64 (s, 1H), 7.60 (s, 1H), 7.16 (d, J = 8.4 Hz, 1H), 7.01 (dd, J = 8.4, 6.4 Hz, 1H), 6.12 (s, 1H), 4.25 (q, J = 7.2 Hz, 2H), 1.69-1.62 (m, 1H), 1.56 (t, J = 7.2 Hz, 3H), 0.92-0.87 (m, 2H), 0.76-0.72 (m, 2H); **LC-MS (ESI):** 98.6%; m/z 304.3 ($M + H^+$); (column: X Select C-18, 50 × 3.0 mm, 3.5 µm); RT 4.23 min; 5 mM NH_4OAc: ACN; 0.8 mL/min).

Step 4: Synthesis of methyl 6-((4-methoxybenzyl) thio) picolinate (8):

[00356] To a stirred solution of methyl 6-bromopicolinate **7** (8 g, 37.2 mmol) in 1, 4-dioxane (110 mL) under inert atmosphere were added (4-methoxyphenyl) methanethiol (5.7 g, 37.0 mmol), xantphos (1.1 g, 1.9 mmol), diisopropyl ethyl amine (13.6 mL, 74.0 mmol), $Pd_2(dba)_3$ (847 mg, 0.9 mmol) at RT, degassed under argon for 15 min; heated to reflux and stirred for 1 h. After

completion of the reaction (TLC), the reaction mixture was diluted with water (500 mL) and extracted with EtOAc (3 x 500 mL). The combined organic extracts were dried over Na_2SO_4, filtered and concentrated under reduced pressure to obtain the crude. The crude was purified (silica gel column chromatography; 10% EtOAc/ hexanes) to afford compound **8** (8 g, 75%) as yellow solid. **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.78 (d, J = 7.6 Hz, 1H), 7.57 (t, J = 8.0 Hz, 1H), 7.42-7.40 (m, 2H), 7.29-7.25 (m, 1H), 6.82 (d, J = 8.4 Hz, 2H), 4.44 (s, 2H), 4.00 (s, 3H), 3.77 (s, 3H); **LC-MS:** 95.7%; 290.3 (M^++1); (column: X Select C-18, 50 × 3.0 mm, 3.5 μm); RT 4.10 min. 5 mM NH_4OAc: ACN; 0.8 mL/min).

Step 5: Synthesis of methyl 6-mercaptopicolinate (6):

[00357] A stirred solution of compound **8** (6 g, 20.7 mmol) in Trifluoro acetic acid (50 mL) under inert atmosphere was heated to reflux and stirred for 16 h. After completion of the reaction (TLC), the volatiles were removed under reduced pressure. The residue was diluted with EtOAc (500 mL), washed with aqueous $NaHCO_3$ solution (3 x 250 mL). The organic extract were dried over Na_2SO_4, filtered and concentrated under reduced pressure to obtain the compound **6** (3.5 g, crude) as pale brown solid. **LC-MS:** 61.1%; 170 (M^++1); (column: X Select C-18, 50 × 3.0 mm, 3.5 μm); RT 1.41 min. 5 mM NH_4OAc: ACN; 0.8 mL/min).

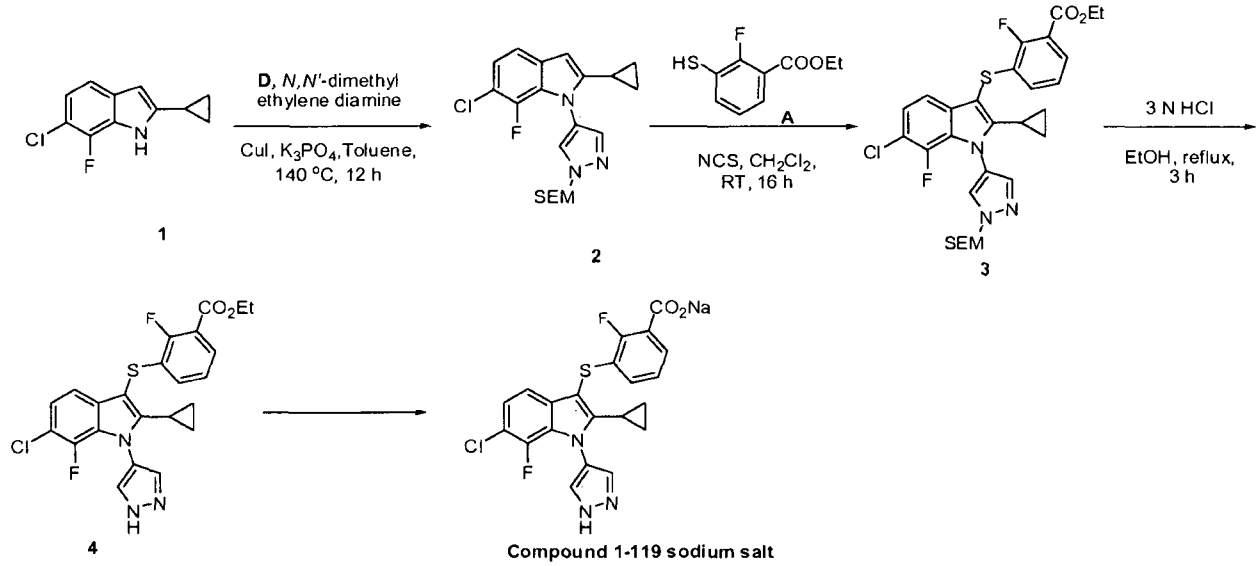
Step 6: Synthesis of methyl 6-((6-chloro-2-cyclopropyl-1-(1-ethyl-1H-pyrazol-4-yl)-7-fluoro-1H-indol-3-yl)thio)picolinate (9):

[00358] To a stirred solution of methyl 6-mercaptopicolinate **6** (3.15 g, crude) in CH_2Cl_2 (50 mL) under inert atmosphere was added NCS (2.49 g, 18.63 mmol) at RT and stirred for 1 h. To this, indole **5** (5.6 g, 18.47 mmol) in CH_2Cl_2 (50 mL) was added at RT and stirred for 16 h. After completion of the reaction (TLC), the reaction mixture was diluted CH_2Cl_2 (100 mL) washed with water (3 x 100 mL). The organic extract was dried over Na_2SO_4, filtered and concentrated under reduced pressure to obtain the crude. The crude was purified (silica gel column chromatography; 10% EtOAc/ hexanes) to afford **9** (2.8 g, 32%) as a pale brown solid. **^{1}H NMR (500 MHz, DMSO-d_6):** δ 7.79 (d, J = 7.5 Hz, 1H), 7.66 (d, J = 10.5 Hz, 2H), 7.51 (t, J = 7.5 Hz, 1H), 7.19 (d, J = 8.5 Hz, 1H), 7.10-7.07 (m, 1H), 6.78 (d, J = 8.0 Hz, 1H), 4.28 (q, 2H), 4.00 (s, 3H), 1.75-1.69 (m, 1H), 1.58 (t, J = 7.0 Hz, 3H), 1.09-1.08 (m, 2H), 0.87-0.84 (m, 2H); **LC-MS:** 98.4%; m/z 471.4 (M + H^+);(column; X-select CSH C-18, (50 × 3.0 mm, 3.5 μm); RT 4.25 min. 5.0 mM NH_4OAc (Aq): ACN; 0.8 mL/min); **HPLC:** 98.1%; (column: Acquity BEH C-18 (50 x 2.1 mm, 1.7 μ); RT 3.02 min. ACN: 0.025% TFA (aq); 0.5 mL/min).

Step 7: Synthesis of 6-((6-chloro-2-cyclopropyl-1-(1-ethyl-1H-pyrazol-4-yl)-7-fluoro-1H-indol-3-yl)thio)picolinic acid sodium salt (Compound 1-92 sodium salt):

[00359] To a stirred solution of compound **9** (2.81 g, 5.97 mmol) in THF : water (4:1) (40 mL) was added 1M aq. NaOH solution (6.03 mL, 6.03 mmol) and the mixture was heated at 60 °C for 1 h. After completion of the reaction, the solvent was removed to afford **Compound 1-92** (2.83 g, 100%) as a light brown solid. **LC-MS:** 457 (M^++1).

Example 11: Synthesis of 3-((6-chloro-2-cyclopropyl-7-fluoro-1-(1*H*-pyrazol-4-yl)-1*H*-indol-3-yl)thio)-2-fluorobenzoic acid sodium salt (Compound 1-119)



Step 1: Synthesis of ethyl 3-((6-chloro-2-cyclopropyl-7-fluoro-1-(1-((2-(trimethylsilyl) ethoxy) methyl)-1*H*-pyrazol-4-yl)-1*H*-indol-3-yl)thio)-2-fluorobenzoate (3):

[00360] Following the procedure of Example 9, Steps 3 and 4 but using Intermediate **D** in place of Intermediate **B** in Step 3, the title compound **3** was obtained as a pale brown syrup. **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.85 (s, 1H), 7.73 (s, 1H), 7.64 (t, J = 7.5 Hz, 1H), 7.20 (d, J = 8.0 Hz, 1H), 7.12-7.09 (m, 1H), 6.95 (t, J = 7.5 Hz, 1H), 6.79 (t, J = 6.5 Hz, 1H), 5.54 (s, 2H), 4.42 (q, 2H), 3.62 (t, J = 7.5 Hz, 2H), 1.70-1.65 (m, 1H), 1.42 (t, J = 7.0 Hz, 3H), 1.06-1.05 (m, 2H), 0.96 (t, J = 8.5 Hz, 2H), 0.89-0.87 (m, 2H), 0.03 (s, 9H); **LC-MS (ESI):** *m/z* 604.6 (M + H^+).

Step 2: Synthesis of ethyl 3-((6-chloro-2-cyclopropyl-7-fluoro-1-(1*H*-pyrazol-4-yl)-1*H*-indol-3-yl)thio)-2-fluorobenzoate (4):

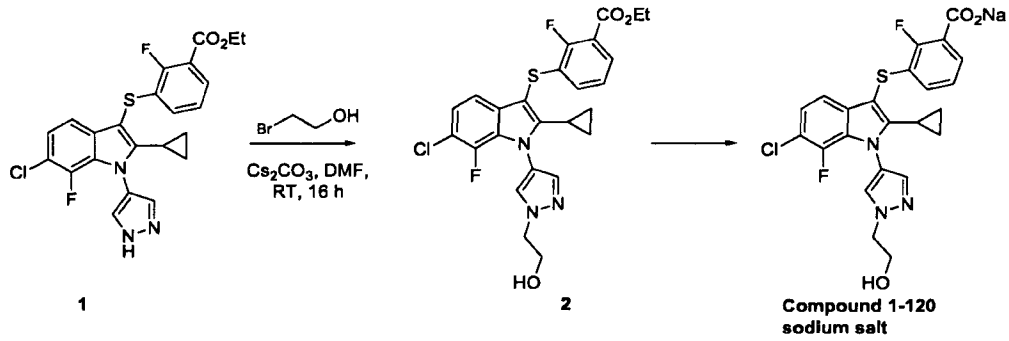
[00361] To a stirred solution of compound **3** (140 mg, 0.23 mmol) in EtOH (17 mL) was added 3 *N* HCl (4 mL) at RT and heated to reflux for 3 h. After completion of the reaction (TLC), the pH of the mixture was neutralized with Et_3N (2 mL) and extracted with EtOAc (2 x 30 mL). The combined organic extracts were dried (Na_2SO_4), filtered and concentrated under reduced pressure

to obtain the crude. The crude was titurated with *n*-pentane, dried under reduced pressure to afford **4** (90 mg, 90%) as a pale brown solid. **^{1}H NMR (500 MHz, DMSO-d_6):** δ 13.21 (br s, 1H), 8.24 (s, 1H), 7.84 (s, 1H), 7.60 (t, J = 6.5 Hz, 1H), 7.21-7.11 (m, 3H), 6.84 (t, J = 6.5 Hz, 1H), 4.34 (q, 2H), 1.81-1.76 (m, 1H), 1.32 (t, J = 8.0 Hz, 3H), 0.93-0.90 (m, 2H), 0.84-0.79 (m, 2H); **LC-MS (ESI):** *m/z* 474.9 (M + H$^+$).

Step 3: Synthesis of 3-((6-chloro-2-cyclopropyl-7-fluoro-1-(1*H*-pyrazol-4-yl)-1*H*-indol-3-yl)thio)-2-fluorobenzoic acid sodium salt (Compound 1-119)

[00362] To a solution of compound **4** (30 mg, 0.063 mmol) in THF : water (3:1) (4 mL) was added 1M aq. NaOH solution (0.063 mL, 0.063 mmol) at RT and then heat at 60 °C overnight. After the completion of the reaction, solvent was removed to afford **Compound 1-119 sodium salt** (29 mg, 100%) as an off-white solid. **LC-MS:** *m/z* 446 (M+1).

Example 12: Synthesis of 3-((6-chloro-2-cyclopropyl-7-fluoro-1-(1-(2-hydroxyethyl)-1*H*-pyrazol-4-yl)-1*H*-indol-3-yl)thio)-2-fluorobenzoic acid sodium salt (Compound 1-120)



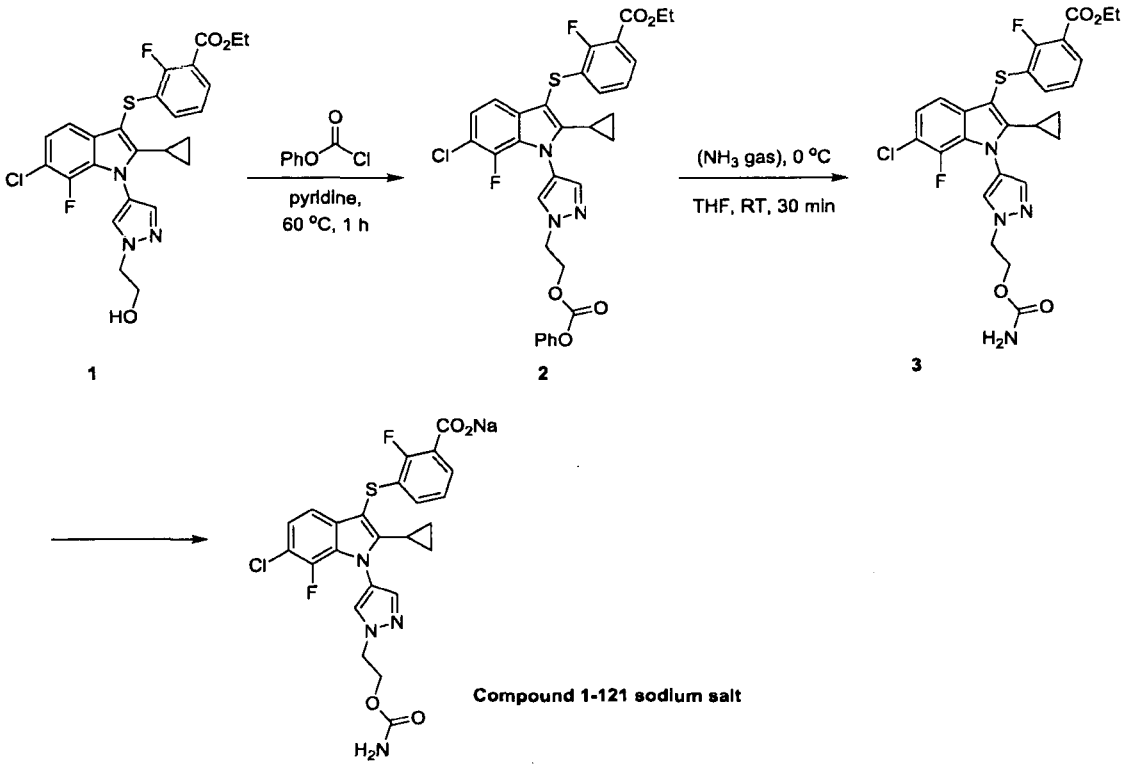
Step 1: Synthesis of ethyl 3-((6-chloro-2-cyclopropyl-7-fluoro-1-(1-(2-hydroxyethyl)-1*H*-pyrazol-4-yl)-1*H*-indol-3-yl)thio)-2-fluorobenzoate (2):

[00363] To a stirred solution of indole 1 (Example 11, Step 3; 480 mg, 1.01 mmol) in DMF (10 mL) under inert atmosphere were added Cs_2CO_3 (1.32 g, 4.05 mmol) and 2-bromoethan-1-ol (152 mg, 1.27 mmol) at RT and stirred for 16 h. The mixture was diluted with water (20 mL) and extracted with EtOAc (3 x 20 mL). The combined organic extracts were dried (Na_2SO_4), filtered and concentrated under reduced pressure to obtain the crude. This was purified (silica gel; 55% EtOAc/ hexanes) to obtain compound **2** (100 mg, 19%) as a colorless syrup. **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.72 (d, J = 6.8 Hz, 2H), 7.62 (dt, J = 8.0 Hz, 1.6 Hz, 1H), 7.18 (d, J = 8.4 Hz, 1H), 7.10-7.07 (m, 1H), 6.94 (t, J = 8.0 Hz, 1H), 6.78 (dt, J = 8.0, 1.6 Hz, 1H), 4.41 (q, 2H), 4.36-4.34 (m, 2H), 4.10 (t, J = 4.8 Hz, 2H), 2.72 (br s, 1H), 1.74-1.67 (m, 1H), 1.41 (t, J = 7.2 Hz, 3H), 1.08-1.04 (m, 2H), 0.90-0.85 (m, 2H); **LC-MS:** *m/z* 518.7 (M + H$^+$).

Step 2: Synthesis of 3-((6-chloro-2-cyclopropyl-7-fluoro-1-(1-(2-hydroxyethyl)-1*H*-pyrazol-4-yl)-1*H*-indol-3-yl)thio)-2-fluorobenzoic acid sodium salt (Compound 1-120)

[00364] Following the procedure of Example 11, Step 3 but using Intermediate **2** in place of Intermediate **4** in Step 3, the title **Compound 1-120 sodium salt** was obtained as a white solid. **LC-MS:** *m/z* 490 (M+1).

Example 13: Synthesis of 3-((1-(1-(2-(carbamoyloxy)ethyl)-1*H*-pyrazol-4-yl)-6-chloro-2-cyclopropyl-7-fluoro-1*H*-indol-3-yl)thio)-2-fluorobenzoic acid sodium salt (Compound 1-121)



Step 1: Synthesis of ethyl 3-((6-chloro-2-cyclopropyl-7-fluoro-1-(1-(2-phenoxycarbonyl)oxy)ethyl)-1*H*-pyrazol-4-yl)-1*H*-indol-3-yl)thio)-2-fluorobenzoate (2):

[00365] To a stirred solution of indole **1** (Example 12, Step 1; 50 mg, 0.096 mmol) in pyridine (2 mL) under inert atmosphere was added phenyl chloroformate (18 mg, 0.11 mmol) at 0 °C; heated to 60 °C and stirred for 1 hr. The mixture was diluted with water (20 mL), acidified with 1 *N* aq. HCl (5 mL) and extracted with EtOAc (2 x 10 mL). The combined organic extracts were washed with brine (10 mL), dried (Na_2SO_4), filtered and concentrated under reduced pressure to obtain the crude. This was purified (silica gel; 30% EtOAc/ hexanes) to afford compound **2** (20 mg, 32%) as a yellow oil. **LC-MS (ESI):** m/z 638.5 ($M + H^+$).

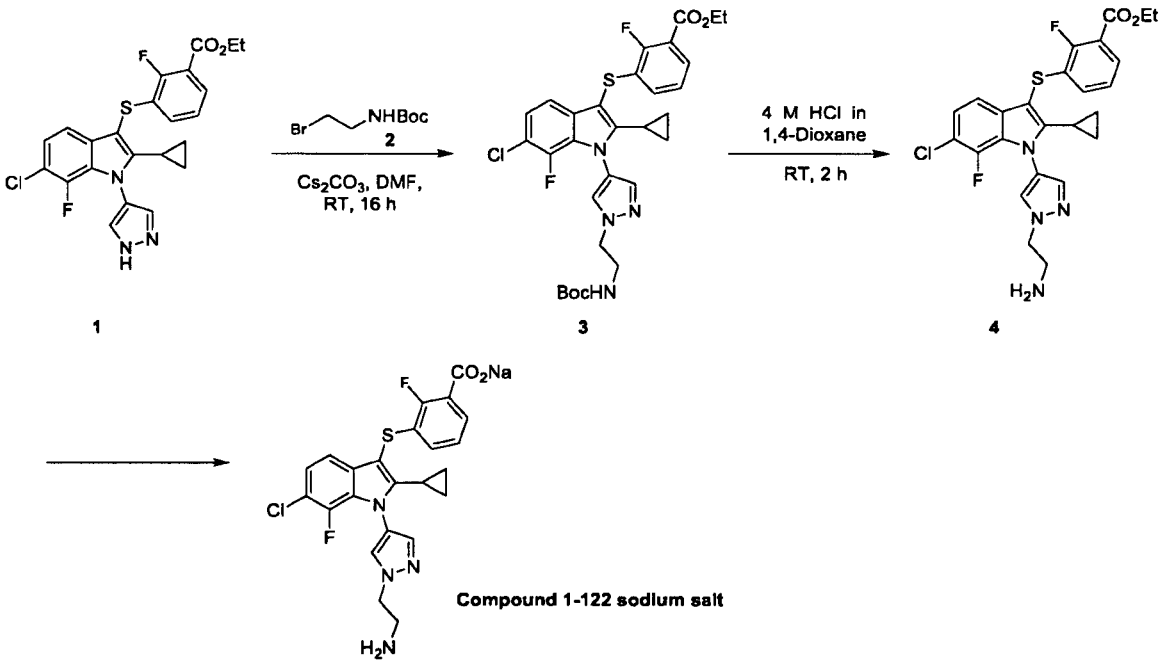
Step 2: Synthesis of ethyl 3-((1-(1-(2-(carbamoyloxy)ethyl)-1*H*-pyrazol-4-yl)-6-chloro-2-cyclopropyl-7-fluoro-1*H*-indol-3-yl)thio)-2-fluorobenzoate (3):

[00366] To a stirred solution of compound **2** (20 mg, 0.031 mmol) in THF (3 mL) under inert atmosphere was passed ammonia gas at 0 °C for 15 min; warmed to RT and stirred for 30 min. The volatiles were removed under reduced pressure and the crude was purified by triturating with *n*-pentane (2 x 5 mL) and dried under reduced pressure to afford **3** (6 mg, 35%) as a pale brown oil. **^{1}H NMR (500 MHz, $CDCl_3$):** δ 7.73 (s, 1H), 7.70 (s, 1H), 7.64 (t, J = 8.0 Hz, 1H), 7.20 (d, J = 8.5 Hz, 1H), 7.11-7.08 (m, 1H), 6.95 (t, J = 8.0 Hz, 1H), 6.79 (t, J = 8.0 Hz, 1H), 4.65 (br s, 2H), 4.54-4.47 (m, 4H), 4.42 (q, 2H), 1.74-1.70 (m, 1H), 1.43 (t, J = 7.5 Hz, 3H), 1.07-1.05 (m, 2H), 0.91-0.88 (m, 2H); **LC-MS:** *m/z* 561.7 ($M + H^+$).

Step 3: Synthesis of 3-((1-(1-(2-(carbamoyloxy)ethyl)-1*H*-pyrazol-4-yl)-6-chloro-2-cyclopropyl-7-fluoro-1*H*-indol-3-yl)thio)-2-fluorobenzoic acid sodium salt (Compound 1-121)

[00367] To a solution of compound **3** (5 mg, 0.009 mmol) in THF : water (3:1) (4 mL) was added 1M aq. NaOH solution (0.009 mL, 0.009 mmol) at RT overnight. After the completion of the reaction, solvent was removed to afford **Compound 1-121 sodium salt** (5 mg, 100%) as an off-white solid. **LC-MS:** *m/z* 533 (M+1).

Example 14: Synthesis of 3-((1-(1-(2-aminoethyl)-1*H*-pyrazol-4-yl)-6-chloro-2-cyclopropyl-7-fluoro-1*H*-indol-3-yl)thio)-2-fluorobenzoic acid sodium salt (Compound 1-122)



Step 1: Synthesis of ethyl 3-((1-(1-(2-((tert-butoxycarbonyl)amino)ethyl)-1*H*-pyrazol-4-yl)-6-chloro-2-cyclopropyl-7-fluoro-1*H*-indol-3-yl)thio)-2-fluorobenzoate (3):

[00368] To a stirred solution of indole **1** (Example 11, Step 3; 300 mg, 0.63 mmol) in DMF (5 mL) under inert atmosphere were added Cs_2CO_3 (310 mg, 0.95 mmol) and *tert*-butyl (2-bromo ethyl)carbamate **2** (213 mg, 0.95 mmol) at RT and stirred for 16 h. The mixture was quenched with sat. aq. NH_4Cl (10 mL) and extracted with EtOAc (2 x 30 mL). The combined organic extracts were dried (Na_2SO_4), filtered and concentrated under reduced pressure to obtain the crude which was purified (silica gel; 30% EtOAc/ hexanes) to afford compound **3** (200 mg, 51%) as a colorless syrup. **^{1}H NMR (500 MHz, $CDCl_3$):** δ 7.71 (s, 1H), 7.65-7.62 (m, 2H), 7.19 (d, J = 8.5 Hz, 1H), 7.11-7.08 (m, 1H), 6.95 (t, J = 8.0 Hz, 1H), 6.79 (t, J = 6.5 Hz, 1H), 4.82 (br s, 1H), 4.41 (q, 2H), 4.34 (t, J = 5.0 Hz, 2H), 3.65-2.04 (m, 2H), 1.72-1.68 (m, 1H), 1.43 (t, J = 7.5 Hz, 3H), 1.29 (s, 9H), 1.06-1.03 (m, 2H), 0.89-0.85 (m, 2H); **LC-MS:** 517.4 (Des-Boc) (M + H^+).

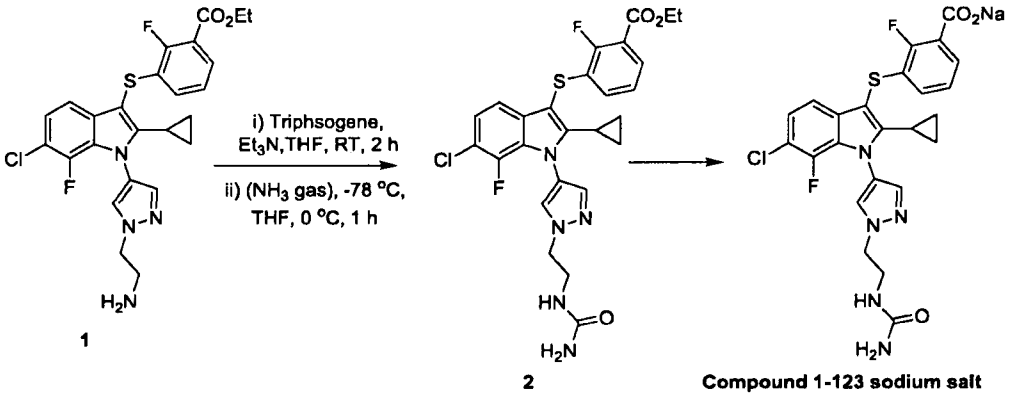
Step 2: Synthesis of ethyl 3-((1-(1-(2-aminoethyl)-1*H*-pyrazol-4-yl)-6-chloro-2-cyclopropyl-7-fluoro-1*H*-indol-3-yl)thio)-2-fluorobenzoate (4):

[00369] A solution of compound **3** (200 mg, 0.32 mmol) in 4.0 *M* HCl in 1,4-dioxane (5 mL) under inert atmosphere was stirred at 0 °C-RT for 2 h. The volatiles were removed under reduced pressure. The residue was diluted with water (5 mL), basified with aq. $NaHCO_3$ (5 mL) and extracted with EtOAc (2 x 20 mL). The combined organic extracts were dried (Na_2SO_4), filtered and concentrated under reduced pressure to afford **4** (130 mg, 81%) as an off-white solid. **^{1}H NMR (400 MHz, DMSO-d_6):** δ 8.24 (s, 1H), 7.82 (s, 1H), 7.60 (t, J = 6.8 Hz, 1H), 7.22-7.11 (m, 3H), 6.84 (t, J = 6.8 Hz, 1H), 4.33 (q, 2H), 4.17 (t, J = 6.0 Hz, 2H), 2.98 (t, J = 6.0 Hz, 2H), 1.84-1.80 (m, 3H), 1.32 (t, J = 7.2 Hz, 3H), 0.92-0.91 (m, 2H), 0.84-0.82 (m, 2H); **MS:** *m/z* 517.6 (M + H^+).

Step 3: Synthesis of 3-((1-(1-(2-aminoethyl)-1*H*-pyrazol-4-yl)-6-chloro-2-cyclopropyl-7-fluoro-1*H*-indol-3-yl)thio)-2-fluorobenzoic acid sodium salt (Compound 1-122)

[00370] Following the procedure of Example 11, Step 3 but using Intermediate **4** in place of Intermediate **4** in Step 3, the title **Compound 1-122 sodium salt** was obtained as an off-white solid. **LC-MS:** *m/z* 489 (M+1).

Example 15: Synthesis of 3-((6-chloro-2-cyclopropyl-7-fluoro-1-(1-(2-ureidoethyl)-1H-pyrazol-4-yl)-1H-indol-3-yl)thio)-2-fluorobenzoic acid sodium salt (Compound 1-123)



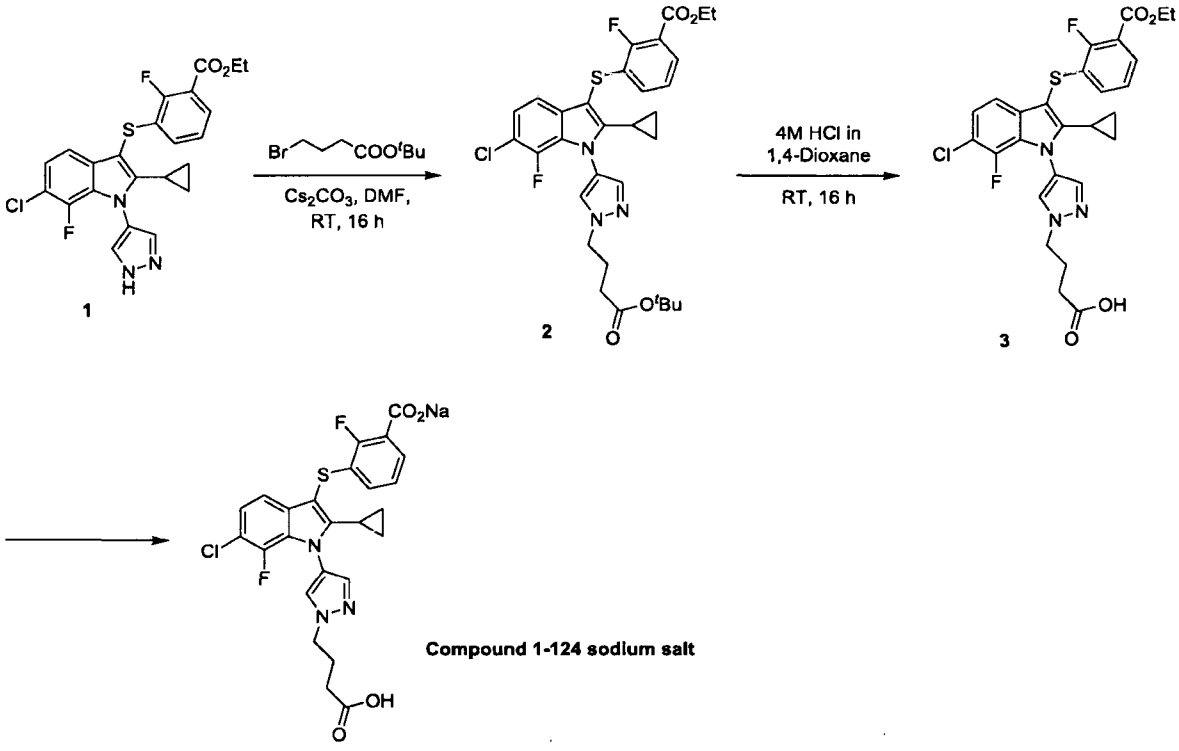
Step 1: Synthesis of ethyl 3-((6-chloro-2-cyclopropyl-7-fluoro-1-(1-(2-ureidoethyl)-1H-pyrazol-4-yl)-1H-indol-3-yl)thio)-2-fluorobenzoate (2)

[00371] To a stirred solution of indole **1** (Example 14, Step 2; 80 mg, 0.15 mmol) in THF (5 mL) under inert atmosphere were added Et_3N (0.04 mL, 0.31 mmol) and triphosgene (18.3 mg, 0.06 mmol) at 0 °C, stirred for 1 h, warmed to RT and stirred for 2 h. To this solution of crude isocyanate was passed ammonia gas at -78 °C for 10 min; warmed to 0 °C and stirred for 1 hr. The mixture was diluted with water and extracted with EtOAc (2 x 20 mL). The combined organic extracts were dried (Na_2SO_4), filtered and concentrated under reduced pressure to obtain the crude. This was purified by triturating with Et_2O (2 x 5 mL) and dried under reduced pressure to afford **2** (30 mg, 34%) as an off-white solid. **^{1}H NMR (400 MHz, DMSO-d_6):** δ 8.19 (s, 1H), 7.82 (s, 1H), 7.60 (t, J = 7.2 Hz, 1H), 7.22-7.11 (m, 3H), 6.84 (t, J = 7.2 Hz, 1H), 6.04-6.03 (m, 1H), 5.53 (br s, 2H), 4.33 (q, 2H), 4.21 (t, J = 6.0 Hz, 2H), 3.43 (t, J = 6.0 Hz, 2H), 1.84-1.78 (m, 1H), 1.32 (t, J = 7.2 Hz, 3H), 0.92-0.91 (m, 2H), 0.87-0.85 (m, 2H); **MS:** *m/z* 560.6 (M + H^+).

Step 2: Synthesis of 3-((6-chloro-2-cyclopropyl-7-fluoro-1-(1-(2-ureidoethyl)-1H-pyrazol-4-yl)-1H-indol-3-yl)thio)-2-fluorobenzoic acid sodium salt (Compound 1-123)

[00372] Following the procedure of Example 13, Step 3 but using Intermediate **2** in place of Intermediate **3** in Step 3, the title **Compound 1-123 sodium salt** was obtained as an off-white solid. **LC-MS:** *m/z* 532 (M+1).

Example 16: Synthesis of 3-((1-(1-(3-carboxypropyl)-1H-pyrazol-4-yl)-6-chloro-2-cyclopropyl-7-fluoro-1H-indol-3-yl)thio)-2-fluorobenzoic acid sodium salt (Compound 1-124)



Step 1: Synthesis of ethyl 3-((1-(1-(4-(tert-butoxy)-4-oxobutyl)-1*H*-pyrazol-4-yl)-6-chloro-2-cyclopropyl-7-fluoro-1*H*-indol-3-yl)thio)-2-fluorobenzoate (2):

[00373] To a stirred solution of indole **1** (Example 11, Step 3; 200 mg, 0.42 mmol) in DMF (5 mL) under inert atmosphere were added Cs_2CO_3 (206 mg, 0.63 mmol) and *tert*-butyl 4-bromobutanoate (141 mg, 0.63 mmol) at RT and stirred for 16 h. The mixture was diluted with ice cold water (20 mL) and extracted with EtOAc (3 x 30 mL). The combined organic extracts were dried (Na_2SO_4), filtered and concentrated under reduced pressure to obtain the crude. This was purified (silica gel chromatography; 20% EtOAc/ hexanes) to afford compound **2** (180 mg, 70%) as a pale brown oil. **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.67 (s, 1H), 7.64 (s, 1H), 7.63-7.60 (m, 1H), 7.18 (d, J = 8.4 Hz, 1H), 7.10-7.06 (m, 1H), 6.93 (t, J = 8.0 Hz, 1H), 6.77 (t, J = 7.6 Hz, 1H), 4.41 (q, 2H), 4.28 (t, J = 6.8 Hz, 2H), 2.28-2.19 (m, 4H), 1.74-1.66 (m, 1H), 1.46 (s, 9H), 1.41 (t, J = 7.2 Hz, 3H), 1.06-1.02 (m, 2H), 0.89-0.84 (m, 2H); **LC-MS (ESI):** *m/z* 618.6 (M + H^+).

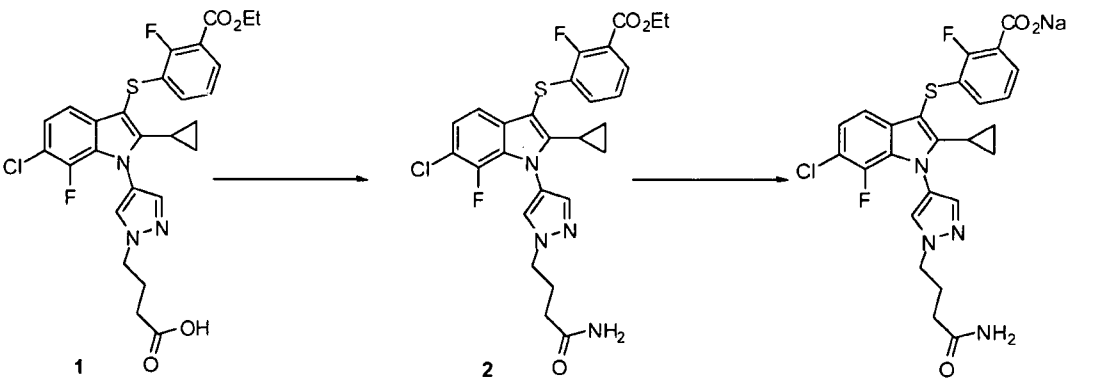
Step 2: Synthesis of 4-(4-(6-chloro-2-cyclopropyl-3-((3-(ethoxycarbonyl)-2-fluorophenyl) thio)-7-fluoro-1*H*-indol-1-yl)-1*H*-pyrazol-1-yl)butanoic acid (3):

[00374] A solution of compound **2** (100 mg, 0.29 mmol) in 4.0 *M* HCl in 1,4-dioxane (2 mL) under inert atmosphere was stirred at 0 °C-RT for 16 h. The volatiles were removed in vacuo and the residue was diluted with water (5 mL), basified with aq. $NaHCO_3$ (5 mL) and extracted with EtOAc (2 x 20 mL). The combined organic extracts were dried (Na_2SO_4), filtered and concentrated under reduced pressure to obtain the crude. This was purified by acid-base treatment to afford **3** (50 mg, 56%) as a white solid. **^{1}H NMR (500 MHz, DMSO-d_6):** δ 12.75 (br s, 1H), 8.24 (s, 1H), 7.82 (s, 1H), 7.59 (t, J = 7.0 Hz, 1H), 7.22-7.10 (m, 3H), 6.84 (t, J = 7.5 Hz, 1H), 4.33 (q, 2H), 4.22 (t, J =7.0 Hz, 2H), 2.21 (t, J = 7.5 Hz, 2H), 2.06-2.03 (m, 2H), 1.81-1.78 (m, 1H), 1.32 (t, J = 7.0 Hz, 3H), 0.89-0.88 (m, 2H), 0.82-0.81 (m, 2H); **MS:** m/z 560.7 (M + H^+).

Step 3: Synthesis of 3-((1-(1-(3-carboxypropyl)-1H-pyrazol-4-yl)-6-chloro-2-cyclopropyl-7-fluoro-1H-indol-3-yl)thio)-2-fluorobenzoic acid sodium salt (Compound 1-124)

[00375] To a solution of compound **3** (10 mg, 0.018 mmol) in THF : water (3:1) (4 mL) was added 1M aq. NaOH solution (0.036 mL, 0.036 mmol) at RT and then heated at 60°C overnight. After the completion of the reaction, solvent was removed to afford **Compound 1-124 sodium salt** (10 mg, 100%) as a white solid. **LC-MS:** *m/z* 532 (M+1).

Example 17: Synthesis of 3-((1-(1-(4-amino-4-oxobutyl)-1*H*-pyrazol-4-yl)-6-chloro-2-cyclopropyl-7-fluoro-1*H*-indol-3-yl)thio)-2-fluorobenzoic acid sodium salt (Compound 1-125)



Step 1: Synthesis of ethyl 3-((1-(1-(4-amino-4-oxobutyl)-1*H*-pyrazol-4-yl)-6-chloro-2-cyclopropyl-7-fluoro-1*H*-indol-3-yl)thio)-2-fluorobenzoate (2):

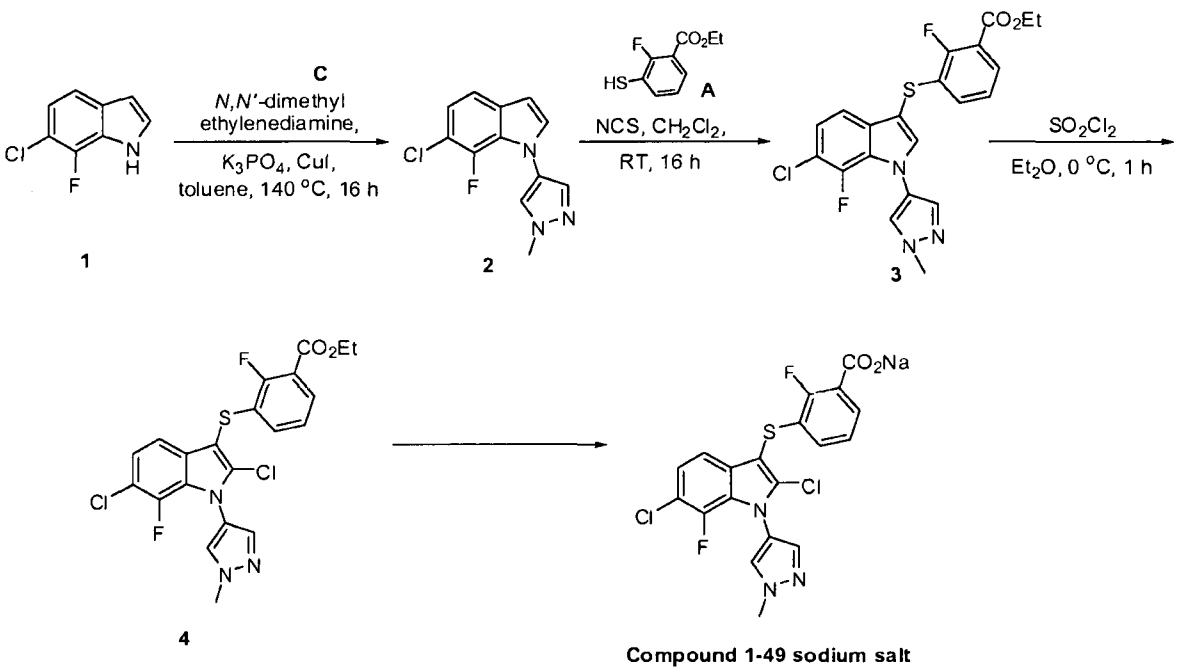
[00376] To a stirred solution of indole **1** (Example 16, Step 2; 150 mg, 0.26 mmol) in DMF (3 mL) under inert atmosphere were added EDCI.HCl (36 mg, 0.40 mmol), HOBt (61.5 mg, 0.40

mmol), NMM (0.07 mL, 0.67 mmol) at RT and stirred for 10 min. To this, NH_4Cl (17.1 mg, 0.32 mmol) was added at RT and stirred for 16 h. The mixture was diluted with water (30 mL) and extracted with EtOAc (2 x 30 mL). The combined organic extracts were washed with brine (20 mL), dried (Na_2SO_4), filtered and dried under reduced pressure to obtain the crude. This was purified (silica gel; 2% MeOH/ CH_2Cl_2) to afford compound **2** (15 mg, 10%) as an off-white solid. **^{1}H NMR (400 MHz, DMSO-d_6):** δ 8.23 (s, 1H), 7.81 (s, 1H), 7.60 (dt, J = 8.0, 1.6 Hz, 1H), 7.29 (br s, 1H), 7.22-7.11 (m, 3H), 6.84 (dt, J = 8.0, 1.6 Hz, 1H), 6.78 (br s, 1H), 4.33 (q, 2H), 4.20 (t, J = 6.4 Hz, 2H), 2.08-2.02 (m, 4H), 1.82-1.77 (m, 1H), 1.32 (t, J = 7.2 Hz, 3H), 0.92-0.88 (m,2H), 0.86-0.80 (m, 2H); **MS:** *m/z* 559.6 (M + H^+).

Step 2: Synthesis of 3-((1-(1-(4-amino-4-oxobutyl)-1*H*-pyrazol-4-yl)-6-chloro-2-cyclopropyl-7-fluoro-1*H*-indol-3-yl)thio)-2-fluorobenzoic acid sodium salt (Compound 1-125)

[00377] Following the procedure of Example 11, Step 3 but using Intermediate **2** in place of Intermediate **4** in Step 3, the title **Compound 1-125 sodium salt** was obtained as a white solid. **LC-MS:** *m/z* 531 (M+1).

Example 18: Synthesis of 3-((2,6-dichloro-7-fluoro-1-(1-methyl-1*H*-pyrazol-4-yl)-1*H*-indol-3-yl)thio)-2-fluorobenzoic acid sodium salt (Compound 1-49)



Step 1: Synthesis of ethyl 3-((6-chloro-7-fluoro-1-(1-methyl-1*H*-pyrazol-4-yl)-1*H*-indol-3-yl)thio)-2-fluorobenzoate (3):

[00378] Following the procedure of Example 9, Steps 3 and 4 but using Intermediate **A** in place of Intermediate **B** in Step 3, the title compound **3** was obtained as a light brown solid. **^{1}H NMR**

(400 MHz, $CDCl_3$): δ 7.68 (s, 1H), 7.67-7.64 (m, 2H), 7.43 (s, 1H), 7.28 (d J = 8.4 Hz, 1H), 7.16 (dd, J = 8.4, 6.0 Hz, 1H), 7.00-6.93 (m, 2H), 4.40 (q, J = 6.8 Hz, 2H), 3.99 (s, 3H), 1.40 (t, J = 6.8 Hz, 3H); **LC-MS (ESI):** *m/z* 448.4 ($M + H^+$).

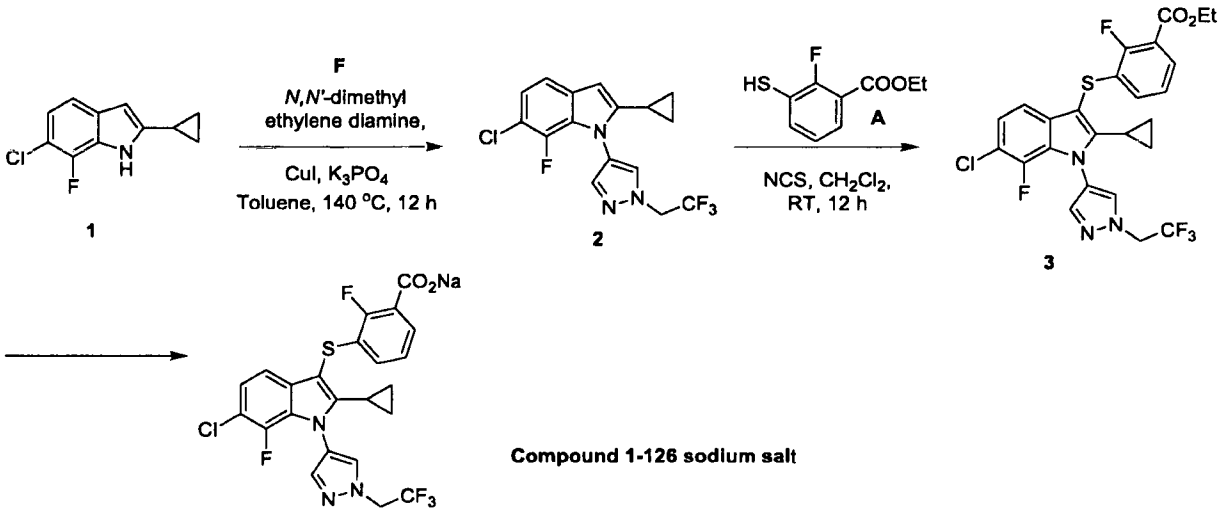
Step 2: Synthesis of ethyl 3-((2,6-dichloro-7-fluoro-1-(1-methyl-1*H*-pyrazol-4-yl)-1*H*-indol-3-yl)thio)-2-fluorobenzoate (4):

[00379] To a stirred solution of compound **3** (150 mg, 0.33 mmol) in Et_2O (10 mL) under inert atmosphere was added SO_2Cl_2 (87 mg, 0.65 mmol) at 0 °C and stirred for 1 h. The reaction mixture was quenched with water (10 mL) and extracted with EtOAc (2 x 20 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated under reduced pressure to obtain the crude. The crude was purified (silica gel; 15% EtOAc/ *n*-Hexane) to afford **4** (35 mg, 22%) as an off-white solid. **^{1}H NMR (500 MHz, $CDCl_3$):** δ 7.72-7.68 (m, 1H), 7.62 (s, 1H), 7.58 (s, 1H), 7.36 (d, J = 8.5 Hz, 1H), 7.24-7.19 (m, 1H), 7.08-6.79 (m, 2H), 4.42 (q, J = 7.0 Hz, 2H), 4.08 (s, 3H), 1.42 (t, J = 7.0 Hz, 3H); **LC-MS:** *m/z* 482.4 (M^+).

Step 3: Synthesis of 3-((2,6-dichloro-7-fluoro-1-(1-methyl-1*H*-pyrazol-4-yl)-1*H*-indol-3-yl)thio)-2-fluorobenzoic acid sodium salt (Compound 1-49):

[00380] Following the procedure of Example 11, Step 3 but using Intermediate **4** in place of Intermediate **4** in Step 3, the title **Compound 1-49 sodium salt** was obtained as a tan solid. **LC-MS:** *m/z* 454 (M+1).

Example 19: Synthesis of 3-((6-chloro-2-cyclopropyl-7-fluoro-1-(1-(2,2,2-trifluoroethyl)-1*H*-pyrazol-4-yl)-1*H*-indol-3-yl)thio)-2-fluorobenzoic acid sodium salt (Compound 1-126)



Compound 1-126 sodium salt

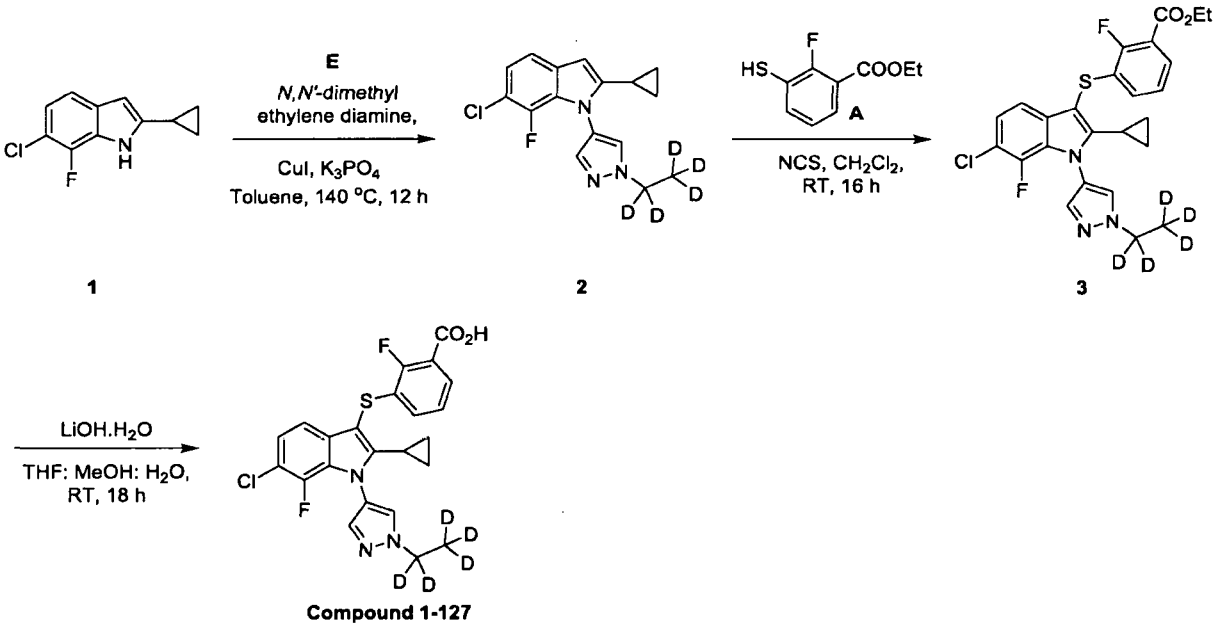
Step 1: Synthesis of ethyl 3-((6-chloro-2-cyclopropyl-7-fluoro-1-(1-(2,2,2-trifluoroethyl)-1*H*-pyrazol-4-yl)-1*H*-indol-3-yl)thio)-2-fluorobenzoate (3):

[00381] Following the procedure of Example 9, Steps 3 and 4 but using Intermediate **F** in place of Intermediate **B** in Step 3, the title compound **3** was obtained as an off-white solid. **^{1}H NMR (400 MHz, CD_3OD):** δ 8.23 (s, 1H), 7.88 (s, 1H), 7.61 (dt, J = 8.0, 1.6 Hz, 1H), 7.20 (d, J = 8.4 Hz, 1H), 7.15-7.11 (m, 1H), 7.02 (t, J = 8.0 Hz, 1H), 6.84 (dt, J = 8.4, 1.6 Hz, 1H), 5.04 (q, 2H), 4.39 (q, 2H), 1.81-1.73 (m, 1H), 1.41-1.38 (m, 3H), 0.98-0.90 (m, 2H), 0.88-0.84 (m, 2H); **MS:** m/z 556.5 ($M + H^+$).

Step 2: Synthesis of 3-((6-chloro-2-cyclopropyl-7-fluoro-1-(1-(2,2,2-trifluoroethyl)-1*H*-pyrazol-4-yl)-1*H*-indol-3-yl)thio)-2-fluorobenzoic acid sodium salt (Compound 1-126)

[00382] Following the procedure of Example 11, Step 3 but using Intermediate **3** in place of Intermediate **4** in Step 3, the title **Compound 1-126 sodium salt** was obtained as an off-white solid. **LC-MS:** *m/z* 528 (M+1).

Example 20: Synthesis of 3-((6-chloro-2-cyclopropyl-1-(1-(ethyl-d_5)-1*H*-pyrazol-4-yl)-7-fluoro-1*H*-indol-3-yl)thio)-2-fluorobenzoic acid (Compound 1-127)



1 2 3

Compound 1-127

Step 1: Synthesis of ethyl 3-((6-chloro-2-cyclopropyl-1-(1-(ethyl-d_5)-1*H*-pyrazol-4-yl)-7-fluoro-1*H*-indol-3-yl)thio)-2-fluorobenzoate (3):

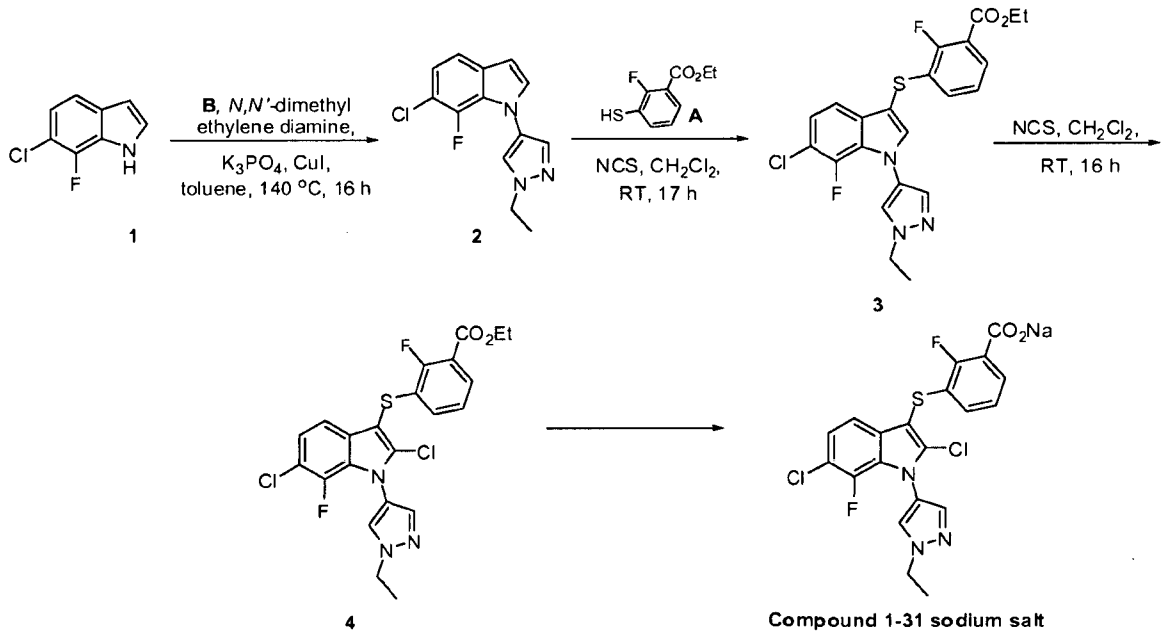
[00383] Following the procedure of Example 9, Steps 3 and 4 but using Intermediate **E** in place of Intermediate **B** in Step 3, the title compound **3** was obtained as a red solid. **^{1}H NMR (500 MHz $CDCl_3$):** δ 7.67-7.61 (m, 3H), 7.18 (d, J = 8.0 Hz, 1H), 7.09-7.07 (m, 1H), 6.94 (t, J = 8.0

Hz, 1H), 6.92-6.75 (m, 1H), 4.41 (q, 2H), 1.72-1.68 (m, 1H), 1.41 (t, J = 7.5 Hz, 3H), 1.08-1.05 (m, 2H), 0.89-0.85 (m, 2H); **LC-MS (ESI):** 509.5 ($M + H^+$).

Step 2: Synthesis of 3-((6-chloro-2-cyclopropyl-1-(1-(ethyl-d_5)-1*H*-pyrazol-4-yl)-7-fluoro-1*H*-indol-3-yl)thio)-2-fluorobenzoic acid (Compound 1-127):

[00384] To a stirred solution of indole **3** (200 mg, 0.39 mmol) in THF:MeOH:H_2O (2:2:1, 5 mL) was added $LiOH.H_2O$ (66 mg, 1.57 mmol) at RT and stirred for 8 h. The volatiles were removed *in vacuo*. The residue was diluted with water (5 mL), acidified with 2 *M* aq. HCl (5 mL); the obtained solid was filtered, washed with water (25 mL), triturated with *n*-pentane (2 x 5 mL) and dried under reduced pressure to afford the title **Compound 1-127** (110 mg, 59%) as an off-white solid. **^{1}H NMR (400 MHz, DMSO-d_6):** δ 13.49 (br s, 1H), 8.22 (s, 1H), 7.73 (s, 1H), 7.51 (t, J = 6.8 Hz, 1H), 7.19-7.13 (m, 2H), 7.04 (t, J = 8.0 Hz, 1H), 6.74 (t, J =7.2 Hz, 1H), 1.80-1.73 (m, 1H), 0.91-0.90 (m, 2H), 0.82-0.80 (m, 2H); **MS (ESI):** *m/z* 480.8 ($M + H^+$).

Example 21: Synthesis of 3-((2,6-dichloro-1-(1-ethyl-1H-pyrazol-4-yl)-7-fluoro-1H-indol-3-yl)thio)-2-fluorobenzoic acid sodium salt (Compound 1-31)



Step 1: Synthesis of ethyl 3-((6-chloro-1-(1-ethyl-1*H*-pyrazol-4-yl)-7-fluoro-1*H*-indol-3-yl)thio)-2-fluorobenzoate (3):

[00385] Following the procedure of Example 9, Steps 3 and 4 but using indole **1** (Example 4, Step 1) in place of indole **3** in Step 3, the title compound **3** was obtained as a light brown solid. **^{1}H NMR (500 MHz, $CDCl_3$):** δ 7.69-7.64 (m, 3H), 7.44 (s, 1H), 7.27 (t, J = 8.0 Hz, 1H), 7.16 (dd, J = 8.5, 6.0 Hz, 1H), 7.01-6.94 (m, 2H), 4.40 (q, J = 7.5 Hz, 2H), 4.26 (q, J = 8.0 Hz, 2H), 1.57 (t, J = 8.0 Hz, 3H), 1.57 (t, J = 7.5 Hz, 3H); **LC-MS (ESI):** *m/z* 462.5 ($M + H^+$).

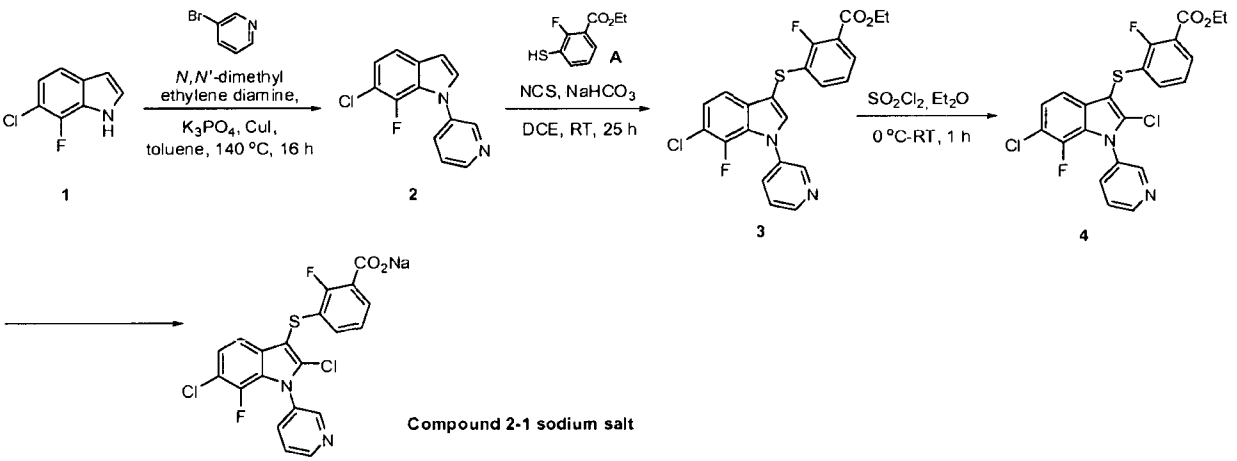
Step 2: Synthesis of ethyl 3-((2,6-dichloro-1-(1-ethyl-1H-pyrazol-4-yl)-7-fluoro-1H-indol-3-yl)thio)-2-fluorobenzoate (4):

[00386] To a solution of compound **3** (100 mg, 0.21 mmol) in CH_2Cl_2 (3 mL) under inert atmosphere was added NCS (58 mg, 0.43 mmol) at RT and stirred for 16 h. The reaction mixture was diluted with water (10 mL) and extracted with CH_2Cl_2 (2 x 15 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated under reduced pressure to obtain the crude. The crude was purified (silica gel; 14-17% EtOAc/Hexanes) to afford **5** (35 mg, 33%) as an off-white solid. **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.71-7.66 (m, 3H), 7.30 (d, J = 7.6 Hz, 1H), 7.19 (dd, J = 8.8, 6.4 Hz, 1H), 7.04-6.97 (m, 2H), 4.40 (q, J = 7.2 Hz, 2H), 4.27 (q, J = 7.6 Hz, 2H), 1.58 (t, J = 7.6 Hz, 3H), 1.49 (t, J = 7.2 Hz, 3H); **LC-MS (ESI):** *m/z* 496.7 ($M + H^+$).

Step 3: Synthesis of 3-((2,6-dichloro-1-(1-ethyl-1H-pyrazol-4-yl)-7-fluoro-1H-indol-3-yl)thio)-2-fluorobenzoic acid (Compound 1-31)

[00387] Following the procedure of Example 11, Step 3 but using Intermediate **4** in place of Intermediate **4** in Step 3, the title **Compound 1-31 sodium salt** was obtained as an off-white solid. **LC-MS:** *m/z* 468 (M+1).

Example 22: Synthesis of 3-((2,6-dichloro-7-fluoro-1-(pyridin-3-yl)-1*H*-indol-3-yl)thio)-2-fluorobenzoic acid sodium salt (Compound 2-1)



Step 1: Synthesis of 6-chloro-7-fluoro-1-(pyridin-3-yl)-1*H*-indole (2):

[00388] To a stirred solution of indole **1** (Example 4, Step 1; 2.0 g, 11.8 mmol) in toluene (50 mL) were added 3-bromopyridine (2.9 g, 17.7 mmol), *N,N'*-dimethylethylenediamine (418 mg, 4.73 mmol), K_3PO_4 (6.3 g, 29.5 mmol), CuI (225 mg, 1.18 mmol) at RT under inert atmosphere. The mixture was purged with argon for 15 min and heated to 140 °C in a sealed tube for 16 h. The reaction mixture was cooled to RT, added *n*-hexane (20 mL), stirred for 5 minutes and then filtered. The filtrate was diluted with water (20 mL) and extracted with EtOAc (2 x 50 mL). The

combined organic extracts were washed with water and brine solution, dried over Na_2SO_4, filtered and concentrated under reduced pressure to obtain the crude. The crude was purified (silica gel; 10% EtOAc/ Hexanes) to afford compound **2** (2.0 g, 69%) as light brown solid. **^{1}H NMR (500 MHz, DMSO-d_6):** δ 8.84 (s, 1H), 8.66 (d, J = 5.0 Hz, 1H), 8.06-8.02 (m, 1H), 7.74-7.72 (m, 1H), 7.64-7.58 (m, 1H), 7.52 (d, J = 8.0 Hz, 1H), 7.28-7.24 (m, 1H), 6.82 (m, 1H).

Step 2: Synthesis of ethyl 3-((6-chloro-7-fluoro-1-(pyridin-3-yl)-1H-indol-3-yl)thio)-2-fluorobenzoate (3):

[00389] To a stirred solution of Intermediate **A** (243 mg, 1.21 mmol) in 1,2-dichloroethane (8 mL) under inert atmosphere was added NCS (163 mg, 1.21 mmol) at RT and stirred for 1 h. To this, compound **2** (200 mg, 0.81 mmol) in 1,2-dichloroethane (2 mL) and $NaHCO_3$ (204 mg, 2.45 mmol) were added at RT. After 24 h stirring at RT, the reaction mixture was diluted with water (15 mL) and extracted with EtOAc (2 x 30 mL). The combined organic extracts were washed with water (30 mL) and brine (30 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to obtain the crude. The crude was purified (silica gel; 10% EtOAc/Hexanes) to afford compound **3** (50 mg, 9%) as an off-white solid. **^{1}H NMR (500 MHz, DMSO-d_6):** δ 8.91 (s, 1H), 8.70 (d, J = 5.0 Hz, 1H), 8.30 (s, 1H), 8.18-8.15 (m, 1H), 7.66-7.762 (m, 2H), 7.36-7.34 (m, 2H), 7.17-7.13 (m, 2H), 4.34 (q, J = 7.5 Hz, 2H), 1.32 (t, J = 7.5 Hz, 3H).

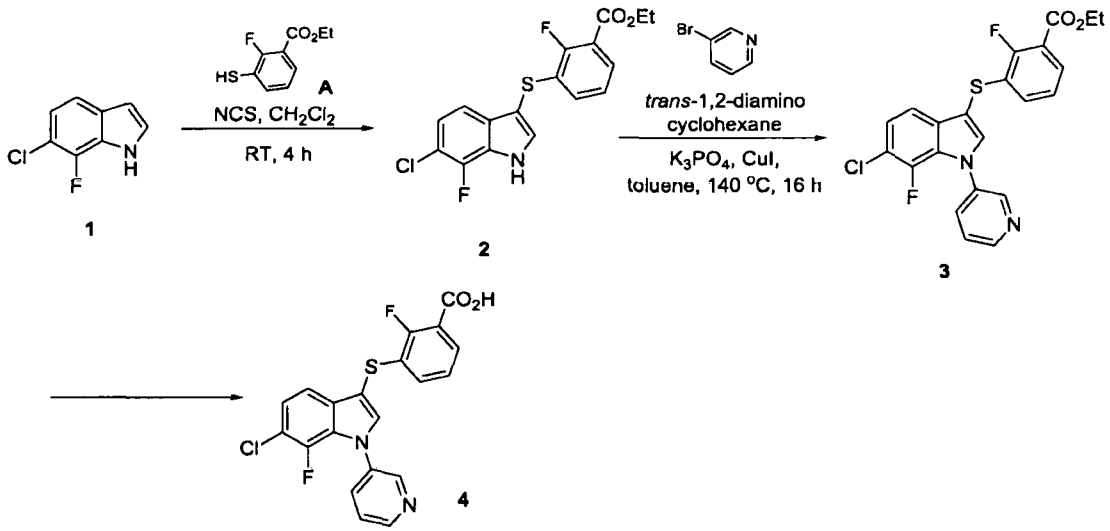
Step 3: Synthesis of ethyl 3-((2,6-dichloro-7-fluoro-1-(pyridin-3-yl)-1*H*-indol-3-yl)thio)-2-fluorobenzoate (4):

[00390] To a stirred solution of compound **3** (50 mg, 0.11 mmol) in Et_2O (10 mL) under inert atmosphere was added SO_2Cl_2 (18 mg, 0.13 mmol) slowly at 0 °C and stirred for 1 h. After completion of the reaction by TLC, the reaction mixture was quenched with water (10 mL) and extracted with EtOAc (2 x 20 mL). The combined organic extracts were washed with water, brine solution, dried over Na_2SO_4 and concentrated under reduced pressure to obtain the crude. The crude was purified by preparative HPLC to afford **4** (17 mg, 32%) as an off-white solid. **^{1}H NMR (400 MHz, DMSO-d_6):** δ 8.93 (d, J = 2.4 Hz, 1H), 8.80 (dd, J = 4.8, 1.6 Hz, 1H), 8.23-8.21 (m, 1H), 7.71-7.66 (m, 2H), 7.39-7.38 (m, 2H), 7.20-7.18 (m, 2H), 4.34 (q, J = 7.2 Hz, 2H), 1.32 (t, J = 7.2 Hz, 3H); **LC-MS:** *m/z* 479.4 (M^+).

Step 4: Synthesis of 3-((2,6-dichloro-7-fluoro-1-(pyridin-3-yl)-1*H*-indol-3-yl)thio)-2-fluorobenzoic acid sodium salt (Compound 2-1):

[00391] To a solution of compound 4 (16 mg, 0.033 mmol) in THF : water (3:1) (4 mL) was added 1M aq. NaOH solution (0.033 mL, 0.033 mmol) at RT and then heated at 60°C for 3 hours. After the completion of the reaction, solvent was removed to afford **Compound 2-1 sodium salt** (16 mg, 100%) as an off-white solid. **LC-MS:** *m/z* 451 (M+1).

Alternate route for Compound 4 preparation:



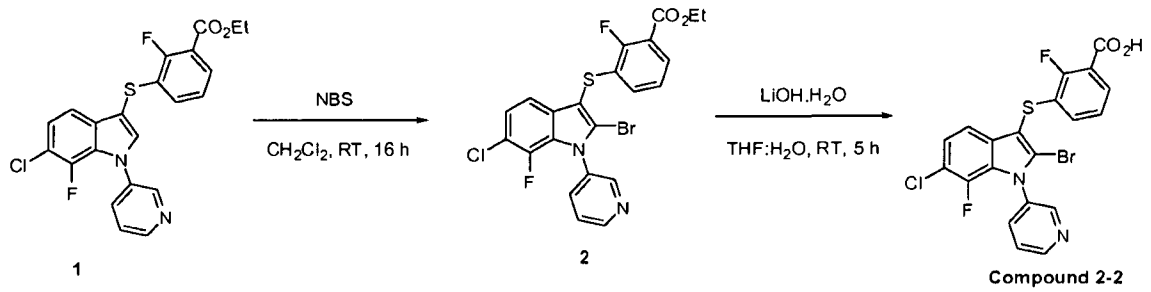
Step 1: Synthesis of ethyl 3-((6-chloro-7-fluoro-1*H*-indol-3-yl)thio)-2-fluorobenzoate (2):

[00392] To a stirred solution of Intermediate **A** (1.18 g, 5.91 mmol) in CH_2Cl_2 (30 mL) under inert atmosphere was added NCS (792 mg, 5.91 mmol) at RT and stirred for 1 h. To this, indole **1** (Example 4, Step 1; 1.0 g, 5.91 mmol) in CH_2Cl_2 (20 mL) was added at RT and stirred for 4 h. After completion of the reaction by TLC, the reaction mixture was diluted with water (40 mL) and extracted with CH_2Cl_2 (2 x 60 mL). The combined organic extracts were washed with water (50 mL) and brine (50 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to obtain the crude. The crude was purified (silica gel; 10% EtOAc/Hexanes) to afford compound **2** (1.2 g, 55%) as a light brown solid. **^{1}H NMR (500 MHz, DMSO-d_6):** δ 12.60 (br s, 1H), 8.00 (d, J = 4.0 Hz, 1H), 7.61-7.57 (m, 1H), 7.24-7.17 (m, 2H), 7.09 (t, J = 8.0 Hz, 1H), 6.90-6.86 (m, 1H), 4.34 (q, J = 7.5 Hz, 2H), 1.32 (t, J = 7.5 Hz, 3H); **MS:** *m/z* 368.6 (M + H$^+$).

Synthesis of ethyl 3-((6-chloro-7-fluoro-1-(pyridin-3-yl)-1*H*-indol-3-yl)thio)-2-fluorobenzoate (3):

[00393] To a stirred solution of compound **2** (200 mg, 0.54 mmol) in toluene (5 mL) were added 3-bromopyridine (131 mg, 0.81 mmol), *trans*-1,2-diaminocyclohexane (24.8 mg, 0.21 mmol), K_3PO_4 (288 mg, 1.35 mmol), Cu(I)I (10.3 mg, 0.05 mmol) at RT under inert atmosphere. The mixture was purged with argon for 15 min and heated to 140 °C in a sealed tube for 16 h. The reaction mixture was cooled to RT, added *n*-hexane (6 mL), stirred for 5 minutes and then filtered. The filtrate was diluted with water (20 mL) and extracted with EtOAc (2 x 50 mL). The combined organic extracts were washed with water and brine solution, dried over Na_2SO_4, filtered and concentrated under reduced pressure to obtain the crude. The crude was purified (silica gel; 10-12% EtOAc/ Hexanes) to afford compound **3** (130 mg, 54%) as an off-white solid.

Example 23: Synthesis of 3-((2-bromo-6-chloro-7-fluoro-1-(pyridin-3-yl)-1*H*-indol-3-yl)thio)-2-fluorobenzoic acid (Compound 2-2)



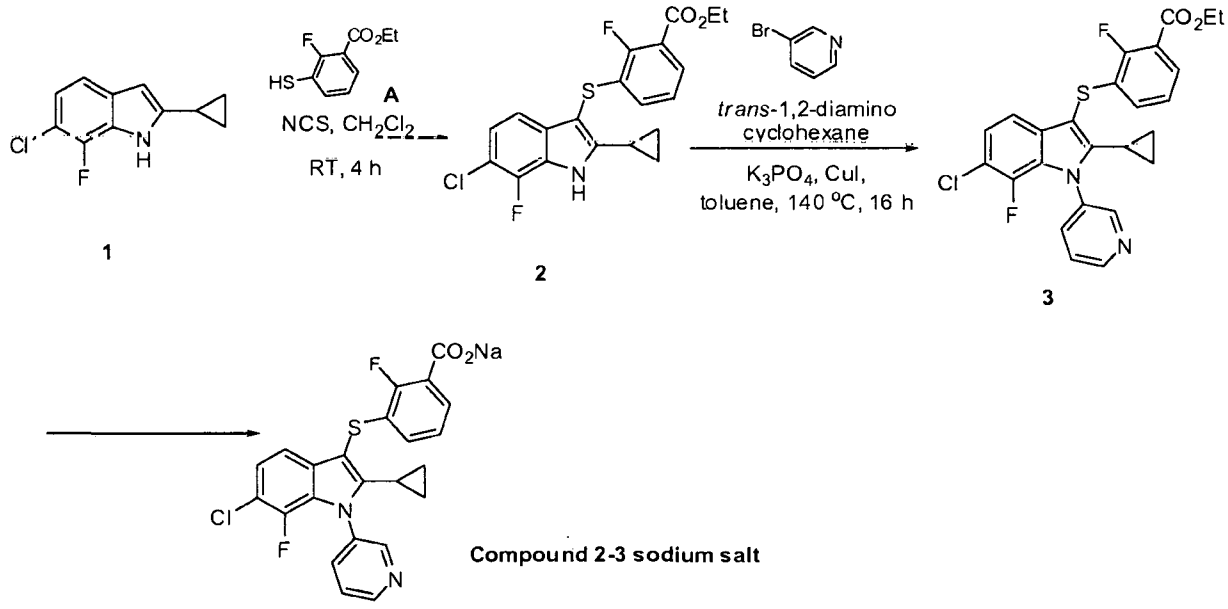
Step 1: Synthesis of ethyl 3-((2-bromo-6-chloro-7-fluoro-1-(pyridin-3-yl)-1*H*-indol-3-yl)thio)-2-fluorobenzoate (2):

[00394] To a stirred solution of indole **1** (Example 22, Step 2; 60 mg, 0.13 mmol) in CH_2Cl_2 (5 mL) under inert atmosphere was added NBS (60 mg, 0.33 mmol) at RT and stirred for 16 h. The mixture was diluted with water (10 mL) and extracted with CH_2Cl_2 (2 x 25 mL). The combined organic extracts were washed with brine (10 mL), dried (Na_2SO_4), filtered and concentrated under reduced pressure to obtain the crude. This was purified (silica gel; 10% EtOAc/ hexanes) to afford compound **2** (35 mg, 50%) as a pale brown solid. **^{1}H NMR (500 MHz, DMSO-d_6):** δ 8.91 (s, 1H), 8.81-8.80 (m, 1H), 8.20 (d, J = 8.5 Hz, 1H), 7.70-7.66 (m, 2H), 7.40-7.37 (m, 2H), 7.18 (t, J = 8.0 Hz, 1H), 7.16-7.13 (m, 1H), 4.33 (q, 2H), 1.32 (t, J = 7.5 Hz, 3H); **MS:** *m/z* 525.3 ($M^+ + 2$).

Step 2: Synthesis of 3-((2-bromo-6-chloro-7-fluoro-1-(pyridin-3-yl)-1*H*-indol-3-yl)thio)-2-fluorobenzoic acid (Compound 2-2):

[00395] To a stirred solution of compound **2** (35 mg, 0.06 mmol) in THF: H_2O (1:1, 4 mL) was added $LiOH.H_20$ (11.2 mg, 0.26 mmol) at RT and stirred for 5 h. The volatiles were removed under reduced pressure and the residue was diluted with water (5 mL), acidified with citric acid and extracted with EtOAc (2 x 25 mL). The combined organic extracts were washed with brine (10 mL), dried (Na_2SO_4), filtered and concentrated under reduced pressure to obtain the crude. This was triturated with *n*-pentane (2 x 5 mL) and dried *in vacuo* to afford the title **Compound 2-2** (25 mg, 76%) as a pale brown solid. **^{1}H NMR (500 MHz, DMSO-d_6):** δ 13.41 (br s, 1H), 8.93 (s, 1H), 8.81-8.80 (m, 1H), 8.20 (d, J = 7.5 Hz, 1H), 7.70-7.64 (m, 2H), 7.40-7.35 (m, 2H), 7.17-7.11 (m, 2H); **LC-MS (ESI):** *m/z* 497.3 ($M^+ + 2$).

Example 24: Synthesis of 3-((6-chloro-2-cyclopropyl-7-fluoro-1-(pyridin-3-yl)-1*H*-indol-3-yl)thio)-2-fluorobenzoic acid sodium salt (Compound 2-3)



Step 1: Synthesis of ethyl 3-((6-chloro-2-cyclopropyl-7-fluoro-1*H*-indol-3-yl)thio)-2-fluorobenzoate (3):

[00396] To a stirred solution of Intermediate **A** (190 mg, 0.95 mmol) in CH_2Cl_2 (10 mL) under inert atmosphere was added NCS (128 mg, 0.95 mmol) at RT and stirred for 1 h. To this, indole **1** (Example 9, Step 2; 200 mg, 0.95 mmol) in CH_2Cl_2 (5 mL) was added at RT and stirred for 12 h. The mixture was diluted with water (50 mL) and extracted with CH_2Cl_2 (3 x 50 mL). The combined organic extracts were washed with brine (100 mL), dried (Na_2SO_4), filtered and concentrated under reduced pressure to obtain the crude. This was purified (silica gel chromatography; 5-10% EtOAc/ hexanes) to obtain compound **2** (300 mg, 77%) as a pale pink solid. **^{1}H NMR (400 MHz, DMSO-d_6):** δ 11.91 (s, 1H), 7.89-7.84 (m, 1H), 7.57 (t, J = 8.0 Hz, 1H), 7.14-7.07 (m, 2H), 6.78 (t, J = 8.0 Hz, 1H), 4.35-4.29 (m, 2H), 2.32-2.25 (m, 1H), 1.33-1.28 (m, 3H), 1.15-1.10 (m, 2H), 1.08-1.03 (m, 2H); **LC-MS (ESI):** *m/z* 406.3 (M - H^+).

Step 2: Synthesis of ethyl 3-((6-chloro-2-cyclopropyl-7-fluoro-1-(pyridin-3-yl)-1*H*-indol-3-yl)thio)-2-fluorobenzoate (3):

[00397] To a stirred solution of compound **2** (100 mg, 0.24 mmol) in toluene (5 mL) were added 3-bromopyridine (59.3 mg, 0.36 mmol), *trans*-1,2-diaminocyclohexane (11.2 mg, 0.098 mmol), K_3PO_4 (130 mg, 0.65 mmol), CuI (4.6 mg, 0.024 mmol) at RT under argon in a sealed tube. The solution was purged with argon; heated to 140 °C and stirred for 40 h. The mixture was cooled to RT, added *n*-hexane (6 mL), stirred for 5 minutes and then filtered. The filtrate was diluted with

R^9 is C_1-C_6alkyl, C_1-C_6fluoroalkyl, C_1-C_6deuteroalkyl, C_3-C_6cycloalkyl, a substituted or unsubstituted phenyl, a substituted or unsubstituted monocyclic heteroaryl, or a substituted or unsubstituted bicyclic heteroaryl;

each R^{10} is independently H, C_1-C_6alkyl, C_1-C_6fluoroalkyl, C_1-C_6deuteroalkyl, C_3-C_6cycloalkyl, a substituted or unsubstituted phenyl, or a substituted or unsubstituted monocyclic heteroaryl; or

two R^{10} groups attached to the same N atom are taken together with the N atom to which they are attached to form a substituted or unsubstituted heterocycle.

2. The compound of claim 1, or a pharmaceutically acceptable salt, or solvate thereof, wherein:

R^1 is -Cl, -Br, -CN, or cyclopropyl.

3. The compound of claim 1, or a pharmaceutically acceptable salt, or solvate thereof, wherein:

R^1 is cyclopropyl.

4. The compound of claim 1, or a pharmaceutically acceptable salt, or solvate thereof, wherein:

R^1 is -Cl.

5. The compound of any one of claims 1-4, or a pharmaceutically acceptable salt, or solvate thereof, wherein:

L^1 is absent, $-CH_2-$, $-CH_2CH_2-$, $-CH_2CH_2CH_2-$, $-CH(CH_3)-$, $-CH(CH_2CH_3)-$, $-C(CH_3)_2-$, $-C(CH_2CH_3)_2-$, cyclopropyl-1,1-diyl, cyclobutyl-1,1-diyl, cyclopentyl-1,1-diyl or cyclohexyl-1,1-diyl; and

Q is $-CO_2H$, $-CO_2(C_1$-C_6alkyl), $-C(=O)NHSO_2R^9$ or tetrazolyl.

6. The compound of any one of claims 1-5, or a pharmaceutically acceptable salt, or solvate thereof, wherein:

L^1 is absent, $-CH_2-$, $-CH(CH_3)-$, $-C(CH_3)_2-$, or cyclopropyl-1,1-diyl; and

Q is $-CO_2H$, or $-CO_2(C_1$-C_6alkyl).

7. The compound of any one of claims 1-5, or a pharmaceutically acceptable salt, or solvate thereof, wherein:

L^1 is absent or $-CH_2-$; and

Q is $-CO_2H$, or $-CO_2(C_1$-C_6alkyl).

8. The compound of any one of claims 1-7, or a pharmaceutically acceptable salt, or solvate thereof, wherein: