D. NO - 54132

0105 57 03

To,
The Controller of Patents,
Baudhik Sampada Bhavan
Antop Hill, S.M. Road
Mumbai

200324597

Re: PRE-GRANT OPPOSITION UNDER SECTION 25 (1) Against Indian Patent Application Number 202221034803 dated 17/06/2022 covering the invention titled *"Thiazolidin-3-yl-Imidazole-pyridine-3-carboxamide as antimalarial agents"* filed by MAHARAJA KRISHNAKUMARSINHJI BHAVNAGAR UNIVERSITY

MAHARAJA KRISHNAKUMARSINHJI BHAVNAGAR UNIVERSITY
an Indian University of .... **APPLICANT**
MAHARAJA KRISHNAKUMARSINHJI BHAVNAGAR UNIVERSITY
Gaurishankar Lake Road, Bhavnagar- 364001, Gujarat, INDIA

DR. OMPRAKASH SINGH BARKHAMBA ..... **OPPONENT**
Indian Resident having address of
OF Salarpur, Mawana Road, Meerut – 250001, Uttar Pradesh, India

LIST

Sr. No.	Description	Page No.
1	Form 7A	3
2	Representation u/s 25(1)	4-16
3	Exhibit 1: Complete specification as filed by the Applicant as downloaded from InPass site including Form 1 & 2	17-43
4	Exhibit 2: Nisheeth C. Desai, Jahnvi D. Monapara, Aratiba M. Jethawa, Unnat Pandit, Chapter 9 - Contemporary development in the synthesis and biologicalapplications of pyridine-based heterocyclic motifs, Recent Developments in the Synthesis and Applications of Pyridines, 2023, Pages 253-298	44-45
5	Exhibit 3: Chemical Substance Information, J-GLOBAL ID : **2009**07080661487392	46-47
6	Exhibit 4: https://pubchem.ncbi.nlm.nih.gov/compound/11726416#section=Structures (2006)	48-57
7	Exhibit 5: Cesur N, Synthesis and Antifungal Activity of Some 2-Aryl-3-substitute d 4-Thiazolidinones, 1994, 327, Pg No. 271-272	58-59

भारत सरकार, पेटेन्ट कार्यालय, मुंबई
10 JUL 2023
GOVT. OF INDIA, PATENT OFFICE, MUMBAI

8	Exhibit 6: Birgul Ozden Kasimogullari et al, Fused Heterocycles: Synthesis of Some New Imidazo[1,2-a]-pyridine Derivatives, Molecules 2004, Vol-9, 894-901 (D1)	60-67
9	Exhibit 7: Khalid Karrouchi et al, Synthesis and Pharmacological Activities of Pyrazole Derivatives: A Review, Molecules 2018, 23, 134; doi:10.3390/molecules23010134	68-153

DR. OMPRAKASH SINGH BARKHAMBA

Opponent

To
The Controller of Patents,
The Patent Office, Mumbai

FORM – 7A

THE PATENTS ACT, 1970

(39 OF 1970)

&

THE PATENTS RULES, 2003

REPRESENTATION FOR OPPOSITION TO GRANT OF PATENT

(See section 25 (1) and rule 55)

I, DR. OMPRAKASH SINGH BARKHAMBA Indian Resident having address of Salarpur, Mawana Road, Meerut – 250001, Uttar Pradesh, India hereby submit representation by way of opposition to the grant of patent in respect of Patent Application No. **202221034803** dated **17/06/2022** for the invention titled "*Thiazolidin-3-yl-Imidazole-pyridine-3-carboxamide as antimalarial agents*" made by Maharaja Krishnakumarsinhji Bhavnagar University, Bhavnagar, Gujarat. It is published in the Official Journal of Indian Patent Office dated 22/07/2022.

The impugned Patent Application is opposed on the following grounds:-

Section 25(1)(b): **Lacks novelty;**

Section 25(1)(e): **lacks inventive step;**

Section 25(1)(f): **Not an invention**

Address for service in India is:

DR. OMPRAKASH SINGH BARKHAMBA
Salarpur, Mawana Road, Meerut – 250001,
Uttar Pradesh
Email: omprakashsinghbarkhamba05@gmail.com

Tel: +91-7094324285/+91-9319788742

omprakash

Date: 27th June, 2023

To
The Controller of Patents, The Patent Office, Mumbai

REPRESENTATION UNDER SECTION 25(1)

I, DR. OMPRAKASH SINGH BARKHAMBA Indian Resident having address of Salarpur, Mawana Road, Meerut – 250001, Uttar Pradesh, India ('Opponent') submit the following representation under Section 25(1) of the Act in opposing the grant of patent on the application indicated in the cause title.

1. Locus Standi:

I am a researcher in the field of Pharmaceutical Chemistry and would like to assist the Controller of Patents in order to take valid decision because I do not found any merit of the 'invention' of Patent Application No. **202221034803.**

Brief History:

i. The alleged invention was filed on June 17, 2022 by Maharaja Krishnakumarsinhji Bhavnagar University, Bhavnagar and allotted application number is 202221034803 by the Indian Patent Office and said application was published on July 22, 2022 in the Official Journal; The Expedited RQ was filed on July 27, 2022;

ii. The First Examination Report was issued by the Deputy Controller of Patents & Designs (Mr. Soumen Ghose), IPO, Kolkata and the reply was filed on Nov. 17, 2022;

iii. A pre-grant representation was filed by Mr. T.Iyar from Madurai on Jan. 09, 2023;

iv. On March 24,2023, an opposition notice u/r 55(3) was issued by another Controller i.e. Dr. Amarandra Samal, Deputy Controller of Patents & Designs, IPO, Mumbai without stating as to why the prosecuting Officer has been changed and **on the same day** (March 24, 2023) when Dr. Amarandra Samal is involved in Administrative work in CGPDTM not in Examination & Grant since last 5 years;

v. the reply statement was filed on the **same day** (March 24, 2023) of the pre-grant notice u/r 55(3) by the Applicant; it is hardly possible for one to see the

pre-grant notice and pre-grant representation thoroughly, analyse the objection and file a suitable reply statement within same day; whether the Applicant was aware about the pre-grant notice u/r 55(3) in advance;

vi. Pre-grant Hearing notice was issued on May 18, 2023 by Dr. Amarandra Samal, Deputy Controller of Patents & Designs, IPO, Mumbai;

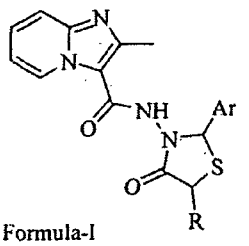
Preliminary observation:

Prof. Nisheeth C. Desai form Department of Chemistry, Maharaja Krishnakumarsinhji Bhavnagar University,Bhavnagar, India is a researcher in the field of pyridine-based heterocyclic motifs (Exhibit 2-***Nisheeth C. Desai,*** *Jahnvi D. Monapara, Aratiba M. Jethawa,* ***Unnat Pandit****, Chapter 9 - Contemporary development in the synthesis and biologicalapplications of pyridine-based heterocyclic motifs, Recent Developments in the Synthesis and Applications of Pyridines, 2023, Pages 253-298*) who is one of the inventor of the impugned application. It is coming out clearly that Prof. Desai and Unnat Pandit (who is currently the Controller General of Patents, Designs & Trademarks, Govt. of India) together were involved in research with regard to the medicinal field. The above is the evident. Currently, Unnat Pandit is the Controller General in India and the impugned case belongs to Prof. Desai and his Bhavnagar Team. This might be the answer as to why the Controller has been changed from Mr. Soumen Ghose to Dr. Amarendra Samal after filling the pre-grant representation by Mr. T. Iyer. It is clear that the CGPDTM favors the Applicant in order to 'grant' a patent of the compound which is not at all deserve to be granted. Now, let me explain as to why it has not been deserved:

The alleged invention is related to:

We claim,

1. The Thiazolidin-3-yl-Imidazo-pyridine-3-carboxamide of formula I, or its pharmaceutically acceptable salt, 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 pharmaceutically acceptable salts, derivatives, metabolites thereof.

The problem to be solved by the alleged invention is to combine thiozolidinone and imidazo-pyridine for achieving a compound having anti-malarial activity.

The teaching of **last paragraph, page no. 05** of alleged invention:

> Researchers synthesized imidazo-pyridine (formulas 2, 3 and 4) and quinoline based 4-thiazolidinones (formulae 5 and 6) and tested them for antimalarial activity, which inspired us to develop hybrids of imidazo-pyridine and 4-thiazolidinones.
>
> 5 of 27

Accordingly, the Applicant himself admitted that there is a motivation to combine 4-thiazolidinone and imidazo-pyridine for achieving a compound having anti-malarial activity. Since it is admitted by the Applicant himself, the claimed compound of alleged

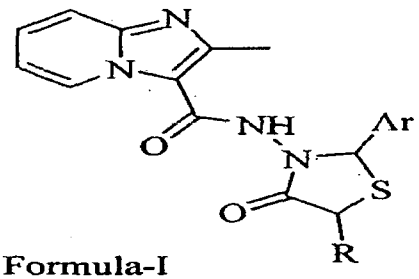
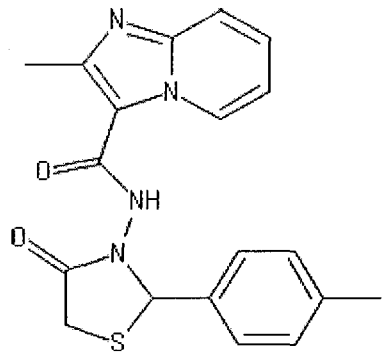
invention is not new rather obvious to the person-skilled-in-art and therefore is not patentable. The alleged invention is liable to be refused on this ground alone.

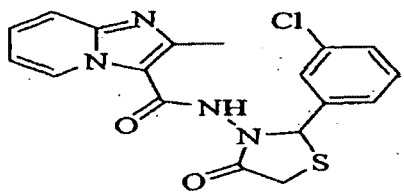
Without prejudice to the above, the Opponents submit para-wise as to how the alleged invention doesn't meet the requirement of Indian Patent Act, 1970.

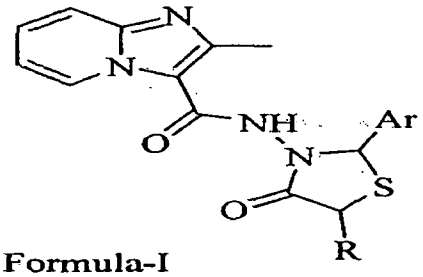
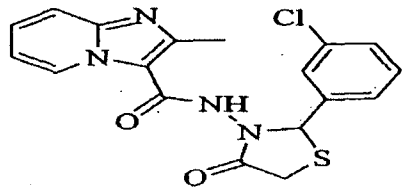
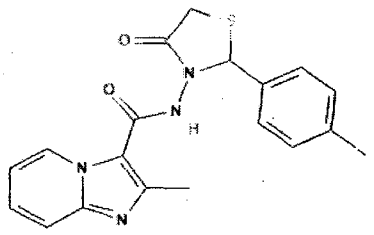
Understanding the invention:

The inventor of alleged invention inserts thiazolidinone to 3rd position of imidazole-pyridine using an amide linker for achieving a compound having anti-malarial activity.

Section 25(1)(b): **lacks novelty.**

Claimed compound of impugned application	J-GLOBAL ID : **2009**07080661487392 (Exhibit 3)
General compound:  **Formula-I** Specific compound:	

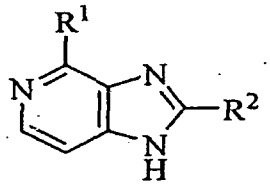
 1a	

Claimed compound of impugned application	PubChem (Exhibit 4)
General compound:  **Formula-I** *Specific compound:*  1a	

The Japanese document J-GLOBAL ID **2009**07080661487392 (Exhibit 3) which is the document of year 2009 and Pubchem (Exhibit 4) in 2006 (well before the priority date of impugned application i.e. June 17, 2022) doesn't disclose any specific medicinal activity of the compound and but discloses same structure and nomenclature. The inventors of impugned application just discovered the medicinal property (anti-malarial) of same compound. Discovering a medicinal property of a structurally same compound is not patentable under Section 2(1)(j) of Indian Patent Act, 1970. Hence the claimed compound of impugned application is not novel over Exhibit 3 or Exhibit 4.

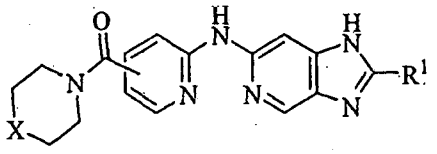
Section 25(1)(e): **lacks inventive step**;

At first, the Applicant is of admitted position **(Last para, Page no. 05 of impugned application)** that they have inspired (in other word motivation) to combine 4-thiazolidinone *(Formula 5 of Anna Caroline C Aguiar et al, 2017; & Formula 6 of Sandeep Jain et al, 2018)* and imidazo-pyridine *(Formula 2 of Andre Horatscheck et al, 2020; & Formula 3 of Claire Le Manach et al., 2018; Formula 4 of Tao Wu et al, 2011)* for achieving a compound (Formula I of impugned application) with anti-malarial activity



Formula-2

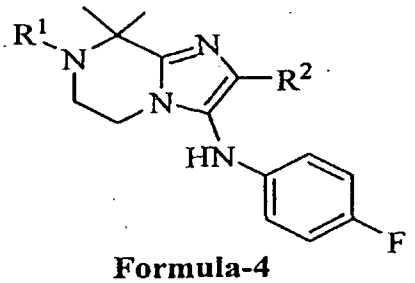
R^1 and R^2 = Different substituents



Formula-3

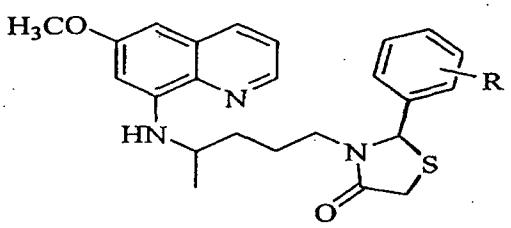
R^1 = Various derivatives

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



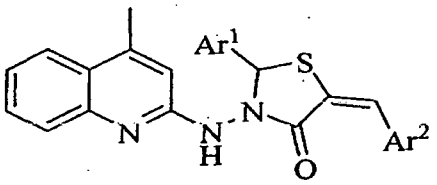
Formula-4

R^1, R^2 = Various substituents



Formula-5

R = Various substituents



Formula-6

Ar^1, Ar^2 = Various substituents

Since the Applicant himself has admitted (as above) that the compound (Formula I) of the impugned application is an effect of the inspiration/motivation of Formula 2-6 as above, the alleged invention is obvious and is liable to be refused on this ground alone.

Without prejudice:

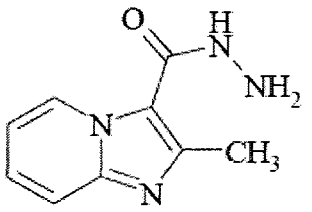
The argument in view of Exhibit 3 or Exhibit 4 for novelty ground as above can be considered for the inventive assessment. From the above comparative chart, it is clear that the structure of compound is same which is already available in the state-of-the art since 2006. Therefore, the subject matter of the impugned application is just a discovery of the medicinal or pharmacological property (anti-malarial) of same compound and discovering a medicinal property of the structurally same compound cannot be considered as technical advanced rather is obvious to a skilled person as Section 2(1)(ja) of the Indian Patent Act 1970 is concerned.

Also, the inventive concept of impugned application is to insert thiazolidinone at 3rd position of imidazole-pyridine using an amide linker for achieving a compound having anti-malarial activity. Exhibit 5 *(CESUR N, 1994)* teaches the compounds where thiazolidinone is being inserted at 3rd position of imidazole-pyridine ring in order to achieve a medicinal activity (anti-fungal). The compounds of CESUR N, 1994 are as follows:

a. 2-Methyl-N-[2-(4-chlorophenyl)-4-oxo-3-thiazolidinyl]imidazo[1,2-a]pyridine-3-carboxamide ,
b. 2-Methyl-N-[2-(4-fluorophenyl)-4-oxo-3-thiazolidinyl]imidazo[1,2-a]pyridine-3-carboxamide ,
c. 2-Methyl-N-[2-(2-nitrophenyl)-4-oxo-3-thiazolidinyl]imidazo[1,2-a]pyridine-3-carboxamide ,
d. 2-Methyl-N-[2-(4-methylphenyl)-4-oxo-3-thiazolidinyl]imidazo[1,2-a]pyridine-3-carboxamide ,
e. 2-Methyl-N-[2-(3-methoxy-4-hydroxyphenyl)-4-oxo-3-thiazolidinyl]imidazo[1,2-a]pyridine-3-carboxamide ,
f. 2-Methyl-N-[2-(3-ethoxy-4-hydroxyphenyl)-4-oxo-3-thiazolidinyl]imidazo[1,2-a]pyridine-3-carboxamide ,
g. 2-Methyl-N-[2-(1,3-benzodioxol-5-yl)-4-oxo-3-thiazolidinyl]imidazo[1,2-a]pyridine-3-carboxamide

Since the concept of insertion of thiazolidinone into imidazole-pyridine ring is already known for achieving a medicinal activity, it is obvious to a skilled person to use the same concept (thiazolidinone into imidazole-pyridine) for another medicinal activity (anti-malarial).

Further, Exhibit 6 *(Birgul Ozden Kasimogullari and Zafer Cesur, 2004)* is related to synthesis of some New Imidazo[1,2-*a*]-pyridine Derivatives in which compound 2 is as follows:



2

Birgul Ozden Kasimogullari and Zafer Cesur, 2004 teaches basic moiety but doesn't suggest the peripheral moiety. Exhibit 7 *(Khalid Karrouchi et al, 2018)* teaches peripheral moiety which can impart antimalarial activity. Accordingly the skilled person would combine the teaching of *Birgul Ozden Kasimogullari and Zafer Cesur, 2004* & *Khalid Karrouchi et al, 2018* in order to get the compound (Formula I) of the impugned application.

Note: I observed (over the reply statement filed by the Applicant dated 24/03/2023 in respect of pre-grant filed by T. Iyer) that the contention of the Applicant is to prove that *the compound 2 of Birgul Ozden Kasimogullari and Zafer Cesur, 2004 is for different medicinal activity therefore the person-skilled-in-art would not motivate over it.* This is not valid argument because since compound 2 is already medicinally used therefore the skilled person would use the same for achieving different medicinal activity which herein

is anti-malarial. The Applicant is failed to establish as to why the skilled person would not motivate over *Birgul Ozden Kasimogullari and Zafer Cesur, 2004* to select the moiety for any medicinal use since ultimately the claimed compound of impugned application is a pharmaceutical product.

With addition to the above, the Opponent submits that It is settled law 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 inventive step. To be patentable the improvement or the combination must produce a new result or 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 *(Biswanath Prasad Radhey Shyam Vs Hindustan Metal Industries, AIR 1982 SC 144).*

Section 25(1)(f): **Not an invention**:

Section 3(d):

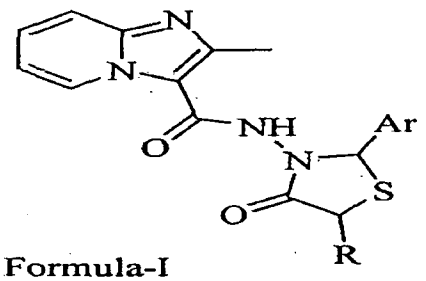
3. What are not inventions.- The following are not inventions within the meaning of this Act,-

(d): [(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.

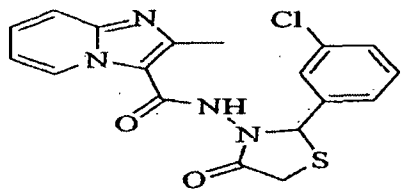
Explanation. -For the purposes of this clause, salts, esters, ethers, polymorphs, metabolites, pure form, particle size, isomers, mixtures of isomers, complexes, combinations and other derivatives of known substance shall be considered to be the same substance, unless they differ significantly in properties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

Analysis:

Claimed compound of impugned application: Anti-malarial compound of Formula I as follows:

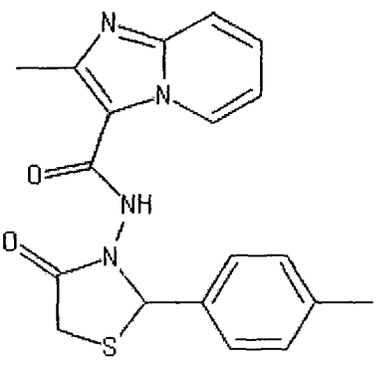


Formula-I



1a

Closest Prior art (J-GLOBAL ID : **2009**07080661487392 OR PubChem :



Accordingly, the claimed compound of impugned application is mere discovery of new property (anti-malarial) or new use for the substance as disclosed in J-GLOBAL ID :

200907080661487392 (Exhibit 3) OR PubChem (Exhibit 4) therefore clearly falls within the scope of *"mere discovery of any new property or new use for a known substance".*

Section 3(e):

It is already admitted from the Applicant's end (as above discussed) that the component thiazolidinone and imidazole-pyridine is known for malaria. Prima facie, the claimed compound is an effect of aggregation of the properties of thiazolidinone and imidazole-pyridine and is therefore mere admixture because no synergism or specific working interrelation of thiazolidinone and imidazole-pyridine is taught in the as filed specification.

RELIEF SOUGHT:

The opponent states that it has established and made out a case on each of the aforesaid grounds of opposition and pray to the Ld. Controller for the following relief(s):

1) Take on record the present representation;
2) Refusal of the application;

3) Forward copy of reply of applicant and evidence if any and any amendments filed;
4) Leave to file a replication to the reply of the applicant and evidence; and
5) Grant of hearing

Date: 27th June, 2023

OmPrakash

.....

DR. OMPRAKASH SINGH BARKHAMBA

To,
The Controller of Patents,
The Patent Office, Mumbai

FORM 2

THE PATENTS ACT, 1970

(39 OF 1970)

COMPLETE SPECIFICATION

(See section 10 and rule 13)

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

Applicant

MAHARAJA KRISHNAKUMARSINHJI BHAVNAGAR UNIVERSITY,

Gaurishankar Lake Road, Bhavnagar – 364002, Gujarat, India

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.

Mosquito control strategies (pesticide-treated nets and indoor residual spraying) had been extremely effective, but are currently ineffectual due to increased insecticide resistance. Similarly, first-line drug-based medications, especially Artemisinin combination therapy (ACTs), are at risk (Fernandez-Alvaro, Journal of medicinal chemistry 2016, 59:5587-5603) affected due to the emergence of resistance. Nonetheless, several natural medications, such as Marinoquinoline A-F and Aplidiopsamine A, are accessible to treat malarial illnesses. Hybrid heterocycles have also played an important role in the fight against malarial resistance. Quinine, artemether, lumefantrine, primaquine, doxycycline, atovaquone, and quinidine based compounds have shown significant antimalarial potential (Kumar, Sahil, *J. Enzyme Inhib. Med. Chem.* 2016, 31:173-186).

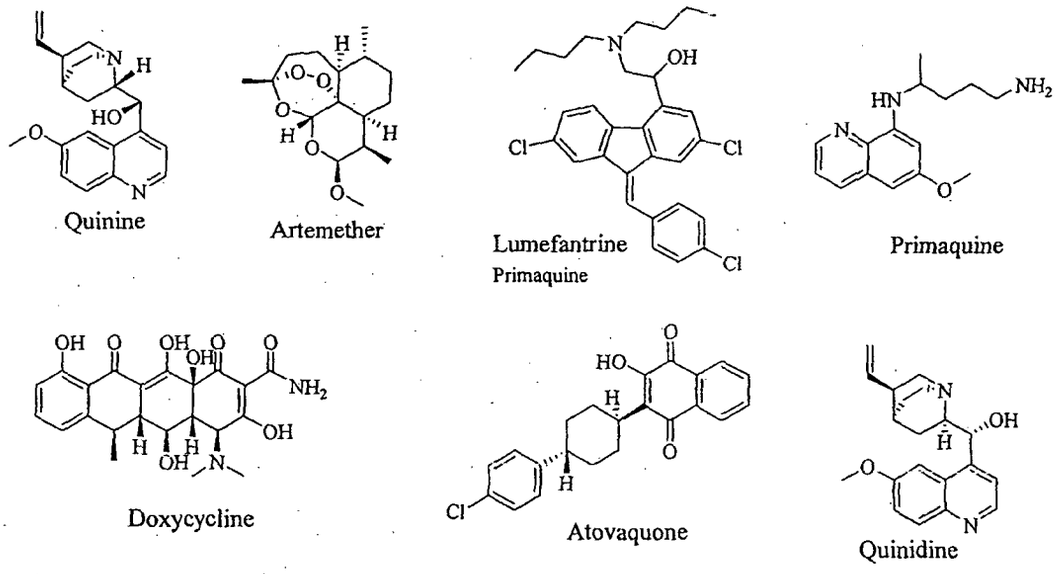
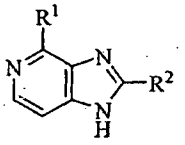


Fig. 1: Structures of commercially available medications used for the treatment of malaria

Nesrin Cesur et al., have synthesized some 2-aryl-3-substituted 4-thiazolidinones and screened for antifungal activity of the compounds (Nesrin Cesur et al, *Arch. Pharm.* (Weinheim) 1994, 327, 271-272.

André Horatscheck et al., have synthesized 2-(3,4-difluorophenyl)-4-(hexahydropyrrolo[1,2

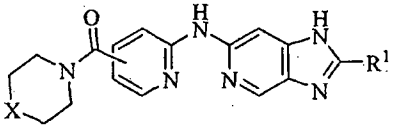
a]pyrazin-2(1*H*)-yl)-1*H*-imidazo[4,5-*c*]pyridines (Formula-2) (André Horatscheck et al., *J. Med. Chem.* 2020, *63* (21), 13013–13030). These reactions were carried out through multi-step reactions and characterized through various spectroscopic techniques. All synthesized compounds were screened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

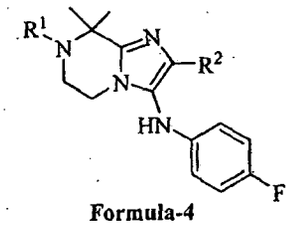


Formula-3

R^1 = Various derivatives

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

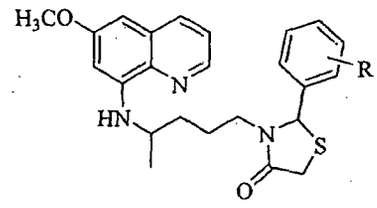
Tao Wu et al., have synthesized some novel *N*,2-bis(4-fluorophenyl)-5,6,7,8-tetrahydroimidazo[1,2-a] pyrazin-3-amines (Formula-4) (Tao Wu et al. *J. Med. Chem.* 2011, *54*, 5116-5130) via multi-step reactions and characterized through various analytical techniques. All the synthesized substituents were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



Formula-4

R^1, R^2 = Various substituents

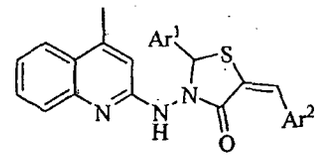
Anna Caroline C. Aguiar et al., have synthesized 3-(4-((6-methoxyquinolin-8-yl)amino)pentyl)-2-phenylthiazolidin-4-ones (Formula-5) (Anna Caroline C. Aguiar et al. *Malar. J.* 2017, *16* (110), 1–11) via one-pot synthesis. The synthesized compounds were evaluated for their *in-vitro* and *in-vivo* antimalarial activity against *P. vivax*.



Formula-5

R = Various substituents

Sandeep Jain et al. have synthesized aryl-3-(4-methylquinolin-2-ylamino)-2-phenylthiazolidin-4-ones (Formula-6) (Sandeep Jain et al. *Exp. Parasitol.* 2018, *185*, 107–114) and characterized with various spectroscopic techniques. The synthesized derivatives were evaluated for *in-vitro*, *in-vivo* and *in-silico* study as antimalarials.



Formula-6

Ar^1, Ar^2 = Various substituents

Researchers synthesized imidazo-pyridine (formulas 2, 3 and 4) and quinoline based 4-thiazolidinones (formulae 5 and 6) and tested them for antimalarial activity, which inspired us to develop hybrids of imidazo-pyridine and 4-thiazolidinones.

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

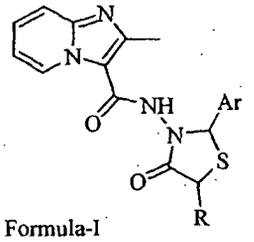
Fig. 1 Graphical Biological Results of Thiazolidin-3-yl-Imidazo-pyridine-3-carboxamide (Give the graphical results at the end of specification)

SUMMARY OF THE INVENTION

The quinine, artemether, lumefantrine, primaquine, doxycycline, atovaquone, and quinidine used to treat malaria. The present invention relates to a novel hybrid heterocyclic of Thiazolidin-3-yl-Imidazo-pyridine-3-carboxamide compounds amalgamating two separate hetero moieties of imdazo-pyridine and 4-thiazolidine, wherein both hydrides are connected with amide linker strategically designed to yield the novel compound showing higher potency as antimalarial agent.

The main embodiment of the present invention is to design and synthesize a novel nitrogen and sulfur-containing heterocyclic hybrids of 2-methyl-*N*-(4-oxo-2-arylthiazolidin-3-yl)imidazo[1,2-*a*]pyridine-3-carboxamide (Formula-I).

Another embodiment of the invention is to disclose a novel process for preparing nitrogen and sulfur-containing heterocyclic hybrids of the Formula-I.

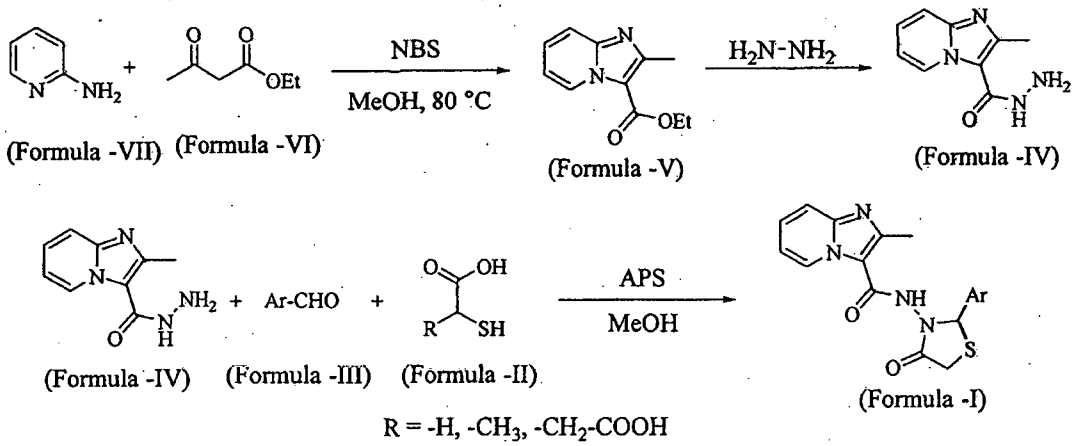


Formula-I

wherein,

R = H, $-CH_3$ and $-CH_2$-COOH and Ar is aryl/heteroaryl ring is substituted by mono or di-substituents with nitroaryl, halogen, *N,N*-dimethyl, cinnamyl, methyl and methoxy and like with various electron-withdrawing and electron-donating groups.

Yet another embodiment of the present invention provides a new process for the preparation of stable imidazo-pyridine clubbed with 4-thiazolidinone derivatives of Formula-I or pharmaceutically acceptable salts thereof following step as depicted in Scheme 1:



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

present invention relates to one-pot synthesis optimizing the in-process the isolation of intermediate steps to yield compound of Formula (I).

The present invention provides a strategically designed novel approach in structural diversity of heterocyclic hybrids consisting of Thiazolidin-3-yl-Imidazo-pyridine-3-carboxamide formula (I) to combat the resistance of malarial species.

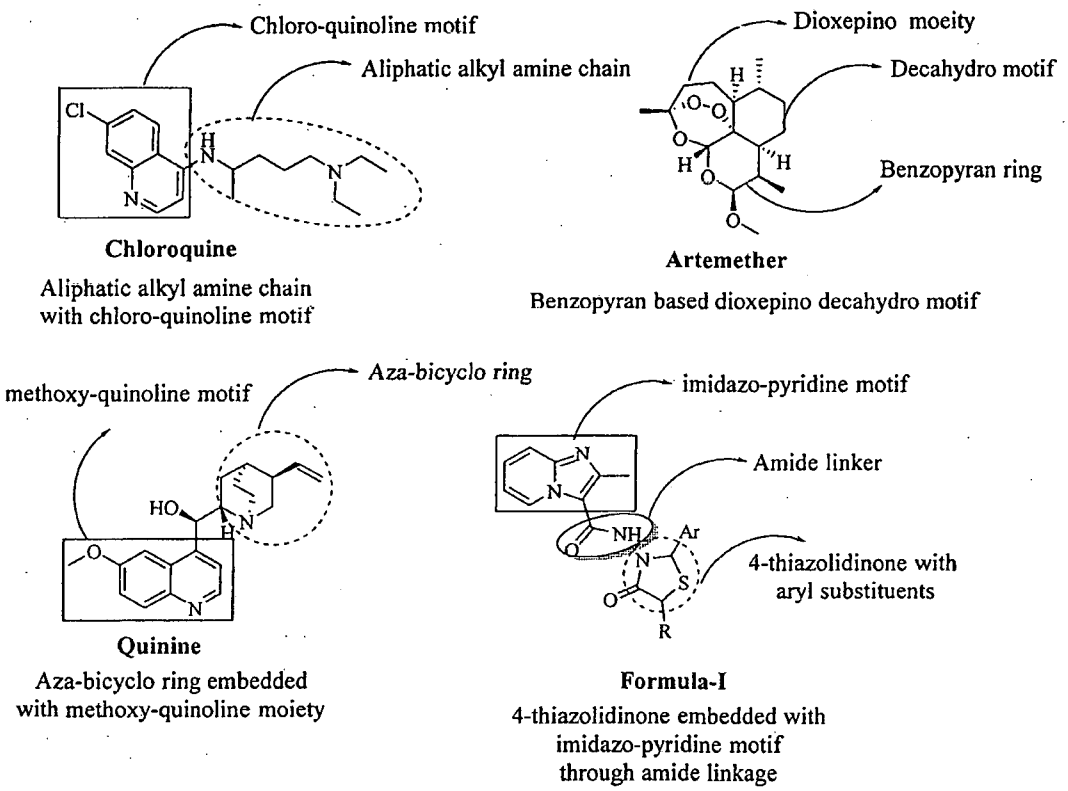
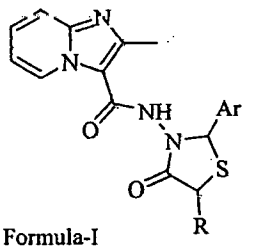


Fig. 2 Novel approach to strategically design the structural hybrid of Thiazolidin-3-yl-Imidazo-pyridine-3-carboxamide

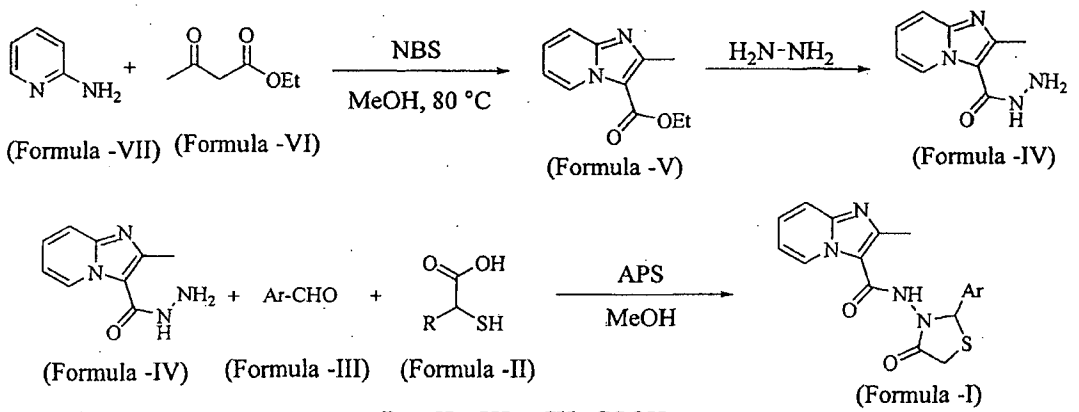
The present invention relates to a series of novel Thiazolidin-3-yl-Imidazo-pyridine-3-carboxamide scaffolds having antimalarial activity. The said compounds are screened to study the antimalarial potency against *P. falciparum*.



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.



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

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

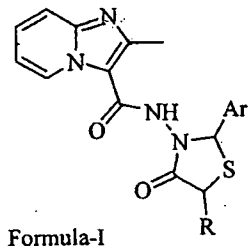
General Formula-I was obtained by the reaction of Formula-IV, substituted aromatic aldehydes (Formula-III), thioglycolic acid (Formula-II) and catalytic amount of ammonium persulphate (APS) in methanol, wherein Ar is defined as per Formula (I):

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.

All the synthesized compounds were screened for antimalarial activity in the Microcare laboratory & Tuberculosis Research Centre, Surat, Gujarat.

The *in-vitro* antimalarial assay was carried out according to the micro assay protocol of Rieckmann and co-workers with minor modifications (Rieckmann et al., *Lancet* 1978, *1*, 221-223). The cultures of *P. falciparum* 3D7 strain were maintained in medium RPMI 1640 supplemented with 25 mM HEPES, 1% D-glucose, 0.23% sodium bicarbonate and 10% heat inactivated human serum. The asynchronous parasites of *P. falciparum* were synchronized after 5% D-sorbitol treatment to obtain only the ring stage parasitized cells. The procedure is given as per the reference and the slides were microscopically observed to record maturation of ring stage parasites into trophozoites and schizonts in presence of different concentrations of the test agents. The test concentration which inhibited the complete maturation into schizonts was recorded as the minimum inhibitory concentrations (MIC). Quinine was used as the reference drug (positive control).

The invention relates to the development of antimalarial drugs based on completely new structures, such as the insertion of thaizolidinone to the 3rd position of imidazo-pyridine, as well as the integration of an amide linker. The amide linker, together with pharmacophores like thaizolidineone and imidazo-pyridine, will play a significant role in the establishment of antimalarial drugs in our innovation. For the first time we have develop the reported formula (I). Until now, no such structures are reported for the development of antimalarial drugs. In accordance with the objective of present invention to provide novel 2-methyl-*N*-(4-oxo-2-arylthiazolidin-3-yl)imidazo[1,2-*a*]pyridine-3-carboxamide (Formula-I).

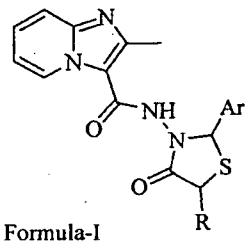


Formula-I

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.



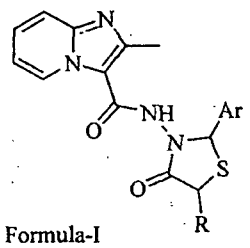
Formula-I

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

1 j	-3-NO_2-C_6H_4	-H
1 k	-4-NO_2-C_6H_4	-H
1 l	-CH=CH-C_6H_5 / -C_8H_7	-H

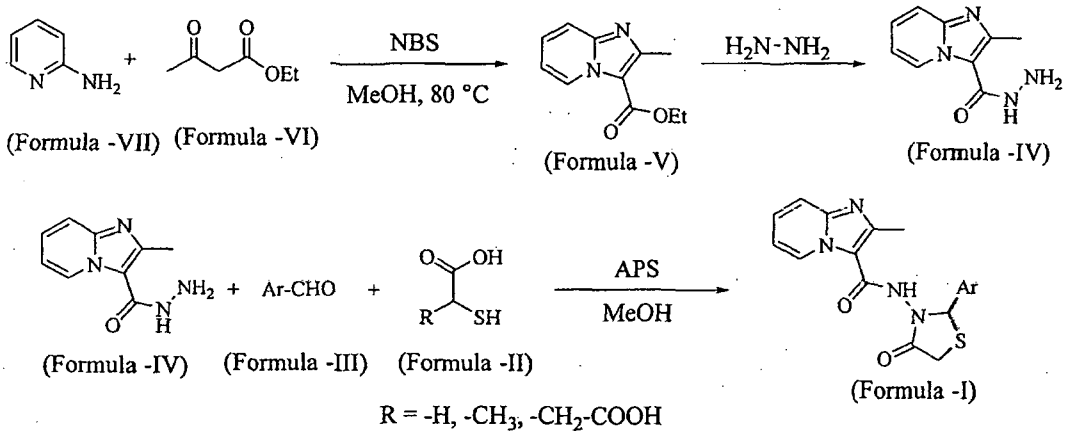
In one exemplary embodiment, wherein Formula-I is further defined as



Formula-I

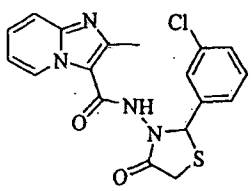
wherein -R is either -H or $-CH_3$ or $-CH_2$-COOH. Aryl/heteroaryl ring is substituted by mono or di-substituents with nitro, halogen, *N,N*-dimethyl, cinnamyl, methyl and methoxy groups or pharmaceutically acceptable salts, derivatives, metabolites thereof.

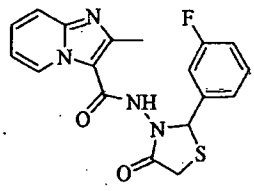
The desirable product of formula (I) is obtained by the following one pot synthesis

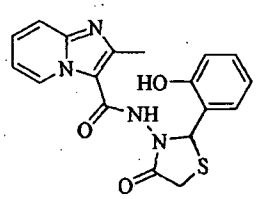


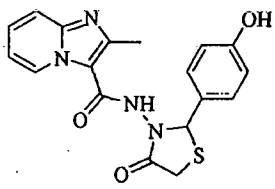
R = -H, -CH_3, -CH_2-COOH

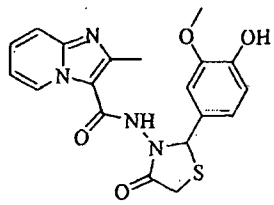
General Formula-I was obtained by the reaction of Formula-IV, substituted aromatic aldehydes (Formula-III), thioglycolic acid (Formula-II) and catalytic amount of ammonium persulphate (APS) in methanol, wherein Ar is defined as per Formula (I):

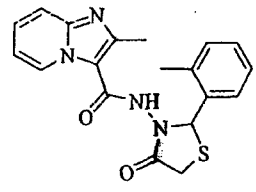

1a

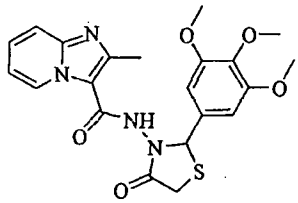

1b

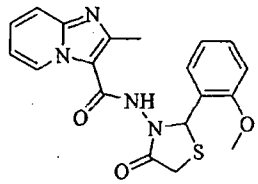

1c

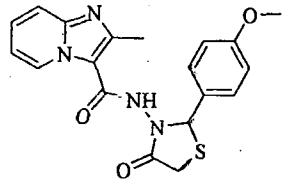

1d

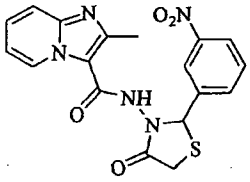

1e

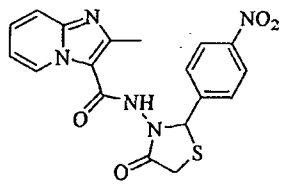

1f

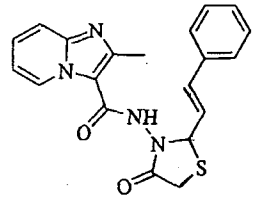

1g


1h


1i


1j


1k


1l

The compounds of Formula-I obtained as above are further purified by using alcohol (95%). The alcohol used for the purification of general compound of formula-I is selected but not limited to C1-C4 Alcohol namely methanol, ethanol, propanol, butanol or mixture of thereof.

The term "alkyl", is referred to C1-C3 alkyl such as $-CH_3$ or $-CH_2$-COOH

The term aryl is selected alone or in combination with aryl/heteroaryl ring is substituted by mono or di-substituents with nitro, halogen, *N,N*-dimethyl, cinnamyl, methyl and methoxy,

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

characterized by IR, ^{1}H NMR, ^{13}C NMR, and Mass spectroscopy. IR spectra revealed that the presence of the amine group was confirmed at 3190 cm^{-1}. The frequency at 1658 cm^{-1} and 1593 cm^{-1} confirmed carbonyl and cyano groups. Moreover, the presence of nitro group and C-S was validated at 1550 cm^{-1} and 686 cm^{-1}. The protons present in the claimed structure were confirmed by proton NMR. Peaks appeared at 2.58 ppm and 2.95-2.98 ppm showing the presence of methyl group and methylene group of 4-thiazolidinone moiety. Furthermore, methine proton of 4-thiazolidinone and amine was confirmed at 7.05 ppm and 11.52 ppm. The carbon skeleton of the claimed compound is also characterized by ^{13}C NMR spectroscopy. Peaks appeared at 16.3 ppm and 168.6 ppm revealed the presence of methyl group and carbonyl group while peaks appeared at 72.6 ppm and 174.1 ppm confirmed the methine carbon and the carbonyl group of 4-thiazolidinone. The mass spectra of the compound are in accordance with the claimed structure.

Example-1: Ethyl 2-methylimidazo[1,2-*a*]pyridine-3-carboxylate was prepared according to the literature method (Bhagat et al., *Tetrahedron Lett.* 2017, 37:3662-3666), (Formula VI).

Ethyl acetoacetate (1.05 mmol) reacted with N-bromo succinamide (1.2 mmol) in methanol (5 mL) at 80 °C for 30 min, followed by the addition of 2-aminopyridine (1.0 mmol) and heated at same temperature for another 30 min. Reaction mixture was cooled to room temperature and product generated was recrystallized from ethanol (95%). Yield: 56%; Solid; M.P. 66-68°C.

Example-2: Procedure for the synthesis of 2-methylimidazo[1,2-*a*]pyridine-3-carbohydrazide, (Formula V).

To a solution of formula V (1.0 mmol) in methanol (5 mL), hydrazine hydrate (20.0 mmol) was added and refluxed it for 2 h. Reaction mixture was then stirred for 15 minutes at room

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]**

A mixture of formula IV (1 mmol), 2-hydroxybenzaldehyde (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 52%; solid; M.P. 182-186 °C.

Example-7: *N*-(2-(4-hydroxyphenyl)-4-oxothiazolidin-3-yl)-2-methylimidazo[1,2-*a*]pyridine-3-carboxamide **[1 d]**

A mixture of formula IV (1 mmol), 4-hydroxybenzaldehyde (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 54%; solid; M.P. 203-206 °C.

Example-8: *N*-(2-(4-hydroxy-3-methoxyphenyl)-4-oxothiazolidin-3-yl)-2-methylimidazo[1,2-*a*]pyridine-3-carboxamide **[1 e]**

A mixture of formula IV (1 mmol), 4-hydroxy-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 78%; solid; M.P. 167-170 °C.

Example-9: 2-methyl-*N*-(4-oxo-2-(*o*-tolyl)thiazolidin-3-yl)imidazo[1,2-*a*]pyridine-3-carboxamide **[1 f]**

A mixture of formula IV (1 mmol), 2-methylbenzaldehyde (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 70%; solid; M.P. 184-187 °C.

Example-10: 2-methyl-*N*-(4-oxo-2-(3,4,5-trimethoxyphenyl)thiazolidin-3-yl)imidazo[1,2-*a*]pyridine-3-carboxamide **[1 g]**

A mixture of formula IV (1 mmol), 3,4,5-trimethoxybenzaldehyde (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 80%; solid; M.P. 215-219 °C.

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.

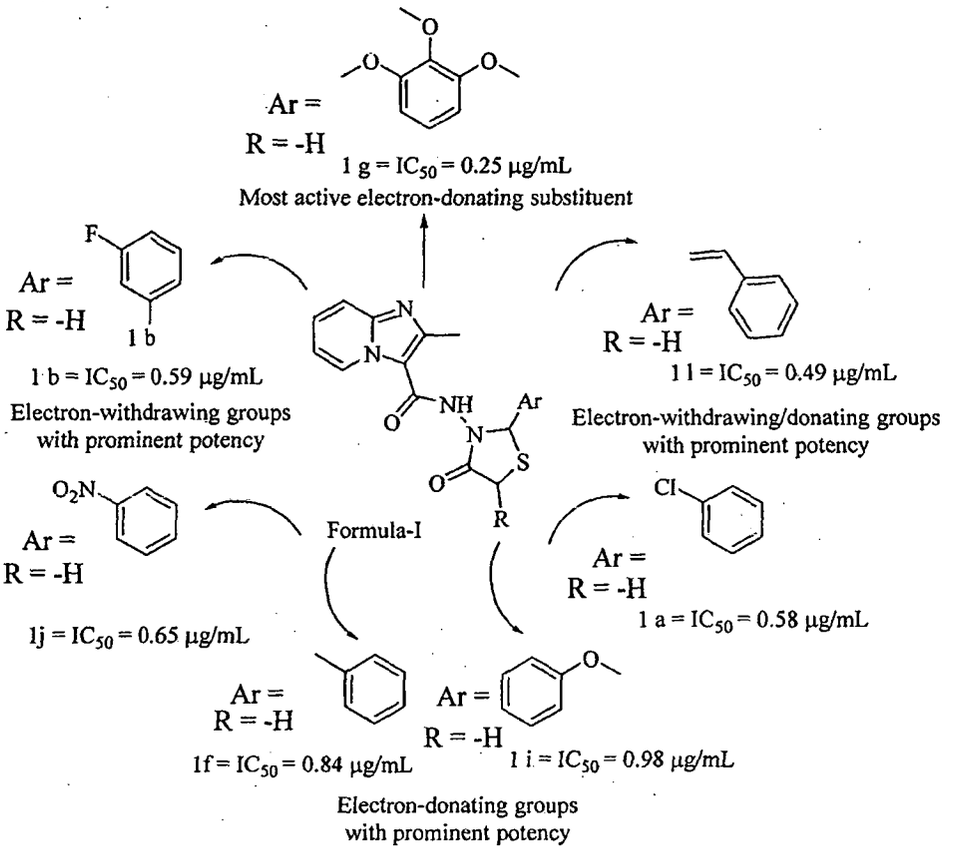
Example-15: 2-methyl-*N*-(4-oxo-2-styrylthiazolidin-3-yl)imidazo[1,2-*a*]pyridine-3-carboxamide **[1 l]**

A mixture of formula IV (1 mmol), cinnamaldehyde (1 mmol), thioglycolic acid and APS (10 mol%) in methanol (10 mL) was refluxed for 60 min. Then do the further process as disclose in example-3. Yield 80%; solid; M.P. 210-213 °C.

Antimalarial activity

All the synthesized compounds were screened for antimalarial activity in the Microcare laboratory & Tuberculosis Research Centre. The *in-vitro* antimalarial assay was carried out in 96 well microtiter plates according to the micro assay protocol of Rieckmann and co-workers with minor modifications (Rieckmann et al., Lancet 1978, *1*, 221-223). The cultures of *P. falciparum* 3D7 strain was maintained in medium RPMI 1640 supplemented with 25 mM HEPES, 1% D-glucose, 0.23% sodium bicarbonate and 10% heat inactivated human serum. The asynchronous parasites of *P. falciparum* were synchronized after 5% D-sorbitol treatment to obtain only the ring stage parasitized cells. For carrying out the assay, an initial ring stage parasitaemia of 0.8 to 1.5% at 3% haematocrit in a total volume of 200 µl of medium RPMI-1640 was determined by Jaswant Singh Bhattacharya (JSB) staining to assess the percent parasitaemia (rings) and uniformly maintained with 50% RBCs (O+). A stock solution of 5 mg/ml of each of the test samples was prepared in DMSO and subsequent dilutions were prepared with culture medium. The diluted samples in 20 µl volume were added to the test wells so as to obtain final concentrations (at five-fold dilutions) ranging between 0.4 µg/ml to 100 µg/ml in duplicate well containing parasitized cell preparation. The culture plates were incubated at 37 °C in a candle jar. After 36 to 40 h incubation, thin blood smears from each well were prepared and stained with JSB stain. The slides were microscopically observed to record maturation of ring stage parasites into trophozoites and schizonts in presence of different concentrations of the test agents. The test concentration which inhibited the complete maturation into schizonts was recorded as the minimum inhibitory concentrations (MIC). Quinine was used as the reference drug (positive control).

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



(Remove background colour)

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

P. falciparum. Compound **1 l** exhibited better potency than the standard drug quinine (MEAN IC_{50} = 0.26 µg/mL). Furthermore, compound 1 a demonstrated promising antimalarial activity. Compounds **1 b** showed a high level of inhibition against a malarial strain. The electron-withdrawing $-NO_2$ group is present at 3rd position, displayed better activity. Regardless, hybrids **1 f** and **1 I** was shown to be significant against the malarial pathogen. Furthermore, substituents **1 c, 1 d, 1 e,** and **1 k** showed high to moderate inhibitory potential. The remaining substituents were moderately effective against *P. falciparum*. It can be stated from the results that electron-donating methoxy group had enhanced the antimalarial potency of the synthesized entity.

Table-2: Results of the antimalarial activity (*Plasmodium falciparum 3D7*)

Sr No.	Compound or Formula (I), ID	-R	-Ar	Mean IC50, (µg/mL)
1	1a	-H	-3-Cl-C_6H_4	0.58 µg/mL
2	1b	-H	-3-F-C_6H_4	0.59 µg/mL
3	1c	-H	-2-OH-C_6H_4	1.30 µg/mL
4	1d	-H	-4-OH-C_6H_4	1.08 µg/mL
5	1e	-H	-3-OCH_3-4-OH-C_6H_3	1.43 µg/mL
6	1f	-H	-2-CH_3-C_6H_4	0.84 µg/mL
7	1g	-H	-2,3,4-$(OCH_3)_3$-C_6H_2	0.25 µg/mL
8	1h	-H	-2-OCH_3-C_6H_4	2.56 µg/mL
9	1i	-H	-3-OCH_3-C_6H_4	0.98 µg/mL
10	1j	-H	-3-NO_2-C_6H_4	0.65 µg/mL
11	1k	-H	-4-NO_2-C_6H_4	1.23 µg/mL
12	1l	-H	-CH=CH-C_6H_5 / -C_8H_7	0.49 µg/mL
Standard Drug: Quinine				0.268 µg/mL

In accordance with the present invention which offers novel approach in design and synthesize of a nitrogen and sulfur-containing heterocyclic hybrids consisting of Thiazolidin-

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*.

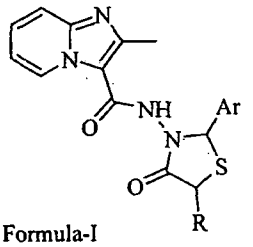
For, M K Bhavnagar University, Bhavnagar,

Prof. Nisheeth C. Desai

Date: 9th June, 2022

We claim,

1. The Thiazolidin-3-yl-Imidazo-pyridine-3-carboxamide of formula I, or its pharmaceutically acceptable salt, 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 pharmaceutically acceptable salts, derivatives, metabolites thereof.

2. The Thiazolidin-3-yl-Imidazo-pyridine-3-carboxamide of formula I as claimed in claim-1 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

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 I 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.*

For, MK Bhavnagar University, Bhavnagar,

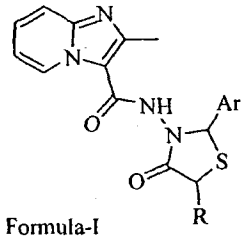
Date: 9th June, 2022

Prof. Nisheeth C. Desai

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

Exhibit 2

ScienceDirect

Recent Developments in the Synthesis and Applications of Pyridines
2023, Pages 253-298

Chapter 9 - Contemporary development in the synthesis and biological applications of pyridine-based heterocyclic motifs

Nisheeth C. Desai [a], Jahnvi D. Monapara [a], Aratiba M. Jethawa [a], Unnat Pandit [b]

[a] Division of Medicinal Chemistry, Department of Chemistry, Maharaja Krishnakumarsinhji Bhavnagar University, Bhavnagar, India
[b] Special Centre for Systems Medicine, Jawaharlal Nehru University, New Delhi, India

Available online 23 September 2022, Version of Record 23 September 2022.

https://doi.org/10.1016/B978-0-323-91221-1.00007-5 ↗
Get rights and content ↗

Abstract

Pyridine, which is made from unrefined coal tar, has various uses in organic chemistry, pharmaceutical chemistry, polymers, metal complexes, catalysts, and other fields. Pyridine-containing compounds have been used in medicinal chemistry for antimicrobial, antitubercular, anticancer, antiviral, antimalarial, antidiabetic, antioxidant, analgesic, anti-inflammatory, anti-infection, and anti-infection applications due to their water solubility, stability, basicity, ability to form a hydrogen bond, lower molecular weight, and availability in many natural products such as vitamins, coenzymes, and alkaloids. The pyridine nucleus was found in commercially accessible pharmaceuticals such as isoniazid (used to treat tuberculosis), etoricoxib (used to suppress the impact of COX-2 enzymes), and perampanel (used as an antiepileptic drug-first approved by FDA in 2012). Proton-pump inhibitors using pyridine as the fundamental unit include omeprazole, rabeprazole, pantoprazole, and lansoprazole.

Tazemetostat (an anticancer agent), rimegepant (a migraine treatment), opicapone (a Parkinson's disease treatment), and selpercatinib (a lung and thyroid cancer treatment) were all approved by the FDA in 2020 contains pyridine unit. In the contemporary era of drug design and research, pyridine, and its derivatives have played an important role in the development of medications for the treatment of a variety of infectious disorders. Several pyridine hybrids are currently undergoing clinical trials, and they may be used as a lead chemical in the future. The synthesis and applications of pyridine are summarized in this chapter. It also

cusses the therapeutic value of pyridine hybrids with various pharmacological actions, as well as molecular docking investigation.

The medicinal potency has been discussed for organic and bioorganic potent pyridine derivatives like pyridine-pyrazole hybrids, pyridine-pyrazoline hybrids, pyridine-oxazine hybrids, pyridine-oxadiazole hybrids, pyridine-indole hybrids, pyridine-coumarin hybrids, pyridine-imidazole hybrids, pyridine-benzimidazole hybrids, pyridine-thiazolidinone hybrids, pyridine-quinoline hybrids, and pyridine-quinazoline hybrids available in literature since 2015 to current.

Previous Next

Keywords

Pyridine; FDA; Green synthesis; Antitubercular activity; Anticancer activity; Antimalarial activity

Recommended articles

Cited by (0)

View full text

Chem J-GLOBAL ID : 200907080661487392 Nikkaji number : J582.976C

2-Methyl-N-[2-(4-methylphenyl)-4-oxo-3-thiazolidinyl]imidazo[1,2-a]pyridine-3-carboxamide

2-メチル-N-[2-(4-メチルフェニル)-4-オキソ-3-チアゾリジニル]イミダゾ[1,2-a]ピリジン-3-カルボアミド

Substance type : Decided structure

Molecular formula : $C_{19}H_{18}N_4O_2S$

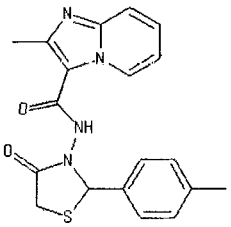
Molecular formula furigana : C19-H18-N4-O2-S

Molecular weight : 366.440

InChI : InChI=1S/C19H18N4O2S/c1-12-6-8-14(9-7-12)19-23(16(24)11-26-19)21-18(25)17-13(2)20-15-5-3-4-10-22(15)17/h3-10,19H,11H2,1-2H3,(H,21,25)

InChI key : LRFROTYNYXFHLO-UHFFFAOYSA-N

SMILES : Cc1nc2ccccn2c1C(=O)NN1C(SCC1=O)c1ccc(C)cc1



Download MOL file

Create JDreamIII upload file

Systematic name (3) :

- 2-メチル-N-[2-(4-メチルフェニル)-4-オキソ-3-チアゾリジニル]イミダゾ[1,2-a]ピリジン-3-カルボアミド
- 2-メチル-N-[2-(4-メチルフェニル)-4-オキソ-1,3-チアゾリジン-3-イル]イミダゾ[1,2-a]ピリジン-3-カルボキサミド
- 2-methyl-N-[2-(4-methylphenyl)-4-oxo-1,3-thiazolidin-3-yl]imidazo[1,2-a]pyridine-3-carboxamide

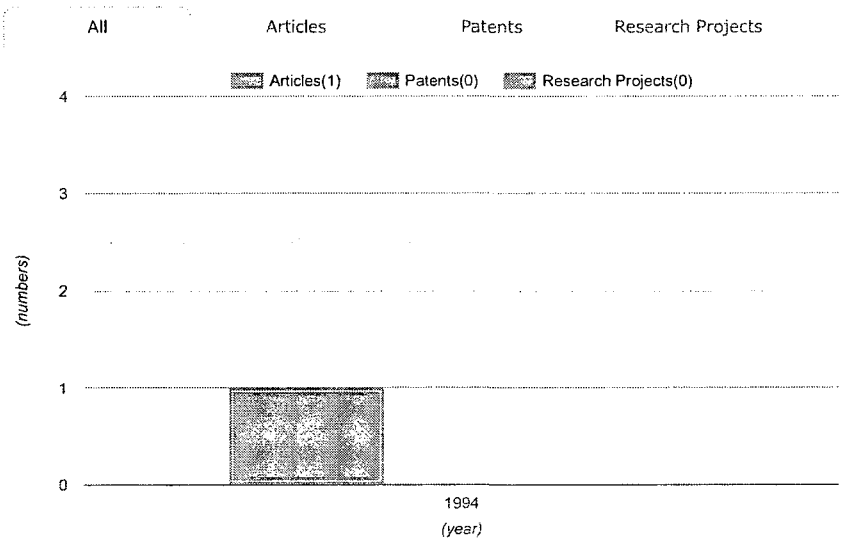
Other name (1) :

- 2-Methyl-N-[2-(4-methylphenyl)-4-oxo-3-thiazolidinyl]imidazo[1,2-a]pyridine-3-carboxamide

Thsaurus map :

Thesaurus Map

Related Article, Patent and Research Project :



Return to Previous Page

Search ウィキペディア

Article using the Chemical Substance

Patent using the Chemical Substance

Research Project using the Chemical Substance

BOTTOM

48

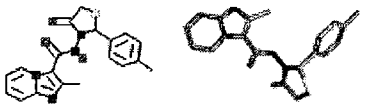
COMPOUND SUMMARY

Exhibit 4

2-Methyl-N-[2-(4-methylphenyl)-4-oxo-3-thiazolidinyl]imidazo[1,2-a]pyridine-3-carboxamide

PubChem CID
11726416

Structure



2D 3D

Molecular Formula
$C_{19}H_{18}N_4O_2S$

Synonyms
2-Methyl-N-[2-(4-methylphenyl)-4-oxo-3-thiazolidinyl]imidazo[1,2-a]pyridine-3-carboxamide

Molecular Weight
366.4 g/mol
Computed by PubChem 2.1 (PubChem release 2021.05.07)

Dates

Create:	Modify:
2006-10-26	2023-06-17

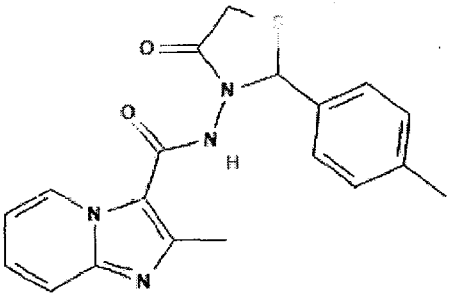
Contents

Title and Summary

1 Structures

1.1 2D Structure

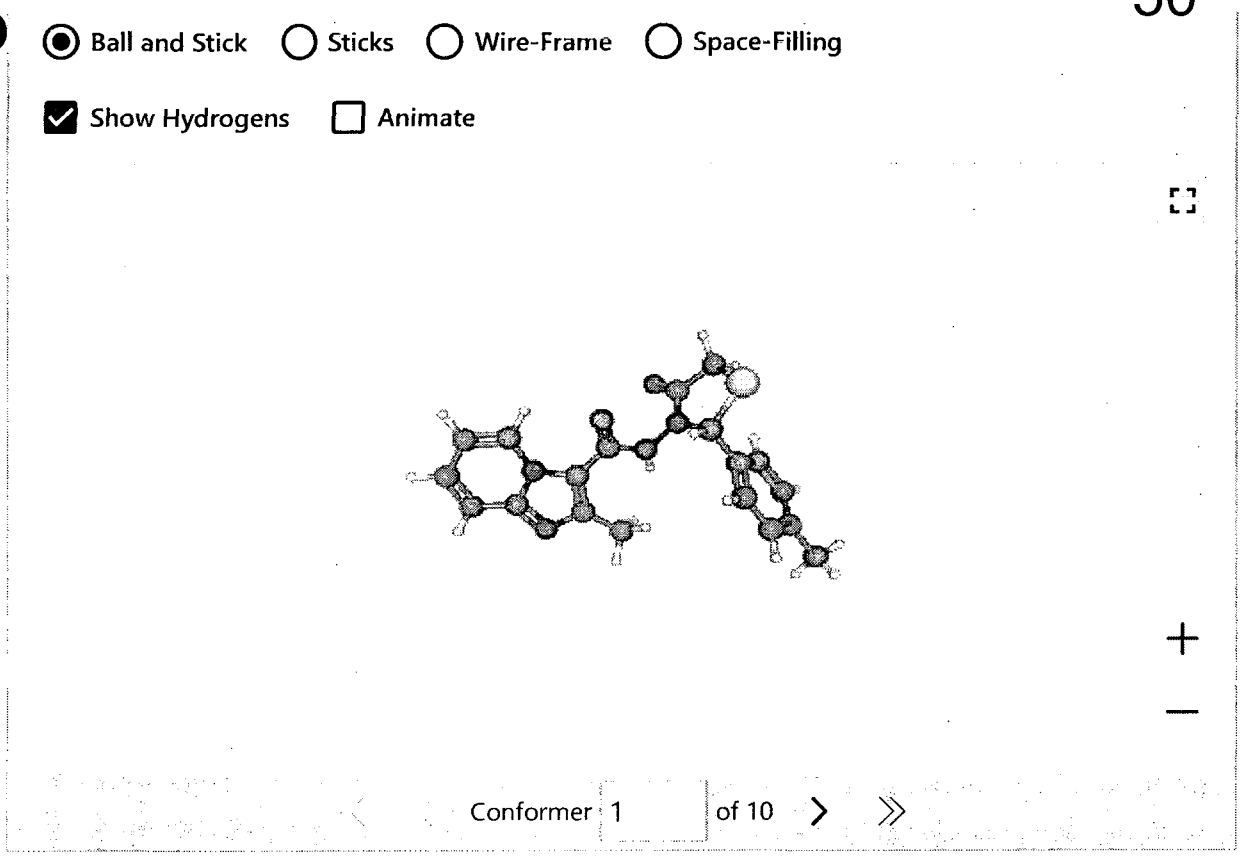
Chemical Structure Depiction



PubChem

1.2 3D Conformer

Interactive Chemical Structure Model



▸ PubChem

2 Names and Identifiers

2.1 Computed Descriptors

2.1.1 IUPAC Name

2-methyl-*N*-[2-(4-methylphenyl)-4-oxo-1,3-thiazolidin-3-yl]imidazo[1,2-a]pyridine-3-carboxamide

Computed by Lexichem TK 2.7.0 (PubChem release 2021.05.07)

▸ PubChem

2.1.2 InChI

InChI=1S/C19H18N4O2S/c1-12-6-8-14(9-7-12)19-23(16(24)11-26-19)21-18(25)17-13(2)20-15-5-3-4-10-22(15)17/h3-10,19H,11H2,1-2H3,(H,21,25)

Computed by InChI 1.0.6 (PubChem release 2021.05.07)

▸ PubChem

2.1.3 InChIKey

LRFROTYNYXFHLO-UHFFFAOYSA-N

Computed by InChI 1.0.6 (PubChem release 2021.05.07)

▸ PubChem

2.1.4 Canonical SMILES

CC1=CC=C(C=C1)C2N(C(=O)CS2)NC(=O)C3=C(N=C4N3C=CC=C4)C

Computed by OEChem 2.3.0 (PubChem release 2021.05.07)

▸ PubChem

2.2 Molecular Formula

$C_{19}H_{18}N_4O_2S$

Computed by PubChem 2.1 (PubChem release 2021.05.07)

▸ PubChem

2.3 Other Identifiers

2.3.1 Nikkaji Number

J582.976C

▸ Japan Chemical Substance Dictionary (Nikkaji)

2.4 Synonyms

2.4.1 Depositor-Supplied Synonyms

2-Methyl-N-[2-(4-methylphenyl)-4-oxo-3-thiazolidinyl]imidazo[1,2-a]pyridine-3-carboxamide

PubChem

3 Chemical and Physical Properties

3.1 Computed Properties

Property Name
Molecular Weight

Property Value
366.4 g/mol

Reference
Computed by PubChem 2.1 (PubChem release 2021.05.07)

Property Name
XLogP3-AA

Property Value
3.9

Reference
Computed by XLogP3 3.0 (PubChem release 2021.05.07)

Property Name
Hydrogen Bond Donor Count

Property Value
1

Reference
Computed by Cactvs 3.4.8.18 (PubChem release 2021.05.07)

Property Name
Hydrogen Bond Acceptor Count

Property Value
4

Reference
Computed by Cactvs 3.4.8.18 (PubChem release 2021.05.07)

Property Name
Rotatable Bond Count

Property Value
2

Reference

53

Computed by Cactvs 3.4.8.18 (PubChem release 2021.05.07)

Property Name
Exact Mass

Property Value
366.11504700 g/mol

Reference
Computed by PubChem 2.1 (PubChem release 2021.05.07)

Property Name
Monoisotopic Mass

Property Value
366.11504700 g/mol

Reference
Computed by PubChem 2.1 (PubChem release 2021.05.07)

Property Name
Topological Polar Surface Area

Property Value
92Å²

Reference
Computed by Cactvs 3.4.8.18 (PubChem release 2021.05.07)

Property Name
Heavy Atom Count

Property Value
26

Reference
Computed by PubChem

Property Name
Formal Charge

Property Value
0

Reference
Computed by PubChem

Property Name
Complexity

Property Value
552

54

Reference
Computed by Cactvs 3.4.8.18 (PubChem release 2021.05.07)

Property Name
Isotope Atom Count

Property Value
0

Reference
Computed by PubChem

Property Name
Defined Atom Stereocenter Count

Property Value
0

Reference
Computed by PubChem

Property Name
Undefined Atom Stereocenter Count

Property Value
1

Reference
Computed by PubChem

Property Name
Defined Bond Stereocenter Count

Property Value
0

Reference
Computed by PubChem

Property Name
Undefined Bond Stereocenter Count

Property Value
0

Reference
Computed by PubChem

Property Name
Covalently-Bonded Unit Count

Property Value

1

Reference

Computed by PubChem

Property Name

Compound Is Canonicalized

Property Value

Yes

Reference

Computed by PubChem (release 2019.01.04)

▸ PubChem

4 Related Records

4.1 Related Compounds with Annotation

UPDATING...

▸ PubChem

4.2 Related Compounds

Similar Conformers Count

39

▸ PubChem

4.3 Substances

4.3.1 Related Substances

Same Count
5

▸ PubChem

4.3.2 Substances by Category

UPDATING...

▸ PubChem

5 Information Sources

FILTER BY SOURCE

ALL SOURCES

1. Japan Chemical Substance Dictionary (Nikkaji)

http://jglobal.jst.go.jp/en/redirect?Nikkaji_No=J582.976C

2. PubChem

https://pubchem.ncbi.nlm.nih.gov

Art J-GLOBAL ID : 200902168049479921 Reference number : 94A0443523

Synthesis and Antifungal Activity of Some 2-Aryl-3-substituted 4-Thiazolidinones.

2-アリール-3-置換-4-チアゾリジノン類の合成および抗真菌作用

Author (7) : CESUR N (Univ. Istanbul, Istanbul, TUR) , CESUR Z (Univ. Istanbul, Istanbul, TUR) , ERGENC N (Univ. Istanbul, Istanbul, TUR) , UZUN M (Univ. Istanbul, Istanbul, TUR) , KIRAZ M (Univ. Istanbul, Istanbul, TUR) , KASIMOGLU O (Univ. Istanbul, Istanbul, TUR) , KAYA D (Univ. Istanbul, Istanbul, TUR)

Material : Archiv der Pharmazie (Arch Pharm)

Volume : 327 **Issue :** 4 **Page :** 271-272 **Publication year :** Apr. 1994

JST Material Number : A0451A **ISSN :** 0365-6233 **CODEN :** ARPMAS **Document type :** Article

Article type : 短報 **Country of issue :** United States (USA) **Language :** ENGLISH (EN)

Thesaurus term : hydrazone ,...

Semi thesaurus term : thiazolidines

To see more with JDream III (charged).

JST classification (2) : Basic research of antifungal drugs (GW17060K) , Structure-activity relationship of drugs (GV01050B)

Substance index (14) : 2-Methyl-N'-benzylideneimidazo[1,2-a]pyridine-3-carbohydrazide , 2-Methyl-N'-(4-chlorobenzylidene)imidazo[1,2-a]pyridine-3-carbohydrazide , 2-Methyl-N'-(4-fluorobenzylidene)imidazo[1,2-a]pyridine-3-carbohydrazide , 2-Methyl-N'-(2-nitrobenzylidene)imidazo[1,2-a]pyridine-3-carbohydrazide , 2-Methyl-N'-(4-methylbenzylidene)imidazo[1,2-a]pyridine-3-carbohydrazide , 2-Methyl-N'-(3-methoxy-4-hydroxybenzylidene)imidazo[1,2-a]pyridine-3-carbohydrazide , 2-Methyl-N-[2-(4-chlorophenyl)-4-oxo-3-thiazolidinyl]imidazo[1,2-a]pyridine-3-carboxamide , 2-Methyl-N-[2-(4-fluorophenyl)-4-oxo-3-thiazolidinyl]imidazo[1,2-a]pyridine-3-carboxamide , 2-Methyl-N-[2-(2-nitrophenyl)-4-oxo-3-thiazolidinyl]imidazo[1,2-a]pyridine-3-carboxamide , 2-Methyl-N-[2-(4-methylphenyl)-4-oxo-3-thiazolidinyl]imidazo[1,2-a]pyridine-3-carboxamide , 2-Methyl-N-[2-(3-methoxy-4-hydroxyphenyl)-4-oxo-3-thiazolidinyl]imidazo[1,2-a]pyridine-3-carboxamide , 2-Methyl-N-[2-(3-ethoxy-4-hydroxyphenyl)-4-oxo-3-thiazolidinyl]imidazo[1,2-a]pyridine-3-carboxamide , 2-Methyl-N'-[(1,3-benzodioxol-5-yl)methylene]imidazo[1,2-a]pyridine-3-carbohydrazide , 2-Methyl-N-[2-(1,3-benzodioxol-5-yl)-4-oxo-3-thiazolidinyl]imidazo[1,2-a]pyridine-3-carboxamide

Terms in the title (2) : 置換 , 抗真菌作用

Return to Previous Page

BOTTOM

BOTTOM

Exhibit 6

Molecules **2004**, *9*, 894-901

molecules

ISSN 1420-3049
http://www.mdpi.org

Fused Heterocycles: Synthesis of Some New Imidazo[1,2-*a*]-pyridine Derivatives

Birgul Ozden Kasimogullari* and Zafer Cesur

Istanbul University, Faculty of Pharmacy, Department of Pharmaceutical Chemistry, 30416, Istanbul, Turkey .Tel. (+90) 212-440-0265, Fax: (+90) 212-440-0252.

* Author to whom correspondence should be addressed; e-mail: okasimogullari@yahoo.com

Received: 4 August 2004 / Accepted: 13 September 2004 / Published: 30 September 2004

Abstract: 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, ^{1}H- and ^{13}C-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).

Keywords: Imidazo[1,2-*a*]pyridine, hydrazones, thiazolidines, spirothiazolidines, antituberculous activity.

Introduction

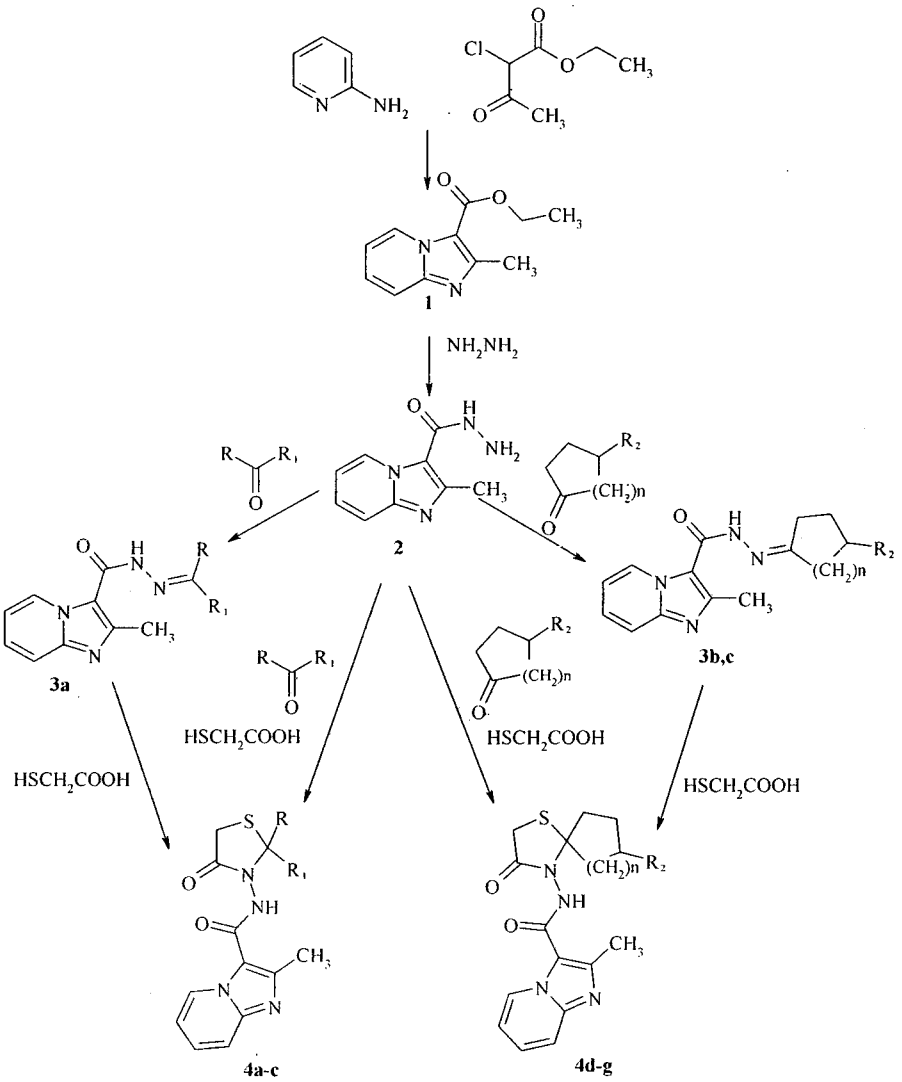
Mycobacterium tuberculosis infects over one-third of the world's population and causes almost three million deaths every year [1]. Isonicotinic acid hydrazide (isonazid) is one of the primary drugs used in combination with ethambutol, rifampin, streptomycin and pyrazinamide to treat tuberculosis, but the treatment of this disease is still a major health problem due to multi-drug resistant bacterial strains and new antimycobacterial agents, different from available first-line drugs, are urgently needed. As part of our studies on imidazo[1,2-*a*]pyridine we have recently reported the synthesis of some imidazo[1,2-*a*]pyridine-3-carboxylic acid hydrazides and related compounds and their antimycobacterial activities [2]. Continuing our search for new antimycobacterial agents we have now

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



Condensation of **2** with the appropriate ketones in ethanol yielded the corresponding ketone-hydrazones **3**. The hydrazones were reacted with mercaptoacetic acid in dry benzene (Method A) to give cyclocondensation products **4b,d** and **e** in 69.8-72.3 % yields. On the other hand, refluxing a mixture of **2** and the appropriate ketone together with mercaptoacetic acid in dry benzene (Method B) also produced the target compounds **4** but in higher yields (69.7-99.1 %), except in the case of **4b** (55.5 %). All the compounds were characterized by their physical data and elemental analyses (Table 1), IR, ^{1}H- and ^{13}C-NMR and EI mass spectra.

Table 1. Some physical and analytical data of compounds **3** and **4**

Comp.	R	R_1	R_2	n	M.p. (°C)	Yield %	Formula (molecular weigh)	Analysis (calcd./found)(%)		
								C	H	N
3a	CH_3	C_2H_5	-	-	120-5	75.8	$C_{13}H_{16}N_4O$	63.91	6.60	22.94
							(244.30)	63.81	6.96	22.55
3b	-	-	-	1	162-6	62.1	$C_{14}H_{16}N_4O.1.5H_2O$	59.35	6.76	19.78
							(283.61)	60.84	6.96	19.70
3c	-	-	-	2	76-8	63.8	$C_{15}H_{18}N_4O.2H_2O$	58.81	7.24	18.29
							(306.33)	58.94	7.56	18.21
4a	CH_3	CH_3	-	-	222-5	87.3	$C_{14}H_{16}N_4O_2S.H_2O$	52.16	5.63	17.38
						(Method B)	(322.38)	52.70	6.04	17.30
4b	CH_3	C_2H_5	-	-	138-43	69.8	$C_{15}H_{18}N_4O_2S.H_2O$	53.56	5.99	16.65
						(Method A)	(336.39)	53.45	6.10	16.83
						55.5				
						(Method B)				
4d	-	-	-	1	137-43	75.5	$C_{16}H_{18}N_4O_2S.H_2O$	55.15	5.79	16.08
						(Method A)	(348.42)	55.10	5.82	15.92
						80.0				
						(Method B)				
4e	-	-	-	2	258-65	77.3	$C_{17}H_{20}N_4O_2S$	59.28	5.85	16.27
						(Method A)	(344.43)	58.97	5.77	16.10
						99.1				
						(Method B)				
4f	-	-	CH_3	2	154-6	72.3	$C_{18}H_{22}N_4O_2S.0.5H_2O$	58.85	6.31	15.26
						(Method B)	(367.46)	58.64	7.26	15.42
4g	-	-	C_2H_5	2	142-6	81.7	$C_{19}H_{24}N_4O_2S.2H_2O$	55.86	6.91	13.71
						(Method B)	(408.52)	55.44	6.56	12.09

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-methyimidazo[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^+, 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^+, 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^+, 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 (thiazolidinc 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 (imidazopyridine 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).

References

1. Montoya, M. E.; Sainz, Y.; Ortega, M. A.; De Cerain, A. L. Monge, A. Synthesis and antituberculosis activity of some new 2-quinoxalinecarbonitriles. *Farmaco* **1998**, *53*, 570-573.
2. Cesur, N.; Cesur, Z. Some imidazo[1,2-*a*]pyridine derivatives as possible antimycobacterials. *J Fac. Pharm. Istanbul* **1998**, *32*, 29-35.
3. Lombardino, G.J. Preparation and New Reactions Imidazo[1,2-*a*]pyridines. *J. Org. Chem.* **1965**, *30*, 2403-2407.
4. Oa, H.; Obato, M.; Yamanaka, T.; Mikashima, H. Oxadiazinylimidazopyridines, -pyrimidines and thiazoles. PCT. Int. Appl. WO8607,059, 04 Dec 1986 ; [Chem. Abstr. **1987,** *106*, 176381w].
5. Inderleid, C.B. *Antibiotics in Laboratory Medicine, 3rd ed.*; V Lorian (ed.); William and Wilkins: Baltimore, **1991**; pp. 134-197.
6. Silverstein, R.M.; Bassler, G.C.; Morril, T.C. *Spectrometric Identification of Organic Compounds,. 4th ed.* ; John Wiley and Sons: New York, **1981**; p. 119.
7. Ur, F.; Cesur, N.; Birteksoz, S.; Otuk, G. Synthesis new 6-methylimidazo[2,1-*b*]thiazole-5-carbohydrazide derivatives and their antimicrobial activities. *Arzneim.-Forsch/Drug Res.* **2004**, *54*, 125-129.

Samples Availability: Available from the authors.

molecules

MDPI

Review

Synthesis and Pharmacological Activities of Pyrazole Derivatives: A Review

Khalid Karrouchi [1,2,3], Smaail Radi [2,*], Youssef Ramli [1], Jamal Taoufik [1], Yahia N. Mabkhot [4,*], Faiz A. Al-aizari [4] and M'hammed Ansar [1]

1 Medicinal Chemistry Laboratory, Faculty of Medicine and Pharmacy, Mohammed V University, 10100 Rabat, Morocco; Khalid.karrouchi@um5s.net.ma (K.K.); yramli76@yahoo.fr (Y.R.); jataoufik@hotmail.com (J.T.); ansarmhammed@gmail.com (M.A.)

2 LCAE, Department of Chemistry, Faculty of Sciences, University Mohamed I, 60000 Oujda, Morocco

3 Physicochemical Service, Drugs Quality Control Laboratory, Division of Drugs and Pharmacy, Ministry of Health, 10100 Rabat, Morocco

4 Department of Chemistry, Faculty of Science, King Saud University, P.O. Box 2455, Riyadh 11451, Saudi Arabia; faizalaizari@yahoo.com

* Correspondence: s.radi@ump.ac.ma or radi_smaail@yahoo.fr (S.R.); yahia@ksu.edu.sa (Y.N.M.); Tel.: +212-536-500-601 (S.R.)

Received: 22 November 2017; Accepted: 5 January 2018; Published: 12 January 2018

Abstract: Pyrazole and its derivatives are considered a pharmacologically important active scaffold that possesses almost all types of pharmacological activities. The presence of this nucleus in pharmacological agents of diverse therapeutic categories such as celecoxib, a potent anti-inflammatory, the antipsychotic CDPPB, the anti-obesity drug rimonabant, difenamizole, an analgesic, betazole, a H2-receptor agonist and the antidepressant agent fezolamide have proved the pharmacological potential of the pyrazole moiety. Owing to this diversity in the biological field, this nucleus has attracted the attention of many researchers to study its skeleton chemically and biologically. This review highlights the different synthesis methods and the pharmacological properties of pyrazole derivatives. Studies on the synthesis and biological activity of pyrazole derivatives developed by many scientists around the globe are reported.

Keywords: pyrazole derivatives; synthesis; biological activities

1. Introduction

Pyrazoles are five-membered heterocycles that constitute a class of compounds particularly useful in organic synthesis. They are one of the most studied groups of compounds among the azole family. Indeed, a huge variety of synthesis methods and synthetic analogues have been reported over the years.

The presence of the pyrazole nucleus in different structures leads to diversified applications in different areas such as technology, medicine and agriculture. In particular, they are described as inhibitors of protein glycation, antibacterial, antifungal, anticancer, antidepressant, antiinflammatory, anti-tuberculosis, antioxidant as well as antiviral agents [1,2].

Nowadays, pyrazole systems, as biomolecules, have attracted more attention due to their interesting pharmacological properties. This heterocycle can be traced in a number of well-established drugs belonging to different categories with diverse therapeutic activities (Figure 1) [3–10].

In this review, we present descriptions and discussions on the most relevant synthesis methods and pharmacological properties of pyrazole-derived heterocyclic systems.

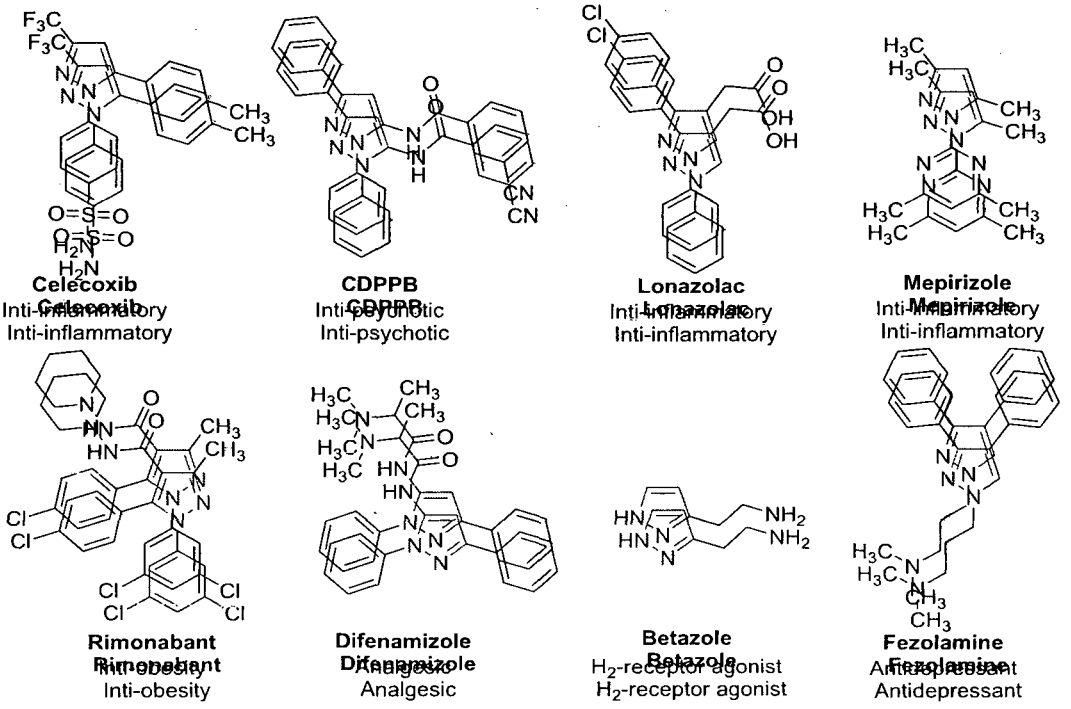


Figure 1. Pharmaceutical drugs containing pyrazole unit.
Figure 1. Pharmaceutical drugs containing pyrazole unit.
Figure 1. Pharmaceutical drugs containing pyrazole unit.

2. The Main Methods of Access to the Pyrazole Nucleus
2. The Main Methods of Access to the Pyrazole Nucleus
2. The Main Methods of Access to the Pyrazole Nucleus

Pyrazole is a π-excess aromatic heterocycle. Electrophilic substitution reactions occur preferentially at position 4 and nucleophilic attacks at positions 3 and 5 (Figure 2).
Pyrazole is a π-excess aromatic heterocycle. Electrophilic substitution reactions occur preferentially at position 4 and nucleophilic attacks at positions 3 and 5 (Figure 2).
Pyrazole is a π-excess aromatic heterocycle. Electrophilic substitution reactions occur preferentially at position 4 and nucleophilic attacks at positions 3 and 5 (Figure 2).

Figure 2. Structure of pyrazole.
Figure 2. Structure of pyrazole.
Figure 2. Structure of pyrazole.

The pyrazoles diversely substituted by aromatic and heteroaromatic groups possess numerous biological activities, which makes them particularly interesting. The various access routes to the pyrazole nucleus have undergone numerous modifications since the first syntheses described by Knorr [1,2]. In this section, we will study this evolution and present the methods generally used to access substituted pyrazoles, that is to say:
The pyrazoles diversely substituted by aromatic and heteroaromatic groups possess numerous biological activities, which makes them particularly interesting. The various access routes to the pyrazole nucleus have undergone numerous modifications since the first syntheses described by Knorr [1,2]. In this section, we will study this evolution and present the methods generally used to access substituted pyrazoles, that is to say:
The pyrazoles diversely substituted by aromatic and heteroaromatic groups possess numerous biological activities, which makes them particularly interesting. The various access routes to the pyrazole nucleus have undergone numerous modifications since the first syntheses described by Knorr [1,2]. In this section, we will study this evolution and present the methods generally used to access substituted pyrazoles, that is to say:

- Cyclocondensation of hydrazine and similar derivatives with carbonyl systems.
- Dipolar cycloadditions.
- Multicomponent reactions.

- Cyclocondensation of hydrazine and similar derivatives with carbonyl systems.
- Dipolar cycloadditions.
- Multicomponent reactions.
- Cyclocondensation of hydrazine and similar derivatives with carbonyl systems.
- Dipolar cycloadditions.
- Multicomponent reactions.

2.1. Cyclocondensation of Hydrazine and Its Derivatives on 1,3-Difunctional Systems
2.1. Cyclocondensation of Hydrazine and Its Derivatives on 1,3-Difunctional Systems
2.1. Cyclocondensation of Hydrazine and Its Derivatives on 1,3-Difunctional Systems

The leading method used for obtaining substituted pyrazoles is a cyclocondensation reaction between an appropriate hydrazine acting as a bidentate nucleophile and a carbon unit like a 1,3-dicarbonyl compound, a 1,3-dicarbonyl derivatives or an α,β-unsaturated ketone (Figure 3).
The leading method used for obtaining substituted pyrazoles is a cyclocondensation reaction between an appropriate hydrazine acting as a bidentate nucleophile and a carbon unit like a 1,3-dicarbonyl compound, a 1,3-dicarbonyl derivatives or an α,β-unsaturated ketone (Figure 3).
The leading method used for obtaining substituted pyrazoles is a cyclocondensation reaction between an appropriate hydrazine acting as a bidentate nucleophile and a carbon unit like a 1,3-dicarbonyl compound, a 1,3-dicarbonyl derivatives or an α,β-unsaturated ketone (Figure 3).

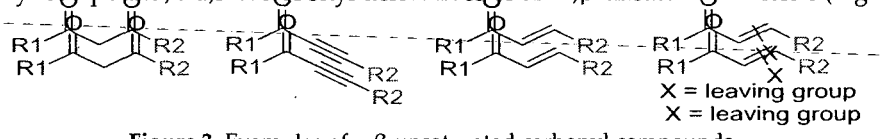


Figure 3. Examples of α,β-unsaturated carbonyl compounds.
Figure 3. Examples of α,β-unsaturated carbonyl compounds.

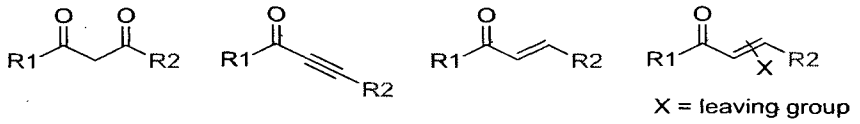
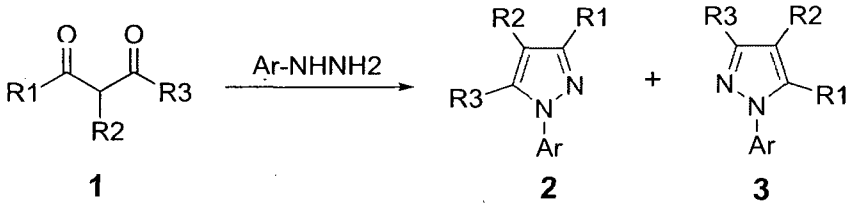


Figure 3. Examples of α,β-unsaturated carbonyl compounds.

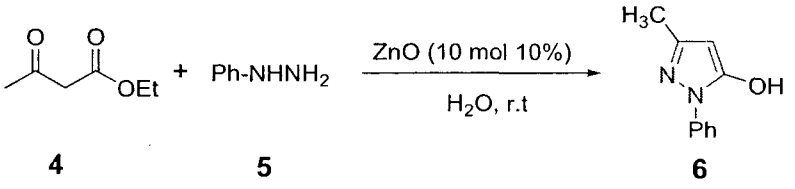
2.1.1. From 1,3-Diketones

The cyclocondensation of the 1,3-dicarbonyl compounds with the hydrazine derivatives is a simple and rapid approach to obtain polysubstituted pyrazoles. The first synthesis of the substituted pyrazoles was carried out in 1883 by Knorr et al. [11] who reacted β-diketone **1** with hydrazine derivatives to give two regioisomers **2** and **3** (Scheme 1).



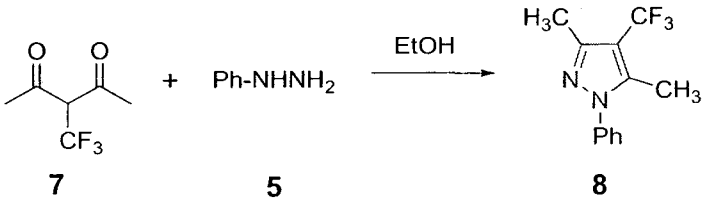
Scheme 1. Synthesis of polysubstituted pyrazoles form 1,3-dicarbonyl compounds.

Girish et al. [12] described an efficient nano-ZnO catalyzed green protocol for the synthesis of 1,3,5-substituted pyrazoles derivatives **6** by condensation of phenylhydrazine **5** with ethyl acetoacetate (**4**) (Scheme 2). The main advantage of this protocol is the excellent yield (95%) achieved, short reaction time and easy work-up procedure.



Scheme 2. Synthesis of 1,3,5-substituted pyrazoles from ethyl acetoacetate.

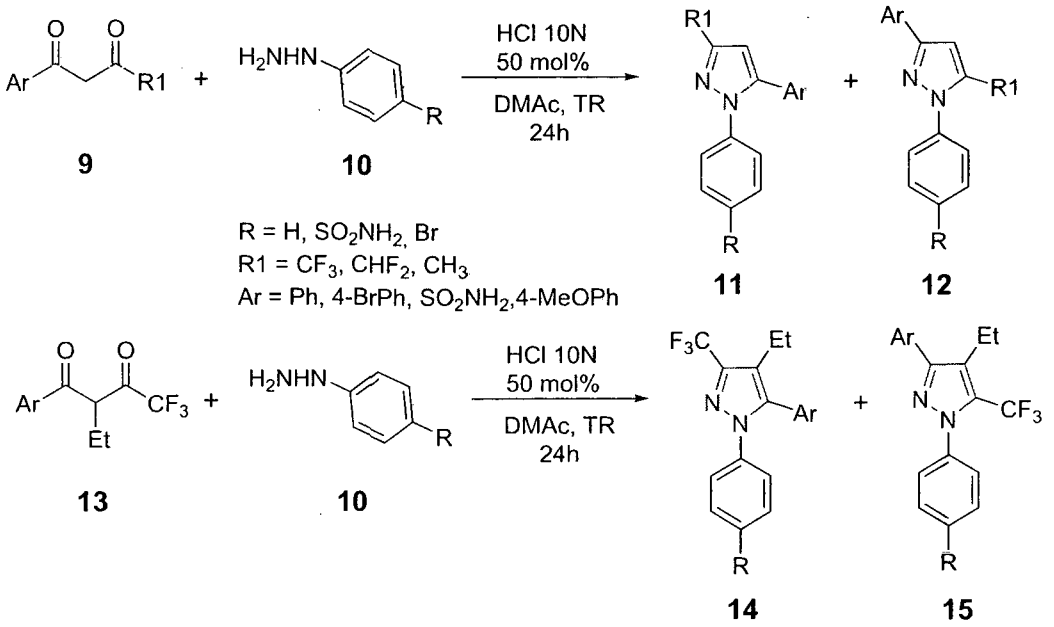
Similarly, Ohtsuka et al. [13] studied the condensation of phenylhydrazine **5** with the 2-(trifluoromethyl)-1,3-diketone **7** in ethanol, affording 1,3,4,5-substituted pyrazole **8** in good yield (63%). Compound **8** was exclusively formed presumably owing to the fact that the sterically small NH_2 is more nucleophilic than NHPh (Scheme 3).



Scheme 3. Synthesis of 1,3,4,5-substituted pyrazoles from 2-(trifluoromethyl)-1,3-diketone.

Gosselin and co-workers have proposed new reaction conditions for the regioselective synthesis of 1,3-substituted 1-arylpyrazoles from 1,3-dicarbonyl compounds. Indeed, the authors have found

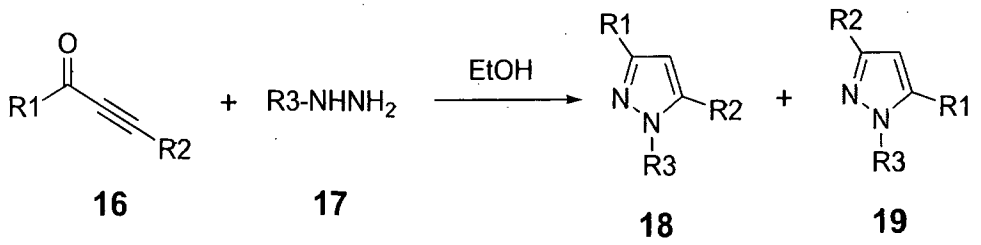
that the cyclocondensation of an aryl hydrochloride hydrazine with 1,3-diketones in aprotic dipolar solvents gives better results than in the polar protic solvents (like ethanol) generally used for this type of reaction. After optimization of the conditions, the addition of a solution of HCl 10 N to the amide solvent (DMF, NMP, DMAc) or urea (DMPU, TMU) makes it possible to increase the yields by accelerating the dehydration steps. The cyclocondensation of the diketones with hydrazine thus takes place at ambient temperature in *N*,*N*-dimethylacetamide, in an acid medium, to give the corresponding pyrazoles with good yields and good regioselectivity. The condensation of various arylhydrazine with 4,4,4-trifluoro-1-arylbutan-1,3-diketones **9**, afforded two isomers **11**, **12** with 74–77% yields. The selectivity obtained is of the order of 98:2 in favor of the isomer **11**. By comparison, the reactions carried out under conventional conditions in ethanol, at ambient temperature, give equimolar mixtures of the regioisomers. Nevertheless, a loss of control of the regioselectivity is observed when the CF_3 group is replaced by a CH_3 or CHF_2. Finally, the condensations of aryl hydrazines with the 1,3-diketones **13** that are 2-substituted by an alkyl group give the trisubstituted pyrazoles **14** and **15** in 79–89% yields and a regioselectivity greater than 99.8:0.2 in favor of isomer **15** in all cases (Scheme 4) [14].



Scheme 4. Synthesis of pyrazoles from 1,3-diketones and arylhydrazines.

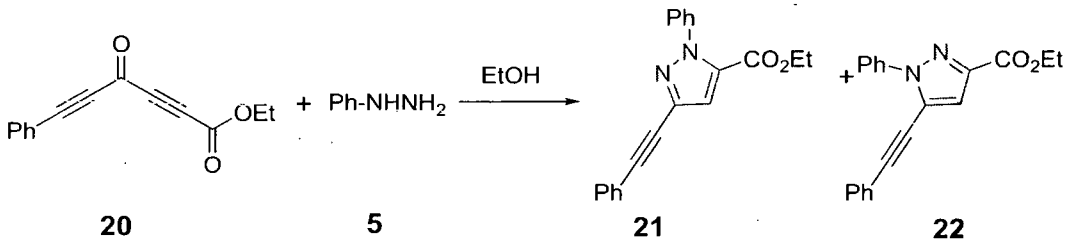
2.1.2. From Acetylenic Ketones

The cyclocondensation reaction of hydrazine derivatives **17** on acetylenic ketones **16** to form pyrazoles has been known for more than 100 years [15]. However, the reaction again results in a mixture of two regioisomers **18** and **19** (Scheme 5).



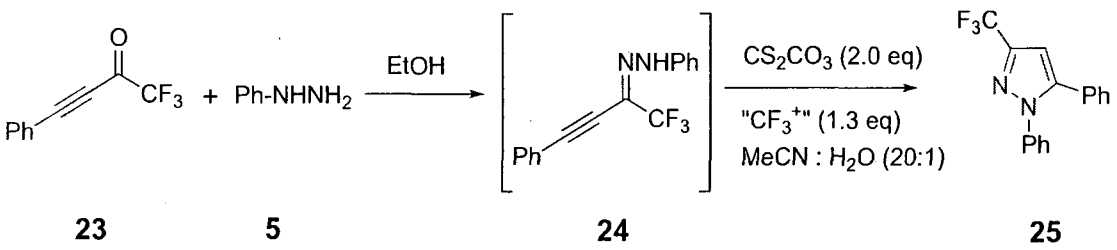
Scheme 5. Synthesis of pyrazoles from acetylenic ketones.

The diacetylene ketones **20** reacted with phenylhydrazine **5** in ethanol to give two regioisomeric pyrazoles **21** and **22**. When phenylhydrazine was used, a mixture of regio-isomers **21**/**22** was generated in approximately 3:2 ratio. When hydrazine hydrate was used as the nucleophile, only regioisomer **21** was isolated, presumably due to hydrogen bonding to the ethyl ester group (Scheme 6) [16].



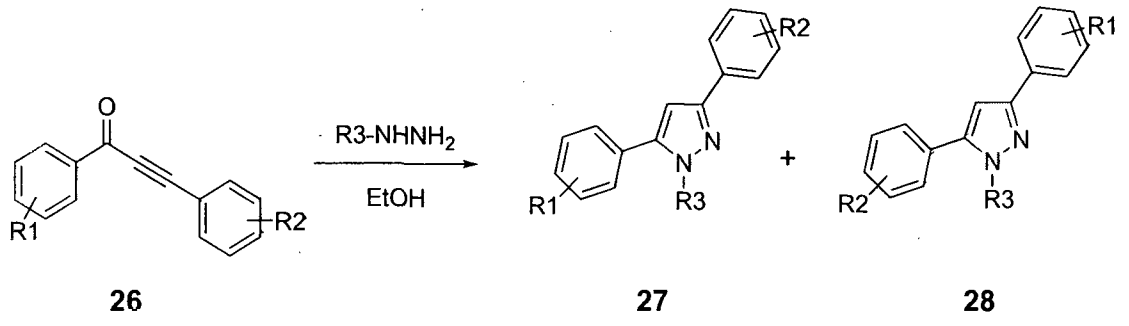
Scheme 6. Synthesis of pyrazoles from diacetylene ketones.

Guojing et al. reported a new efficient method for the synthesis of 3-trifluoromethylpyrazoles **25** with good yields via trifluoromethylation/cyclization of acetylenic ketones **25** on phenylhydrazine **5** using a hypervalent iodine reagent under transition-metal-free conditions. The optimal conditions were obtained when the ratio **24**/Togni reagent was maintained at 1:1.3, giving **25** in 70% isolated yield (Scheme 7) [17].



Scheme 7. Synthesis of 3-trifluoromethylpyrazoles via cyclization of acetylenic ketones.

Bishop et al. were interested in the factors determining the regioselectivity of this type of reaction in the framework of the synthesis of 3,5-diarylpyrazoles. They studied the cyclocondensation of acetylenic ketones **26** on methylhydrazine or aryl hydrazines in ethanol, which provides two difficultly separable regioisomeric pyrazoles **27** and **28** (Scheme 8) [18].



26 **27** **28**

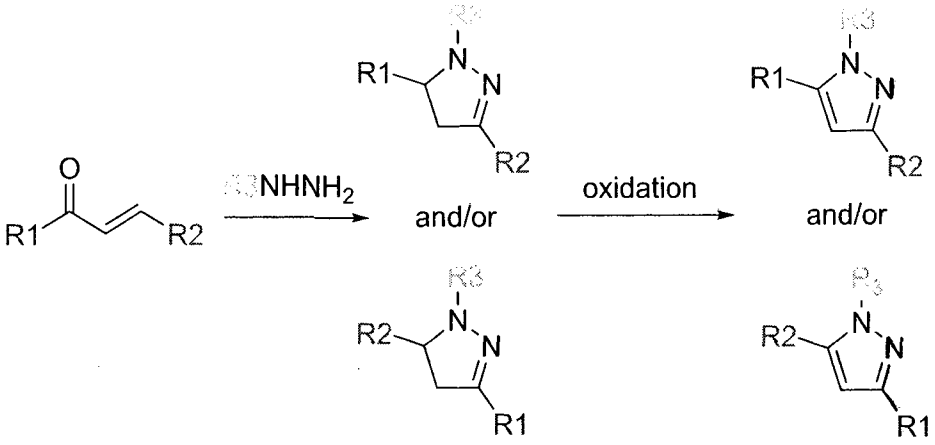
R1 or R2 = H, NO_2, Cl, OMe, F
R1 = Ph, 4-$MeOC_6H_4$, 4-$NO_2C_6H_4$, 2,4-$(NO_2)_2C_6H_3$, Me

Scheme 8. Synthesis of 3,5-diarylpyrazoles from acetylenic ketones and hydrazines derivatives.

The difference in regioselectivity observed when using methylhydrazine (ratio **27**/**28** = 93:3 to 97:3) or an arylic hydrazine (ratio **28**/**27** = 87:13 to 99:1) is explained by the fact that the nitrogen carrying a methyl group is much more nucleophilic and will react by Michael addition on the triple bond of the acetylenic ketone followed by the intramolecular formation of an imine. In the case of a hydrazine substituted by an aryl group, the primary amine is the most nucleophilic and will react on the triple bond followed by the attack of the secondary amine on the carbonyl.

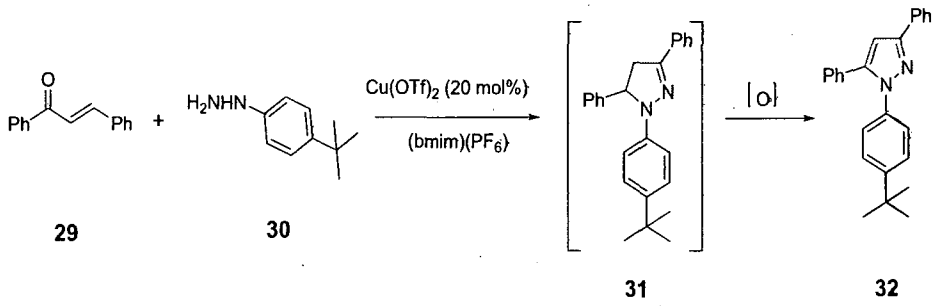
2.1.3. From Vinyl Ketones

The cyclocondensation reaction between an α,β-ethylenic ketone and a hydrazine derivative results in the synthesis of pyrazolines which, after oxidation, provide the pyrazole ring (Scheme 9).



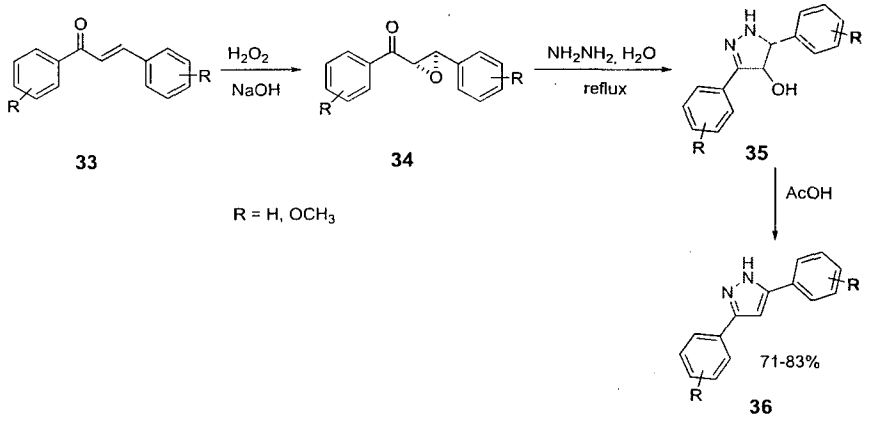
Scheme 9. Synthesis of pyrazoles by cyclocondensation reaction of α,β-ethylenic ketone.

Rao et al. described the condensation of an α,β-ethylenic ketone **29** with *p*-(4-(*tert*-butyl)phenyl) hydrazine **30** in the presence of copper triflate and 1-butyl-3-methylimidazolium hexafluorophosphate [bmim] (PF6) as catalysts, to access pyrazoline **31**. The corresponding 1,3,5-trisubstituted pyrazole **32** was obtained after oxidation in situ of this pyrazoline. The reaction protocol gave 1,3,5-triarylpyrazoles in good yields (about 82%) via a one-pot addition–cyclocondensation between chalcones and arylhydrazines, and oxidative aromatization stands without the requirement of an additional oxidizing reagent. The catalyst can be reused more than four cycles without much loss in the catalytic activity (Scheme 10) [19].



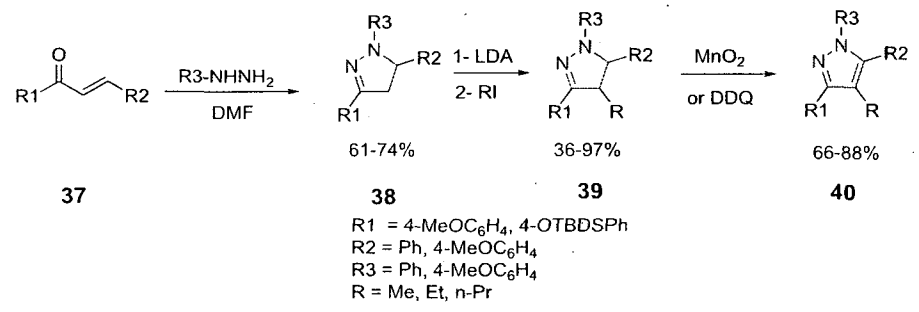
Scheme 10. Synthesis of pyrazoles from α,β-ethylenic ketone.

On the other hand, Bhat et al. described a method for the synthesis of 3,5-diaryl-1*H*-pyrazoles from the reaction β-arylchalcones **33** with hydrogen peroxide that gave epoxides **34**. Then, addition of hydrazine hydrate afforded pyrazoline intermediates **35**, dehydration of which yielded desired 3,5-diaryl-1*H*-pyrazoles **36** (Scheme 11) [20].



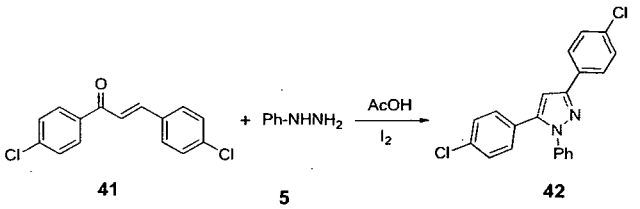
Scheme 11. Synthesis of 3,5-diaryl-*1H*-pyrazoles from β-arylchalcones.

Huang et al. developed a new regioselective synthesis of 4-alkyl-1,3,5-triarylpyrazoles for the preparation of unsymmetrically substituted systems of interest as ligands for the estrogen receptor. The condensation of hydrazines with α,β-ethylenic ketones **37** in DMF gave pyrazolines **38**. However, the corresponding pyrazole derivatives **40** were obtained in good yield (66–88%) by alkylation of the pyrazolines **38** in the presence of LDA, before undergoing the oxidation reaction (Scheme 12) [21].



Scheme 12. Synthesis of 4-alkyl-1,3,5-triarylpyrazoles from α,β-ethylenic ketones.

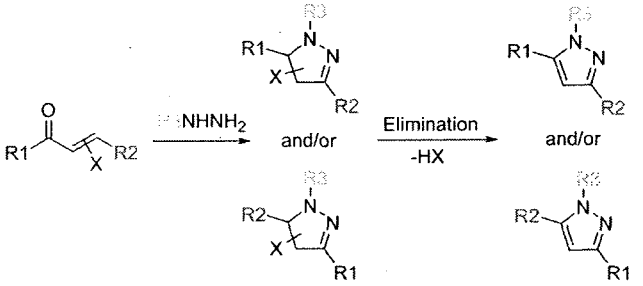
Similarly, a method for the synthesis of 1,3,5-trisubstituted pyrazoles from an α,β-ethylenic ketone was described. Cyclocondensation of the α,β-ethylenic ketone **41** with phenylhydrazine (1.2 eq.) **5** in acetic acid and in the presence of iodine (1.0 eq.) afforted the corresponding pyrazole **42** in good yield (70%) (Scheme 13) [22].



Scheme 13. Synthesis of pyrazoles by cyclocondensation reaction of the α,β-ethylenic ketone.

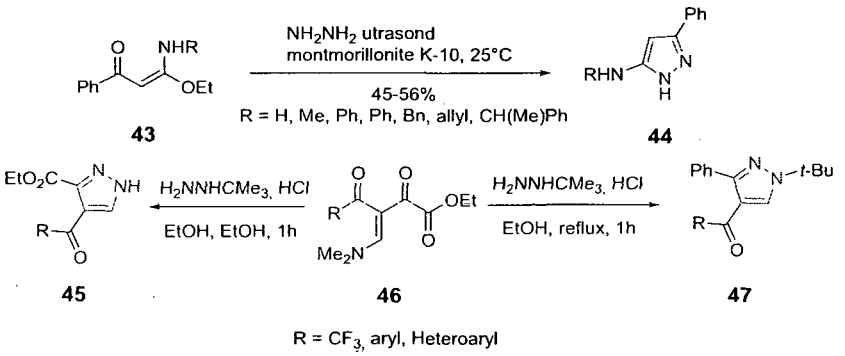
2.1.4. From Vinyl Ketones Having a Leaving Group

The α,β-ethylenic ketones having a leaving group may react with hydrazine derivatives to form pyrazolines which, after removal of the leaving group, provide the desired pyrazoles (Scheme 14).



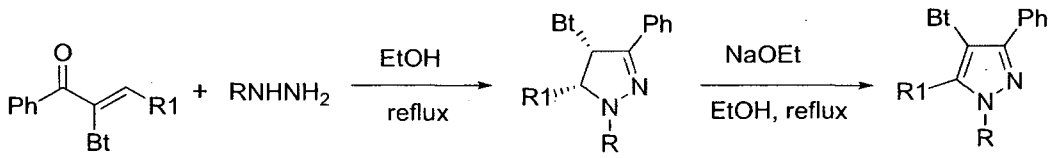
Scheme 14. Synthesis of pyrazoles via cyclocondensation of α,β-ethylenic ketones having a leaving group.

5-Amino-3-phenylpyrazoles **44** were prepared from α-oxoketene *O*,*N*-acetals **43** using montmorillonite K-10 under sonication conditions [23]. The cyclocondensation of non-symmetrical enaminodicketones **46** on various hydrazine derivatives has been studied in the case of *tert*-butylhydrazine and carboxymethylhydrazine. The various pyrazoles **45** and **47** are obtained regiospecifically and in good yields (74–94%). It should be noted that in the case of carboxymethylhydrazine, the reaction leads directly to the corresponding NH-pyrazoles [24] (Scheme 15).



Scheme 15. Synthesis of pyrazoles from α-oxoketene *O*,*N*-acetals and enaminodicketones.

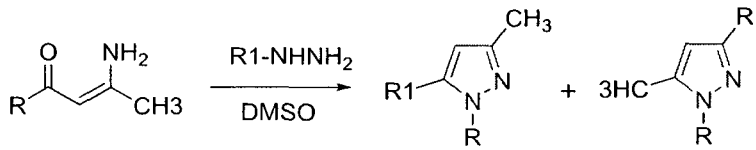
Katritzky et al. [25] described the synthesis of 1-methyl(aryl)-3-phenyl-5-alkyl(aryl)pyrazoles **50** by a regioselective condensation reaction of α-benzotriazolylenones **48** with methyl and phenylhydrazines. The intermediate pyrazolines **49** are then treated in a basic medium to give the expected pyrazoles in 50–94% yields after removal of benzotriazole. The advantage of using the benzotriazole group lies in the fact that the proton in the α-position is made more acidic and thus permits functionalization in the 4-position of the pyrazoline nucleus, thus allowing access to tetrasubstituted pyrazoles **50** (Scheme 16).



48 **49** **50**

Scheme 16. Synthesis of pyrazoles starting from α-benzotriazolylenones.

Alberola et al. [26] studied the regioselectivity of the reaction of various β-aminoenones on different monoalkyl, acetyl-, methoxycarbonyl-hydrazine and semicarbazide. Indeed, when the least bulky substituent is attached at the β position of the enone, high regioselectivity is obtained. This is the case of pyrazoles **51** and **52** which have been obtained with a regioselectivity greater than 90% from the reaction of alkylhydrazines (R1 = Me, t-Bu), in DMSO, with β-aminoenones **50a**, **50b** and **50c** which possess the smallest group (CH_3) in the β position (Scheme 17 and Table 1).



50a, R = $(CH_2)_2Ph$
50b, R = *i*Pr
50c, R = *t*-Bu

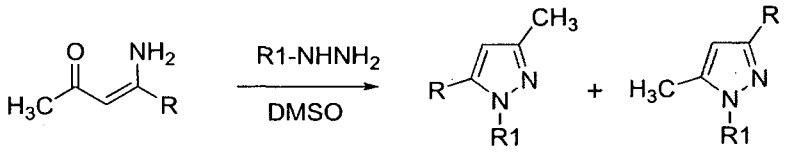
51 **52**

Scheme 17. Synthesis of pyrazoles from β-aminoenones.

Table 1. Preparation of pyrazoles **55** from β-aminoenones **49a**, **49b** and **49c**.

Starting Compound	R	R1	Yields of 51 (%)
50a	$(CH_2)_2Ph$	Me	81
	$(CH_2)_2Ph$	t-Bu	78
50b	iPr	Me	84
	iPr	t-Bu	86
50c	t-Bu	Me	72
	t-Bu	t-Bu	86

In the inverse case where the substituent in position β is the largest, the regioselectivity decreases. Indeed, when β-aminoenones **50a**, **50b** and **50c** were replaced by their position isomers **50d**, **50e** and **50f** in the previous reactions, a drop in regioselectivity was observed (Scheme 18 and Table 2).



50d, R = $(CH_2)_2Ph$
50e, R = *i*Pr
50f, R = *t*-Bu

53 **54**

Scheme 18. Synthesis of pyrazoles from β-aminoenones.

Table 2. Preparation of pyrazoles **54** from β-aminoenones **54d**, **54e** and **54f**.

Starting Compound	R	R1	Yields of 54 (%)	Ratio 54:53
50d	$(CH_2)_2Ph$	Me	81	1:0
	$(CH_2)_2Ph$	t-Bu	23	1:1.4
50e	iPr	Me	71	1:0
	iPr	t-Bu	-	1:9
50f	t-Bu	Me	72	11:1

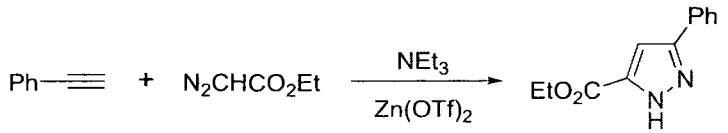
This phenomenon is all the more important as R and alkylhydrazine are more voluminous. In this context, in order to increase the regioselectivity (to increase the ratio **54**/**53**) several experimental attempts have been carried out and have suggested that the selectivity would be improved if the reactions are catalyzed by acetic acid and carried out in DMSO or in ethanol.

2.2. The 1,3-Dipolar Cycloaddition

Other methods allowing access to the pyrazole nucleus involve [3 + 2] cyloaddition reactions between an alkyne (or an olefin) and 1,3-dipolar compounds such as the diazo compounds, the sydnones or the nitrilimines.

2.2.1. Cycloaddition of Diazocarbonyl Compounds

He et al. [27] investigated the action of ethyl α-diazoacetate **56** on phenylpropargyl **55** in triethylamine and in the presence of zinc triflate as a catalyst; the 1,3-dipolar cycloaddition reaction, leads to the corresponding pyrazole **57** in good yield (89%). The simple reaction conditions, straightforward procedure, synthetically useful products, good yielding, and easy manipulation make this method potentially useful in organic synthesis (Scheme 19).

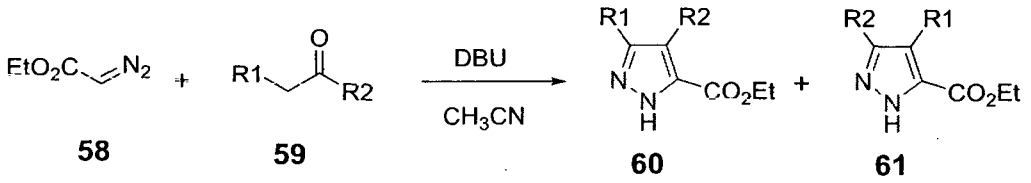


55 **56** **57**

Scheme 19. Synthesis of pyrazoles by 1,3-dipolar cycloaddition of ethyl α-diazoacetate.

Gioiello and co-workers described a facile one-pot procedure for the synthesis of pyrazole-5-carboxylates by 1,3-dipolar cycloaddition of ethyl diazoacetate **58** with α-methylene carbonyl **59** compounds utilizing 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) as base and acetonitrile as solvent. Pyrazoles **60** and **61** were obtained with excellent regioselectivity and good yields. In particular, when

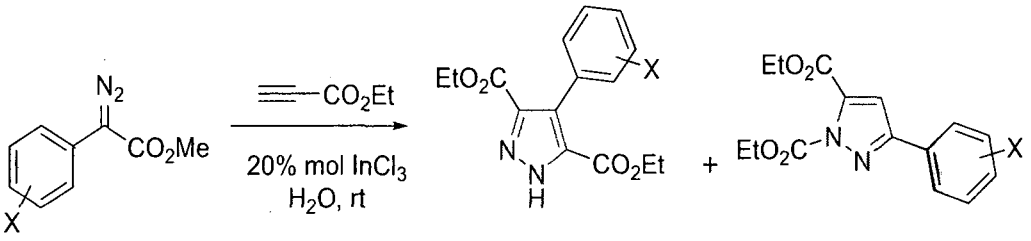
58 was reacted with 59 (with R1 = R2 = Ph) in the presence of 1.7 eq. of DBU in acetonitrile under argon atmosphere at room temperature, ethyl 3,4-diphenyl-1*H*-pyrazole-5-carboxylate was obtained in 65% yield after flash chromatography. The reaction was found to proceed by a domino 1,3-dipolar cycloaddition water elimination (Scheme 20) [28].



58 59 60 61

Scheme 20. Synthesis of pyrazole-5-carboxylates using 1,3-dipolar cycloaddition of ethyl diazoacetate and α-methylene carbonyl.

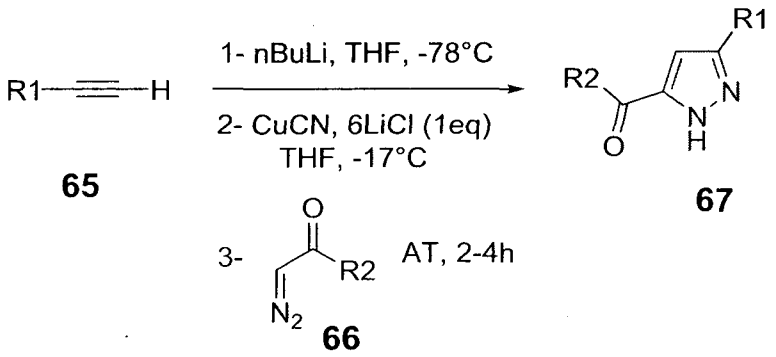
Under the same conditions, the reaction of various aryl α-diazoarylacetacetates on methyl propionate led to the formation of two regioisomers 63 and 64. After cyclization, minor compound 64 (4–12%) is obtained by migration of the ester group on nitrogen atom. The majority compound 63 (77–90%) would be obtained by migration of the aryl group to the adjacent carbon atom followed by a prototropic rearrangement (Scheme 21) [29].



62 63 64

Scheme 21. Synthesis of pyrazoles using 1,3-dipolar cycloaddition of α-diazoarylacetacetates.

In another approach, Qi and Ready developed a direct and efficient access towards 3-acylpyrazoles 67 that involves the copper-promoted cycloaddition of acetylides 65 with diazocarbonyl compounds 66 under mild conditions. A wide variety of substituents is tolerated at both the acetylide and the diazo compound. The method is a rare example of an inverse-electron-demand cycloaddition (Scheme 22) [30].

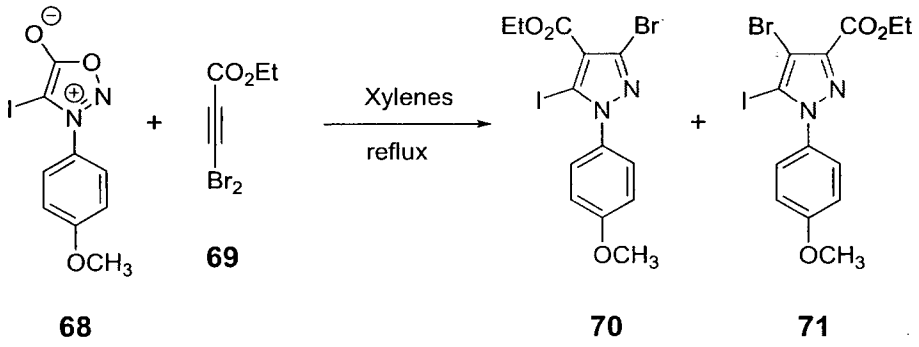


65 66 67

Scheme 22. Synthesis of 3-acylpyrazoles using 1,3-dipolar cycloaddition of diazocarbonyl and acetylides.

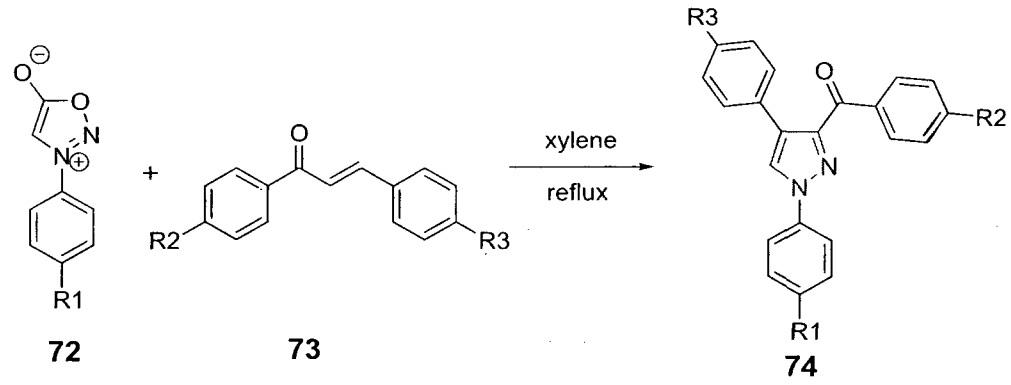
2.2.2. The Sydnones

The pyrazoles ca obtained by a cycloaddition reaction of sydnones. Delaunay and co-workers presented the synthesis of the two regioisomeric 1,3,4,5-substituted pyrazoles **70** and **71** via a cycloaddition reaction between a sydnone **68** and alkyne 69. The reaction was completed within 15 h, giving rise to a 3:1 mixture of regioisomeric 5-iodopyrazoles **70** and **71** in 84% combined yield. The pyrazoles were easily separated by silica gel chromatography, and the structure assignment of the desired major isomer **70** (63% isolated yield) was made on the basis of the ^{1}H-NMR spectrum [31] (Scheme 23).



Scheme 23. Synthesis of pyrazoles by cycloaddition reaction of sydnones and alkyne.

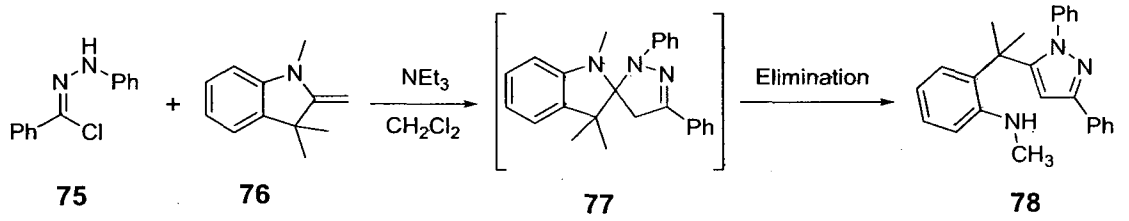
On the other hand, Chen et al. [32] described the synthesis of a trisubstituted pyrazole **74**, by 1,3-dipolar cycloaddition of arylsydnones **72** and α,β-unsaturated ketone **73** in dry xylene (Scheme 24).



Scheme 24. Synthesis of pyrazoles by 1,3-dipolar cycloaddition of arylsydnones and chalcone.

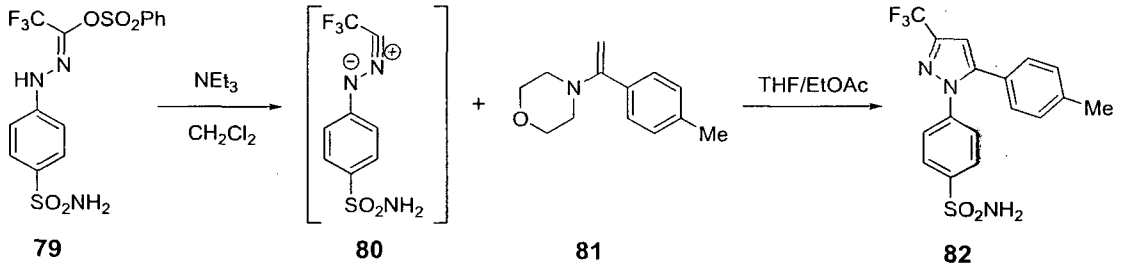
2.2.3. Nitrilimines

Dadiboyena et al. described the synthesis of 1,3,5-trisubstituted pyrazole **78** by 1,3-dipolar cycloaddition of diphenylnitrilimine **75** with an alkene **76** in dichloromethane in the presence of triethylamine. The trisubstituted pyrazole **78**, isolated in 88% yield, was the only product rather than the expected spiro-pyrazoline **77** (Scheme 25) [33].



Scheme 25. Synthesis of pyrazole by 1,3-dipolar cycloaddition of diphenylnitrilimine and alkene.

Oh et al. reported the synthesis of the 1,3,5-substituted pyrazole **82** via 1,3-dipolar cycloaddition reaction of a vinyl derivative **81** with the nitrilimine **80** generated in situ from an arylhydrazone **79**. The reaction yielded the corresponding pyrazole in 72% yield. The protocol is simple and practical, employing economical and readily available reagents (Scheme 26) [34].

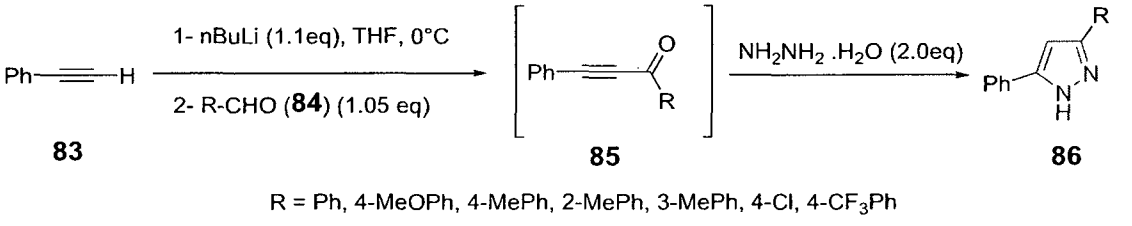


Scheme 26. Synthesis of pyrazole via 1,3-dipolar cycloaddition reaction of nitrilimine and vinyl.

2.3. Multicomponent Approaches

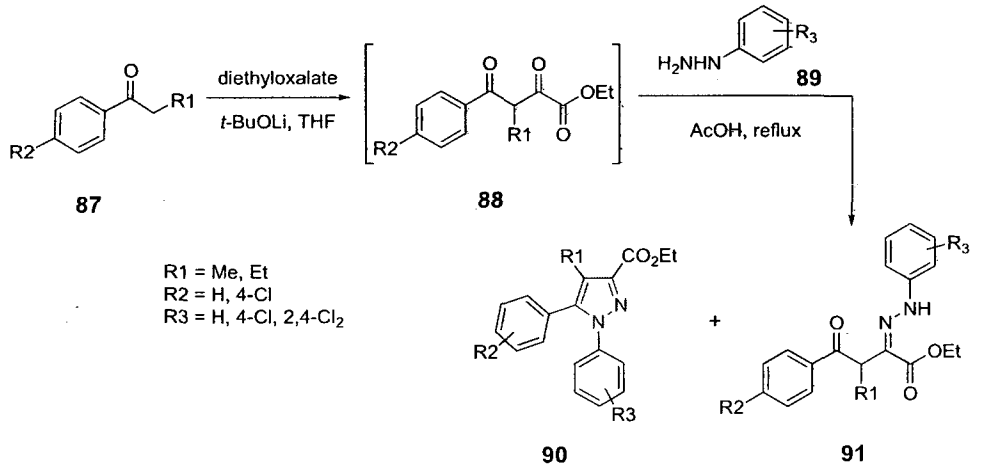
2.3.1. In Situ Formation of Carbonyl Derivatives

Harigae and co-workers reported the preparation of 3,5-substituted pyrazole **86** in good yields (68–99%) with high regioselectivity in one pot by the treatment of terminal alkynes **83** with aromatic aldehydes **84**, molecular iodine, and hydrazines. The present reaction is a simple and practical method for the preparation of various 1,3-disubstituted pyrazoles from easily available compounds (Scheme 27) [35].



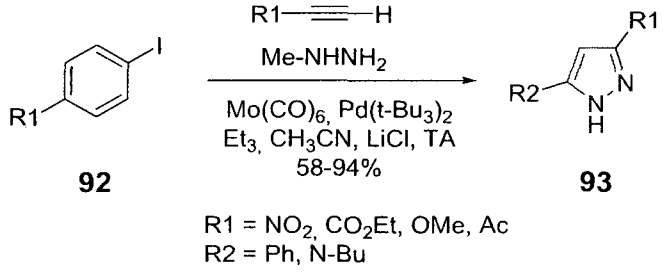
Scheme 27. Synthesis of pyrazole from α,β-unsaturated carbonyl and hydrazine.

1,3,4,5-Substituted pyrazole **90** was synthetized via a cyclocondensation reaction of arylhydrazine **89** and carbonyl derivatives **88** generated in situ from a ketone **87** and diethyl oxalate. The diketoesters **88** was converted into the desired 1,5-isomers **90** in the yields of 60–66%. Meanwhile, *N*-arylhydrazones **91** were obtained in the yields of 24–31% (Scheme 28) [36].



Scheme 28. Synthesis of pyrazole via cyclocondensation reaction of 1,3-dicarbonyl and arylhydrazine.

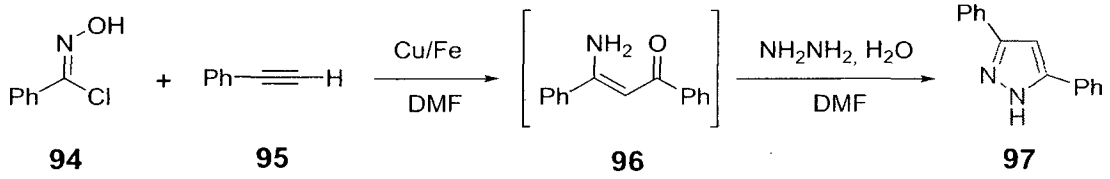
Lizuka and Kondo demonstrate palladocatalyzed carbonylation of acetylenic acids on aryl iodides **92** in the presence of hexacarbonyl molybdenum as a source of CO and tri-*tert*-butylphosphine as a palladium ligand, to similarly access 1,3,5-substituted pyrazoles **93** with excellent yields (58–94%). The one-pot formation of pyrazole in the presence of methylhydrazine was also successful and aryl iodides with electron withdrawing groups were easily converted into pyrazoles (Scheme 29) [37].



Scheme 29. Synthesis of pyrazoles by one-pot reaction of aryl iodides, acetylenic acids and methylhydrazine.

2.3.2. In Situ Formation of β-Aminoenones

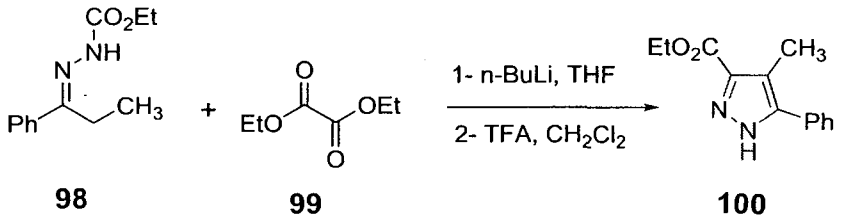
Kovacs et al. developed a novel process for the synthesis of 3,5-substituted pyrazoles **97** via cuprocatalyzed coupling between an alkyne **95** and an oxime **94** in dimethylformamide, which provides the β-aminoenone **96**. The valuable β-aminoenone was transformed into pyrazoles with the addition of hydrazine in a straightforward one-pot procedure; the product **97** was isolated with 70% yield (Scheme 30) [38].



Scheme 30. Synthesis of 3,5-diphenylpyrazoles via cuprocatalyzed coupling between alkyne and oxime.

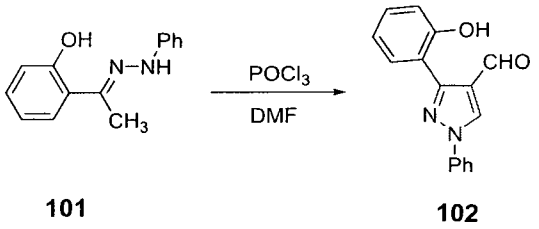
2.3.3. In Situ Formation of a Hydrazone

Dang et al. described a novel reaction for the synthesis of pyrazole-3-carboxylates by one-pot cyclization of hydrazone dianions **98** with diethyl dioxalate **99**. The cyclization of diethyl oxalate with the dianions of hydrazones **98** afforded the pyrazole-3-carboxylates **100** in good yields (53%) (Scheme 31) [39].



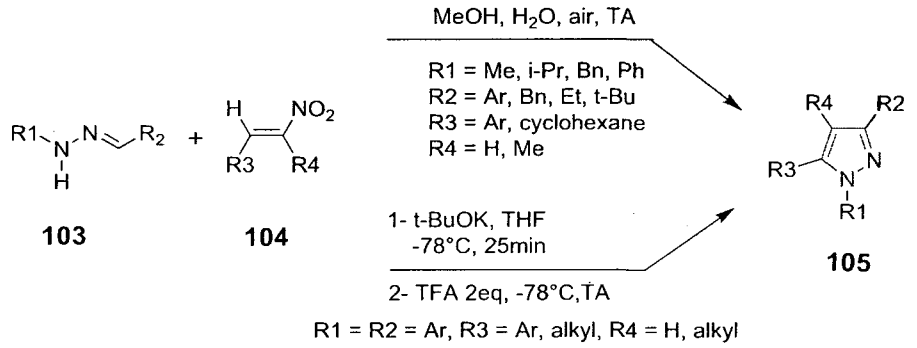
Scheme 31. Synthesis of pyrazoles by one-pot cyclization of hydrazone with diethyl dioxalate.

Lokhande et al. used the Vilsmeier-Haack reaction to synthesize carboxaldehyde pyrazoles **101**. Condensation of a hydrazine **102** in the presence of phosphorus oxychloride gives the 4-formyl pyrazole (Scheme 32) [40].



Scheme 32. Synthesis of carboxaldehyde pyrazoles by Vilsmeier-Haack reaction.

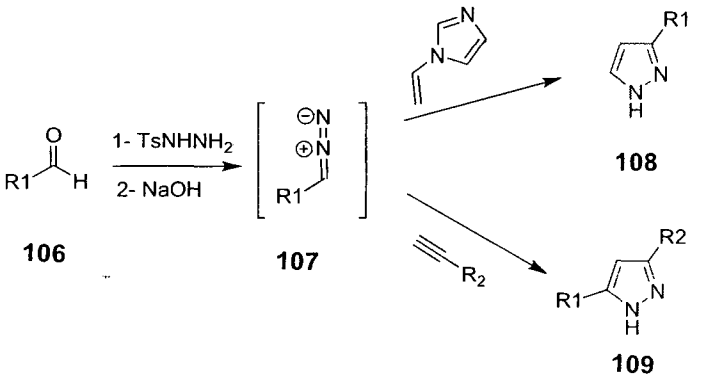
1,3,4,5-Substituted pyrazoles **105** were regioselectively synthesized in modest to good yields (26–92%) by Deng and Mani from hydrazone **103** and a nitroolefin **104** in methanol [41]. As a result of this work, the same authors proposed another strategy for synthesis based on the use of the same substrates and selectively leading to 1,3,4-substituted pyrazoles. In this new approach, the cyclocondensation of nitroolefins **104** with hydrazones **103** is carried out using a strong base such as *t*-BuOK. After treatment with a strong acid, the desired pyrazole **105** is obtained in the form of a single regioisomer in excellent yields (42–88%) (Scheme 33) [42].



Scheme 33. Synthesis of 1,3,4,5-Substituted pyrazole derivatives.

2.3.4. In Situ Formation of Diazo Compounds

The Aggarwal team has developed a multicomponent process in which diazo **107** derivatives are generated in situ from various aldehydes **106** and tosylhydrazines, thus limiting the risks associated with the isolation of these compounds. These are then used in a 1,3-dipolar cycloaddition reaction to give corresponding pyrazoles **108** and **109** Diazo compounds derived from aldehydes were reacted with terminal alkynes to furnish regioselectively 3,5-disubstituted pyrazoles in 24–67% yields. Furthermore, the reaction of *N*-vinylimidazole and diazo compounds derived from aldehydes gave exclusively 3-substituted pyrazoles in a one-pot process with 32–79% yields (Scheme 34) [43].

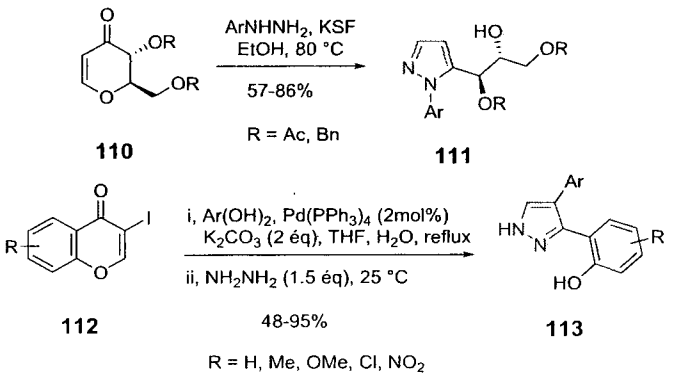


Scheme 34. Synthesis of pyrazoles by 1,3-dipolar cycloaddition of diazo derivatives.

2.4. From Heterocyclic Systems

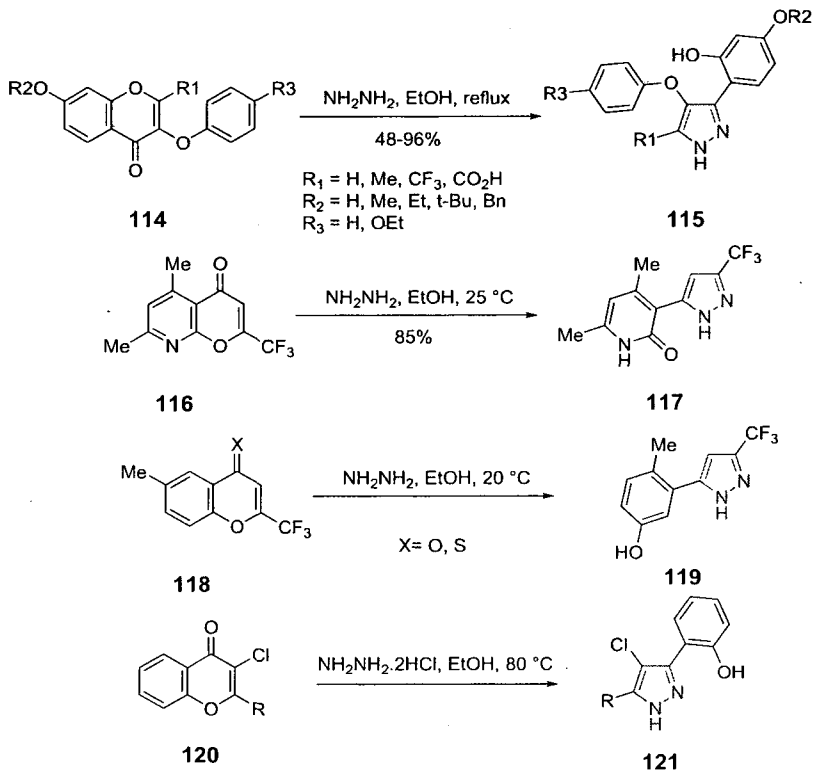
2.4.1. From the Pyranones

Pyranones are among the most widely used heterocycles for the preparation of pyrazoles. The condensation of 2,3-dihydro-4*H*-pyran-4-ones **110** with arylhydrazines in ethanol and in the presence of montmorillonite KSF as catalyst, gives access to 5-substituted pyrazoles **111** in yields of (57–86%) (Scheme 35) [44]. Similarly, Xie et al. have developed a general method for the synthesis of pyrazoles. This involves the use of Suzuki coupling of arylboronic acids with chromones **112**, followed by the action of hydrazine hydrate, yields the corresponding 3,4-diarylpyrazoles **113** in a yield of 48–95% (Scheme 35) [45].



Scheme 35. Synthesis of pyrazoles from pyranones.

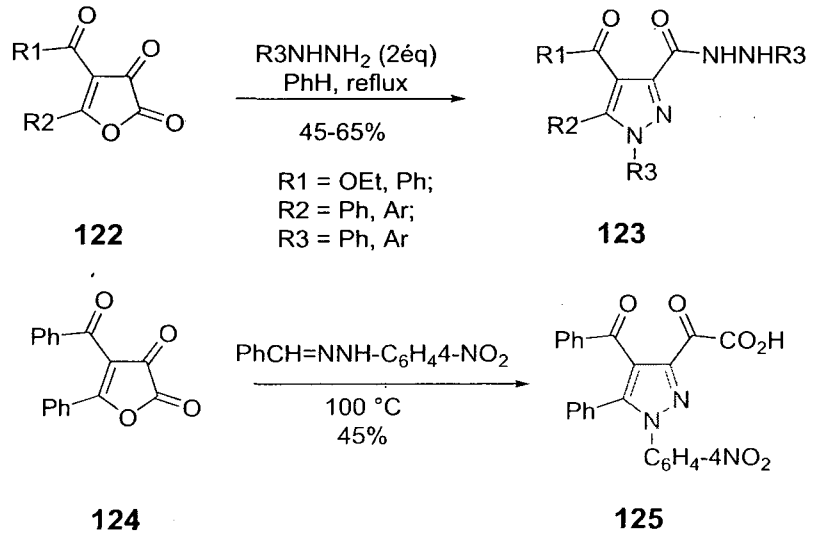
Similarly, reaction of pyranones derivatives **114**, **116**, **118** and **120** with hydrazine in ethanol the give corresponding pyrazoles **115**, **117**, **119** and **121** respectively (Scheme 36) [46–49].



Scheme 36. Synthesis of pyrazoles by reaction of pyranones derivatives with hydrazine.

2.4.2. From Furandiones

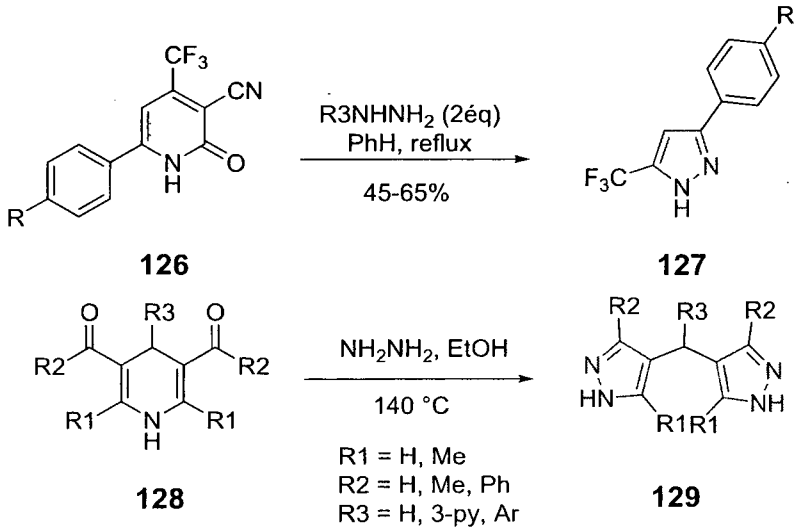
Ilham et al. [50] carried out condensation in refluxing benzene, furan-2,3-diones **126** with arylhydrazines, allowing access to pyrazole-3-hydrazides **127** in acceptable to good yields (45–65%) (Scheme 37). Similarly, condensation of furan-2,3-dione **128** with *N*-benzylidene-*N*′-(4-nitrophenyl) hydrazine afforted 4-benzoyl-1-(4-nitrophenyl)-5-phenyl-1*H*-pyrazole-3-carboxylic acid **129** in a 45% yield (Scheme 37) [51].



Scheme 37. Synthesis of pyrazoles from furandiones.

2.4.3. From Pyrimidines and Pyrimidones

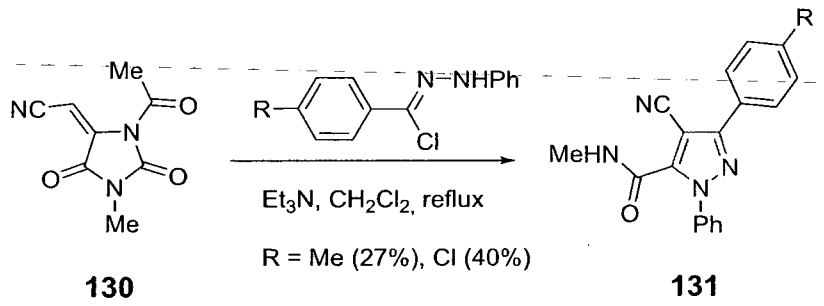
3-Cyano-4-trifluoromethyl-6-aryl-2(1*H*)-pyridones **126** react with hydrazine hydrate under reflux to give 5-trifluoromethyl-3-arylpyrazoles **127** in 45–65% yields (Scheme 38) [52]. Similarly, the reaction of 3,5-diacyl-1,4-dihydropyridine **128** with hydrazine in ethanol at 140 °C afforded bis-pyrazolyl methanes **129** in good yields (Scheme 38) [53].



Scheme 38. Synthesis of pyrazoles from furandiones.

2.4.4. From Imidazole

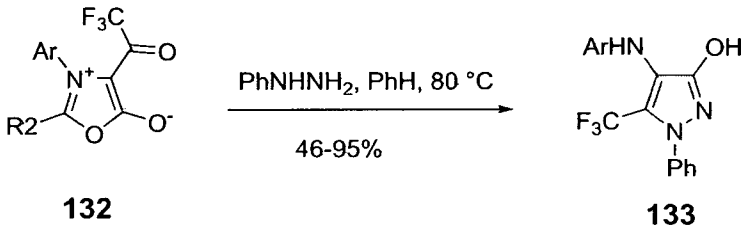
Cycloaddition of (5Z)-1-acyl-5-(cyanomethylidene)-3-methylimidazolidine-2,4-diones **130** with arylhydrazonyl chloride under basic conditions to give pyrazole-5-carboxamides **131** in moderate 27–40% yields (Scheme 39) [54].



Scheme 39. Synthesis of pyrazoles from furandiones.

2.4.5. From Oxazoles

5-Trifluoromethyl-3-hydroxypyrazoles **132** were obtained in good yield (46–95%) by heating phenylhydrazine and 4-trifluoroacetyl-1,3-oxazolium-5-olates **133** under reflux of benzene (Scheme 40) [55].

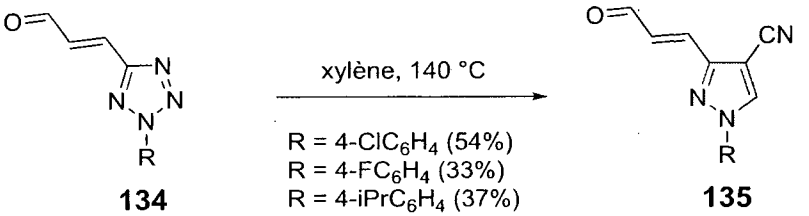


132 **133**

Scheme 40. Synthesis of pyrazoles from furandiones.

2.4.6. From Tetrazoles

Cyanopyrazoles **135** are readily prepared from tetrazolo[1,5-*b*]pyridazines, tetrazolo[1,5-*a*] pyrimidines, or tetrazolo[1,5-*a*]pyridines. Tetrazolyl acroleins **134** reacts with fumaronitrile in xylene at 140 °C to give the corresponding pyrazole formation **135** (Scheme 41) [56].

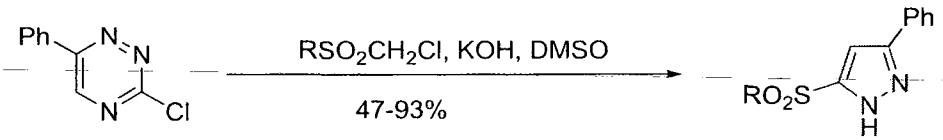


134 **135**

Scheme 41. Synthesis of pyrazoles from furandiones.

2.4.7. From Triazines

Rykowski et al. [57] proposed a synthesis of pyrazoles, based on the condensation of 3-chloro-6-phenyl-1,2,4-triazines **136** on α-chlorosulfonyls in the presence of potassium hydroxide for obtain the corresponding pyrazoles **137** (Scheme 42).

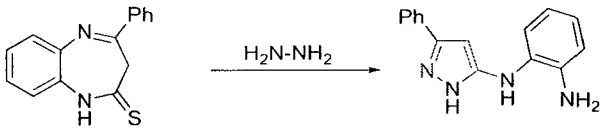


136 R = Ph, 4-morpholinyl, 1-pyrolidinyl, OPh, OCH_2CMe_3 **137**

Scheme 42. Synthesis of pyrazoles from furandiones.

2.4.8. From 1,5-Benzodiazepin-2-one

Ferfra et al. [58] prepared pyrazole from benzodiazepine-2-thione in one step. They opened the seven-membered ring by reacting hydrazine with benzodiazepine-2-thione **138** to give *o*-aminophenylaminopyrazole **139** (Scheme 43).

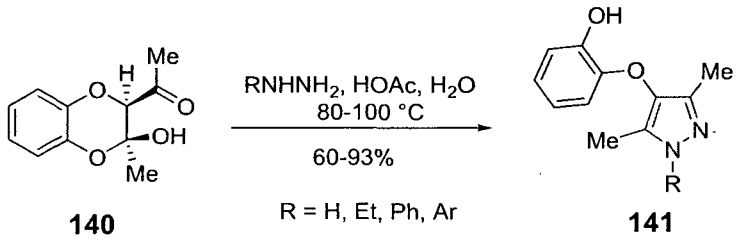


138 **139**

Scheme 43. Synthesis of pyrazoles from furandiones.

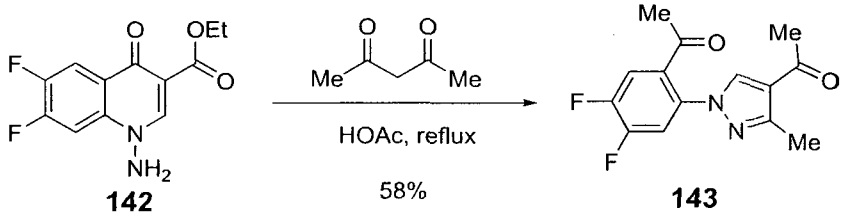
2.4.9. From Other Heterocycles

Substituted pyrazoles **141** were synthesized in high yields through the condensation reaction of (Z)-3-Acetyl-2-methyl-2,3-dihydro-1,4-benzodioxin-2-ol **140** with arylhydrazines in a mixture of water and acetic acid (Scheme 44) [59].



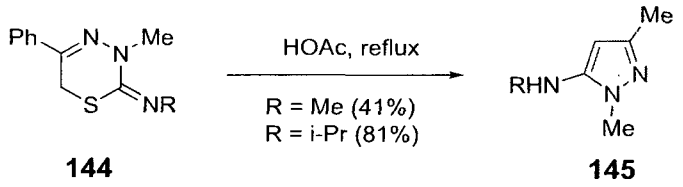
Scheme 44. Synthesis of pyrazoles from furandiones.

Similarly, condensation of ethyl-1-amino-6,7-difluorooxoquinolin-4-one-3-carboxylate **142** with pentane-2,4-dione in acetic acid at reflux afforded 1-(2-acetyl-4,5-difluorophenyl)-3-methyl-4-acetylpyrazole **143** (Scheme 45) [60].



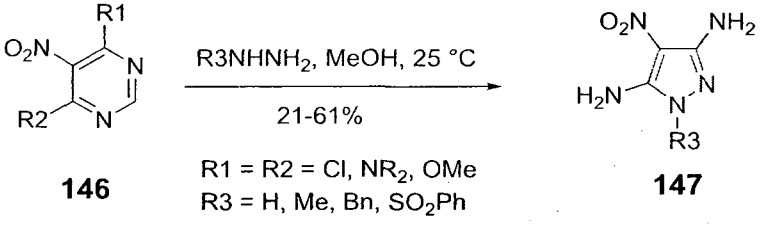
Scheme 45. Synthesis of pyrazoles from furandiones.

5-Aminopyrazoles **145** were obtained in good yield by heating of 3-methyl-6*H*-1,3,4-thiadiazine **146** under reflux of acetic acid (Scheme 46) [61].



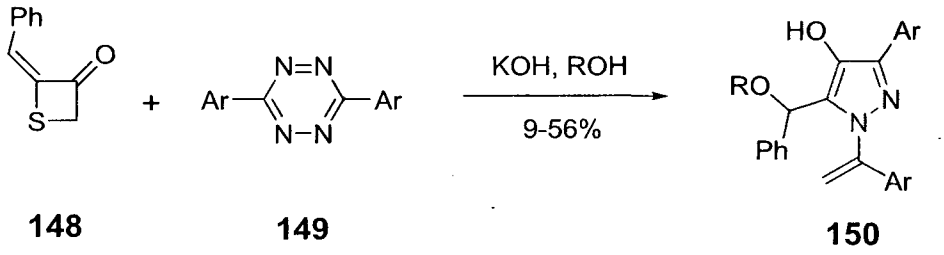
Scheme 46. Synthesis of pyrazoles from furandiones.

On the other hand, the reaction of nitropyrimidine **146** with arylhydrazines in methanol at room temperature, to afford 4-nitro-3,5-diaminopyrazoles **147** in yields of 21–61% (Scheme 47) [62].



Scheme 47. Synthesis of pyrazoles from furandiones.

Suen et al. prepared a series of substituted 1*H*-pyrazoles **150** by condensing thietanone **148** with 1,2,4,5-tetrazines **149** in the presence of potassium hydroxide (Scheme 48) [63].



Scheme 48. Synthesis of pyrazoles from furandiones.

3. Pharmacological Activities

3.1. Antibacterial and Antifungal Activity

Akbas et al. synthesized of series 1*H*-pyrazole-3-carboxylic acid derivatives (Figure 4) and evaluated for their antibacterial activities against *Bacillus cereus*, *Staphylococcus aureus*, *Escherichia coli* and *Pseudomonas putida*. The results showed that the compound **151** was the best compound in the series, exhibiting antibacterial activity against both Gram-positive and Gram-negative bacteria [64]. A series of new pyrazoles containing a quinolinyl chalcone group were synthesized and assessed for antibacterial activity. Compound **152** was the most potent against bacterial and fungal strains [65]. A series of pyrazole-3-carboxylic acid and pyrazole-3,4-dicarboxylic acid derivatives were synthesized and evaluated for their antibacterial and antifungal activities against five bacterial and five fungal pathogens. However, only the molecules **153**, **154**, **155** and **156** demonstrated some inhibitory effects on *Candida parapsilosis*, *Candida tropicalis*, and *Candida glabrata* strains [66]. Rahimizadeh et al. reported the synthesis and antibacterial activity of a series of 5-amido-1-(2,4-dinitrophenyl)-1*H*-pyrazole-4-carbonitriles. Results showed that the compound **157** exhibit antimicrobial activities against methicillin susceptible *S. aureus* and methicillin resistant *S. aureus* with MIC values of 25.1 μM [67].

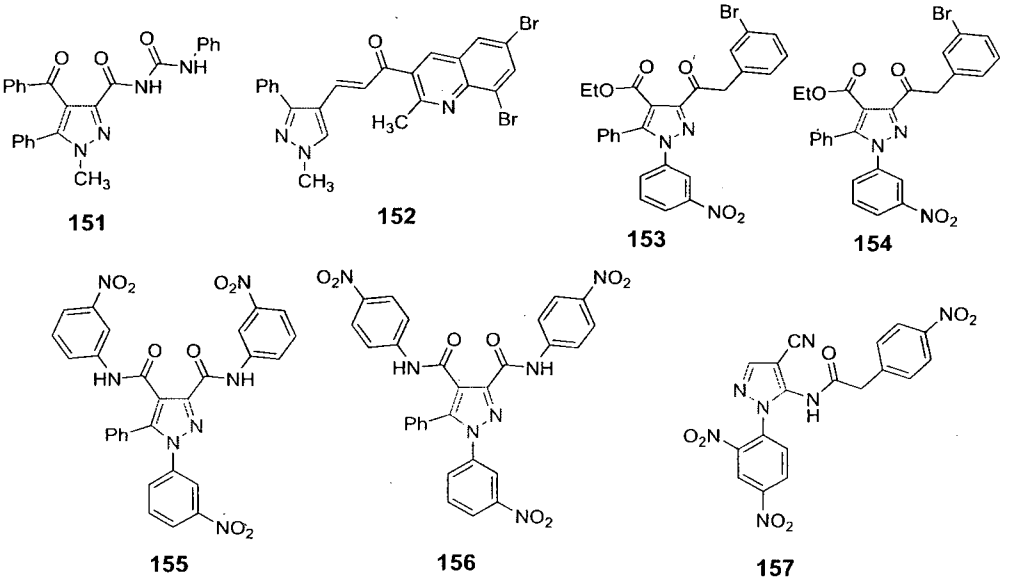


Figure 4. Structures of some pyrazole derivatives as antimicrobial compounds.

A series of pyrazole derivatives were synthesized and screened for their antibacterial properties against *S. aureus*, *Bacillus subtilis*, *E. coli* and *P. aeruginosa*. Among the tested compounds **158**, **159**, **160** and **161** (Figure 5) have shown excellent antibacterial activity against all the tested bacterial strains as compared with the standard drug ceftriaxone, which was active at 3.125, 1.6125, 1.6125 and 1.6125 μg/mL against *S. aureus*, *B. subtilis*, *E. coli*, and *P. aeruginosa* strains, respectively [68].

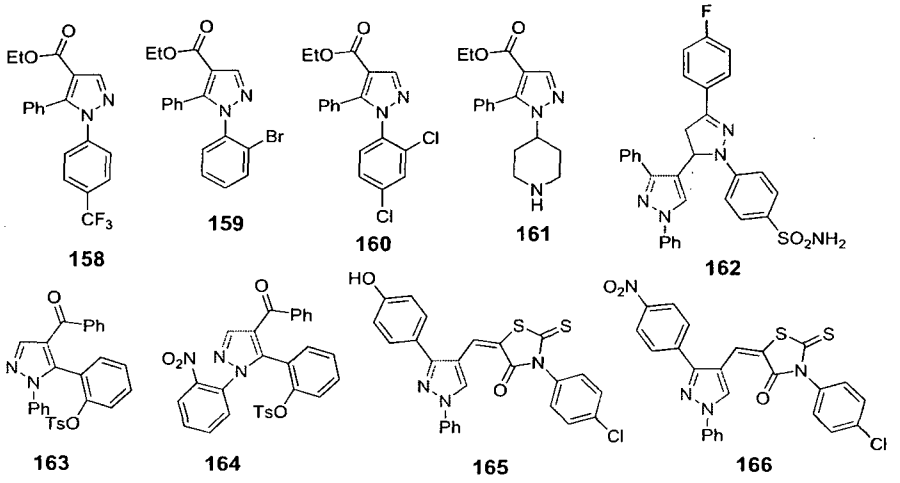


Figure 5. Structures of some pyrazole derivatives with antibacterial activity.

A series of pyrazolylpyrazolines was synthesized and evaluated for their in vitro anti-microbial activity against two Gram-positive bacteria and two Gram-negative bacteria. The results schowed that the compound **162** was able to inhibit the growth of both the Gram-positive as well as Gram-negative bacteria [69]. A series of pyrazole derivatives were prepared and screened for their anti-bacterial and antifungal activities using ampicillin and norcadine as standard drugs. All the compounds were screened for their antimicrobial activities. The results for these derivatives showed good antibacterial activity for **163** and **164** [70].

B'Bhatt and Sharma synthesized a series of 3-(4-chlorophenyl)-5-((1-phenyl-3-aryl-1*H*-pyrazol-4-yl)methylene)-2-thioxothiazolidin-4-ones. All the synthesized compounds were screened for in vitro antibacterial activity against *E. coli*, *P. aeruginosa*, *S. aureus*, and *S. pyogenes* and in vitro anti-fungal activity, these compounds were tested against *C. albicans*, *A. niger* and *A. clavatus* using ampicillin and griseofulvin as standard drugs. Compound **165** was found as a potent compound against *E. coli*, while compound **166** was found to be potent against *S. aureus*, *S. pyogenes* and was found to have very good activity against *C. albicans* [71].

1,3,4,5-Tetrasubstituted pyrazole derivatives were synthesized and tested for anti-microbial activity against *S. aureus*, *E. coli*, *Aspergillus flavus* and *C. albicans*. Compound **167** showed promising antibacterial and antifungal activity [72]. Padmaja et al. reported the synthesis and antimicrobial activity of substituted pyrazoles. Results showed that the compound with sulfone moieties **168** displayed the maximum activity [73]. Novel 1,5-diaryl pyrazole derivatives were synthesized and screened for their antimicrobial activity against *E. coli*, *S. aureus*, *P. aeruginosa*, *K. pneumonia* and for their antifungal activity against *A. flavus*, *A. fumigates*, *P. marneffei* and *T. mentagrophytes*. Compound **169** (Figure 6) exhibited good antibacterial and antifungal activity with MIC value of 12.5 mg/mL [74]. A series of 1,3-diarylpyrazoles derivatives were synthesized and evaluated for their in vitro antibacterial activity against *S. aureus*, *B. subtilis*, *E. coli*, *P. aeruginosa*, and in vitro antifungal activity against *A. niger* and *A. flavus*. Compound **169** exhibited moderate antibacterial and antifungal activities against the tested bacteria and fungi [75]. A series of 3-(4-chlorophenyl)-4-substituted pyrazoles were synthesized and tested for antifungal activity against a pathogenic strain of fungi and antibacterial activity against Gram-positive and Gram-negative organisms. Among those tested,

compound **171** (Figure 6) showed good to excellent antimicrobial at MIC values of 0.0025 to 12.5 μg/mL against all the selected pathogenic bacteria and fungi [76].

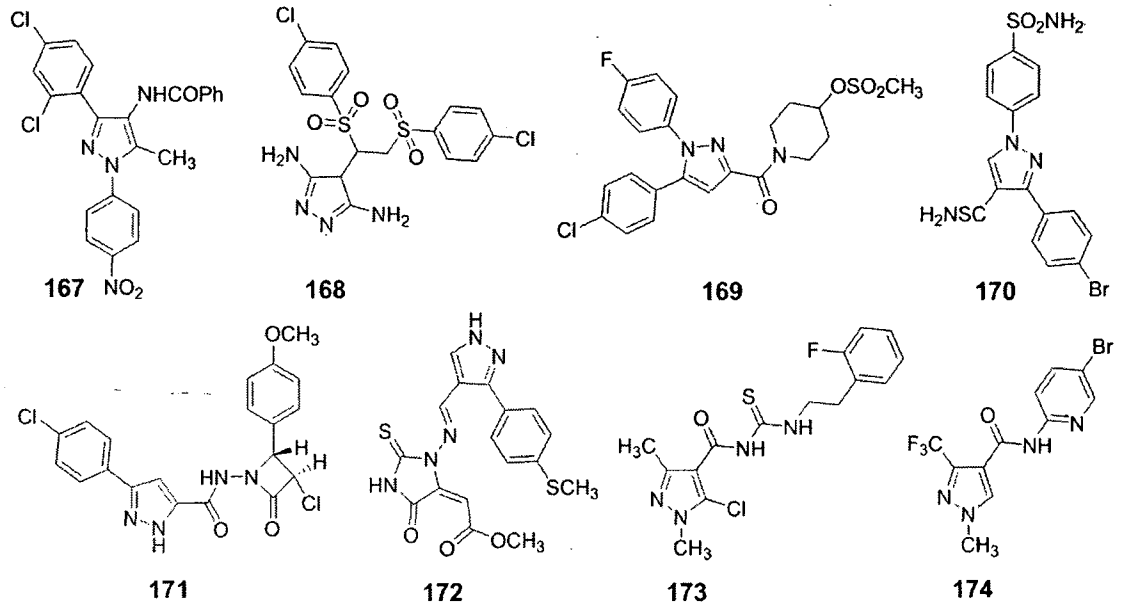


Figure 6. Pyrazole derivatives with antimicrobial activity.

A series of novel imidazole derivatives containing substituted pyrazole moiety were synthesized by Vijesh et al. and screened for antifungal and antibacterial activities. Among the synthesized compounds, compound **172** was found to be potent antimicrobial agent [77]. Several pyrazole acyl thiourea derivatives were synthesized and antifungal activity against *G. zeae*, *F. oxysporum*, *C. mandshurica*. Compound **173** displayed good antifungal activities against the tested fungi [78]. A series of *N*-(substituted-pyridinyl)-1-methyl(phenyl)-3-trifluoromethyl-1*H*-pyrazole-4-carboxamide derivatives were synthesized by Wu et al. and evaluated in vitro against three kinds of phytopathogenic fungi (*G. zeae*, *F. oxysporum*, *C. mandshurica*). The results showed that the compound **174** displayed more than 73% inhibition activities against *G. zeae* at 100 μg/mL [79]. A series of 1,3-diaryl pyrazole derivatives bearing rhodanine-3-fatty acid moieties (Figure 7) were synthesized and investigated for their in vitro antimicrobial activities against various Gram-positive and Gram-negative bacteria. Compound **175** was found active against the methicillin-resistant *Staphylococcus aureus* (MRSA) with a MIC of 2 mg/mL [80]. A series of novel pyrazole derivatives were synthesized by Desai et al. and screened for their in vitro antibacterial activity against *S. aureus*, *S. pyogenes*, *E. coli*, *P. aeruginosa*. The results indicated the compound **176** showed potent antibacterial activity against *S. aureus*, *E. coli* at 12.5 mg/mL [81]. Pyrido[1,2-*a*]benzimidazole derivatives bearing the aryloxypyrazole nucleus were synthesized and investigated for in vitro antimicrobial activity. Compound **177** was found active against employed pathogens [82]. Malladi et al. synthesized a series of new Schiff bases containing pyrazole rings and screened them for their antibacterial (*S. aureus*, *B. subtilis*, *E. coli* and *P. aeruginosa*) activity. The results revealed that, compound **178** exhibited significant antibacterial activity against the tested microorganisms with MIC value of 1.61 mg/mL [83]. A series of formyl-pyrazoles derivatives were synthesized and screened in vitro for their antibacterial and antifungal activities. The compounds **179** exhibited promising antifungal and antibacterial activity with MIC values of 15–60 μg/mL against the different organisms tested [84]. The anti-bacterial activity of 5-aryloxypyrazole derivatives was reported by Song et al. Compound **180** showed good inhibitory activity against selected methicillin resistant and quinolone-resistant *S. aureus* (MRSA, QRSA) with MIC values in the range of 2–4 μg/mL [85]. Sayed and co-workers described the synthesis and antimicrobial

activity of new pyrazole derivatives. The results revealed that the compound **181** showed significant antimicrobial activity against the tested microorganisms [86]. A series of novel 5-imidazopyrazole derivatives were synthesized and evaluated for their in vitro antibacterial activity against a panel of pathogenic strains of bacteria and fungi. Compound **182** exhibited excellent antimicrobial activity as compared with the first line drugs [87].

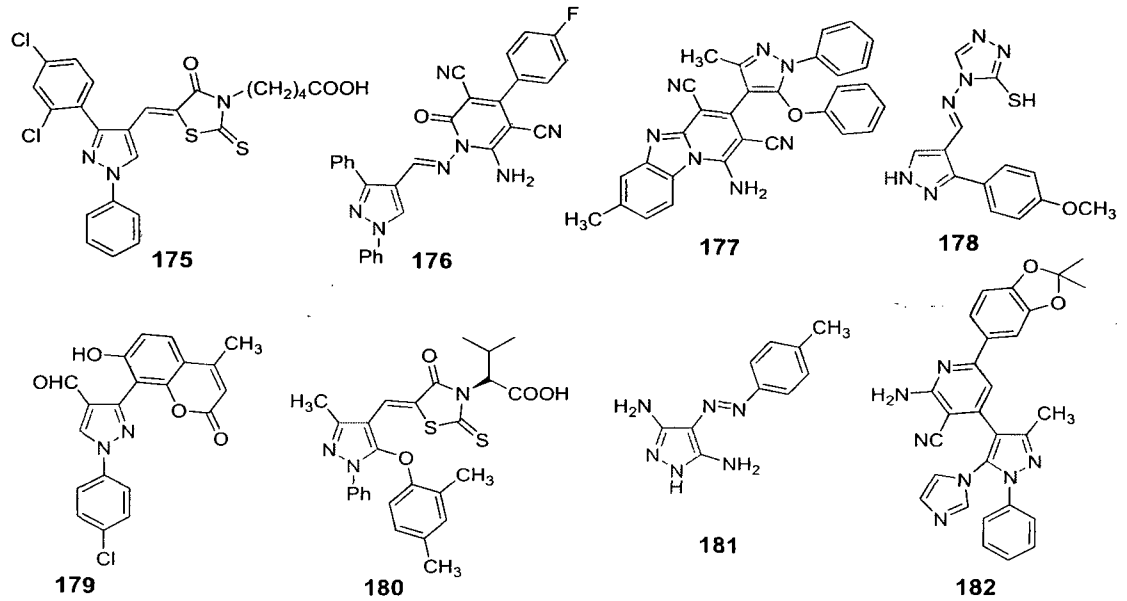


Figure 7. Pyrazole derivatives showing antimicrobial activity.

Pyrimidine pyrazole derivatives (Figure 8) were synthesized by Kumar et al. and screened for their antimicrobial activity against bacteria and fungi. Among all the compounds, compound **183** was found to be the most active with MIC value of 31.25 μg/mL against *S. aureus* and *B. cereus* [88]. Several pyrazole derivatives were synthesized and evaluated for their fungicidal activities against *Botrytis cinerea, Rhizoctonia solani, Valsa mali Miyabe et Yamada, Thanatephorus cucumeris, Fusarium oxysporum*, and *Fusarium graminearum*. The results indicated that the compound **184** showed the highest activity, with EC_{50} values of 2.432, 2.182, 1.787, 1.638, 6.986 and 6.043 μg/mL against *B. cinerea, R. solani, V. mali, T. cucumeris, F. oxysporum*, and *F. graminearum*, respectively [89]. A series of 2,5-disubstitued-1,3,4-oxadiazole derivatives bearing a pyrazole moiety were synthesized and screened for their antibacterial activity against *E. coli, S. aureus* and *P. aeruginosa*, and for antifungal activity against *A. flavus, C. keratinophilum* and *C. albicans*. The evaluation of antimicrobial screening revealed that compounds **185** exhibited excellent activity [90]. A new series of quinazolin-4(3H)-one derivatives containing a (1,3-diphenyl-1*H*-pyrazol-4-yl) core were synthesized by Mehta et al. and screened for their antimicrobial, antifungal activities. The results showed that the compound **186** was found the most active against the tested pathogens [91]. A series of pyrazole derivatives containing 1,3,4-oxadiazoles moiety were synthesized by Ningaiah et al. and evaluated for their antimicrobial activity. Among the synthesized compounds, compound **187** showed good to moderate activity with MIC in the range of 20–50 μg/mL against bacteria and 25–55 μg/mL against fungi [92]. A series of pyrazole derivatives linked thiazole and imidazole were prepared and tested for antimicrobial activity. The compounds **188** and **189** exhibited excellent antibacterial and antifungal activities [93]. Du et al. synthesized a series of novel 3-(difluoromethyl)-1-methyl-1*H*-pyrazole-4-carboxylic acid amides and tested in vitro for their activities against seven phytopathogenic fungi. Among them *N*-(2-(5-bromo-1*H*-indazol-1-yl)-phenyl)-3-(difluoromethyl)-1-methyl-1*H*-pyrazole-4-carboxamide (**190**) exhibited higher antifungal activity against the seven phytopathogenic fungi than boscalid [94].

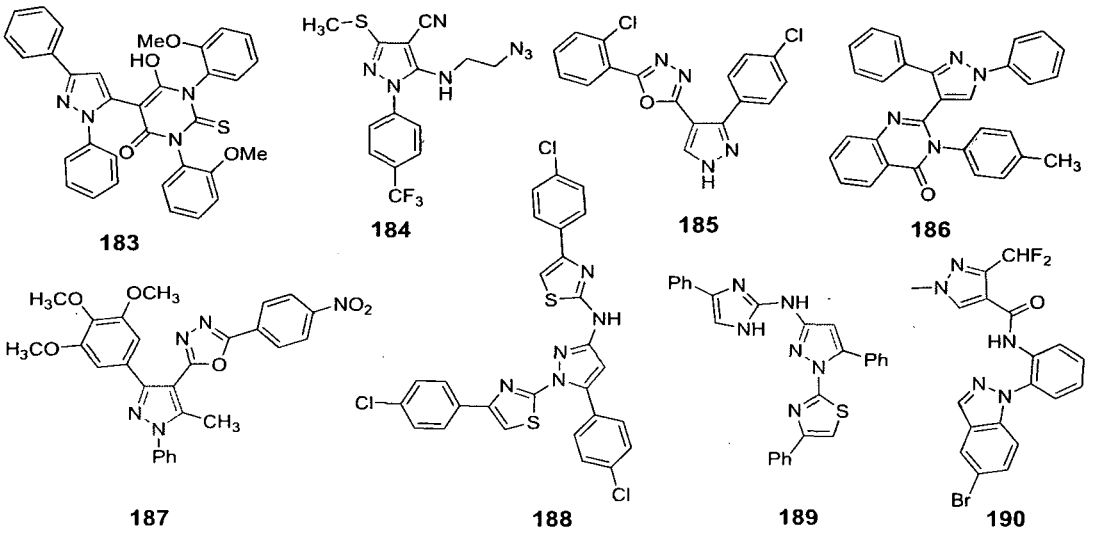


Figure 8. Pyrazole derivatives with antimicrobial activity.

Miniyar et al. synthesized a novel series of pyrazole derivatives bearing a 2-chloroquinoline ring (Figure 9) and screened them for antibacterial and antifungal activity. Among the series, compound **191** was found moderately active against *A. fumigatus*, *P. notatum*, *B. subtilis* and *E. coli* with MIC values of 48, 46, 44 and 87 μg/mL, respectively [95]. Radi et al. reported the synthesis and antifungal activity of novel pyrazole derivatives. Compound **192** had the most potent activity against *Fusarium oxysporum* f.sp *albedinis FAO* with n IC_{50} value of 0.055 μM [96]. A series of new pyrazole derivatives were synthesized and evaluated for antimicrobial activity. Compound **193** showed the highest activities against tested organisms [97]. A series of isoxazolol pyrazole carboxylate derivatives were synthesized and bioassayed in vitro against four types of phytopathogenic fungi (*Alternaria porri*, *Marssonina coronaria*, *Cercospora petroselini* and *Rhizoctonia solani*). The results showed that the compound **194** exhibited significant antifungal activity against *R. solani*, with an EC_{50} value of 0.37 μg/mL [98]. A series of novel diterpene derivatives containing pyrazole ring were synthesized and investigated for their activity against *S. aureus* Newman strain and multidrug-resistant strains (*NRS-1*, *NRS-70*, *NRS-100*, *NRS-108* and *NRS-271*). Among the compounds tested, compound **195** showed the most potent activity with MIC values of 0.71–3.12 μg/mL against five multidrug-resistant *S. aureus* [99]. Elshaier et al. described the synthesis and antimicrobial activity of new series of pyrazole-thiobarbituric acid derivatives. Compound **196** was the most active against *C. albicans* with MIC = 4 μg/L, and exhibited the best activity against *S. aureus*, *B. subtilis* and *E. faecalis* with MIC = 16 μg/L [100]. A series of novel pyrazole-5-carboxylate derivatives containing a *N*-triazole scaffold were synthesized and screened for their in vitro antimicrobial activity against three Gram-positive and Gram-negative bacteria as well as three fungi. The results revealed that the compound **197** was more potent antibacterial activity against all bacterial strains, and showed excellent antifungal activities against *A. niger* and *C. albicans* in MIC = 4 μg/L [101]. Several new pyrazole derivatives incorporating a thiophene moiety were synthesized and evaluated for their antibacterial and antifungal activities. The results showed that compound **198** revealed a high degree of antibacterial activity towards *Pseudomonas aeruginosa* and inhibition effects against *Escherichia coli* [102].

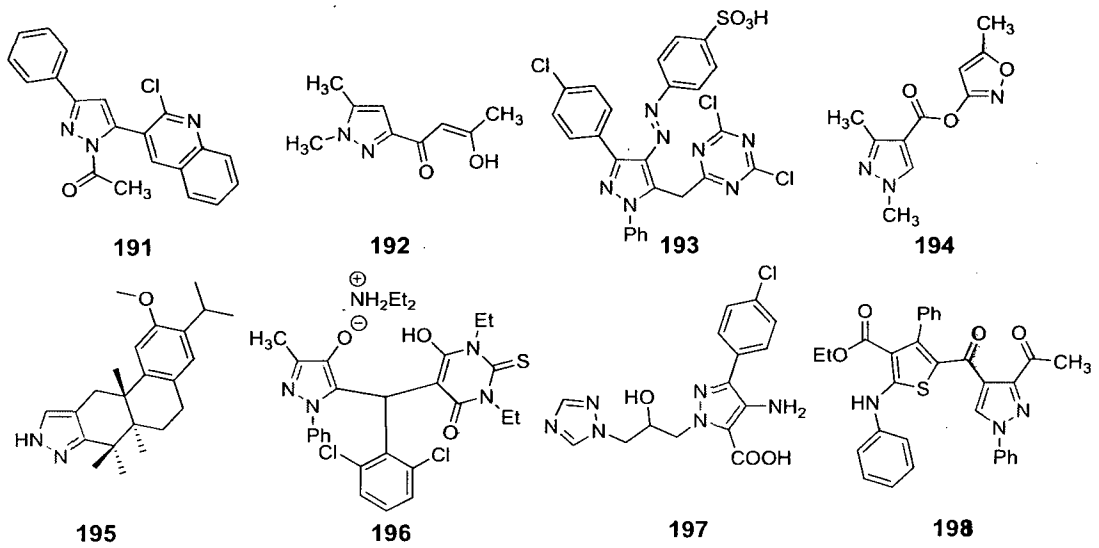


Figure 9. Pyrazole derivatives with antimicrobial activity.

A series of novel pyrazole amide derivatives (Figure 10) were synthesized and evaluated in vivo for their antifungal activity against *P. ultimum* Trow, *Phytophthora infestans* (Mont.) De Bary, *Corynespora cassiicola*, *Botrytis cinerea* and *Rhizoctonia solani*. The fungicidal results indicated that the compound **199** exhibited good control efficacy (77.78%) against *P. ultimum* Trow at a concentration of 100 μg/mL [103]. Nagamallu et al. synthesized a series of novel coumarin pyrazole hybrids were synthesized and evaluated for antimicrobial activities. Among the series, compound **200** showed excellent antimicrobial activity against different bacterial and fungal strains with MIC values in range of 12.5–50 μg/mL [104]. In another sequence of pyrazole derivatives synthesized by Radi et al., a series of new *N,N,N′,N′*-tetradentate pyrazoly derivatives were screened for their antimicrobial activity. Among the compound **201** was exceedingly antifungal active against budding yeast (*Saccharomyces cerevisiae*) cells with MIC = 500 μM [105]. A series of quinoline derivatives bearing pyrazole moiety were synthesized and evaluated for their antibacterial and antifungal activities. Pyrazole compound **202** showed better results when compared with the reference drugs as revealed from their MIC values (0.12–0.98 μg/mL) against the following human pathogens strains: *S. flexneri*, *A. clavatus*, *C. albicans*, *P. vulgaris*, *S. epidermidis* and *A. fumigatus* [106]. Ahn et al. reported the synthesis and antimicrobial activities of pyrazole-derived amino acids and peptidomimetics. Compound **203** showed the good activity against *E. coli*, *P. aeruginosa*, *S. epidermidis* and *S. aureus* with MIC values range from 4 to 32 μg/mL [107]. Nada et al. synthesized new series pyrazol-based derivatives and tested for their antimicrobial against bacterial strains *E. coli* and *S. aureus*. Data showed that pyrazole compound **204** was potent only at 0.075 mg/mL against the tested microorganisms [108]. A new series of pyrazole-containing s-triazine derivatives were synthesized by Sharma et al. and investigated for antimicrobial and antifungal activity against the growth of several microorganisms. Compound **205** exhibited antibacterial activity against bacterial strains: *P. aeruginosa*, *M. luteus* and methicillin-resistant *S. aureu* [109].

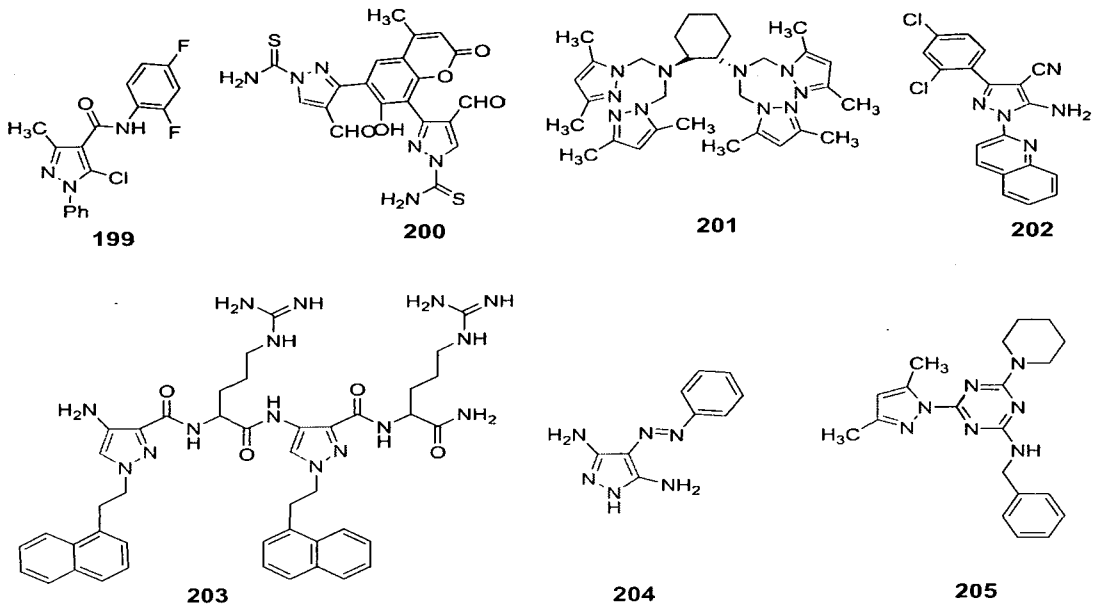


Figure 10. Pyrazole derivatives with antimicrobial activity.

A series of pyridinium-tailored 5-trifluoromethylpyrazoles containing 1,3,4-oxadiazole moieties (Figure 11) were constructed by Zhou et al. and evaluated in vitro for antimicrobial activities against three types of pathogenic bacteria and six fungal strains. Among these derivatives, compound **206** showed potent antibacterial effects against *Xanthomonas oryzae* pv. oryzae and *Xanthomonas axonopodis* pv. citri with EC_{50} values within 0.467 and 0.600 μg/mL, respectively [110]. Recently, Mondal et al. reported the syntheses and antimicrobial activity of some Ni(II), Cd(II) and Hg(II) complexes of a pyrazole containing Schiff base ligands. The results showed that the complex **207** demonstrated highest antimicrobial agents against both Gram positive and Gram negative bacteria [111]. A series of isoxazolyl thiazolyl pyrazoles were synthesized by Mor et al. and evaluated in vitro for antimicrobial activity. Amongst the newly synthesized compounds, compound **208** was found to exhibit the promising antibacterial activity against *S. aureus* [112]. A series of *N*-(1-methyl-1*H*-pyrazole-4-carbonyl)-thiourea derivatives were prepared and evaluated for antibacterial and antifungal activities. Compound **209** was found to be the most potent antimicrobial agent [113]. The synthesis and antibacterial activity of pyrazole derivative were described by Tanitame et al. Results showed that the compound **210** possesses potent antibacterial activity and selective inhibitory activity against bacterial *topoisomerases* (*MRSA*, *PRSA* and *VRE*) with MIC = 1–2 μg/mL [114]. Antibacterial activity of a-Acyl-pyrazole-3-carboxylic acids was described by Çetin et al. Results showed that the compound **211** has very potent antibacterial activity against *B. subtilis*, *S. aureus*, *E. coli*, *P. aeruginosa*, and *K. pneumonia* [115]. A series of novel pyrazolyl alcohols were prepared and evaluated for their anti-bacterial activity. The compound **212** displayed the potent anti-bacterial activity against *Micrococcus luteus* (MIC 3.9 and MBC 7.81 μg/mL) [116]. A series of novel pyrazole oxime derivatives were synthesized and evaluated for fungicidal activities in vivo against *Pseudoperonospora cubensis*. Among the synthesized compounds, compound **213** (EC_{50} = 0.51 μg/mL) showed excellent fungicidal activity against *P. cubensis* comparable or better than that of the control pyraclostrobin (EC_{50} = 4.59 μg/mL) [117].

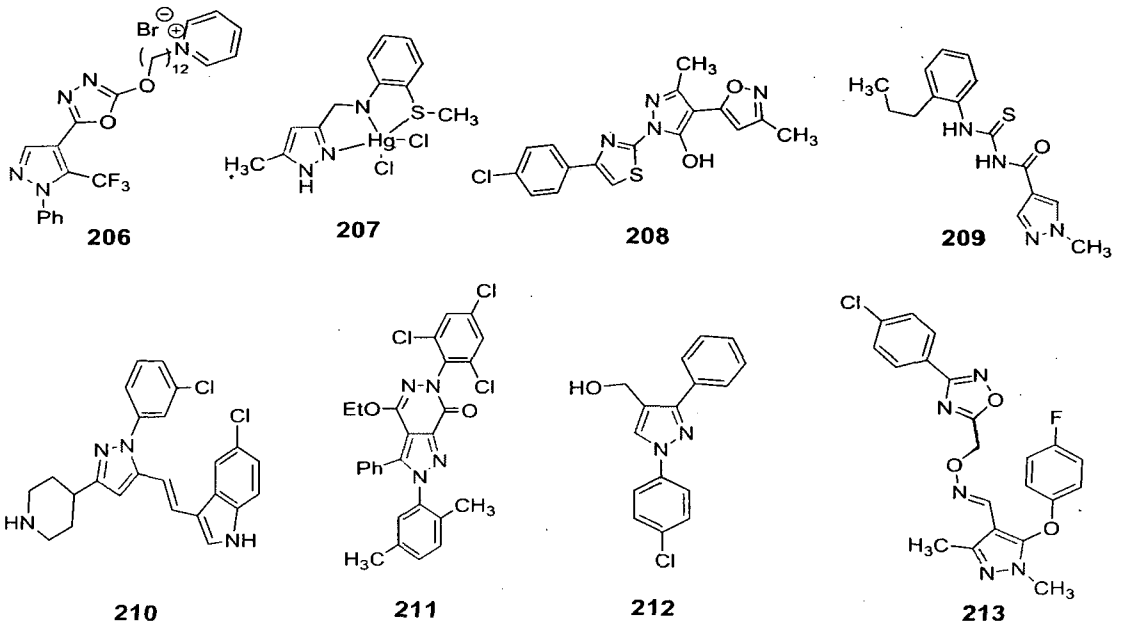


Figure 11. Pyrazole derivatives with antimicrobial activity.

3.2. *Anticancer Activity*

A new class of pyrazole-oxindole (Figure 12) were synthesized and investigated for their antiproliferative activity on different human cancer cell lines. Among the active compound **214** manifested significant cytotoxicity and inhibited tubulin assembly with IC_{50} 3 μM [118]. Xu et al. reported compound **215** as hPKM2 activator with (AC_{50} = 0.011 μM) as the most active anticancer agent with IC_{50} of 5.94 and 6.40 μM against A549 and NCI-H1299 cell lines respectively [119]. Pyrazoles derivatives synthetized by Viale et al. were secrenned for their anti-proliferative activity. The comparative data once again demonstrate the good antiproliferative activity of these compounds, confirming that **216** may be considered as a good lead compound for subsequent development [120]. Several pyrazole derivatives were reported. The bioactivities of the new compounds were evaluated through in vitro assays for endothelial cell proliferation and tube formation. Results indicated that the synthetized compound **217** exhibit potent cytostatic properties displaying IC_{50} values of 1.5 μM [121]. A series of pyrazolo[1,5-*a*]pyrazin-4(5*H*)-ones were synthesized and tested to determine their ability to inhibit the growth of A549 and H322 cancer cells. Results showed that the compound **218** exerted good activity, with an IC_{50} of of 24.2 and 29.4 μM against A549 and H322 cells lines, respectively [122]. Balbi et al. synthesized a series of pyrazole derivatives and studied their antiproliferative activity in human ovarian adenocarcinoma A2780 cells, human lung carcinoma A549 cells, and murine P388 leukemia cells. compound **216** demonstated significant antiproliferative agent [123]. A series of substituted pyrazole compounds were synthesized and evaluated in vitro for their anticancer effects on a panel of 60 cellular lines. Results showed that the compound **219** presented significant growth inhibitory effects on the tested cancer cells [124]. A series of 3,5-diarylpyrazole derivatives were synthesized and evaluated for their anticancer activity against five cell lines (breast cancer, prostate cancer, promyelocytic leukemia, lung cancer, colon cancer). Compound **220** was identified as a potent anticancer agent against all selected cell lines [125].

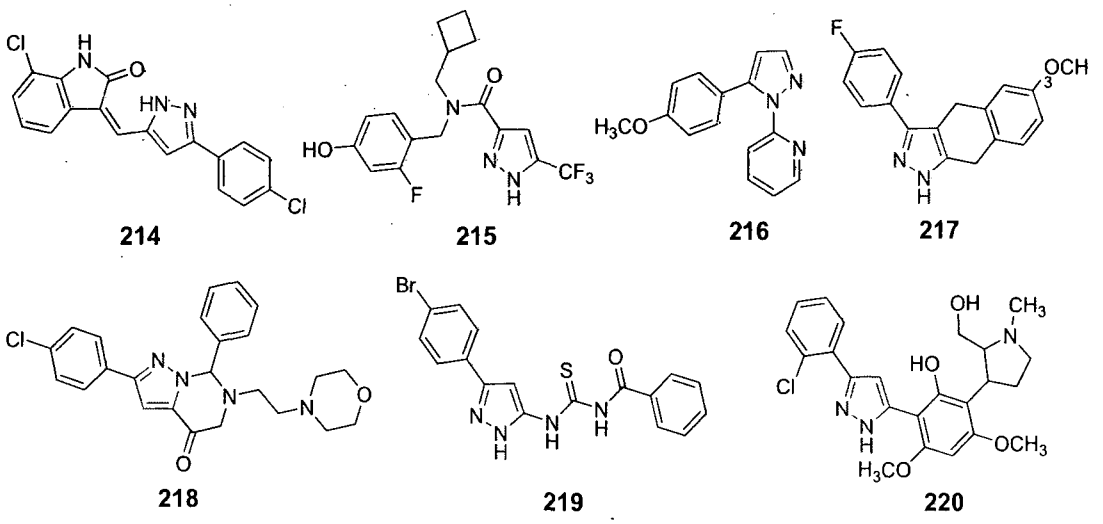


Figure 12. Structures of pyrazole derivatives with anticancer activity.

Miao and co-worker synthesized a series of pyrazoles derivatives (Figure 13) and investigated the effects of all the compounds on A549 cell growth. The results showed that the compounds **221–229** possessed the highest growth inhibitory effect and induced apoptosis of A549 lung cancer cells [126–134].

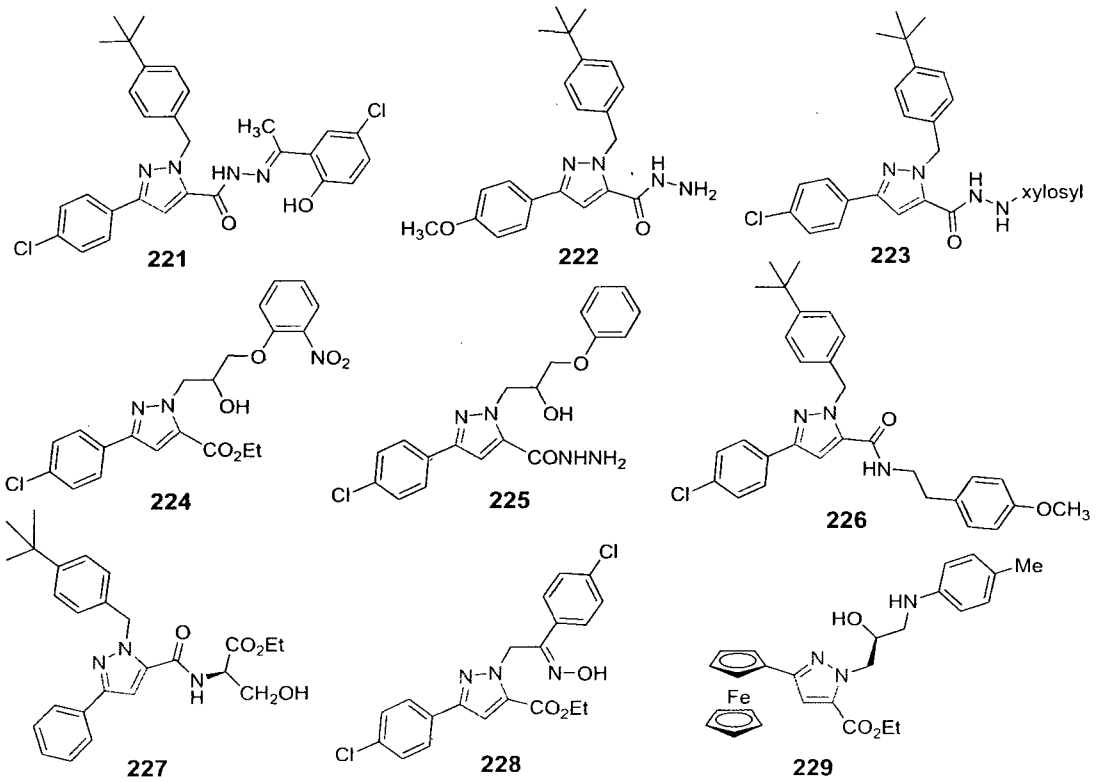


Figure 13. Pyrazole derivatives showing anticancer activity.

Farag et al. synthesized a series of pyrazole derivatives (Figure 14) and evaluated them for their antitumor activity. Compound **230** was reported as the most potent anticancer agent against Ehrlich

ascites carcinoma tumor cells [135]. Several [1,2,4]triazolo[1,5-*a*]pyridine-bearing pyrazole moieties were prepared by Jin et al. and evaluated for their ALK5 inhibitory activity in an enzyme assay and in a cell-based luciferase reporter assay. The compound **231** exerted the maximun anticancer actvity with IC_{50} of 0.57 nM [136]. Newhouse et al. reported the synthesis and anticancer activity of pyrazole derivatives. Results showed that the compound **232** exhibit excellent enzyme activity (B-Raf inhibitor) [137]. A series of novel 3-(1*H*-indole-3-yl)-1*H*-pyrazole-5-carbohydrazide derivatives were synthesized and evaluated for their in vitro cytotoxic activity against A549, HepG-2, BGC823 and BT474 cell lines. Compound **233** exhibited more potent antiproliferative activity [138]. A new family of protein farnesyltransferase inhibitors, based on a phenothiazine containing pyrazole scaffold, was synthesized and evaluated for their antiproliferative activity on a NCI-60 cancer cell line panel. Indenopyrazole **234** exhibited the most potent in vitro cytostatic activity inhibiting the growth of HCT-116, LOX IMVI and SK-MEL-5 cell lines [139]. A series of 1,4,5,6-tetrahydropyrrolo[3,4-*c*]pyrazole derivatives were synthesized and initially evaluated for their in vitro anticancer activity against human colon carcinoma HCT-116 cell line. These results indicated that the compound **235** showed considerable in vitro anticancer activity with IC_{50} of 0.58 μM [140].

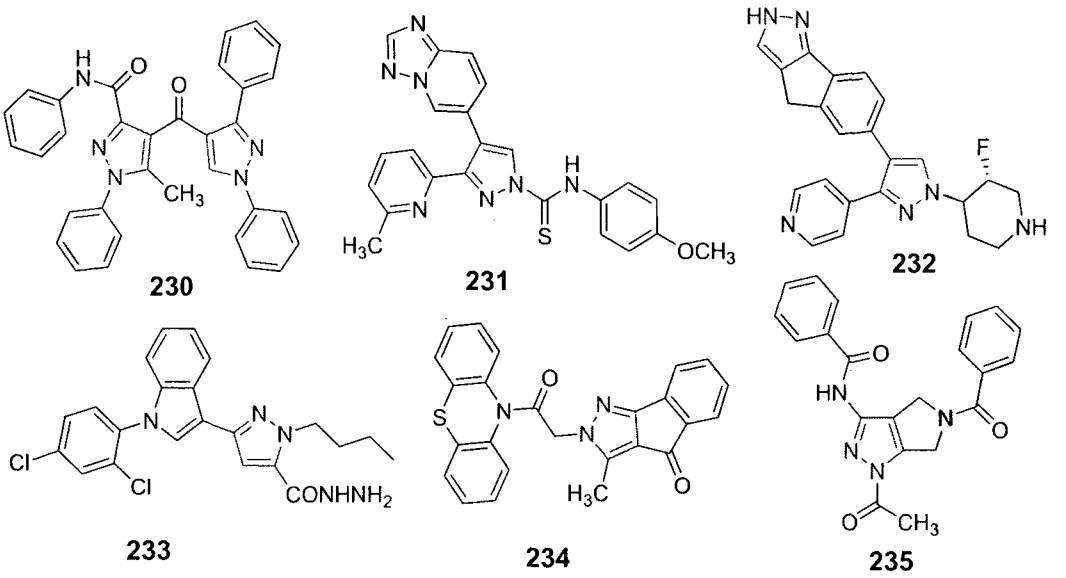


Figure 14. Pyrazole derivatives with anticancer activity.

A 1,3-dimethyl-1*H*-pyrazole-based series of imidazo[4,5-*b*]pyridines (Figure 15) were synthesized by Bevetsias et al. and assessed for their FLT3/Aurora inhibitory activity. Amongst the series, compound **236** displayed antiproliferative activity in a range of human tumor cell lines, including HCT116 human colon carcinoma (GI_{50} = 0.300 μM) and the human FLT3-ITD positive AML cell lines MOLM-13 (GI_{50} = 0.104 μM) and MV4−11 (GI_{50} = 0.291 μM) [141]. Some novel 1,3,4-oxadiazole derivatives carrying pyrazole rings were developed and evaluated for their antitumor and cytotoxic activities. The results revealed that the compound **237** displayed promising in vitro antitumor activity in the 4-cell lines assay [142]. Cui et al. identified a new c-MET inhibitor. Compound **238** demonstrated effective tumor growth inhibition in c-MET dependent tumor models with good oral PK properties and an acceptable safety profile in preclinical studies. Compound **238** progressed to clinical evaluation in a Phase I oncology setting [143]. A series of new pyrazolo[3,4-*d*]pyrimidines were synthesized and investigated for their anti-tumor activity. Compound **239** was the most active compound with IC_{50} equal to 7.5 nM [144]. A series of pyrazolo[3,4-*b*]pyridine derivatives were prepared by El-Borai et al. and tested for antitumor activity against liver cell line. Compounds **240**

showed the highest activity with IC_{50} 3.43 μg/mL [145]. Hanan et al. developed a new series of pyrazoles derivatives bearing pyrazolo[1,5-*a*]pyrimidine scaffold and optimized for their activity against Janus kinase 2 inhibitors. Compound **241** was identified as a potent inhibitor of Jak2 (Ki = 0.1 nM) and demonstrated a time-dependent knock-down of pSTAT5 (IC_{50} = 7.4 nM) [146]. A novel series of pyrazolo[3,4-*d*]pyrimidines derivatives were developed by Huang et al. and evaluated for their anticancer activity. Among the examples, compound **242** possessed better potency against NCI-H226 and NPC-TW01 cancer cells with GI_{50} values 18 mM [147]. Li et al. synthesized a series of 1*H*-pyrazole-4-carboxamide derivatives and evaluated for their potential antiproliferation activity and Aurora-A kinase inhibitory activity. Among all the compounds, compound **243** possessed the most potent biological activity against HCT116 and MCF-7 cell lines with IC_{50} values of 0.39 μM and 0.46 μM, respectively. Compound **243** also exhibited significant Aurora-A kinase inhibitory activity (IC_{50} = 0.16 ± 0.03 μM) [148].

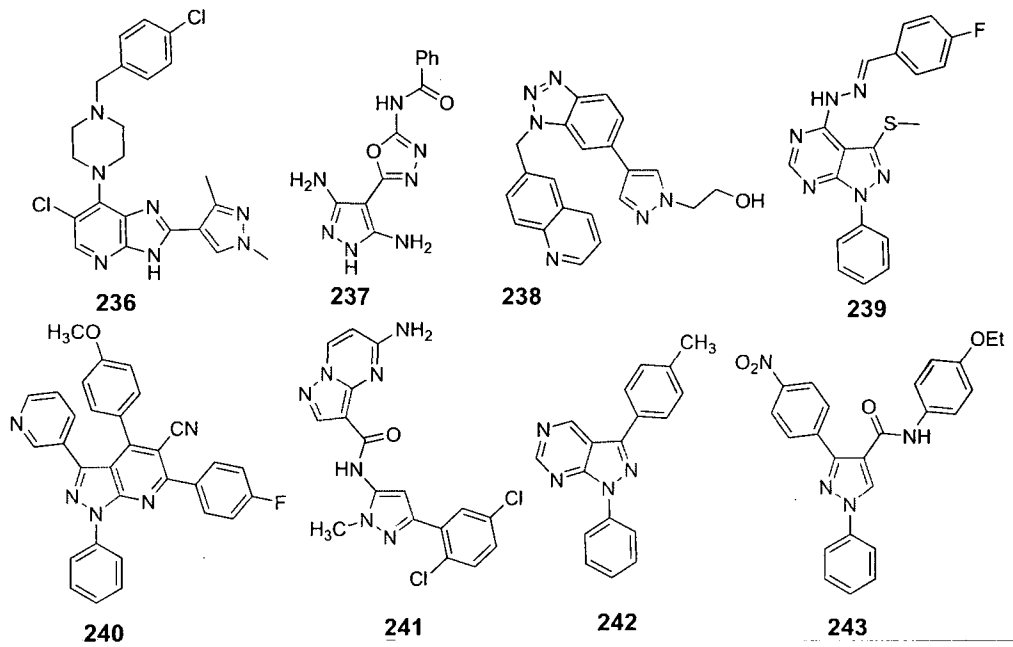


Figure 15. Pyrazole derivatives with anticancer activity.

A series of pyrazoles derivatives (Figure 16) were synthesized and screened for their cytotoxic activity. The results showed clearly that compound **244** displayed promising in vitro anticancer activity against four different cell lines (HepG2, WI 38, VERO and MCF-7) [149]. Mohareb et al. synthesized of new series of pyrazoles derivatives containing pregnenolone moiety and evaluated for their cytotoxicity against three human tumor cell lines. Compound **245** was found to exhibit much higher inhibitory effects towards adenocarcinoma (MCF-7), non-small cell lung cancer (NCI-H460) and CNS cancer (SF-268), with IC_{50} values 0.01, 0.02 and 0.04 μM, respectively [150]. The same authors synthesized a series of pyrazolyl semicarbazidoandrrostane derivatives and tested their cytotoxicity activity, whereby compound **246** displayed excellent cytotoxicity with IC_{50} values 0.02, 0.01 and 0.03 μM against MCF-7, NCI-H460 and SF-268 cells, respectively [151]. Puthiyapurayil et al. reported the synthesis and anticancer activity of pyrazoles derivatives bearing a *S*-substituted-1,3,4-oxadiazole moiety. Amongst the tested compounds, the compound **247** was the most promising anticancer agent, with an IC_{50} value of 15.54 μM in MCF-7 cells, compared to doxorubicin as standard drug [152]. Small pyrazole derivatives were developed and evaluated in vitro for their anticancer activity on HCC-derived cell lines. The compound **248** selected as potential agents active against hepatocellular carcinoma (HCC) and showed a promising inhibitory growth efficacy (IC_{50} = 50 mM) in SNU449 cell

line [153]. Synthesis and anticancer activities of new pyrazole derivatives bearing 1,2,4-oxadiazole moiety were reported by Vujasinovic et al. Therefore, compound **249** presents a good starting point for design of new, more potent and safer anticancer therapeutics [154].

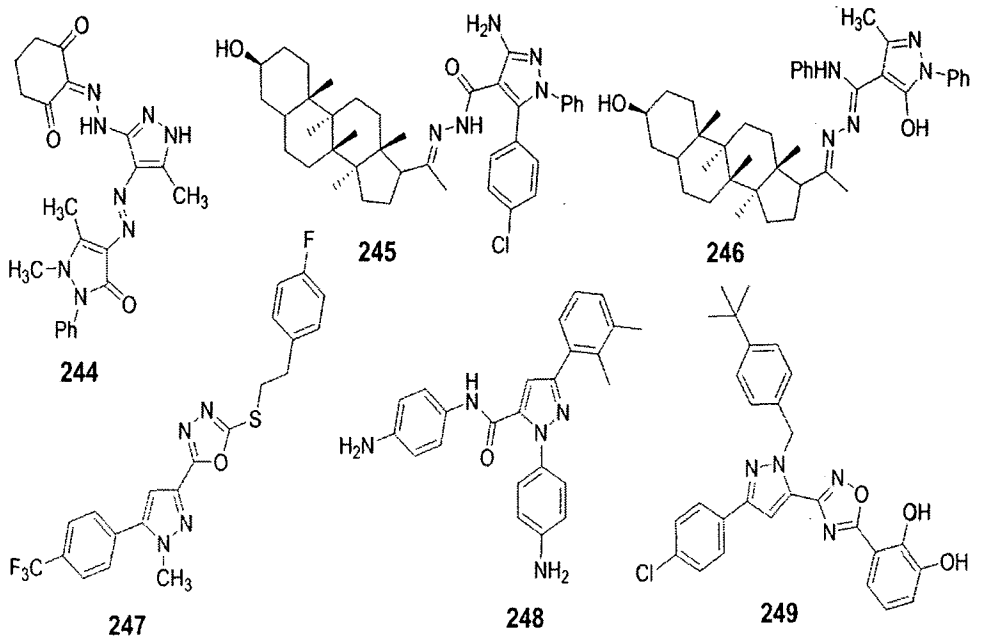


Figure 16. Pyrazole derivatives with anticancer activity.

Yamamoto et al. synthesized a series of 4-arylmethyl-1-phenylpyrazole derivatives (Figure 17) and evaluated their potential as new-generation androgen receptor (AR) antagonists therapeutically effective against castration-resistant prostate cancer (CRPC). Compound **250** exhibited potent antitumor effects against a CRPC model of LNCaP-hr cell line in a mouse xenograft model [155]. Some new pyrazolo[1,5-*a*]-pyrimidines were prepared and evaluated for their cytotoxicity activity against Vero cells. Compound **251** was reported as the most active compounds of the series [156]. Bevetsias et al. synthesized a new 1,3-dimethyl-1*H*-pyrazole-based series of imidazo[4,5-*b*]pyridines and tested them for their Aurora-A kinase inhibitory activity. Amongst the series, compound **252** displayed antiproliferative activity in a range of human tumor cell lines, including Aurora-A (GI_{50} = 0.067 μM) Aurora-A (IC_{50} = 12.71 μM) and in HCT116 human colon carcinoma cells (p-T288, IC_{50} = 0.065 μM; p-HH3, IC_{50} = 24.65 μM) [157]. Desai et al. synthesized of novel *Abl* kinase inhibitors. Within just **253** compounds, identified a novel template and hinge binding motif with pIC_{50} > 8 against Abl kinase both wild type and clinically relevant mutants [158]. A series of pyrazoles derivatives bearing 4b-amidopodophyllotoxin rings were synthesized and evaluated for anticancer activity against five human cancer cell lines. Among the series, one of the compounds, 254, showed significant antiproliferative activity in A549 (lung cancer) cell line [159]. Koca et al. a new series of acyl thiourea derivatives containing pyrazole ring were prepared and evaluated for their anticancer activity. Compound **255** was reported as the most potent anticancer agent [160]. Miyamoto et al. described the synthesis and anticancer activity of 1*H*-pyrazole-5-carboxamide deriavtives. Compound **256** emerged as a highly potent VEGF receptor 2 kinase inhibitor with an IC_{50} value of 0.95 nM and suppressed proliferation of VEGF-stimulated human umbilical vein endothelial cells with an IC_{50} of 0.30 nM [161].

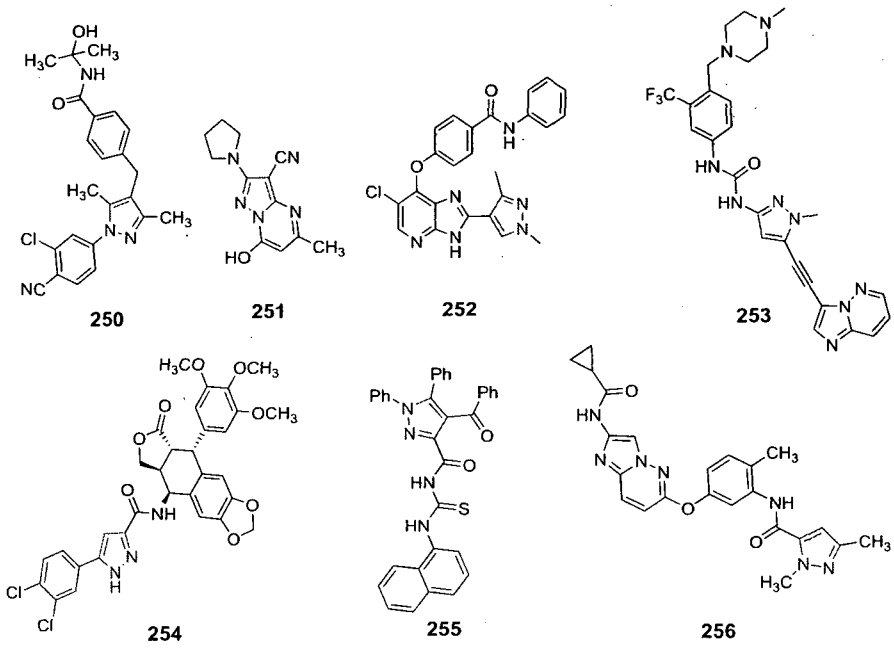


Figure 17. Pyrazole derivatives with anticancer activity.

A series of novel pyrazolo[1,5-*a*][1,4]dia-zepin-4-one derivatives containing ferrocene scaffolds (Figure 18) were synthesized and evaluated for their anticancer activity against A549, H322 and H1299 lung cancer cells. Of them, compound **257** possessed notable cytotoxicity and selectivity for A549 vs. H1299 and H322 lung cancer cells [162]. Zhu et al. prepared a series of novel carbothioamide-pyrazole derivatives and tested for their in vitro cytotoxic activities against four human tumor cell lines. Results indicated that compound **258** exhibited potent cytotoxicity (IC_{50} = 6.51 μM) against Raji cell [163].

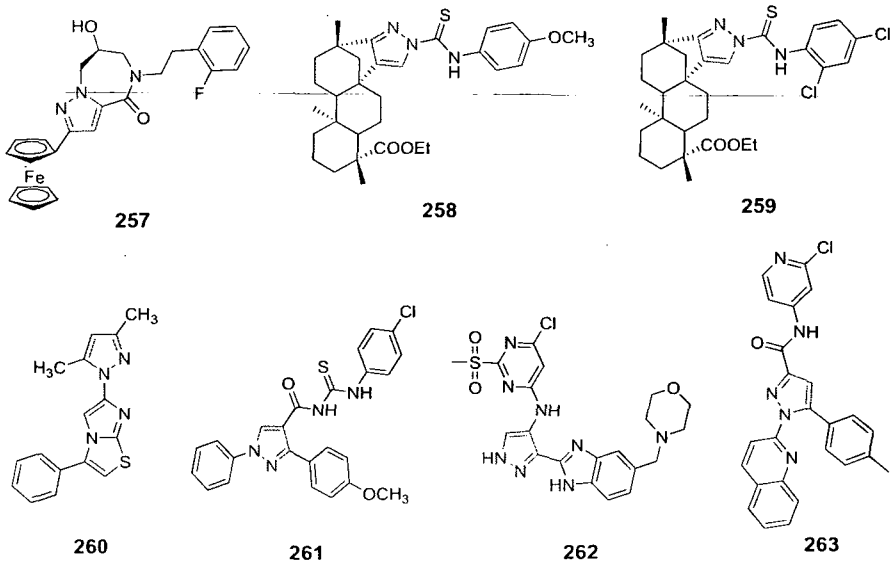


Figure 18. Pyrazole derivatives with anticancer activity.

A series of novel isosteviol-fused pyrazole derivatives were synthesized and evaluated in vitro for their antiproliferative activities on four human malignant cell lines. Results revealed that

compound **259** displayed better cytotoxities with IC_{50} values: 2.71, 3.18, 1.09 and 13.52 mM against SGC 7901, A549, Raji and HeLa, respectively, compared to cisplatin (IC_{50} values: 7.56, 17.78, 17.32 and 14.31 mM, respectively) [164]. A series of imidazo[2,1-*b*]thiazoles bearing pyrazole moieties were synthesized and tested in vitro for their anticancer activity. Result showed that compounds **260** had the highest anticancer effect against CNS SNB-75 and renal UO-31 cancer cell lines [165]. Sun et al. synthesized a series of 1*H*-pyrazole-4-carboxamide derivatives and evaluated for their antiproliferative activities as CDKs inhibitors. Among all the synthesized compounds, compound **261** inhibited CDK2 with an IC_{50} value 25 nM [166]. Novel pyrazole–benzimidazole derivatives were synthesized and evaluated for their anticancer activities against cancer cell lines U937, K562, A549, LoVo and HT29 and were screened for Aurora A/B kinase inhibitory activity in vitro. The **262** demonstrated significant cancer cell lines and Aurora A/B kinase inhibitory activities [167]. A series of novel 5-(*p*-tolyl)-1-(quinolin-2-yl)pyrazole-3-carboxylic acid derivatives were synthesized and assessed for their antiproliferative activities against three human cancer cell lines (Huh7, human liver; MCF7, breast and HCT116, colon carcinoma cell lines). Compound **263** exhibited promising cytotoxic activity against all cell lines with IC_{50} values of 1.6 μM, 3.3 μM and 1.1 μM for Huh7, MCF7 and HCT116 cells, respectively [168].

Cd(II) complexes of tridentate nitrogen donor ligand, 2,6-bis(3,4,5-trimethylpyrazolyl)pyridine (Figure 19) were synthesized and tested for cytotoxic activity against the human carcinoma cell lines HEP3B (hepatocellular carcinoma), PC3 (prostate adenocarcinoma), MCF7 (breast adenocarcinoma) and Saos2 (osteosarcoma). The results showed that, complex **264** is the most cytotoxic complex for PC3 [169]. A series of pyrazoles derivatives were synthesized and evaluated for their ALK5 inhibitory activity. Among them, compound **265** inhibited ALK5 phosphorylation with an IC_{50} value of 0.018 μM [170].

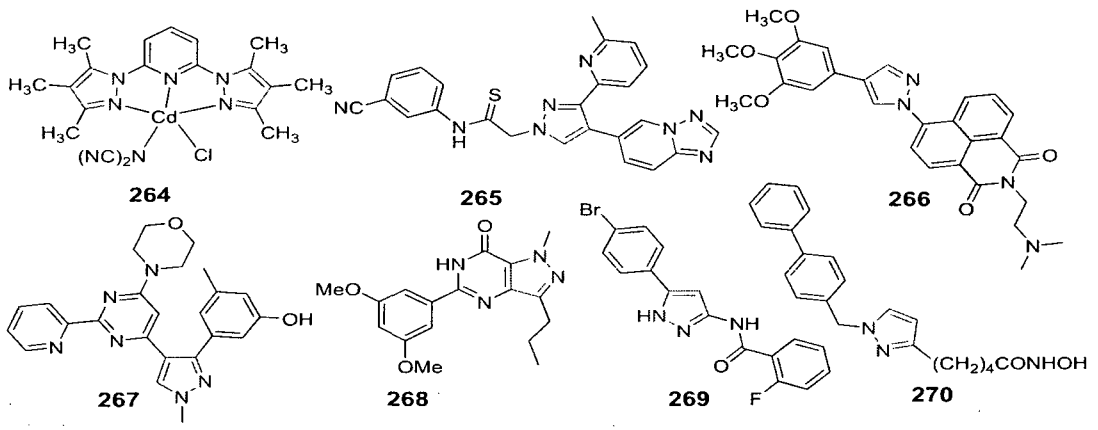


Figure 19. Pyrazole derivatives with anticancer activity.

Li et al. synthesized a novel series of 4-pyrazolyl-1,8-naphthalimide derivatives and tested in vitro for their anticancer activity. Compound **266** showed improved cytotoxic activity with IC_{50} value of 0.51 μM against MCF-7 cells line [171]. Park et al. reported trisubstituted pyrazole-based ROS1 inhibitors. Among these compounds, compound **267** (IC_{50} = 13.6 nM) has exerted 5 fold potency than crizotinib and exhibited high degree of selectivity (selectivity score value = 0.028) representing the number of non-mutant kinases with biological activity over 90% at 10 μM [172]. A series of 1*H*-pyrazolo[4,3-*d*]pyrimidin-7(6*H*)-ones were developed and evaluated in vitro for their anticancer activity against human cancer cell lines HeLa, CAKI-I, PC-3, MiaPaca-2, A549 gave good results. Compound **268** revealed that the compound shows anticancer activity through apoptosis mechanism and also inhibits mTOR with nonomolar potency [173].

A series of novel 5-phenyl-1*H*-pyrazole derivatives were synthesized by Wang et al. and evaluated for their antiproliferative as potential BRAFV600E inhibitors. Among them, compound **269** exhibited the most potent inhibitory activity with an IC_{50} value of 0.33 μM for BRAFV600E and has better antiproliferative activity against WM266.4 and A375 with IC_{50} value of 2.63 and 3.16 μM, respectively [174]. Yao et al. reported compound **270** to have appreciable inhibitory activity against class I and IIb HDAC and in vitro anticancer activities against several cancer cell lines [175].

A series of novel pyrazolyl hydroxamic acid derivatives (Figure 20) were synthesized and investigated in vitro for their anticancer activities against human lung cancer cell line A549. The results showed that the compounds **271** (10 μM) exerted more effective anti-proliferation activity against A549 cell line [176]. Abd El-Karim et al. synthesized a series of novel benzofuran-pyrazole and evaluated for their in vitro antiproliferative activity. Compound **272** exhibited remarkable growth inhibitory activity pattern against leukemia CCRF-CEM, MOLT-4, lung cancer HOP-92, colon cancer HCC-2998, CNS cancer SNB-75, melanoma SK-MEL-2, ovarian cancer IGROV1, renal cancer 786-0, RXF 393, breast cancer HS 578T and T-47D (GI_{50}: 1.00–2.71 μM) [177]. A series of novel 4-pyrazolecyclopentylpyrimidines were prepared and evaluated in vitro as IGF-1R tyrosine kinase inhibitors. Compound **273** was found to be most active, with an IC_{50} value of 10 nM [178]. Several new series of benzenesulfonamide derivatives incorporating pyrazole were prepared by Ibrahim et al. and screened for anti-tumor activity against the metalloenzyme carbonic anhydrase and human isoforms hCA I, II, IX and XII. The in vitro evaluation demonstrated compounds **274** was found to inhibit hCA XII with Ki of 3.7 nM [179]. New arylpyrazole linked benzimidazole conjugates were synthesized and evaluated for their ability to inhibit the growth of sixty cancer cell line panel. Compound **275** exhibited significant growth inhibitory activity against most of the cell lines ranging from 0.3 to 3 μM and expressed appreciable cytotoxic potential [180]. A series of pyrazolylpyrazolines were synthesized and evaluated for carbonic anhydrase inhibitory activity against cytosolic human isozymes. Compound **276** exhibited better inhibition profile against hCA II (Ki = 0.17 nM) [181]. 3-(2-chloroethyl)-5-methyl-6-phenyl-8- (trifluoromethyl)-5,6-[3,4-*f*][1,2,3,5]tetrazepin-4-(3*H*)-one **277** synthesized by Maggio et al. was tested antiproliferative activity. The compound exerted the maximum antiproliferative activity with GI_{50} value of 2.3 μM [182].

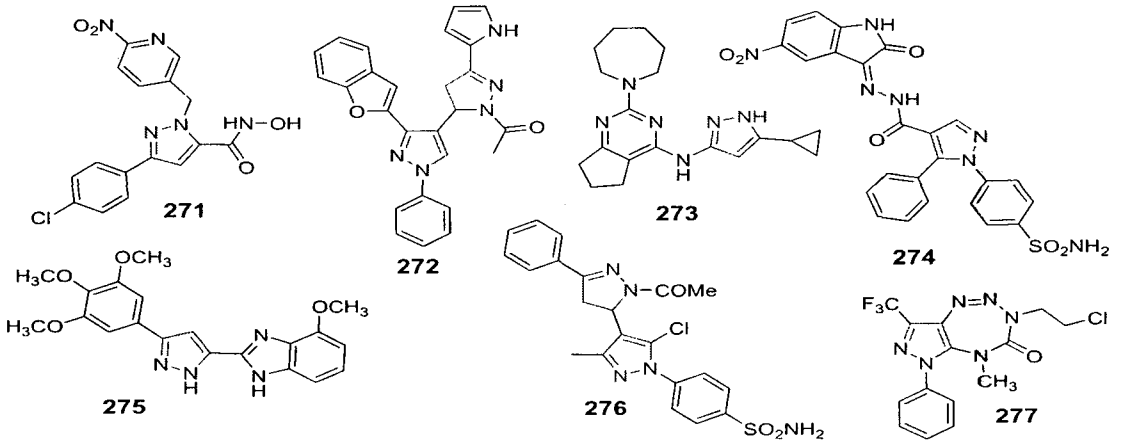


Figure 20. Some structures of pyrazoles with anticancer activity.

Nitulescu et al. synthesized new pyrazole thiourea derivatives (Figure 21) and studied their apoptotic effects in human cancer cells. The results showed that the compound **278** exhibited the highest apoptosis-inducing effect [183]. The same author described the synthesis of new pyrazole derivatives as inhibitors of the cell cycle kinases. The compound **279** induced a significant increase of cells in G2/M phases in conjunction with an increased expression of cyclin A and cyclin B, emerging as a promising anticancer drug [184]. New pyrazole chalcones derivatives were described and assessed

in vitro for their anticancer activity. The compound **280** was reported as potent anticancer agent with IC_{50} values of 18 and 47 μM against HeLa and MCF-7 cell lines, respectively [185]. A series of pyrazole derivatives containing benzimidazole moiety were synthesized and evaluated for their potential anti-proliferative activity against three human tumor cell lines. Compound **281** showed potent growth inhibition against A549, MCF-7, HeLa and HaCaT cell lines with IC_{50} values of 1.13, 0.95 and 1.57 μM, respectively [186]. Steroidal derivatives containing a pyrazole moiety were synthesized and evaluated for anticancer activity against a human leukemia cell line (HL-60). Compound **282** displayed promising behavior by showing better anticancer activity [187]. Shi et al. synthesized a series of pyrazole-carboxamide derivatives and evaluated for anticancer activity. Compound **283** exhibited strong inhibitory activity against MGC-803 cells, and showed the most potent telomerase inhibitory activity [188]. A series of pyrazoles derivatives synthesized by Alam et al. and evaluated for topoisomerase IIa inhibitory activity and in vitro cytotoxicity against a panel of cancerous cell lines (MCF-7, NCI-H460, HeLa) and a normal cell line (HEK-293T). Compound **284** showed superior cytotoxicity with an IC_{50} value of 7.01 μM for HeLa, 8.55 μM for NCI-H460 and 14.31 μM for MCF-7 cancer cell lines [189]. *N*-(Benzyloxy)-1,3-diphenyl-1*H*-pyrazole-4-carboxamide derivatives were synthesized and evaluated for anticancer activity as MEK inhibitors. Among these compounds, compound **285** showed the most potent inhibitory activity with IC_{50} of 91 nM for MEK1 and GI_{50} value of 0.26 μM for A549 cells [190].

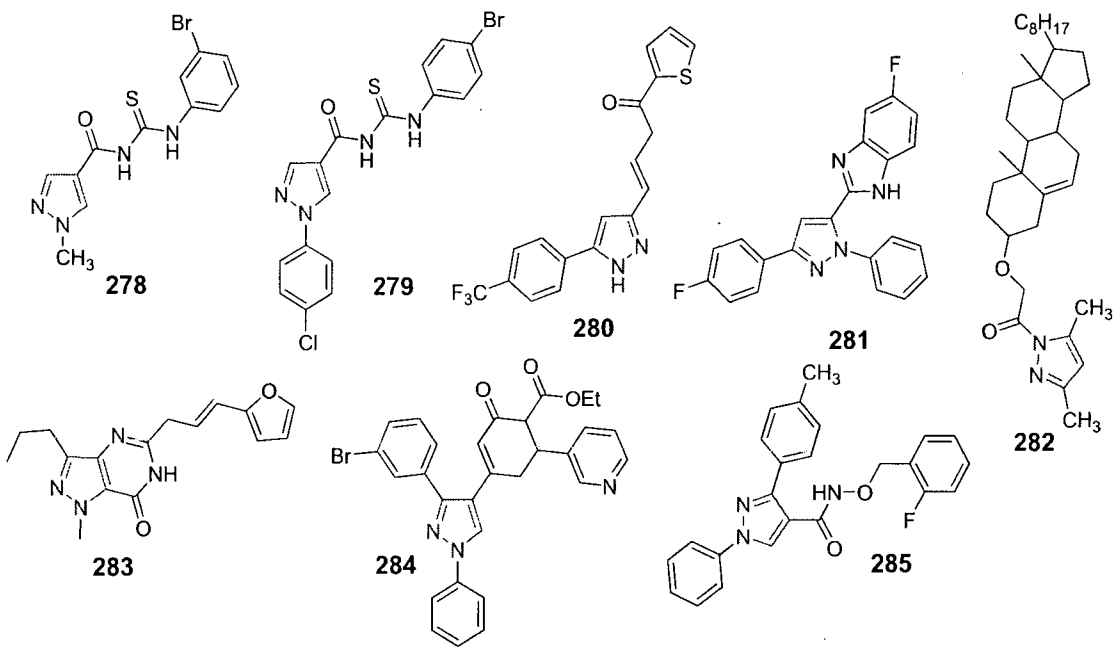


Figure 21. Pyrazole derivatives with anticancer activity.

A series of 1,4,6,7-tetrahydropyrano[4,3-*c*]pyrazole derivatives (Figure 22) were synthesized and tested in vitro for antitumor activity against four human cancer cell lines (MCF-7, EC-109, HGC-27, and PC-3). Compound **286** showed the most potent inhibitory activity against HGC-27 and PC-3 [191]. A new collection of *N*-(6-mercaptohexyl)-3-substituted-1*H*-pyrazole-5-carboxamide HDAC inhibitors was developed by Wen et al. The disulfide compound **287** was found to be potent cytotoxic agent against a panel of seven tumor cells, causing hyperacetylation of histone and non-histone proteins in cellular level, and demonstrated a notable in vivo anti-tumor activity in HCT-116 xeno-grafted model [192]. Pyrazole-benzimidazole derivatives are novel potent active Chk2 inhibitors were described by Galal et al. Out of the synthesized compounds, compound **288** was reported as the most potent effects as Chk2 inhibitors with cytotoxic properties besides their potentiation effects on

the cytotoxicity of both cisplatin and doxorubicin, and showed marked antitumor activity as single agent in breast cancer–bearing animals [193]. A novel series of 1*H*-pyrazole-3-carboxylate derivatives were synthesized and screened for antitumor activity against BEL-7404, HepG2, NCI-H460, T-24, A549 tumor cell lines. Compound **289** exhibited lower IC_{50} value (129.75 μM) against HepG2 [194]. Li et al. synthesized novel steroidal pyrazole derivatives and evaluated for their cytotoxicity activity against 293T cell lines and three cancers cell lines: A549, Hela and MCF-7. Compound **290**, showed the highest potency, with an IC_{50} values of 0.87 μM and 0.53 μM for 293T cell lines and Hela cell lines, respectively [195]. A series of scopoletin-pyrazole hybrids were synthesized and their anticancer activities were evaluated in vitro against three human cancer cell lines including HCT-116, Hun7 and SW620. Results showed that the compound **291** exhibited potent cytotoxic activities with IC_{50} values below 20 μM [196]. A series of pyrazole derivatives bearing Sorafenib scaffold were synthesized by Wang et al. and evaluated for the cytotoxicity against A549, HepG2, MCF-7, and PC-3 cancer cell lines and some selected compounds were further evaluated for the activity against VEGFR-2/KDR, BRAF, CRAF, c-Met, EGFR and Flt-3 kinases. Compound **292** exhibited moderate to good activity toward c-Met and showed moderate to no activity against CRAF, EGFR, Flt-3 kinases, and showed strong antitumor activities against A549, HepG2 and MCF-7 cell lines with IC_{50} values of 2.84, 1.85 and 1.96 μM, respectively [197]. Several new 4-(3,3-dimethyltriazeno)-5-benzamidopyrazole derivatives were prepared and tested at 10 μM for their vitro anti-leukemic activity against K562 and Raji cell lines. The most active compound **293** showed growth inhibition values of 97.8% and 99.4% against the K562 and Raji cell lines, respectively [198].

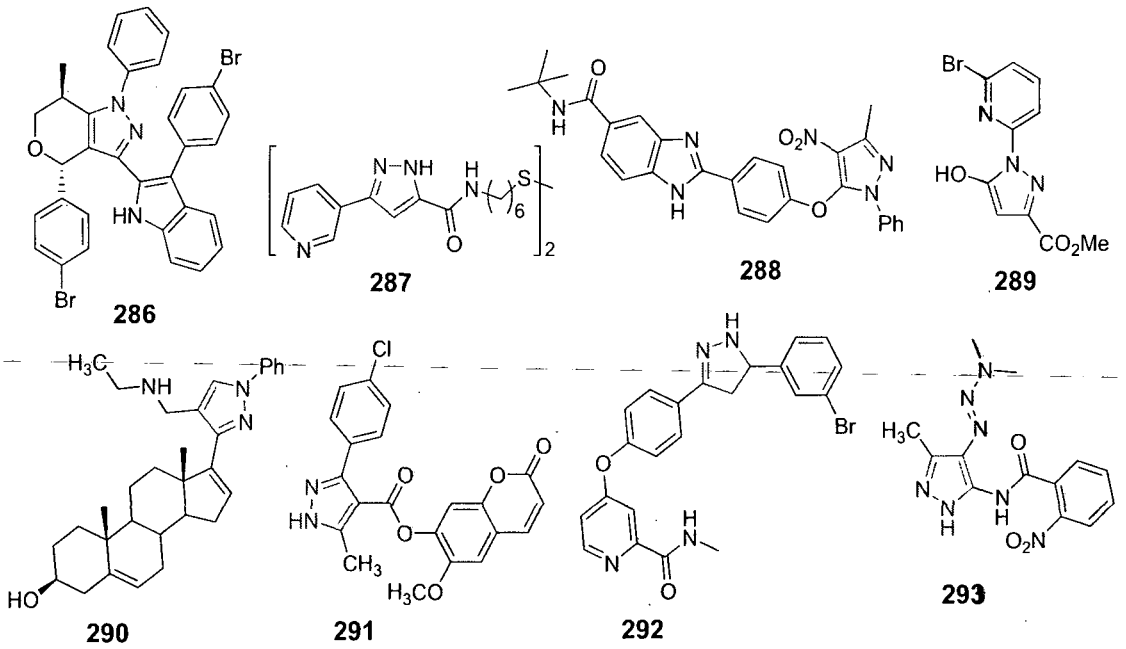


Figure 22. Pyrazole derivatives with anticancer activity.

3.3. *Anti-Inflammatory and Analgesic Activity*

A new group of pyrazole derivatives were designed (Figure 23) for evaluation as selective cyclooxygenase-2 (COX-2) inhibitors. Results indicated that the compound **294** exhibited significant COX-II inhibition (78.91±0.80 %) [199]. A series of 1*H*-pyrazolyl derivatives were described by Bekhit et al. and tested for their in vivo anti-inflammatory activity. Compound **295** exhibited anti-inflammatory activity comparable to that of indomethacin (LD_{50} > 500 mg/Kg), and showed good selective inhibitory activity against COX-2 enzyme [200]. Bekhit et al. synthesized a series of novel

pyrazolyl benzenesulfonamide derivatives bearing thiazolyl ring and evaluated for anti-inflammatory activity. Among the synthesized compounds, compound **296** exhibited higher anti-inflammatory activity than the reference compound (indomethacin) [201]. 3,5-Diaryl pyrazole derivatives were prepared and evaluated for anti-inflammatory activity. Compound **297** was identified as the potent ant-inflammatory agent against TNF-α and IL-6 at 10 μM concentration [125]. Girisha et al. synthesized a novel series of 1-acetyl/propyl-3-aryl-5-(5-chloro-3-methyl-1- phenyl-1*H*-pyrazol-4-yl)-2-pyrazolines and screened for analgesic and anti-inflammatory activity. Compound **298** showed good activity comparable with that of standard drugs pentazocin and diclofenac sodium, respectively [202]. Sharma et al. synthesized and evaluated pyrazolyl-pyrazoline derivatives for their anti-inflammatory activity using carrageenan-induced rat paw edema assay. Amongst the tested compounds, **299** showed pronounced anti-inflammatory activity (32%) that was comparable to nimesulide (36%) [69]. Synthesis and anti-inflammatory evaluation of new 2,3-dihydro-imidazo[1,2-*b*]pyrazole derivatives were reported by Brullo et al., in which compound **300** showed an interesting dual activity inhibiting both fMLP-OMe and IL8-induced chemotaxis with IC_{50} values of 3.9 and 1.2 nM, respectively [203]. A novel series of pyrazoles containing benzenesulfonamides were synthesized by El-Moghazy et al., and evaluated in vivo for their anti-inflammatory activity. Compound **301** was found to be the most active anti-inflammatory agent (62.67% inhibition of edema) comparable to that of indomethacin (60.8% inhibition of edema) [204].

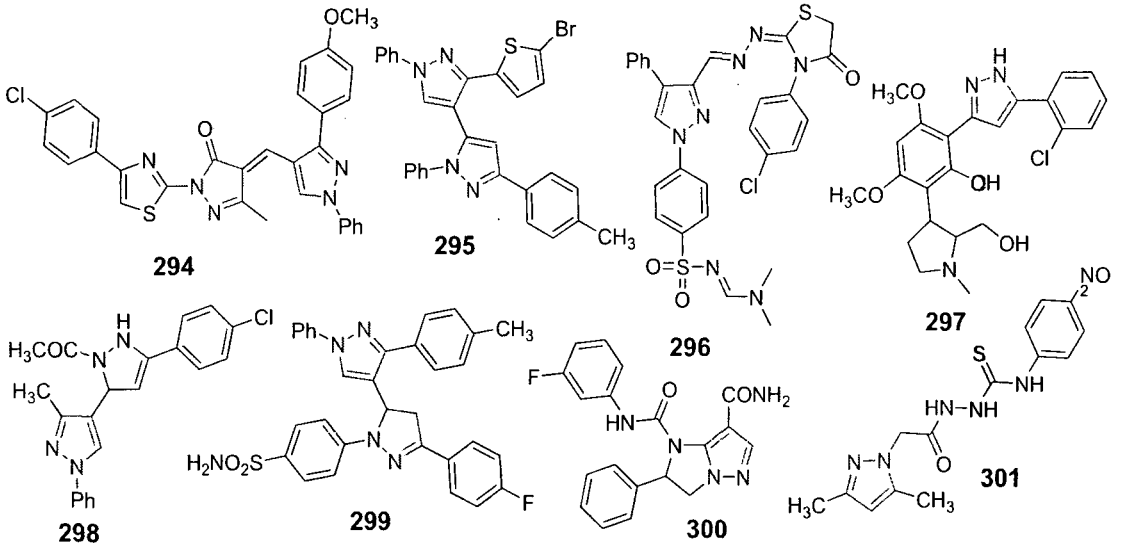


Figure 23. Pyrazole derivatives with anti-inflammatory activity.

Pyrazole analogues (Figure 24) synthesized by Magda, et al., were evaluated in vitro for their ability to inhibit ovine COX-1/COX-2 isozymes. Among the tested compounds, compound **302** exhibited optimal COX-2 inhibitory potency (IC_{50} = 0.26 μM) and selectivity (SI = 192.3) comparable with reference drug celecoxib (IC_{50} value of 0.28 μM and selectivity index of 178.57) [205]. A series of dihydropyrazolyl-thiazolinone derivatives were synthesized and evaluated as potential cyclooxygenase-2 (COX-2) inhibitors. Among these compounds, compound **303** displayed the most potent COX-2 inhibitory activity with IC_{50} of 0.5 μM [206]. 1,3,4-Trisubstituted pyrazole derivatives were synthesized and screened for the anti-inflammatory activity by carrageenan-induced paw edema method. Compounds **304** showed excellent anti-inflammatory actvity (≥84.2% inhibition) compared to that of the standard drug diclofenac (86.72%) [207]. Novel series of celecoxib analogs were synthesized and evaluated for COX-1/COX 2 inhibitory activity and assessed for their anti-inflammatory activity and ulcerogenic liability in vivo. The 3-(pyridin-3-yl)pyrazole derivative **305** exhibited the highest

anti-inflammatory activity and demonstrated about 40% reduction in ulcerogenic potential relative to the reference drug [208]. Karrouchi et al. synthesized pyrazole-hydrazone derivatives and evaluated for their anti-inflammatory activity. The anti-inflammatory activity of **306** at the dose of 100 mg/kg showed excellent protection against inflammation (92.59% inhibition) in comparison with Indomethacin [209]. A series of 1-(4-substituted-phenyl)-3-phenyl-1*H*-pyrazole-4-carbaldehydes were prepared and tested for their anti-inflammatory and analgesic activities. Among the prepared compounds, compound **307** exhibited the maximum anti-inflammatory and analgesic activities [210]. A novel series of pyrazole derivatives were synthesized by Tewari et al. and evaluated in vivo for their anti-inflammatory activity. Among all compounds, **308** showed comparable anti-inflammatory activity to nimesulide [211].

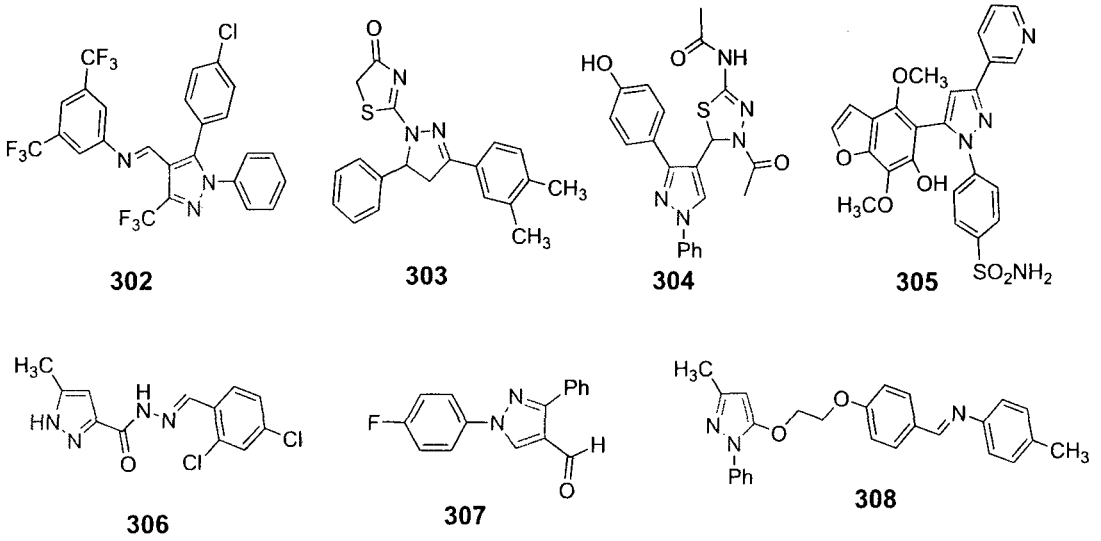


Figure 24. Pyrazole derivatives with anti-inflammatory and analgesic activities.

Several new pyrazole derivatives (Figure 25) containing a quinolone moiety were synthesized and tested for their anti-inflammatory and ulcerogenic effect. The most active compound **309** was found to be superior to celecoxib, and demonstrated the highest anti-inflammatory activity as well as the best binding profiles into the COX-2 binding site [212]. Hussain et al. synthesized pyrazole derivatives and investigated them for their, anti-inflammatory and analgesic activities. Results indicated that the compound **310** (80.29% inhibition) showed anti-inflammatory activity almost equal to that of the standard drug, ibuprofen (80.38%). Compound **311** showed moderate analgesic activity in comparison to their standard drugs [213]. Surendra Kumar et al. reported the synthesis and anti-inflammatory activity of pyrazole derivatives. The derivative **312** showed significant anti-inflammatory activity when compared to the standard drug diclofenc sodium [214]. A series of 1,3-diaryl pyrazole derivatives bearing aminoguanidine moiety were synthesized and evaluated for and anti-inflammatory activities. Compound **313** showed the greatest anti-inflammatory activity (93.59% inhibition), which was more potent than the reference drugs ibuprofen and indomethacin [215]. Compound **314** were identified by Pelcman et al., as the most potent inhibitors of human 15-lipoxygenase [216]. Wang et al. identified a series of novel pyrazole containing benzamides as potent RORγ inverse agonists. Compound **315** was found to be more potent, selective and have adequate profiles RORγ inverse agonists [217]. A series of novel ethyl-5-amino-3-methylthio-1*H*-pyrazole-4-carboxylates were synthesized and were screened for in vivo analgesic and anti-inflammatory activities. Compound **316** exhibited significant analgesic and anti-inflammatory activities at a dose of 25 mg/kg [218].

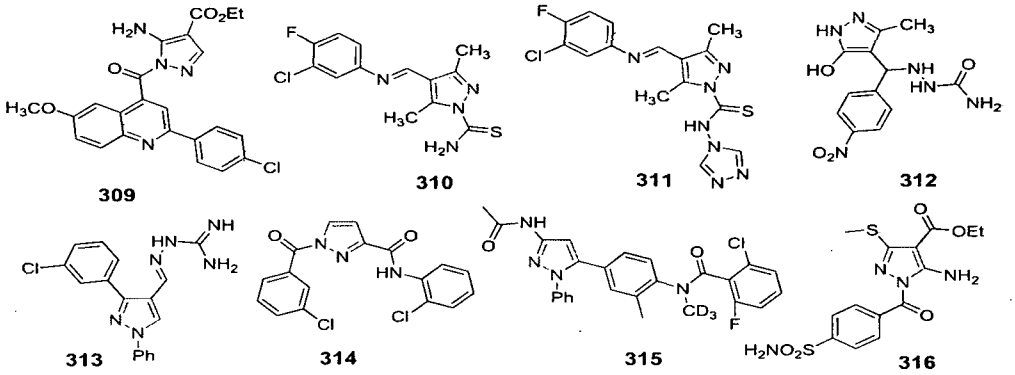


Figure 25. Pyrazole derivatives with anti-inflammatory and analgesic activities.

A new series of pyrazole-substituted were synthesized and investigated for their anti-inflammatory activity using the carrageenan-induced paw edema standard technique. Results revealed that, compound **317** seems to be the most effective prepared anti-inflammatory agent, revealing better activity (89.57% inhibition of edema) (Figure 26) [219]. Several new 1*H*-pyrazole-4-acetates containing quinazolinone rings were synthesized and screened for their analgesic and anti-inflammatory activities. Compound **318** showed appreciable anti-inflammatory and analgesic activities [220]. Compound **319** was identified by Hall et al. as brain penetrant compounds and both demonstrated efficacy in the CFA model of inflammatory pain [221]. De Moura et al. identified new pyrazole-containing tetrazole compound **320** as a non-steroidal anti-inflammatory drug [222]. Some novel 1,3,4-trisubstituted pyrazoles were synthesized by Ragab et al. and screened for their anti-inflammatory and analgesic activities. Compound **321** was found to be the most active one as anti-inflammatory and analgesic agents [223]. Vijesh et al. described the synthesis and analgesic activity of new 1,2,4-triazole and benzoxazole derivatives containing pyrazole moieties. The results revealed that the compound **322** showed significant analgesic activity [224]. A series of new substituted pyrazoline derivatives linked to a substituted pyrazole scaffold were prepared by Vieka et al. and screened for their anti-inflammatory and analgesic activities. The results revealed that the compound **323** could be identified as the most active member within this study with a dual anti-inflammatory and analgesic profile [225]. A series of novel 5-methyl-2-phenylthiazole-4-substituted-pyrazole derivatives were synthesized and evaluated for their anti-inflammatory and analgesic activities. Derivative **324** exhibited moderate to good anti-inflammatory and analgesic activities [226].

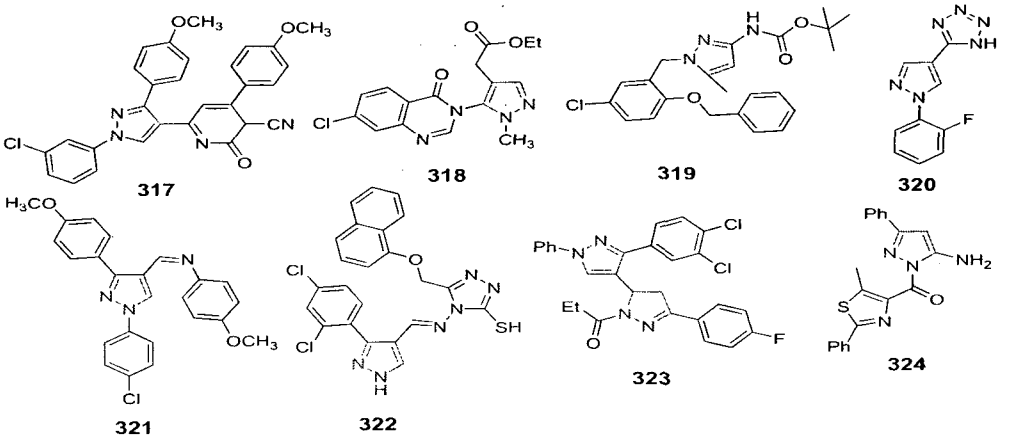


Figure 26. Pyrazole derivatives with anti-inflammatory and analgesic activities.

A series of pyrazole derivatives were synthesized (Figure 27) by Chowdhury et al. All the compounds were evaluated for their anti-inflammatory potential using carrageenan-induced rat paw edema assay. Among the series compound **325** was found to possess potent anti-inflammatory potential (ED_{50} value 61.2 mg/kg) [227]. In order to improve anti-inflammatory profile some modified and novel nitric oxide releasing coxib prodrugs were synthesize. In contrary to previously described results, compound **326** exhibited higher oral anti-inflammatory potency [228]. A series of novel pyrazole amalgamated flavones were synthesized and tested for their in vitro COX inhibition and in vivo carrageenan induced hind paw edema in rats and acetic acid induced vascular permeability in mice. Among the synthesized compound **327** showed significant inhibitory profiles against COX-2, indicating that they are selective inhibitors for COX-2 [229]. Recently, novel, pyrazole-hydrazone derivatives as anti-inflammatory agents were synthesized and evaluated for their in vitro COX-1, COX-2 and 5-LOX enzymes inhibitition potential. Especially, Compound **328** (IC_{50} = 0.58 lM) showed better COX-2 inhibitory activity than celecoxib (IC_{50} = 0.87 lM) [230]. In search of novel anti-inflammatory motifs, several new pyrazole compounds were synthesized by Singh et al. and evaluated for cyclooxygenase inhibition against recombinant human COX-2 enzyme. Outcome of the study revealed that compound **329** having hydroxymethyl group ortho to sulfonamide group exhibited good inhibitory potency and selectivity toward COX-2 enzyme (SI = 297, COX-2 IC_{50} = 0.036 mM) [231]. In order to explore the canine selective COX-2 inhibitory potential of *N*-methanesulfonylpyridinyl-substituted trifluoro-methylpyrazole derivatives, several compounds have been screened for their canine selective COX-2 inhibitory activity using in vitro canine whole blood (CWB) COX inhibition assay. Among all the synthesized derivatives, compound **330** was found to be most potent COX-2 inhibitor with high selectivity index (IC_{50} = 0.06 mM, SI = 132) [232]. Cheng et al. synthesized some new *N*-methanesulfonyl pyridinyl-substituted pyrazole derivatives bearing heteroaryl moiety at 5-position of pyrazole and evaluated in vitro canine selective COX-2 inhibitory activity. Compound **331** is the most potent and selective canine COX-2 inhibitor (IC_{50} = 0.012 mM) which displayed COX-1/COX-2 selectivity ratio greater than 4000-fold and thus provided an excellent efficacy profile for the treatment of pain and inflammation [233]. Sakya and coworkers evaluated canine selective COX-2 inhibitory potential of some new substituted pyrazole derivatives. The results revealed that among prepared compounds, the compound **332** (COX-2 IC_{50} = 0.063 mM, SI = 262) was found to be most potent and COX-2 selective [234].

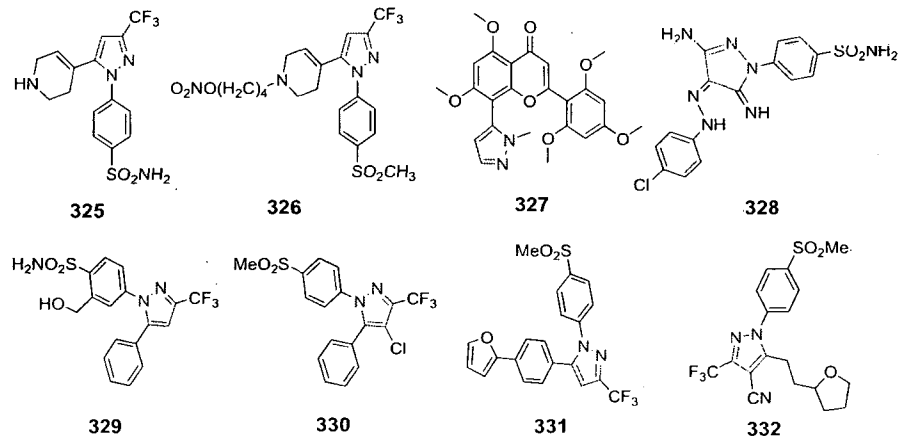


Figure 27. Pyrazole derivatives with anti-inflammatory activity.

Sakya et al. also evaluated in vitro canine selective COX-2 inhibitory activity of some new *N*-methanesulfonylpyridinyl-substituted pyrazole derivatives bearing ether/thioether substituents using CWB assay (Figure 28). The results revealed that among alkyl ethers, the compound **333** showed highest inhibitory potency and selectivity for COX-2 enzyme (IC_{50} = 0.09 mM, SI = 127) [235].

In a study, Aggarwal et al. explored the effect of 3/5-trifluoromethylpyrazole derivatives on in vivo anti-inflammatory potency at a dose level 50 mg/kg. Among all the tested compounds, **334** possessed very high anti-inflammatory potential 78% comparable to indomethacin (78%) after 3 h induction [236]. Knaus et al. synthesized and evaluated in vitro COX-1/COX-2 inhibitory potential of the celecoxib analogs having an azido group in place of the SO_2NH_2 moiety. The compound **335** was emerged as a selective COX-2 inhibitor [COX-1 IC_{50} > 100 μM, COX-2 IC_{50} = 1.5 μM, SI = 64] and displayed good anti-inflammatory properties [237]. In continuation to previous results, Knaus and coworkers have synthesized a series of celecoxib analogs and evaluated for their in vitro COX-1/COX-2 inhibitory activity with an expectation to find an efficient class of anti-inflammatory agents. Results revealed that compound **336** bearing SO_2N_3 group at para-position inhibited the activity of COX-1 enzyme selectively [COX-1 IC_{50} = 3.3 μM, COX-2 IC_{50} > 100, SI > 0.033] [238]. Some novel 2-phenyl-5-(1,3-diphenyl-1*H*-pyrazol-4-yl)-1,3,4-oxadiazoles derivatives have been synthesized for selective COX-2 inhibition with potent anti-inflammatory activity. Among all the tested compounds, compound **337** optimal COX-2 inhibitory potency (IC_{50} = 0.31 μM, ED_{50} = 74.3 mg/kg) [239]. Other 4-substituted novel trifluoromethylpyrazole derivatives have also been evaluated for their anti-inflammatory and COX-2 inhibitory potential. Results revealed that compound **338** displayed a promising degree of activity with ED_{50} value in the range 0.261 mmol/kg, in comparison to the standard drug, diclofenac (ED_{50} = 0.358 mmol/kg) and resulted 89.7% inhibition of edema at dose level of 200 mg/kg [240]. A series of pyrazolylbenzenesulfonamide derivatives were synthesized and evaluated for their anti-inflammatory and COX-1 and COX-2 inhibitory activities. Among investigated compounds, compound **339** was found to possess anti-inflammatory activity comparable to that of indomethacin and celecoxib, and exhibited COX-1/COX-2 selectivity [241]. Tewari et al. synthesized a series of pyrazole ester prodrugs analogues and evaluated in vitro for COX-2 inhibitory activity. The results indicated that compound **340** showed to possess maximum inhibitory effect when compared to control group [242]. A series of 1,3,4-trisubstituted pyrazole derivatives have been synthesized and evaluated for their cyclooxygenase (COX-1 and COX-2) inhibitory activity. Among these derivatives, compound **341** was the most potent and selective COX-2 inhibitor (IC_{50} = 1.33 μM), with a significant selectivity index (SI > 60) [243].

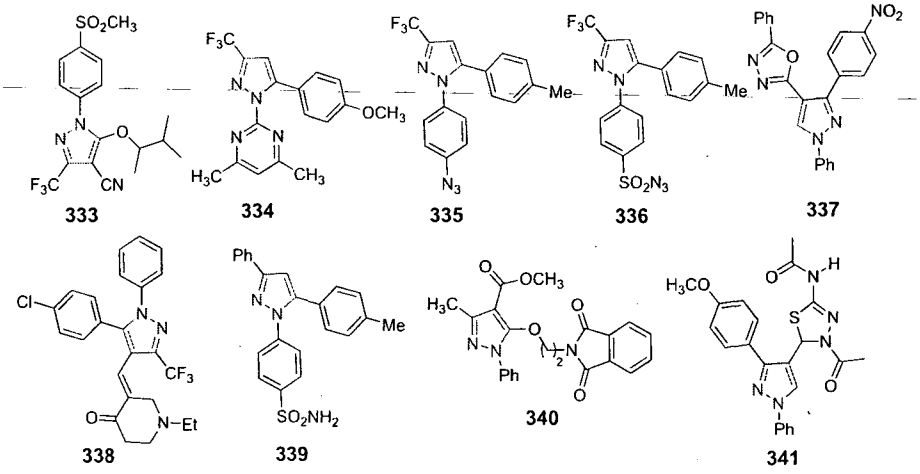


Figure 28. Pyrazole derivatives with anti-inflammatory activity.

3.4. Anti-Tubercular Activity

Manetti et al. identified new inhibitors of *Mycobacterium tuberculosis* (Figure 29). Compound **342** was found to be most active agent with a MIC value of 25 μg/mL [244]. A series of 3-substituted 5-hydroxy-5-trifluoro[chloro]methyl-1*H*-1-isonicotinoyl-4,5-dihydropyrazoles were synthesized by

Almeida da Silva et al. and tested for their in vitro antimycrobial activity against *Mycobacterium tuberculosis H37Rv*, INH-resistant clinical *M. tuberculosis* isolates non-tuberculous mycobacteria. Amongst the synthesized compounds, compound **343** was found to be the most active agents against susceptible *M. tuberculosis* and several INH-resistant strains [245]. As a continuation of our previous work that turned toward the identification of antimycobacterial compounds with innovative structures, two series of pyrazole derivatives were synthesized by Castagnolo et al. and assayed as inhibitors of *M. tuberculosis* H37Rv. The pyrazole derivative **344**, with the *p*-bromophenyl group at the N1 position, was showed to be very active (MIC = 4 μg/mL) [246]. Velaparthi et al. presented a series of 5-*tert*-butyl-*N*-pyrazol-4-yl-4,5,6,7-tetrahydrobenzo[*d*]isoxazole-3-carboxamide derivatives as novel potent *M. tuberculosis* pantothenate synthestase inhibitors. The new compound **345** exhibited the maximum activity with IC_{50} of 90 nM [247]. Castagnolo et al. synthesized two series of novel rigid pyrazolone derivatives and evaluated as inhibitors of *M. tuberculosis*, the causative agent of tuberculosis. The results showed that compound **346** bearing *N*-Me-piperazine and morpholine moieties proved to be very active with MIC = 4 μg/mL [248]. A series of 3a,4-dihydro-3*H*-indeno[1,2-*c*]pyrazole-2-carboxamide analogues were synthesized and evaluated for antitubercular activity. The compound **347** was found to be the most promising compound active against *M. tuberculosis H37Rv* and isoniazid resistant *M. tuberculosis* with MIC concentration 3.12 μM and 6.25 μM, respectively [249]. A new *N*-aryl-1,4-dihydropyridines derivatives bearing 1*H*-pyrazole ring were synthesized and evaluated for antitubercular activity. The lowest MIC value 0.02 μg/mL, was found for compound **348** making it more potent than first line antitubercular drug isoniazid [250]. As a part of our ongoing research to develop novel antitubercular agents, a series of *N*-phenyl-3-(4-fluorophenyl)-4-substituted pyrazoles have been synthesized and tested for antimycobacterial activity in vitro against *M. tuberculosis* H37Rv. Amongst them, compound **349** displayed the most potency with IC_{50} of 0.47 μM [251]. As a part to develop novel antitubercular agent, a series of 3-(4-chlorophenyl)-4-substituted pyrazoles have been synthesized by Pathak et al. and tested for antitubercular activity in vitro against *M. tuberculosis* H37Rv strain. Among them tested, compound **350** showed excellent antitubercular activity with MIC of 0.35 mg/mL [76].

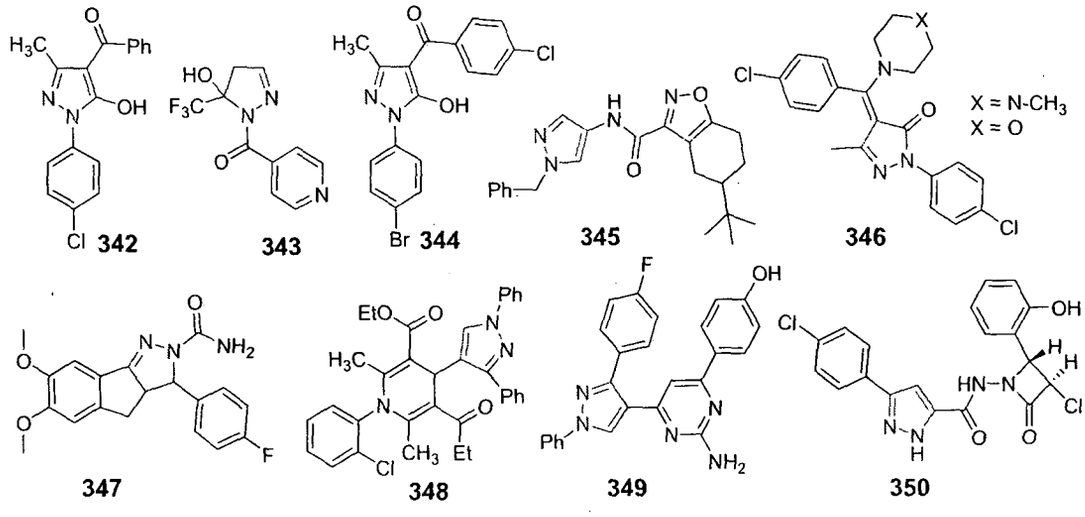


Figure 29. Pyrazole derivatives with anti-tubercular activity.

A new series of fluorinated pyrazoles (Figure 30) were synthesized and screened for their in vitro anti-tubercular activities against *M. tuberculosis* H37Rv. Results showed that pyrazoline **351** displayed significant anti-tubercular activities against the *M. tuberculosis* H37Rv strain (MIC = 6.25 μg/mL) [252]. A series of 1-[(4-benzyloxyphenyl)-but-3-enyl]-1*H*-azoles has been identified by Anand et al. as potent antitubercular agents against *M. tuberculosis*. Compound **352** exhibited significant antitubercular

activities with MIC value 0.61 μg/mL, comparable to many standard drugs [253]. Fullam et al. described the synthesis and inhibitory potencies of a novel series of 3,5-diaryl-1*H*-pyrazoles as specific inhibitors of prokaryotic arylamine *N*-acetyltransferase enzymes. Compound **353** was found to have good anti-mycobacterial activity and inhibited the growth of both *M. tuberculosis* with an MIC < 10 μg/mL (34 μM) [254]. Hernández et al. reported the preparation and anti-tubercular activity on *M. tuberculosis* H37Rv of hybrid furoxanyl *N*-acylhydrazones bearing pyrazole moiety. Among them, compound **354** displayed good selectivity against *M. tuberculosis* with MIC value 17.9 μM [255]. Various substituted pyrazole derivatives have been synthesized and evaluated for their in vitro anti-tubercular activity against *M. tuberculosis* H37Rv strain. Compound **355** exhibited significant anti-tubercular activity at MIC value 25 μM concentration [256]. A new series of 1-adamantyl-3-heteroaryl ureas containing pyrazole ring were synthesized by North et al. and evaluated for their anti-mycobacterial activity against MTB H37Rv. Among the synthesized compounds, compound **356** exhibited excellent activity against MTB H37Rv with MIC value 1.56 μg/mL [257]. A series of pyrazole derivatives containing thiochromeno and benzothiepino moieties were prepared and evaluated for antituberculosis activity. The compound **357** showed moderate inhibitory activity against MTB at MIC 14 μM [258]. Samala and coworkers have reported the synthesis and evaluation of the bioactivity of 3-phenyl-4,5,6,7-tetrahydro-1*H*-pyrazolo[4,3-*c*]pyridine derivatives against M. tuberculosis (MTB) pantothenate synthetase Trypanosoma. Among the compounds, **358** was found to be the most active compound with IC_{50} of 21.8 μM against MTB PS [259].

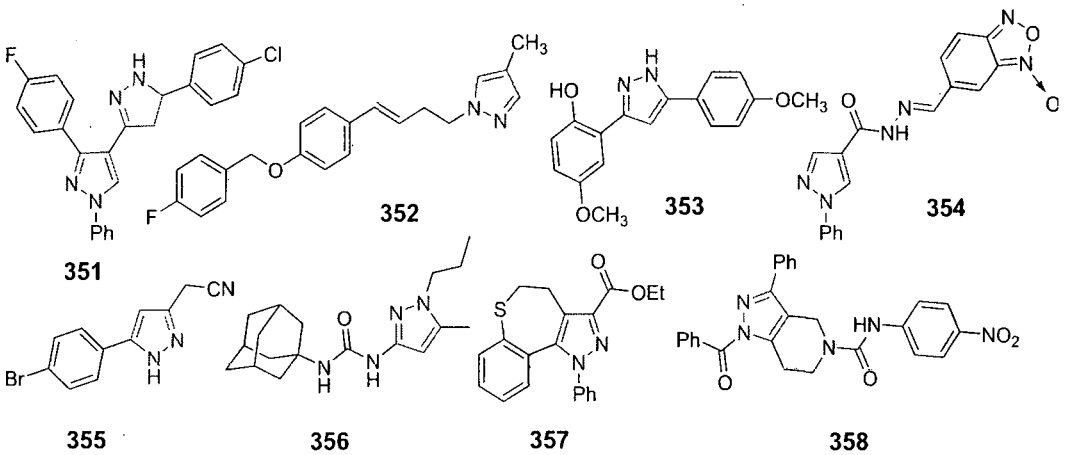


Figure 30. Pyrazole derivatives with anti-tubercular activity.

The design, synthesis and anti-mycobacterial activities of pyrazole bearing a methylthiazole scaffold (Figure 31) were reported by Shirude et al. Among the synthesized compounds, **359** showed similar enzyme inhibition against *M. tuberculosis* with a MIC value of 0.5 μM [260]. Novel 5-imidazopyrazoles incorporating 2-amino-3-cyano pyridine derivatives were synthesized and tested for their in vitro, anti-tuberculosis activity. Compound **360** displayed excellent inhibition (96% at 25 μg/mL) against anti-tubercular activity as compared to standard drugs [87]. A new category of polyhydroquinoline derivatives were synthesized were evaluated for their in vitro anti-tubercular activity against *M. tuberculosis* H37Rv strain. Compound **361** exhibited moderate anti-tuberculosis activity compared with the first line drugs. The outcome of the result revealed that, compound **361** was found to possess excellent activity (94% at 250 mg/mL and 100 mg/mL) against *M. tuberculosis* H37Rv [261]. Karad et al. reported the synthesized and anti-tuberculosis activity against *M. tuberculosis* H37Rv of a novel series of fluoro-substituted pyrazolylpyrazolines. Good anti-tubercular activity was exhibited by compound **362** (96% at 250 mg/mL) [262]. Mehta et al. synthesized a

new series of quinazolin-4(3*H*)-one derivatives containing a (1,3-diphenyl-1*H*-pyrazol-4-yl) core and screened for their anti-tubercular activities. Compound **363** was reported as the most active compound with MIC of 12.5 μg/mL against MTB H37Rv strain [91]. Various substituted 1-(3,5-diaryl-4,5-dihydro-1*H*-pyrazol-1-yl)ethanone derivatives were synthesized by Pathak et al. and evaluated for their in vitro anti-tubercular activity against *M. tuberculosis* H37Rv strain. Compound **364** exhibited significant anti-tubercular activity at MIC value 12.5 μM concentration [263]. The design, synthesis, and in vitro anti-tubercular activity of compound **365** were reported by Villemagne and coworkers. The compound displayed moderate anti-tubercular activity (EC_{50} > 10 μM) [264].

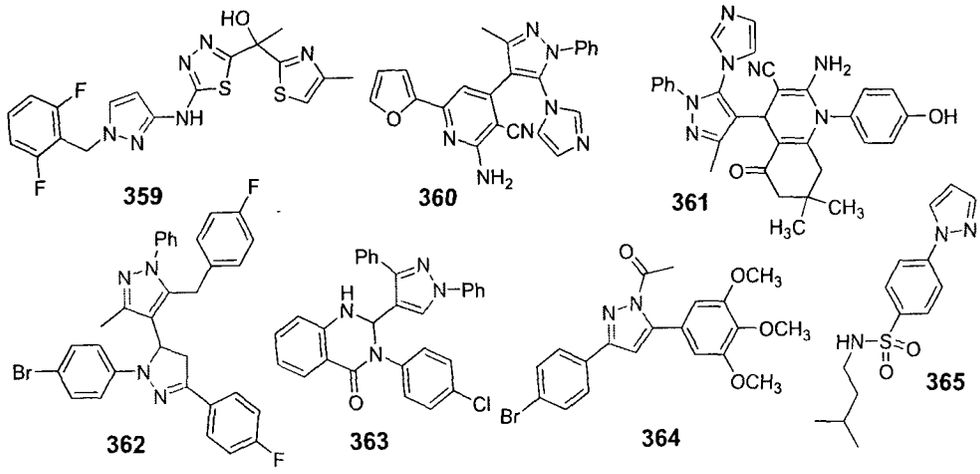


Figure 31. Pyrazole derivatives with anti-tubercular activity.

A series of novel pyrazole linked triazolo-pyrimidine hybrids (Figure 32) were synthesized and evaluated for their anti-tuberculosis activity against *M. tuberculosis* H37Rv strain. Compound **366** inhibited *M. tuberculosis* (99%) at MIC 0.39 μg/mL [265]. A series pyrazolyl-based Pd(II) complexes were synthesized by Da Silva et al. and evaluated in vitro for antimycobacterial activity. Anti-tuberculosis evaluation demonstrated that compound **367** displayed excellent activity with MIC of 7.61 μM [266]. A novel aminopyrazolo[1,5-*a*]pyrimidine derivatives were synthesis by Street et al. and tested for their anti-mycobacterial activity. Among the prepared compounds, compound **368** displayed promising anti-mycobacterial activity (MIC_{99} = 5 μM) [267]. Mutai et al. reported the synthesis and antimycobacterial activity of formononetin analogues bearing pyrazole ring. When all compounds were tested at a concentration of 10 μM, the pyrazole linked compound **369**, exhibited 40% inhibition of the H37Rv strain of *M. tuberculosis* [268]. The design, synthesis and evaluation of anti-tubercular activity of new INH-pyrazole analogs were reported by Nayak et al. the in vitro anti-mycobacterial evaluation demonstrated that compound **370** emerged as promising anti-tubercular agents with MIC of 0.8 μg/mL which is much lower than the MIC of the first line anti-tubercular drug, ethambutol [269]. Several 1,2,4-oxadiazole/pyrazole derivatives have been screened for anti-tubercular activity, and most of them showed weak to moderate activity. Amongst them, 1,2,4-oxadiazole pyrazole **371** displayed moderate potency against *M. tuberculosis* H37Rv strain [270]. A series of *N*-benzyl-4-((heteroaryl)methyl)-benzamides as a novel class of direct InhA inhibitors by high-throughput screening were identified by Guardia et al. These compounds displayed potent activity against MTB (MIC_{90}: 6 to 125 μM), maintaining activity versus *KatG* mutant clinical strains (IC_{50}: 12–31 μM) and emerging as a potential tool against MDR-TB and XDR-TB. The pyrazole derivative **372** (IC_{50} = 0.04 μM) is a potent direct InhA inhibitor with moderate whole-cell activity and an encouraging safety profile, but unfortunately it was not efficacious in an in vivo murine model of TB infection [271]. Using a fragment-based approach, a novel series of potent and isoform selective inhibitors of the essential MTB enzyme CYP121 have been developed by Kavanagh et al. The good

selectivity of CYP121 inhibitors, particularly compound **373**, demonstrated here against human P450s, is promising for the development of this series of CYP121 inhibitors [272].

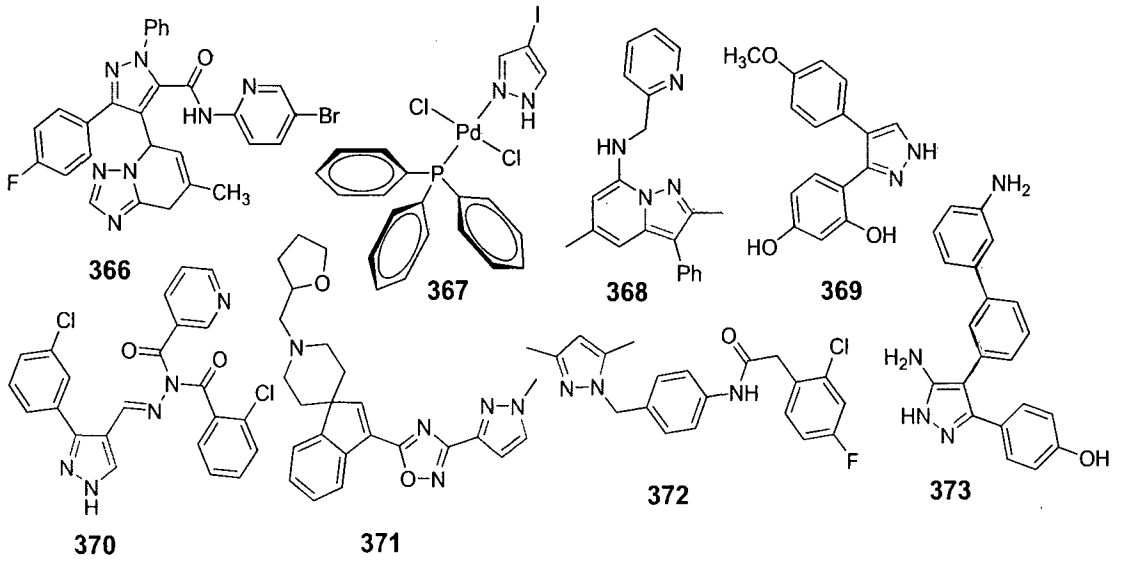


Figure 32. Pyrazole derivatives with anti-tubercular activity.

A series of biheterocyclic (1*H*-indole, benzofuran, pyrazolo[1,5-*a*]pyrimidine, pyrazolo[1,5-*a*] pyrimidin-5-4*H*)-one, imidazo[2,1-*b*]thiazole and pyrazolo[5,1-*b*]thiazole) derivatives (Figure 33) were synthesized and evaluated for their anti-tubercular activities. The imidazo[2,1-*b*]thiazoles and pyrazolo[5,1-*b*]thiazoles exhibited promising anti-tubercular activity in varying degrees. Especially, the 2,6-dimethylpyrazolo[5,1-*b*]thiazole **374** exhibited strong suppressing function against H37Ra strain with MIC value of 0.03 μg/mL [273]. Nayak et al. reported the synthesis and anti-tubercular activity of some active fluorine containing quinoline-pyrazole hybrid derivatives. Among the synthesized compounds, derivatives **375** emerged as active anti-TB leads which exhibited low toxicity profile and high selectivity index value [274]. A novel sila analogues of Rimonabant as potent anti-tubercular agents were identified by Ramesh et al. the sila-analogue **376** was found to be the most potent anti-mycobacterial compound with MIC = 31 nM from this series with an excellent selectivity index [275]. Various 1-((1-(substituted)-1*H*-1,2,3-triazol-4-yl) methyl)-*N*,3-diphenyl-6,7-dihydro-1*H*-pyrazolo[4,3-*c*]pyridine-5(4*H*)-carboxamides were prepared and screened for in vitro anti-tubercular activity against *M. tuberculosis* H37Rv strain. Among the compounds, **377** was found to be the most active compound with IC_{50} 1.01 μM against MTB PS; it inhibited MTB with MIC 24.72 μM [276]. A new 2-aroyl-[1]benzopyrano[4,3-*c*]pyrazol-4(1*H*)-one derivatives containing hydrazide-hydrazone analogues were prepared and tested in vitro for their anti-mycobacterial activity against reference strain *M. tuberculosis* H37Rv. Compound **378** demonstrated significant MIC value 0.32 μM, which was comparable to those of isoniazid [277]. A new bedaquiline derivatives containing a pyrazole moiety were identified by He et al. and tested for their inhibitory activities against ATP synthesis inhibition in mycobacteria. The results showed that compound **379** inhibited ATP synthesis with IC_{50} > 62.9 μM [278]. Various pyrazole derivatives derived from isoniazide pharmacophore along with coumarin scaffold were investigated for their anti-mycobacterial activity against MTB H37Rv by a resazurin MIC assay. Amongst them, compound **380** showed excellent activity at MIC 0.625 μg/mL and exhibited 80% growth inhibition of MTB H37Rv [279]. A series of pyrazole derivatives were synthesized by Sriram et al. and subjected to in vitro screening against MTB H37Rv. The most potent analogue **381** exhibits MIC value of 3.13 μg/mL compared to 3.25 and 50 μg/mL for ethambutol and pyrazinamide [280].

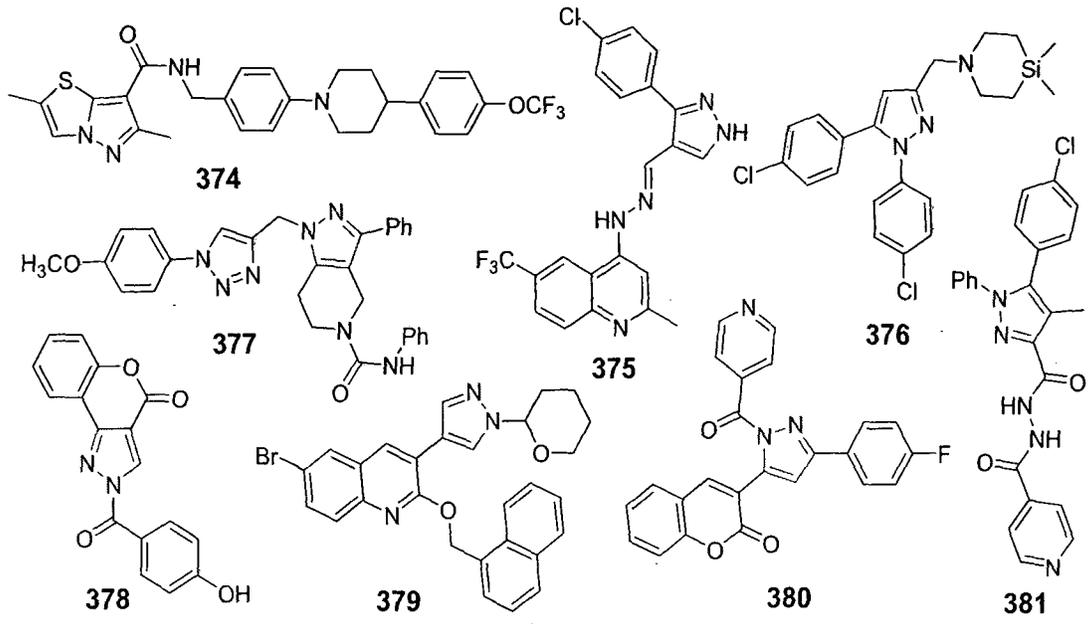


Figure 33. Pyrazole derivatives with anti-tubercular activity.

The design, synthesis, and in vitro anti-tubercular activity of a new series of 8-trifluoromethyl quinoline substituted pyrazole-3-carboxamides (Figure 34) were described by Nayak et al., Among the tested compounds, compound **382** showed significant inhibition activity against *M. tuberculosis* H37Rv strain with MIC of 3.13 μg/mL, which is comparable with the activity of standard drug, ethambutol [281]. A series of phenothiazine clubbed pyrazolo[3,4-*d*]pyrimidines were synthesized by Trivedi et al. and their ability to inhibit growth of *M.* tuberculosis in vitro have been determined. The results showed that compound **383** exhibited excellent anti-tubercular activity with percentage inhibition of 96%, at a MIC < 6.25 μg/mL [282]. Labana et al. described the synthesis and anti-tubercular activity of benzopyran-annulated pyrano[2,3-*c*]pyrazoles derivatives. Results indicated that compound **384** showed excellent anti-tubercular activity with a percent inhibition growth around 93% [283]. According to the research by Encinas et al., benzofuran pyrazole derivatives showed considerable in vitro activity against MTB H37Rv, and compound **385** showed the most potency with MIC_{90} of 0.05 μM [284]. A series of quinolinyl heterocycles were evaluated for their anti-mycobacterial activity against *M. smegmatis*, and some quinolinyl pyrazole hybrids showed excellent anti-mycobacterial activity such as **386** (MIC = 14.66 μg/mL) was as potent as isoniazide (MIC = 12.07 μg/mL) [285].The in vitro abilities of quinazolinone pyrazole derivatives to inhibit growth of MTB H37Rv have been reported by Pandit et al. The results exhibited all hybrids showed considerable anti-TB activity, particularly, hybrid **387** (96%, MIC_{90} < 3.125 μg/mL) warrant further investigation [286]. Dihydropyrimidine pyrazole derivatives were synthesized and evaluated for their in vitro anti-tubercular activity against MTB H37Rv, compound **388** were found to be the most active compounds in vitro with MIC of 0.02 μg/mL, with the highest SI > 500 were more potent than INH (0.03 μg/mL) [287]. A series of 4-aminoquinolone piperidine amides were synthesized by Naik et al. and evaluated for their anti-tubercular activity against non-replicating phase (NRP) and drug-resistant strains of MTB. The most active **389** (MIC of 0.4–50 μM) showed promising activity against MTB H37Rv, DprE1 overexpressed (OE), InhA OE, TopA OE, PimA OE, BTZ043 (C387S), TMC207-resistant mutant clone 8.1 and moxifloxacin-resistant mutant clone 4.1 strains [288].

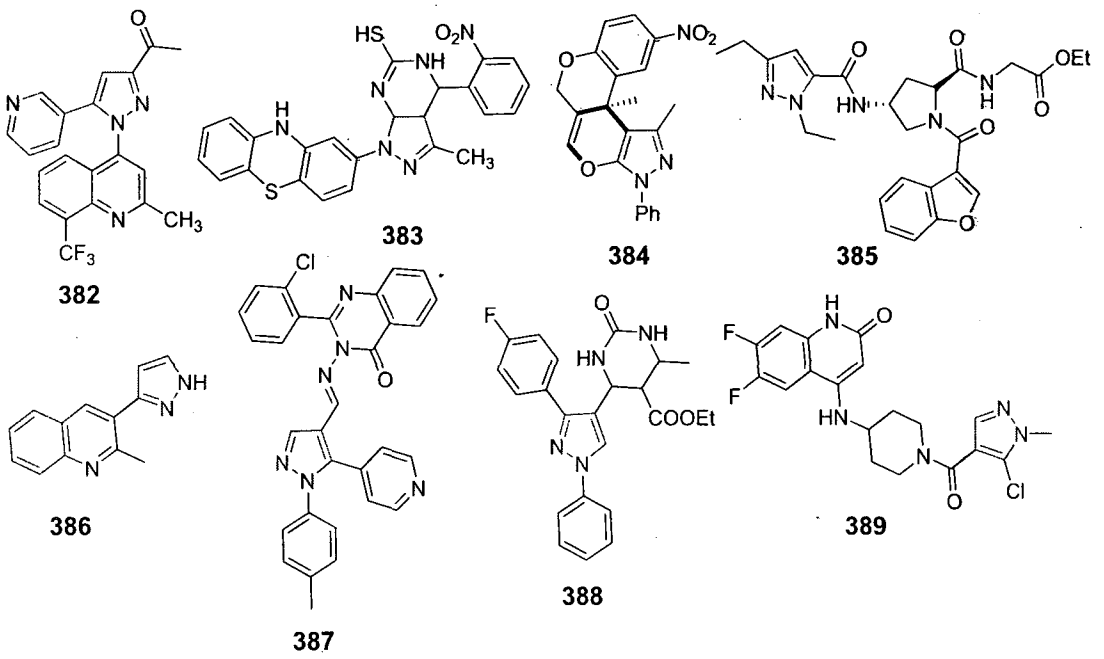


Figure 34. Pyrazole derivatives with anti-tubercular activity.

3.5. Anti-Viral Activity

Several pyrazole and pyrazolo[4,3-*d*]-1,2,3-triazine-4-one ribonucleozides (Figure 35) were prepared by Manfredini et al. and tested in vitro for antiviral activities against herpes simplex type 1 (HSV-1), africain swine fever (ASFV), polio, coxsackie, vescicular stomatitis virus (VSV), and HIV-1. Among pyrazole nucleosides, compound **390** showed a selective and inhibited the HIV-1 multiplication in acutely infected C8166 cells [289]. In searching for derivatives of pyrazofurin that could display antiviral properties by means that do not require 5′-deoxypyrazofurin derivatives has been synthesized by Chen and Schneller and evaluated for their antiviral activity against a large number of viruses including herpes-, pox-, myxo-, toga-, arena-, rhabdo-, picorna-, reo-, and retroviruses. Compound **391** proved active against respiratory syncytial virus (in HeLa cells), vaccinia virus (in embryonic skin-muscle fibroblast cells), vesicular stomatitis virus (in HeLa cells), and influenza A virus (in Madin-Darby canine kidney cells) at concentrations ranging from 4 to 20 μg/mL [290]. A novel fluoropyrazole ribonucleoside has been synthesized and evaluated in vitro for their anti-influenza activity. The fluoropyrazole nucleoside **392** was found to have excellent activity against influenza A and B in vitro with I_{50} values of 0.2 and 0.4 μg/mL, respectively [291]. Genin et al. discovered a novel 1,5-diphenylpyrazole class of HIV-1 nonnucleoside reverse transcriptase inhibitors (NNRTIs). Compound **393** was found to have good activity versus wild-type (IC_{50} = 2.3 μM) and delavirdine-resistant P236L (IC_{50} = 1.1 μM) reverse transcriptase (RT) [292]. Anovel series of 1-(4-chlorophenyl)-4-hydroxy-1*H*-pyrazole-3-carboxylic acid hydrazide analogs has been synthesized and were investigated for their in vitro effect on the replication of hepatitis-C virus (HCV) in HepG2 hepatocellular carcinoma cell line infected with the virus using the reverse transcription-polymerase chain reaction (RT-PCR) technique. The results revealed that compounds **394** were capable of inhibiting the replication of both the HCV RNA (+) and (−) strands at 10–100 μg/mL concentration range [293]. Some novel pyrazolo[4′,3′:5,6]pyrano[2,3-*d*]pyrimidine derivatives were prepared and tested for antiviral activity against Herpes Simplex Virus type-1 (HSV-1). The obtained results revealed that the pyrazolopyranopyrimidine **395** showed the highest effect on HSV-1 than the other tested compounds, where its antiviral activity increased from 63% at concentration of 20 $\mu g/10^5$ cells to 95% at concentration of 40 $\mu g/10^5$ cells [294]. Sun et al. identified

1-methyl-3-(trifluoromethyl)-*N*-[4-(pyrrolidinylsulfonyl)phenyl]-1*H*-pyrazole-5-carboxamide as a novel and potent inhibitor against multiple primary isolates of diverse measles virus (MV) genotypes currently circulating worldwide. The most active piperidine derivative **396**, when subjected to a secondary virus titer reduction assay, revealed activity against live MV (0.012 ± 0.017 μM, strain Alaska) and no cytotoxicity [295]. A novel series of pyrazolaldoxime ester derivatives were synthesized by Ouyang et al. and evaluated for their antiviral activities against TMV. The results of bioassay showed that these title compounds exhibited weak to good anti-TMV bioactivity. Title compound **397** showed better biological activity and exhibited a higher affinity for TMV CP [296]. Some novel substituted pyrazole and pyrazolo[3,4-*d*]pyrimidine derivatives 2, 4, 8, and 9 were synthesized and tested for their antiviral activity against hepatitis-A virus (HAV) and herpes simplex virus type-1 (HSV-1). Compound **398** revealed the highest anti-HAV activity at a concentration of 20 μg/10^5 cells, in comparison with the other tested compounds [297].

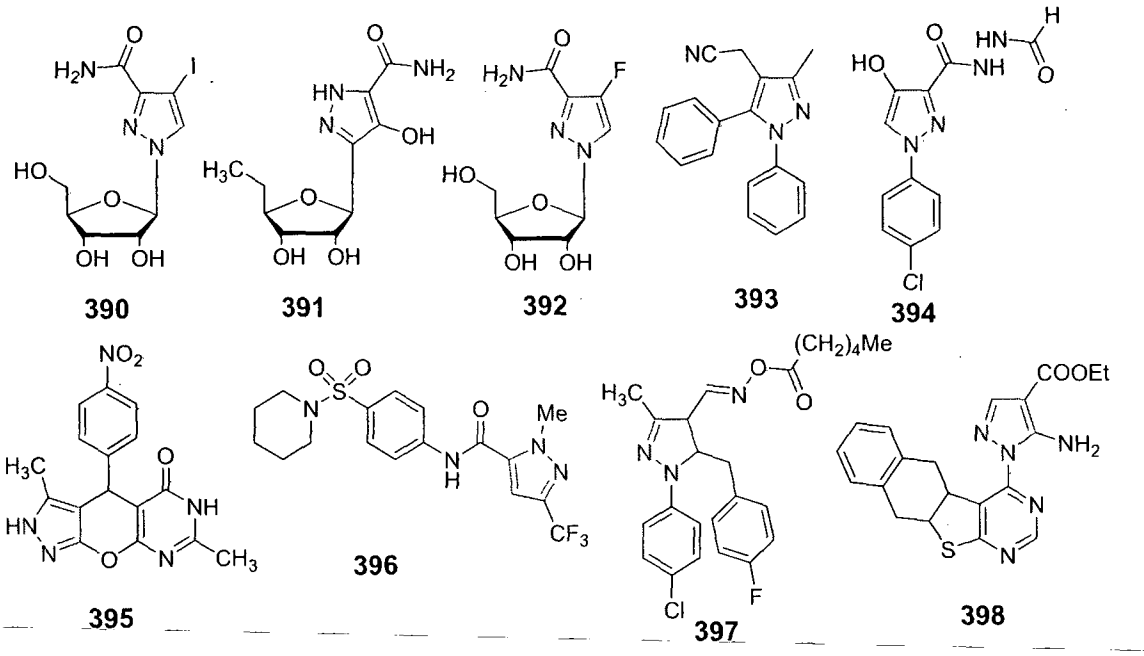


Figure 35. Pyrazole derivatives with anti-viral activity.

Zeng et al. have been synthesized a novel phenyl-substituted 1*H*-pyrazole-3-carboxylic acids (Figure 36) and were conveniently examined with respect to the effect on the IN inhibition and HIV replication. The best antiviral effect was exhibited by 5-(4-nitrophenyl)-1*H*-pyrazole-3-carboxylic acid **399** and 3-(3-(benzyloxy)phenyl)isoxazole-5-carboxylic acid **400** with an EC_{50} value of 3.6 and 253 μM [298]. A new series of *N*-hydroxyethyl pyrazoles derivatives were prepared by Mowbray et al. and evaluated in vivo for their anti-HIV activity. Compound **401** demonstrated excellent activities against large panels of wild type and drug-resistant HIV consistent with the encouraging profile demonstrated against the isolated RT enzymes shown above [299]. In another study, the same authors described the design and synthesis of a novel series of non-nucleoside HIV reverse transcriptase inhibitors (NNR-TIs) based on a pyrazole template. The compounds are active against wild type reverse transcriptase (RT) and retain activity against clinically important mutants. Combining the best 3- and 5-substituents gave the 3,5-diethylpyrazole **402** as the most potent compound in this early series [300]. Sidique et al. described the design and synthesis of 3-substituted pyrazole ester derivatives which are active as allosteric inhibitors of West Nile Virus NS2B-NS3 proteinase. Compound **403** was found to be more promising in comparison to the other one, with the IC_{50} value 1.96 μM [301]. 4,4′-(Arylmethylene)bis(1*H*-pyrazol-5-ol) derivatives has been synthesized by

Sujatha et al. and evaluated for in vitro antiviral activity against peste des petits ruminant virus (PPRV). Compound **404** emerged as the most interesting compound in this series exhibiting excellent antiviral activity against PPRV and found to be more potent than the standard drug ribavirin used [302]. Three series of novel pyrazole derivatives were synthesized by Riyadh et al. and tested for anti-viral activity against HCV. Compound **405** was proved to be a notable anti-HCV activity with MIC value of 0.144 μg/mL [303]. Shih et al. identified novel pyrazole compound with potent and selective anti-influenza virus activity using a similar cell-based neutralization (inhibition of virus-induced cytopathic effect) assay. After screening 20,800 randomly selected compounds from a library, we found that **406** has potent inhibitory activity [304].

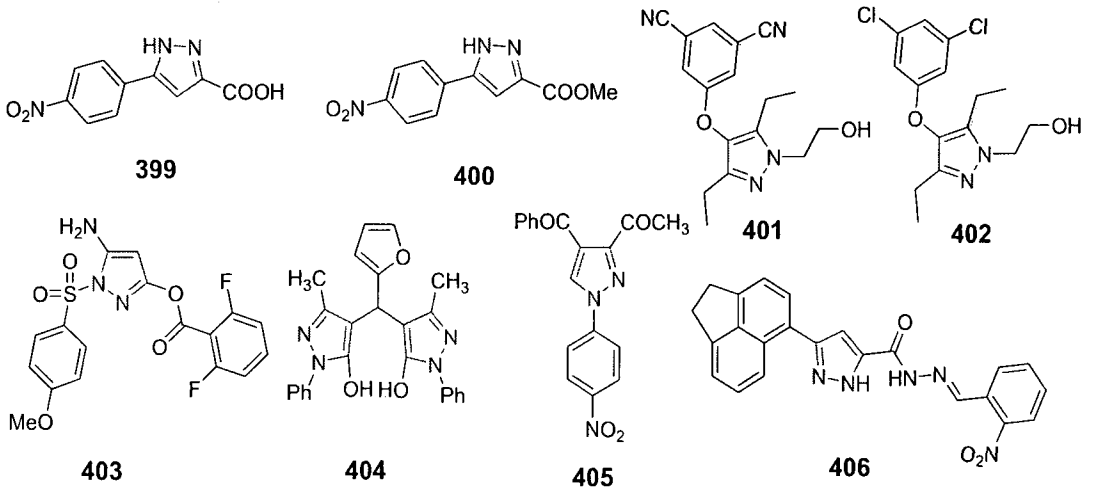


Figure 36. Pyrazole derivatives with anti-viral activity.

Su et al. reported a series of novel pyrazole derivatives (Figure 37) as potent inhibitors of HIV-1 RT with nanomolar intrinsic activity on the WT and key mutant enzymes and potent antiviral activity in infected cells. Compound **407** showed excellent intrinsic antiviral activity against WT, K103N, and Y181C mutants, and exhibited excellent activity in the cell base assay against the same panel of mutants with small shift in activity between 10% FBS and 50% NHS [305]. Several new pyrazole- and isoxazole-based heterocycles were synthesized by Dawood et al. and screened for their inti-viral activity against Herpes simplex type-1 (HSV-1). Among the tested compounds, compound **408** showed the highest activity and reduced the number of HSV-1 plaques by 69% [306]. A series of novel pyrazole amides containing α-aminophosphonate moiety were synthesized by Wu et al. and evaluated for their antiviral activity. The title compound **409** showed some curative activities (50.1%) against tobacco mosaic virus at 0.5 mg/mL [307]. A novel series of potent nucleoside inhibitors of Hepatitis C virus (HCV) NS5B polymerase bearing pyrazole ring were reported by Di Francesco et al. Amongst these, the pyrazole analog **410** showed significantly improved intrinsic potency, both inhibiting NS5B polymerase with NTP IC_{50} = 0.5 μM and displayed interesting levels of anti-viral activity in the replicon assay, with EC_{50} = 7.8 μM [308]. Kim et al. identified a novel class of aryl substituted pyrazole compounds as potent non-nucleoside reverse transcriptase inhibitors (NNRTIs) for anti-human immunodeficiency virus (HIV) activity using a cell-based full replication assay. The optimization of the antiviral activity leading to the discovery of compound **411** which possessed excellent potency against wild-type HIV-1 (EC_{50} = 0.2 nM) as well as viruses *bearing Y181C* and *K103N* resistance mutations in the reverse transcriptase gene [309]. Ndungu et al. the synthesis and a SAR strategy that led to the discovery of novel pyrazole derivatives as potent measles virus (MeV). Optimization of in vitro potency and aqueous solubility led to the discovery of pyrazole **412**, a potent inhibitor of MeV (EC_{50} = 60 nM) with an aqueous solubility of approximately 60 μg/mL [310].

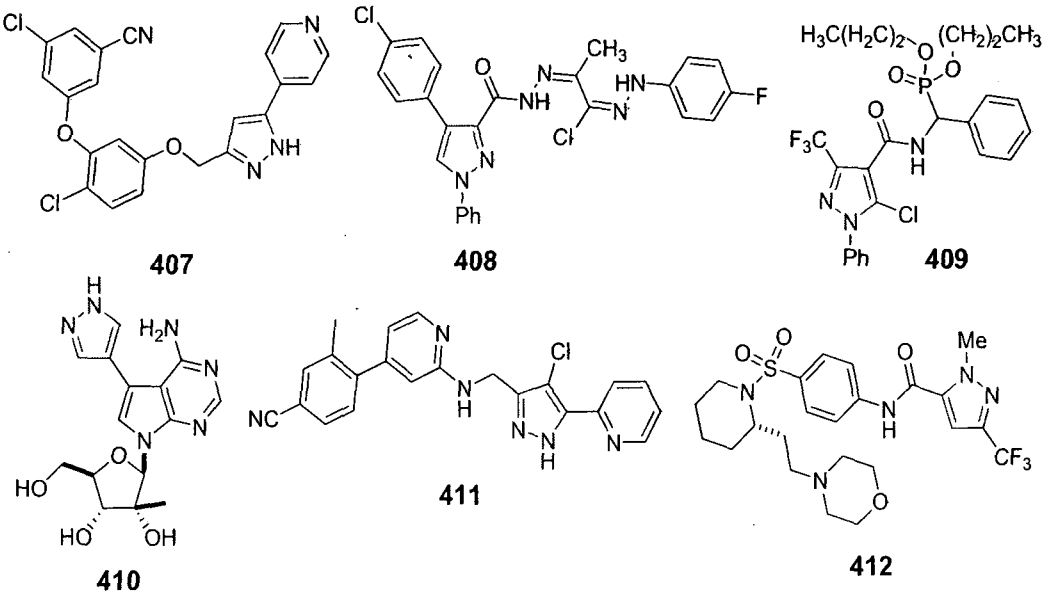


Figure 37. Pyrazole derivatives with anti-viral activity.

A new series of 4-substituted 3-methyl-1,5-diphenyl-1*H*-pyrazoles (Figure 38) has been synthesized by Tantawy et al. and evaluated in vitro for antiviral activity against herpes simplex virus type-1 grown on Vero African green monkey kidney cells through plaque-reduction assay method using acyclovir as a positive control. The results of the antiviral activity of the prepared compounds showed that compound **413** exhibited strong antiviral activity with IC_{50} value of 0.02 compared to the used reference drug [311]. A novel series of bis-pyrazole compounds were synthesized by Zhang et al. and tested for anti-viral activity against tobacco mosaic virus (TMV). Compound **414** showed higher activity superior to ningnanmycin at a concentration of 0.5 μg/mL and equal activity at 0.1 μg/mL [312]. Hwang et al. identified a series of 1,3,4-trisubstituted pyrazoles as potent hepatitis C virus (HCV) inhibitor by our phenotypic high-throughput screening using infectious HCVcc. Among them compound **415** was the most potent compound with EC_{50} value of 0.11 μM [313]. Mizuhara et al. synthesized a series of phenylpyrazole derivatives for the development of novel anti-HIV agents. Among the synthesized compounds, the 3,4-dichloro derivative **416** also exhibited more potent anti-HIV activity when (EC_{50} = 0.047 μM) [314]. Given the emergence of resistance observed for the current clinical-stage hepatitis C virus (HCV) NS3 protease inhibitors, there is a need for new inhibitors with a higher barrier to resistance. Moreau et al. reported a rational approach to the discovery of macrocyclic acylsulfonamides bearing pyrazole moiety as HCV protease inhibitors addressing potency against clinically relevant resistant variants. Compound **417** displayed most remarkable antiviral activity with an EC_{50} values of 0.14 and 1.0 nM against mutant D168V 1b and R155K 1a, respectively [315]. A series 24 compounds of diarylaniline analogues bearing pyrazole scaffold as non-nucleoside reverse transcriptase inhibitors (NNRTIs) were developed by Bhadoriya et al. using 3D-QSAR and pharmacophore modelling of *NNRTIs*. The survived 12 hits show new scaffolds 2,4-dihydropyrano[2,3-*c*]pyrazole **418** for anti-HIV-1 chemotherapy as NNRTIs [316]. A series of *N*-((1,3-diphenyl-1*H*-pyrazol-4-yl)methyl)anilines were synthesized by Fioravanti et al. and evaluated in vitro for cytotoxicity and antiviral activity against a large panel of viruses. Most of the tested compounds **419** interfered with RSV replication in the micromolar concentrations (EC_{50}s ranging from 5 μM to 28 μM) [317]. A series of novel pyrazole fused heterocyclic derivatives were synthesized and evaluated for their catalytic DNA cleavage abilities and anti-BVDV activities. Among them, compound **420** showed the highest antiviral activity (EC_{50} = 0.12 mmol/L) and was 10 fold more than that of the positive control ribavirin (EC_{50} = 1.3 mmol/L) [318].

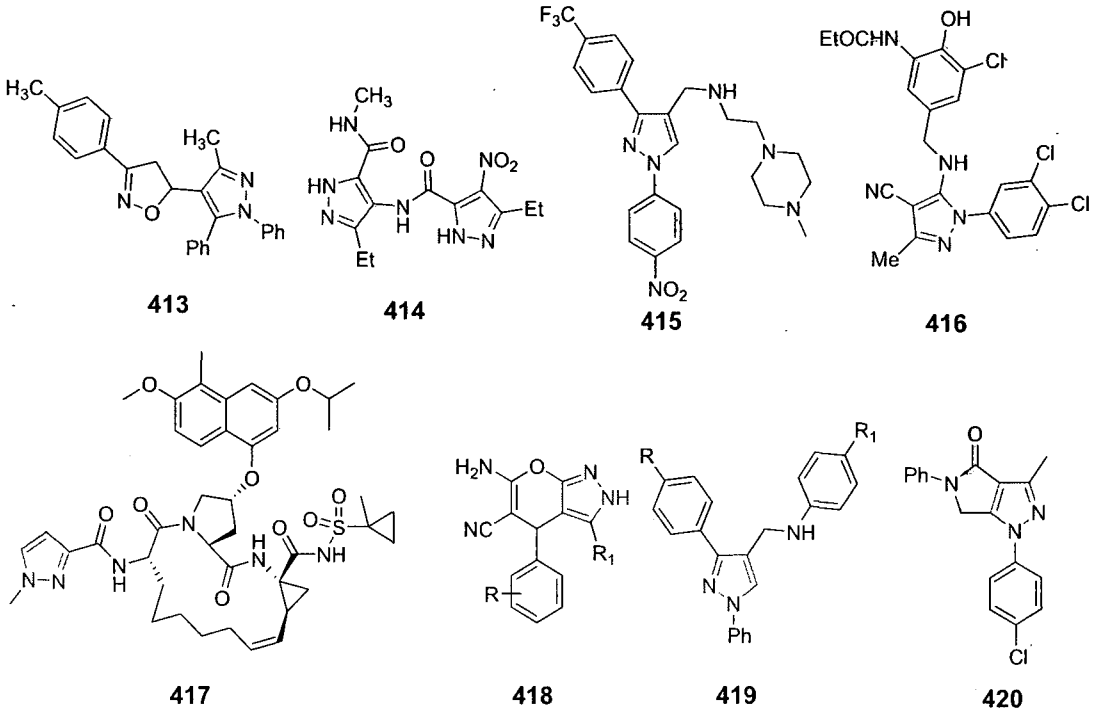


Figure 38. Pyrazole derivatives with anti-viral activity.

Manvar et al. reported the synthesis and mechanism of inhibition of pyrazolecarboxamide derivatives (Figure 39) as a new class of HCV inhibitors. Compound **421** exhibited an EC_{50} of 6.7 μM and selectivity index of 23 against HCV 1b, and reduced the RNA copies of the infectious Jc1 chimeric 2a clone by 82% at 7 μM [319]. A new series of pyridine-pyrazole-sulfonate compounds were synthesized evaluated for their anti-HBV activities and established the structure-activity relationship (SAR) in HepG2 2.2.15 cells. Among these compounds, compound **422** showed the most potent inhibitory activity with IC_{50} value of 9.19 μM, and high selectivity index, SI (TC_{50}/IC_{50}) 35.46 [320]. Ouyang et al. reported the synthesis and antiviral activities of pyrazole derivatives containing oxime moiety. The bioassay revealed that the compounds possessed antiviral activities. Compound **423** was found to possess inactivation effects against tobacco mosaic virus (TMV) (EC_{50} = 58.7 μg/mL) as the commercial product ningnanmycin (EC_{50} = 52.7 μg/mL) [321]. Jia et al. identified a series of novel pyrazole derivatives as non-nucleoside HBV inhibitors via bioisosterism and pharmacophore hybrid strategy. In particular, compound **424** displayed the most potent activity against the secretion of HBsAg and HBeAg with IC_{50} of 24.33 μM and 2.22 μM, respectively [322]. A series of pyrrolopyrazole derivatives were synthesized by Liu et al. and evaluated for their anti-viral activity against HIV-1. Among of them, compound **425** had potent anti-HIV-1 activities (EC_{50} = 3.98 μM) and excellent therapeutic index (TI, CC_{50}/EC_{50} > 105.25). The compound has potential as lead compounds for further optimization into clinical anti-HIV-1 agents [323]. Novel pyrazole acyl thiourea derivatives were synthesized and tested for their anti-TMV activity. Amongst the new products compound **426** showed curative rates by 41.23% [78]. Pyrazolo[1,5-*a*]pyridine derivatives synthesized by Johns et al. were evaluated for antiviral activity against herpes virus. Compound **427** was reported as the most potent anti-viral agent with EC_{50} = 0.26 μM [324].

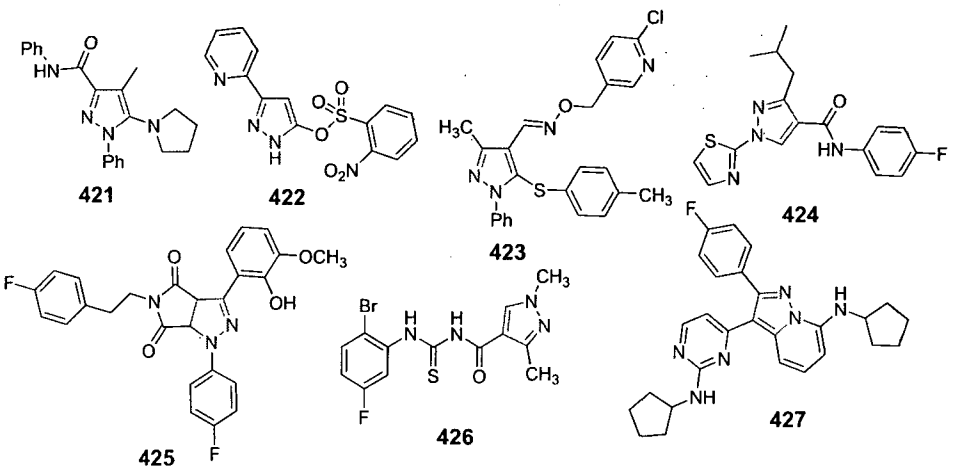


Figure 39. Pyrazole derivatives with anti-viral activity.

3.6. Anti-Azheimer's Activity

Chimenti et al. prepared a series of 3,5-diaryl pyrazoles (Figure 40) and assayed for their ability to inhibit reversibly monoamine oxidase-A (MAO-A) and monoamine oxidase B (MAO-B). Several compounds show inhibitory activity with concentration values in the nanomolar range. Compound **428** showed good inhibitory activity against MAO-A and MAO-B, but low selectivity (pIC_{50} MAO-A = 9.00 nM, pIC_{50} MAO-B = 8.00 nM, and pSI = 1.00) [325]. Kuduk et al. identified compound **429** as a potent and selective full agonist of the M_1 positive allosteric modulators. Compound **429** also exhibited high potency, which gave an M1 IP = 94 nM and a high free fraction (10%) in rat and human plasma [326]. Malamas et al. developed new pyrazolyl and thienyl aminohydatoins as potent BACE1 inhibitors. The *n*-butyl analog **430** was the most potent analog, with an IC_{50} value of 8 nM [327]. A series of metabolically stable γ-secretase inhibitors selective for inhibition of the production of amyloid-β over notch were reported by Probst et al. Compound **431** both entered human clinical trials and lowered Aβ in the CSF of healthy human volunteers [328]. A series of pyrazole based compounds were synthesized by Zou et al. and identified them as novel C-terminus Beta-secretase 1 (BACE1) inhibitors. Further, modification over pyrazole scaffold lead to the identification of compound **432** as a potent inhibitor of BACE1 with IC_{50} value of 0.025 μM [329]. In an effort to develop novel inhibitors of receptor for advanced glycation end products (RAGE) for the treatment of Alzheimer's disease, a series of pyrazole-5-carboxamides were synthesized by Han et al. and evaluated for anti-Alzheimer's activity. Results indicated that the most active analogs **433** exhibited higher inhibitory activities and exhibited significant brain Aβ-lowering effects as well as favorable aqueous solubility [330].

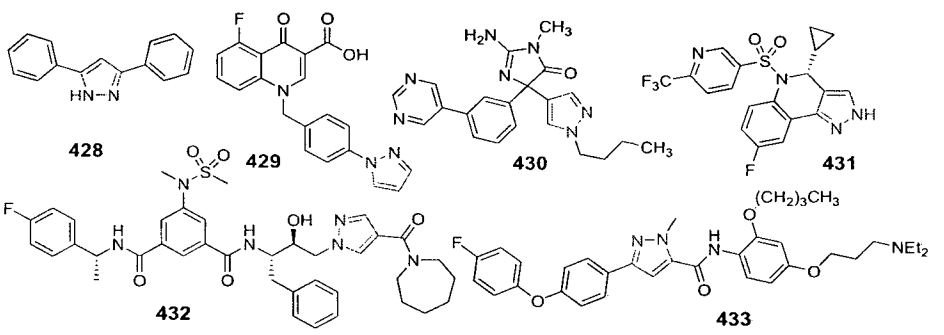


Figure 40. Pyrazole derivatives with anti-azheimer activity.

A new series of pyrazolotacrine as acetylcholinesterase (AChE) inhibitors (Figure 41) were reported by Silva et al. The results showed that compound **434** was the most potent inhibitor of AChE, which inhibited the aforementioned enzyme with an IC_{50} value of 0.069 μM [331]. Khoobi et al. synthesized a new tetracyclic tacrine analogs containing pyrano[2,3-*c*]pyrazole and evaluated for inhibition of acetylcholinesterase (AChE). Compound **435** bearing 3,4-dimethoxyphenyl group was the most potent compound against AChE, being more active than the reference drug tacrine [332]. Zanaletti et al. developed a new α7 nicotinic acetylcholine receptors (α7 nAChR) represented promising therapeutic candidates for the treatment of cognitive impairment associated with Alzheimer's disease (AD) and schizophrenia. Compound **436** was found a potent and selective full agonist of the α7 nAChR that demonstrated improved plasma stability, brain levels, and efficacy in behavioral cognition models [333]. The same author reported the synthesis and α7 nAChR inhibitory activity of novel class of pyrazole derivative. Compound **437** proved to be potent and selective, and it demonstrated a fair pharmacokinetic profile accompanied by efficacy in rodent behavioral cognition models [334]. Nencini et al. reported the design and synthesis of a pyrazole hybrid series of potent and selective agonists of α7 nicotinic acetylcholine receptor. The results revealed that compound **438** was the most potent inhibitor of α7 nAChR with an IC_{50} value of 0.07 μM [335]. AstraZeneca AB developed diverse series of pyrazole derivatives as positive allosteric modulators (PAMs). Compound **439** expressed good activity by inhibiting nicotinic acetylcholine receptors (*nAChRs*) [336]. Janssen Pharmaceutica identified a new series of trisubstituted pyrazole derivatives to PAM types 1–4 related to their kinetic properties in whole-cell voltage-clamp recordings using the agonist choline at a concentration of 1 mM. The trisubstituted pyrazole **440** showed remarkable activity with a pEC_{50} value of 7.11 (6268% efficacy) and a PAM type 4 profile [337].

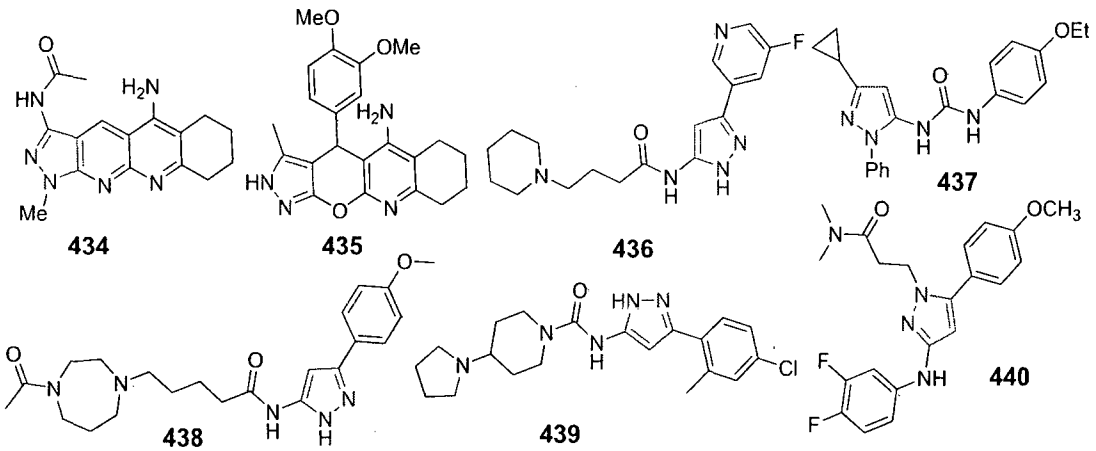


Figure 41. Pyrazole derivatives as anti-azheimer's compounds.

3.7. Anti-Diabetic Activity

A new series of substituted pyrazole-4-carboxylic acids were synthesized (Figure 42) by Cottineau et al. and evaluated for their antidiabetic activity. The results indicated that compound **441** emerges as the best hypoglycemic agent in the series [338]. Sharon et al. synthesized a new series of 5-[(5-aryl-1*H*-pyrazol-3-yl)methyl]-1*H*-tetrazoles and evaluated them for their in vivo anti-hyperglycemic activity. Out of screened compounds, compound **442** demonstrated 24.6% of blood glucose lowering activity at 100 mg/kg [339]. Humphries et al. reported the development of a series of novel 4-pyrazolyl-2-aminopyrimidines as inhibitors of c-Jun *N*-terminal kinases. This study led to the identification of **443**, which showed good selectivity across a panel of diverse protein and lipid kinases [340]. Several pyrazolopyrimidines were synthesized by Brigance et al. and evaluated as inhibitors of dipeptidyl peptidase-4 (DPP4). Among the synthesized compounds,

the **444** displayed the greatest potency (Ki = 20 nM) and demonstrated excellent selectivity over the other dipeptidyl peptidases [341]. Choi et al. identified 1,3-diphenyl-1*H*-pyrazole derivatives as a new series of potent *PPARγ* partial agonists using an improved virtual screening method combining ligand-centric and receptor-centric methods. The pyrazole-based compound **445** showed relatively strong binding activities against PPARγ among the virtual candidates [342]. A novel class of 1,3,5-pyrazoles has been discovered by Shen et al. as potent human glucagon receptor antagonists. Compound **446** was identified as a potent human glucagon receptor antagonist with good pharmacokinetic profiles in four preclinical species, and showed excellent oral pharmacodynamics efficacy in rhesus monkeys and transgenic mice by blocking glucagon-induced hyperglycemia [343]. A series of 4-benzyl-1*H*-pyrazol-3-yl β-D-glucopyranoside derivatives were synthesized and evaluated for their inhibitory activity toward sodium glucose co-transporter 1 (SGLTs). Compound **447** was identified as potent and selective SGLT1 inhibitors, both of which showed improved in vitro intestinal stability over phlorizin, high solubility to water [344].

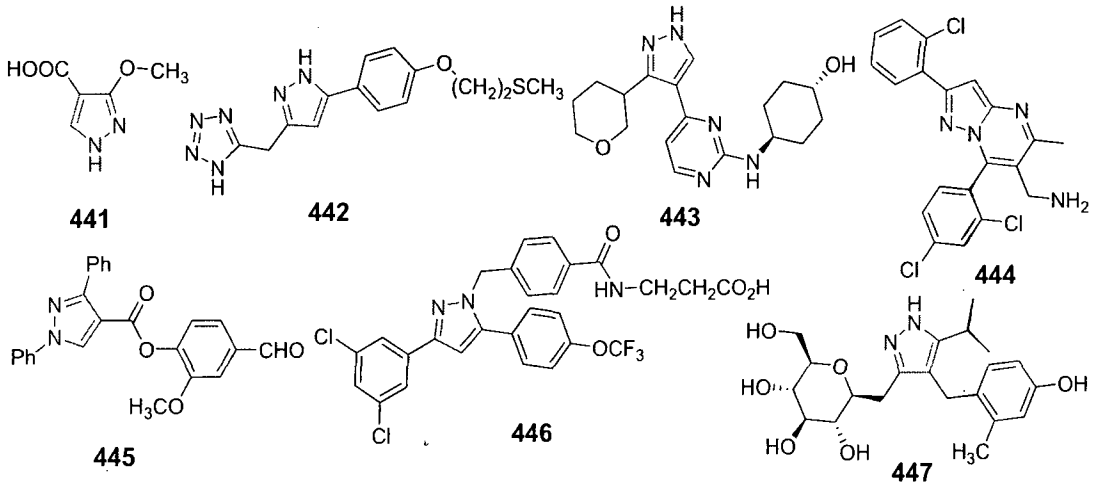


Figure 42. Pyrazole derivatives with anti-diabetic activity.

Rikimaru et al. described the design, synthesis, and structure-activity relationships of novel benzylpyrazole acylsulfonamides as non-thiazolidinedione, non-carboxylic-acid-based *peroxisome* proliferator activated receptor (PPAR) γ agonists (Figure 43). Overall, the compound **448** exhibited favorable metabolic stability and potent PPARγ agonist with EC_{50} values of 8.3 nM [345]. Xiong et al. discovered a new pyrazole compound **449** as a potent, selective glucagon receptor antagonist by optimization of a previously identified lead. Compound **449** is a reversible and competitive antagonist with high binding affinity (IC_{50} of 6.6 nM) and functional *cAMP* activity (IC_{50} of 15.7 nM) [346]. Yoshida et al. reported the discovery and preclinical profile of teneligliptin as a highly potent, selective, long-lasting and orally active dipeptidyl peptidase IV inhibitor for the treatment of type 2 diabetes. Compound **450** (teneligliptin), at 0.03 mg/kg or higher doses, significantly inhibited the increase of plasma glucose levels after an oral glucose load in Zucker fatty rats, and has been approved for the treatment of type 2 diabetes in Japan [347]. A series of pyrazole-based *GPR119* agonists were designed by Futatsugi et al., a novel and potent GPR119 full agonist **451** was identified through a conformational restriction-core flipping strategy. Compound **451** was roughly 10-fold less potent than exemplars from other series [348]. Griffith et al. disclosed a series of acetyl-CoA carboxylase (ACC) inhibitors based on a spirocyclic pyrazololactam core. Compound **452** showed excellent oral bioavailability, moderate systemic clearance, and acceptable exposure in rat pharmacokinetic studies. The oral dosing of rats with **452** resulted in potent, dose-proportional inhibition of ACC activity as measured by incorporation of ^{14}C in DNL product [349].

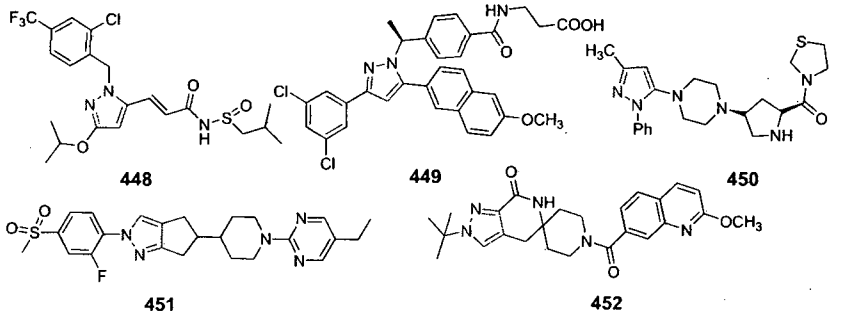


Figure 43. Pyrazole derivatives with anti-diabetic activity.

Novel 1,5-diaryl pyrazole derivatives were synthesized (Figure 44) by Hernández-Vázquez et al. and evaluated in vivo for their hypoglycemic activity. Compound **453** showed the most significant plasma glucose reduction, with decreases of 64% [350]. Toda et al. identified a new pyrazole compounds as novel insulin secretagogues for the treatment of type 2 diabetes. Compound **454** showed potent glucose lowering effects during an oral glucose tolerance test in mice and monkeys [351]. Yu et al. reported the lead optimization of pyrazole based GPR142 agonists. Structure–activity relationship studies indicated that amino-pyrazole-phenylalanine carboxylic acid **455**, exhibited good agonistic activity (h-GPR142-EC_{50} = 0.052 μM), high target selectivity, desirable pharmacokinetic properties, and no cytochrome P450 or hERG liability [352]. Bhosle et al. synthesized a new series of 2-hydrazolyl-4-thiazolidinone-5-carboxylic acids having pyrazolyl pharmacophores and evaluated their anti-hyperglycemic activity. Among the prepared compounds, **456** have displayed significant anti-hyperglycemic activity at 100 mg/kg [353]. A novel Zn mononuclear complex with 3-carboxy-pyrazole ligand has been prepared and evaluated in vivo for their antidiabetic activity. This compound **457** exhibits a potential in vivo anti-diabetic activity (62% reduction in blood glucose in the diabetic group treated compared with untreated diabetic) [354]. Kenchappa et al. reported the synthesis of coumarin derivatives containing pyrazole and indenone rings as potent anti-hyperglycemic agents. The compound **458** showed significant decrease in glucose concentration (115 and 138 mg/dL) with the dose of 100 mg/kg [355]. A series of substituted pyrazoles derivatives were synthesized by Doddaramappa et al. and tested in vitro for their anti-diabetic activity by measuring the α-amylase and α-glucosidase inhibitory potential. Among the synthesized compounds, compound **459** emerged as an excellent antidiabetic agent with IC_{50} values of 10 and 15 μg/mL against α-amylase and α-glucosidase inhibitors, respectively [356].

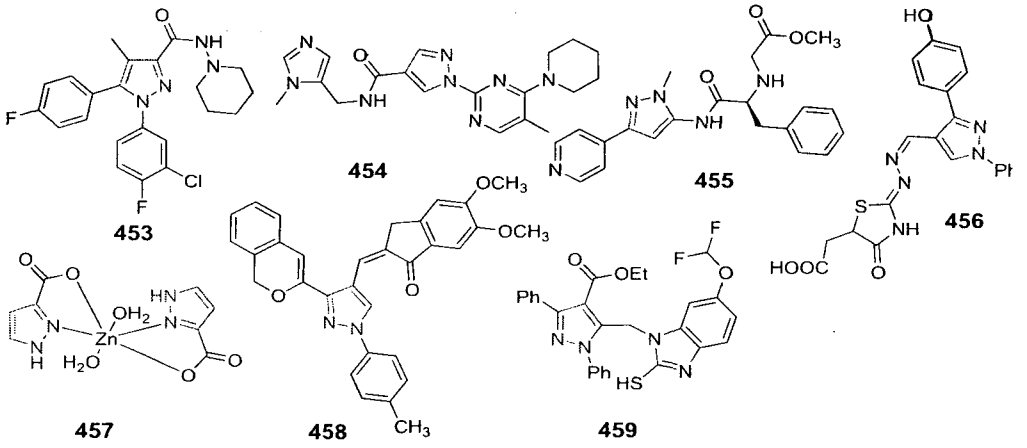


Figure 44. Pyrazole derivatives with anti-diabetic activity.

Hernández-Vázquez et al. reported the design, synthesis and anti-diabetic activity of novel *N'*-arylidene pyrazole-3-carbohydrazides (Figure 45). Compound **460** exhibited a remarkable hypoglycemic effect with a 90% of plasma glucose reduction [357]. A series of dihydropyrano[2,3-*c*] pyrazoles derivatives were synthesized and evaluated for their α-glucosidase inhibitory activity. Compound **461** was the most potent analog of this series (IC_{50} = 54.2 μM), when compared with standard drug, i.e., acarbose (IC_{50} = 937.0 μM) [358]. A series of imidazolylpyrazoles were synthesized by Chaudhry et al. and tested for their α-glucosidase inhibitory activity. The in vitro enzyme inhibition indicated that the compound **462** showed significant inhibitory potentials and binding affinities (IC_{50} = 23.95 μM) as compared to that of reference acarbose [359]. During current investigation concerning the synthesis of novel 1,5-diarylpyrazole derivatives as antidiabetic entities, Hernández-Vázquez et al. synthesized the hybrid **463**, a novel dual compound that exhibited both anti-diabetic and in vitro antioxidant effects. Compound **463** showed a pronounced anti-hyperglycemic effect even at a dose of 5 mg/kg ($p < 0.001$) in a glucose tolerance test on normoglycemic rats [360].

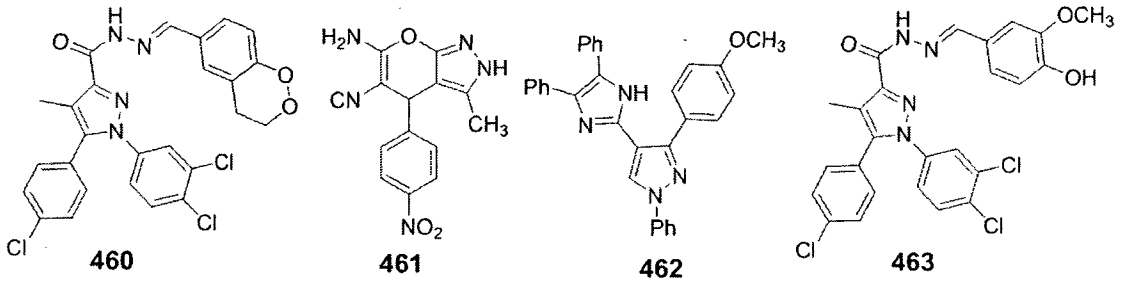


Figure 45. Pyrazole derivatives with anti-diabetic activity.

3.8. Anti-Leishmanial Activity

A series of 4-anilino-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxylic esters (Figure 46) were synthesized by De Mello et al. and tested against promastigote forms of *Leishmania amazonensis* as part of a program to study potential anti-Leishmania drugs. The very promising results showed the compound **464** as the most active [IC_{50} = 0.12 μM (22)] [361]. Bernardino et al. reported the synthesis and in vitro leishmanicidal acitivities of 1*H*-pyrazole-4-carbohydrazides. Among all the 1*H*-pyrazole-4-carbohydrazides derivatives examined, the compound **465** was found the most active against *L. amazonensis*, *L. chagasi* and *L. braziliensis* species [362]. Dardari et al. reported the synthesis and the antileishmanial activity of a new pyrazole derivative **466**. This compound inhibited the in vitro multiplication of *Leishmania tropica*, *Leishmania major*, and *Leishmania infantum* with IC_{50} values of 0.48 μg/mL, 0.63 μg/mL and 0.40 μg/mL, respectively [363]. 1-Aryl-1*H*-pyrazole-4-carboximidamide derivatives were synthesized by Dos Santos et al. and evaluated in vitro for their anti-leishmanial activities. Compound **467** showed an activity profile that can be improved through medicinal chemistry strategies [364]. This same author, synthesized a series of 1-aryl-4-(4,5-dihydro-1*H*-imidazol-2-yl)-1*H*-pyrazoles and evaluated in vitro against three Leishmania species: *L. amazonensis*, *L. braziliensis* and *L. infantum* (*L. chagasi syn.*). Among the derivatives examined, compound **468** emerged as the most active on promastigotes forms of *L. amazonensis*, with an IC_{50} value of 15 μM [365]. A new series of pyrazolo[3,4-*d*]pyridazin-7-one derivatives were synthesised and evaluated for their *in vitro* anti-leishmanial activity against *Leishmania amazonensis* promastigote and axenic amastigote forms. The results showed that compound **469** exhibit better anti-leishmanial activity with IC_{50} 3.63 and 2.32 μM, against the *promastigote* form and axenic amastigote form, respectively [366].

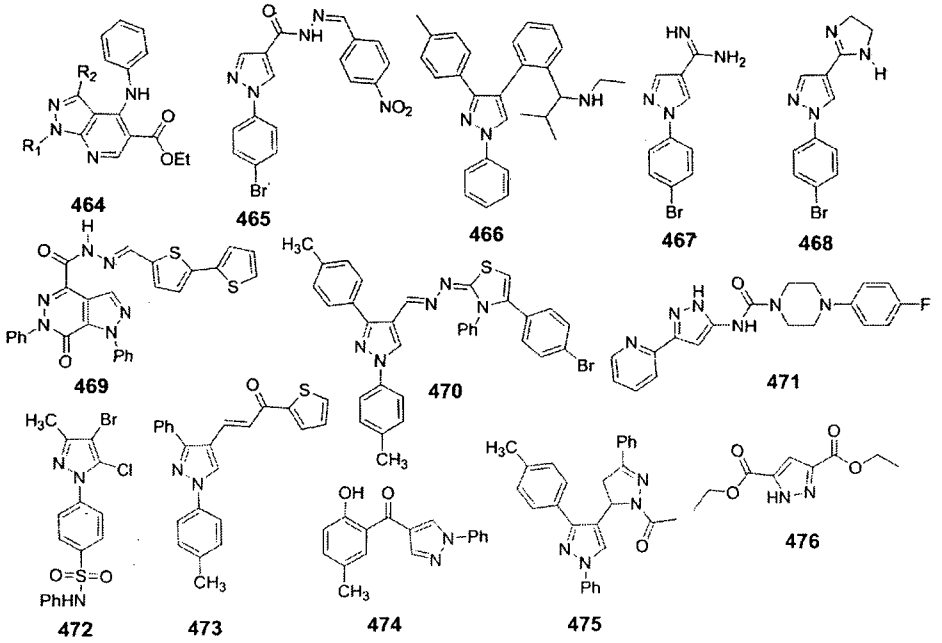


Figure 46. Pyrazole derivatives with anti-leishmanial activity.

A new series of pyrazole derivatives were synthesized by Bekhit et al. and evaluated for their in vitro anti-leishmanial activity against Leishmania aethiopica promastigotes and amastigotes. The results showed that compound **470** had the highest anti-leishmanial activity, with an IC_{50} value of [367]. Mowbray et al. identified a novel series of amino-pyrazole ureas with potent in vitro anti-leishmanial activity. Furthermore, compound **471** showed high levels of in vivo efficacy (>90%) against *Leishmania infantum*, thus demonstrating proof of concept for this series [368]. A series of 4-(1*H*-pyrazol-1-yl)-benzenesulfonamides were synthesized and evaluated in vitro for their anti-leishmanial profile against *Leishmania infantum* and *Leishmania amazonensis*. Interestingly, **472** showed the best in vitro active profile against the infective *L. amazonensis* promastigotes and *L. infantum* forms, with IC_{50} values of 0.059 and 0.070 mM, respectively [369]. Bekhit et al. prepared a novel series of 1*H*-pyrazole derivatives and tested for their in vitro anti-leishmanial activities against *L. aethiopica* promastigotes. The highest anti-leishmanial activity was exhibited by compound **473**, with an IC_{50} of 0.079 μg/mL [370]. Pyrazole derivatives were prepared and tested for their in vitro antiparasitic activity against promastigotes of *Leishmania mexicana* (Bel 21) and epimastigotes of *Trypanosoma cruzi* (DM28) using a modified MTT assay. Only **474** displayed selectivity on *L. mexicana* with a SI of 3, however, the IC_{50} obtained here was around four times higher (25 μM) [371]. A new series of pyrazole derivatives were prepared and tested in vitro for their anti-leishmanial activity. Compound **475** was found to be the most active (IC_{50} = 0.0112 μg/mL) than the standards miltefosine (IC_{50} = 0.3 ± 0.04 μg/mL) and amphotericin B deoxycholate (IC_{50} = 0.2 ± 0.02 μg/mL) for *Leishmania donovani* [372]. Reviriego et al. reported the synthesis and antiprotozoal activity of some simple dialkyl pyrazole-3,5-dicarboxylates against *Trypanosoma cruzi*, *Leishmania infantum* and *Leishmania braziliensis*. The diethyl ester **476** showed high efficiency against the mentioned protozoa [373].

3.9. Anti-Malarial Activity

A series of pyrazoles were described (Figure 47) as part of efforts directed toward the synthesis of some potent antimalarial agents. Further modification of the heterocyclic ring to give substituted aryl derivatives afforded potent antimalarial derivatives **477** with IC_{50} = 0.149 μmol/L [374]. Novel curcumin analogues bearing pyrazole ring were prepared and evaluated for their anti-malarial

activity against *CQ-S* and *CQ-R Plasmodium falciparum* culture. Compound **478** was found to be the most potent analogue with IC_{50} values 0.48 and 0.45 μM against *CQ-S* and *CQ-R*, respectively [375]. Gonzalez Cabrera et al. identified an aminomethylthiazole pyrazole carboxamide lead **479** with good in vitro antiplasmodial activity [IC_{50}: 0.08 μM (*K1*, chloroquine and multidrug resistant strain) and 0.07 μM (NF54, chloroquine-sensitive strain)] and microsomal metabolic stability from whole cell screening of a SoftFocus kinase library. Compound **479** also exhibited in vivo activity in the *P. berghei* mouse model at 4 × 50 mg/kg administration via the oral route, showing 99.5% activity [376]. Quirante et al. described the synthesis and in vitro antimalarial activities of platinum(II) and palladium(II) complexes with ligands derived from pyrazole. Compound **480** exhibited only moderate antimalarial activities against two *P. falciparum* strains (3D7 and W2) [377]. A new category of polyhydroquinoline derivatives containing pyrazole moieties were prepared by Kalaria et al. and evaluated for their *in vitro* antimalarial activity against *Plasmodium falciparum*. Among the tested compounds, compound **481** exhibited excellent antimalarial activity with an IC_{50} value of 0.033 μg/mL [261]. A series of imidazopyridazine inhibitors of *Plasmodium falciparum* calcium-dependent protein kinase 1 (PfCDPK1) has been explored and extended by Large et al. Diaminocyclohexane **482** showed a good in vitro potency and metabolic stability profile against *Plasmodium falciparum* (PfCDPK1 enzyme IC_{50} = 0.056 μM, Pf anti-parasite EC_{50} = 0.262 μM) [378]. A novel series of fluoro-substituted pyrazolylpyrazolines were synthesized and screened for their antimalarial activity against *Plasmodium falciparum*. Compound **483** displayed excellent activity with an IC_{50} value of 0.022 μg/mL against *P. falciparum* stain as compared to quinine IC_{50} = 0.268 μg/mL [262]. A new series of pyrazole derivatives were synthesized and evaluated for their in vivo antimalarial activity against *Plasmodium berghei*-infected mice and the most active derivatives were further examined for their in vitro antimalarial activity against chloroquine resistant (RKL9) strain of *Plasmodium falciparum*. Compound **484** had more than 90% parasite suppression activity of that found with the antimalarial reference standard drug, chloroquine phosphate and had lower IC_{50} values than chloroquine [367]. Belaji et al. reported the molecular modelling, synthesis, and antimalarial potentials of curcumin analogues containing pyrazole ring. The compound **485** showed the most significant result, with maximum schizonticidal (IC_{50} = 1.48 μM) and parasiticidal activities (MKC; 3.87 = μM) [379].

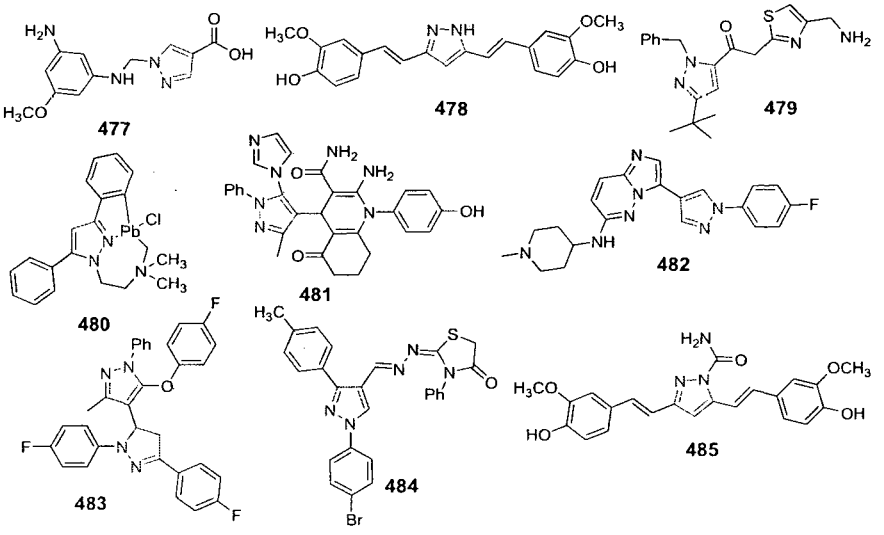


Figure 47. Pyrazole derivatives with anti-malarial activity.

3.10. Anti-Parkinson Activity

Niswender et al. discovered a new pyrazolo[3,4-*d*]pyrimidines derivatives (Figure 48) as novel modulators of the metabotropic glutamate receptor subtype 4 (mGluR4) positive allosteric modulators.

Results indicated that the compound **486** showed a remarkable anti-parkinson activity [380]. A series of *N*1-thiocarbamoyl-3,5-di(hetero)aryl-4,5-dihydro-(1*H*)-pyrazole derivatives has been synthesized by Chimenti et al. and tested for their ability to inhibit the activity of the A and B isoforms of human monoamine oxidase (hMAO). Compound **487** was found the most active of the series with IC_{50} value of 2.75 μM and selectivity ratio of 25 [381]. Maher et al. synthesized a pyrazole structure **488** as aderivative of curcumin and was tested for its ability to enhance the activity of Ca^{2+}/calmodulin dependent protein kinase II (CaMKII). Results indicated that the compound **488** enhanced the induction both long-term potentiation (LTP) in rat hippocampal slices and memory in a rat object [382]. Chan et al. identified a new aminopyrazole as a Leucine-Rich Repeat Kinase 2 (LRRK2) inhibitor. In in vivo rodent PKPD studies, compound **489** demonstrated good brain exposure and engendered significant reduction in brain pLRRK2 levels post-ip administration [383]. 4-(1-Phenyl-1*H*-pyrazol-4-yl)quinoline **490** was identified by screening the Lundbeck compound collection, and characterized as having mGlu4 receptor positive allosteric modulator properties. Compound **490** showed excellent anti-parkinson activity with an EC_{50} value of 220 nM [384]. Dore et al. designed and synthesized a novel tricyclic pyrazoles as potent phosphodiesterase 10A (*PDE10A*). Pyrazolo[5,1-*f*] [1,6]naphthyridine **491** showed the highest affinity for PDE10A enzyme (IC_{50} = 40 nM) [385]. Estrada et al. discovered a new aminopyrazoles as Leucine-Rich Repeat Kinase 2 (LRRK2) inhibitors. Compound **492** was identified as as highly potent and selective LRRK2 inhibitors with IC_{50} value of 3 nM [386]. Fujinaga et al. reported the radio-synthesis and evaluation of 5-methyl-*N*-(4-[^{11}C]methylpyrimidin-2-yl)-4-(1*H*-pyrazol-4-yl)thiazol-2-amine (493) as a novel radio-ligand for imaging of metabotropic glutamate receptor subtype 4 (mGluR4). In vitro autoradiography and ex vivo bio-distribution study in rat brains showed specific binding of compound **493** in the cerebellum, striatum, thalamus, cerebral cortex, and medulla oblongata, which showed dose-dependent decreases by administration with multiple dosing [387].

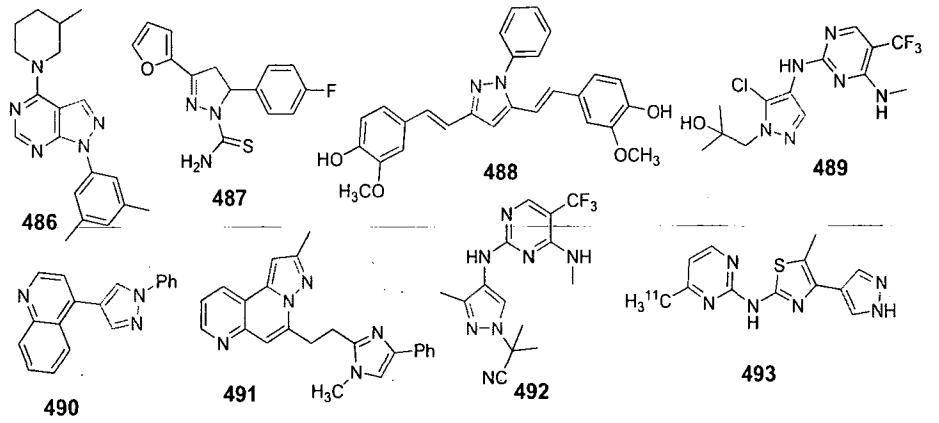


Figure 48. Pyrazole derivatives with anti-parkinson activity.

3.11. Agrochemical Activity

In the past few years, the interest in pyrazole derivatives has increased due to their proven usefulness as intermediates in the preparation of new biological materials. Specifically, pyrazole derivatives have a long history of application in the agrochemical industry as herbicides, insecticides, fungicides and acaracides. The pyrazole ring is present in many agrochemically important compounds, such as the pesticides, furametpyr [388], cyantraniliprole [389], cyenopyrafen [390], tebufenpyrad [391], tolfenpyrad [392], and fenpyroximate [388] (Figure 49).

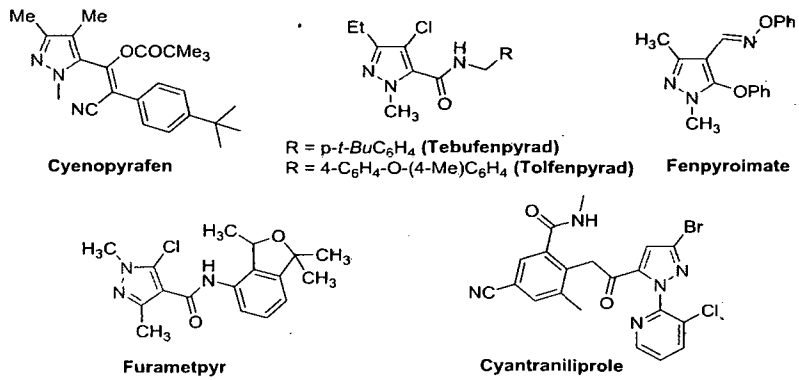


Figure 49. Agrochemical molecules containning pyrazole scaffold.

Finkelstein et al. described the synthesis and insecticidal activity of novel pyrazole methanesulfonates (Figure 50) against *Diabrotica undecimpunctata Howardi, Nilaparvata lugens, Nephotettix cincticeps*. Compound **494** showed a very high level of activity with LD values of 0.5, 2.5 and 5.5 mg/L against *Diabrotica undecimpunctata Howardi, Nilaparvata lugens, Nephotettix cincticeps*, respectively [393]. A series of novel *N*-pyridylpyrazolecarboxamides were designed and synthesized by Mao et al. The bioassays showed that some of the compounds exhibited excellent insecticidal activities against oriental armyworm (*Mythimna separata*) and diamondback moth (*Plutella xylostella*). Compound **495** showed 86% larvicidal activities against *P. xylostella* at the concentration of 0.1 mg/L, while the activity of compound **496** against *M. separata* was 80% at 1 mg/L [394]. Wu et al. reported the synthesis and insecticidal activities of novel pyrazole amide derivatives containing hydrazone substructures. In vivo tests indicated that the compound **497** exhibited good activity against different insect species, such as *P. xylostella, H. armigera, C. pipiens pallens, N. lugens* and *R. maidis* [395]. A series of new pyrazole oximes bearing substituted thiazole ring were prepared and tested for their insecticidal and acaricidal activities. The results of primary bioassay indicated that the compound **498** was more potent against *Tetranychus cinnabarinus* and *Plutella xylostella* than other analogues [396]. Song et al. synthesized a novel pyrazole derivatives and evaluated for their insecticidal activity against cotton bollworm (*Helicoverpa armigera*), diamondback moth (*Plutella xylostella*), bean aphid (*Aphis craccivora*), mosquito (*Culex pipiens pallens*), and spider mite (*Tetranychus cinnabarinus*). The results of bioassays indicated that the compound **499** showed high insecticidal activity against cotton bollworm was 60% at 5 mg/kg [397]. Fu et al. reported the synthesis and insecticidal activities of novel pyrazole oxime ether derivatives. Bioassays showed that at a 10 mg/L, the insecticidal activity of compounds **500** exceeded 90% [398].

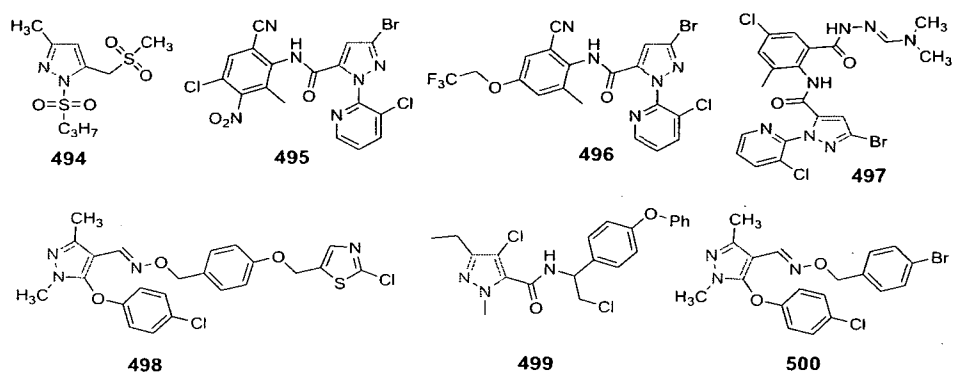


Figure 50. Pyrazole derivatives with insecticidal and acaricidal activities.

A series of novel *N*-(2,2,2)-trifluoroethylpyrazole derivatives (Figure 51) were synthesized and tested for their herbicidal activity. The bioassay results indicated that the compound **501** showed the best preemergence herbicidal effects against both dicotyledonous and monocotyledonous weeds with good safety to maize and rape at the dosage of 150 g·ha^{-1} in greenhouse [399]. Dai et al. synthesized a new series of pyrazole oxime derivatives containing a 5-trifluoromethylpyridyl moiety and evaluated for their insecticidal and acaricidal activities against *Plutella xylostella*, *Aphis craccivora* and *Tetranychus cinnabarinus*. Results showed that the compound **502** possessed excellent acaricidal activity against *T. cinnabarinus* and displayed potential insecticidal activity against *P. xylostella* and *A. craccivora* [400]. Li et al. reported Synthesis and fungicidal activities of new pyrazole derivatives. The test results indicated that the compound **503** exhibited strong fungicidal activities against *Pyricularia oryzae*, *Phytophthora infestans*, *Pseudoperonospora cubensis*, and *Erysiphe graminis* [401]. Fustero et al. described the synthesis of new fluorinated tebufenpyrad analogs with acaricidal activity. Among the synthesized compounds, two of these compounds **504** and **505** display a fertility inhibition superior to that of tebufenpyrad [402]. Two series of new pyrazoles, namely pyrazolo[1,5-*a*][1,3,5]triazine-2,4-dione and pyrazolo-[1,5-*c*][1,3,5]thiadiazine-2-one derivatives, were synthesized as potential inhibitors of the photosynthetic electron transport chain at the photosystem II level. Among the pyrazolo[1,5-*a*][1,3,5]triazine-2,4-dione derivatives, those including cyclohexyl substituents like **506** showed maximal activity [403]. A series of novel phenylpyrazoles containing a 2,2,2-trichloro-1-alkoxyethyl moiety were designed and synthesized by Zhao et al. and tested for their insecticidal activity. The results of bioassays indicated that the target compounds possessed excellent activities against a broad spectrum of insects such as bean aphid (*Aphis craccivora*), mosquito (*Culex pipiens pallens*) and diamondback moth (*Plutella xylostella*). Especially, the foliar contact activity against bean aphid of compound **507** at 2.5 mg/kg was 89% [404].

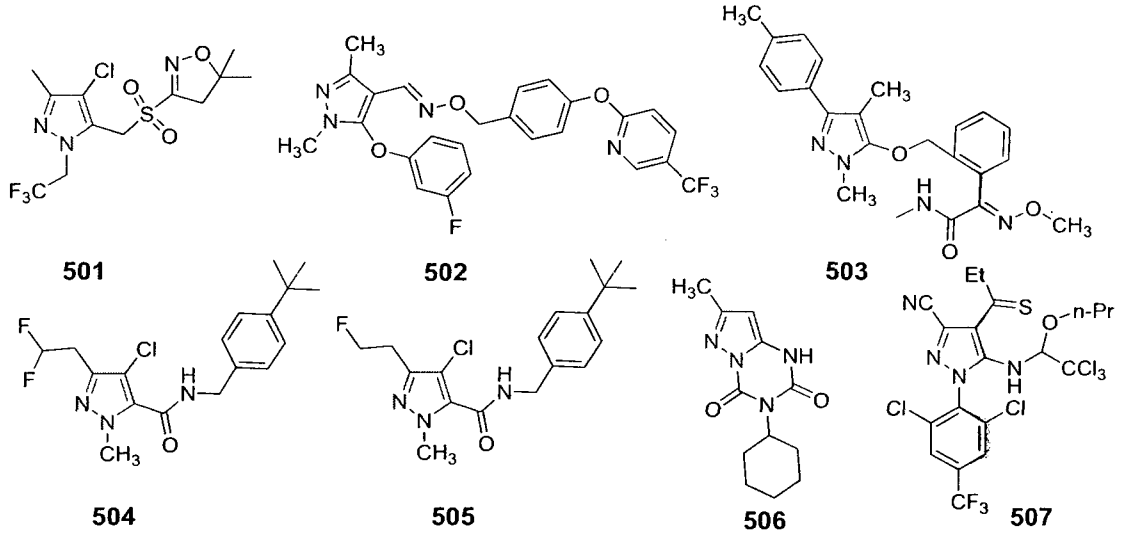


Figure 51. Pyrazole derivatives with pesticidal activity.

4. Conclusions

Pyrazoles represent a major pharmacophore with various biological properties, and some pyrazole-containing derivatives have already been used for therapeutic purposes. This literature review shows that pyrazole derivatives are pharmacologically very potent and, therefore, their design and synthesis is the potential area of research. It has been noted so far that the structural modifications of the basic structure of pyrazole, have allowed the preparation of new derivatives with a broad spectrum of biological activity, with the most important structural variations concerning the substituents at the 1-position, the carbon at the 3-position and the substituent at the 5-position.

Previous studies have shown that the structural modification on the different positions of the basic molecule allows for improving its pharmacological profile, giving it antimicrobial, anticonvulsant, analgesic, anti-inflammatory, anti-viral, anti-malarial and anti-cancer properties. For the moment, researchers have been drawn to the design of more potent pyrazole derivatives having great diversity of biological activity.

Acknowledgments: The authors extend their appreciation to the Deanship of Scientific Research at King Saud University for funding this work through research group No. (RGP-007). Sincere appreciation is also extended to the PPR2-MESRSFC-CNRST-P10 project (Morocco).

Author Contributions: K.K., S.R., Y.R., J.T. and M.A. cooperated in the preparation and writing of the manuscript. Y.N.M. participated in the preparation of the manuscript and took charge of payment of the publication fees. F.A.A. contributed in the revision of the manuscript and payment of the publication fees.

Conflicts of Interest: The authors declare no conflict of interest.

References

1. Fustero, S.; Sánchez-Roselló, M.; Barrio, P.; Simón-Fuentes, A. From 2000 to Mid-2010: A fruitful decade for the synthesis of pyrazoles. *Chem. Rev.* **2011**, *111*, 6984–7034. [CrossRef] [PubMed]
2. Ansari, A.; Ali, A.; Asif, M. biologically active pyrazole derivatives. *New J. Chem.* **2017**, *41*, 16–41. [CrossRef]
3. Steinbach, G.; Lynch, P.M.; Robin, K.S.P.; Wallace, M.H.; Hawk, E.; Gordon, G.B.; Wakabayashi, N.; Saunders, B.; Shen, Y.; Fujimura, T.; Su, L.-K.; Levin, A.B. The effect of celecoxib, a cyclooxygenase-2 inhibitor, in familial adenomatous polyposis. *N. Engl. J. Med.* **2000**, *342*, 1946–1952. [CrossRef] [PubMed]
4. Uslaner, J.M.; Parmentier-Batteur, S.; Flick, R.B.; Surles, N.O.; Lam, J.S.; McNaughton, C.H. Dose-dependent effect of CDPPB, the mGluR5 positive allosteric modulator, on recognition memory is associated with GluR1 and CREB phosphorylation in the prefrontal cortex and hippocampus. *Neuropharmacology* **2009**, *57*, 531–538. [CrossRef] [PubMed]
5. Friedrich, G.; Rose, T.; Rissler, K. Determination of lonazolac and its hydroxy and O-sulfated metabolites by on-line sample preparation liquid chromatography with fluorescence detection. *J. Chromatogr. B* **2002**, *766*, 295–305. [CrossRef]
6. Hampp, C.; Hartzema, A.G.; Kauf, T.L. Cost-utility analysis of rimonabant in the treatment of obesity. *Value Health* **2008**, *11*, 389–399. [CrossRef] [PubMed]
7. Spitz, I.; Novis, B.; Ebert, R.; Trestian, S.; LeRoith, D.; Creutzfeld, W. Betazole-induced GIP secretion is not mediated by gastric HCl. *Metabolism* **1982**, *31*, 380–382. [CrossRef]
8. Luttinger, D.; Hlasta, D.J. Antidepressant Agents. *Annu. Rep. Med. Chem.* **1987**, *22*, 21–30. [CrossRef]
9. Tsutomu, K.; Toshitaka, N. Effects of 1,3-diphenyl-5-(2-dimethylaminopropionamide)-pyrazole [difenamizole] on a conditioned avoidance response. *Neuropharmacology* **1978**, *17*, 249–256. [CrossRef]
10. García-Lozano, J.; Server-Carrió, J.; Escrivà, E.; Folgado, J.-V.; Molla, C.; Lezama, L. X-ray crystal structure and electronic properties of chlorobis (mepirizole) copper (II) tetrafluoroborate (mepirizole = 4-methoxy-2-(5-methoxy-3-methyl-1*H*-pyrazol-1-yl)-6-methylpyrimidine). *Polyhedron* **1997**, *16*, 939–944. [CrossRef]
11. Knorr, L. Einwirkung von acetessigester auf phenylhydrazin. *Eur. J. Inorg. Chem.* **1883**, *16*, 2597–2599. [CrossRef]
12. Girish, Y.R.; Kumar, K.S.S.; Manasa, H.S.; Shashikanth, S. ZnO: An Ecofriendly, Green Nano-catalyst for the Synthesis of Pyrazole Derivatives under Aqueous Media. *J. Chin. Chem. Soc.* **2014**, *61*, 1175–1179. [CrossRef]
13. Ohtsuka, Y.; Uraguchi, D.; Yamamoto, K.; Tokuhisa, K.; Yamakawa, T. Syntheses of 2-(trifluoromethyl)-1, 3-dicarbonyl compounds through direct trifluoromethylation with CF_3I and their application to fluorinated pyrazoles syntheses. *Tetrahedron* **2012**, *68*, 2636–2649. [CrossRef]
14. Gosselin, F.; O'Shea, P.D.; Webster, R.A.; Reamer, R.A.; Tillyer, R.D.; Grabowski, E.J.J. Highly Regioselective Synthesis of 1-Aryl-3,4,5-Substituted Pyrazoles. *Synlett* **2006**, *19*, 3267–3270. [CrossRef]
15. Moureu, C.; Delange, R. Over some Acetylenketone and over a new method to the synthesis of β-Diketones. *Bull. Soc. Chim. Fr.* **1901**, *25*, 302–313.

16. Baldwin, J.E.; Pritchard, G.J.; Rathmell, R.E. The reactions of diacetylenic ketones with nitrogen nucleophiles; facile preparation of alkynyl substituted pyrimidines and pyrazoles. *J. Chem. Soc. Perkin Trans. 1* **2001**, 2906–2908. [CrossRef]
17. Ji, G.; Wang, X.; Zhang, S.; Xu, Y.; Ye, Y.; Li, M. Synthesis of 3-trifluoromethylpyrazoles via trifluoromethylation/cyclization of α,β-alkynic hydrazones using a hypervalent iodine reagent. *Chem. Commun.* **2014**, *50*, 4361–4363. [CrossRef] [PubMed]
18. Bishop, B.C.; Brands, K.M.; Gibb, A.D.; Kennedy, D.J. Regioselective synthesis of 1,3,5-substituted pyrazoles from acetylenic ketones and hydrazines. *Synthesis* **2004**, *2004*, 43–52. [CrossRef]
19. Rao, V.K.; Tiwari, R.; Chhikara, B.S.; Shirazi, A.N.; Parang, K.; Kumar, A. Copper triflate-mediated synthesis of 1,3,5-triarylpyrazoles in [bmim][PF_6] ionic liquid and evaluation of their anticancer activities. *RSC Adv.* **2013**, *3*, 15396–15403. [CrossRef] [PubMed]
20. Bhat, B.A.; Puri, S.C.; Qurishi, M.A.; Dhar, K.L.; Qazi, G.N. Synthesis of 3,5-diphenyl-1*H*-pyrazoles. *Synth. Commun.* **2005**, *35*, 1135–1142. [CrossRef]
21. Huang, Y.R.; Katzenellenbogen, J.A. Regioselective synthesis of 1,3,5-triaryl-4-alkylpyrazoles: Novel ligands for the estrogen receptor. *Org. Lett.* **2000**, *2*, 2833–2836. [CrossRef] [PubMed]
22. Ponnala, S.; Prasad, S.D. Iodine-Mediated Synthesis of 2-Arylbenzoxazoles, 2-Arylbenzimidazoles, and 1,3,5-Trisubstituted Pyrazoles. *Synth. Commun.* **2006**, *36*, 2189–2194. [CrossRef]
23. Braibante, M.E.; Braibante, H.T.; Da Roza, J.K.; Henriques, D.M.; de Carvalho, T.L. Synthesis of Aminopyrazoles from α-Oxoketene *O,N*-Acetals Using Montmorillonite K-10/Ultrasound. *Synthesis* **2003**, *2003*, 1160–1162. [CrossRef]
24. Rosa, F.A.; Machado, P.; Vargas, P.S.; Bonacorso, H.G.; Zanatta, N.; Martins, M.A. Straightforward and regiospecific synthesis of pyrazole-5-carboxylates from unsymmetrical enaminodiketones. *Synlett* **2008**, *2008*, 1673–1678. [CrossRef]
25. Katritzky, A.R.; Wang, M.; Zhang, S.; Voronkov, M.V.; Steel, P.J. Regioselective synthesis of polysubstituted pyrazoles and isoxazoles. *J. Org. Chem.* **2001**, *66*, 6787–6791. [CrossRef] [PubMed]
26. Alberola, A.; Gonzalez-Ortega, A.; Luisa Sadaba, M.; Carmen Sanudo, M. [small beta]-Aminoenones in the regioselective synthesis of 1,3,5-trialkylpyrazoles. The influence of the substituents in the mechanism and the regioselectivity of the reaction. *J. Chem. Soc. Perkin Trans. 1.* **1998**, *0*, 4061–4066. [CrossRef]
27. He, S.; Chen, L.; Niu, Y.-N.; Wu, L.-Y.; Liang, Y.-M. 1,3-Dipolar cycloaddition of diazoacetate compounds to terminal alkynes promoted by Zn $(OTf)_2$: An efficient way to the preparation of pyrazoles. *Tetrahedron Lett.* **2009**, *50*, 2443–2445. [CrossRef]
28. Gioiello, A.; Khamidullina, A.; Fulco, M.C.; Venturoni, F.; Zlotsky, S.; Pellicciari, R. New one-pot synthesis of pyrazole-5-carboxylates by 1,3-dipole cycloadditions of ethyl diazoacetate with α-methylene carbonyl compounds. *Tetrahedron Lett.* **2009**, *50*, 5978–5980. [CrossRef]
29. Jiang, N.; Li, C.-J. Novel 1,3-dipolar cycloaddition of diazocarbonyl compounds to alkynes catalyzed by $InCl_3$ in wate. *Chem. Commun.* **2004**, 394–395. [CrossRef] [PubMed]
30. Qi, X.; Ready, J.M. Copper-Promoted Cycloaddition of Diazocarbonyl Compounds and Acetylides. *Angew. Chem. Int. Ed.* **2007**, *46*, 3242–3244. [CrossRef] [PubMed]
31. Delaunay, T.; Genix, P.; Es-Sayed, M.; Vors, J.-P.; Monteiro, N.; Balme, G. A Modular Sydnone Cycloaddition/Suzuki-Miyaura Cross-Coupling Strategy to Unsymmetrical 3,5-Bis (hetero) aromatic Pyrazoles. *Org. Lett.* **2010**, *12*, 3328–3331. [CrossRef] [PubMed]
32. Chen, F.; Liu, F.-M.; Shi, H.; Chen, S.-L. A facile access to 1,3,4-trisubstituted pyrazoles via 1,3-dipolar cycloaddition of 3-arylsydnones with α,β-unsaturated ketones. *Monatsh. Chem. Chem. Mon.* **2013**, *144*, 879–884. [CrossRef]
33. Dadiboyena, S.; Valente, E.J.; Hamme, A.T. A novel synthesis of 1,3,5-trisubstituted pyrazoles through a spiro-pyrazoline intermediate via a tandem 1,3-dipolar cycloaddition/elimination. *Tetrahedron Lett.* **2009**, *50*, 291–294. [CrossRef] [PubMed]
34. Oh, L.M. Synthesis of celecoxib via 1,3-dipolar cycloaddition. *Tetrahedron Lett.* **2006**, *47*, 7943–7946. [CrossRef]
35. Harigae, R.; Moriyama, K.; Togo, H. Preparation of 3,5-Disubstituted Pyrazoles and Isoxazoles from Terminal Alkynes, Aldehydes, Hydrazines, and Hydroxylamine. *J. Org. Chem.* **2014**, *79*, 2049–2058. [CrossRef] [PubMed]

36. Jiang, J.-A.; Huang, W.-B.; Zhai, J.-J.; Liu, H.-W.; Cai, Q.; Xu, L.-X. 'One-pot' synthesis of 4-substituted 1,5-diaryl-1*H*-pyrazole-3-carboxylates via lithium tert-butoxide-mediated sterically hindered Claisen condensation and Knorr reaction. *Tetrahedron* **2013**, *69*, 627–6235. [CrossRef]
37. Iizuka, M.; Kondo, Y. Palladium-Catalyzed Alkynylcarbonylation of Aryl Iodides with the Use of Mo (CO) 6 in the Presence of tBu3P Ligand. *Eur. J. Org. Chem.* **2007**, *2007*, 5180–5182. [CrossRef]
38. Kovacs, S.; Novak, Z. Copper on iron promoted one-pot synthesis of β-aminoenones and 3,5-disubstituted pyrazoles. *Tetrahedron* **2013**, *69*, 8987–9893. [CrossRef]
39. Dang, T.T.; Dang, T.T.; Fischer, C.; Görls, H.; Langer, P. Synthesis of pyrazole-3-carboxylates and pyrazole-1,5-dicarboxylates by one-pot cyclization of hydrazone dianions with diethyl oxalate. *Tetrahedron* **2008**, *64*, 2207–2215: [CrossRef]
40. Lokhande, P.; Hasanzadeh, K.; Konda, S.G. A novel and efficient approach for the synthesis of new halo substituted 2-arylpyrazolo[4,3-*c*]coumarin derivatives. *Eur. J. Chem.* **2011**, *2*, 223–228. [CrossRef]
41. Deng, X.; Mani, N.S. Reaction of *N*-monosubstituted hydrazones with nitroolefins: A novel regioselective pyrazole synthesis. *Org. Lett.* **2006**, *8*, 3505–3508. [CrossRef] [PubMed]
42. Deng, X.; Mani, N.S. Base-mediated reaction of hydrazones and nitroolefins with a reversed regioselectivity: A novel synthesis of 1,3,4-trisubstituted pyrazoles. *Org. Lett.* **2008**, *10*, 1307–13010. [CrossRef] [PubMed]
43. Aggarwal, V.K.; de Vicente, J.; Bonnert, R.V. A novel one-pot method for the preparation of pyrazoles by 1,3-dipolar cycloadditions of diazo compounds generated in situ. *J. Org. Chem.* **2003**, *68*, 5381–5383. [CrossRef] [PubMed]
44. Yadav, J.; Reddy, B.S.; Srinivas, M.; Prabhakar, A.; Jagadeesh, B. Montmorillonite KSF clay-promoted synthesis of enantiomerically pure 5-substituted pyrazoles from 2,3-dihydro-4*H*-pyran-4-ones. *Tetrahedron Lett.* **2004**, *45*, 6033–6036. [CrossRef]
45. Xie, F.; Cheng, G.; Hu, Y. Three-component, one-pot reaction for the combinatorial synthesis of 1,3,4-substituted pyrazoles. *J. Comb. Chem.* **2006**, *8*, 286–288. [CrossRef] [PubMed]
46. Arkhipov, V.; Garazd, M.; Smirnov, M.; Khilya, V. Chemistry of Modified Flavonoids. 24. Synthesis of 4-Aryloxy-3-(2-hydroxy-4-hydroxy/alkoxyphenyl) pyrazoles. *Chem. Heterocycl. Compd.* **2004**, *40*, 183–187. [CrossRef]
47. Sosnovskikh, V.Y.; Barabanov, M.; Usachev, B. Reactions of 5,7-dimethyl-2-polyfluoroalkyl-8-azachromones with *N*-nucleophiles. *Russ. Chem. Bull.* **2003**, *52*, 1758–1767. [CrossRef]
48. Usachev, B.; Shafeev, M.; Sosnovskikh, V.Y. Synthesis and reactivity of 2-polyfluoroalkylchromene-4 (4*H*)-thiones. *Russ. Chem. Bull.* **2004**, *53*, 2285–2292. [CrossRef]
49. Sosnovskikh, V.Y.; Usachev, B.; Sizov, A.Y. 2-Polyfluoroalkylchromones. 14. Synthesis of 4-chloro-3(5)-(2-hydroxyaryl)-5(3)-polyfluoroalkylpyrazoles. *Russ. Chem. Bull.* **2003**, *52*, 508–510. [CrossRef]
50. İlhan, İ.Ö.; Saripinar, E.; Akçamur, Y. Synthesis of some pyrazole-3-carboxylic acid-hydrazide and pyrazolopyridazine compounds. *J. Heterocycl. Chem.* **2005**, *42*, 117–120. [CrossRef]
51. Sener, A.; Kasimogullari, R.; Sener, M.; Genç, H. Studies on reactions of cyclic oxalyl compounds with hydrazines or hydrazones. 2. Synthesis and reactions of 4-benzoyl-1-(4-nitrophenyl)-5-phenyl-1*H*-pyrazole-3-carboxylic acid. *Chem. Heterocycl. Compd.* **2004**, *40*, 1039–1046. [CrossRef]
52. Krishnaiah, A.; Narsaiah, B. A novel approach to the synthesis of 5-trifluoromethyl-3-substituted pyrazoles. *J. Fluor. Chem.* **2002**, *115*, 9–11. [CrossRef]
53. Bisenieks, E.; Uldrikis, J.; Dubur, G. Reaction of 3,5-carbonyl-substituted 1,4-dihydropyridines with hydrazine hydrate. *Chem. Heterocycl. Compd.* **2004**, *40*, 869–875. [CrossRef]
54. Grošelj, U.; Drobnič, A.; Rečnik, S.; Svete, J.; Stanovnik, B.; Golobič, A.; Nina, L.; Ivan, L.; Anton, M.; Simona, G.-G. 1,3-Dipolar Cycloadditions to (5*Z*)-1-Acyl-5-(cyanomethylidene)-imidazolidine-2,4-diones: Synthesis and Transformations of Spirohydantoin Derivatives. *Helv. Chim. Acta* **2001**, *84*, 3403–3417. [CrossRef]
55. Kawase, M.; Koiwai, H.; Yamano, A.; Miyamae, H. Regioselective reaction of mesoionic 4-trifluoroacetyl-1,3-oxazolium-5-olates and phenylhydrazine: Synthesis of trifluoromethyl substituted pyrazole and 1,2,4-triazine derivatives. *Tetrahedron Lett.* **1998**, *39*, 663–666. [CrossRef]
56. Simoni, D.; Rondanin, R.; Furnò, G.; Aiello, E.; Invidiata, F.P. Facile synthesis of pyrazoles and pyrroles via thermolysis of tetrazolo[1,5-*b*]pyridazines, tetrazolo[1,5-*a*]pyrimidines and tetrazolo[1,5-*a*]pyridines. *Tetrahedron Lett.* **2000**, *41*, 2699–2703. [CrossRef]

57. Rykowski, A.; Branowska, D. Ring transformation of 3-halo-1,2,4-triazines with α-chlorocarbanions: A novel route to pyrazoles with sulfonyl, sulfonamido and sulfonyloxy groups. *Heterocycles* **1996**, *10*, 2095–2098. [CrossRef]
58. Ferfra, S.; Ahabchane, N.H.; Garrigues, B.; Essassi, E.M. Nouvelle méthode de synthèse de quinoxalines associées à différents hétérocycles à cinq chaînons. *C. R. Acad. Sci. IIC* **2001**, *4*, 905–911. [CrossRef]
59. Dzvinchuk, I.; Lozinskii, M. Hydrazinolytic Recyclization of (Z)-3-Acetyl-2-methyl-2,3-dihydro-1,4-benzodioxin-2-ol. *Chem. Heterocycl. Compd.* **2001**, *37*, 459–462. [CrossRef]
60. Azev, Y.A.; Lork, E.; Gabel, D.; Duelcks, T. New way of the reaction of 1-amino-6,7-difluoro-4-oxoquinolyl-3-ethylcarboxylate with acetoacetone. *Mendeleev Commun.* **2003**, *13*, 184–185. [CrossRef]
61. Pfeiffer, W.-D.; Dilk, E.; Rossberg, H.; Langer, P. Synthesis and Reactivity of 3,4-Dimethyl-4*H*-1,3,4-thiadiazines. *Synlett* **2003**, *2003*, 2392–2394. [CrossRef]
62. Guillard, J.; Goujon, F.; Badol, P.; Poullain, D. New synthetic route to diaminonitropyrazoles as precursors of energetic materials. *Tetrahedron Lett.* **2003**, *44*, 5943–5945. [CrossRef]
63. Suen, Y.F.; Hope, H.; Nantz, M.H.; Haddadin, M.J.; Kurth, M.J. A novel route to fully substituted 1*H*-pyrazoles. *J. Org. Chem.* **2005**, *70*, 8468–8471. [CrossRef] [PubMed]
64. Akbas, E.; Berber, I.; Sener, A.; Hasanov, B. Synthesis and antibacterial activity of 4-benzoyl-1-methyl-5-phenyl-1*H*-pyrazole-3-carboxylic acid and derivatives. *Farmaco* **2005**, *60*, 23–26. [CrossRef] [PubMed]
65. Prasath, R.; Bhavana, P.; Sarveswari, S.; Ng, S.W.; Tiekink, E.R.T. Efficient ultrasound-assisted synthesis, spectroscopic, crystallographic and biological investigations of pyrazole-appended quinolinyl chalcones. *J. Mol. Struct.* **2015**, *1081*, 201–210. [CrossRef]
66. Mert, S.; Kasimogullari, R.; Ica, T.; Colak, F.; Altun, A.; Ok, S. Synthesis, structure-activity relationships, and in vitro antibacterial and antifungal activity evaluations of novel pyrazole carboxylic and dicarboxylic acid derivatives. *Eur. J. Med. Chem.* **2014**, *78*, 86–96. [CrossRef] [PubMed]
67. Rahimizadeh, M.; Pordel, M.; Bakavoli, M.; Rezaeian, S.; Sadeghian, A. Synthesis and antibacterial activity of some new derivatives of pyrazole. *World J. Microbiol. Biotechnol.* **2010**, *26*, 317–321. [CrossRef]
68. Chandrakantha, B.; Isloor, A.; Shetty, P.; Isloor, S.; Malladi, S.; Fun, H. Synthesis, characterization and antimicrobial activity of novel ethyl 1-(*N*-substituted)-5-phenyl-1*H*-pyrazole-4-carboxylate derivatives. *Med. Chem. Res.* **2012**, *21*, 2702–2708. [CrossRef]
69. Sharma, P.K.; Kumar, S.; Kumar, P.; Kaushik, P.; Kaushik, D.; Dhingra, Y. Synthesis and biological evaluation of some pyrazolylpyrazolines as anti-inflammatory–antimicrobial agents. *Eur. J. Med. Chem.* **2010**, *45*, 2650–2655. [CrossRef] [PubMed]
70. Kendre, B.V.; Landge, M.G.; Bhusare, S.R. Synthesis and biological evaluation of some novel pyrazole, isoxazole, benzoxazepine, benzothiazepine and benzodiazepine derivatives bearing an aryl sulfonate moiety as antimicrobial and anti-inflammatory agents. *Arab. J. Chem.* **2015**. [CrossRef]
71. B'Bhatt, H.; Sharma, S. Synthesis and antimicrobial activity of pyrazole nucleus containing 2-thioxothiazolidin-4-one derivatives. *Arab. J. Chem.* **2017**, *10*, S1590–S1596. [CrossRef]
72. Abunada, N.; Hassaneen, H.; Kandile, N.; Miqdad, O. Synthesis and Antimicrobial Activity of Some New Pyrazole, Fused Pyrazolo[3,4-*d*]-pyrimidine and Pyrazolo[4,3-*e*][1,2,4]-triazolo[1,5-*c*]pyrimidine Derivatives. *Molecules* **2008**, *13*, 1501–1517. [CrossRef] [PubMed]
73. Padmaja, A.; Payani, T.; Reddy, G.D.; Padmavathi, V. Synthesis, antimicrobial and antioxidant activities of substituted pyrazoles, isoxazoles, pyrimidine and thioxopyrimidine derivatives. *Eur. J. Med. Chem.* **2009**, *44*, 4557–4566. [CrossRef] [PubMed]
74. Ragavan, R.V.; Vijayakumar, V.; Kumari, N.S. Synthesis and antimicrobial activities of novel 1,5-diaryl pyrazoles. *Eur. J. Med. Chem.* **2010**, *45*, 1173–1180. [CrossRef] [PubMed]
75. Sharma, P.K.; Chandak, N.; Kumar, P.; Sharma, C.; Aneja, K.R. Synthesis and biological evaluation of some 4-functionalized-pyrazoles as antimicrobial agents. *Eur. J. Med. Chem.* **2011**, *46*, 1425–1432. [CrossRef] [PubMed]
76. Pathak, R.B.; Chovatia, P.T.; Parekh, H.H. Synthesis, antitubercular and antimicrobial evaluation of 3-(4-chlorophenyl)-4-substituted pyrazole derivatives. *Bioorg. Med. Chem. Lett.* **2012**, *22*, 5129–5133. [CrossRef] [PubMed]
77. Vijesh, A.M.; Isloor, A.M.; Telkar, S.; Peethambar, S.K.; Rai, S.; Isloor, N. Synthesis, characterization and antimicrobial studies of some new pyrazole incorporated imidazole derivatives. *Eur. J. Med. Chem.* **2011**, *46*, 3531–3536. [CrossRef] [PubMed]

78. Wu, J.; Shi, Q.; Chen, Z.; He, M.; Jin, L.; Hu, D. Synthesis and Bioactivity of Pyrazole Acyl Thiourea Derivatives. *Molecules* **2012**, *17*, 5139–5150. [CrossRef] [PubMed]
79. Wu, Z.; Hu, D.; Kuangn, J.; Cain, H.; Wun, S.; Xuen, W. Synthesis and Antifungal Activity of *N*-(Substituted pyridinyl)-1-methyl(phenyl)-3-(trifluoromethyl)-1*H*-pyrazole-4-carboxamide Derivatives. *Molecules* **2012**, *17*, 14205–14218. [CrossRef] [PubMed]
80. Xu, L.-L.; Zheng, C.-J.; Sun, L.-P.; Miao, J.; Piao, H.-R. Synthesis of novel 1,3-diaryl pyrazole derivatives bearing rhodanine-3-fatty acid moieties as potential antibacterial agents. *Eur. J. Med. Chem.* **2012**, *48*, 174–178. [CrossRef] [PubMed]
81. Desai, N.C.; Rajpara, K.M.; Joshi, V.V. Synthesis of pyrazole encompassing 2-pyridone derivatives as antibacterial agents. *Bioorg. Med. Chem. Lett.* **2013**, *23*, 2714–2717. [CrossRef] [PubMed]
82. Jardosh, H.H.; Sangani, C.B.; Patel, M.P.; Patel, R.G. One step synthesis of pyrido [1,2-*a*] benzimidazole derivatives of aryloxypyrazole and their antimicrobial evaluation. *Chin. Chem. Lett.* **2013**, *24*, 123–126. [CrossRef]
83. Malladi, S.; Isloor, A.M.; Isloor, S.; Akhila, D.; Fun, H.-K. Synthesis, characterization and antibacterial activity of some new pyrazole based Schiff bases. *Arab. J. Chem.* **2013**, *6*, 335–340. [CrossRef]
84. Renuka, N.; Kumar, K.A. Synthesis and biological evaluation of novel formyl-pyrazoles bearing coumarin moiety as potent antimicrobial and antioxidant agents. *Bioorg. Med. Chem. Lett.* **2013**, *23*, 6406–6409. [CrossRef] [PubMed]
85. Song, M.-X.; Zheng, C.-J.; Deng, X.-Q.; Sun, L.-P.; Wu, Y.; Hong, L.; Li, Y.J.; Liu, Y.; Wei, Z.Y.; Jin, M.J.; et al. Synthesis and antibacterial evaluation of rhodanine-based 5-aryloxy pyrazoles against selected methicillin resistant and quinolone-resistant Staphylococcus aureus (MRSA and QRSA). *Eur. J. Med. Chem.* **2013**, *60*, 376–385. [CrossRef] [PubMed]
86. Sayed, G.H.; Azab, M.E.; Anwer, K.E.; Raouf, M.A.; Negm, N.A. Pyrazole, pyrazolone and enaminonitrile pyrazole derivatives: Synthesis, characterization and potential in corrosion inhibition and antimicrobial applications. *J. Mol. Liq.* **2018**, *252*, 329–338. [CrossRef]
87. Kalaria, P.N.; Satasia, S.P.; Avalani, J.R.; Raval, D.K. Ultrasound-assisted one-pot four-component synthesis of novel 2-amino-3-cyanopyridine derivatives bearing 5-imidazopyrazole scaffold and their biological broadcast. *Eur. J. Med. Chem.* **2014**, *83*, 655–664. [CrossRef] [PubMed]
88. Kumar, R.; Arora, J.; Ruhil, S.; Phougat, N.; Chhillar, A.K.; Prasad, A.K. Synthesis and antimicrobial studies of pyrimidine pyrazole heterocycles. *Adv. Chem.* **2014**, *2014*, 1–12. [CrossRef]
89. Liu, X.-R.; Wu, H.; He, Z.-Y.; Ma, Z.-Q.; Feng, J.-T.; Zhang, X. Design, Synthesis and Fungicidal Activities of Some Novel Pyrazole Derivatives. *Molecules* **2014**, *19*, 14036–14051. [CrossRef] [PubMed]
90. Malladi, S.; Isloor, A.M.; Peethambar, S.; Fun, H.K. Synthesis and biological evaluation of newer analogues of 2,5-disubstituted 1,3,4-oxadiazole containing pyrazole moiety as antimicrobial agents. *Arab. J. Chem.* **2014**, *7*, 1185–1191. [CrossRef]
91. Mehta, H.B.; Dixit, B.C.; Dixit, R.B. L-Proline catalyzed one-pot multi-component synthesis of 2-(1,3-diphenyl-1*H*-pyrazol-4-yl)quinazolin-4(3*H*)-one derivatives and their biological studies. *Chin. Chem. Lett.* **2014**, *25*, 741–744. [CrossRef]
92. Ningaiah, S.; Bhadraiah, U.K.; Doddaramappa, S.D.; Keshavamurthy, S.; Javarasetty, C. Novel pyrazole integrated 1,3,4-oxadiazoles: Synthesis, characterization and antimicrobial evaluation. *Bioorg. Med. Chem. Lett.* **2014**, *24*, 245–248. [CrossRef] [PubMed]
93. Prakash, T.B.; Reddy, G.D.; Padmaja, A.; Padmavathi, V. Synthesis and antimicrobial activity of amine linked bis-and tris-heterocycles. *Eur. J. Med. Chem.* **2014**, *82*, 347–3454. [CrossRef] [PubMed]
94. Du, S.; Tian, Z.; Yang, D.; Li, X.; Li, H.; Jia, C.; Che, C.; Wang, M.; Qin, Z. Synthesis, Antifungal Activity and Structure-Activity Relationships of Novel 3-(Difluoromethyl)-1-methyl-1*H*-pyrazole-4-carboxylic Acid Amides. *Molecules* **2015**, *20*, 8395–8408. [CrossRef] [PubMed]
95. Miniyar, P.B.; Barmade, M.A.; Mahajan, A.A. Synthesis and biological evaluation of 1-(5-(2-chloroquinolin-3-yl)-3-phenyl-1*H*-pyrazol-1-yl) ethanone derivatives as potential antimicrobial agents. *J. Saudi Chem. Soc.* **2015**, *19*, 655–660. [CrossRef]
96. Radi, S.; Tighadouini, S.; Feron, O.; Riant, O.; Bouakka, M.; Benabbes, R.; Mabkhot, Y.N. Synthesis of Novel β-Keto-Enol Derivatives Tethered Pyrazole, Pyridine and Furan as New Potential Antifungal and Anti-Breast Cancer Agents. *Molecules* **2015**, *20*, 19684–19694. [CrossRef] [PubMed]

97. Rizk, H.F.; Ibrahim, S.A.; El-Borai, M.A. Synthesis, fastness properties, color assessment and antimicrobial activity of some azo reactive dyes having pyrazole moiety. *Dyes Pigment.* **2015**, *112*, 86–92. [CrossRef]
98. Sun, J.; Zhou, Y. Synthesis and Antifungal Activity of the Derivatives of Novel Pyrazole Carboxamide and Isoxazolol Pyrazole Carboxylate. *Molecules* **2015**, *20*, 4383–4394. [CrossRef] [PubMed]
99. Yu, L.-G.; Ni, T.-F.; Gao, W.; He, Y.; Wang, Y.-Y.; Cui, H.-W.; Yang, C.-G.; Qiu, W.-W. The synthesis and antibacterial activity of pyrazole-fused tricyclic diterpene derivatives. *Eur. J. Med. Chem.* **2015**, *90*, 10–20. [CrossRef] [PubMed]
100. Elshaier, Y.; Barakat, A.; Al-Qahtany, B.; Al-Majid, A.; Al-Agamy, M. Synthesis of Pyrazole-Thiobarbituric Acid Derivatives: Antimicrobial Activity and Docking Studies. *Molecules* **2016**, *21*, 1337. [CrossRef] [PubMed]
101. Hafez, H.; El-Gazzar, A.-R. Synthesis and Biological Evaluation of *N*-Pyrazolyl Derivatives and Pyrazolopyrimidine Bearing a Biologically Active Sulfonamide Moiety as Potential Antimicrobial Agent. *Molecules* **2016**, *21*, 1156. [CrossRef] [PubMed]
102. Mabkhot, Y.; Alatibi, F.; El-Sayed, N.; Kheder, N.; Al-Showiman, S. Synthesis and Structure-Activity Relationship of Some New Thiophene-Based Heterocycles as Potential Antimicrobial Agents. *Molecules* **2016**, *21*, 1036. [CrossRef] [PubMed]
103. Mu, J.-X.; Shi, Y.-X.; Yang, M.-Y.; Sun, Z.-H.; Liu, X.-H.; Li, B.-J.; Sun, N.-B. Design, Synthesis, DFT Study and Antifungal Activity of Pyrazolecarboxamide Derivatives. *Molecules* **2016**, *21*, 68. [CrossRef] [PubMed]
104. Nagamallu, R.; Srinivasan, B.; Ningappa, M.B.; Kariyappa, A.K. Synthesis of novel coumarin appended bis(formylpyrazole) derivatives: Studies on their antimicrobial and antioxidant activities. *Bioorg. Med. Chem. Lett.* **2016**, *26*, 690–694. [CrossRef] [PubMed]
105. Abrigach, F.; Bouchal, B.; Riant, O.; Macé, Y.; Takfaoui, A.; Radi, S.; Oussaid, A.; Bellaoui, M.; Touzani, R. New *N*,*N*,*N*′,*N*′-tetradentate Pyrazoly Agents: Synthesis and Evaluation of their Antifungal and Antibacterial Activities. *Med. Chem.* **2016**, *12*, 83–89. [CrossRef] [PubMed]
106. El Shehry, M.F.; Ghorab, M.M.; Abbas, S.Y.; Fayed, E.A.; Shedid, S.A.; Ammar, Y.A. Quinoline derivatives bearing pyrazole moiety: Synthesis and biological evaluation as possible antibacterial and antifungal agents. *Eur. J. Med. Chem.* **2018**, *143*, 1463–1473. [CrossRef] [PubMed]
107. Ahn, M.; Gunasekaran, P.; Rajasekaran, G.; Kim, E.Y.; Lee, S.-J.; Bang, G.; Cho, K.; Hyun, J.-K.; Lee, H.-J.; Jeon, Y.H.; et al. Pyrazole derived ultra-short antimicrobial peptidomimetics with potent anti-biofilm activity. *Eur. J. Med. Chem.* **2017**, *125*, 551–564. [CrossRef] [PubMed]
108. Nada, A.; Al-Moghazy, M.; Soliman, A.A.F.; Rashwan, G.M.T.; Eldawy, T.H.A.; Hassan, A.A.E.; Sayed, G.H. Pyrazole-based compounds in chitosan liposomal emulsion for antimicrobial cotton fabrics. *Int. J. Biol. Macromol.* **2018**, *107*, 585–594. [CrossRef] [PubMed]
109. Sharma, A.; Ghabbour, H.; Khan, S.T.; de la Torre, B.G.; Albericio, F.; El-Faham, A. Novel pyrazolyl-s-triazine derivatives, molecular structure and antimicrobial activity. *J. Mol. Struct.* **2017**, *1145*, 244–253. [CrossRef]
110. Zhou, L.; Wang, P.-Y.; Zhou, J.; Shao, W.-B.; Fang, H.-S.; Wu, Z.-B.; Yang, S. Antimicrobial activities of pyridinium-tailored pyrazoles bearing 1,3,4-oxadiazole scaffolds. *J. Saudi Chem. Soc.* **2017**, *21*, 852–860. [CrossRef]
111. Mandal, S.; Mondal, M.; Biswas, J.K.; Cordes, D.B.; Slawin, A.M.Z.; Butcher, R.J.; Saha, M.; Saha, N.C. Synthesis, characterization and antimicrobial activity of some nickel, cadmium and mercury complexes of 5-methyl pyrazole-3yl-*N*-(2′-methylthiophenyl) methyleneimine, (MPzOATA) ligand. *J. Mol. Struct.* **2018**, *1152*, 189–198. [CrossRef]
112. Mor, S.; Mohil, R.; Kumar, D.; Ahuja, M. Synthesis and antimicrobial activities of some isoxazolyl thiazolyl pyrazoles. *Med. Chem. Res.* **2012**, *21*, 3541–3548. [CrossRef]
113. Nitulescu, G.M.; Draghici, C.; Chifiriuc, M.C.; Marutescu, L.; Bleotu, C.; Missir, A.V. Synthesis and antimicrobial screening of *N*-(1-methyl-1*H*-pyrazole-4-carbonyl)-thiourea derivatives. *Med. Chem. Res.* **2012**, *21*, 308–314. [CrossRef]
114. Tanitame, A.; Oyamada, Y.; Ofuji, K.; Fujimoto, M.; Iwai, N.; Hiyama, Y.; Suzuki, K.; Ito, H.; Terauchi, H.; Kawasaki, M.; et al. Synthesis and Antibacterial Activity of a Novel Series of Potent DNA Gyrase Inhibitors. Pyrazole Derivatives. *J. Med. Chem.* **2004**, *47*, 3693–3696. [CrossRef] [PubMed]
115. Çetin, A.; Bildirici, İ. A study on synthesis and antimicrobial activity of 4-acyl-pyrazoles. *J. Saudi Chem. Sci.* **2016**. [CrossRef]

116. Dayakar, C.; Kumar, B.S.; Sneha, G.; Sagarika, G.; Meghana, K.; Ramakrishna, S.; Prakasham, R.S.; China, R.B. Synthesis, pharmacological activities and molecular docking studies of pyrazolyltriazoles as anti-bacterial and anti-inflammatory agents. *Bioorg. Med. Chem.* **2017**, *25*, 5678–5691. [CrossRef] [PubMed]
117. Dai, H.; Chen, J.; Li, G.; Ge, S.; Shi, Y.; Fang, Y.; Ling, Y. Design, synthesis, and bioactivities of novel oxadiazole-substituted pyrazole oximes. *Bioorg. Med. Chem. Lett.* **2017**, *27*, 950–953. [CrossRef] [PubMed]
118. Kamal, A.; Shaik, A.B.; Jain, N.; Kishor, C.; Nagabhushana, A.; Supriya, B.; Kumar, G.B.; Chourasiya, S.S.; Suresh, Y.; Mishra, R.K. Anthony Addlagatta. Design and synthesis of pyrazole–oxindole conjugates targeting tubulin polymerization as new anticancer agents. *Eur. J. Med. Chem.* **2015**, *92*, 501–513. [CrossRef] [PubMed]
119. Xu, Y.; Liu, X.-H.; Saunders, M.; Pearce, S.; Foulks, J.M.; Parnell, K.M.; Clifford, A.; Nix, R.N.; Bullough, J.; Hendrickson, T.F.; et al. Discovery of 3-(trifluoromethyl)-1*H*-pyrazole-5-carboxamide activators of the M2 isoform of pyruvate kinase (PKM2). *Bioorg. Med. Chem. Lett.* **2014**, *24*, 515–519. [CrossRef] [PubMed]
120. Viale, M.; Anzaldi, M.; Aiello, C.; Fenoglio, C.; Albicini, F.; Emionite, L.; Gangemi, R.; Balbi, A. Evaluation of the anti-proliferative activity of three new pyrazole compounds in sensitive and resistant tumor cell lines. *Pharmacol. Rep.* **2013**, *65*, 717–723. [CrossRef]
121. Tzanetou, E.; Liekens, S.; Kasiotis, K.M.; Fokialakis, N.; Haroutounian, S.A. Novel Pyrazole and Indazole Derivatives: Synthesis and Evaluation of Their Anti-Proliferative and Anti-Angiogenic Activities. *Arch. Pharm.* **2012**, *345*, 804–811. [CrossRef] [PubMed]
122. Zheng, L.-W.; Shao, J.-H.; Zhao, B.-X.; Miao, J.-Y. Synthesis of novel pyrazolo[1,5-*a*]pyrazin-4(5*H*)-one derivatives and their inhibition against growth of A549 and H322 lung cancer cells. *Bioorg. Med. Chem. Lett.* **2011**, *21*, 3909–3913. [CrossRef] [PubMed]
123. Balbi, A.; Anzaldi, M.; Macciò, C.; Aiello, C.; Mazzei, M.; Gangemi, R.; Castagnola, P.; Miele, M.; Rosano, C.; Viale, M. Synthesis and biological evaluation of novel pyrazole derivatives with anticancer activity. *Eur. J. Med. Chem.* **2011**, *46*, 5293–5309. [CrossRef] [PubMed]
124. Nitulescu, G.M.; Draghici, C.; Missir, A.V. Synthesis of new pyrazole derivatives and their anticancer evaluation. *Eur. J. Med. Chem.* **2010**, *45*, 4914–4919. [CrossRef] [PubMed]
125. Bandgar, B.P.; Totre, J.V.; Gawande, S.S.; Khobragade, C.N.; Warangkar, S.C.; Kadam, P.D. Synthesis of novel 3,5-diaryl pyrazole derivatives using combinatorial chemistry as inhibitors of tyrosinase as well as potent anticancer, anti-inflammatory agents. *Bioorg. Med. Chem.* **2010**, *18*, 6149–6155. [CrossRef] [PubMed]
126. Zheng, L.-W.; Wu, L.-L.; Zhao, B.-X.; Dong, W.-L.; Miao, J.-Y. Synthesis of novel substituted pyrazole-5-carbohydrazide hydrazone derivatives and discovery of a potent apoptosis inducer in A549 lung cancer cells. *Bioorg. Med. Chem.* **2009**, *17*, 1957–1962. [CrossRef] [PubMed]
127. Xia, Y.; Dong, Z.-W.; Zhao, B.-X.; Ge, X.; Meng, N.; Shin, D.-S.; Miao, J.-Y. Synthesis and structure-activity relationships of novel 1-arylmethyl-3-aryl-1*H*-pyrazole-5-carbohydrazide derivatives as potential agents against A549 lung cancer cells. *Bioorg. Med. Chem.* **2007**, *15*, 6893–6899. [CrossRef] [PubMed]
128. Lian, S.; Su, H.; Zhao, B.X.; Liu, W.Y.; Zheng, L.W.; Miao, J.Y. Synthesis and discovery of pyrazole-5-carbohydrazide *N*-glycosides as inducer of autophagy in A549 lung cancer cells. *Bioorg. Med. Chem.* **2009**, *17*, 7085–7092. [CrossRef] [PubMed]
129. Wei, F.; Zhao, B.-X.; Huang, B.; Zhang, L.; Sun, C.-H.; Dong, W.-L.; Shin, D.-S.; Miao, J.-Y. Design, synthesis, and preliminary biological evaluation of novel ethyl 1-(2′-hydroxy-3′-aroxypropyl)-3-aryl-1*H*-pyrazole-5-carboxylate. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 6342–6347. [CrossRef] [PubMed]
130. Ding, X.-L.; Zhang, H.-Y.; Qi, L.; Zhao, B.-X.; Lian, S.; Lv, H.-S.; Miao, J.-Y. Synthesis of novel pyrazole carboxamide derivatives and discovery of modulators for apoptosis or autophagy in A549 lung cancer cells. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 5325–5328. [CrossRef] [PubMed]
131. Zheng, L.-W.; Li, Y.; Ge, D.; Zhao, B.-X.; Liu, Y.-R.; Lv, H.-S.; Ding, J.; Miao, J.-Y. Synthesis of novel oxime-containing pyrazole derivatives and discovery of regulators for apoptosis and autophagy in A549 lung cancer cells. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 4766–4770. [CrossRef] [PubMed]
132. Liu, Y.-R.; Luo, J.-Z.; Duan, P.-P.; Shaon, J.; Zhao, B.-X.; Miao, J.-Y. Synthesis of pyrazole peptidomimetics and their inhibition against A549 lung cancer cells. *Bioorg. Med. Chem. Lett.* **2012**, *22*, 6882–6887. [CrossRef] [PubMed]

133. Fan, C.-D.; Zhao, B.-X.; Wei, F.; Zhang, G.-H.; Dong, W.-L.; Miao, J.-Y. Synthesis and discovery of autophagy inducers for A549 and H460 lung cancer cells, novel 1-(2′-hydroxy-3′-aroxypropyl)-3-aryl-1*H*-pyrazole-5-carbohydrazide derivatives. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 3860–3864. [CrossRef] [PubMed]
134. Shen, S.-L.; Zhu, J.; Li, M.; Zhao, B.-X.; Miao, J.-Y. Synthesis of ferrocenyl pyrazole-containing chiral aminoethanol derivatives and their inhibition against A549 and H322 lung cancer cells. *Eur. J. Med. Chem.* **2012**, *54*, 287–294. [CrossRef] [PubMed]
135. Farag, A.M.; Mayhoub, A.S.; Barakat, S.E.; Bayomi, A.H. Regioselective synthesis and antitumor screening of some novel *N*-phenylpyrazole derivatives. *Bioorg. Med. Chem.* **2008**, *16*, 881–889. [CrossRef] [PubMed]
136. Jin, C.H.; Krishnaiah, M.; Sreenu, D.; Subrahmanyam, V.B.; Rao, K.S.; Mohan, A.V.N.; Park, C.-Y.; Son, J.-Y.; Sheen, Y.Y. Synthesis and biological evaluation of 1-substituted-3-(6-methylpyridin-2-yl)-4-([1,2,4] triazolo[1,5-*a*]pyridin-6-yl) pyrazoles as transforming growth factor-β type 1 receptor kinase inhibitors. *Bioorg. Med. Chem. Lett.* **2011**, *21*, 6049–6053. [CrossRef] [PubMed]
137. Newhouse, B.J.; Hansen, J.D.; Grina, J.; Welch, M.; Topalov, G.; Littman, N.; Callejo, M.; Martinsona, M.; Galbraitha, S.; Laird, E.R.; et al. Non-oxime pyrazole based inhibitors of B-Raf kinase. *Bioorg. Med. Chem. Lett.* **2011**, *21*, 3488–3492. [CrossRef] [PubMed]
138. Zhang, D.; Wang, G.; Zhao, G.; Xu, W.; Huo, L. Synthesis and cytotoxic activity of novel 3-(1*H*-indol-3-yl)-1*H*-pyrazole-5-carbohydrazide derivatives. *Eur. J. Med. Chem.* **2011**, *46*, 5868–5877. [CrossRef] [PubMed]
139. Baciu-Atudosie, L.; Ghinet, A.; Farce, A.; Dubois, J.; Belei, D.; Bîcu, E. Synthesis and biological evaluation of new phenothiazine derivatives bearing a pyrazole unit as protein farnesyltransferase inhibitors. *Bioorg. Med. Chem. Lett.* **2012**, *22*, 6896–6902. [CrossRef] [PubMed]
140. Bai, X.-G.; Yu, D.-K.; Wang, J.-X.; Zhang, H.; He, H.-W.; Shao, R.-G.; Li, X.-M.; Wang, Y.-C. Design, synthesis and anticancer activity of 1-acyl-3-amino-1,4,5,6-tetrahydropyrrolo[3,4-*c*]pyrazole derivatives. *Bioorg. Med. Chem. Lett.* **2012**, *22*, 6947–6951. [CrossRef] [PubMed]
141. Bavetsias, V.; Crumpler, S.; Sun, C.; Avery, S.; Atrash, B.; Faisal, A.; Moore, A.S.; Kosmopoulou, M.; Brown, N.; Sheldrake, P.W.; et al. Optimization of imidazo[4,5-*b*]pyridine-based kinase inhibitors: Identification of a dual FLT3/Aurora kinase inhibitor as an orally bioavailable preclinical development candidate for the treatment of acute myeloid leukemia. *J. Med. Chem.* **2012**, *55*, 8721–8734. [CrossRef] [PubMed]
142. Bondock, S.; Adel, S.; Etman, H.A.; Badria, F.A. Synthesis and antitumor evaluation of some new 1,3,4-oxadiazole-based heterocycles. *Eur. J. Med. Chem.* **2012**, *48*, 192–199. [CrossRef] [PubMed]
143. Cui, J.J.; McTigue, M.; Nambu, M.; Tran-Dubé, M.; Pairish, M.; Shen, H.; Jia, L.; Cheng, H.; Hoffman, J.; Le, P.; et al. Discovery of a Novel Class of Exquisitely Selective Mesenchymal-Epithelial Transition Factor (c-MET) Protein Kinase Inhibitors and Identification of the Clinical Candidate 2-(4-(1-(Quinolin-6-ylmethyl)-1*H*-[1,2,3]triazolo[4,5-*b*]pyrazin-6-yl)-1*H*-pyrazol-1-yl)ethanol (PF-04217903) for the Treatment of Cancer. *J. Med. Chem.* **2012**, *55*, 8091–8109. [CrossRef] [PubMed]
144. El Hamid, M.K.A.; Mihovilovic, M.D.; El-Nassan, H.B. Synthesis of novel pyrazolo[3,4-*d*]pyrimidine derivatives as potential anti-breast cancer agents. *Eur. J. Med. Chem.* **2012**, *57*, 323–328. [CrossRef] [PubMed]
145. El-Borai, M.; Rizk, H.; Abd-Aal, M.; El-Deeb, I. Synthesis of pyrazolo[3,4-*b*]pyridines under microwave irradiation in multi-component reactions and their antitumor and antimicrobial activities–Part 1. *Eur. J. Med. Chem.* **2012**, *48*, 92–96. [CrossRef] [PubMed]
146. Hanan, E.J.; Van Abbema, A.; Barrett, K.; Blair, W.S.; Blaney, J.; Chang, C.; Eigenbrot, C.; Flynn, S.; Gibbons, P.; Hurley, C.A.; et al. Discovery of potent and selective pyrazolopyrimidine janus kinase 2 inhibitors. *J. Med. Chem.* **2012**, *55*, 10090–100107. [CrossRef] [PubMed]
147. Huang, Y.-Y.; Wang, L.-Y.; Chang, C.-H.; Kuo, Y.-H.; Kaneko, K.; Takayama, H.; Kimura, M.; Juang, S.-H.; Wong, F.F. One-pot synthesis and antiproliferative evaluation of pyrazolo[3,4-*d*]pyrimidine derivatives. *Tetrahedron* **2012**, *68*, 9658–9664. [CrossRef]
148. Li, X.; Lu, X.; Xing, M.; Yang, X.-H.; Zhao, T.-T.; Gong, H.-B.; Zhu, H.-L. Synthesis, biological evaluation, and molecular docking studies of *N*,1,3-triphenyl-1*H*-pyrazole-4-carboxamide derivatives as anticancer agents. *Bioorg. Med. Chem. Lett.* **2012**, *22*, 3589–3593. [CrossRef] [PubMed]
149. Metwally, M.; Gouda, M.; Harmal, A.N.; Khalil, A. Synthesis, antitumor, cytotoxic and antioxidant evaluation of some new pyrazolotriazines attached to antipyrine moiety. *Eur. J. Med. Chem.* **2012**, *56*, 254–262. [CrossRef] [PubMed]

150. Mohareb, R.M.; Al-Omran, F. Reaction of pregnenolone with cyanoacetylhydrazine: Novel synthesis of hydrazide–hydrazone, pyrazole, pyridine, thiazole, thiophene derivatives and their cytotoxicity evaluations. *Steroids* **2012**, *77*, 1551–1559. [CrossRef] [PubMed]
151. Mohareb, R.M.; Wardakhan, W.W.; Elmegeed, G.A.; Ashour, R.M. Heterocyclizations of pregnenolone: Novel synthesis of thiosemicarbazone, thiophene, thiazole, thieno[2,3-*b*]pyridine derivatives and their cytotoxicity evaluations. *Steroids* **2012**, *77*, 1560–1569. [CrossRef] [PubMed]
152. Puthiyapurayil, P.; Poojary, B.; Chikkanna, C.; Buridipad, S.K. Design, synthesis and biological evaluation of a novel series of 1,3,4-oxadiazole bearing *N*-methyl-4-(trifluoromethyl) phenyl pyrazole moiety as cytotoxic agents. *Eur. J. Med. Chem.* **2012**, *53*, 203–210. [CrossRef] [PubMed]
153. Strocchi, E.; Fornari, F.; Minguzzi, M.; Gramantieri, L.; Milazzo, M.; Rebuttini, V.; Breviglieri, S.; Camaggi, C.M.; Locatelli, E.; Bolondi, L.; et al. Design, synthesis and biological evaluation of pyrazole derivatives as potential multi-kinase inhibitors in hepatocellular carcinoma. *Eur. J. Med. Chem.* **2012**, *48*, 391–401. [CrossRef] [PubMed]
154. Vujasinović, I.; Paravić-Radičević, A.; Mlinarić-Majerski, K.; Brajša, K.; Bertoša, B. Synthesis and biological validation of novel pyrazole derivatives with anticancer activity guided by 3D-QSAR analysis. *Bioorg. Med. Chem.* **2012**, *20*, 2101–2110. [CrossRef] [PubMed]
155. Yamamoto, S.; Tomita, N.; Suzuki, Y.; Suzaki, T.; Kaku, T.; Hara, T.; Yamaokaa, M.; Kanzakia, N.; Hasuokaa, A.; Babaa, A.; et al. Design, synthesis, and biological evaluation of 4-arylmethyl-1-phenylpyrazole and 4-aryloxy-1-phenylpyrazole derivatives as novel androgen receptor antagonists. *Bioorg. Med. Chem.* **2012**, *20*, 2338–2352. [CrossRef] [PubMed]
156. Al-Adiwish, W.M.; Tahir, M.; Siti-Noor-Adnalizawati, A.; Hashim, S.F.; Ibrahim, N.; Yaacob, W. Synthesis, antibacterial activity and cytotoxicity of new fused pyrazolo[1,5-*a*]pyrimidine and pyrazolo[5,1-*c*][1,2,4]triazine derivatives from new 5-aminopyrazoles. *Eur. J. Med. Chem.* **2013**, *64*, 464–476. [CrossRef] [PubMed]
157. Bavetsias, V.; Faisal, A.; Crumpler, S.; Brown, N.; Kosmopoulou, M.; Joshi, A.; Atrash, B.; Pérez-Fuertes, Y.; Schmitt, J.A.; Boxall, K.J.; et al. Aurora isoform selectivity: Design and synthesis of imidazo[4,5-*b*]pyridine derivatives as highly selective inhibitors of Aurora-A kinase in cells. *J. Med. Chem.* **2013**, *56*, 9122–9135. [CrossRef] [PubMed]
158. Desai, B.; Dixon, K.; Farrant, E.; Feng, Q.; Gibson, K.R.; Van Hoorn, W.P.; Mills, J.; Morgan, T.; Parry, D.M.; Ramjee, M.K.; et al. Rapid discovery of a novel series of Abl kinase inhibitors by application of an integrated microfluidic synthesis and screening platform. *J. Med. Chem.* **2013**, *56*, 3033–3047. [CrossRef] [PubMed]
159. Kamal, A.; Tamboli, J.R.; Vishnuvardhan, M.; Adil, S.; Nayak, V.L.; Ramakrishna, S. Synthesis and anticancer activity of heteroaromatic linked 4β-amido podophyllotoxins as apoptotic inducing agents. *Bioorg. Med. Chem. Lett.* **2013**, *23*, 273–280. [CrossRef] [PubMed]
160. Koca, I.; Özgür, A.; Coşkun, K.A.; Tutar, Y. Synthesis and anticancer activity of acyl thioureas bearing pyrazole moiety. *Bioorg. Med. Chem.* **2013**, *21*, 3859–3865. [CrossRef] [PubMed]
161. Miyamoto, N.; Sakai, N.; Hirayama, T.; Miwa, K.; Oguro, Y.; Oki, H.; Okada, K.; Takagi, T.; Iwata, H.; Awazu, Y.; et al. Discovery of *N*-[5-({2-[(cyclopropylcarbonyl) amino]imidazo[1,2-*b*]pyridazin-6-yl}oxy)-2-methylphenyl]-1,3-dimethyl-1*H*-pyrazole-5-carboxamide (TAK-593), a highly potent VEGFR2 kinase inhibitor. *Bioorg. Med. Chem.* **2013**, *21*, 2333–2345. [CrossRef] [PubMed]
162. Shen, S.-L.; Shao, J.-H.; Luo, J.-Z.; Liu, J.-T.; Miao, J.-Y.; Zhao, B.-X. Novel chiral ferrocenylpyrazolo[1,5-*a*][1,4]diazepin-4-one derivatives–synthesis, characterization and inhibition against lung cancer cells. *Eur. J. Med. Chem.* **2013**, *63*, 256–268. [CrossRef] [PubMed]
163. Zhu, S.-L.; Wu, Y.; Liu, C.-J.; Wei, C.-Y.; Tao, J.-C.; Liu, H.-M. Synthesis and in vitro cytotoxic activity evaluation of novel heterocycle bridged carbothioamide type isosteviol derivatives as antitumor agents. *Bioorg. Med. Chem. Lett.* **2013**, *23*, 1343–1346. [CrossRef] [PubMed]
164. Zhu, S.-L.; Wu, Y.; Liu, C.-J.; Wei, C.-Y.; Tao, J.-C.; Liu, H.-M. Design and stereoselective synthesis of novel isosteviol-fused pyrazolines and pyrazoles as potential anticancer agents. *Eur. J. Med. Chem.* **2013**, *65*, 70–82. [CrossRef] [PubMed]
165. Ali, A.R.; El-Bendary, E.R.; Ghaly, M.A.; Shehata, I.A. Synthesis, in vitro anticancer evaluation and in silico studies of novel imidazo[2,1-*b*]thiazole derivatives bearing pyrazole moieties. *Eur. J. Med. Chem.* **2014**, *75*, 492–500. [CrossRef] [PubMed]

166. Sun, J.; Lv, X.-H.; Qiu, H.-Y.; Wang, Y.-T.; Du, Q.-R.; Li, D.-D.; Yang, Y.-H.; Zhu, H.-L. Synthesis, biological evaluation and molecular docking studies of pyrazole derivatives coupling with a thiourea moiety as novel CDKs inhibitors. *Eur. J. Med. Chem.* **2013**, *68*, 1–9. [CrossRef] [PubMed]
167. Zheng, Y.; Zheng, M.; Ling, X.; Liu, Y.; Xue, Y.; An, L.; Gu, N.; Jin, M. Design, synthesis, quantum chemical studies and biological activity evaluation of pyrazole–benzimidazole derivatives as potent Aurora A/B kinase inhibitors. *Bioorg. Med. Chem. Lett.* **2013**, *23*, 3523–3530. [CrossRef] [PubMed]
168. Cankara, P.Ş.; Çalışkan, B.; Durmaz, I.; Atalay, R.; Banoglu, E. Synthesis and preliminary mechanistic evaluation of 5-(p-tolyl)-1-(quinolin-2-yl)pyrazole-3-carboxylic acid amides with potent antiproliferative activity on human cancer cell lines. *Eur. J. Med. Chem.* **2014**, *87*, 140–149. [CrossRef] [PubMed]
169. Hopa, C.; Yildirim, H.; Kara, H.; Kurtaran, R.; Alkan, M. Synthesis, characterization and anti-proliferative activity of Cd (II) complexes with NNN type pyrazole-based ligand and pseudohalide ligands as coligand. *Spectrochim. Acta A Mol. Biomol. Spectrosc.* **2014**, *121*, 282–287. [CrossRef] [PubMed]
170. Jin, C.H.; Krishnaiah, M.; Sreenu, D.; Subrahmanyam, V.B.; Park, H.-J.; Park, S.-J.; Sheena, Y.Y.; Kim, D.-K. 4-([1,2,4]Triazolo[1,5-*a*]pyridin-6-yl)-5(3)-(6-methylpyridin-2-yl) imidazole and-pyrazole derivatives as potent and selective inhibitors of transforming growth factor-β type I receptor kinase. *Bioorg. Med. Chem.* **2014**, *22*, 2724–2732. [CrossRef] [PubMed]
171. Li, S.; Xu, S.; Tang, Y.; Ding, S.; Zhang, J.; Wang, S.; Zhou, G.; Zhou, C.; Li, X. Synthesis, anticancer activity and DNA-binding properties of novel 4-pyrazolyl-1,8-naphthalimide derivatives. *Bioorg. Med. Chem. Lett.* **2014**, *24*, 586–590. [CrossRef] [PubMed]
172. Park, B.S.; Al-Sanea, M.M.; Abdelazem, A.Z.; Park, H.M.; Roh, E.J.; Park, H.-M.; Yoo, K.H.; Sim, T.; Tae, J.S.; Lee, S.H. Structure-based optimization and biological evaluation of trisubstituted pyrazole as a core structure of potent ROS1 kinase inhibitors. *Bioorg. Med. Chem.* **2014**, *22*, 3871–3878. [CrossRef] [PubMed]
173. Reddy, G.L.; Guru, S.K.; Srinivas, M.; Pathania, A.S.; Mahajan, P.; Nargotra, A.; Bhushan, S.; Vishwakarma, R.A.; Sawantad, S.D. Synthesis of 5-substituted-1*H*-pyrazolo[4,3-*d*]pyrimidin-7(6*H*)-one analogs and their biological evaluation as anticancer agents: MTOR inhibitors. *Eur. J. Med. Chem.* **2014**, *80*, 201–208. [CrossRef] [PubMed]
174. Wang, S.-F.; Zhu, Y.-L.; Zhu, P.-T.; Makawana, J.A.; Zhang, Y.-L.; Zhao, M.-Y.; Lv, P.-C.; Zhu, H.-L. Design, synthesis and biological evaluation of novel 5-phenyl-1*H*-pyrazole derivatives as potential BRAF V600E inhibitors. *Bioorg. Med. Chem.* **2014**, *22*, 6201–6208. [CrossRef] [PubMed]
175. Yao, Y.; Liao, C.; Li, Z.; Wang, Z.; Sun, Q.; Liu, C.; Yang, Y.; Tu, Z.; Jiang, S. Design, synthesis, and biological evaluation of 1,3-disubstituted-pyrazole derivatives as new class I and IIb histone deacetylase inhibitors. *Eur. J. Med. Chem.* **2014**, *86*, 639–652. [CrossRef] [PubMed]
176. Zhang, J.-F.; Li, M.; Miao, J.-Y.; Zhao, B.-X. Biological activities of novel pyrazolyl hydroxamic acid derivatives against human lung cancer cell line A549. *Eur. J. Med. Chem.* **2014**, *83*, 516–525. [CrossRef] [PubMed]
177. Abd El-Karim, S.S.; Anwar, M.M.; Mohamed, N.A.; Nasr, T.; Elseginy, S.A. Design, synthesis, biological evaluation and molecular docking studies of novel benzofuran–pyrazole derivatives as anticancer agents. *Bioorg. Chem.* **2015**, *63*, 1–12. [CrossRef] [PubMed]
178. Aware, V.; Gaikwad, N.; Chavan, S.; Manohar, S.; Bose, J.; Khanna, S.; B-Rao, C.; Dixit, N.; Singhd, K.S.; Damred, A.; et al. Cyclopentyl-pyrimidine based analogues as novel and potent IGF-1R inhibitor. *Eur. J. Med. Chem.* **2015**, *92*, 246–256. [CrossRef] [PubMed]
179. Ibrahim, H.S.; Abou-Seri, S.M.; Tanc, M.; Elaasser, M.M.; Abdel-Aziz, H.A.; Supuran, C.T. Isatin-pyrazole benzenesulfonamide hybrids potently inhibit tumor-associated carbonic anhydrase isoforms IX and XII. *Eur. J. Med. Chem.* **2015**, *103*, 583–593. [CrossRef] [PubMed]
180. Kamal, A.; Shaik, A.B.; Polepalli, S.; Kumar, G.B.; Reddy, V.S.; Mahesh, R.; Garimella, S.; Jain, N. Synthesis of arylpyrazole linked benzimidazole conjugates as potential microtubule disruptors. *Bioorg. Med. Chem.* **2015**, *23*, 1082–1095. [CrossRef] [PubMed]
181. Khloya, P.; Ceruso, M.; Ram, S.; Supuran, C.T.; Sharma, P.K. Sulfonamide bearing pyrazolylpyrazolines as potent inhibitors of carbonic anhydrase isoforms I, II, IX and XII. *Bioorg. Med. Chem. Lett.* **2015**, *25*, 3208–3212. [CrossRef] [PubMed]
182. Maggio, B.; Raimondi, M.V.; Raffa, D.; Plescia, F.; Cascioferro, S.; Cancemi, G.; Tolomeo, M.; Grimaudo, S.; Daidone, G. Synthesis and antiproliferative activity of 3-(2-chloroethyl)-5-methyl-6-phenyl-8-(trifluoromethyl)-5,6-dihydropyrazolo[3,4-*f*][1,2,3,5]tetrazepin-4-(3*H*)-one. *Eur. J. Med. Chem.* **2015**, *96*, 98–104. [CrossRef] [PubMed]

183. Nitulescu, G.M.; Draghici, C.; Olaru, O.T.; Matei, L.; Ioana, A.; Dragu, L.D.; Bleotu, C. Synthesis and apoptotic activity of new pyrazole derivatives in cancer cell lines. *Bioorg. Med. Chem.* **2015**, *23*, 5799–5808. [CrossRef] [PubMed]
184. Nitulescu, G.M.; Matei, L.; Aldea, I.M.; Draghici, C.; Olaru, O.T.; Bleotu, C. Ultrasound-assisted synthesis and anticancer evaluation of new pyrazole derivatives as cell cycle inhibitors. *Arab. J. Chem.* **2015**. [CrossRef]
185. Rai, U.S.; Isloor, A.M.; Shetty, P.; Pai, K.; Fun, H.-K. Synthesis and in vitro biological evaluation of new pyrazole chalcones and heterocyclic diamides as potential anticancer agents. *Arab. J. Chem.* **2015**, *8*, 317–321. [CrossRef]
186. Reddy, T.S.; Kulhari, H.; Reddy, V.G.; Bansal, V.; Kamal, A.; Shukla, R. Design, synthesis and biological evaluation of 1,3-diphenyl-1*H*-pyrazole derivatives containing benzimidazole skeleton as potential anticancer and apoptosis inducing agents. *Eur. J. Med. Chem.* **2015**, *101*, 790–805. [CrossRef] [PubMed]
187. Siddiqui, T.; Alam, M.G.; Dar, A.M. Synthesis, characterization and anticancer studies of new steroidal oxadiazole, pyrrole and pyrazole derivatives. *J. Saudi Chem. Soc.* **2015**, *19*, 387–391. [CrossRef]
188. Shi, J.B.; Tang, W.J.; Li, R.; Liu, X.H. Novel pyrazole-5-carboxamide and pyrazole–pyrimidine derivatives: Synthesis and anticancer activity. *Eur. J. Med. Chem.* **2015**, *90*, 889–896. [CrossRef] [PubMed]
189. Alam, R.; Wahi, D.; Singh, R.; Sinha, D.; Tandon, V.; Grover, A. Design, synthesis, cytotoxicity, HuTopoIIα inhibitory activity and molecular docking studies of pyrazole derivatives as potential anticancer agents. *Bioorg. Chem.* **2016**, *69*, 77–90. [CrossRef] [PubMed]
190. Lv, X.-H.; Ren, Z.-L.; Zhou, B.-G.; Li, Q.-S.; Chu, M.-J.; Liu, D.-H.; Zhang, L.-S.; Yao, X.-K.; Cao, H.-Q. Discovery of *N*-(benzyloxy)-1,3-diphenyl-1*H*-pyrazole-4-carboxamide derivatives as potential antiproliferative agents by inhibiting MEK. *Bioorg. Med. Chem.* **2016**, *24*, 4652–4659. [CrossRef] [PubMed]
191. Wang, F.-Q.; Yang, H.; He, B.; Jia, Y.-K.; Meng, S.-Y.; Zhang, C.; Liu, H.-M.; Liu, F.-W. A novel domino approach for synthesis of indolyl tetrahydropyrano[4,3-*c*]pyrazole derivatives as anticancer agents. *Tetrahedron* **2016**, *72*, 5769–5775. [CrossRef]
192. Wen, J.; Bao, Y.; Niu, Q.; Yang, J.; Fan, Y.; Li, J.; Jing, Y.; Zhao, L.; Liu, D. Identification of *N*-(6-mercaptohexyl)-3-(4-pyridyl)-1*H*-pyrazole-5-carboxamide and its disulfide prodrug as potent histone deacetylase inhibitors with in vitro and in vivo anti-tumor efficacy. *Eur. J. Med. Chem.* **2016**, *109*, 350–359. [CrossRef] [PubMed]
193. Galal, S.A.; Abdelsamie, A.S.; Shouman, S.A.; Attia, Y.M.; Ali, H.I.; Tabll, A.; El-Shenawye, R.; El Abd, Y.S.; Ali, M.M.; Mahmoud, A.E.; et al. Part I: Design, synthesis and biological evaluation of novel pyrazole-benzimidazole conjugates as checkpoint kinase 2 (Chk2) inhibitors with studying their activities alone and in combination with genotoxic drugs. *Eur. J. Med. Chem.* **2017**, *134*, 392–405. [CrossRef] [PubMed]
194. Huang, Q.; Zhang, S.; Zhang, S.; Wang, K.; Xiao, Y. Solvent and Copper Ion-Induced Synthesis of Pyridyl–Pyrazole-3-One Derivatives: Crystal Structure, Cytotoxicity. *Molecules* **2017**, *22*, 1813. [CrossRef] [PubMed]
195. Li, J.; Huo, H.; Guo, R.; Liu, B.; Li, L.; Dan, W.; Xiao, X.; Zhang, J.; Shi, B. Facile and efficient access to Androsten-17-(1′,3′,4′)-pyrazoles and Androst-17β-(1′,3′,4′)-pyrazoles via Vilsmeier reagents, and their antiproliferative activity evaluation in vitro. *Eur. J. Med. Chem.* **2017**, *130*, 1–14. [CrossRef] [PubMed]
196. Shi, W.; Hu, J.; Bao, N.; Li, D.; Chen, L.; Sun, J. Design, synthesis and cytotoxic activities of scopoletin-isoxazole and scopoletin-pyrazole hybrids. *Bioorg. Med. Chem. Lett.* **2017**, *27*, 147–151. [CrossRef] [PubMed]
197. Wang, M.; Xu, S.; Lei, H.; Wang, C.; Xiao, Z.; Jia, S.; Zhi, J.; Zheng, P.; Zhu, W. Design, synthesis and antitumor activity of Novel Sorafenib derivatives bearing pyrazole scaffold. *Bioorg. Med. Chem.* **2017**, *25*, 5754–5763. [CrossRef] [PubMed]
198. Daidone, G.; Maggio, B.; Raffa, D.; Plescia, S.; Schillaci, D.; Raimondi, M.V. Synthesis and in vitro antileukemic activity of new 4-triazenopyrazole derivatives. *Farmaco* **2004**, *59*, 413–417. [CrossRef] [PubMed]
199. Kamble, R.D.; Meshram, R.J.; Hese, S.V.; More, R.A.; Kamble, S.S.; Gacche, R.N.; Dawane, B.S. Synthesis and in silico investigation of thiazoles bearing pyrazoles derivatives as anti-inflammatory agents. *Comput. Biol. Chem.* **2016**, *61*, 86–96. [CrossRef] [PubMed]
200. Bekhit, A.A.; Abdel-Aziem, T. Design, synthesis and biological evaluation of some pyrazole derivatives as anti-inflammatory-antimicrobial agents. *Bioorg. Med. Chem.* **2004**, *12*, 1935–1945. [CrossRef] [PubMed]

201. Bekhit, A.A.; Ashour, H.M.A.; Abdel Ghany, Y.S.; Bekhit, A.-A.; Baraka, A. Synthesis and biological evaluation of some thiazolyl and thiadiazolyl derivatives of 1*H*-pyrazole as anti-inflammatory antimicrobial agents. *Eur. J. Med. Chem.* **2008**, *43*, 456–463. [CrossRef] [PubMed]
202. Girisha, K.S.; Kalluraya, B.; Narayana, V.; Padmashree, V. Synthesis and pharmacological study of 1-acetyl/propyl-3-aryl-5-(5-chloro-3-methyl-1-phenyl-1*H*-pyrazol-4-yl)-2-pyrazoline. *Eur. J. Med. Chem.* **2010**, *45*, 4640–4644. [CrossRef] [PubMed]
203. Brullo, C.; Spisani, S.; Selvatici, R.; Bruno, O. *N*-Aryl-2-phenyl-2,3-dihydro-imidazo[1,2-*b*]pyrazole-1-carboxamides 7-substituted strongly inhibiting both fMLP-OMe-and IL-8-induced human neutrophil chemotaxis. *Eur. J. Med. Chem.* **2012**, *47*, 573–579. [CrossRef] [PubMed]
204. El-Moghazy, S.; Barsoum, F.; Abdel-Rahman, H.; Marzouk, A. Synthesis and anti-inflammatory activity of some pyrazole derivatives. *Med. Chem. Res.* **2012**, *21*, 1722–1733. [CrossRef]
205. Magda, A.-A.; Abdel-Aziz, N.I.; Alaa, A.-M.; El-Azab, A.S.; ElTahir, K.E. Synthesis, biological evaluation and molecular modeling study of pyrazole and pyrazoline derivatives as selective COX-2 inhibitors and anti-inflammatory agents. Part 2. *Bioorg. Med. Chem.* **2012**, *20*, 3306–3316. [CrossRef]
206. Qiu, K.-M.; Yan, R.; Xing, M.; Wang, H.-H.; Cui, H.-E.; Gong, H.-B.; Zhu, H.-L. Synthesis, biological evaluation and molecular modeling of dihydro-pyrazolyl-thiazolinone derivatives as potential COX-2 inhibitors. *Bioorg. Med. Chem.* **2012**, *20*, 6648–6654. [CrossRef] [PubMed]
207. Alegaon, S.G.; Alagawadi, K.R.; Garg, M.K.; Dushyant, K.; Vinod, D. 1,3,4-Trisubstituted pyrazole analogues as promising anti-inflammatory agents. *Bioorg. Chem.* **2014**, *54*, 51–59. [CrossRef] [PubMed]
208. Hassan, G.S.; Abou-Seri, S.M.; Kamel, G.; Ali, M.M. Celecoxib analogs bearing benzofuran moiety as cyclooxygenase-2 inhibitors: Design, synthesis and evaluation as potential anti-inflammatory agents. *Eur. J. Med. Chem.* **2014**, *76*, 482–493. [CrossRef] [PubMed]
209. Karrouchi, K.; Chemlal, L.; Doudach, L.; Taoufik, J.; Cherrah, Y.; Radi, S.; Fouzi, M.A.; Ansar, M. Synthesis, anti-inflammatory and antioxidant activities of some new pyrazole derivatives. *J. Pharm. Res.* **2014**, *8*, 1171–1177.
210. Selvam, T.P.; Kumar, P.V.; Saravanan, G.; Prakash, C.R. Microwave-assisted synthesis, characterization and biological activity of novel pyrazole derivatives. *J. Saudi Chem. Soc.* **2014**, *18*, 1015–1021. [CrossRef]
211. Tewari, A.K.; Singh, V.P.; Yadav, P.; Gupta, G.; Singh, A.; Goel, R.K.; Shinde, P.; Mohan, C.G. Synthesis, biological evaluation and molecular modeling study of pyrazole derivatives as selective COX-2 inhibitors and anti-inflammatory agents. *Bioorg. Chem.* **2014**, *56*, 8–15. [CrossRef] [PubMed]
212. El-Feky, S.A.; El-Samii, Z.K.A.; Osman, N.A.; Lashine, J.; Kamel, M.A.; Thabet, H.K. Synthesis, molecular docking and anti-inflammatory screening of novel quinoline incorporated pyrazole derivatives using the Pfitzinger reaction II. *Bioorg. Chem.* **2015**, *58*, 104–116. [CrossRef] [PubMed]
213. Hussain, S.; Kaushik, D. Noval 1-substituted-3,5-dimethyl-4-[(substituted phenyl)diazenyl] pyrazole derivatives: Synthesis and pharmacological activity. *J. Saudi Chem. Soc.* **2015**, *19*, 274–281. [CrossRef]
214. Surendra Kumar, R.; Arif, I.A.; Ahamed, A.; Idhayadhulla, A. Anti-inflammatory and antimicrobial activities of novel pyrazole analogues. *Saudi J. Biol. Sci.* **2016**, *23*, 614–620. [CrossRef] [PubMed]
215. Li, Y.-R.; Li, C.; Liu, J.-C.; Guo, M.; Zhang, T.-Y.; Sun, L.-P.; Zheng, C.-J.; Piao, H.-R. Synthesis and biological evaluation of 1,3-diaryl pyrazole derivatives as potential antibacterial and anti-inflammatory agents. *Bioorg. Med. Chem. Lett.* **2015**, *25*, 5052–5057. [CrossRef] [PubMed]
216. Pelcman, B.; Sanin, A.; Nilsson, P.; Schaal, W.; Olofsson, K.; Krog-Jensen, C.; Forsell, P.; Hallberg, A.; Larhed, M.; Boesend, T.; et al. *N*-Substituted pyrazole-3-carboxamides as inhibitors of human 15-lipoxygenase. *Bioorg. Med. Chem. Lett.* **2015**, *25*, 3017–3023. [CrossRef] [PubMed]
217. Wang, T.; Banerjee, D.; Bohnert, T.; Chao, J.; Enyedy, I.; Fontenot, J.; Guertina, K.; Jones, H.; Lina, E.Y.; Marcotte, D.; et al. Discovery of novel pyrazole-containing benzamides as potent RORγ inverse agonists. *Bioorg. Med. Chem. Lett.* **2015**, *25*, 2985–2990. [CrossRef] [PubMed]
218. Thore, S.; Gupta, S.V.; Baheti, K.G. Novel ethyl-5-amino-3-methylthio-1*H*-pyrazole-4-carboxylates: Synthesis and pharmacological activity. *J. Saudi Chem. Sci.* **2016**, *20*, 259–264. [CrossRef]
219. Nossier, E.; Fahmy, H.; Khalifa, N.; El-Eraky, W.; Baset, M. Design and Synthesis of Novel Pyrazole-Substituted Different Nitrogenous Heterocyclic Ring Systems as Potential Anti-Inflammatory Agents. *Molecules* **2017**, *22*, 512. [CrossRef] [PubMed]

220. Maggio, B.; Daidone, G.; Raffa, D.; Plescia, S.; Mantione, L.; Cutuli, V.M.C.; Mangano, N.G.; Caruso, A. Synthesis and pharmacological study of ethyl 1-methyl-5-(substituted 3,4-dihydro-4-oxoquinazolin-3-yl)-1*H*-pyrazole-4-acetates. *Eur. J. Med. Chem.* **2001**, *36*, 737–742. [CrossRef]
221. Hall, A.; Billinton, A.; Brown, S.H.; Clayton, N.M.; Chowdhury, A.; Giblin, G.M.P.; Goldsmith, P.; Hayhow, T.G.; Hurst, D.N.; Kilford, I.R.; et al. Non-acidic pyrazole EP1 receptor antagonists with in vivo analgesic efficacy. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 3392–3399. [CrossRef] [PubMed]
222. De Moura, S.S.; de Ávila, R.I.; Brito, L.B.; de Oliveira, R.; de Oliveira, G.A.R.; Pazini, F.; Aline, R.M.; Cesar, C.B.; Marize, K.G.; Valadares, C. In vitro genotoxicity and in vivo subchronic evaluation of the anti-inflammatory pyrazole compound LQFM021. *Chem. Biol. Interact.* **2017**, *277*, 185–194. [CrossRef] [PubMed]
223. Ragab, F.A.; Abdel Gawad, N.M.; Georgey, H.H.; Said, M.F. Synthesis of novel 1,3,4-trisubstituted pyrazoles as anti-inflammatory and analgesic agents. *Eur. J. Med. Chem.* **2013**, *63*, 645–654. [CrossRef] [PubMed]
224. Vijesh, A.M.; Isloor, A.M.; Shetty, P.; Sundershan, S.; Fun, H.K. New pyrazole derivatives containing 1,2,4-triazoles and benzoxazoles as potent antimicrobial and analgesic agents. *Eur. J. Med. Chem.* **2013**, *62*, 410–415. [CrossRef] [PubMed]
225. Viveka, S.; Dinesha, S.P.; Nagaraja, G.K.; Ballav, S.; Kerkar, S. Design and synthesis of some new pyrazolyl-pyrazolines as potential anti-inflammatory, analgesic and antibacterial agents. *Eur. J. Med. Chem.* **2015**, *101*, 442–451. [CrossRef] [PubMed]
226. Thore, S.N.; Gupta, S.V.; Baheti, K.G. Synthesis and pharmacological evaluation of 5-methyl-2-phenylthiazole-4-substituted heteroazoles as a potential anti-inflammatory and analgesic agents. *J. Saudi Chem. Soc.* **2016**, *20*, S46–S52. [CrossRef]
227. Chowdhury, M.A.; Abdellatif, K.R.; Dong, Y.; Knaus, E.E. Synthesis of new 4-[2-(4-methyl(amino) sulfonylphenyl)-5-trifluoromethyl-2*H*-pyrazol-3-yl]-1,2,3,6-tetrahydropyridines: A search for novel nitric oxide donor anti-inflammatory agents. *Bioorg. Med. Chem.* **2008**, *16*, 8882–8888. [CrossRef] [PubMed]
228. Chowdhury, M.A.; Abdellatif, K.R.; Dong, Y.; Yu, G.; Huang, Z.; Rahman, M.; Das, D.; Velázquez, C.A.; Suresh, M.R.; Knaus, E.E. Celecoxib analogs possessing a *N*-(4-nitrooxybutyl) piperidin-4-yl or *N*-(4-nitrooxybutyl)-1,2,3,6-tetrahydropyridin-4-yl nitric oxide donor moiety: Synthesis, biological evaluation and nitric oxide release studies. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 1324–1329. [CrossRef] [PubMed]
229. Chavan, H.V.; Bandgar, B.P.; Adsul, L.K.; Dhakane, V.D.; Bhale, P.S.; Thakare, V.N.; Masand, V. Design, synthesis, characterization and anti-inflammatory evaluation of novel pyrazole amalgamated flavones. *Bioorg. Med. Chem. Lett.* **2013**, *23*, 1315–1321. [CrossRef] [PubMed]
230. Abdelgawad, M.A.; Labib, L.B.; Abdel-Latif, M. Pyrazole-hydrazone derivatives as anti-inflammatory agents: Design, synthesis, biological evaluation, COX-1,2/5-LOX inhibition and docking study. *Bioorg. Chem.* **2017**, *74*, 212–220. [CrossRef] [PubMed]
231. Singh, S.K.; Reddy, P.G.; Rao, K.S.; Lohray, B.B.; Misra, P.; Rajjak, S.A.; Rao, Y.K.; Venkateswarlu, A. Polar substitutions in the benzenesulfonamide ring of celecoxib afford a potent 1,5-diarylpyrazole class of COX-2 inhibitors. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 499–504. [CrossRef] [PubMed]
232. Li, J.; DeMello, K.M.L.; Cheng, H.; Sakya, S.M.; Bronk, B.S.; Rafka, R.J.; Jaynes, B.H.; Ziegler, C.B.; Kilroy, C.; Mann, D.W.; et al. Discovery of a potent, selective and orally active canine COX-2 inhibitor, 2-(3-difluoromethyl-5-phenyl-pyrazol-1-yl)-5-methanesulfonyl-pyridine. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 95–98. [CrossRef] [PubMed]
233. Cheng, H.; DeMello, K.M.L.; Li, J.; Sakya, S.M.; Ando, K.; Kawamura, K.; Kato, T.; Rafka, R.J.; Jaynes, B.H.; Ziegler, C.B.; et al. Synthesis and SAR of heteroaryl-phenyl-substituted pyrazole derivatives as highly selective and potent canine COX-2 inhibitors. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 2076–2080. [CrossRef] [PubMed]
234. Sakya, S.M.; DeMello, K.M.L.; Minich, M.L.; Rast, B.; Shavnya, A.; Rafka, R.J. 5-Heteroatom substituted pyrazoles as canine COX-2 inhibitors. Part 1: Structure-activity relationship studies of 5-alkylamino pyrazoles and discovery of a potent, selective, and orally active analog. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 288–292. [CrossRef] [PubMed]
235. Sakya, S.M.; Cheng, H.; DeMello, K.M.L.; Shavnya, A.; Minich, M.L.; Rast, B. 5-Heteroatom-substituted pyrazoles as canine COX-2 inhibitors: Part 2. Structure-activity relationship studies of 5-alkylethers and 5-thioethers. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 1202–1206. [CrossRef] [PubMed]

236. Aggarwal, R.; Bansal, A.; Rozas, I.; Kelly, B.; Kaushik, P.; Kaushik, D. Synthesis, biological evaluation and molecular modeling study of 5-trifluoromethyl-Δ^2-pyrazoline and isomeric 5/3-trifluoromethylpyrazole derivatives as anti-inflammatory agents. *Eur. J. Med. Chem.* **2013**, *70*, 350–357. [CrossRef] [PubMed]
237. Habeeb, A.G.; Praveen, R.P.; Knaus, E.E. Design and synthesis of celecoxib and rofecoxib analogues as selective cyclooxygenase-2 (COX-2) inhibitors: Replacement of sulfonamide and methylsulfonyl pharmacophores by an azido bioisostere. *J. Med. Chem.* **2001**, *44*, 3039–3042. [CrossRef] [PubMed]
238. Uddin, M.J.; Rao, P.P.; Knaus, E.E. Design and synthesis of novel celecoxib analogues as selective cyclooxygenase-2 (COX-2) inhibitors: Replacement of the sulfonamide pharmacophore by a sulfonylazide bioisostere. *Bioorg. Med. Chem.* **2003**, *11*, 5273–5280. [CrossRef] [PubMed]
239. Bansal, S.; Bala, M.; Suthar, S.K.; Choudhary, S.; Bhattacharya, S.; Bhardwaj, V. Design and synthesis of novel 2-phenyl-5-(1,3-diphenyl-1*H*-pyrazol-4-yl)-1,3,4-oxadiazoles as selective COX-2 inhibitors with potent anti-inflammatory activity. *Eur. J. Med. Chem.* **2014**, *80*, 167–174. [CrossRef] [PubMed]
240. El-Sayed, M.A.A.; Abdel-Aziz, N.I.; Abdel-Aziz, A.A.M.; El-Azab, A.S.; Asiri, Y.A.; ElTahir, K.E.H. Design, synthesis, and biological evaluation of substituted hydrazone and pyrazole derivatives as selective COX-2 inhibitors: Molecular docking study. *Bioorg. Med. Chem.* **2011**, *19*, 3416–3424. [CrossRef] [PubMed]
241. Bekhit, A.A.; Ashour, H.M.; Bekhit, A.E.D.A.; Abdel-Rahman, H.M.; Bekhit, S.A. Synthesis of some pyrazolyl benzenesulfonamide derivatives as dual anti-inflammatory antimicrobial agents. *J. Enzym. Inhib. Med. Chem.* **2009**, *24*, 296–309. [CrossRef] [PubMed]
242. Tewari, A.K.; Srivastava, P.; Singh, V.P.; Singh, A.; Goel, R.K.; Mohan, C.G. Novel anti-inflammatory agents based on pyrazole based dimeric compounds; design, synthesis, docking and in vivo activity. *Chem. Pharm. Bull.* **2010**, *58*, 634–638. [CrossRef] [PubMed]
243. Alegaon, S.G.; Hirpara, M.B.; Alagawadi, K.R.; Hullatti, K.K.; Kashniyal, K. Synthesis of novel pyrazole–thiadiazole hybrid as potential potent and selective cyclooxygenase-2 (COX-2) inhibitors. *Bioorg. Med. Chem. Lett.* **2014**, *24*, 5324–5329. [CrossRef] [PubMed]
244. Manetti, F.; Magnani, M.; Castagnolo, D.; Passalacqua, L.; Botta, M.; Corelli, F. Ligand-Based Virtual Screening, Parallel Solution-Phase and Microwave-Assisted Synthesis as Tools to Identify and Synthesize New Inhibitors of Mycobacterium tuberculosis. *Chem. Med. Chem.* **2006**, *1*, 973–989. [CrossRef] [PubMed]
245. Almeida, P.E.; Ramos, D.F.; Bonacorso, H.G.; de la Iglesia, A.I.; Oliveira, M.R.; Coelho, T. Synthesis and in vitro antimycobacterial activity of 3-substituted 5-hydroxy-5-trifluoro[chloro]methyl-4,5-dihydro-1*H*-1-(isonicotinoyl)pyrazoles. *Int. J. Antimicrob. Agents* **2008**, *32*, 139–144. [CrossRef] [PubMed]
246. Castagnolo, D.; De Logu, A.; Radi, M.; Bechi, B.; Manetti, F.; Magnani, M. Synthesis, biological evaluation and SAR study of novel pyrazole analogues as inhibitors of Mycobacterium tuberculosis. *Bioorg. Med. Chem.* **2008**, *16*, 8587–85891. [CrossRef] [PubMed]
247. Velaparthi, S.; Brunsteiner, M.; Uddin, R.; Wan, B.; Franzblau, S.G.; Petukhov, P.A. 5-tert-Butyl-*N*-pyrazol-4-yl-4,5,6,7-tetrahydrobenzo[*d*]isoxazole-3-carboxamide derivatives as novel potent inhibitors of Mycobacterium tuberculosis pantothenate synthetase: Initiating a quest for new antitubercular drugs. *J. Med. Chem.* **2008**, *51*, 1999–2002. [CrossRef] [PubMed]
248. Castagnolo, D.; Manetti, F.; Radi, M.; Bechi, B.; Pagano, M.; De Logu, A.; Meleddu, R.; Saddi, M.; Botta, M. Synthesis, biological evaluation, and SAR study of novel pyrazole analogues as inhibitors of *Mycobacterium tuberculosis*: Part 2. Synthesis of rigid pyrazolones. *Bioorg. Med. Chem.* **2009**, *17*, 5716–5721. [CrossRef] [PubMed]
249. Ahsan, M.J.; Samy, J.G.; Soni, S.; Jain, N.; Kumar, L.; Sharma, L.K.; Yadav, H.; Saini, L.; Kalyansing, R.G.; Devenda, N.S. Discovery of novel antitubercular 3a,4-dihydro-3*H*-indeno[1,2-*c*] pyrazole-2-carboxamide/carbothioamide analogues. *Bioorg. Med. Chem. Lett.* **2011**, *21*, 5259–5261. [CrossRef] [PubMed]
250. Trivedi, A.R.; Dodiya, D.K.; Dholariya, B.H.; Kataria, V.B.; Bhuva, V.R.; Shah, V.H. Synthesis and biological evaluation of some novel *N*-aryl-1,4-dihydropyridines as potential antitubercular agents. *Bioorg. Med. Chem. Lett.* **2011**, *21*, 5181–5183. [CrossRef] [PubMed]
251. Khunt, R.C.; Khedkar, V.M.; Chawda, R.S.; Chauhan, N.A.; Parikh, A.R.; Coutinho, E.C. Synthesis, antitubercular evaluation and 3D-QSAR study of *N*-phenyl-3-(4-fluorophenyl)-4-substituted pyrazole derivatives. *Bioorg. Med. Chem. Lett.* **2012**, *22*, 666–678. [CrossRef] [PubMed]
252. Shelke, S.N.; Mhaske, G.R.; Bonifácio, V.D.; Gawande, M.B. Green synthesis and anti-infective activities of fluorinated pyrazoline derivatives. *Bioorg. Med. Chem. Lett.* **2012**, *22*, 5727–5730. [CrossRef] [PubMed]

253. Anand, N.; Ramakrishna, K.; Gupt, M.P.; Chaturvedi, V.; Singh, S.; Srivastava, K.K.; Sharma, P.; Rai, N.; Ramachandran, R.; Dwivedi, A. Identification of 1-[4-benzyloxyphenyl)-but-3-enyl]-1*H*-azoles as new class of antitubercular and antimicrobial agents. *ACS Med. Chem. Lett.* **2013**, *4*, 958–963. [CrossRef] [PubMed]
254. Fullam, E.; Talbot, J.; Abuhammed, A.; Westwood, I.; Davies, S.G.; Russell, A.J.; Sim, E. Design, synthesis and structure-activity relationships of 3,5-diaryl-1*H*-pyrazoles as inhibitors of arylamine *N*-acetyltransferase. *Bioorg. Med. Chem. Lett.* **2013**, *23*, 2759–2764. [CrossRef] [PubMed]
255. Hernández, P.; Rojas, R.; Gilman, R.H.; Sauvain, M.; Lima, L.M.; Barreiro, E.J.; González, M.; Cerecetto, H. Hybrid furoxanyl *N*-acylhydrazone derivatives as hits for the development of neglected diseases drug candidates. *Eur. J. Med. Chem.* **2013**, *59*, 64–74. [CrossRef] [PubMed]
256. Maurya, H.K.; Verma, R.; Alam, S.; Pandey, S.; Pathak, V.; Sharma, S.; Srivastava, K.K.; Negi, A.S.; Gupta, A. Studies on substituted benzo[*h*]quinazolines, benzo[*g*]indazoles, pyrazoles, 2,6-diarylpyridines as anti-tubercular agents. *Bioorg. Med. Chem. Lett.* **2013**, *23*, 5844–5849. [CrossRef] [PubMed]
257. North, E.J.; Scherman, M.S.; Bruhn, D.F.; Scarborough, J.S.; Maddox, M.M.; Jones, V.; Grzegorzewicz, A.; Yang, L.; Hess, T.; Morisseau, C. Design, synthesis and anti-tuberculosis activity of 1-adamantyl-3-heteroaryl ureas with improved in vitro pharmacokinetic properties. *Bioorg. Med. Chem.* **2013**, *21*, 2587–2599. [CrossRef] [PubMed]
258. Palanisamy, P.; Jenniefer, S.J.; Muthiah, P.T.; Kumaresan, S. Synthesis, characterization, antimicrobial, anticancer, and antituberculosis activity of some new pyrazole, isoxazole, pyrimidine and benzodiazepine derivatives containing thiochromeno and benzothiepino moieties. *RSC Adv.* **2013**, *3*, 19300–19310. [CrossRef]
259. Samala, G.; Devi, P.B.; Nallangi, R.; Yogeeswari, P.; Sriram, D. Development of 3-phenyl-4,5,6,7-tetrahydro-1*H*-pyrazolo[4,3-*c*]pyridine derivatives as novel Mycobacterium tuberculosis pantothenate synthetase inhibitors. *Eur. J. Med. Chem.* **2013**, *69*, 356–364. [CrossRef] [PubMed]
260. Shirude, P.S.; Madhavapeddi, P.; Naik, M.; Murugan, K.; Shinde, V.; Nandishaiah, R.; Bhat, J.; Kumar, A.; Hameed, S.; Holdgate, G. Methyl-thiazoles: A novel mode of inhibition with the potential to develop novel inhibitors targeting InhA in Mycobacterium tuberculosis. *J. Med. Chem.* **2013**, *56*, 8533–8542. [CrossRef] [PubMed]
261. Kalaria, P.N.; Satasia, S.P.; Raval, D.K. Synthesis, characterization and pharmacological screening of some novel 5-imidazopyrazole incorporated polyhydroquinoline derivatives. *Eur. J. Med. Chem.* **2014**, *78*, 207–216. [CrossRef] [PubMed]
262. Karad, S.C.; Purohit, V.B.; Raval, D.K. Design, synthesis and characterization of fluoro substituted novel pyrazolylpyrazolines scaffold and their pharmacological screening. *Eur. J. Med. Chem.* **2014**, *84*, 51–58. [CrossRef] [PubMed]
263. Pathak, V.; Maurya, H.K.; Sharma, S.; Srivastava, K.K.; Gupta, A. Synthesis and biological evaluation of substituted 4,6-diarylpyrimidines and 3,5-diphenyl-4,5-dihydro-1*H*-pyrazoles as anti-tubercular agents. *Bioorg. Med. Chem. Lett.* **2014**, *24*, 2892–2896. [CrossRef] [PubMed]
264. Villemagne, B.; Flipo, M.; Blondiaux, N.; Crauste, C.; Malaquin, S.; Leroux, F.; Piveteau, C.; Villeret, V.; Brodin, P.; Villoutreix, B.O.; et al. Ligand Efficiency Driven Design of New Inhibitors of Mycobacterium tuberculosis Transcriptional Repressor EthR Using Fragment Growing, Merging, and Linking Approaches. *J. Med. Chem.* **2014**, *57*, 4876–4888. [CrossRef] [PubMed]
265. Bhatt, J.D.; Chudasama, C.J.; Patel, K.D. Pyrazole clubbed triazolo[1,5-*a*]pyrimidine hybrids as an anti-tubercular agents: Synthesis, in vitro screening and molecular docking study. *Bioorg. Med. Chem.* **2015**, *23*, 7711–7716. [CrossRef] [PubMed]
266. Da Silva, C.; Ribeiro, L.B.; Furuno, C.C.; da Cunha, G.A.; de Souza, R.F.; Netto, A.V.; Mauro, A.E.; Frem, R.C.; Fernandes, J.A.; Paz, F.A.A. Pyrazolyl Pd (II) complexes containing triphenylphosphine: Synthesis and antimycobacterial activity. *Polyhedron* **2015**, *100*, 10–16. [CrossRef]
267. De Melo, C.S.; Feng, T.-S.; van der Westhuyzen, R.; Gessner, R.K.; Street, L.J.; Morgans, G.L.; Warner, D.F.; Moosa, A.; Naran, K.; Lawrence, N. Aminopyrazolo[1,5-*a*]pyrimidines as potential inhibitors of Mycobacterium tuberculosis: Structure activity relationships and ADME characterization. *Bioorg. Med. Chem.* **2015**, *23*, 7240–7250. [CrossRef] [PubMed]
268. Mutai, P.; Pavadai, E.; Wiid, I.; Ngwane, A.; Baker, B.; Chibale, K. Synthesis, antimycobacterial evaluation and pharmacophore modeling of analogues of the natural product formononetin. *Bioorg. Med. Chem. Lett.* **2015**, *25*, 2510–2513. [CrossRef] [PubMed]

269. Nayak, N.; Ramprasad, J.; Dalimba, U. New INH-pyrazole analogs: Design, synthesis and evaluation of antitubercular and antibacterial activity. *Bioorg. Med. Chem. Lett.* **2015**, *25*, 5540–5545. [CrossRef] [PubMed]
270. Tantry, S.J.; Degiacomi, G.; Sharma, S.; kumar Jena, L.; Narayan, A.; Guptha, S.; Shanbhag, G.; Menasinakai, S.; Mallya, M.; Awasthy, D. Whole cell screen based identification of spiropiperidines with potent antitubercular properties. *Bioorg. Med. Chem. Lett.* **2015**, *25*, 3234–3245. [CrossRef] [PubMed]
271. Guardia, A.; Gulten, G.; Fernandez, R.; Gómez, J.; Wang, F.; Convery, M.; Blanco, D.; Martínez, M.; Pérez-Herrán, E.; Alonso, M. *N*-Benzyl-4-((heteroaryl)methyl) benzamides: A New Class of Direct NADH-Dependent 2-trans Enoyl–Acyl Carrier Protein Reductase (InhA) Inhibitors with Antitubercular Activity. *Chem. Med. Chem.* **2016**, *11*, 687–701. [CrossRef] [PubMed]
272. Kavanagh, M.E.; Coyne, A.G.; McLean, K.J.; James, G.G.; Levy, C.W.; Marino, L.B.; De Carvalho, L.P.S.; Chan, D.S.; Hudson, S.A.; Surade, S. Fragment-based approaches to the development of Mycobacterium tuberculosis CYP121 inhibitors. *J. Med. Chem.* **2016**, *59*, 3272–3302. [CrossRef] [PubMed]
273. Lu, X.; Tang, J.; Liu, Z.; Li, M.; Zhang, T.; Zhang, X.; Ding, K. Discovery of new chemical entities as potential leads against Mycobacterium tuberculosis. *Bioorg. Med. Chem. Lett.* **2016**, *26*, 5916–5919. [CrossRef] [PubMed]
274. Nayak, N.; Ramprasad, J.; Dalimba, U. Synthesis and antitubercular and antibacterial activity of some active fluorine containing quinoline–pyrazole hybrid derivatives. *J. Fluor. Chem.* **2016**, *183*, 59–68. [CrossRef]
275. Ramesh, R.; Shingare, R.D.; Kumar, V.; Anand, A.; Swetha, B.; Veeraraghavan, S.; Viswanadha, S.; Ummanni, R.; Gokhale, R.; Reddy, D.S. Repurposing of a drug scaffold: Identification of novel sila analogues of rimonabant as potent antitubercular agents. *Eur. J. Med. Chem.* **2016**, *122*, 723–730. [CrossRef] [PubMed]
276. Amaroju, S.; Kalaga, M.N.; Srinivasarao, S.; Napiorkowska, A.; Augustynowicz-Kopec, E.; Murugesan, S.; Chander, S.; Krishnan, R.; Chandra Sekhar, K.V.G. Identification and development of pyrazolo[4,3-*c*]pyridine carboxamides as Mycobacterium tuberculosis pantothenate synthetase inhibitors. *New J. Chem.* **2017**, *41*, 347–357. [CrossRef]
277. Angelova, V.T.; Valcheva, V.; Pencheva, T.; Voynikov, Y.; Vassilev, N.; Mihaylova, R.; Momekov, G.; Shivachev, B. Synthesis, antimycobacterial activity and docking study of 2-aroyl-[1]benzopyrano[4,3-*c*] pyrazol-4(1*H*)-one derivatives and related hydrazide-hydrazones. *Bioorg. Med. Chem. Lett.* **2017**, *27*, 2996–3002. [CrossRef] [PubMed]
278. He, C.; Preiss, L.; Wang, B.; Fu, L.; Wen, H.; Zhang, X.; Cui, H.; Meier, T.; Yin, D. Structural Simplification of Bedaquiline: The Discovery of 3-(4-(*N*,*N*-Dimethylaminomethyl)phenyl) quinoline-Derived Antitubercular Lead Compounds. *Chem. Med. Chem.* **2017**, *12*, 106–119. [CrossRef] [PubMed]
279. Aragade, P.; Palkar, M.; Ronad, P.; Satyanarayana, D. Coumarinyl pyrazole derivatives of INH: Promising antimycobacterial agents. *Med. Chem. Res.* **2013**, *22*, 2279–2283. [CrossRef]
280. Gajbhiye, J.; More, N.; Patil, M.D.; Ummanni, R.; Kotapalli, S.; Yogeeswari, P.; Sriram, D.; Masand, V. Discovery of Rimonabant and its potential analogues as anti-TB drug candidates. *Med. Chem. Res.* **2015**, *24*, 2960–2971. [CrossRef]
281. Nayak, N.; Ramprasad, J.; Dalimba, U. Design, Synthesis, and Biological Evaluation of New 8-Trifluoromethylquinoline Containing Pyrazole-3-carboxamide Derivatives. *J. Heterocycl. Chem.* **2017**, *54*, 171–182. [CrossRef]
282. Trivedi, A.R.; Dholariya, B.H.; Vakhariya, C.P.; Dodiya, D.K.; Ram, H.K.; Kataria, V.B.; Siddiqui, A.B.; Shah, V.H. Synthesis and anti-tubercular evaluation of some novel pyrazolo[3,4-*d*]pyrimidine derivatives. *Med. Chem. Res.* **2012**, *21*, 1887–1891. [CrossRef]
283. Labana, B.M.; Brahmbhatt, G.C.; Sutariya, T.R.; Parmar, N.J.; Padrón, J.M.; Kant, R.; Gupta, V.K. Efficient synthesis and biological evaluation of new benzopyran-annulated pyrano[2,3-*c*]pyrazole derivatives. *Mol. Divers.* **2017**, *21*, 339–354. [CrossRef] [PubMed]
284. Encinas, L.; O'Keefe, H.; Neu, M.; Remuiñán, M.J.; Patel, A.M.; Guardia, A.; Davie, C.P.; Pérez-Macías, N.; Yang, H.; Convery, M.A. Encoded library technology as a source of hits for the discovery and lead optimization of a potent and selective class of bactericidal direct inhibitors of Mycobacterium tuberculosis InhA. *J. Med. Chem.* **2014**, *57*, 1276–1288. [CrossRef] [PubMed]
285. Rachakonda, V.; Alla, M.; Kotipalli, S.S.; Ummani, R. Design, diversity-oriented synthesis and structure activity relationship studies of quinolinyl heterocycles as antimycobacterial agents. *Eur J Med Chem* **2013**, *70*, 536–547. [CrossRef] [PubMed]

286. Pandit, U.; Dodiya, A. Synthesis and antitubercular activity of novel pyrazole–quinazolinone hybrid analogs. *Med. Chem. Res.* **2013**, *22*, 3364–3371. [CrossRef]
287. Mistry, P.T.; Kamdar, N.R.; Haveliwala, D.D.; Patel, S.K. Synthesis, characterization, and in vitro biological studies of some novel pyran fused pyrimidone derivatives. *J. Heterocycl. Chem.* **2012**, *49*, 349–357. [CrossRef]
288. Naik, M.; Humnabadkar, V.; Tantry, S.J.; Panda, M.; Narayan, A.; Guptha, S.; Panduga, V.; Manjrekar, P.; Jena, L.K.; Koushik, K. 4-aminoquinolone piperidine amides: Noncovalent inhibitors of DprE1 with long residence time and potent antimycobacterial activity. *J. Med. Chem.* **2014**, *57*, 5419–5434. [CrossRef] [PubMed]
289. Manfredini, S.; Bazzanini, R.; Baraldi, P.G.; Guarneri, M.; Simoni, D.; Marongiu, M.E.; Pani, A.; La Colla, P.; Tramontano, E. Pyrazole-related nucleosides. Synthesis and antiviral/antitumor activity of some substituted pyrazole and pyrazolo[4,3-*d*]-1,2,3-triazin-4-one nucleosides. *J. Med. Chem.* **1992**, *35*, 917–924. [CrossRef] [PubMed]
290. Chen, X.; Schneller, S.W.; Ikeda, S.; Snoeck, R.; Andrei, G.; Balzarini, J.; De Clercq, E. Synthesis and antiviral activity of 5′-deoxypyrazofurin. *J. Med. Chem.* **1993**, *36*, 3727–3730. [CrossRef] [PubMed]
291. Storer, R.; Ashton, C.J.; Baxter, A.D.; Hann, M.M.; Marr, C.L.P.; Mason, A.M.; Mo, C.-L.; Myers, P.L.; Noble, S.A.; Penn, C.R.; et al. The Synthesis and Antiviral Activity of 4-Fluoro-1-β-D-ribofuranosyl-1*H*-pyrazole-3-carboxamide. *Nucleosides Nucleotides* **1999**, *18*, 203–216. [CrossRef] [PubMed]
292. Genin, M.J.; Biles, C.; Keiser, B.J.; Poppe, S.M.; Swaney, S.M.; Tarpley, W.G.; Yagi, Y.; Romero, D.L. Novel 1,5-Diphenylpyrazole Nonnucleoside HIV-1 Reverse Transcriptase Inhibitors with Enhanced Activity versus the Delavirdine-Resistant P236L Mutant: Lead Identification and SAR of 3- and 4-Substituted Derivatives. *J. Med. Chem.* **2000**, *43*, 1034–1040. [CrossRef] [PubMed]
293. Rostom, S.A.F.; Shalaby, M.A.; El-Demellawy, M.A. Polysubstituted pyrazoles, part 5. Synthesis of new 1-(4-chlorophenyl)-4-hydroxy-1*H*-pyrazole-3-carboxylic acid hydrazide analogs and some derived ring systems. A novel class of potential antitumor and anti-HCV agents. *Eur. J. Med. Chem.* **2003**, *38*, 959–974. [CrossRef] [PubMed]
294. Shamroukh, A.H.; Zaki, M.E.; Morsy, E.M.; Abdel-Motti, F.M.; Abdel-Megeid, F.M. Synthesis of Pyrazolo [4′,3′:5,6] pyrano[2,3-*d*]pyrimidine Derivatives for Antiviral Evaluation. *Arch. Pharm.* **2007**, *340*, 236–243. [CrossRef] [PubMed]
295. Sun, A.; Chandrakumar, N.; Yoon, J.-J.; Plemper, R.K.; Snyder, J.P. Non-nucleoside inhibitors of the measles virus RNA-dependent RNA polymerase complex activity: Synthesis and in vitro evaluation. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 5199–5203. [CrossRef] [PubMed]
296. Ouyang, G.; Chen, Z.; Cai, X.-J.; Song, B.-A.; Bhadury, P.S.; Yang, S.; Jin, L.-H.; Xue, W.; Hu, D.-Y.; Zeng, S. Synthesis and antiviral activity of novel pyrazole derivatives containing oxime esters group. *Bioorg. Med. Chem.* **2008**, *16*, 9699–9707. [CrossRef] [PubMed]
297. Rashad, A.E.; Hegab, M.I.; Abdel-Megeid, R.E.; Micky, J.A.; Abdel-Megeid, F.M. Synthesis and antiviral evaluation of some new pyrazole and fused pyrazolopyrimidine derivatives. *Bioorg. Med. Chem.* **2008**, *16*, 7102–7106. [CrossRef] [PubMed]
298. Zeng, L.-F.; Zhang, H.-S.; Wang, Y.-H.; Sanchez, T.; Zheng, Y.-T.; Neamati, N.; Long, Y.-Q. Efficient synthesis and utilization of phenyl-substituted heteroaromatic carboxylic acids as aryl diketo acid isosteres in the design of novel HIV-1 integrase inhibitors. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 4521–4524. [CrossRef] [PubMed]
299. Mowbray, C.E.; Burt, C.; Corbau, R.; Gayton, S.; Hawes, M.; Perros, M.; Tran, I.; Price, D.A.; Quinton, F.J.; Selby, M.D. Pyrazole NNRTIs 4: Selection of UK-453,061 (lersivirine) as a development candidate. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 5857–5860. [CrossRef] [PubMed]
300. Mowbray, C.E.; Burt, C.; Corbau, R.; Perros, M.; Tran, I.; Stupple, P.A.; Webster, R.; Wood, A. Pyrazole NNRTIs 1: Design and initial optimisation of a novel template. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 5599–5602. [CrossRef] [PubMed]
301. Sidique, S.; Shiryaev, S.A.; Ratnikov, B.I.; Herath, A.; Su, Y.; Strongin, A.Y.; Cosford, N.D. Structure–activity relationship and improved hydrolytic stability of pyrazole derivatives that are allosteric inhibitors of West Nile Virus NS2B-NS3 proteinase. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 5773–5777. [CrossRef] [PubMed]
302. Sujatha, K.; Shanthi, G.; Selvam, N.P.; Manoharan, S.; Perumal, P.T.; Rajendran, M. Synthesis and antiviral activity of 4,4′-(arylmethylene)bis(1*H*-pyrazol-5-ols) against peste des petits ruminant virus (PPRV). *Bioorg. Med. Chem. Lett.* **2009**, *19*, 1501–1503. [CrossRef] [PubMed]

303. Riyadh, S.M.; Farghaly, T.A.; Abdallah, M.A.; Abdalla, M.M.; El-Aziz, M.R.A. New pyrazoles incorporating pyrazolylpyrazole moiety: Synthesis, anti-HCV and antitumor activity. *Eur. J. Med. Chem.* **2010**, *45*, 1042–1050. [CrossRef] [PubMed]
304. Shih, S.-R.; Chu, T.-Y.; Reddy, G.R.; Tseng, S.-N.; Chen, H.-L.; Tang, W.-F.; Wu, M.-S.; Yeh, J.-Y.; Chao, Y.-S.; Hsu, J.T. Pyrazole compound BPR1P0034 with potent and selective anti influenza virus activity. *J. Biomed. Sci.* **2010**, *17*, 13–21. [CrossRef] [PubMed]
305. Su, D.-S.; Lim, J.J.; Tinney, E.; Tucker, T.J.; Saggar, S.; Sisko, J.T.; Wan, B.-L.; Young, M.B.; Anderson, K.D.; Rudd, D. Biaryl ethers as potent allosteric inhibitors of reverse transcriptase and its key mutant viruses: Aryl substituted pyrazole as a surrogate for the pyrazolopyridine motif. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 4328–4332. [CrossRef] [PubMed]
306. Dawood, K.M.; Abdel-Gawad, H.; Mohamed, H.A.; Badria, F.A. Synthesis, anti-HSV-1, and cytotoxic activities of some new pyrazole-and isoxazole-based heterocycles. *Med. Chem. Res.* **2011**, *20*, 912–919. [CrossRef]
307. Wu, L.; Song, B.; Bhadury, P.S.; Yang, S.; Hu, D.; Jin, L. Synthesis and antiviral activity of novel pyrazole amides containing α-aminophosphonate moiety. *J. Heterocycl. Chem.* **2011**, *48*, 389–396. [CrossRef]
308. Di Francesco, M.E.; Avolio, S.; Pompei, M.; Pesci, S.; Monteagudo, E.; Pucci, V.; Giuliano, C.; Fiore, F.; Rowley, M.; Summa, V. Synthesis and antiviral properties of novel 7-heterocyclic substituted 7-deaza-adenine nucleoside inhibitors of Hepatitis C NS5B polymerase. *Bioorg. Med. Chem.* **2012**, *20*, 4801–4811. [CrossRef] [PubMed]
309. Kim, J.; Lee, D.; Park, C.; So, W.; Jo, M.; Ok, T.; Kwon, J.; Kong, S.; Jo, S.; Kim, Y. Discovery of phenylaminopyridine derivatives as novel HIV-1 non-nucleoside reverse transcriptase inhibitors. *ACS Med. Chem. Lett.* **2012**, *3*, 678–682. [CrossRef] [PubMed]
310. Ndungu, J.M.; Krumm, S.A.; Yan, D.; Arrendale, R.F.; Reddy, G.P.; Evers, T.; Howard, R.; Natchus, M.G.; Saindane, M.T.; Liotta, D.C. Non-nucleoside inhibitors of the measles virus RNA-dependent RNA polymerase: Synthesis, structure-activity relationships, and pharmacokinetics. *J. Med. Chem.* **2012**, *55*, 4220–4230. [CrossRef] [PubMed]
311. Tantawy, A.S.; Nasr, M.N.; El-Sayed, M.A.; Tawfik, S.S. Synthesis and antiviral activity of new 3-methyl-1,5-diphenyl-1*H*-pyrazole derivatives. *Med. Chem. Res.* **2012**, *21*, 4139–4149. [CrossRef]
312. Zhang, D.Q.; Xu, G.F.; Fan, Z.J.; Wang, D.Q.; Yang, X.L.; Yuan, D.K. Synthesis and anti-TMV activity of novel *N*-(3-alkyl-1*H*-pyrazol-4-yl)-3-alkyl-4-substituted-1*H*-pyrazole-5-carboxamides. *Chin. Chem. Lett.* **2012**, *23*, 669–672. [CrossRef]
313. Hwang, J.Y.; Kim, H.-Y.; Park, D.-S.; Choi, J.; Baek, S.M.; Kim, K.; Kim, S.; Seong, S.; Choi, I.; Lee, H.-G. Identification of a series of 1,3,4-trisubstituted pyrazoles as novel hepatitis C virus entry inhibitors. *Bioorg. Med. Chem. Lett.* **2013**, *23*, 6467–6473. [CrossRef] [PubMed]
314. Mizuhara, T.; Kato, T.; Hirai, A.; Kurihara, H.; Shimada, Y.; Taniguchi, M.; Maeta, H.; Togami, H.; Shimura, K.; Matsuoka, M. Structure-activity relationship study of phenylpyrazole derivatives as a novel class of anti-HIV agents. *Bioorg. Med. Chem. Lett.* **2013**, *23*, 4557–4561. [CrossRef] [PubMed]
315. Moreau, B.; O'Meara, J.A.; Bordeleau, J.E.; Garneau, M.; Godbout, C.; Gorys, V.; Leblanc, M.L.; Villemure, E.; White, P.W.; Llinàs-Brunet, M. Discovery of hepatitis C virus NS3-4A protease inhibitors with improved barrier to resistance and favorable liver distribution. *J. Med. Chem.* **2013**, *57*, 1770–1776. [CrossRef] [PubMed]
316. Bhadoriya, K.S.; Sharma, M.C.; Jain, S.V. 2,4-Dihydropyrano[2,3-*c*]pyrazole: Discovery of new lead as through pharmacophore modelling, atom-based 3D-QSAR, virtual screening and docking strategies for improved anti-HIV-1 chemotherapy. *J. Taibah Univ. Sci.* **2015**, *9*, 521–530. [CrossRef]
317. Fioravanti, R.; Desideri, N.; Biava, M.; Droghini, P.; Atzori, E.M.; Ibba, C.; Collu, G.; Sanna, G.; Delogu, I.; Loddo, R. *N*-((1,3-Diphenyl-1*H*-pyrazol-4-yl)methyl) anilines: A novel class of anti-RSV agents. *Bioorg. Med. Chem. Lett.* **2015**, *25*, 2401–2404. [CrossRef] [PubMed]
318. Han, C.; Guo, Y.-C.; Wang, D.-D.; Dai, X.-J.; Wu, F.-J.; Liu, H.-F.; Dai, G.-F.; Tao, J.-C. Novel pyrazole fused heterocyclic ligands: Synthesis, characterization, DNA binding/cleavage activity and anti-BVDV activity. *Chin. Chem. Lett.* **2015**, *26*, 534–538. [CrossRef]
319. Manvar, D.; Pelliccia, S.; La Regina, G.; Famiglini, V.; Coluccia, A.; Ruggieri, A.; Anticoli, S.; Lee, J.-C.; Basu, A.; Cevik, O. New 1-phenyl-5-(1*H*-pyrrol-1-yl)-1*H*-pyrazole-3-carboxamides inhibit hepatitis C virus replication via suppression of cyclooxygenase-2. *Eur. J. Med. Chem.* **2015**, *90*, 497–506. [CrossRef] [PubMed]

320. Chuang, H.; Huang, L.-C.S.; Kapoor, M.; Liao, Y.-J.; Yang, C.-L.; Chang, C.-C.; Wu, C.-Y.; Hwu, J.R.; Huang, T.-J.; Hsu, M.-H. Design and synthesis of pyridine-pyrazole-sulfonate derivatives as potential anti-HBV agents. *MedChemComm* **2016**, *7*, 832–836. [CrossRef]
321. Ouyang, G.; Cai, X.-J.; Chen, Z.; Song, B.-A.; Bhadury, P.S.; Yang, S.; Jin, L.-H.; Xue, W.; Hu, D.-Y.; Zeng, S. Synthesis and Antiviral Activities of Pyrazole Derivatives Containing an Oxime Moiety. *J. Agric. Food Chem.* **2008**, *56*, 10160–10167. [CrossRef] [PubMed]
322. Jia, H.; Bai, F.; Liu, N.; Liang, X.; Zhan, P.; Ma, C.; Jiang, X.; Liu, X. Design, synthesis and evaluation of pyrazole derivatives as non-nucleoside hepatitis B virus inhibitors. *Eur. J. Med. Chem.* **2016**, *123*, 202–210. [CrossRef] [PubMed]
323. Liu, G.-N.; Luo, R.-H.; Zhou, Y.; Zhang, X.-J.; Li, J.; Yang, L.-M.; Zheng, Y.-T.; Liu, H. Synthesis and Anti-HIV-1 Activity Evaluation for Novel 3a,6a-Dihydro-1*H*-pyrrolo[3,4-*c*]pyrazole-4,6-dione Derivatives. *Molecules* **2016**, *21*, 1198. [CrossRef] [PubMed]
324. Johns, B.A.; Gudmundsson, K.S.; Allen, S.H. Pyrazolo[1,5-*a*]pyridine antiherpetics: Effects of the C3 substituent on antiviral activity. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 2858–2862. [CrossRef] [PubMed]
325. Chimenti, F.; Fioravanti, R.; Bolasco, A.; Manna, F.; Chimenti, P.; Secci, D.; Befani, O.; Turini, P.; Ortuso, F.; Alcaro, S. Monoamine Oxidase Isoform-Dependent Tautomeric Influence in the Recognition of 3,5-Diaryl Pyrazole Inhibitors. *J. Med. Chem.* **2007**, *50*, 425–428. [CrossRef] [PubMed]
326. Kuduk, S.D.; Di Marco, C.N.; Cofre, V.; Pitts, D.R.; Ray, W.J.; Ma, L.; Wittmann, M.; Veng, L.; Seager, M.A.; Koeplinger, K. *N*-Heterocyclic derived M 1 positive allosteric modulators. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 1334–1337. [CrossRef] [PubMed]
327. Malamas, M.S.; Erdei, J.; Gunawan, I.; Barnes, K.; Hui, Y.; Johnson, M.; Robichaud, A.; Zhou, P.; Yan, Y.; Solvibile, W. New pyrazolyl and thienyl aminohydantoins as potent BACE1 inhibitors: Exploring the S2′ region. *Bioorg. Med. Chem. Lett.* **2011**, *21*, 5164–5170. [CrossRef] [PubMed]
328. Probst, G.; Aubele, D.L.; Bowers, S.; Dressen, D.; Garofalo, A.W.; Hom, R.K.; Konradi, A.W.; Marugg, J.L.; Mattson, M.N.; Neitzel, M.L. Discovery of (*R*)-4-Cyclopropyl-7,8-difluoro-5-(4-(trifluoromethyl)phenylsulfonyl) -4,5-dihydro-1*H*-pyrazolo[4,3-*c*]quinoline (ELND006) and (*R*)-4-Cyclopropyl- 8-fluoro-5-(6-(trifluoromethyl) pyridin-3-ylsulfonyl)-4,5-dihydro-2*H*-pyrazolo[4,3-*c*]quinoline (ELND007): Metabolically Stable γ-Secretase Inhibitors that Selectively Inhibit the Production of Amyloid-β over Notch. *J. Med. Chem.* **2013**, *56*, 5261–5274. [CrossRef] [PubMed]
329. Zou, Y.; Xu, L.; Chen, W.; Zhu, Y.; Chen, T.; Fu, Y.; Li, L.; Ma, L.; Xiong, B.; Wang, X. Discovery of pyrazole as C-terminus of selective BACE1 inhibitors. *Eur. J. Med. Chem.* **2013**, *68*, 270–283. [CrossRef] [PubMed]
330. Han, Y.T.; Kim, K.; Choi, G.-I.; An, H.; Son, D.; Kim, H.; Ha, H.-J.; Son, J.-H.; Chung, S.-J.; Park, H.-J. Pyrazole-5-carboxamides, novel inhibitors of receptor for advanced glycation end products (RAGE). *Eur. J. Med. Chem.* **2014**, *79*, 128–142. [CrossRef] [PubMed]
331. Silva, D.; Chioua, M.; Samadi, A.; Carreiras, M.C.; Jimeno, M.-L.; Mendes, E.; de los Ríos, C.; Romero, A.; Villarroya, M.; López, M.G. Synthesis and pharmacological assessment of diversely substituted pyrazolo[3,4-*b*]quinoline, and benzo[b]pyrazolo[4,3-*g*][1,8]naphthyridine derivatives. *Eur. J. Med. Chem.* **2011**, *46*, 4676–4681. [CrossRef] [PubMed]
332. Khoobi, M.; Ghanoni, F.; Nadri, H.; Moradi, A.; Hamedani, M.P.; Moghadam, F.H.; Emami, S.; Vosooghi, M.; Zadmard, R.; Foroumadi, A. New tetracyclic tacrine analogs containing pyrano[2,3-*c*]pyrazole: Efficient synthesis, biological assessment and docking simulation study. *Eur. J. Med. Chem.* **2015**, *89*, 296–303. [CrossRef] [PubMed]
333. Zanaletti, R.; Bettinetti, L.; Castaldo, C.; Ceccarelli, I.; Cocconcelli, G.; Comery, T.A.; Dunlop, J.; Genesio, E.; Ghiron, C.; Haydar, S.N. *N*-[5-(5-Fluoropyridin-3-yl)-1*H*-pyrazol-3-yl]-4-piperidin-1-ylbutyramide (SEN78702, WYE-308775): A Medicinal Chemistry Effort toward an α7 Nicotinic Acetylcholine Receptor Agonist Preclinical Candidate. *J. Med. Chem.* **2012**, *55*, 10277–10281. [CrossRef] [PubMed]
334. Zanaletti, R.; Bettinetti, L.; Castaldo, C.; Cocconcelli, G.; Comery, T.; Dunlop, J.; Gaviraghi, G.; Ghiron, C.; Haydar, S.N.; Jow, F. Discovery of a novel alpha-7 nicotinic acetylcholine receptor agonist series and characterization of the potent, selective, and orally efficacious agonist 5-(4-acetyl[1,4]diazepan-1-yl)pentanoic acid[5-(4-methoxyphenyl)-1*H*-pyrazol-3-yl] amide (SEN15924, WAY-361789). *J. Med. Chem.* **2012**, *55*, 4806–4823. [CrossRef] [PubMed]

335. Nencini, A.; Castaldo, C.; Comery, T.A.; Dunlop, J.; Genesio, E.; Ghiron, C.; Haydar, S.; Maccari, L.; Micco, I.; Turlizzi, E.; et al. Design and synthesis of a hybrid series of potent and selective agonists of α7 nicotinic acetylcholine receptor. *Eur. J. Med. Chem.* **2014**, *78*, 401–418. [CrossRef] [PubMed]
336. Ernst, G.; Frietze, W.; Simpson, T. Novel Pyrazole Derivatives and Their Use as Modulators of Nicotinic Acetylcholine Receptors. *Google Patents*. 2008. Available online: https://www.google.com/patents/US20080081833 (accessed on 2 October 2017).
337. Thuring, J.W.J.F.; MacDonald, G.J.; Zhuang, W. Trisubstituted Pyrazoles as Acetylcholine Receptor Modulators. *Google Patents*. 2014. Available online: https://www.google.com/patents/US8779158 (accessed on 2 October 2017).
338. Cottineau, B.; Toto, P.; Marot, C.; Pipaud, A.; Chenault, J. Synthesis and hypoglycemic evaluation of substituted pyrazole-4-carboxylic acids. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 2105–2108. [CrossRef]
339. Sharon, A.; Pratap, R.; Tiwari, P.; Srivastava, A.; Maulik, P.R.; Ram, V.J. Synthesis and in vivo antihyperglycemic activity of 5-(1*H*-pyrazol-3-yl)methyl-1*H*-tetrazoles. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 2115–2117. [CrossRef] [PubMed]
340. Humphries, P.S.; Lafontaine, J.A.; Agree, C.S.; Alexander, D.; Chen, P.; Do, Q.-Q.T.; Li, L.Y.; Lunney, E.A.; Rajapakse, R.J.; Siegel, K. Synthesis and SAR of 4-substituted-2-aminopyrimidines as novel c-Jun *N*-terminal kinase (JNK) inhibitors. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 2099–2102. [CrossRef] [PubMed]
341. Brigance, R.P.; Meng, W.; Fura, A.; Harrity, T.; Wang, A.; Zahler, R.; Kirby, M.S.; Hamann, L.G. Synthesis and SAR of azolopyrimidines as potent and selective dipeptidyl peptidase-4 (DPP4) inhibitors for type 2 diabetes. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 4395–4398. [CrossRef] [PubMed]
342. Choi, J.; Park, Y.; Lee, H.S.; Yang, Y.; Yoon, S. 1,3-Diphenyl-1*H*-pyrazole derivatives as a new series of potent PPARγ partial agonists. *Bioorg. Med. Chem.* **2010**, *18*, 8315–8323. [CrossRef] [PubMed]
343. Shen, D.-M.; Brady, E.J.; Candelore, M.R.; Dallas-Yang, Q.; Ding, V.D.H.; Feeney, W.P.; Jiang, G.; McCann, M.E.; Mock, S.; Qureshi, S.A.; et al. Discovery of novel, potent, selective, and orally active human glucagon receptor antagonists containing a pyrazole core. *Bioorg. Med. Chem. Lett.* **2011**, *21*, 76–81. [CrossRef] [PubMed]
344. Fushimi, N.; Fujikura, H.; Shiohara, H.; Teranishi, H.; Shimizu, K.; Yonekubo, S.; Ohno, K.; Miyagi, T.; Itoh, F.; Shibazaki, T. Structure-activity relationship studies of 4-benzyl-1*H*-pyrazol-3-ylβ-d-glucopyranoside derivatives as potent and selective sodium glucose co-transporter 1 (SGLT1) inhibitors with therapeutic activity on postprandial hyperglycemia. *Bioorg. Med. Chem.* **2012**, *20*, 6598–6612. [CrossRef] [PubMed]
345. Rikimaru, K.; Wakabayashi, T.; Abe, H.; Imoto, H.; Maekawa, T.; Ujikawa, O.; Murase, K.; Matsuo, T.; Matsumoto, M.; Nomura, C. A new class of non-thiazolidinedione, non-carboxylic-acid-based highly selective peroxisome proliferator-activated receptor (PPAR) γ agonists: Design and synthesis of benzylpyrazole acylsulfonamides. *Bioorg. Med. Chem.* **2012**, *20*, 714–733. [CrossRef] [PubMed]
346. Xiong, Y.; Guo, J.; Candelore, M.R.; Liang, R.; Miller, C.; Dallas-Yang, Q.; Jiang, G.; McCann, P.E.; Qureshi, S.A.; Tong, X. Discovery of a Novel Glucagon Receptor Antagonist *N*-[(4-{(1*S*)-1-[3-(3,5-Dichlorophenyl)-5-(6-methoxynaphthalen-2-yl)-1*H*-pyrazol-1-yl]ethyl}phenyl)carbonyl]-β-alanine (MK-0893) for the Treatment of Type II Diabetes. *J. Med. Chem.* **2012**, *55*, 6137–6148. [CrossRef] [PubMed]
347. Yoshida, T.; Akahoshi, F.; Sakashita, H.; Kitajima, H.; Nakamura, M.; Sonda, S.; Takeuchi, M.; Tanaka, Y.; Ueda, N.; Sekiguchi, S. Discovery and preclinical profile of teneligliptin (3-[(2*S*,4*S*)-4-[4-(3-methyl-1-phenyl-1*H*-pyrazol-5-yl)piperazin-1-yl]pyrrolidin-2-ylcarbonyl]thiazolidine): A highly potent, selective, long-lasting and orally active dipeptidyl peptidase IV inhibitor for the treatment of type 2 diabetes. *Bioorg. Med. Chem.* **2012**, *20*, 5705–5719. [CrossRef] [PubMed]
348. Futatsugi, K.; Mascitti, V.; Guimarães, C.R.; Morishita, N.; Cai, C.; DeNinno, M.P.; Gao, H.; Hamilton, M.D.; Hank, R.; Harris, A.R. From partial to full agonism: Identification of a novel 2,4,5,6-tetrahydropyrrolo[3,4-*c*]pyrazole as a full agonist of the human GPR119 receptor. *Bioorg. Med. Chem. Lett.* **2013**, *23*, 194–197. [CrossRef] [PubMed]
349. Griffith, D.A.; Dow, R.L.; Huard, K.; Edmonds, D.J.; Bagley, S.W.; Polivkova, J.; Zeng, D.; Garcia-Irizarry, C.N.; Southers, J.A.; Esler, W. Spirolactam-based acetyl-CoA carboxylase inhibitors: Toward improved metabolic stability of a chromanone lead structure. *J. Med. Chem.* **2013**, *56*, 7110–7119. [CrossRef] [PubMed]
350. Hernández-Vázquez, E.; Aguayo-Ortiz, R.; Ramírez-Espinosa, J.J.; Estrada-Soto, S.; Hernández-Luis, F. Synthesis, hypoglycemic activity and molecular modeling studies of pyrazole-3-carbohydrazides designed by a CoMFA model. *Eur. J. Med. Chem.* **2013**, *69*, 10–21. [CrossRef] [PubMed]

351. Toda, N.; Hao, X.; Ogawa, Y.; Oda, K.; Yu, M.; Fu, Z.; Chen, Y.; Kim, Y.; Lizarzaburu, M.; Lively, S. Potent and orally bioavailable GPR142 agonists as novel insulin secretagogues for the treatment of type 2 diabetes. *ACS Med. Chem. Lett.* **2013**, *4*, 790–794. [CrossRef] [PubMed]
352. Yu, M.; Lizarzaburu, M.; Motani, A.; Fu, Z.; Du, X.; Liu, J.; Jiao, X.; Lai, S.; Fan, P.; Fu, A. Aminopyrazole–Phenylalanine Based GPR142 Agonists: Discovery of Tool Compound and in Vivo Efficacy Studies. *ACS Med. Chem. Lett.* **2013**, *4*, 829–834. [CrossRef] [PubMed]
353. Bhosle, M.R.; Mali, J.R.; Pal, S.; Srivastava, A.K.; Mane, R.A. Synthesis and antihyperglycemic evaluation of new 2-hydrazolyl-4-thiazolidinone-5-carboxylic acids having pyrazolyl pharmacophores. *Bioorg. Med. Chem. Lett.* **2014**, *24*, 2651–2654. [CrossRef] [PubMed]
354. López-Viseras, M.E.; Fernández, B.; Hilfiker, S.; González, C.S.; González, J.L.; Calahorro, A.J.; Colacio, E.; Rodríguez-Diéguez, A. In vivo potential antidiabetic activity of a novel zinc coordination compound based on 3-carboxy-pyrazole. *J. Inorg. Biochem.* **2014**, *131*, 64–67. [CrossRef] [PubMed]
355. Kenchappa, R.; Bodke, Y.D.; Chandrashekar, A.; Sindhe, M.A.; Peethambar, S. Synthesis of coumarin derivatives containing pyrazole and indenone rings as potent antioxidant and antihyperglycemic agents. *Arab. J. Chem.* **2017**, *10*, S3895–S3906. [CrossRef]
356. Doddaramappa, S.D.; Lokanatha Rai, K.M.; Srikantamurthy, N.; Chethan, J. Novel 5-functionalized-pyrazoles: Synthesis, characterization and pharmacological screening. *Bioorg. Med. Chem. Lett.* **2015**, *25*, 3671–3675. [CrossRef] [PubMed]
357. Hernández-Vázquez, E.; Salgado-Barrera, S.; Ramírez-Espinosa, J.J.; Estrada-Soto, S.; Hernández-Luis, F. Synthesis and molecular docking of *N*′-arylidene-5-(4-chlorophenyl)-1-(3,4-dichlorophenyl)-4-methyl-1*H*-pyrazole-3-carbohydrazides as novel hypoglycemic and antioxidant dual agents. *Bioorg. Med. Chem.* **2016**, *24*, 2298–2306. [CrossRef] [PubMed]
358. Kashtoh, H.; Muhammad, M.T.; Khan, J.J.A.; Rasheed, S.; Khan, A.; Perveen, S.; Javaid, K.; Atia tul, W.; Khan, K.M.; Choudhary, M.I. Dihydropyrano[2,3-*c*]pyrazole: Novel in vitro inhibitors of yeast α-glucosidase. *Bioorg. Chem.* **2016**, *65*, 61–72. [CrossRef] [PubMed]
359. Chaudhry, F.; Naureen, S.; Huma, R.; Shaukat, A.; Al-Rashida, M.; Asif, N.; Ashraf, M.; Munawar, M.A.; Khan, M.A. In search of new α-glucosidase inhibitors: Imidazolylpyrazole derivatives. *Bioorg. Chem.* **2017**, *71*, 102–109. [CrossRef] [PubMed]
360. Hernández-Vázquez, E.; Ocampo-Montalban, H.; Cerón-Romero, L.; Cruz, M.; Gómez-Zamudio, J.; Hiriart-Valencia, G.; Villalobos-Molina, R.; Flores-Flores, A.; Estrada-Soto, S. Antidiabetic, antidyslipidemic and toxicity profile of ENV-2: A potent pyrazole derivative against diabetes and related diseases. *Eur. J. Pharmacol.* **2017**, *803*, 159–166. [CrossRef] [PubMed]
361. De Mello, H.; Echevarria, A.; Bernardino, A.M.; Canto-Cavalheiro, M.; Leon, L.L. Antileishmanial pyrazolopyridine derivatives: Synthesis and structure-activity relationship analysis. *J. Med. Chem.* **2004**, *47*, 5427–5432. [CrossRef] [PubMed]
362. Bernardino, A.M.R.; Gomes, A.O.; Charret, K.S.; Freitas, A.C.C.; Machado, G.M.C.; Canto-Cavalheiro, M.M.; Leon, L.L.; Amaral, V.F. Synthesis and leishmanicidal activities of 1-(4-X-phenyl)-*N*′-[(4-Y-phenyl) methylene]-1*H*-pyrazole-4-carbohydrazides. *Eur. J. Med. Chem.* **2006**, *41*, 80–87. [CrossRef] [PubMed]
363. Dardari, Z.; Lemrani, M.; Sebban, A.; Bahloul, A.; Hassar, M.; Kitane, S.; Berrada, M.; Boudouma, M. Antileishmanial and Antibacterial Activity of a New Pyrazole Derivative Designated 4-[2-(1-(Ethylamino)-2-methyl-propyl) phenyl]-3-(4-methyphenyl)-1-phenylpyrazole. *Arch. Pharm.* **2006**, *339*, 291–298. [CrossRef] [PubMed]
364. Dos Santos, M.S.; Gomes, A.O.; Bernardino, A.M.; Souza, M.C.D.; Khan, M.A.; Brito, M.A.D.; Castro, H.C.; Abreu, P.A.; Rodrigues, C.R.; de Léo, R.M. Synthesis and antileishmanial activity of new 1-aryl-1*H*-pyrazole-4-carboximidamides derivatives. *J. Braz. Chem. Soc.* **2011**, *22*, 352–358. [CrossRef]
365. Dos Santos, M.S.; Oliveira, M.L.; Bernardino, A.M.; de Léo, R.M.; Amaral, V.F.; de Carvalho, F.T.; Leon, L.L.; Canto-Cavalheiro, M.M. Synthesis and antileishmanial evaluation of 1-aryl-4-(4,5-dihydro-1*H*-imidazol-2-yl)-1*H*-pyrazole derivatives. *Bioorg. Med. Chem. Lett.* **2011**, *21*, 7451–7454. [CrossRef] [PubMed]
366. Jacomini, A.P.; Silva, M.J.V.; Silva, R.G.M.; Gonçalves, D.S.; Volpato, H.; Basso, E.A.; Paula, F.R.; Nakamura, C.V.; Sarragiotto, M.H.; Rosa, F.A. Synthesis and evaluation against Leishmania amazonensis of novel pyrazolo[3,4-*d*]pyridazinone-*N*-acylhydrazone-(bi)thiophene hybrids. *Eur. J. Med. Chem.* **2016**, *124*, 340–349. [CrossRef] [PubMed]

367. Bekhit, A.A.; Hassan, A.M.M.; Abd El Razik, H.A.; El-Miligy, M.M.M.; El-Agroudy, E.J.; Bekhit, A.E.-D.A. New heterocyclic hybrids of pyrazole and its bioisosteres: Design, synthesis and biological evaluation as dual acting antimalarial-antileishmanial agents. *Eur. J. Med. Chem.* **2015**, *94*, 30–44. [CrossRef] [PubMed]
368. Mowbray, C.E.; Braillard, S.; Speed, W.; Glossop, P.A.; Whitlock, G.A.; Gibson, K.R.; Mills, J.E.J.; Brown, A.D.; Gardner, J.M.F.; Cao, Y.; et al. Novel Amino-pyrazole Ureas with Potent In Vitro and In Vivo Antileishmanial Activity. *J. Med. Chem.* **2015**, *58*, 9615–9624. [CrossRef] [PubMed]
369. Marra, R.; Bernardino, A.; Proux, T.; Charret, K.; Lira, M.-L.; Castro, H.; Souza, A.; Oliveira, C.; Borges, J.; Rodrigues, C.; et al. 4-(1*H*-Pyrazol-1-yl)Benzenesulfonamide Derivatives: Identifying New Active Antileishmanial Structures for Use against a Neglected Disease. *Molecules* **2012**, *17*, 12961–12973. [CrossRef] [PubMed]
370. Bekhit, A.A.; Haimanot, T.; Hymete, A. Evaluation of some 1*H*-pyrazole derivatives as a dual acting antimalarial and anti-leishmanial agents. *Pak. J. Pharm. Sci.* **2014**, *27*, 1767–1773. [PubMed]
371. Figarella, K.; Marsiccobetre, S.; Galindo-Castro, I.; Urdaneta, N.; Herrera, J.; Canudas, N.; Galarraga, E. Antileishmanial and antitrypanosomal activity of synthesized hydrazones, pyrazoles, pyrazolo [1,5-*a*]-pyrimidines and pyrazolo[3,4-*b*]-pyridine. *Curr. Bioact. Compd.* **2017**, *13*. [CrossRef]
372. Tuha, A.; Bekhit, A.A.; Seid, Y. Screening of some pyrazole derivatives as promising antileishmanial agent. *Afr. J. Pharm. Pharmacol.* **2017**, *11*, 32–37. [CrossRef]
373. Reviriego, F.; Olmo, F.; Navarro, P.; Marín, C.; Ramírez-Macías, I.; García-España, E.; Albelda, M.T.; Gutiérrez-Sánchez, R.; Sánchez-Moreno, M.; Arán, V.J. Simple dialkyl pyrazole-3,5-dicarboxylates show in vitro and in vivo activity against disease-causing trypanosomatids. *Parasitology* **2017**, *144*, 1133–1143. [CrossRef] [PubMed]
374. Domínguez, J.N.; Charris, J.E.; Caparelli, M.; Riggione, F. Synthesis and antimalarial activity of substituted pyrazole derivatives. *Arzneimittel-Forschung* **2002**, *52*, 482–488. [CrossRef] [PubMed]
375. Mishra, S.; Karmodiya, K.; Surolia, N.; Surolia, A. Synthesis and exploration of novel curcumin analogues as anti-malarial agents. *Bioorg. Med. Chem.* **2008**, *16*, 2894–2902. [CrossRef] [PubMed]
376. González Cabrera, D.; Douelle, F.; Feng, T.-S.; Nchinda, A.T.; Younis, Y.; White, K.L.; Wu, Q.; Ryan, E.; Burrows, J.N.; Waterson, D. Novel orally active antimalarial thiazoles. *J. Med. Chem.* **2011**, *54*, 7713–7719. [CrossRef] [PubMed]
377. Quirante, J.; Ruiz, D.; Gonzalez, A.; López, C.; Cascante, M.; Cortés, R.; Messeguer, R.; Calvis, C.; Baldomà, L.; Pascual, A. Platinum (II) and palladium (II) complexes with (*N*,*N*′) and (*C*,*N*,*N*′)–ligands derived from pyrazole as anticancer and antimalarial agents: Synthesis, characterization and in vitro activities. *J. Inorg. Biochem.* **2011**, *105*, 1720–1728. [CrossRef] [PubMed]
378. Large, J.M.; Osborne, S.A.; Smiljanic-Hurley, E.; Ansell, K.H.; Jones, H.M.; Taylor, D.L.; Clough, B.; Green, J.L.; Holder, A.A. Imidazopyridazines as potent inhibitors of Plasmodium falciparum calcium-dependent protein kinase 1 (PfCDPK1): Preparation and evaluation of pyrazole linked analogues. *Bioorg. Med. Chem. Lett.* **2013**, *23*, 6019–6024. [CrossRef] [PubMed]
379. Balaji, S.N.; Ahsan, M.J.; Jadav, S.S.; Trivedi, V. Molecular modelling, synthesis, and antimalarial potentials of curcumin analogues containing heterocyclic ring. *Arab. J. Chem.* **2015**. [CrossRef]
380. Niswender, C.M.; Lebois, E.P.; Luo, Q.; Kim, K.; Muchalski, H.; Yin, H.; Conn, P.J.; Lindsley, C.W. Positive allosteric modulators of the metabotropic glutamate receptor subtype 4 (mGluR4): Part I. Discovery of pyrazolo[3,4-*d*]pyrimidines as novel mGluR4 positive allosteric modulators. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 5626–5630. [CrossRef] [PubMed]
381. Chimenti, F.; Carradori, S.; Secci, D.; Bolasco, A.; Bizzarri, B.; Chimenti, P.; Granese, A.; Yanez, M.; Orallo, F. Synthesis and inhibitory activity against human monoamine oxidase of *N*1-thiocarbamoyl-3,5-di(hetero)aryl-4,5-dihydro-(1*H*)-pyrazole derivatives. *Eur. J. Med. Chem.* **2010**, *45*, 800–804. [CrossRef] [PubMed]
382. Maher, P.; Akaishi, T.; Schubert, D.; Abe, K. A pyrazole derivative of curcumin enhances memory. *Neurobiol. Aging* **2010**, *31*, 706–709. [CrossRef] [PubMed]
383. Chan, B.K.; Estrada, A.A.; Chen, H.; Atherall, J.; Baker-Glenn, C.; Beresford, A.; Burdick, D.J.; Chambers, M.; Dominguez, S.L.; Drummond, J. Discovery of a highly selective, brain-penetrant aminopyrazole LRRK2 inhibitor. *ACS Med. Chem. Lett.* **2012**, *4*, 85–90. [CrossRef] [PubMed]

384. Jimenez, H.N.; Liu, K.G.; Hong, S.-P.; Reitman, M.S.; Uberti, M.A.; Bacolod, M.D.; Cajina, M.; Nattini, M.; Sabio, M.; Doller, D. 4-(1-Phenyl-1*H*-pyrazol-4-yl) quinolines as novel, selective and brain penetrant metabotropic glutamate receptor 4 positive allosteric modulators. *Bioorg. Med. Chem. Lett.* **2012**, *22*, 3235–3239. [CrossRef] [PubMed]
385. Dore, A.; Asproni, B.; Scampuddu, A.; Pinna, G.A.; Christoffersen, C.T.; Langgård, M.; Kehler, J. Synthesis and SAR study of novel tricyclic pyrazoles as potent phosphodiesterase 10A inhibitors. *Eur. J. Med. Chem.* **2014**, *84*, 181–193. [CrossRef] [PubMed]
386. Estrada, A.A.; Chan, B.K.; Baker-Glenn, C.; Beresford, A.; Burdick, D.J.; Chambers, M.; Chen, H.; Dominguez, S.L.; Dotson, J.; Drummond, J. Discovery of highly potent, selective, and brain-penetrant aminopyrazole leucine-rich repeat kinase 2 (LRRK2) small molecule inhibitors. *J. Med. Chem.* **2014**, *57*, 921–936. [CrossRef] [PubMed]
387. Fujinaga, M.; Yamasaki, T.; Nengaki, N.; Ogawa, M.; Kumata, K.; Shimoda, Y.; Yui, J.; Xie, L.; Zhang, Y.; Kawamura, K.; et al. Radiosynthesis and evaluation of 5-methyl-*N*-(4-[11C]methylpyrimidin-2-yl)-4-(1*H*-pyrazol-4-yl)thiazol-2-amine ([11C]ADX88178) as a novel radioligand for imaging of metabotropic glutamate receptor subtype 4 (mGluR4). *Bioorg. Med. Chem. Lett.* **2016**, *26*, 370–374. [CrossRef] [PubMed]
388. Kim, M.; Sim, C.; Shin, D.; Suh, E.; Cho, K. Residual and sublethal effects of fenpyroximate and pyridaben on the instantaneous rate of increase of Tetranychus urticae. *Crop Prot.* **2006**, *25*, 542–548. [CrossRef]
389. Selby, T.P.; Lahm, G.P.; Stevenson, T.M.; Hughes, K.A.; Cordova, D.; Annan, I.B. Discovery of cyantraniliprole, a potent and selective anthranilic diamide ryanodine receptor activator with cross-spectrum insecticidal activity. *Bioorg. Med. Chem. Lett.* **2013**, *23*, 6341–6345. [CrossRef] [PubMed]
390. Yu, H.; Xu, M.; Cheng, Y.; Wu, H.; Luo, Y.; Li, B. Synthesis and acaricidal activity of cyenopyrafen and its geometric isomer. *Arkivoc* **2012**, *6*, 26–34. [CrossRef]
391. Marcic, D. Sublethal effects of tebufenpyrad on the eggs and immatures of two-spotted spider mite, Tetranychus urticae. *Exp. Appl. Acarol.* **2005**, *36*, 177–185. [CrossRef] [PubMed]
392. Nonaka, N. Tolfenpyrad—A New Insecticide with Wide Spectrum and Unique Action. *Agrochem. Jpn.* **2003**, *83*, 17–19.
393. Finkelstein, B.L.; Strock, C.J. Synthesis and Insecticidal Activity of Novel Pyrazole Methanesulfonates. *Pest. Sci.* **1997**, *50*, 324–328. [CrossRef]
394. Mao, M.; Li, Y.; Liu, Q.; Zhou, Y.; Zhang, X.; Xiong, L. Synthesis and insecticidal evaluation of novel *N*-pyridylpyrazolecarboxamides containing cyano substituent in the ortho-position. *Bioorg. Med. Chem. Lett.* **2013**, *23*, 42–46. [CrossRef] [PubMed]
395. Wu, J.; Song, B.A.; Hu, D.Y.; Yue, M.; Yang, S. Design, synthesis and insecticidal activities of novel pyrazole amides containing hydrazone substructures. *Pest. Manag. Sci.* **2012**, *68*, 801–810. [CrossRef] [PubMed]
396. Dai, H.; Xiao, Y.-S.; Li, Z.; Xu, X.-Y.; Qian, X.-H. The thiazoylmethoxy modification on pyrazole oximes: Synthesis and insecticidal biological evaluation beyond acaricidal activity. *Chin. Chem. Lett.* **2014**, *25*, 1014–1016. [CrossRef]
397. Song, H.; Liu, Y.; Xiong, L.; Li, Y.; Yang, N.; Wang, Q. Design, synthesis, and insecticidal activity of novel pyrazole derivatives containing α-hydroxymethyl-*N*-benzyl carboxamide, α-chloromethyl-*N*-benzyl carboxamide, and 4,5-dihydrooxazole moieties. *J. Agric. Food. Chem.* **2012**, *60*, 1470–1479. [CrossRef] [PubMed]
398. Fu, C.; Pei, J.; Ning, Y.; Liu, M.; Shan, P.; Liu, J. Synthesis and insecticidal activities of novel pyrazole oxime ether derivatives with different substituted pyridyl rings. *Pest. Manag. Sci.* **2014**, *70*, 1207–1214. [CrossRef] [PubMed]
399. Ma, H.-J.; Li, Y.-H.; Zhao, Q.-F.; Zhang, T.; Xie, R.-L.; Mei, X.-D. Synthesis and herbicidal activity of novel *N*-(2,2,2)-trifluoroethylpyrazole derivatives. *J. Agric. Food Chem.* **2010**, *58*, 4356–4360. [CrossRef] [PubMed]
400. Dai, H.; Chen, J.; Li, H.; Dai, B.; He, H.; Fang, Y. Synthesis and Bioactivities of Novel Pyrazole Oxime Derivatives Containing a 5-Trifluoromethylpyridyl Moiety. *Molecules* **2016**, *21*, 276. [CrossRef] [PubMed]
401. Li, M.; Liu, C.-L.; Yang, J.-C.; Zhang, J.-B.; Li, Z.-N.; Zhang, H. Synthesis and biological activity of new (*E*)-α-(methoxyimino)benzeneacetate derivatives containing a substituted pyrazole ring. *J. Agric. Food Chem.* **2009**, *58*, 2664–2667. [CrossRef] [PubMed]
402. Fustero, S.; Román, R.; Sanz-Cervera, J.F.; Simón-Fuentes, A.; Bueno, J.; Villanova, S. Synthesis of new fluorinated tebufenpyrad analogs with acaricidal activity through regioselective pyrazole formation. *J. Org. Chem.* **2008**, *73*, 8545–8552. [CrossRef] [PubMed]

403. Vicentini, C.B.; Mares, D.; Tartari, A.; Manfrini, M.; Forlani, G. Synthesis of pyrazole derivatives and their evaluation as photosynthetic electron transport inhibitors. *J. Agric. Food Chem.* **2004**, *52*, 1898–1906. [CrossRef] [PubMed]
404. Zhao, Q.; Li, Y.; Xiong, L.; Wang, Q. Design, synthesis and insecticidal activity of novel phenylpyrazoles containing a 2,2,2-trichloro-1-alkoxyethyl moiety. *J. Agric. Food Chem.* **2010**, *58*, 4992–4998. [CrossRef] [PubMed]