

February 7, 2019

To,  
The Controller of Patents,  
Patent Office,  
Mumbai

Re: Opposition under Section 25(1) against Patent Application No. **1220/MUMNP/2009** dated **29.06.2009**, titled "*Fumarate salt of (alpha s, beta r)-6-bromo-alpha-[2-(dimethylamino)-ethyl]-2-methoxy-alpha-1-naphthalenyl-beta-phenyl-3-quinolineethanol*", filed by Janssen Pharmaceutica N.V.

Opponent: Nandita Venkatesan and Phumeza Tisile

In reference to the above mentioned patent application number, we herein submit the following:

1. Representation of pre-grant opposition on Form 7-A as prescribed under Section 25(1) of the Patents Act and Rule 55 of the Patents Rule, 2003
2. Exhibits: Exhibit A, Exhibit B, Exhibit C, Exhibit D, Exhibit E, Exhibit F, Exhibit G
3. Form-26

You are kindly requested to take this opposition on record, and grant a hearing in due course.

Yours sincerely,

Priyam Lizmary Cherian  
Agent for the Opponent  
A-13, First Floor, Nizamuddin West,  
Delhi 110013  
priyamlizcherian@gmail.com  
Phone: 011-46805555

**BEFORE THE CONTROLLER OF PATENTS,  
THE PATENT OFFICE, MUMBAI  
THE PATENTS ACT, 1970 AND THE PATENTS RULES, 2003**

IN THE MATTER OF A PRE- GRANT  
OPPOSITION UNDER SECTION 25 (1) AND  
RULE 55 OF THE PATENTS ACT, 1970

And

IN THE MATTER OF PATENT APPLICATION  
NO. **1220/MUMNP/2009** DATED **29.06.2009**  
TITLED **FUMARATE SALT OF (ALPHA S,  
BETA R)-6-BROMO-ALPHA-[2-  
(DIMETHYLAMINO)-ETHYL]-2-METHOXY-  
ALPHA-1-NAPHTHALENYL-BETA-PHENYL-  
3-QUINOLINEETHANOL** in the name of  
**JANSSEN PHARMACEUTICA N.V.,**  
OF TURHOUTSEWEG 30, 2340 BEERSE,  
BELGIUM

.....APPLICANT

And

IN THE MATTER OF REPRESENTATION BY  
WAY OF NOTICE OF  
OPPOSITION UNDER SECTION 25(1) OF  
PATENTS ACT, 1970 FILED BY NANDITA  
VENKATESAN AND PHUMEZA TISILE

.....OPPONENT

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For the Opponent  
Priyam Lizmary Cherian  
Counsel for the Opponent  
A-13, First Floor,  
Nizamuddin West, Delhi 110013

February 7, 2019

**FORM 7A**  
**THE PATENTS ACT, 1970 & THE PATENT RULES, 2003**  
**NOTICE OF OPPOSITION**  
**Section 25(1) and rule 55**

We, Nandita Venkatesan and Phumeza Tisile hereby give representation by way of opposition to the grant of patent in respect of Indian Patent Application numbered **1220/MUMNP/2009** titled **FUMARATE SALT OF (ALPHA S, BETA R)-6-BROMO-ALPHA-[2-(DIMETHYLAMINO)-ETHYL]-2-METHOXY-ALPHA-1-NAPHTHALENYL-BETA-PHENYL-3-QUINOLINEETHANOL** dated **29.06.2009** and published on **14.08.2009** in the name of **JANSSEN PHARMACEUTICA N.V.**, a Belgian company of Turhoutseweg 30, 2340 Beerse, BELGIUM, on the following grounds:

1. That the invention claimed in any and all claims of the complete specification was published before the priority date of the claim in India or elsewhere in any other document – Section 25(1)(b);
2. That the invention claimed in any and all claims of the complete specification is obvious and clearly does not involve any inventive step – Section 25(1)(e);
3. That the subject of any and all claims of the complete specification is not an invention within the meaning of this Act, or is not patentable under this Act – Section 25(1)(f).
4. That the complete specification does not sufficiently and clearly describe the invention or the method by which it is to be performed- Section 25(1)(g)
5. That the Applicant did not disclose information required by Section 8– Section 25(1)(h).

Our address for service in India is:

Priyam Lizmary Cherian  
A-13, First Floor,  
Nizamuddin West,  
Delhi 110013

We request that all communications be addressed to us at the above mentioned address.

Dated this 7<sup>th</sup> day of February 2019  
Opponent

**To**  
**The Controller,**  
**The Patent Office Branch**  
**MUMBAI**

**BEFORE THE CONTROLLER OF PATENTS,  
THE PATENT OFFICE, MUMBAI  
THE PATENTS ACT, 1970 AND THE PATENTS RULES, 2003**

IN THE MATTER OF A PRE- GRANT  
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BETA R)-6-BROMO-ALPHA-[2-  
(DIMETHYLAMINO)-ETHYL]-2-  
METHOXY-ALPHA-1-NAPHTHALENYL-  
BETA-PHENYL-3-QUINOLINEETHANOL**  
in the name of **JANSSEN PHARMACEUTICA  
N.V., OF TURHOUTSEWEG 30, 2340  
BEERSE, BELGIUM**

.....APPLICANT

And

IN THE MATTER OF REPRESENTATION BY  
WAY OF NOTICE OF  
OPPOSITION UNDER SECTION 25(1) OF  
PATENTS ACT, 1970 FILED BY **NANDITA  
VENKATESAN AND PHUMEZA TISILE**

.....OPPONENT

**REPRESENTATION BY WAY OF OPPOSITION U/S 25(1)**

1. A pre-grant opposition under Section 25(1) of the Patents Act, 1970, is being submitted by Opponent, Nandita Venkatesan and Phumeza Tisile

(hereinafter collectively referred as “Opponent”) against Indian Patent Application No. **1220/MUMNP/2009** (hereinafter referred to as the “Present Application”) in the name of Janssen Pharmaceutica N.V. (hereinafter referred to as the “Applicant”).

## **BACKGROUND AND LOCUS STANDI**

2. The Opponent Nandita Venkatesan and Phumeza Tisile are survivors of Tuberculosis (TB).
3. Opponent Nandita Venkatesan had to fight two bouts of intestinal TB with the first one diagnosed in 2007 when she was an undergraduate student. After a 14-month treatment the first time she was affected by TB, in 2013 she suffered a relapse. She underwent at least five surgeries during the course of her treatment, in addition to multiple medicines including painful injections. She lost her hearing as a result of injectable TB drugs.
4. The Opponent Phumeza Tisile is an extreme drug-resistant TB (XDR-TB) survivor. She was diagnosed with TB in 2010 which forced her to drop her studies. She was diagnosed with TB, then multi-drug-resistant TB (MDR-TB), and thereafter with XDR-TB. In 2013, the XDR-TB treatment left her bereft of hearing.
5. Both the Opponent after their TB related treatment underwent cochlear implant surgery to facilitate hearing.
6. The Opponent herein have the lived experience of overcoming the obstacles faced when diagnosed with TB and accessing new oral medicines that are safer than injectable drugs. The Opponent believe that every individual should get treatment and no one should suffer ailment, debility or die due to lack of medicines. One of the main concerns of the Opponent is the impact of product patent protection on access to effective and affordable life-saving medicines for people not just in India but across the developing world.
7. Section 25(1) of the Patents Act provides that *any person* may make a pre-grant representation against grant of patent to an application. The Opponent herein therefore have the *locus standi* to make the instant representation.

## **GENERAL BACKGROUND ON TUBERCULOSIS AND MULTI-DRUG RESISTANT TUBERCULOSIS TREATMENT**

8. Tuberculosis (TB) epidemic, poses one of the greatest challenges to global public health today. In 2017, India had about 2.74 million cases of TB (Global Tuberculosis Report, WHO 2018). In the same year, India had 27% of the global TB cases.
9. TB is the leading killer of People Living with HIV (PLHIV) with one-third of HIV related deaths occurring due to TB co-infection in 2015. The risk of developing TB is estimated to be between 26 and 31 times greater in PLHIV than among those without HIV infection. TB and HIV co-infection leads to synergy of the disease with rapid progression of TB and re-activation of latent TB risk being 12 and 20 times greater in PLHIV. Similarly, TB also accelerates the disease progression of HIV.
10. Globally in 2014, there were an estimated 3.3% of new cases and 20% of previously treated cases with multidrug-resistant TB (MDR-TB). Cases of Extremely drug resistant TB (XDR-TB) and Totally drug resistant TB (TDR-TB) have also been reported to be on the rise in India.
11. Almost after 50 years a new antibiotic viz. Bedaquiline has been introduced for treatment of DR-TB. This drug is particularly critical for children with DR-TB, extensively and pre-extensively drug resistant (XDR/pre-XDR) TB patients and those with drug intolerance and people living with HIV co-infected with DR-TB. Recognizing the pressing need to reduce treatment failures, subsequent to registration of Bedaquiline by US-FDA based on limited phase II data, the World Health Organization (WHO) in 2013 included Bedaquiline as an add-on agent in its multidrug-resistant tuberculosis (MDR-TB) treatment guidelines.
12. According to the updated WHO guidance, Bedaquiline-based treatments are now recommended for a larger number of people. In August 2018, the World Health Organization (WHO) announced an update to its treatment guidelines for multidrug- and rifampicin-resistant TB (MDR/RR-TB) to

include the use of Bedaquiline as a core drug in standard treatment regimens for MDR-TB, highlighting “the immediate steps to be taken to ensure that MDR/RR-TB patients receive treatment in accordance with the latest evidence on effectiveness and safety.” The guidelines now include Bedaquiline as a highest-ranked option (Group A) and recommend limiting the use of injectable aminoglycosides (included in Group C, the least preferred option).

13. Although there is a gradual decrease in tuberculosis cases worldwide, nearly half a million people acquire Drug Resistant Tuberculosis (DR-TB) each year. Drug resistance, which results from inadequate, incomplete or poor treatment quality, is emerging as a significant public health crisis. Two-thirds of the DR-TB affected people reside in low and middle income countries like India.
14. India, with approximately 147,000 people suffering from MDR-TB, is one of the countries with highest DR-TB burden. Subsequent to WHO’s guidelines in 2013, India issued conditional approval to Bedaquiline in 2014, permitting use of Bedaquiline under the Revised National TB Control Program (RNTCP) framework. In 2018, Indian Ministry of Health released the “*Report of the First National Anti-Tuberculosis Drug Resistance Survey*” which indicated almost 22% resistance to fluoroquinolones in India. Resistance to Fluoroquinolones (FQ) could mean development of XDR-TB. Therefore, there is an increasing need ensure better availability of drugs like Bedaquiline, a composition of which has been claimed in the Present Application.
15. The Present Application relates to a composition comprising *inter alia*, fumarate salt of Bedaquiline. Bedaquiline is a diarylquinoline anti-mycobacterial drug indicated as part of combination therapy in the treatment of adults ( $\geq 18$  years) with pulmonary MDR TB. The chemical name of Bedaquiline fumarate is (1R, 2S)-1-(6-bromo-2-methoxy-3-quinolinyl)-4-(dimethylamino)-2-(1-naphthalenyl)-1-phenyl-2-butanol compound with fumaric acid. Within the Biopharmaceutics Classification System (BCS),



Bedaquiline is classified as a Class 2 compound (expressing low solubility and high permeability).

#### **ACCESS TO MEDICINES AND STRICT INTERPRETATION OF INDIAN PATENTABILITY STANDARDS**

16. Patent rights, particularly in case of pharmaceutical products are often granted for minor and inconsequential changes to known substances, thereby extending the patentee's monopoly. This practice does not align with the balancing of the rights of the patentee with that of the public at large. More significantly, in the face of an epidemic such as TB, such extended monopolies may hinder the accessibility of critical drugs.
17. Cognisant of public health concerns and the Doha Declaration on the TRIPS Agreement and Public Health (2001), Parliament amended the Patents Act, 1970, and *inter alia* included a provision that would ensure that patents are granted only for genuine inventions and "evergreening" of patents is prevented.
18. It is submitted that the Hon'ble Patent Controller, may scrutinise the Present Application with strict scrutiny as its decision will affect the availability of affordable access to lifesaving treatment to MDR-TB not only in India but across the world.

#### **PRESENT APPLICATION**

19. The Present Application bearing application no. 1220/MUMNP/2009 titled "*Fumarate salt of (Alpha S, Beta R)-6-Bromo-Alpha-[2-(Dimethylamino)Ethyl]-2-Methoxy-Alpha-1-Naphthalenyl-Beta-Phenyl-3-Quinolineethanol*", was filed by Janssen Pharmaceutica N.V. (hereinafter "the Applicant") in India on 29.06.2009 with 21 claims. The Present Application derives priority from European Application 06125443.9. The Present Application therefore claims a priority date of 05.12.2006. The application was filed under the PCT convention on 03.10.2007 and was published on 12.06.2008 with publication number WO 2008/068231.

20. The Present Application was published on 14.08.2009 and the First Examination Report (FER) was issued on 12.03.2012. The Applicant amended the claims twice. The claims were first amended on 23.12.2009 and the number of claims was increased to 22. Later, in response to the FER, the claims were again amended and brought down to 7. Presently there are 7 claims, with claim 1 as the independent claim and claims 2-7 dependent on claim 1.

#### **ALLEGED INVENTION**

21. The Present Application relates to a composition *inter alia* comprising *Fumarate salt of (Alpha S, Beta R)-6-Bromo-Alpha-[2-(Dimethylamino)Ethyl]-2-Methoxy-Alpha-1-Naphthalenyl-Beta-Phenyl-3-Quinolineethanol*, used in treatment of mycobacterial infections such as that of mycobacterium tuberculosis.
22. The Applicant has admitted the following in the complete specification of the Present Application:
- 6-bromo- $\alpha$ -[2-(dimethylamino)ethyl]-2-methoxy- $\alpha$ -1-naphthalenyl- $\beta$ -phenyl-3-quinolineethanol and stereoisomeric forms thereof were disclosed in WO2004/011436 as useful agents to treat mycobacterial diseases, in particular tuberculosis (see complete specification at internal page 2, lines 15-19);
  - Enantiomer (alpha S, beta R)- 6-bromo- $\alpha$ -[2-(dimethylamino)ethyl]-2-methoxy- $\alpha$ -1-naphthalenyl- $\beta$ -phenyl-3-quinolineethanol corresponds to compound 12 (A1 enantiomer) of WO2004/011436 and is a preferred compound to treat mycobacterial diseases, in particular tuberculosis (see complete specification at internal page 2, lines 21-24);
  - The composition comprising salt of (alpha S, beta R)- 6-bromo- $\alpha$ -[2-(dimethylamino)ethyl]-2-methoxy- $\alpha$ -1-naphthalenyl- $\beta$ -phenyl-3-quinolineethanol, is non-hygroscopic with an acceptable bioavailability (see complete specification at internal page 2, lines 25-30).

### Claims of the Present Application

23. Claim 1 of the Present Application relates to a composition comprising The Present Application relates to a composition *inter alia* comprising *Fumarate salt of (Alpha S, Beta R)-6-Bromo-Alpha-[2-(Dimethylamino)Ethyl]-2-Methoxy-Alpha-1-Naphthalenyl-Beta-Phenyl-3-Quinolineethanol*, used in treatment of mycobacterial treatment, pharmaceutically acceptable carrier and a wetting agent.
24. Claim 2 of the claims a pharmaceutical composition of claim 1 suitable for oral administration.
25. Claim 3 of the Present Application claims a composition of claim 1 or claim 2, comprising active ingredient (5 to 50% of total weight), wetting agent (0.01% to 5% of total weight), diluent (40-92% of the total weight), and glidant (0.1-5% of the total weight).
26. Claim 4 of the Present Application claims a composition of claims 1-3 in the form of a tablet.
27. Claim 5 of the Present Application claims a composition of claim 4 with  
5 to 50% of active ingredient;  
0.01% to 5% of a wetting agent;  
From 40 to 92% of a diluent;  
From 0 to 10% of a polymer;  
From 2 to 10% of a disintegrant;  
From 0.1 to 5% of a glidant;  
From 0.1 to 1.5% of a lubricant.
28. Claim 6 claims a composition of claims 4 or 5 with  
Active ingredient 120.89 mg (i.e. 100mg base equivalent)  
Lactose monohydrate (200 mesh) 152.91 mg  
Maize starch 66mg  
Hypermellose 2910 15mPa.s 8 mg  
Polysorbate 20 1 mg  
Microcrystalline cellulose 82.2 mg

Croscarmellose sodium 23mg

Colloidal silicon dioxide 1.4mg

Magnesium stearate 4.6mg

29. Claim 7 of the Present Application claims a film-coated composition of any one of claims 4-6.

#### **SUMMARY OF GROUNDS CONSIDERED FOR OPPOSITION**

30. The Opponent bring this opposition under the following grounds, each of which are without prejudice to one another:
- i. Claims 1-7 of the Present Application are not novel as the composition claimed has been published before the priority date. Therefore, the Opponent bring this Opposition under **Section 25(1)(b)(ii)**- that the invention as claimed in the complete specification has been published before the priority date of the claim in any other document;
  - ii. Claims 1-7 the Present Application lack inventive step, and therefore fail under Sections 2(1)(j) and 2(1)(ja) of the Patents Act. Therefore, the Opponent bring this opposition under **Section 25(1)(e)**-that the invention so far as claimed in any claim of the complete specification is obvious and clearly does not involve any inventive step, having regard to the matter published before the priority date in India or elsewhere in any document.
  - iii. Claims 1-7 of the Present Application do not satisfy the test of Section 3(d) of the Patents Act as the subject matter does not exhibit enhancement of the known efficacy of known substance. Therefore, the Opponent bring this opposition under **Section 25(1) (f)** -that the subject of any claim of the complete specification is not an invention within the meaning of this Act.
  - iv. Claims 1-7 of the Present Application do not satisfy the test of Section 3(e) of the Patents Act as the subject matter does not exhibit any synergistic effect. Therefore, the Opponent bring this opposition under **Section 25(1)**

- (f) -that the subject of any claim of the complete specification is not an invention within the meaning of this Act.
- v. The rationale of choosing composition of claims 1-7 of the Present Application has not been clearly described in the Present Application. Therefore, the Opponent bring this Opposition under **Section 25(1) (g)** - That the complete specification does not sufficiently and clearly describe the invention.
  - vi. That the Applicant did not disclose information required by Section 8. Therefore, the Opponent bring this Opposition under **Section 25(1)(h)**.

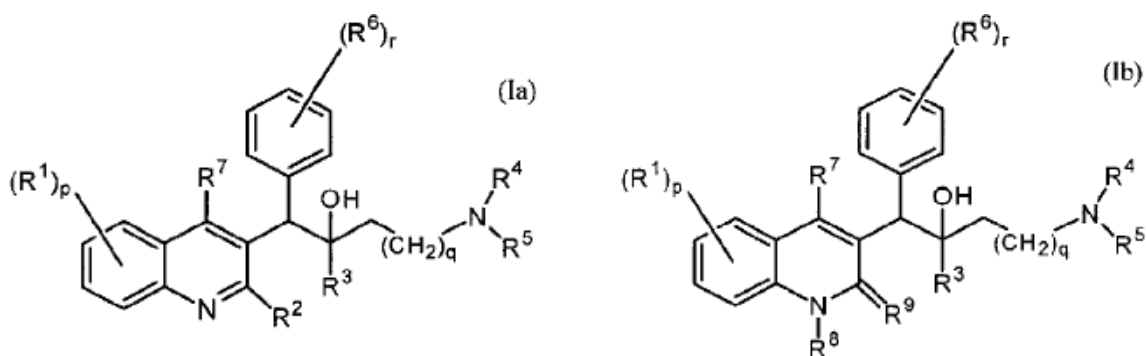
#### **DETAILED GROUNDS**

##### **I. CLAIMS 1 TO 7 ARE NOT NOVEL, AND THEREFORE HAVE TO BE REJECTED UNDER SECTION 25(1)(e) OF THE PATENTS ACT**

- 31. Section 2(1) (j) of the Patents Act defines an “invention” as “a new product or process involving an inventive step and capable of industrial application”. Section 25 (1)(b)(ii) of the Patents Act allows opposition of a patent if the alleged invention, as claimed in any claim of the complete specification has been published before the priority date of the claim in India or elsewhere, in any other document.
- 32. Therefore, claims of a patent application are to be rejected if a publication dated before the priority date of the application in question discloses the alleged invention. Disclosure of alleged invention by such a document may be determined by comparing the claims of the patent application in question to the disclosures in the prior art, read in light of the general knowledge available to a person skilled in the art.
- 33. It is the Opponent’s claim that document published before the date of priority of the Present Application discloses the compounds of claims 1-7. Therefore, claims 1-7 should be rejected for lack of novelty.

**WO 2004/011436**

34. The Opponent relies on PCT publication no. WO 2004/011436 (hereinafter “WO ’436”), published on February 5, 2004 viz. much before the priority date of the Present Application viz. 05.12.2006. WO ’436 may be relied on as a prior art document. WO ’436 is annexed herein as **Exhibit-A**.
35. WO ’436 is a patent publication titled “*Quinoline derivatives and their use as mycobacterial inhibitors*” and was filed on 18.07.2003 by the Applicant of the Present Application, viz. Janssen Pharmaceutica N.V.
36. WO ’436 states that it discloses an invention related to novel substituted quinoline derivatives according to formulae Ia and Ib (reproduced below) (see abstract of WO ’436 and internal page 3 of WO ’436)



37. In fact, the Applicant itself has admitted that Enantiomer (alpha S, beta R)-6-bromo- $\alpha$ -[2-(dimethylamino)ethyl]-2-methoxy- $\alpha$ -1-naphthalenyl- $\beta$ -phenyl-3-quinolineethanol corresponds to compound 12 (A1 enantiomer) in WO2004/011436 and is a preferred compound to treat mycobacterial diseases, in particular tuberculosis (see internal page 2 of the complete specification of present application, lines 21-24);
38. Further, WO ’436 states that the invention includes “*pharmaceutically acceptable acid or base addition salts thereof, the stereochemically isomeric forms thereof, the tautomeric forms thereof and the N-oxide forms thereof*” of the above disclosed compounds. (See WO’436 at abstract at lines 1-3, and claim 1 at internal page 52)

39. WO'436 is stated to claim compounds that is particularly useful in the treatment of *Mycobacterium tuberculosis* (See WO'436 abstract at lines 3-4 and internal page 1 at lines 5-8)
40. WO'436 indicates that pharmaceutically acceptable salts could be obtained by treating the base form of the compounds (Ia or Ib) with appropriate inorganic acids or organic acids such as fumarate acid (see internal page 8, lines 30-38, and internal page 9 at lines 1-4).
41. WO'436 particularly discloses that the invention therein relates to a composition. It states, *"The invention also relates to a composition comprising a pharmaceutically acceptable carrier and, as active ingredient, a therapeutically effective amount of a compound according to the invention. The compounds according to the invention may be formulated into various pharmaceutical forms for administration purposes. As appropriate compositions there may be cited all compositions usually employed for systemically administering drugs. To prepare the pharmaceutical compositions of this invention, an effective amount of the particular compound, optionally in addition salt form, as the active ingredient is combined in intimate admixture with a pharmaceutically acceptable carrier, which carrier may take a wide variety of forms depending on the form of preparation desired for administration. These pharmaceutical compositions are desirable in unitary dosage form suitable, in particular, for administration orally or by parenteral injection. For example, in preparing the compositions in oral dosage form, any of the usual pharmaceutical media may be employed such as, for example, water, glycols, oils, alcohols and the like in the case of oral liquid preparations such as suspensions, syrups, elixirs, emulsions and solutions; or solid carriers such as starches, sugars, kaolin, diluents, lubricants, binders, disintegrating agents and the like in the case of powders, pills, capsules and tablets. Because of their ease in administration, tablets and capsules represent the most advantageous oral dosage unit forms in which case solid pharmaceutical carriers are obviously employed. For parenteral*

*compositions, the carrier will usually comprise sterile water, at least in large part, though other ingredients, for example, to aid solubility, may be included... Depending on the mode of administration, the pharmaceutical composition will preferably comprise from 0.05 to 99 % by weight, more preferably from 0.1 to 70 % by weight of the active ingredient, and, from 1 to 99.95 % by weight, more preferably from 30 to 99.9 weight % of a pharmaceutically acceptable carrier, all percentages being based on the total composition. The pharmaceutical composition may additionally contain various other ingredients known in the art, for example, a lubricant, stabilising agent, buffering agent, emulsifying agent, viscosity-regulating agent, surfactant, preservative, flavouring or colorant.*” (emphasis supplied) (see internal page 12, lines 3-36, internal page 13, lines 1-4).

42. Therefore, as seen above, WO'436 discloses:
- pharmaceutical composition comprising compound Ia or Ia, including compound 12, viz. (alpha S, beta R)- 6-bromo- $\alpha$ -[2-(dimethylamino)ethyl]-2-methoxy- $\alpha$ -1-naphthalenyl- $\beta$ -phenyl-3-quinolineethanol;
  - Such composition could include additional salt form of compound 12, including a fumarate salt form;
  - Such composition includes the active ingredient (such as compound 12) combined with a pharmaceutically acceptable carrier;
  - Such composition may include additional ingredients including a surfactant, often used as a wetting agent;
  - The composition will preferably contain 0.1 to 70 % by weight of the active ingredient;
  - The composition will preferably contain 30 to 99.9 weight % of a pharmaceutically acceptable carrier.
43. WO'436 also teaches process for separating the racemic mixtures of enantiomers produced using the process described therein. It notes that, “*The racemic compounds of either Formula (Ia) and (Ib) may be converted*



into the corresponding diastereomeric salts forms by reaction with a suitable chiral acid.” (See WO’436, internal page 10, lines 23-28).

44. A tabular form of comparison between the disclosure in WO ’436 and the claims of the present application is indicated below:

| Claims of the Present Application   | Disclosure in WO ’436   |
|---|---|
| <p>Claim 1<br/>A solid pharmaceutical composition comprising a pharmaceutically acceptable carrier and as active ingredient a therapeutically effective amount of the fumarate salt of (alpha S, beta R)- 6-bromo-alpha-[2-(dimethylamino)ethyl]-2-methoxy-alpha-1-naphthalenyl-β-phenyl-3-quinolineethanol and further comprising a wetting agent, said wetting agent being a polyethylene glycol sorbitan fatty acid ester.</p> | <p>A composition comprising fumarate salt of (alpha S, beta R)-6-bromo-alpha-[2-(dimethylamino)ethyl]-2-methoxy-alpha-1-naphthalenyl-β-phenyl-3-quinolineethanol (also known as 1-(6-bromo-2-methoxy-quinolin-3-yl)-4-dimethylamino-2-naphthalen- 1 -yl- 1 - phenyl-butan-2-ol) and wetting agent is disclosed, as can be seen from the relevant portions of WO’436 disclosed below:</p> <p>Claim 6: “A compound according to claim 1, characterized in that the compound is :... <u>1-(6-bromo-2-methoxy-quinolin-3-yl)-4-dimethylamino-2-naphthalen- 1 -yl- 1 - phenyl-butan-2-ol...</u>” (See WO ’436, internal page 55)</p> <p>Claim 8: “A composition comprising a <u>pharmaceutically acceptable carrier</u> and, as active ingredient, a therapeutically</p> |

|  |  |
|--|--|
|  | <p><i>effective amount of a <u>compound as defined in any one of claims 1 to 7.</u></i>” (WO '436, internal page 56)</p> <p>“<i>Most preferable, the compound is :...<br/> <u>o 1-(6-bromo-2-methoxy-quinolin-3-yl)-4-dimethylamino-2-naphthalen-1-yl-1-phenylbutan-2-ol</u> ;... the pharmaceutically <u>acceptable acid or base addition salts</u> thereof, the stereochemically isomeric forms thereof, the tautomeric forms thereof and the N-oxide forms thereof.” (See WO '436, internal page 8, lines 13-14, 27-29)</i></p> <p>“<i>Some acid addition salts can be obtained by treating the base form of the compounds with...fumaric acid</i>” (See WO '436, internal page 8, lines 33-34, internal page 9, line 1)</p> <p>“<i>The invention also relates to a <u>composition comprising a pharmaceutically acceptable carrier</u> and, as active ingredient, a therapeutically effective amount of a <u>compound according to the</u></i></p> |
|--|--|

|   |   |
|---|---|
|   | <p><i>invention... For example, in preparing the compositions in oral dosage form, any of the <u>usual pharmaceutical media</u> may be employed such as, for example, water, glycol...” (See WO '436, see internal page 12, lines 3-23)</i></p> <p><i>“The pharmaceutical composition may additionally contain various other ingredients known in the art, for example, a lubricant, stabilising agent, buffering agent, emulsifying agent, viscosity-regulating agent, <u>surfactant, preservative, flavouring or colorant.</u>” (internal page 13, lines 1-4)</i></p> |
| <p>Claim 2</p> <p>A pharmaceutical composition according to claim 1 wherein the composition is suitable for oral admission.</p> | <p>WO'436 also discloses that the composition may also be used for oral admission as seen below.</p> <p><i>“These pharmaceutical compositions are desirable in unitary dosage form suitable, in particular, for administration orally or by parenteral injection.”</i> (See WO '436, internal page 12, lines 13-15)</p>   |
| <p>Claim 3</p> <p>A pharmaceutical composition</p>  | <p>WO'436 also discloses the range of the constituent ingredients by</p>  |

|  |  |
|--|--|
| <p>according to claim 1 or claim 2 comprising by weight based on the total weight of the composition:</p> <ul style="list-style-type: none"> <li>(a) From 5 to 50% of active ingredient;</li> <li>(b) From 0.01 to 5% of a wetting agent;</li> <li>(c) From 40 to 92% of a diluent;</li> <li>(d) From 0.1 to 5% of a glidant.</li> </ul> | <p>weight in the composition as disclosed below:</p> <p><i>“Depending on the mode of administration, the pharmaceutical composition will preferably comprise from 0.05 to 99% by weight, more preferably from 0.1 to 70% by weight of the active ingredient, and, from 1 to 99.95% by weight, more preferably from 30 to 99.9 weight % of a pharmaceutically acceptable carrier, all percentages being based on the total composition.”</i></p> <p>(See WO '436, internal page 12, lines 31-36)</p> <p><i>“The pharmaceutical composition may additionally contain various other ingredients known in the art, for example, a lubricant, stabilising agent, buffering agent, emulsifying agent, viscosity-regulating agent, surfactant, preservative, flavouring or colorant.”</i> (See WO'436, internal page 13, lines 1-4)</p> |
| <p>Claim 4</p> <p>A pharmaceutical composition according to any one of claims 1 to 3 wherein the composition is in the</p>   | <p>WO'436 also discloses that the composition may be in the form of a tablet, as has been shown below.</p> <p><i>“Examples of such unit dosage</i></p>   |

|   |  |
|---|--|
| <p>form of a tablet.</p>  | <p><i>forms are tablets (including scored or coated tablets), capsules, pills, powder packets, wafers, suppositories, injectable solutions or suspensions and the like, and segregated multiples thereof.” (See WO ’436 at internal page 13, lines 11-13)</i></p>  |
| <p>Claim 5</p> <p>A pharmaceutical composition according to claim 4 comprising by weight based on the total weight of the tablet core</p> <ul style="list-style-type: none"> <li>a) from 5 to 50% of active ingredient;</li> <li>b) from 0.01% to 5% of a wetting agent;</li> <li>c) from 40 to 92% of a diluent;</li> <li>d) from 0 to 10% of a polymer;</li> <li>e) from 2 to 10% of a disintegrant;</li> <li>f) from 0.1 to 5% of a glidant;</li> <li>g) from 0.1 to 1.5% of a lubricant.</li> </ul> | <p>WO’436 discloses the weight by percentage of the constituents of the composition, as disclosed below:</p> <p><i>“Depending on the mode of administration, the pharmaceutical composition will preferably comprise from 0.05 to 99% by weight, more preferably from 0.1 to 70% by weight of the active ingredient, and, from 1 to 99.95% by weight, more preferably from 30 to 99.9 weight % of a pharmaceutically acceptable carrier, all percentages being based on the total composition.”</i></p> <p>(See WO ’436, internal page 12, lines 31-36)</p> <p><i>“The pharmaceutical composition may additionally contain various other ingredients known in the art, for example, a lubricant,</i></p> |

|   |   |
|---|---|
|   | <p><i>stabilising agent, buffering agent, emulsifying agent, viscosity-regulating agent, surfactant, preservative, flavouring or colorant.”</i> (See WO’436, internal page 13, lines 1-4)</p>   |
| <p>Claim 7</p> <p>A pharmaceutical composition according to any one of claims 4-6 which is film-coated.</p> | <p>WO’436 not only discloses that the composition could be in tablet form but also discloses that such a tablet could be also coated. This can be seen in the portion reproduced below.</p> <p><i>“Examples of such unit dosage forms are tablets (including scored or <u>coated tablets</u>), capsules, pills, powder packets, wafers, suppositories, injectable solutions or suspensions and the like, and segregated multiples thereof.”</i> (See WO’436, internal page 13, lines 11-13)</p> |

45. Hence, WO’436 discloses-

- the fumarate salt of (alpha S, beta R)- 6-bromo-alpha-[2-(dimethylamino)ethyl]-2-methoxy-alpha-1-naphthalenyl-β-phenyl-3-quinolineethanol;
- a composition comprising the fumarate salt of (alpha S, beta R)- 6-bromo-alpha-[2-(dimethylamino)ethyl]-2-methoxy-alpha-1-naphthalenyl-β-phenyl-3-quinolineethanol and a pharmaceutical carrier;

- a composition of (alpha S, beta R)- 6-bromo-alpha-[2-(dimethylamino)ethyl]-2-methoxy-alpha-1-naphthalenyl-beta-phenyl-3-quinolineethanol and the pharmaceutical carrier by weight in tablet form;
- Composition as above mentioned with a wetting agent;
- Composition as above mentioned in a coated tablet form;
- Suitability of such composition for oral administration.

46. Therefore, it is submitted that WO'436 discloses all the elements of the claims 1-7 of the Present Application. Hence, Claims 1 to 7 of the Present Application should be rejected under Section 25(1) (b) (ii) of the Patents Act on grounds of anticipation by prior publication.

**II. CLAIMS 1-7 OF THE PRESENT APPLICATION ARE CHALLENGED UNDER SECTION 25(1)(e) OF THE PATENTS ACT, ON GROUND OF LACKING INVENTIVE STEP AS DEFINED UNDER SECTIONS 2(1)(ja) OF THE PATENTS ACT**

47. It is submitted that Section 2(1) (j), Patents Act defines an "invention" as "*a new product or process involving an inventive step and capable of industrial application*" (emphasis supplied). For an alleged invention to qualify for a patent, it must involve an inventive step. Section 2(1)(ja) of the Patents Act defines an inventive step as "*a feature of an invention that involves technical advance as compared to the existing knowledge ... and that makes the invention not obvious to a person skilled in the art*".

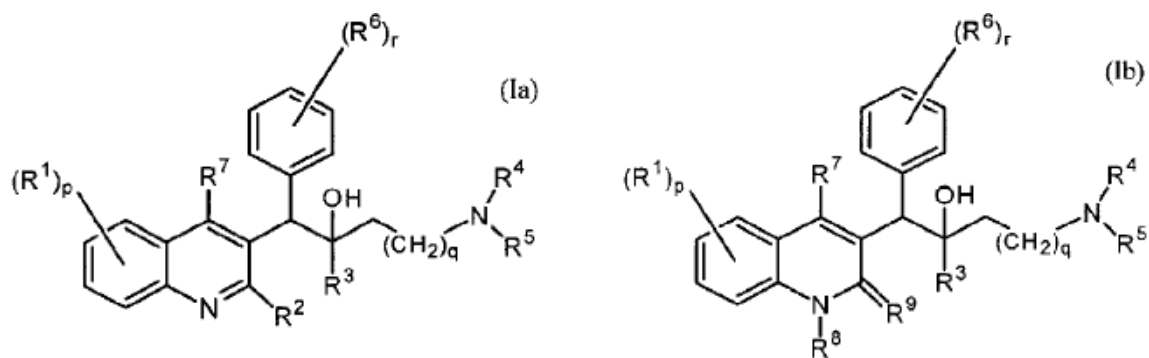
48. Section 25(1)(e) of the Patents Act provides that an application may be opposed if the alleged invention is obvious and does not involve an inventive step having regard to matter published in India or elsewhere in any document before the priority date of the alleged invention. Without prejudice to other grounds raised herein, the Opponent submits that claims 1-7 of the Present Application lack an inventive step and therefore should be rejected.

49. It is submitted that at the priority date of the Present Application, as will be explained below, the following were well known to persons skilled in the art:
- fumarate salt of (alpha S, beta R)- 6-bromo-alpha-[2-(dimethylamino)ethyl]-2-methoxy-alpha-1-naphthalenyl-beta-phenyl-3-quinolineethanol;
  - a composition of (alpha S, beta R)- 6-bromo-alpha-[2-(dimethylamino)ethyl]-2-methoxy-alpha-1-naphthalenyl-beta-phenyl-3-quinolineethanol and the pharmaceutical carrier in tablet form;
  - Composition of fumarate salt of (alpha S, beta R)- 6-bromo-alpha-[2-(dimethylamino)ethyl]-2-methoxy-alpha-1-naphthalenyl-beta-phenyl-3-quinolineethanol with constituents including lactose monohydrate, hypromellose, polysorbate 20, microcrystalline cellulose, colloidal silicon dioxide and magnesium stearate.

**Composition comprising Fumarate salt of (alpha S, beta R)- 6-bromo-alpha-[2-(dimethylamino)ethyl]-2-methoxy-alpha-1-naphthalenyl-beta-phenyl-3-quinolineethanol was known**

**WO 2004/011436**

50. The Opponent relies on WO'436 (Exhibit-A) again. It is submitted that WO'436 discloses the use of Formulae Ia and Ib as antimycobacterial agents and the method of using the same for treatment of mycobacterial infection, particularly, M. tuberculosis (See WO'436 at page 2, lines 20-24). The structures of Ia and Ib are reproduced below for easy reference:





51. Further, it is submitted that WO'456 discloses a composition comprising as an active ingredient, a therapeutically effective amount of a compound, which includes compounds of formula 1(a) or 1(b) and a pharmaceutical carrier. (See WO'436, internal page 12, lines 4-13).
52. It is submitted that WO '436 also discloses pharmaceutically acceptable acid or base addition salts of formulae Ia and Ib. (See WO'436 at abstract and claim 1 of WO'436 at internal page 52). Such acid salts include those obtained by treating compounds (Ia or Ib) with appropriate inorganic acids or organic acids such as fumaric acid (see internal page 8, lines 30-38, and internal page 9 at lines 1-4). In fact claim 6 of WO'436 claims, "*a compound according to claim 1, characterized in that the compound is...1-(6-bromo-2-methoxy-quinolin-3-yl)-4-dimethylamino-2-naphthalen-1-yl-1-phenyl-butan-2-ol...the pharmaceutically acceptable acid or base addition salts thereof, the stereochemically isomeric forms thereof, the tautomeric forms thereof and the N-oxide forms thereof.*" The stereoisomeric form of 1-(6-bromo-2-methoxy-quinolin-3-yl)-4-dimethylamino-2-naphthalen-1-yl-1-phenyl-butan-2-ol would include (alpha S, beta R)- 6-bromo- $\alpha$ -[2-(dimethylamino)ethyl]-2-methoxy- $\alpha$ -1-naphthalenyl- $\beta$ -phenyl-3-quinolineethanol, the active ingredient claimed the composition claimed in the Present Application.
53. Therefore, on the date of priority of the Present Application, fumarate salt of (alpha S, beta R)- 6-bromo- $\alpha$ -[2-(dimethylamino)ethyl]-2-methoxy- $\alpha$ -1-naphthalenyl- $\beta$ -phenyl-3-quinolineethanol was known.
54. It is submitted that the Applicant of the Present Application has admitted that enantiomer (alpha S, beta R)- 6-bromo- $\alpha$ -[2-(dimethylamino)ethyl]-2-methoxy- $\alpha$ -1-naphthalenyl- $\beta$ -phenyl-3-quinolineethanol corresponds to compound 12 (A1 enantiomer) in WO'436.
55. WO'436 also discloses a composition comprising a pharmaceutically acceptable carrier and therapeutically effective amount of compounds Ia or Ib. WO'436 indicates that the composition in unitary dosage form can be administered orally or by parenteral injection. WO'436 also indicates that

pharmaceutical media may be employed such as, for example, water, glycols, oils, alcohols could be used in preparation of oral liquid preparations, and that solid carriers such as starches, sugars, kaolin, diluents, lubricants, binders, disintegrating agents can be used for powders, pills, capsules and tablets (see WO'436, internal page 12, lines 3-30).

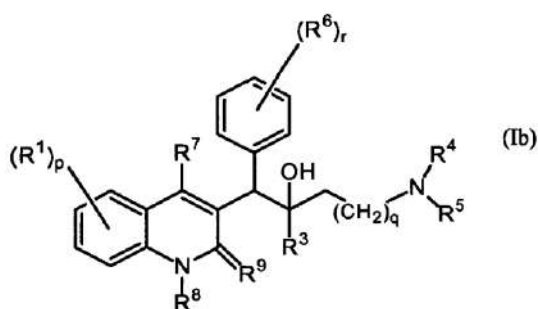
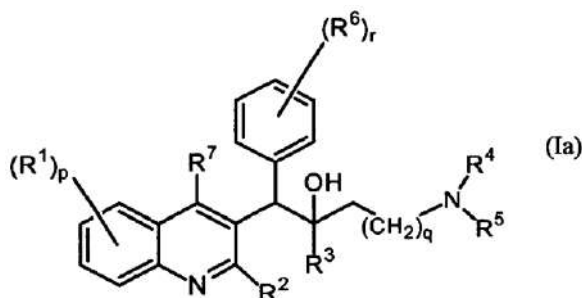
56. WO'436 also discloses the amount by weight of the components of the composition where it provides, *“Depending on the mode of administration, the pharmaceutical composition will preferably comprise from 0.05 to 99 % by weight, more preferably from 0.1 to 70 % by weight of the active ingredient, and, from 1 to 99.95 % by weight, more preferably from 30 to 99.9 weight % of a pharmaceutically acceptable carrier, all percentages being based on the total composition. The pharmaceutical composition may additionally contain various other ingredients known in the art, for example, a lubricant, stabilising agent, buffering agent, emulsifying agent, viscosity-regulating agent, surfactant, preservative, flavouring or colorant.”* (See WO'439 internal page 12, at lines 31-36 and page 13, lines 1-4). Further, this document also teaches a film coated tablet of the composition (See WO'436, internal page 13, lines 11-13).
57. Thus a person skilled in the art (POSITA) on reading WO'436 would be taught a composition comprising *inter alia* fumarate salt of (alpha S, beta R)- 6-bromo- $\alpha$ -[2-(dimethylamino)ethyl]-2-methoxy- $\alpha$ -1-naphthalenyl- $\beta$ -phenyl-3-quinolineethanol along with pharmaceutical media. The POSITA will also be taught the composition by weight of the pharmaceutically active ingredient and the pharmaceutically acceptable carrier. The POSITA would also be taught that other ingredients including a surfactant (wetting agent) could be used in such a composition.

#### **WO/2005/117875**

58. The Opponent relies on the publication WO/2005/117875 (hereinafter “WO '875” and annexed herewith as **Exhibit-B**) titled *“Use of substituted quinoline derivatives for the treatment of drug resistant mycobacterial*

diseases”, filed in the name of the Applicant of the Present Application. WO’875 was published on 15.12.2005 viz. much before the priority date of the Present Application viz. 05.12.2006. Thus WO ’875 may be relied on as a prior art document.

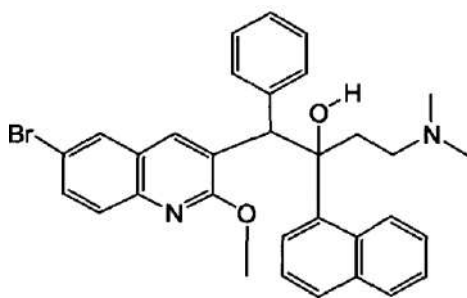
59. WO’875 relates to the use of a substituted quinoline derivative for preparing medicament for treating a drug resistant Mycobacterium strain. This is done so using a substituted quinoline derivative according to Formula (Ia) or Formula (Ib) the pharmaceutically acceptable acid or base addition salts thereof, the stereochemically isomeric forms thereof, the tautomeric forms thereof. WO’875 also discloses a composition comprising a pharmaceutically acceptable carrier, therapeutically effective amount of compounds (Ia) or (Ib) and one or more other antimycobacterial agents. (See WO’875 at abstract and internal page 3 at lines 15-20). The structures of compounds (Ia) and (Ib) are reproduced below for reference:



60. WO’875 discloses that, “An interesting group of compounds are the compounds according to Formula (Ia), the pharmaceutically acceptable acid or base addition salts thereof, the stereochemically 1-(6-bromo-2-methoxy-quinolyn-3-yl)-4-dimethylamino-2-naphthalen-1-yl-1-phenylbutan-2-ol corresponding to 6-bromo- $\alpha$ -[2-(dimethylamino)ethyl]-2-

*methoxy- $\alpha$ -1-naphthalenyl- $\beta$ -phenyl-3-quinolineethanol;* a  
*pharmaceutically acceptable acid or base addition salt thereof, a*  
*stereochemically isomeric form thereof, a tautomeric form thereof or a N-*  
*oxide form thereof.”* (See WO’875, internal page 13, line 36-37 and internal  
page 14, lines 1-5)

61. WO’875 further discloses that, “An alternative chemical name for *l*-(6-bromo-2-methoxy-quinolin-3-yl)-4-dimethylamino-2-naphthalen-1-yl-*l*-phenyl-butan-2-ol is 6-bromo- $\alpha$ -[2-(dimethylamino)ethyl]-2-methoxy- $\alpha$ -1-naphthalenyl- $\beta$ -phenyl-3-quinolineethanol. Said compound can also be represented as follows :



” (See WO’875, internal page 14, lines

6-14)

62. Further, it notes that most preferably the compound is, “...( $\alpha$ S,  $\beta$ R)-6-bromo- $\alpha$ -[2-(dimethylamino)ethyl]-2-methoxy- $\alpha$ -1-naphthalenyl- $\beta$ -phenyl-3-quinolineethanol, *i.e.* compound 12, or a pharmaceutically acceptable acid addition salt thereof...” (See WO’875 at internal page 14, lines 14, 24-26). ( $\alpha$ S,  $\beta$ R)-6-bromo- $\alpha$ -[2-(dimethylamino)ethyl]-2-methoxy- $\alpha$ -1-naphthalenyl- $\beta$ -phenyl-3-quinolineethanol has also been identified as the most preferable compound (See WO’875, internal page 15, lines 1-5). It also discloses that this compound is useful for the treatment of drug-resistant mycobacterium strain (See WO’875, internal page 18, lines 14-34, internal page 19, lines 1-2).
63. WO’875 also discloses that pharmaceutically acceptable acid addition salts of compounds (Ia) or (Ib) can be formed by treating their base forms with

appropriate acids, including fumaric acid. (See WO'875, internal page 15, lines 8-16).

64. WO'875 also teaches that the compounds of formula (1a) and (1b) may be synthesized in the form of racemic mixtures of enantiomers. It indicates that these mixtures can be separated based on known resolution procedures. Further, it indicates that, "*The racemic compounds of either Formula (1a) and (1b) may be converted into the corresponding diastereomeric salt forms by reaction with a suitable chiral acid. Said diastereomeric salt forms are subsequently separated, for example, by selective or fractional crystallization and the enantiomers are liberated therefrom by alkali. An alternative manner of separating the enantiomeric forms of the compounds of either Formula (1a) and (1b) involves liquid chromatography using a chiral stationary phase. Said pure stereochemically isomeric forms may also be derived from the corresponding pure stereochemically isomeric forms of the appropriate starting materials, provided that the reaction occurs stereospecifically. Preferably if a specific stereoisomer is desired, said compound will be synthesized by stereospecific methods of preparation.*" (See WO'875 at internal page 17, lines 9-21)
65. In fact, use of ( $\alpha$ S,  $\beta$ R)-6-bromo- $\alpha$ -[2-(dimethylamino)ethyl]-2-methoxy- $\alpha$ -1-naphthalenyl- $\beta$ -phenyl-3-quinolineethanol, i.e. compound 12, or a pharmaceutically acceptable acid addition salt in a composition with other antimycobacterial agents has been suggested (See WO'875, internal page 19, lines 19-35)
66. WO'875 also discloses that, "*These pharmaceutical compositions are desirable in unitary dosage form suitable, in particular, for administration orally or by parenteral injection. For example, in preparing the compositions in oral dosage form, any of the usual pharmaceutical media may be employed such as, for example, water, glycols, oils, alcohols and the like in the case of oral liquid preparations such as suspensions, syrups, elixirs, emulsions and solutions; or solid carriers such as starches, sugars, kaolin, diluents, lubricants, binders, disintegrating agents and the like in the*

*case of powders, pills, capsules and tablets. Because of their ease in administration, tablets and capsules represent the most advantageous oral unit dosage forms in which case solid pharmaceutical carriers are obviously employed.*” (See WO’875, internal page 21, lines 28-37). Further, such composition may also contain a lubricant, stabilising agent, buffering agent, emulsifying agent, viscosity-regulating agent, surfactant, preservative, flavouring or colorant (WO’875, internal page 22, lines 35-36 and internal page 23, lines 1-2).

67. That is, on reading WO’875, a POSITA would be taught about a composition comprising ( $\alpha$ S,  $\beta$ R)-6-bromo- $\alpha$ -[2-(dimethylamino)ethyl]-2-methoxy- $\alpha$ -1-naphthalenyl- $\beta$ -phenyl-3-quinolineethanol, a pharmaceutically acceptable carrier in a tablet form.
68. WO’875 also discloses identification of the stereoisomer and states, *“Of some compounds the absolute stereochemical configuration of the stereogenic carbon atom(s) therein was not experimentally determined. In those cases the stereochemically isomeric form which was first isolated is designated as "A" and the second as "B", without further reference to the actual stereochemical configuration. However, said "A" and "B" isomeric forms can be unambiguously characterized by a person skilled in the art, using art-known methods such as, for example, X-ray diffraction. In case "A" and "B" are stereoisomeric mixtures, they can be further separated whereby the respective first fractions isolated are designated "A1" and "B1" and the second as "A2" and "B2", without further reference to the actual stereochemical configuration.”* (See WO’875, internal page 23, lines 21-31).
69. Further, it discloses the boiling point of stereoisomer A1, ( $\alpha$ S,  $\beta$ R)-6-bromo- $\alpha$ -[2-(dimethylamino)ethyl]-2-methoxy- $\alpha$ -1-naphthalenyl- $\beta$ -phenyl-3-quinolineethanol viz. compound 12 (see internal page 25, entry 13).
70. WO’875 also discloses the minimum inhibitory concentration (MICs) of ( $\alpha$ S,  $\beta$ R)-6-bromo- $\alpha$ -[2-(dimethylamino)ethyl]-2-methoxy- $\alpha$ -1-naphthalenyl- $\beta$ -phenyl-3-quinolineethanol against different clinical isolates

of resistant Mycobacterium strains, as reproduced below (see internal pages 35-36):

Table 7 :

| Strains  | Rifampin | Compound 12 | Compound 109 | Compound 2 |
|--|----------|-------------|--------------|------------|
| <i>M.tuberculosis</i><br>isoniazid-resistant<br>low level  | 0.5      | 0.06        | 0.12         | 0.25       |
| <i>M.tuberculosis</i><br>isoniazid-resistant<br>high level | 0.5      | ≤ 0.01      | 0.03         | ≤ 0.01     |
| <i>M.tuberculosis</i><br>rifampin-resistant                | >256     | 0.06        | 0.12         | 0.06       |

Table 8:

| Strains   | Rifampin | Compound 12 |
|---|----------|-------------|
| <i>M.tuberculosis</i><br>isoniazid-resistant High<br>Level                                | 0.25     | 0.01        |
| <i>M.tuberculosis</i><br>isoniazid-resistant high<br>level                                | 0.5      | 0.06        |
| <i>M.tuberculosis</i><br>isoniazid-resistant high<br>level                                | 0.12     | 0.03        |
| <i>M.tuberculosis</i><br>isoniazid-resistant high<br>level                                | ≤ 0.06   | 0.01        |
| <i>M.tuberculosis</i><br>isoniazid-Resistant high<br>level and streptomycin-<br>resistant | 0.25     | 0.01        |
| <i>M. tuberculosis</i><br>rifampin-resistant  | 256      | 0.03        |
| <i>M.tuberculosis</i><br>rifampin-resistant   | 16       | 0.03        |
| <i>M.tuberculosis</i><br>rifampin-resistant   | 256      | 0.01        |
| <i>M.tuberculosis</i><br>streptomycin-resistant   | 0.5      | 0.01        |
| <i>M.tuberculosis</i><br>ethambutol-resistant   | 0.25     | 0.01        |
| <i>M.tuberculosis</i><br>pyrazinamide-resistant   | 0.5      | 0.03        |

71. Further, WO'875 discloses the minimum inhibitory concentration (MICs) of ( $\alpha$ S,  $\beta$ R)-6-bromo- $\alpha$ -[2-(dimethylamino)ethyl]-2-methoxy- $\alpha$ -1-naphthalenyl- $\beta$ -phenyl-3-quinolineethanol against different clinical isolates of Mycobacterium strains resistant to fluoroquinolones as indicated below (see internal page 37)

**Table 9 :**

| Strains               | Rifampin | Compound 12 | Ofloxacin              |
|-----------------------|----------|-------------|------------------------|
| <i>M.tuberculosis</i> | 1        | 0.06        | 8 (Ala83Val Ser84Pro)* |
| <i>M.tuberculosis</i> | 2        | 0.12        | 32 (Asp87Gly)*         |
| <i>M.avium</i>        | 16       | 0.007       | 128 (Ala83Val)*        |

\* The indications between parentheses indicate the mutations in the protein responsible for ofloxacin resistance

**Table 10 :**

| Strains            | Rifampin | Compound 12 | Ofloxacin                     |
|--------------------|----------|-------------|-------------------------------|
| <i>M.smegmatis</i> | 64       | 0.01        | 8 (Asp87Gly)*                 |
| <i>M.smegmatis</i> | 64       | 0.01        | 32 (Ala 83 Val and Asp87Gly)* |
| <i>M.smegmatis</i> | 64       | 0.01        | 32 (Ala83Val and Asp87Gly)*   |
| <i>M.smegmatis</i> | 128      | 0.007       | 2 (Ala83Val)*                 |
| <i>M.smegmatis</i> | ND       | 0.003       | 32 (Asp87Gly)*                |
| <i>M.fortuitum</i> | 128      | 0.01        | 1                             |
| <i>M.fortuitum</i> | 128      | 0.007       | 1 (Ser84Pro)*                 |
| <i>M.fortuitum</i> | >64      | 0.01        | 1.5 (Asp87Gly)*               |

\* The indications between parentheses indicate the mutations in the protein responsible for ofloxacin resistance.

72. Claim 13 of WO'875 claims, "Use according to claim 1, characterized in that that compound is selected from the group consisting of:..1-(6-bromo-2-



*methoxy-quinolin-3-yl)-4-dimethylamino-2-naphthalen-1-yl-1-phenyl-butan-2-ol...a pharmaceutical acceptable acid or base addition salt thereof, a stereochemically isomeric form thereof, a tautomeric form thereof or a N-oxide form thereof.”* (See WO’875 at internal page 47)

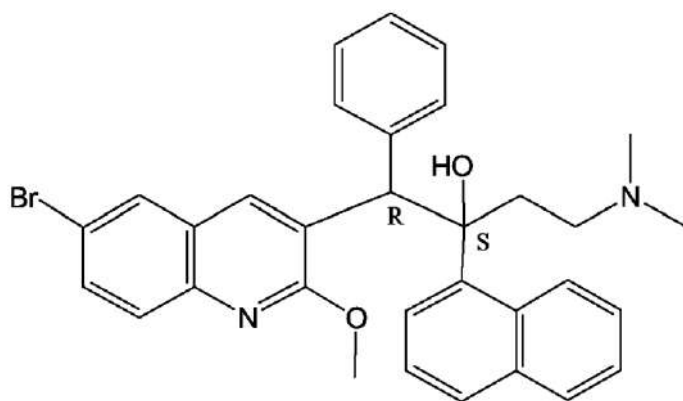
73. Further, claim 16 also claims, “*Use according to claim 15 wherein the compound is 6-bromo- $\alpha$ -[2-(dimethylamino)ethyl]-2-methoxy- $\alpha$ -1-naphthalenyl- $\beta$ -phenyl-3-quinolineethanol, or a pharmaceutically acceptable acid addition salt thereof.*” (See WO’875 at internal page 48).
74. In particular claim 19 claims, “*( $\alpha$ S, $\beta$ R)-6-bromo- $\alpha$ -[2-(dimethylamino)ethyl]-2-methoxy- $\alpha$ -1-naphthalenyl- $\beta$ -phenyl-3-quinolineethanol, or pharmaceutically acceptable acid additional salt thereof.*” (See WO’875 at internal page 48)
75. Claim 25 therein also claims, “*A pharmaceutical composition comprising pharmaceutically acceptable carrier and, as active ingredient, a therapeutically effective amount of (a) a compound of formula (Ia) or (Ib) as defined in any one of claims 1 to 20 and (b) one or more other antimycobacterial agents.*” (See WO’875 at internal page 49).
76. Hence, a POSITA on reading WO’875 would not only be taught that fumarate salt of ( $\alpha$ S,  $\beta$ R)-6-bromo- $\alpha$ -[2-(dimethylamino)ethyl]-2-methoxy- $\alpha$ -1-naphthalenyl- $\beta$ -phenyl-3-quinolineethanol can be used in a composition with pharmaceutically acceptable carrier, as an effective treatment against resistant Mycobacterium strains, but also would be taught the minimum inhibitory concentration of this compound. Therefore, a POSITA working on treating resistant mycobacterium strains, on reading WO’436 and WO’875 would be motivated to use a pharmaceutically acceptable salt, including fumarate salt of ( $\alpha$ S,  $\beta$ R)-6-bromo- $\alpha$ -[2-(dimethylamino)ethyl]-2-methoxy- $\alpha$ -1-naphthalenyl- $\beta$ -phenyl-3-quinolineethanol in a composition.

#### **WO2006067048**

77. The Opponent relies on the publication WO2006067048 (hereinafter “WO’048” and annexed herein as **Exhibit-C**) titled, “*Quinoline derivatives*

*for the treatment of latent tuberculosis*” in the name of the Applicant of the Present Application. WO’048 was published on 29.06.2006 viz. much before the priority date of the Present Application viz. 05.12.2006. Thus WO ’048 may be relied on as a prior art document.

78. WO’048 discloses compounds Ia and Ib for treatment of latent tuberculosis. (See WO’048, abstract and internal page 1, lines 4-5). WO’048 discloses that these compounds Ia and Ib are the same as those disclosed in WO’436. WO’048 claims pharmaceutically acceptable salt form of compounds Ia and Ib (See WO’048, internal page 50, claims 1, internal page 55 at claims 21, 23, 24, internal page 56 at claim 27).
79. WO’048 as well indicates that pharmaceutically acceptable salts of Ia and Ib may include those derived from organic acids such as fumaric acid (See WO’048, internal page 7, lines 4-15). It also discloses that the racemic compounds of either Ia or Ib may be converted into corresponding diastereoisomeric salt forms by reaction with suitable chiral acids (See WO’048, internal page 9, lines 15-20).
80. Further, WO’048 discloses that compound 1-(6-bromo-2-methoxy-quinolin-3-yl)-4-dimethylamino-2-naphthalen-1-yl-1-phenyl-butan-2-ol also identified as 6-bromo- $\alpha$ -[2-(dimethylamino)emyl]-2-methoxy- $\alpha$ -1-naphthalenyl- $\beta$ -phenyl-3-quinolineethanol is a preferred compound (WO’048, internal page 19, lines 5-17). Further, it discloses that ( $\alpha$ S, $\beta$ R)-6-bromo- $\alpha$ -[2-(dimethylamino)emyl]-2-methoxy- $\alpha$ -1-naphthalenyl- $\beta$ -phenyl-3-quinolineethanol and its pharmaceutically acceptable acid addition salt thereof, is also a preferred compound (WO’048, internal page 20, lines 1-5, lines 15-20). The structure of ( $\alpha$ S, $\beta$ R)-6-bromo- $\alpha$ -[2-(dimethylamino)emyl]-2-methoxy- $\alpha$ -1-naphthalenyl- $\beta$ -phenyl-3-quinolineethanol is reproduced below for easy reference (WO’048, internal page 20):



81. Therefore, a POSITA on reading WO'048, WO'875 and WO'436, working on developing a composition for treating mycobacterium infections would be motivated to use a pharmaceutically acceptable form, including a fumaric salt of (alpha S, beta R)- 6-bromo- $\alpha$ -[2-(dimethylamino)ethyl]-2-methoxy- $\alpha$ -1-naphthalenyl- $\beta$ -phenyl-3-quinolineethanol, a pharmaceutically acceptable carrier and a wetting agent.

**Composition with constituents including lactose monohydrate, hypromellose, polysorbate 20, microcrystalline cellulose, maize starch, colloidal silicon dioxide and magnesium stearate was known**

#### **WO2006024667**

82. The Opponent relies on publication no. WO2006024667 (hereinafter "WO'667" and annexed hereto as **Exhibit-D**) filed in name of the Applicant of the Present Application and titled, "fumarate of 4-((4-((4-(2-cyanoethenyl)-2,6-dimethylphenyl)amino)-2-pyrimidinyl)amino)benzotrile". WO'667 was published on 09.03.2006 viz. much before the priority date of the Present Application viz. 05.12.2006. Thus WO '667 may be relied on as a prior art document.
83. WO'667 relates to a composition comprising fumarate salt of 4-[[4-[[4-(2-cyanoethenyl)-2,6-dimethylphenyl]amino]-2-pyrimidinyl]amino]benzotrile (See WO'667, at abstract). WO'667 notes

that, “Free base 4- [ [4- [ [4-(2-cyanoethenyl)-2,6-dimethylphenyl]amino] -2-pyrimidinyl] -amino]benzotrile can be classified as a BCS class 2 compound and has thus a low solubility in water. 4-[[4-[[4-(2-cyanoethenyl)-2,6-dimethylphenyl]amino]-2-pyrimidinyl]amino]benzotrile does not only exhibit a low solubility in water, but also in an acidic environment. Consequently, when administered orally in a conventional solid dosage form, a low bioavailability may be expected.

When confronted with a BCS class 2 compound intended for oral administration, a person skilled in pharmaceutical technology would turn to exploring possibilities for improving the compound's solubility, for instance by preparing an appropriate salt. This route was also followed for 4-[[4-[[4-(2-cyanoethenyl)-2,6-dimethylphenyl]-amino]-2-pyrimidinyl]amino]benzotrile.

The prepared salts appeared to have only a slight improved solubility in water and in HCl. The prepared salts still belong to BCS class 2. Thus, also for the prepared salts a low bioavailability could be expected.

Unexpectedly, it has now been found that the fumarate salt ( $\text{trans CH}(\text{COOH})=\text{CH}(\text{COOH})$ ) of 4-[[4-[[4-(2-cyanoethenyl)-2,6-dimethylphenyl]amino]-2-pyrimidinyl]amino]benzotrile, in particular its E-isomer, has a significant improved in vivo bioavailability compared to the free base. In fact, the present salt administered as a solid dosage form has an in vivo bioavailability which is comparable with the bioavailability of the free base administered as an oral PEG 400 solution.

Because of the increased bioavailability in vivo, the fumarate salt may be formulated without the need of complex formulation techniques.

The fumarate salt of the present invention was also found to be non-hygroscopic and to be chemically and physically stable in different conditions of humidity and temperatures.” (See WO'667, internal page 2, lines 22-33 and internal page 3, lines 1-19).

84. Hence, the Applicant of the Present Applicant on previous occasion had found in case of a Biopharmaceutics Classification System (BCS) class 2 drug, the fumarate salt of the free base was found to be more bioavailable. Therefore, there is no inventive step in using a fumarate salt of known compound in a composition, especially in the case of a BCS class 2 compound.
85. As discussed in the section related to treatment of MDR-TB, it may be noted here that Bedaquiline (the fumarate salt of which is one of the constituents of the claimed composition in Present Application) is also a BCS class 2 drug.
86. In fact, many portions of the Present Application are verbatim reproduction from WO'667. Particularly, the Present Application has reproduced the portions related to use of a wetting agent in the composition. The same is being reproduced in tabular form below for easy reference:

| <b>WO2006024667</b>   | <b>Present Application</b>  |
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| <p>[Internal page 11, at lines 34 through internal page 16 at line 08]</p> <p><i>'The pharmaceutical compositions of the present invention preferably comprise a wetting agent.</i></p> <p><i>As for the wetting agent in the compositions of the invention, there may be used any of the physiologically tolerable wetting agent suitable for use in a pharmaceutical composition.</i></p> <p><i>It is well-known in the art that a wetting agent is an amphiphilic compound; it</i></p> | <p>[See internal page 7 at line 31 through internal 12 at line 10]</p> <p><i>"The pharmaceutical compositions of the present invention preferably comprise a wetting agent.</i></p> <p><i>As for the wetting agent in the compositions of the invention, there may be used any of the physiologically tolerable wetting agent suitable for use in a pharmaceutical composition.</i></p> <p><i>It is well-known in the art that a wetting agent is an amphiphilic compound; it</i></p> |

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| <p><i>contains polar, hydrophilic moieties as well as non-polar, hydrophobic moieties.</i></p>   | <p><i>contains polar, hydrophilic moieties as well as non-polar, hydrophobic moieties.</i></p>   |
| <p><i>The terms "hydrophilic" or "hydrophobic" are relative terms.</i></p>   | <p><i>The terms "hydrophilic" or "hydrophobic" are relative terms.</i></p>   |
| <p><i>The relative hydrophilicity or hydrophobicity of a wetting agent may be expressed by its hydrophilic-lipophilic balance value ("HLB value"). Wetting agents with a lower HLB value are categorized as being "hydrophobic" wetting agents whereas wetting agents with a higher HLB value are categorized as being "hydrophilic" wetting agents.</i></p> | <p><i>The relative hydrophilicity or hydrophobicity of a wetting agent may be expressed by its hydrophilic- lipophilic balance value ("HLB value). Wetting agents with a lower HLB value are categorized as being "hydrophobic" wetting agents whereas wetting agents with a higher HLB value are categorized as being "hydrophilic" wetting agents.</i></p> |
| <p><i>As a rule of thumb, wetting agents having a HLB value greater than about 10 are generally considered as being hydrophilic wetting agents; wetting agents having a HLB value lower than about 10 are generally considered as being hydrophobic wetting agents.</i></p>  | <p><i>As a rule of thumb, wetting agents having a HLB value greater than about 10 are generally considered as being hydrophilic wetting agents; wetting agents having a HLB value lower than about 10 are generally considered as being hydrophobic wetting agents.</i></p>  |
| <p><i>The present compositions preferably comprise a hydrophilic wetting agent. It should be appreciated that the HLB value of a wetting agent is only a rough guide to indicate the hydrophilicity/hydrophobicity of a wetting agent. The HLB value of a particular</i></p>   | <p><i>The present compositions preferably comprise a hydrophilic wetting agent. It should be appreciated that the HLB value of a wetting agent is only a rough guide to indicate the hydrophilicity/hydrophobicity of a wetting agent. The HLB value of a</i></p>  |

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| <p>wetting agent may vary depending upon the method used to determine the HLB value; may vary depending on its commercial source; is subject to batch to batch variability.</p> <p>A person skilled in the art can readily identify hydrophilic wetting agents suitable for use in the pharmaceutical compositions of the present invention.</p> <p>The wetting agent of the present invention can be an anionic, a cationic, a zwitterionic or a non-ionic wetting agent, the latter being preferred. The wetting agent of the present invention can also be a mixture of two or more wetting agents.</p> <p>Suitable wetting agents for use in the compositions of the present invention are listed below. It should be emphasized that said list of wetting agents is only illustrative, representative and not exhaustive. Thus the invention is not limited to the wetting agents listed below. In the present compositions, also mixtures of wetting agents may be used.</p> <p>Suitable wetting agents which may be used in the present invention comprise :</p> <p>a) Polyethylene glycol fatty acid</p> | <p>particular wetting agent may vary depending upon the method used to determine the HLB value; may vary depending on its commercial source; is subject to batch to batch variability.</p> <p>A person skilled in the art can readily identify hydrophilic wetting agents suitable for use in the pharmaceutical compositions of the present invention.</p> <p>The wetting agent of the present invention can be an anionic, a cationic, a zwitterionic or a non-ionic wetting agent, the latter being preferred. The wetting agent of the present invention can also be a mixture of two or more wetting agents.</p> <p>Suitable wetting agents for use in the compositions of the present invention are listed below. It should be emphasized that said list of wetting agents is only illustrative, representative and not exhaustive. Thus the invention is not limited to the wetting agents listed below. In the present compositions, also mixtures of wetting agents may be used.</p> <p>Suitable wetting agents which may be used in the present invention comprise :</p> <p>a) Polyethylene glycol fatty acid</p> |
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| <p><i>monoesters comprising esters of lauric acid, oleic acid, stearic acid, ricinoic acid and the like with PEG 6, 7, 8, 9, 10, 12, 15, 20, 25, 30, 32, 40, 45, 50, 55, 100, 200, 300, 400, 600 and the like, for instance PEG-6 laurate or stearate, PEG-7 oleate or laurate, PEG-8 laurate or oleate or stearate, PEG-9 oleate or stearate, PEG-10 laurate or oleate or stearate, PEG- 12 laurate or oleate or stearate or ricinoleate, PEG- 15 stearate or oleate, PEG-20 laurate or oleate or stearate, PEG-25 stearate, PEG-32 laurate or oleate or stearate, PEG-30 stearate, PEG-40 laurate or oleate or stearate, PEG-45 stearate, PEG-50 stearate, PEG-55 stearate, PEG-100 oleate or stearate, PEG-200 oleate, PEG-400 oleate, PEG-600 oleate; (the wetting agents belonging to this group are for instance known as Cithrol, Algon, Kessco, Lauridac, Mapeg, Cremophor, Emulgante, Nikkol, Myrj, Crodet, Albunol, Lactomul)</i></p> <p><i>b) Polyethylene glycol fatty acid diesters comprising diesters of lauric acid, stearic acid, palmic acid, oleic acid and the like with PEG-8, 10, 12, 20, 32, 400 and the like, for instance PEG-8 dilaurate or distearate, PEG-10 dipalmitate, PEG- 12 dilaurate or distearate or dioleate, PEG-</i></p> | <p><i>monoesters comprising esters of lauric acid, oleic acid, stearic acid, ricinoic acid and the like with PEG 6, 7, 8, 9, 10, 12, 15, 20, 25, 30, 32, 40, 45, 50, 55, 100, 200, 300, 400, 600 and the like, for instance PEG-6 laurate or stearate, PEG-7 oleate or laurate, PEG-8 laurate or oleate or stearate, PEG-9 oleate or stearate, PEG-10 laurate or oleate or stearate, PEG- 12 laurate or oleate or stearate or ricinoleate, PEG- 15 stearate or oleate, PEG-20 laurate or oleate or stearate, PEG-25 stearate, PEG-32 laurate or oleate or stearate, PEG-30 stearate, PEG-40 laurate or oleate or stearate, PEG-45 stearate, PEG-50 stearate, PEG-55 stearate, PEG-100 oleate or stearate, PEG-200 oleate, PEG-400 oleate, PEG-600 oleate; (the wetting agents belonging to this group are for instance known as Cithrol, Algon, Kessco, Lauridac, Mapeg, Cremophor,Emulgante, Nikkol, Myrj, Crodet, Albunol, Lactomul)</i></p> <p><i>b) Polyethylene glycol fatty acid diesters comprising diesters of lauric acid, stearic acid, palmic acid, oleic acid and the like with PEG-8, 10, 12, 20, 32, 400 and the like, for instance PEG-8 dilaurate or distearate, PEG-10 dipalmitate, PEG- 12</i></p> |
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| <p>20 dilaurate or distearate or dioleate PEG-32 dilaurate or distearate or dioleate, PEG-400 dioleate or distearate; (the wetting agents belonging to this group are for instance known as Mapeg, Polyalso, Kessco, Cithrol)</p> <p>c) Polyethylene glycol fatty acid mono- and diester mixtures such as for example PEG 4-150 mono and dilaurate, PEG 4-150 mono and dioleate, PEG 4-150 mono and distearate and the like; (the wetting agents belonging to this group are for instance known as Kessco)</p> <p>d) Polyethylene glycol glycerol fatty acid esters such as for instance PEG-20 glyceryl laurate or glyceryl stearate or glyceryl oleate, PEG-30 glyceryl laurate or glyceryl oleate, PEG- 15 glyceryl laurate, PEG-40 glyceryl laurate and the like; (the wetting agents belonging to this group are for instance known as Tagat, Glycerox L, Capmul) ,</p> <p>e) Alcohol-oil transesterification products comprising esters of alcohols or polyalcohols such as glycerol, propylene glycol, ethylene glycol, polyethylene glycol, sorbitol, pentaerythritol and the like with natural</p> | <p>dilaurate or distearate or dioleate, PEG-20 dilaurate or distearate or dioleate PEG-32 dilaurate or distearate or dioleate, PEG-400 dioleate or distearate; (the wetting agents belonging to this group are for instance known as Mapeg, Polyalso, Kessco, Cithrol)</p> <p>c) Polyethylene glycol fatty acid mono- and diester mixtures such as for example PEG 4-150 mono and dilaurate, PEG 4-150 mono and dioleate, PEG 4-150 mono and distearate and the like; (the wetting agents belonging to this group are for instance known as Kessco)</p> <p>d) Polyethylene glycol glycerol fatty acid esters such as for instance PEG-20 glyceryl laurate or glyceryl stearate or glyceryl oleate, PEG-30 glyceryl laurate or glyceryl oleate, PEG- 15 glyceryl laurate, PEG-40 glyceryl laurate and the like; (the wetting agents belonging to this group are for instance known as Tagat, Glycerox L, Capmul) ,</p> <p>e) Alcohol-oil transesterification products comprising esters of alcohols or polyalcohols such as glycerol, propylene glycol, ethylene glycol, polyethylene glycol, sorbitol,</p> |
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| <p><i>and/or hydrogenated oils or oil-soluble vitamins such as castor oil, hydrogenated castor oil, vitamin A, vitamin D, vitamin E, vitamin K, an edible vegetable oil e.g. corn oil, olive oil, peanut oil, palm kernel oil, apricot kernel oil, almond oil and the like, such as PEG-20 castor oil or hydrogenated castor oil or corn glycerides or almond glycerides, PEG-23 castor oil, PEG-25 hydrogenated castor oil or trioleate, PEG-35 castor oil, PEG-30 castor oil or hydrogenated castor oil, PEG-38 castor oil, PEG-40 castor oil or hydrogenated castor oil or palm kernel oil, PEG-45 hydrogenated castor oil, PEG-50 castor oil or hydrogenated castor oil, PEG-56 castor oil, PEG-60 castor oil or hydrogenated castor oil or corn glycerides or almond glycerides, PEG- 80 hydrogenated castor oil, PEG-100 castor oil or hydrogenated castor oil, PEG-200 castor oil, PEG- 8 caprylic/capric glycerides, PEG-6 caprylic/capric glycerides, lauroyl macrogol-32 glyceride, stearyl macrogol glyceride, tocopheryl PEG-1000 succinate (TPGS); (the wetting agents belonging to this group are for instance known as Emalex, Cremophor, Emulgante, Eumulgin, Nikkol, Thornley, Simulsol, Cerex, Crovol, Labrasol, Softigen, Gelucire, Vitamin E TPGS),</i></p> | <p><i>pentaerythritol and the like with natural and/or hydrogenated oils or oil-soluble vitamins such as castor oil, hydrogenated castor oil, vitamin A, vitamin D, vitamin E, vitamin K, an edible vegetable oil e.g. corn oil, olive oil, peanut oil, palm kernel oil, apricot kernel oil, almond oil and the like, such as PEG-20 castor oil or hydrogenated castor oil or corn glycerides or almond glycerides, PEG-23 castor oil, PEG-25 hydrogenated castor oil or trioleate, PEG-35 castor oil, PEG-30 castor oil or hydrogenated castor oil, PEG-38 castor oil, PEG-40 castor oil or hydrogenated castor oil or palm kernel oil, PEG-45 hydrogenated castor oil, PEG-50 castor oil or hydrogenated castor oil, PEG-56 castor oil, PEG-60 castor oil or hydrogenated castor oil or corn glycerides or almond glycerides, PEG-80 hydrogenated castor oil, PEG-100 castor oil or hydrogenated castor oil, PEG-200 castor oil, PEG-8 caprylic/capric glycerides, PEG-6 caprylic/capric glycerides, lauroyl macrogol-32 glyceride, stearyl macrogol glyceride, tocopheryl PEG-1000 succinate (TPGS); (the wetting agents belonging to this group are for instance known as Emalex, Cremophor, Emulgante, Eumulgin, Nikkol, Thornley,</i></p> |
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| <p><i>f) polyglycerized fatty acids comprising polyglycerol esters of fatty acids such as for instance poly glyceryl- 10 laurate or oleate or stearate, poly glyceryl- 10 mono and dioleate, polyglyceryl polyricinoleate and the like; (the wetting agents belonging to this group are for instance known as Nikkol Decaglyn, Caprol or Polymuls)</i></p> <p><i>g) Sterol derivatives comprising polyethylene glycol derivatives of sterol such as PEG-24 cholesterol ether, PEG-30 cholestanol, PEG-25 phyto sterol, PEG-30 soya sterol and the like; (the wetting agents belonging to this group are for instance known as Solulan™ or Nikkol BPSH)</i></p> <p><i>h) Polyethylene glycol sorbitan fatty acid esters such as for example PEG-10 sorbitan laurate, PEG-20 sorbitan mono laurate or sorbitan tristearate or sorbitan monooleate or sorbitan trioleate or sorbitan monoisostearate or sorbitan monopalmiate or sorbitan monostearate, PEG-4 sorbitan monolaurate, PEG-5 sorbitan monooleate, PEG-6 sorbitan</i></p> | <p><i>Simulsol, Cerex, Crovol, Labrasol, Softigen, Gelucire, Vitamin E TPGS),</i></p> <p><i>f) polyglycerized fatty acids comprising polyglycerol esters of fatty acids such as for instance polyglyceryl-10 laurate or oleate or stearate, polyglyceryl-10 mono and dioleate, polyglyceryl polyricinoleate and the like;(the wetting agents belonging to this group are for instance known as Nikkol Decaglyn, Caprol or Polymuls)</i></p> <p><i>g) Sterol derivatives comprising polyethylene glycol derivatives of sterol such as PEG-24 cholesterol ether, PEG-30 cholestanol, PEG-25 phyto sterol, PEG-30 soya sterol and the like; (the wetting agents belonging to this group are for instance known as Solulan™ or Nikkol BPSH)</i></p> <p><i>h) Polyethylene glycol sorbitan fatty acid esters such as for example PEG-10 sorbitan laurate, PEG-20 sorbitan mono laurate or sorbitan tristearate or sorbitan monooleate or sorbitan trioleate or sorbitan monoisostearate or sorbitan monopalmiate or sorbitan monostearate, PEG-4 sorbitan mono laurate, PEG-5 sorbitan monooleate, PEG-6 sorbitan</i></p> |
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| <p><i>monooleate or sorbitan monolaurate or sorbitan monostearate, PEG-8 sorbitan monostearate, PEG-30 sorbitan tetraoleate, PEG-40 sorbitan oleate or sorbitan tetraoleate, PEG-60 sorbitan tetrastearate, PEG-80 sorbitan monolaurate, PEG sorbitol hexaoleate (Atlas G- 1086) and the like; (the wetting agents belonging to this group are for instance known as Liposorb, Tween, Dacol MSS, Nikkol, Emalex, Atlas)</i></p> <p><i>i) Polyethylene glycol alkyl ethers such as for instance PEG-10 oleyl ether or cetyl ether or stearyl ether, PEG-20 oleyl ether or cetyl ether or stearyl ether, PEG-9 lauryl ether, PEG-23 lauryl ether (laureth-23), PEG-100 stearyl ether and the like; (the wetting agents belonging to this group are for instance known as Volpo, Brij)</i></p> <p><i>j) Sugar esters such as for instance sucrose distearate/monostearate, sucrose monostearate or monopalmitate or monolaurate and the like; (the wetting agents belonging to this group are for instance known as Sucro ester, Crodesta, Saccharose monolaurate)</i></p> | <p><i>monooleate or sorbitan mono laurate or sorbitan monostearate, PEG-8 sorbitan monostearate, PEG-30 sorbitan tetraoleate, PEG-40 sorbitan oleate or sorbitan tetraoleate, PEG-60 sorbitan tetrastearate, PEG-80 sorbitan monolaurate, PEG sorbitol hexaoleate (Atlas G- 1086) and the like; (the wetting agents belonging to this group are for instance known as Liposorb, Tween, Dacol MSS, Nikkol, Emalex, Atlas)</i></p> <p><i>i) Polyethylene glycol alkyl ethers such as for instance PEG-10 oleyl ether or cetyl ether or stearyl ether, PEG-20 oleyl ether or cetyl ether or stearyl ether, PEG-9 lauryl ether, PEG-23 lauryl ether (laureth-23), PEG-100 stearyl ether and the like; (the wetting agents belonging to this group are for instance known as Volpo, Brij)</i></p> <p><i>j) Sugar esters such as for instance sucrose distearate/monostearate, sucrose monostearate or monopalmitate or monolaurate and the like; (the wetting agents belonging to this group are for instance known as Sucro ester, Crodesta, Saccharose monolaurate)</i></p> |
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| <p><i>k) Polyethylene glycol alkyl phenols such as for instance PEG- 10- 100 nonyl phenol (Triton X series), PEG- 15- 100 oyl phenol ether (Triton N series) and the like;</i></p>  | <p><i>k) Polyethylene glycol alkyl phenols such as for instance PEG- 10- 100 nonyl phenol (Triton X series), PEG- 15- 100 oyl phenol ether (Triton N series) and the like;</i></p>   |
| <p><i>l) Polyoxyethylene-polyoxypropylene block copolymers (poloxamers) such as for instance poloxamer 108, poloxamer 188, poloxamer 237, poloxamer 288 and the like; (the wetting agents belonging to this group are for instance known as Synperonic PE, Pluronic, Emkalyx, Lutrol™, Supronic, Monolan, Pluracare, Plurodac)</i></p>  | <p><i>l) Polyoxyethylene-polyoxypropylene block copolymers (poloxamers) such as for instance poloxamer 108, poloxamer 188, poloxamer 237, poloxamer 288 and the like; (the wetting agents belonging to this group are for instance known as Synperonic PE, Pluronic, Emkalyx, Lutrol™, Supronic, Monolan, Pluracare, Plurodac)</i></p>   |
| <p><i>m) ionic wetting agents including cationic, anionic and zwitterionic surfactans such as the fatty acid salts e.g. sodium oleate, sodium lauryl sulfate, sodium lauryl sarcosinate, sodium dioctyl sulfosuccinate, sodium myristate, sodium palmitate, sodium state, sodium ricinoleate and the like; such as bile salts e.g. sodium cholate, sodium taurocholate, sodium glycocholate and the like; such as phospholipids e.g. egg/soy lecithin, hydroxylated lecithin, lysophosphatidylcholine, phosphatidylcholine, phosphatidyl ethanolamine, phosphatidyl glycerol,</i></p> | <p><i>m) ionic wetting agents including cationic, anionic and zwitterionic surfactans such as the fatty acid salts e.g. sodium oleate, sodium lauryl sulfate, sodium lauryl sarcosinate, sodium dioctyl sulfo succinate, sodium myristate, sodium palmitate, sodium state, sodium ricinoleate and the like; such as bile salts e.g. sodium cholate, sodium taurocholate, sodium glycocholate and the like; such as phospholipids e.g. egg/soy lecithin, hydroxylated lecithin, lysophosphatidylcholine, phosphatidylcholine, phosphatidyl ethanolamine, phosphatidyl glycerol,</i></p> |

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| <p><i>phosphatidyl serine and the like; such as phosphoric acid esters e.g. diethanolammonium polyoxyethylene-10 oleyl ether phosphate, esterification products of fatty alcohols or fatty alcohol ethoxylates with phosphoric acid or anhydride; such as carboxylates e.g. succinylated monoglycerides, sodium stearyl fumarate, stearyl propylene glycol hydrogen succinate, mono/diacetylated tartaric acid esters of mono-and diglycerides, citric acid esters of mono-and diglycerides, glyceryl- lacto esters of fatty acids, lactic esters of fatty acids, calcium/sodium stearyl-2-lactylate, calcium/sodium stearyl lactylate, alginate salts, propylene glycol alginate, ether carboxylates and the like; such as sulfates and sulfonates e.g. ethoxylated alkyl sulfates, alkyl benzene sulfates, alpha-olefin sulfonates, acyl isethionates, acyl taurates, alkyl glyceryl ether sulfonates, octyl sulfosuccinate disodium, disodium undecyleneamido-MEA-sulfosuccinate and the like; such as cationic wetting agents e.g. hexadecyl triammonium bromide, decyl trimethyl ammonium bromide, cetyl trimethyl ammonium bromide, dodecyl ammonium chloride, alkyl benzyldimethylammonium salts, diisobutyl phenoxyethoxydimethyl</i></p> | <p><i>phosphatidyl serine and the like; such as phosphoric acid esters e.g. diethanolammonium polyoxy ethylene- 10 oleyl ether phosphate, esterification products of fatty alcohols or fatty alcohol ethoxylates with phosphoric acid or anhydride; such as carboxylates e.g. succinylated monoglycerides, sodium stearyl fumarate, stearyl propylene glycol hydrogen succinate, mono/diacetylated tartaric acid esters of mono-and diglycerides, citric acid esters of mono-and diglycerides, glyceryl- lacto esters of fatty acids, lactic esters of fatty acids, calcium/sodium stearyl-2-lactylate, calcium/sodium stearyl lactylate, alginate salts, propylene glycol alginate, ether carboxylates and the like; such as sulfates and sulfonates e.g. ethoxylated alkyl sulfates, alkyl benzene sulfates, alpha-olefin sulfonates, acyl isethionates, acyl taurates, alkyl glyceryl ether sulfonates, octyl sulfosuccinate disodium, disodium undecyleneamido-MEA-sulfosuccinate and the like; such as cationic wetting agents e.g. hexadecyl triammonium bromide, decyl trimethyl ammonium bromide, cetyl trimethyl ammonium bromide, dodecyl ammonium chloride, alkyl benzyldimethylammonium salts, diisobutyl phenoxyethoxydimethyl</i></p> |
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| <p><i>benzylammonium salts, alkylpyridinium salts, betaines (lauryl betaine), ethoxylated amines (polyoxyethylene-15 coconut amine) and the like.</i></p> <p><i>When in the above list of suitable wetting agents, different possibilities are listed such as for example PEG-20 oleyl ether or cetyl ether or stearyl ether, this means that PEG-20 oleyl ether and PEG-20 cetyl ether and PEG-20 stearyl ether are intended.</i></p> <p><i>Thus for instance PEG-20 castor oil or hydrogenated castor oil or corn glycerides or almond glycerides has to be read as PEG-20 castor oil and PEG-20 hydrogenated castor oil and PEG-20 corn glycerides and PEG-20 almond glycerides.</i></p> <p><i>Preferred wetting agents in the present compositions are sodium lauryl sulfate, sodium dioctyl sulfosuccinate, or those wetting agents belonging to the group of the polyethylene glycol sorbitan fatty acid esters, such as wetting agents known as Tween, e.g. Tween 20, 60, 80. Most preferred, the wetting agent is Tween 20.</i></p> <p><i>In the compositions of the invention, the</i></p> | <p><i>benzylammonium salts, alkylpyridinium salts, betaines (lauryl betaine), ethoxylated amines (polyoxyethylene-15 coconut amine) and the like.</i></p> <p><i>When in the above list of suitable wetting agents, different possibilities are listed such as for example PEG-20 oleyl ether or cetyl ether or stearyl ether, this means that PEG-20 oleyl ether and PEG-20 cetyl ether and PEG-20 stearyl ether are intended.</i></p> <p><i>Thus for instance PEG-20 castor oil or hydrogenated castor oil or corn glycerides or almond glycerides has to be read as PEG-20 castor oil and PEG-20 hydrogenated castor oil and PEG-20 corn glycerides and PEG-20 almond glycerides.</i></p> <p><i>Preferred wetting agents in the present compositions are those agents belonging to the group of the polyethylene glycol sorbitan fatty acid esters, such as wetting agents known as Tween, e.g. Tween 20, 60, 80. Most preferred, the wetting agent is Tween 20.</i></p> <p><i>In the compositions of the invention, the</i></p> |
|---|--|

|  |  |
|--|--|
| <p>wetting agent is preferably present at a concentration from about 0.01 to about 5% by weight relative to the total weight of the composition, preferably from about 0.1 to about 3 % by weight, more preferably from about 0.1 to about 1 % by weight.</p> <p>The quantity of wetting agent used in the present compositions may depend on the amount of the compound of formula (I), (I-a) or (I-b) present in the composition or on the particle size of the compound of formula (I), (I-a) or (I-b). A higher amount or a smaller particle size may require more wetting agent.”</p> | <p>wetting agent is preferably present at a concentration from about 0.01 to about 5% by weight relative to the total weight of the composition, preferably from about 0.1 to about 3 % by weight, more preferably from about 0.1 to about 1 % by weight.</p> <p>The quantity of wetting agent used in the present compositions may depend on the amount of the compound present in the composition or on the particle size of the compound. A higher amount or a smaller particle size may require more wetting agent.”</p> |
|--|--|

87. In fact, WO’667 claims a composition that has the same composition by weight as claimed in the Present application. As represented below, claim 5 of the Present Application uses the same weight composition as claimed in claim 11 of WO’667.

| <b>Claim 5 of Present Application</b>  | <b>Claim 11 of WO ‘667</b><br>(Also see internal page. 19 lines 15-24)   |
|--|--|
| <p>Claim 5 ” A pharmaceutical composition according to claim 4 comprising by weight based on the total weight of the tablet core</p> <p>(a) from 5 to 50% of active ingredient;</p> <p>(b) from 0.01 to 5 % of a wetting</p> | <p>Claim 11 “A pharmaceutical composition according any one of claims 4-10 having following composition:</p> <p>(a) from 5 to 50% of a compound of formula (I), (I-a) or (I-b);(b) from 0.01</p> |



|   |   |
|---|---|
| <i>agent;</i><br><i>(c) from 40 to 92% of a diluent;</i><br><i>(d) from 0 to 10 % of a polymer;</i><br><i>(e) from 2 to 10 % of a disintegrant;</i><br><i>(f) from 0.1 to 5% of a glidant;</i><br><i>(g) from 0.1 to 1.5 % of a lubricant.”</i> | <i>to 5% of a wetting agent;</i><br><i>(c) from 40 to 92% of a diluent;</i><br><i>(d) from 0 to 10% of a polymer;</i><br><i>(e) from 2 to 10% of a disintegrant;</i><br><i>(f) from 0.1 to 5% of a glidant;</i><br><i>(g) from 0.1 to 1.5% of a lubricant.”</i> |
|---|---|

88. Further, WO'667 also discloses weight wise distribution of each of the constituents of the composition. These constituents included active ingredient, lactose monohydrate, hypromellose 2910, polysorbate, microcrystalline cellulose, croscarmellose sodium, colloidal silicon dioxide, magnesium stearate. It discloses that, “*Tablet compositions illustrating the present invention are:*

*Composition 2a*

*Tablet core:*

*Compound of formula (I-a) 110 mg (i.e. 100 mg base equivalent)*

*Lactose monohydrate 137.8 mg*

*Hypromellose 2910 15mPa.s 5.6 mg*

*Polysorbate 20 1.4 mg*

*Microcrystalline cellulose 52.5 mg*

*Croscarmellose sodium 17.5 mg*

*Colloidal silicon dioxide 1.05 mg*

*Magnesium stearate 2.45 mg”* (See WO'667, internal page 26, and generally internal pages 24-30). WO'667 also gives other examples with different weight of the constituents of the composition. For a POSITA working on developing a composition with similar constituents, varying the weight of the constituents would be a matter of trial and error. Therefore, a POSITA working on developing an anti-mycobacterium treatment using ( $\alpha$ S,  $\beta$ R)-6-bromo- $\alpha$ -[2-(dimethylamino)ethyl]-2-methoxy- $\alpha$ -1-naphthalenyl- $\beta$ -phenyl-3-quinolineethanol salt on reading WO'667 would be taught to make a composition comprising various constituents such as lactose monohydrate,

polysorbate 20, microcrystalline cellulose, croscarmellose sodium, colloidal silicon dioxide and magnesium stearate to arrive at a composition claimed in claim 7 of the Present Application.

89. Hence, a POSITA working on developing a composition for treating mycobacterium resistance, on reading WO'667 would be motivated to use fumarate salt of a known substance with anti-mycobacterium activity in a composition with other constituents as used in WO'667.

#### **US 6,534, 508**

90. The Opponent relies on US patent US 6,534, 508 titled, "*Methods and Composition for treating infection using optically pure (S)-Lomefloxacin*" (hereinafter "US'508" and annexed herein as **Exhibit-E**). The patent was published on 23.05.2002, which is earlier than the priority date of the Present Application. Therefore, US'508 may be relied on as prior art.
91. US'508 relates to composition for treating bacterial infection, in particular, Mycobacteria infection. (See internal page 1, RHS at abstract). It discloses that, "*Usual pharmaceutical media includes, for example, water, glycols, oils, alcohols, flavoring agents, preservatives, coloring agents, and the like in the case of oral liquid preparations (such as for example, suspensions, solutions, and elixirs); aerosols; or carriers such as starches, sugars, microcrystalline cellulose, diluents, granulating agents, lubricants, binders, disintegrating agents and the like, in the case of oral solid preparations (such as for example, powders, capsules, and tablets) with the oral solid preparations being preferred over the oral liquid preparations. The most preferred oral solid preparation is tablets.*" (See US'508, column 10, lines 5-16)
92. Further, it cites examples of oral compositions as reproduced below:

### Example 1

#### Oral Formulation

Capsules:

| Formula   | Quantity per Capsule<br>in mg. |     |
|---|--------------------------------|-----|
| Active Ingredient<br>(S)-lomefloxacin hydrochloride | 100                            | 200 |
| Lactose   | 349                            | 249 |
| Corn Starch   | 50                             | 50  |
| Magnesium Stearate                                  | 1.0                            | 1.0 |
| Compression Weight                                  | 500                            | 500 |

(See US'508, column 11)

### Example 2

#### Oral Formulation

Tablets

| Formula   | Quantity per Capsule<br>in mg. |     |
|---|--------------------------------|-----|
| Active Ingredient<br>(S)-lomefloxacin hydrochloride | 100                            | 200 |
| Lactose BP  | 309                            | 209 |
| Starch BP   | 60                             | 60  |
| Pregelatinized Maize Starch BP                      | 30                             | 30  |
| Magnesium Stearate                                  | 1                              | 1   |
| Compression Weight                                  | 500                            | 500 |

93. Therefore, US'508 discloses oral formulation composition that includes the active ingredient, lactose, corn starch, magnesium stearate. Hence, a POSITA working on developing a composition for treating mycobacteria infection, on reading US'508 would be motivated to include corn starch and magnesium stearate in the composition.

#### Summary

94. A POSITA, working on developing a composition for treating mycobacterium infection, on reading WO'048, WO'875 and WO'436, WO'667, US'508 would be motivated to use a pharmaceutically acceptable form, including a fumaric salt of (alpha S, beta R)- 6-bromo- $\alpha$ -[2-

(dimethylamino)ethyl]-2-methoxy- $\alpha$ -1-naphthalenyl- $\beta$ -phenyl-3-quinolineethanol along in a composition with excipients taught by prior art documents to arrive at the composition claimed in the Present Application. The constituents of the composition *inter alia* as taught by the prior art could include lactose, maize starch, hyperomellose, polysorbate, microcrystalline cellulose, croscarmellose sodium, colloidal silicon dioxide and magnesium stearate. Such composition in tablet form, as per teachings of the prior art document may also be film coated, as claimed in the Present Application. Therefore, the composition of claims 1-7 of the Present Application are obvious and should be rejected for lack of inventive step.

**III. THAT CLAIMS 1-7 OF THE PRESENT APPLICATION DO NOT SATISFY THE TEST OF SECTION 3(d) AND SECTION 3(e) AND THEREFORE ARE OBJECTED TO UNDER SECTION 25(1) (f)**

95. Section 25(1)(f) of the Patents Act allows opposition to grant of patent on the ground of the claimed invention not being an invention within the meaning of the Patents Act, 1970. Section 25(1)(f) reads as follows:

*“(1) Where an application for a patent has been published but a patent has not been granted, any person may, in writing, represent by way of opposition to the Controller against the grant of patent on the ground—*

*..*

*(f) that the subject of any claim of the complete specification is not an invention within the meaning of this Act, or is not patentable under this Act.”*

**Claims of Present Application not an invention under Section 3(d)**

96. Without prejudice to other grounds raised herein, the Opponent raises objection under Section 25(1)(f) as the claims of the Present Application fail under Section 3(d).

97. Section 3(d) of the Patents Act disallows patents on modification of known substances. It is an established position of law that S. 3(d) has to be satisfied

independently of Section 2(1)(j) and S. 2(1)(ja) [see *Novartis AG versus Union of India and Others* (2013) 6 SCC 1]. The burden of showing enhanced (therapeutic) efficacy of modified known substance, under S. 3(d) is on the Applicant (see *Novartis AG versus Union of India and Others* 2007 4 MLJ 1153, para 13). Further, such data has to be provided by the Applicant in the complete specification (Hon'ble IPAB, *Novartis AG versus Union of India*, MIPR 2009 (2) 0345, para 9(xvii)).

98. The Applicant again places reliance on WO '436. It is submitted that the publication discloses (alpha S, beta R)- 6-bromo- $\alpha$ -[2-(dimethylamino)ethyl]-2-methoxy- $\alpha$ -1-naphthalenyl- $\beta$ -phenyl-3-quinolineethanol as one of the compounds that falls within the purview of the claimed formula. This compound is identified as compound 12 (See internal page 34 of WO'436). Further, WO '436 also discloses the pIC<sub>50</sub> value of compound 12 as 8.7 (See WO'436, Table 5, internal page 46).
99. The Applicant itself has admitted that (alpha S, beta R)- 6-bromo- $\alpha$ -[2-(dimethylamino)ethyl]-2-methoxy- $\alpha$ -1-naphthalenyl- $\beta$ -phenyl-3-quinolineethanol, one of the ingredients in the composition claimed by the Applicant, has been already disclosed in WO 2004/011436. The Applicant has failed to show how the composition claimed in the present application shows an enhanced efficacy over the known and disclosed compound in WO'436.
100. Section 3(d) of the patents act provides that a known substance may include combination of known substances. The claims of the present application are related to a combination of known substances and therefore must fulfil Section 3(d). As submitted above, the applicant has failed to show enhanced efficacy of the claimed compound over the known substance and hence fail to meet the standard laid down under Section 3(d). Hence, the claims of the present application are liable to be rejected under Section 3(d).

### **Claims of Present Application not an invention under Section 3(e)**

101. Without prejudice to other grounds raised herein, the Opponent raises objection under Section 25(1)(f) as the claims of the Present Application fail under Section 3(e).
102. It is submitted that claims 1-7 of the Present Application are liable to be rejected as the claimed compounds are mere admixtures resulting in mere aggregation of properties and not an invention under Section 3(e) of the Patents Act.
103. An applicant claiming a combination of compounds is required to show the enhanced additive effect or synergism in the complete specification itself. *“The question of efficacy and or synergism are matters of scientific facts which are required to be embodied in the specification so that the said characteristics are apparent from the specification.”* (See order of the Asst. Controller of Patents & Designs in patent application no. 314/MUM/2008, at lines 3-5 at internal page 7 and annexed herein as **Exhibit-F**).
104. Merely providing the composition of each of the ingredients in terms of weight does not discharge the burden of showing synergism. The Asst. Controller of Patents & Designs, while rejecting application no. 3725/CHENP/2006, on grounds of Section 3(e) noted, *“Applicant doesn’t provide any supportive experimental data or comparative examples highlighting the surprising and or synergistic effect of the claimed formulation over the prior art compositions. Instead examples 1, 2 and 3 provide only the amount of individual components in grams.”* (See the order of the Controller in 327/CHENP/2006, hereto annexed as **Exhibit-G** at internal page 4. Para 8)
105. It is submitted that composition claimed in Claims 1-7 of the Present Application are mere admixture of known substances resulting in aggregation of properties of the individual components. Therefore, the claimed invention does not overcome S.3(e). Further, the Applicant has failed to disclose any synergistic effect of the claimed composition anywhere in the complete specification. Thus, it is submitted that claims 1-7

of the Present Application are not an invention per Section 3(e) and thus be rejected.

**IV. THAT CLAIMS 1-7 OF THE PRESENT APPLICATION MUST BE REJECTED AS THE COMPLETE SPECIFICATION DOES NOT SUFFICIENTLY AND CLEARLY DESCRIBE THE INVENTION**

106. Without prejudice to the grounds raised in this representation, the Opponent invokes Section 25(1) (g). It is submitted that the Present Application does not sufficiently and clearly describe the invention claimed.
107. It is submitted that the Present Application has failed to indicate why only certain weight of the alleged inventive composition has been claimed. The Applicant has failed to provide any reasoning for the amount of constituents of the composition as claimed in claims 3, 5 and 6 of the Present Application.
108. It is submitted that the Applicant has failed to indicate any advantage of the claimed percentage or specific weight over those broadly disclosed range in the complete specification.
109. It is further submitted that the Applicant has failed to disclose any advantage or benefit of use of the composition claimed in claims 1-7 of the Present Application.
110. The Present Application has not discussed the exact problem in prior art WO'436 which had to be overcome by using the composition as claimed in the Present Application. The Applicant has failed to indicate any specific advantage/ merit of the claimed pharmaceutical composition.

**V. THAT THE APPLICANT HAS FAILED TO DISCLOSE TO THE CONTROLLER THE INFORMATION REQUIRED BY SECTION 8, AND THEREFORE OBJECTION IS RAISED UNDER S.25(1)(h)**

111. It is submitted that Section 25(1)(h) allows raising an objection against grant of patent if the applicant has failed to provide information as required under

Section 8 of the Patents Act. Without prejudice to other grounds raised herein, the Present Application should be rejected because the Patent Applicant has not complied with the mandatory requirements of Section 8 of the Patents Act.

112. It is submitted that the Applicant of the Present Application has not provided detailed particulars of the information required under Section 8. The details of the corresponding national applications vis-à-vis which the information has not been provided by the Applicant are indicated below:

| <b>National Application Number</b> | <b>Information not provided by the Applicant</b>   |
|------------------------------------|--|
| AR064149A1                         | Refusal by the patent office was not communicated by the Applicant                                       |
| EP2086940                          | Opposition filed at EPO and documents pertaining thereto were not forwarded to the Indian Patent Office. |
| BRPI0719693                        | Change in status of the application was not indicated  |
| KR10-2009-7011043                  | Office action of the KIPO was not filed at the Indian Patent Office                                      |

113. It is submitted that the complete information related to the corresponding applications in other jurisdictions has not been provided by the Applicant. The Opponent therefore, requests the Controller to direct the Applicant to submit translated copies of the opposition proceedings and office actions in these jurisdictions to facilitate examination of the Present Application.

**PRAYER FOR RELIEF**

In view of the above said references Opponent prays as follows:

- a) To be heard and be allowed to lead evidence (documentary and oral) before any order is passed;
- b) To reject the claims of Application No. 1220/MUMNP/2009 *in toto*;
- c) To allow the Opponent to file further documents as evidence if necessary to support the averments;



- d) To allow amendment of the opposition as and when the need may arise;
- e) To allow the Opponent to make further submissions in case the Applicant amends the claims;
- f) For costs in this matter;
- g) For any further and other relief in the facts and circumstances that may be granted in favour of the Opponent in the interest of justice.

Dated this the 7<sup>th</sup> day of February 2019

[OPPONENT]

**To**  
**The Controller,**  
**The Patent Office Branch**  
**MUMBAI**

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(71) Applicant (for all designated States except US):  
JANSSEN PHARMACEUTICA N.V. [BE/BE]; Turn-  
houtseweg 30, B-2340 Beerse (BE).

(71) Applicant and

(72) Inventor: GUILLEMONT, Jérôme, Emile, Georges  
[FR/FR]; C/O Janssen-Cilag S.A., 1, rue Camille  
Desmoulins, TSA 91003, F-92787 Issy-les-Moulin-  
eaux Cedex 9 (FR).

(72) Inventors; and

(75) Inventors/Applicants (for US only): VAN GESTEL,

Jozef, Frans, Elisabetha [BE/BE]; c/o Janssen Pharma-  
ceutica N.V., Turnhoutseweg 30, B-2340 Beerse (BE).  
VENET, Marc, Gaston [FR/FR]; 10, Square de Bour-  
gogne, F-76240 Le Mesnil-Esnard (FR). POIGNET,  
Hervé, Jean, Joseph [FR/FR]; C/O Janssen-Cilag S.A.,  
1, rue Camille Desmoulins, TSA 91003, F-92787  
Issy-les-Moulineaux Cedex 9 (FR). DECRANE,  
Laurence, Françoise, Bernadette [FR/FR]; C/O  
Janssen-Cilag S.A., 1, rue Camille Desmoulins, TSA  
91003, F-92787 Issy-les-Moulineaux Cedex 9 (FR).  
VERNIER, Daniel, F., J. [FR/FR]; C/O Janssen-Cilag  
S.A., 1, rue Camille Desmoulins, TSA 91003, F-92787  
Issy-les-Moulineaux Cedex 9 (FR).

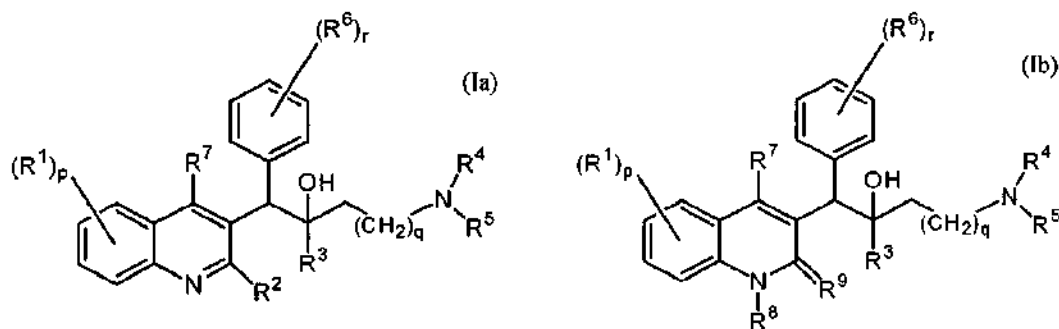
(74) Common Representative: JANSSEN PHARMACEU-  
TICA N.V.; Turnhoutseweg 30, B-2340 Beerse (BE).

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[Continued on next page]

(54) Title: QUINOLINE DERIVATIVES AND THEIR USE AS MYCOBACTERIAL INHIBITORS



(57) Abstract: The present invention relates to novel substituted quinoline derivatives according to the general Formula (Ia) or the general Formula (Ib), the pharmaceutically acceptable acid or base addition salts thereof, the stereochemically isomeric forms thereof, the tautomeric forms thereof and the *N*-oxide forms thereof. The claimed compounds are useful for the treatment of mycobacterial diseases, particularly those diseases caused by pathogenic mycobacteria such as *Mycobacterium tuberculosis*, *M. bovis*, *M. avium* and *M. marinum*. In particular, compounds are claimed in which, independently from each other, R<sup>1</sup> is bromo, p=1, R<sup>2</sup> is alkyloxy, R<sup>3</sup> is optionally substituted naphthyl or phenyl, q=1, R<sup>4</sup> and R<sup>5</sup> each independently are hydrogen, methyl or ethyl, R<sup>6</sup> is hydrogen, r is equal to 0 or 1 and R<sup>7</sup> is hydrogen. Also claimed is a composition comprising a pharmaceutically acceptable carrier and, as active ingredient, a therapeutically effective amount of the claimed compounds, the use of the claimed compounds or compositions for the manufacture of a medicament for the treatment of mycobacterial diseases and a process for preparing the claimed compounds.

WO 2004/011436 A1



SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

**Declarations under Rule 4.17:**

- *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii)) for all designations*
- *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii)) for all designations*
- *of inventorship (Rule 4.17(iv)) for US only*

**Published:**

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- *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

*For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.*

## QUINOLINE DERIVATIVES AND THEIR USE AS MYCOBACTERIAL INHIBITORS

5 The present invention relates to novel substituted quinoline derivatives useful for the treatment of mycobacterial diseases, particularly those diseases caused by pathogenic mycobacteria such as *Mycobacterium tuberculosis*, *M. bovis*, *M. avium* and *M. marinum*.

## 10 BACKGROUND OF THE INVENTION

*Mycobacterium tuberculosis* is the causative agent of tuberculosis (TB), a serious and potentially fatal infection with a world-wide distribution. Estimates from the World Health Organization indicate that more than 8 million people contract TB each year, and 2 million people die from tuberculosis yearly. In the last decade, TB cases have grown 20% worldwide with the highest burden in the most impoverished communities. If these trends continue, TB incidence will increase by 41% in the next twenty years. Fifty years since the introduction of an effective chemotherapy, TB remains after AIDS, the leading infectious cause of adult mortality in the world. Complicating the TB epidemic is the rising tide of multi-drug-resistant strains, and the deadly symbiosis with HIV. People who are HIV-positive and infected with TB are 30 times more likely to develop active TB than people who are HIV-negative and TB is responsible for the death of one out of every three people with HIV/AIDS worldwide

25 Existing approaches to treatment of tuberculosis all involve the combination of multiple agents. For example, the regimen recommended by the U.S. Public Health Service is a combination of isoniazid, rifampicin and pyrazinamide for two months, followed by isoniazid and rifampicin alone for a further four months. These drugs are continued for a further seven months in patients infected with HIV. For patients infected with multi-drug resistant strains of *M. tuberculosis*, agents such as ethambutol, streptomycin, kanamycin, amikacin, capreomycin, ethionamide, cycloserine, ciprofloxacin and ofloxacin are added to the combination therapies. There exists no single agent that is effective in the clinical treatment of tuberculosis, nor any combination of agents that offers the possibility of therapy of less than six months' duration.

35

There is a high medical need for new drugs that improve current treatment by enabling regimens that facilitate patient and provider compliance. Shorter regimens and those that require less supervision are the best way to achieve this. Most of the benefit from

treatment comes in the first 2 months, during the intensive, or bactericidal, phase when four drugs are given together; the bacterial burden is greatly reduced, and patients become noninfectious. The 4- to 6-month continuation, or sterilizing, phase is required to eliminate persisting bacilli and to minimize the risk of relapse. A potent sterilizing drug that shortens treatment to 2 months or less would be extremely beneficial. Drugs that facilitate compliance by requiring less intensive supervision also are needed. Obviously, a compound that reduces both the total length of treatment and the frequency of drug administration would provide the greatest benefit.

10 Complicating the TB epidemic is the increasing incidence of multi-drug- resistant strains or MDR-TB. Up to four percent of all cases worldwide are considered MDR-TB - those resistant to the most effective drugs of the four-drug standard, isoniazid and rifampin. MDR-TB is lethal when untreated and can not be adequately treated through the standard therapy, so treatment requires up to 2 years of "second-line" drugs. These drugs are often toxic, expensive and marginally effective. In the absence of an effective therapy, infectious MDR-TB patients continue to spread the disease, producing new infections with MDR-TB strains. There is a high medical need for a new drug with a new mechanism of action, which is likely to demonstrate activity against MDR strains.

20 The purpose of the present invention is to provide novel compounds, in particular substituted quinoline derivatives, having the property of inhibiting growth of mycobacteria and therefore useful for the treatment of mycobacterial diseases, particularly those diseases caused by pathogenic mycobacteria such as *Mycobacterium tuberculosis*, *M. bovis*, *M. avium* and *M. marinum*.

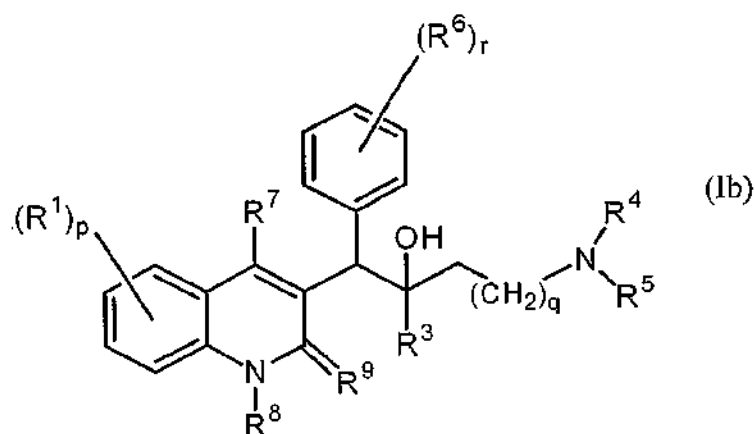
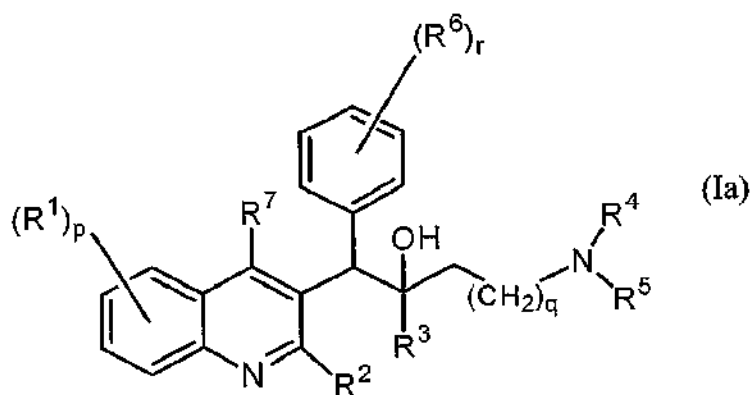
25 Substituted quinolines were already disclosed in US 5,965,572 (The United States of America) for treating antibiotic resistant infections and in WO 00/34265 to inhibit the growth of bacterial microorganisms. None of these publications disclose the substituted quinoline derivatives according to our invention.

30

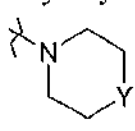
## SUMMARY OF THE INVENTION

The present invention relates to novel substituted quinoline derivatives according to Formula (Ia) or Formula (Ib)

35



the pharmaceutically acceptable acid or base addition salts thereof, the stereochemically isomeric forms thereof, the tautomeric forms thereof and the *N*-oxide forms thereof, wherein :

- 5  $R^1$  is hydrogen, halo, haloalkyl, cyano, hydroxy, Ar, Het, alkyl, alkyloxy, alkylthio, alkyloxyalkyl, alkylthioalkyl, Ar-alkyl or di(Ar)alkyl ;
- $p$  is an integer equal to zero, 1, 2, 3 or 4 ;
- $R^2$  is hydrogen, hydroxy, thio, alkyloxy, alkyloxyalkoxy, alkylthio, mono
- 10 or di(alkyl)amino or a radical of formula  wherein Y is CH<sub>2</sub>, O, S, NH or N-alkyl ;
- $R^3$  is alkyl, Ar, Ar-alkyl, Het or Het-alkyl;
- $q$  is an integer equal to zero, 1, 2, 3 or 4 ;
- $R^4$  and  $R^5$  each independently are hydrogen, alkyl or benzyl; or
- 15  $R^4$  and  $R^5$  together and including the N to which they are attached may form a radical selected from the group of pyrrolidinyl, 2H-pyrrolyl, 2-pyrrolinyl, 3-pyrrolinyl, pyrrolyl, imidazolidinyl, pyrazolidinyl, 2-imidazoliny, 2-pyrazolinyl, imidazolyl, pyrazolyl, triazolyl, piperidinyl, pyridinyl, piperazinyl, imidazolidinyl, pyridazinyl, pyrimidinyl, pyrazinyl,

- triazinyl, morpholinyl and thiomorpholinyl, optionally substituted with alkyl, halo, haloalkyl, hydroxy, alkyloxy, amino, mono- or dialkylamino, alkylthio, alkyloxyalkyl, alkylthioalkyl and pyrimidinyl ;
- 5  $R^6$  is hydrogen, halo, haloalkyl, hydroxy, Ar, alkyl, alkyloxy, alkylthio, alkyloxyalkyl, alkylthioalkyl, Ar-alkyl or di(Ar)alkyl ; or two vicinal  $R^6$  radicals may be taken together to form a bivalent radical of formula  $=C-C=C=C-$  ;
- $r$  is an integer equal to 0, 1, 2, 3, 4 or 5 ; and
- $R^7$  is hydrogen, alkyl, Ar or Het ;
- 10  $R^8$  is hydrogen or alkyl ;
- $R^9$  is oxo ; or
- $R^8$  and  $R^9$  together form the radical  $=N-CH=CH-$  .
- alkyl is a straight or branched saturated hydrocarbon radical having from 1 to 6 carbon atoms ; or is a cyclic saturated hydrocarbon radical having from 3 to 6 carbon atoms ; or is a a cyclic saturated hydrocarbon radical having from 3 to 6 carbon atoms attached to a straight or branched saturated hydrocarbon radical having from 1 to 6 carbon atoms ; wherein each carbon atom can be optionally substituted with halo, hydroxy, alkyloxy or oxo ;
- 15 Ar is a homocycle selected from the group of phenyl, naphthyl, acenaphthyl, tetrahydronaphthyl, each optionally substituted with 1, 2 or 3 substituents, each substituent independently selected from the group of hydroxy, halo, cyano, nitro, amino, mono- or dialkylamino, alkyl, haloalkyl, alkyloxy, haloalkyloxy, carboxyl, alkyloxycarbonyl, aminocarbonyl, morpholinyl and mono- or dialkylaminocarbonyl ;
- 20 Het is a monocyclic heterocycle selected from the group of N-phenoxy piperidinyl, pyrrolyl, pyrazolyl, imidazolyl, furanyl, thienyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, pyridinyl, pyrimidinyl, pyrazinyl and pyridazinyl; or a bicyclic heterocycle selected from the group of quinolinyl, quinoxalinyl, indolyl, benzimidazolyl, benzoxazolyl, benzisoxazolyl, benzothiazolyl, benzisothiazolyl, benzofuranyl, benzothienyl, 2,3-dihydrobenzo[1,4]dioxinyl or benzo[1,3]dioxolyl ; each monocyclic and bicyclic heterocycle may optionally be substituted on a carbon atom with 1, 2 or 3 substituents selected from the group of halo, hydroxy, alkyl or alkyloxy ;
- 25 halo is a substituent selected from the group of fluoro, chloro, bromo and iodo and
- 35 haloalkyl is a straight or branched saturated hydrocarbon radical having from 1 to 6 carbon atoms or a cyclic saturated hydrocarbon radical having from 3 to 6 carbon atoms, wherein one or more carbon atoms are substituted with one or more halo-atoms.

The compounds according to Formula (Ia) and (Ib) are interrelated in that e.g. a compound according to Formula (Ib), with R<sup>9</sup> equal to oxo is the tautomeric equivalent of a compound according to Formula (Ia) with R<sup>2</sup> equal to hydroxy (keto-enol tautomerism).

#### DETAILED DESCRIPTION

In the framework of this application, alkyl is a straight or branched saturated hydrocarbon radical having from 1 to 6 carbon atoms ; or is a cyclic saturated hydrocarbon radical having from 3 to 6 carbon atoms ; or is a cyclic saturated hydrocarbon radical having from 3 to 6 carbon atoms attached to a straight or branched saturated hydrocarbon radical having from 1 to 6 carbon atoms ; wherein each carbon atom can be optionally substituted with halo, hydroxy, alkyloxy or oxo.

Preferably, alkyl is methyl, ethyl or cyclohexylmethyl.

In the framework of this application, Ar is a homocycle selected from the group of phenyl, naphthyl, acenaphthyl, tetrahydronaphthyl, each optionally substituted with 1, 2 or 3 substituents, each substituent independently selected from the group of hydroxy, halo, cyano, nitro, amino, mono- or dialkylamino, alkyl, haloalkyl, alkyloxy, haloalkyloxy, carboxyl, alkyloxycarbonyl, aminocarbonyl, morpholinyl and mono- or dialkylaminocarbonyl. Preferably, Ar is naphthyl or phenyl, each optionally substituted with 1 or 2 halo substituents.

In the framework of this application, Het is a monocyclic heterocycle selected from the group of N-phenoxy piperidinyl, pyrrolyl, pyrazolyl, imidazolyl, furanyl, thienyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, pyridinyl, pyrimidinyl, pyrazinyl and pyridazinyl; or a bicyclic heterocycle selected from the group of quinolinyl, quinoxalinyl, indolyl, benzimidazolyl, benzoxazolyl, benzisoxazolyl, benzothiazolyl, benzisothiazolyl, benzofuranyl, benzothienyl, 2,3-dihydrobenzo[1,4]dioxinyl or benzo[1,3]dioxolyl ; each monocyclic and bicyclic heterocycle may optionally be substituted on a carbon atom with 1, 2 or 3 substituents selected from the group of halo, hydroxy, alkyl or alkyloxy. Preferably, Het is thienyl.

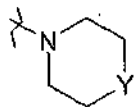
In the framework of this application, halo is a substituent selected from the group of fluoro, chloro, bromo and iodo and haloalkyl is a straight or branched saturated hydrocarbon radical having from 1 to 6 carbon atoms or a cyclic saturated hydrocarbon radical having from 3 to 6 carbon atoms, wherein one or more carbon atoms are



substituted with one or more halo-atoms. Preferably, halo is bromo, fluoro or chloro and preferably, haloalkyl is trifluoromethyl.

Preferably, the invention relates to compounds of Formula (Ia) and (Ib) wherein :

- 5  $R^1$  is hydrogen, halo, cyano, Ar, Het, alkyl, and alkyloxy ;  
 $p$  is an integer equal to zero, 1, 2, 3 or 4 ;  
 $R^2$  is hydrogen, hydroxy, alkyloxy, alkyloxyalkyloxy, alkylthio or a radical



of formula  wherein Y is O ;

- $R^3$  is alkyl, Ar, Ar-alkyl or Het ;  
 10  $q$  is an integer equal to zero, 1, 2, or 3 ;  
 $R^4$  and  $R^5$  each independently are hydrogen, alkyl or benzyl; or  
 $R^4$  and  $R^5$  together and including the N to which they are attached may form a radical  
 selected from the group of pyrrolidinyl, imidazolyl, triazolyl,  
 piperidinyl, piperazinyl, pyrazinyl, morpholinyl and thiomorpholinyl,  
 15 optionally substituted with alkyl and pyrimidinyl ;  
 $R^6$  is hydrogen, halo or alkyl ; or  
 two vicinal  $R^6$  radicals may be taken together to form a bivalent radical of formula  
 $=C-C=C=C-$  ;  
 $r$  is an integer equal to 1 ; and  
 20  $R^7$  is hydrogen ;  
 $R^8$  is hydrogen or alkyl ;  
 $R^9$  is oxo ; or  
 $R^8$  and  $R^9$  together form the radical  $=N-CH=CH-$  .

alkyl is a straight or branched saturated hydrocarbon radical having from 1 to 6  
 25 carbon atoms ; or is a cyclic saturated hydrocarbon radical having from 3 to 6  
 carbon atoms ; or is a cyclic saturated hydrocarbon radical having from 3 to 6  
 carbon atoms attached to a straight or branched saturated hydrocarbon radical  
 having from 1 to 6 carbon atoms ; wherein each carbon atom can be optionally  
 substituted with halo or hydroxy ;

30 Ar is a homocycle selected from the group of phenyl, naphthyl, acenaphthyl,  
 tetrahydronaphthyl, each optionally substituted with 1, 2 or 3 substituents, each  
 substituent independently selected from the group of halo, haloalkyl, cyano,  
 alkyloxy and morpholinyl ;

35 Het is a monocyclic heterocycle selected from the group of N-phenoxy piperidinyl,  
 furanyl, thienyl, pyridinyl, pyrimidinyl ; or a bicyclic heterocycle selected from

the group of benzothienyl, 2,3-dihydrobenzo[1,4]dioxinyl or benzo[1,3]-  
dioxolyl; each monocyclic and bicyclic heterocycle may optionally be  
substituted on a carbon atom with 1, 2 or 3 alkyl substituents ; and  
halo is a substituent selected from the group of fluoro, chloro and bromo.

5

For compounds according to either Formula (Ia) and (Ib), preferably,  $R^1$  is hydrogen,  
halo, Ar, alkyl or alkyloxy. More preferably,  $R^1$  is halo. Most preferably,  $R^1$  is bromo.

Preferably, p is equal to 1.

10

Preferably,  $R^2$  is hydrogen, alkyloxy or alkylthio. More preferably,  $R^2$  is alkyloxy.  
Most preferably,  $R^2$  is methyloxy.

15

Preferably,  $R^3$  is naphthyl, phenyl or thienyl, each optionally substituted with 1 or 2  
substituents, that substituent preferably being a halo or haloalkyl, most preferably being  
a halo. More preferably,  $R^3$  is naphthyl or phenyl. Most preferably,  $R^3$  is naphthyl.

Preferably, q is equal to zero, 1 or 2. More preferably, q is equal to 1.

20

Preferably,  $R^4$  and  $R^5$  each independently are hydrogen or alkyl, more preferably  
hydrogen, methyl or ethyl, most preferably methyl.

25

Preferably  $R^4$  and  $R^5$  together and including the N to which they are attached form a  
radical selected from the group of imidazolyl, triazolyl, piperidiny, piperazinyl and  
thiomorpholinyl, optionally substituted with alkyl, halo, haloalkyl, hydroxy, alkyloxy,  
alkylthio, alkyloxyalkyl or alkylthioalkyl, preferably substituted with alkyl, most  
preferably substituted with methyl or ethyl.

30

Preferably,  $R^6$  is hydrogen, alkyl or halo. Most preferably,  $R^6$  is hydrogen. Preferably r  
is 0, 1 or 2.

Preferably,  $R^7$  is hydrogen or methyl.

35

For compounds according to Formula (Ib) only, preferably,  $R^8$  is alkyl, preferably  
methyl and  $R^9$  is oxygen.

An interesting group of compounds are those compounds according to Formula (Ia), the  
pharmaceutically acceptable acid or base addition salts thereof, the stereochemically

isomeric forms thereof, the tautomeric forms thereof and the *N*-oxide forms thereof, in which R<sup>1</sup> is hydrogen, halo, Ar, alkyl or alkyloxy, p = 1, R<sup>2</sup> is hydrogen, alkyloxy or alkylthio, R<sup>3</sup> is naphthyl, phenyl or thienyl, each optionally substituted with 1 or 2 substituents selected from the group of halo and haloalkyl, q = 0, 1, 2 or 3, R<sup>4</sup> and R<sup>5</sup> each independently are hydrogen or alkyl or R<sup>4</sup> and R<sup>5</sup> together and including the N to which they are attached form a radical selected from the group of imidazolyl, triazolyl, piperidinyl, piperazinyl and thiomorpholinyl, R<sup>6</sup> is hydrogen, alkyl or halo, r is equal to 0 or 1 and R<sup>7</sup> is hydrogen.

10 Most preferable, the compound is :

- 1-(6-bromo-2-methoxy-quinolin-3-yl)-2-(3,5-difluoro-phenyl)-4-dimethylamino-1-phenyl-butan-2-ol ;
- 1-(6-bromo-2-methoxy-quinolin-3-yl)-4-dimethylamino-2-naphthalen-1-yl-1-phenyl-butan-2-ol ;
- 15 ○ 1-(6-bromo-2-methoxy-quinolin-3-yl)-2-(2,5-difluoro-phenyl)-4-dimethylamino-1-phenyl-butan-2-ol ;
- 1-(6-bromo-2-methoxy-quinolin-3-yl)-2-(2,3-difluoro-phenyl)-4-dimethylamino-1-phenyl-butan-2-ol ;
- 1-(6-bromo-2-methoxy-quinolin-3-yl)-4-dimethylamino-2-(2-fluoro-phenyl)-1-phenyl-butan-2-ol ;
- 20 ○ 1-(6-bromo-2-methoxy-quinolin-3-yl)-4-dimethylamino-2-naphthalen-1-yl-1-p-tolyl-butan-2-ol ;
- 1-(6-bromo-2-methoxy-quinolin-3-yl)-4-methylamino-2-naphthalen-1-yl-1-phenyl-butan-2-ol ; and
- 25 ○ 1-(6-bromo-2-methoxy-quinolin-3-yl)-4-dimethylamino-2-(3-fluoro-phenyl)-1-phenyl-butan-2-ol,

the pharmaceutically acceptable acid or base addition salts thereof, the stereochemically isomeric forms thereof, the tautomeric forms thereof and the *N*-oxide forms thereof.

30

The pharmaceutically acceptable acid addition salts are defined to comprise the therapeutically active non-toxic acid addition salt forms which the compounds according to either Formula (Ia) and (Ib) are able to form. Said acid addition salts can be obtained by treating the base form of the compounds according to either Formula (Ia) and (Ib) with appropriate acids, for example inorganic acids, for example hydrohalic acid, in particular hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid and phosphoric acid ; organic acids, for example acetic acid, hydroxyacetic acid, propanoic acid, lactic acid, pyruvic acid, oxalic acid, malonic acid, succinic acid,

35

maleic acid, fumaric acid, malic acid, tartaric acid, citric acid, methanesulfonic acid, ethanesulfonic acid, benzenesulfonic acid, p-toluenesulfonic acid, cyclamic acid, salicylic acid, p-aminosalicylic acid and pamoic acid.

- 5 The compounds according to either Formula (Ia) and (Ib) containing acidic protons may also be converted into their therapeutically active non-toxic base addition salt forms by treatment with appropriate organic and inorganic bases. Appropriate base salts forms comprise, for example, the ammonium salts, the alkaline and earth alkaline metal salts, in particular lithium, sodium, potassium, magnesium and calcium salts,  
0 salts with organic bases, e.g. the benzathine, *N*-methyl-D-glucamine, hybamine salts, and salts with amino acids, for example arginine and lysine.

Conversely, said acid or base addition salt forms can be converted into the free forms by treatment with an appropriate base or acid.

5

The term addition salt as used in the framework of this application also comprises the solvates which the compounds according to either Formula (Ia) and (Ib) as well as the salts thereof, are able to form. Such solvates are, for example, hydrates and alcoholates.

10

The term "stereochemically isomeric forms" as used herein defines all possible isomeric forms which the compounds of either Formula (Ia) and (Ib) may possess. Unless otherwise mentioned or indicated, the chemical designation of compounds denotes the mixture of all possible stereochemically isomeric forms, said mixtures  
25 containing all diastereomers and enantiomers of the basic molecular structure. More in particular, stereogenic centers may have the *R*- or *S*-configuration; substituents on bivalent cyclic (partially) saturated radicals may have either the *cis*- or *trans*-configuration. Stereochemically isomeric forms of the compounds of either Formula (Ia) and (Ib) are obviously intended to be embraced within the scope of this invention.

30

Following CAS-nomenclature conventions, when two stereogenic centers of known absolute configuration are present in a molecule, an *R* or *S* descriptor is assigned (based on Cahn-Ingold-Prelog sequence rule) to the lowest-numbered chiral center, the reference center. The configuration of the second stereogenic center is indicated using  
35 relative descriptors [*R*\*,*R*\*] or [*R*\*,*S*\*], where *R*\* is always specified as the reference center and [*R*\*,*R*\*] indicates centers with the same chirality and [*R*\*,*S*\*] indicates centers of unlike chirality. For example, if the lowest-numbered chiral center in the molecule has an *S* configuration and the second center is *R*, the stereo descriptor would

be specified as  $S$ -[ $R^*$ , $S^*$ ]. If " $\alpha$ " and " $\beta$ " are used : the position of the highest priority substituent on the asymmetric carbon atom in the ring system having the lowest ring number, is arbitrarily always in the " $\alpha$ " position of the mean plane determined by the ring system. The position of the highest priority substituent on the other asymmetric  
5 carbon atom in the ring system relative to the position of the highest priority substituent on the reference atom is denominated " $\alpha$ ", if it is on the same side of the mean plane determined by the ring system, or " $\beta$ ", if it is on the other side of the mean plane determined by the ring system.

10 Compounds of either Formula (Ia) and (Ib) and some of the intermediate compounds invariably have at least two stereogenic centers in their structure which may lead to at least 4 stereochemically different structures.

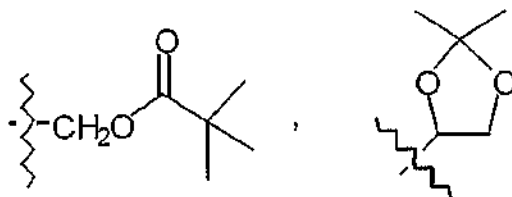
The tautomeric forms of the compounds of either Formula (Ia) and (Ib) are meant to  
15 comprise those compounds of either Formula (Ia) and (Ib) wherein e.g. an enol group is converted into a keto group (keto-enol tautomerism).

The  $N$ -oxide forms of the compounds according to either Formula (Ia) and (Ib) are meant to comprise those compounds of either Formula (Ia) and (Ib) wherein one or  
20 several nitrogen atoms are oxidized to the so-called  $N$ -oxide, particularly those  $N$ -oxides wherein the nitrogen of the amine radical is oxidized.

The compounds of either Formula (Ia) and (Ib) as prepared in the processes described below may be synthesized in the form of racemic mixtures of enantiomers which can  
25 be separated from one another following art-known resolution procedures. The racemic compounds of either Formula (Ia) and (Ib) may be converted into the corresponding diastereomeric salt forms by reaction with a suitable chiral acid. Said diastereomeric salt forms are subsequently separated, for example, by selective or fractional crystallization and the enantiomers are liberated therefrom by alkali. An  
30 alternative manner of separating the enantiomeric forms of the compounds of either Formula (Ia) and (Ib) involves liquid chromatography using a chiral stationary phase. Said pure stereochemically isomeric forms may also be derived from the corresponding pure stereochemically isomeric forms of the appropriate starting materials, provided that the reaction occurs stereospecifically. Preferably if a specific stereoisomer is  
35 desired, said compound will be synthesized by stereospecific methods of preparation. These methods will advantageously employ enantiomerically pure starting materials.

The invention also comprises derivative compounds (usually called "pro-drugs") of the pharmacologically-active compounds according to the invention, which are degraded *in vivo* to yield the compounds according to the invention. Pro-drugs are usually (but not always) of lower potency at the target receptor than the compounds to which they are degraded. Pro-drugs are particularly useful when the desired compound has chemical or physical properties that make its administration difficult or inefficient. For example, the desired compound may be only poorly soluble, it may be poorly transported across the mucosal epithelium, or it may have an undesirably short plasma half-life. Further discussion on pro-drugs may be found in Stella, V. J. *et al.*, "Prodrugs", *Drug Delivery Systems*, 1985, pp. 112-176, and *Drugs*, 1985, **29**, pp. 455-473.

Pro-drugs forms of the pharmacologically-active compounds according to the invention will generally be compounds according to either Formula (Ia) and (Ib), the pharmaceutically acceptable acid or base addition salts thereof, the stereochemically isomeric forms thereof, the tautomeric forms thereof and the *N*-oxide forms thereof, having an acid group which is esterified or amidated. Included in such esterified acid groups are groups of the formula  $-\text{COOR}^x$ , where  $\text{R}^x$  is a  $\text{C}_{1-6}$ alkyl, phenyl, benzyl or one of the following groups :



20

Amidated groups include groups of the formula  $-\text{CONR}^y\text{R}^z$ , wherein  $\text{R}^y$  is H,  $\text{C}_{1-6}$ alkyl, phenyl or benzyl and  $\text{R}^z$  is  $-\text{OH}$ , H,  $\text{C}_{1-6}$ alkyl, phenyl or benzyl.

Compounds according to the invention having an amino group may be derivatised with a ketone or an aldehyde such as formaldehyde to form a Mannich base. This base will hydrolyze with first order kinetics in aqueous solution.

The compounds according to the invention have surprisingly been shown to be suitable for the treatment of mycobacterial diseases, particularly those diseases caused by pathogenic mycobacteria such as *Mycobacterium tuberculosis*, *M. bovis*, *M. avium* and *M. marinum*. The present invention thus also relates to compounds of either Formula (Ia) and (Ib) as defined hereinabove, the pharmaceutically acceptable acid or base

addition salts thereof, the stereochemically isomeric forms thereof, the tautomeric forms thereof and the *N*-oxide forms thereof, for use as a medicine.

The invention also relates to a composition comprising a pharmaceutically acceptable carrier and, as active ingredient, a therapeutically effective amount of a compound according to the invention. The compounds according to the invention may be formulated into various pharmaceutical forms for administration purposes. As appropriate compositions there may be cited all compositions usually employed for systemically administering drugs. To prepare the pharmaceutical compositions of this invention, an effective amount of the particular compound, optionally in addition salt form, as the active ingredient is combined in intimate admixture with a pharmaceutically acceptable carrier, which carrier may take a wide variety of forms depending on the form of preparation desired for administration. These pharmaceutical compositions are desirable in unitary dosage form suitable, in particular, for administration orally or by parenteral injection. For example, in preparing the compositions in oral dosage form, any of the usual pharmaceutical media may be employed such as, for example, water, glycols, oils, alcohols and the like in the case of oral liquid preparations such as suspensions, syrups, elixirs, emulsions and solutions; or solid carriers such as starches, sugars, kaolin, diluents, lubricants, binders, disintegrating agents and the like in the case of powders, pills, capsules and tablets. Because of their ease in administration, tablets and capsules represent the most advantageous oral dosage unit forms in which case solid pharmaceutical carriers are obviously employed. For parenteral compositions, the carrier will usually comprise sterile water, at least in large part, though other ingredients, for example, to aid solubility, may be included. Injectable solutions, for example, may be prepared in which the carrier comprises saline solution, glucose solution or a mixture of saline and glucose solution. Injectable suspensions may also be prepared in which case appropriate liquid carriers, suspending agents and the like may be employed. Also included are solid form preparations which are intended to be converted, shortly before use, to liquid form preparations.

Depending on the mode of administration, the pharmaceutical composition will preferably comprise from 0.05 to 99 % by weight, more preferably from 0.1 to 70 % by weight of the active ingredient, and, from 1 to 99.95 % by weight, more preferably from 30 to 99.9 weight % of a pharmaceutically acceptable carrier, all percentages being based on the total composition.

The pharmaceutical composition may additionally contain various other ingredients known in the art, for example, a lubricant, stabilising agent, buffering agent, emulsifying agent, viscosity-regulating agent, surfactant, preservative, flavouring or colorant.

5  
It is especially advantageous to formulate the aforementioned pharmaceutical compositions in unit dosage form for ease of administration and uniformity of dosage. Unit dosage form as used herein refers to physically discrete units suitable as unitary dosages, each unit containing a predetermined quantity of active ingredient calculated  
10 to produce the desired therapeutic effect in association with the required pharmaceutical carrier. Examples of such unit dosage forms are tablets (including scored or coated tablets), capsules, pills, powder packets, wafers, suppositories, injectable solutions or suspensions and the like, and segregated multiples thereof. The daily dosage of the compound according to the invention will, of course, vary with  
15 the compound employed, the mode of administration, the treatment desired and the mycobacterial disease indicated. However, in general, satisfactory results will be obtained when the compound according to the invention is administered at a daily dosage not exceeding 1 gram, e.g. in the range from 10 to 50 mg/kg body weight.

20 Further, the present invention also relates to the use of a compound of either Formula (Ia) and (Ib), the pharmaceutically acceptable acid or base addition salts thereof, the stereochemically isomeric forms thereof, the tautomeric forms thereof and the *N*-oxide forms thereof, as well as any of the aforementioned pharmaceutical compositions thereof for the manufacture of a medicament for the treatment of mycobacterial  
25 diseases.

Accordingly, in another aspect, the invention provides a method of treating a patient suffering from , or at risk of, a mycobacterial disease, which comprises administering to the patient a therapeutically effective amount of a compound or pharmaceutical  
30 composition according to the invention.

#### GENERAL PREPARATION

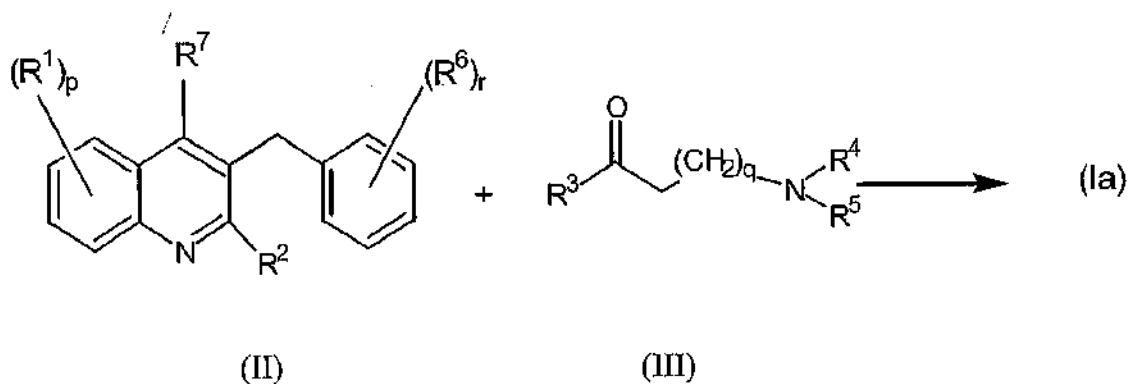
35 The compounds according to the invention can generally be prepared by a succession of steps, each of which is known to the skilled person.



In particular, the compounds according to Formula (Ia) can be prepared by reacting an intermediate compound of Formula (II) with an intermediate compound of Formula (III) according to the following reaction scheme (1):

5

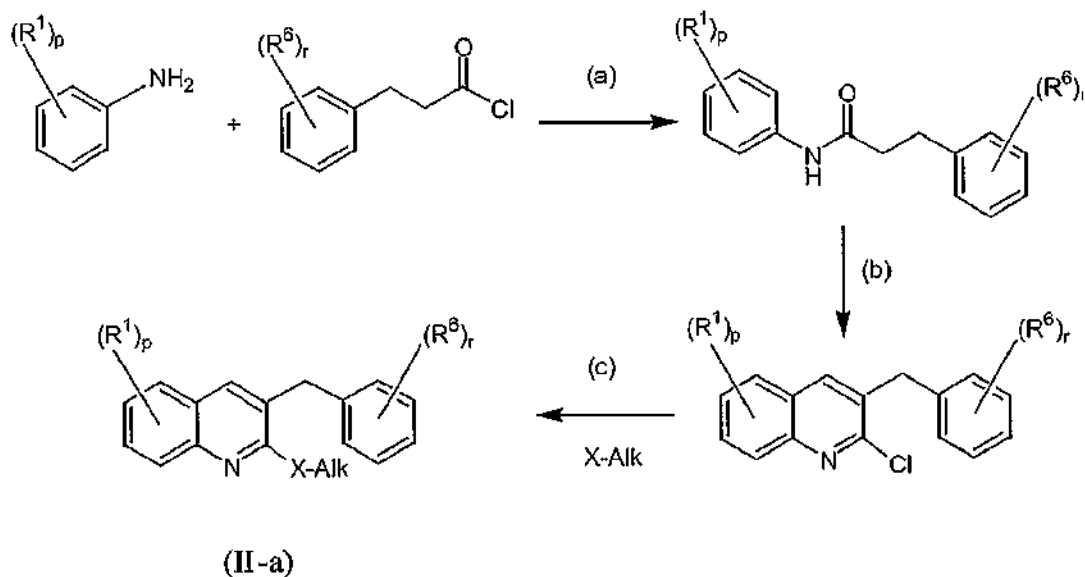
Scheme 1



using BuLi in a mixture of DIPA and THF, wherein all variables are defined as in Formula (Ia). Stirring may enhance the rate of the reaction. The reaction may  
 10 conveniently be carried out at a temperature ranging between  $-20$  and  $-70$  °C.

The starting materials and the intermediate compounds of Formula (II) and (III) are compounds that are either commercially available or may be prepared according to conventional reaction procedures generally known in the art. For example,  
 15 intermediate compounds of Formula (II-a) may be prepared according to the following reaction scheme (2):

Scheme 2



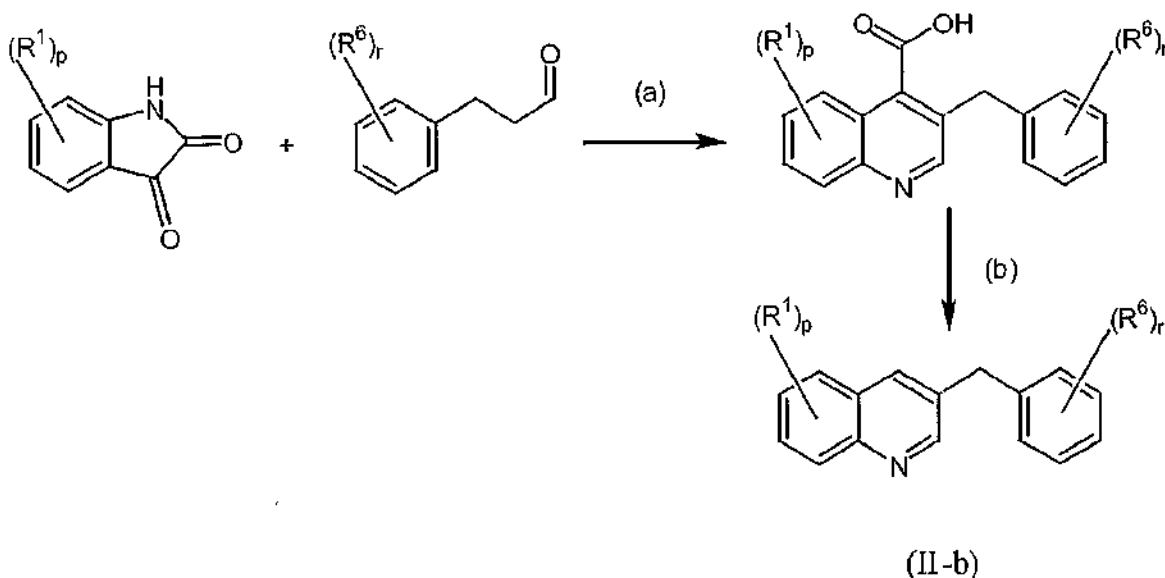
wherein all variables are defined as in Formula (Ia) and (Ib). Reaction scheme (2) comprises step (a) in which an appropriately substituted aniline is reacted with an appropriate acylchloride such as 3-phenylpropionyl chloride, 3-fluorobenzenepropionyl chloride or p-chlorobenzenepropionyl chloride, in the presence of a suitable base, such as triethylamine and a suitable reaction-inert solvent, such as methylene chloride or ethylene dichloride. The reaction may conveniently be carried out at a temperature ranging between room temperature and reflux temperature. In a next step (b) the adduct obtained in step (a) is reacted with phosphoryl chloride ( $\text{POCl}_3$ ) in the presence of N,N-dimethylformamide (Vilsmeier-Haack formylation followed by cyclization). The reaction may conveniently be carried out at a temperature ranging between room temperature and reflux temperature. In a next step (c) a specific  $\text{R}^3$ -group, wherein  $\text{R}^3$  is an alkyloxy or alkylthio radical is introduced by reacting the intermediate compound obtained in step (b) with a compound X-Alk, wherein X=S or O and Alk is an alkylgroup as defined in Formula (Ia) and (Ib).

15

Intermediate compounds according to Formula (II-b) may be prepared according to the following reaction scheme (3), wherein in a first step (a) a substituted indole-2,3-dione is reacted with a substituted 3-phenylpropionaldehyde in the presence of a suitable base such as sodium hydroxide (Pfitzinger reaction), after which the carboxylic acid compound in a next step (b) is decarboxylated at high temperature in the presence of a suitable reaction-inert solvent such as diphenylether.

20

Scheme 3



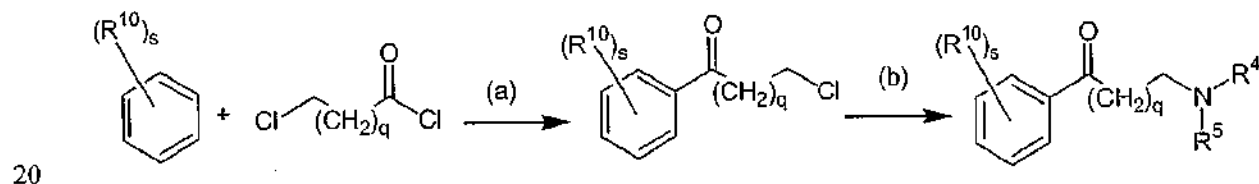
25

It is evident that in the foregoing and in the following reactions, the reaction products

may be isolated from the reaction medium and, if necessary, further purified according to methodologies generally known in the art, such as extraction, crystallization and chromatography. It is further evident that reaction products that exist in more than one enantiomeric form, may be isolated from their mixture by known techniques, in particular preparative chromatography, such as preparative HPLC. Typically, compounds of Formula (Ia) and (Ib) may be separated into their isomeric forms.

The intermediate compounds of Formula (III) are compounds that are either commercially available or may be prepared according to conventional reaction procedures generally known in the art. For example, intermediate compounds of Formula (III-a) in which  $R^3$  is Ar substituted with  $s$  substituents  $R^{10}$ , wherein each  $R^{10}$  is independently selected from the group of hydroxy, halo, cyano, nitro, amino, mono- or dialkylamino, alkyl, haloalkyl, alkyloxy, haloalkyloxy, carboxyl, alkyloxycarbonyl, aminocarbonyl, morpholinyl and mono- or dialkylaminocarbonyl and  $s$  is an integer equal to zero, 1, 2 or 3, may be prepared according to the following reaction scheme (4):

Scheme 4



Reaction scheme (4) comprises step (a) in which an appropriately substituted phenyl is reacted by Friedel-Craft reaction with an appropriate acylchloride such as 3-chloropropionyl chloride or 4-chlorobutyryl chloride, in the presence of a suitable Lewis acid, such as  $AlCl_3$ ,  $FeCl_3$ ,  $SnCl_4$ ,  $TiCl_4$  or  $ZnCl_2$  and a suitable reaction-inert solvent, such as methylene chloride or ethylene dichloride. The reaction may conveniently be carried out at a temperature ranging between room temperature and reflux temperature. In a next step (b) an amino group ( $-NR_4R_5$ ) is introduced by reacting the intermediate compound obtained in step (a) with a primary or secondary amine.

The following examples illustrate the present invention without being limited thereto.

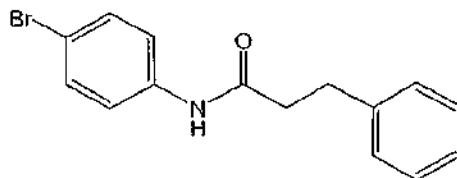
## EXPERIMENTAL PART

Of some compounds the absolute stereochemical configuration of the stereogenic carbon atom(s) therein was not experimentally determined. In those cases the stereochemically isomeric form which was first isolated is designated as "A" and the second as "B", without further reference to the actual stereochemical configuration. However, said "A" and "B" isomeric forms can be unambiguously characterized by a person skilled in the art, using art-known methods such as, for example, X-ray diffraction. The isolation method is described in detail below.

Hereinafter, "DMF" is defined as *N,N*-dimethylformamide, "DIPE" is defined as diisopropyl ether, "THF" is defined as tetrahydrofuran.

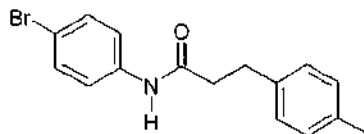
A. Preparation of the intermediate compoundsExample A1

Preparation of intermediate compound 1



Benzenepropanoylchloride (0.488 mol) was added dropwise at room temperature to a solution of 4-bromobenzenamine (0.407 mol) in Et<sub>3</sub>N (70ml) and CH<sub>2</sub>Cl<sub>2</sub> (700ml) and the mixture was stirred at room temperature overnight. The mixture was poured out into water and concentrated NH<sub>4</sub>OH, and extracted with CH<sub>2</sub>Cl<sub>2</sub>. The organic layer was dried (MgSO<sub>4</sub>), filtered, and the solvent was evaporated. The residue was crystallized from diethyl ether. The residue (119.67g) was taken up in CH<sub>2</sub>Cl<sub>2</sub> and washed with HCl 1N. The organic layer was dried (MgSO<sub>4</sub>), filtered, and the solvent was evaporated. Yielding: 107.67g of intermediate compound 1.

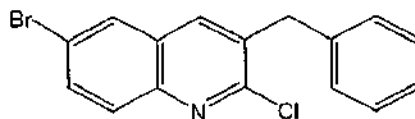
Preparation of intermediate compound 9



Accordingly, intermediate compound 9 was prepared in the same way as intermediate compound 1 but using 4-methyl-benzenepropanoylchloride.

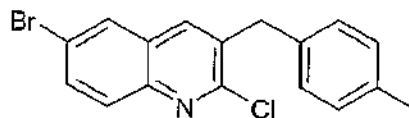
Example A2

Preparation of intermediate compound 2



The reaction was carried out twice . POCl<sub>3</sub> (1.225 mol) was added dropwise at 10°C to DMF (0.525 mol) . Then intermediate compound 1 (prepared according A1) (0.175 mol) was added at room temperature . The mixture was stirred overnight at 80°C, poured out on ice and extracted with CH<sub>2</sub>Cl<sub>2</sub> . The organic layer was dried (MgSO<sub>4</sub>), filtered, and the solvent was evaporated . The product was used without further purification. Yielding: (77.62g; Yield=67%) .

Preparation of intermediate compound 10

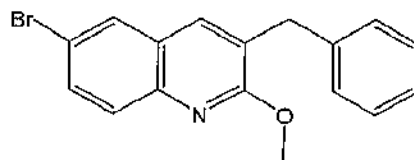


Accordingly, intermediate compound 10 was prepared in the same way as intermediate compound 2, starting from intermediate compound 9 (prepared according to A1).

10

#### Example A3

Preparation of intermediate compound 3

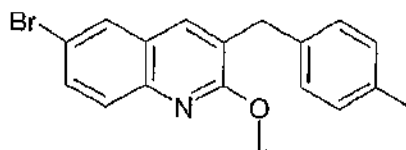


15

A mixture of intermediate compound 2 (prepared according to A2) (0.233 mol) in CH<sub>3</sub>ONa (30%) in methanol (222.32 ml) and methanol (776ml) was stirred and refluxed overnight, then poured out on ice and extracted with CH<sub>2</sub>Cl<sub>2</sub> . The organic layer was separated, dried (MgSO<sub>4</sub>), filtered and the solvent was evaporated . The residue was purified by column chromatography over silica gel (eluent: CH<sub>2</sub>Cl<sub>2</sub>/cyclohexane 20/80 and then 100/0; 20-45μm). The pure fractions were collected and the solvent was evaporated . Yielding: 25g of intermediate compound 3 (Yield=33%; mp.84°C) as a white powder .

20

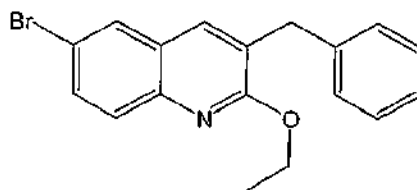
Preparation of intermediate compound 11



Accordingly, intermediate compound 11 was prepared in the same way as intermediate compound 3, starting from intermediate compound 10 (prepared according to A2).

#### Example A4

Preparation of intermediate compound 4

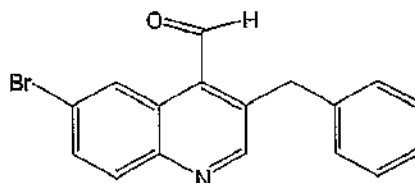


A mixture of intermediate compound 2 (prepared according to A2) (0.045 mol) in NaOEt 21% in ethanol (50ml) and ethanol (150ml) was stirred and refluxed for 12 hours . The mixture was poured out on ice and extracted with CH<sub>2</sub>Cl<sub>2</sub> . The organic layer was separated, dried (MgSO<sub>4</sub>), filtered and the solvent was evaporated .

5 Yielding: 15.2g of intermediate compound 4 (98%).

#### Example A5

Preparation of intermediate compound 5

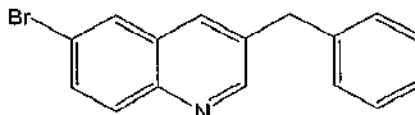


A mixture of 5-bromo-1H-indole-2,3-dione (0.28 mol) in NaOH 3N (650ml) was stirred and heated at 80°C for 30 min, then cooled to room temperature .

10 Benzenepropanal (0.28 mol) was added and the mixture was stirred and refluxed overnight . The mixture was allowed to cool to room temperature and acidified till pH=5 with HOAc . The precipitate was filtered off, washed with H<sub>2</sub>O and dried (vacuum) . Yielding: 50g of intermediate compound 5 (52%).

#### 15 Example A6

Preparation of intermediate compound 6

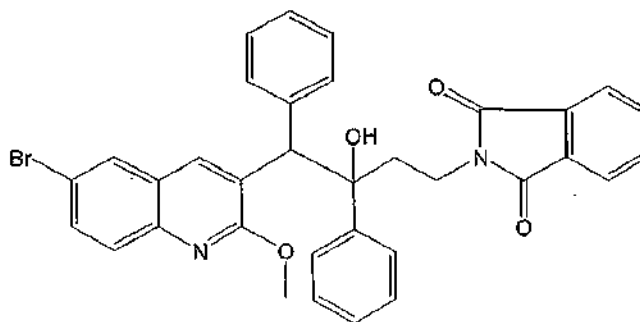


A mixture of intermediate compound 5 (prepared according to A5) (0.035 mol) in diphenylether (100ml) was stirred and heated at 300°C for 8 hours, then allowed to cool to room temperature . This procedure was carried out four times . The four mixtures were combined and then purified by column chromatography over silica gel (eluent: CH<sub>2</sub>Cl<sub>2</sub>/CH<sub>3</sub>OH 100/0, then 99/1) . The pure fractions were collected and the solvent was evaporated . Yielding: 25.6g of intermediate compound 6 (61%).

20

**Example A7**

Preparation of intermediate  
compound 7 and 8



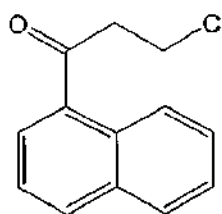
Intermediate 7 = (A)  
Intermediate 8 = (B)

nBuLi 1.6M (0.13 mol) was added dropwise at  $-10^{\circ}\text{C}$  under  $\text{N}_2$  flow to a mixture of *N*-(1-methylethyl)-2-propanamine (0.13 mol) in THF (300ml). The mixture was stirred at  $-10^{\circ}\text{C}$  for 20 min and then cooled to  $-70^{\circ}\text{C}$ . A solution of intermediate compound 3 (prepared according to A3) (0.1 mol) in THF (300ml) was added dropwise. The mixture was stirred at  $-70^{\circ}\text{C}$  for 45 min. A solution of 2-(3-oxo-3-phenylpropyl)-1H-isoindole-1,3(2H)-dione (0.13 mol) in THF (300ml) was added dropwise. The mixture was stirred at  $-70^{\circ}\text{C}$  for 1 hour, then brought to  $-40^{\circ}\text{C}$ , stirred at  $-40^{\circ}\text{C}$  for 2 hours, hydrolyzed at  $-40^{\circ}\text{C}$  with  $\text{H}_2\text{O}$  and extracted with EtOAc. The organic layer was separated, dried ( $\text{MgSO}_4$ ), filtered and the solvent was evaporated. The residue (40g) was purified by column chromatography over silica gel (eluent: cyclohexane/EtOAc 85/15). Two pure fractions were collected and their solvents were evaporated. Yielding: 1.8g of intermediate compound 7 (3%) and 5.3g of intermediate compound 8 (9%).

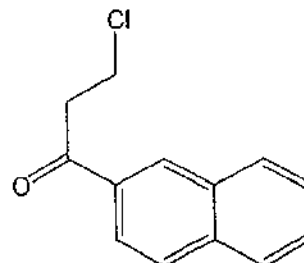
15

**Example A8**

Preparation of intermediate  
compounds 12 and 13



Intermediate 12



Intermediate 13

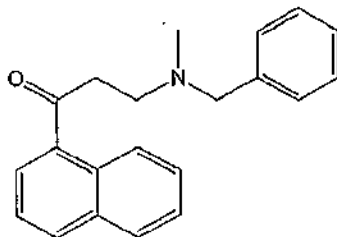
A mixture of aluminium chloride (34.3g, 0.257mol) and 3-chloropropionyl chloride (29.7g, 0.234mol) in dichloroethane (150ml) was stirred at  $0^{\circ}\text{C}$ . A solution of naphthalene (30g, 0.234mol) in dichloroethane (50ml) was added. The mixture was stirred at  $5^{\circ}\text{C}$  for 2 hours and poured out into ice water. The organic layer was separated, dried ( $\text{MgSO}_4$ ), filtered, and the solvent was evaporated. The residue (56g) was purified by column chromatography over silica gel (eluent: cyclohexane/  $\text{CH}_2\text{Cl}_2$ : 60/40; 20-45 $\mu\text{m}$ ). Two fractions were collected and the solvent was evaporated to

20

afford intermediate compound 12 (31g; Yield=61%) as an oil. The second fraction (14g) was taken up in DIPE to afford intermediate compound 13 (8.2g; Yield=16%; mp.68°C) as a pale yellow solid.

5 Example A9

Preparation of intermediate compound 14



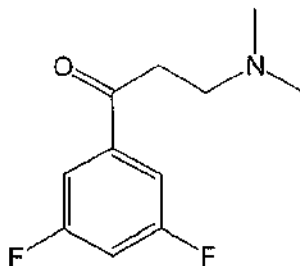
Intermediate 14

A mixture of the intermediate compound 12 (prepared according to A8) (3g; 0.0137mol), N-benzylmethyl amine (2ml; 0.0150mol) in acetonitrile (100ml) was stirred at 80°C for 2 hours. At room temperature (RT) water was added. The mixture was extracted with CH<sub>2</sub>Cl<sub>2</sub>. The organic layer was separated and dried (MgSO<sub>4</sub>), filtered, and the solvent was evaporated. The residue (6g) was purified by column chromatography over silica gel (eluent: CH<sub>2</sub>Cl<sub>2</sub>/ MeOH: 97/3; 20-45µm) to afford BB1 (4.2g; quantitative yield) as an oil, yielding intermediate compound 14.

15

Example A10

Preparation of intermediate compound 15

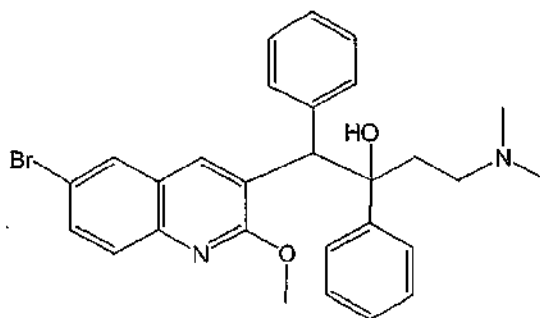


A mixture of 3,5-difluoroacetophenone (commercially available) (25g;0.16mol), diethylamine hydrochloride (52g; 0.64mol), paraformaldehyde (19g; 0.63mol) in HCl conc (5ml) and ethanol (300ml) was stirred at 80°C for 16hours. The mixture was evaporated till dryness and the residue was taken up by HCl 3N (50ml). This mixture was extracted with Et<sub>2</sub>O (3x30ml). The organic layer was collected and basified with K<sub>2</sub>CO<sub>3</sub> (10%aq). The organic layer was dried over MgSO<sub>4</sub> and evaporated. The product, intermediate compound 15 was used without further purification for the next step (23.7g; yield : 69% ) as an oil.



B. Preparation of the final compoundsExample B1

Preparation of final compound 1, 2, 3  
and 4



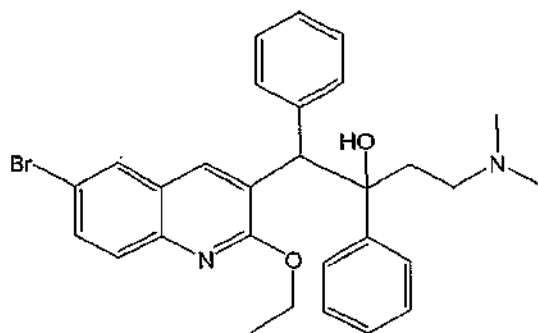
Compound 1 (A1)  
Compound 2 (A2)  
Compound 3 (A)  
Compound 4 (B)

nBuLi 1.6M (0.067 mol) was added slowly at  $-20^{\circ}\text{C}$  under  $\text{N}_2$  flow to a solution of  
 5 *N*-(1-methylethyl)-2-propanamine (0.067 mol) in THF (100ml). The mixture was  
 cooled to  $-70^{\circ}\text{C}$ . A solution of intermediate compound 3 (prepared according to A3)  
 (0.122 mol) in THF (200ml) was added slowly. The mixture was stirred at  $-70^{\circ}\text{C}$  for  
 30 min. A solution of 3-(dimethylamino)-1-phenyl-1-propanone (0.146 mol) in THF  
 (100ml) was added slowly. The mixture was stirred at  $-70^{\circ}\text{C}$  for 1 hour, then  
 10 hydrolysed at  $-30^{\circ}\text{C}$  with ice water and extracted with EtOAc. The organic layer was  
 separated, dried ( $\text{MgSO}_4$ ), filtered and the solvent was evaporated. The residue (67g)  
 was purified by column chromatography over silica gel (eluent:  
 $\text{CH}_2\text{Cl}_2/\text{CH}_3\text{OH}/\text{NH}_4\text{OH}$  99/1/0.1; 20-45 $\mu\text{m}$ ). Two pure fractions were collected and  
 their solvents were evaporated. Fraction 1 (7,2g) was crystallized from DIPE. The  
 15 precipitate was filtered off and dried. Yielding: 6.5g of diastereoisomer A (final  
 compound 3) (mp.  $172^{\circ}\text{C}$ ) (10%) as a white solid. Fraction 2 (13g) was crystallized  
 from 2-propanone and diethyl ether. The precipitate was filtered off and dried.  
 Yielding: 11g of diastereoisomer B (final compound 4) (mp.  $170^{\circ}\text{C}$ ) (17%) as a white  
 solid. Part of fraction of final compound 3 (4g) was separated into its enantiomers by  
 20 column chromatography (eluent: hexane/2-propanol 99.9/0.1; column: CHIRACEL  
 OD). Two pure fractions were collected and their solvents were evaporated. The  
 residue was crystallized from pentane. The precipitate was filtered off and dried.  
 Yielding: 0.7g of enantiomer A1 (final compound 1) (mp.  $194^{\circ}\text{C}$ ) and 0.6g of  
 enantiomer A2 (final compound 2) (mp.  $191^{\circ}\text{C}$ ) as a white solid.

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Example B2

Preparation of final compound 5  
and 6



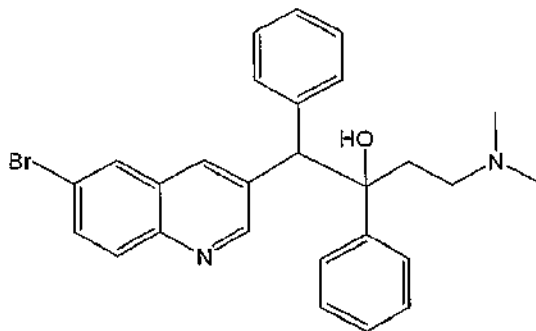
Compound 5 (A)  
Compound 6 (B)

nBuLi 1.6M (0.048 mol) was added slowly at  $-20^{\circ}\text{C}$  to a solution of *N*-(1-methylethyl)-2-propanamine (0.048 mol) in THF (70ml) . The mixture was cooled again to  $-70^{\circ}\text{C}$  . A solution of intermediate compound 4 (prepared according to A4) (0.044 mol) in THF  
5 (150ml) was added slowly . The mixture was stirred at  $-70^{\circ}\text{C}$  for 30 min . A solution of 3-(dimethylamino)-1-phenyl-1-propanone (0.053 mol) in THF (100ml) was added slowly . The mixture was stirred at  $-70^{\circ}\text{C}$  for 1 hour, hydrolysed at  $-30^{\circ}\text{C}$  with ice water and extracted with EtOAc . The organic layer was separated, dried ( $\text{MgSO}_4$ ), filtered and the solvent was evaporated . The residue (23.5g) was purified by column  
10 chromatography over silica gel (eluent:  $\text{CH}_2\text{Cl}_2/\text{CH}_3\text{OH}/\text{NH}_4\text{OH}$  99.5/0.5/0.1; 15-40  $\mu\text{m}$ ) . Two pure fractions were collected and their solvents were evaporated . The residue was crystallized from DIPE . The precipitate was filtered off and dried . Yielding: 0.7g of final compound 5 (3%) (mp.  $162^{\circ}\text{C}$ ) as a white solid and 1g of final  
15 compound 6 (5%) (mp.  $74^{\circ}\text{C}$ ) as a white solid.

15

Example B3

Preparation of final compound 7  
and 8



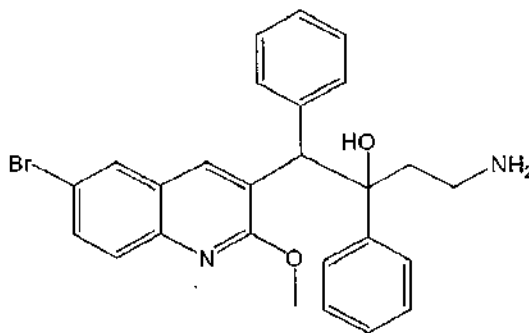
Compound 7 (A)  
Compound 8 (B)

nBuLi (1.6M) (0.070 mol) was added dropwise at  $-30^{\circ}\text{C}$  under  $\text{N}_2$  flow to a solution of *N*-(1-methylethyl)-2-propanamine (0.070 mol) in THF (70ml) . The mixture was stirred at  $-20^{\circ}\text{C}$  for 30 min, then cooled to  $-70^{\circ}\text{C}$  . A solution of intermediate

compound 6 (prepared according to A6) (0.046 mol) in THF (130ml) was added dropwise. The mixture was stirred at  $-70^{\circ}\text{C}$  for 45 min. A solution of 3-(dimethylamino)-1-phenyl-1-propanone (0.056 mol) in THF (100ml) was added dropwise. The mixture was stirred at  $-70^{\circ}\text{C}$  for 2 hours, hydrolyzed with ice-water and extracted with EtOAc. The organic layer was separated, dried ( $\text{MgSO}_4$ ), filtered and the solvent was evaporated. The residue (23.6g) was purified by column chromatography over silica gel (eluent:  $\text{CH}_2\text{Cl}_2/\text{CH}_3\text{OH}/\text{NH}_4\text{OH}$  99/1/0.1; 15-40  $\mu\text{m}$ ). Two pure fractions were collected and their solvents were evaporated. Fraction 1 (4g) was crystallized from diethyl ether. The precipitate was filtered off and dried. Yielding: 1.7g of final compound 7 (mp.  $98^{\circ}\text{C}$ ) (7.6%). Fraction 2 (3.5g) was crystallized from diethyl ether/EtOAc. The precipitate was filtered off and dried. Yielding: 2.2g of final compound 8 (mp.  $180^{\circ}\text{C}$ ) (9.8%) as a white solid.

#### Example B4

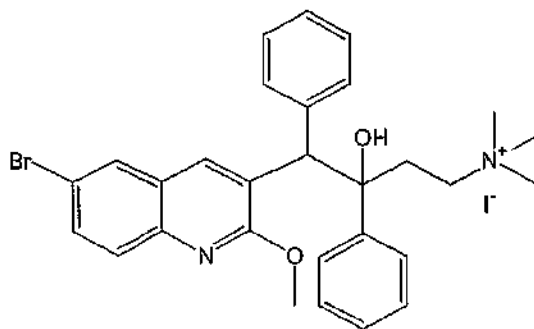
Preparation of final compound 9



A mixture of intermediate compound 8 (prepared according to A7) (0.009 mol) and hydrazine (0.01 mol) in ethanol (70ml) was stirred and refluxed for 1 hour. The solvent was evaporated till dryness. The residue was dissolved in  $\text{CH}_2\text{Cl}_2$ . The organic solution was washed with  $\text{K}_2\text{CO}_3$  10%, dried ( $\text{MgSO}_4$ ), filtered and the solvent was evaporated. The residue (5g) was purified by column chromatography over silica gel (eluent:  $\text{CH}_2\text{Cl}_2/\text{CH}_3\text{OH}/\text{NH}_4\text{OH}$  97/3/0.1; 15-40  $\mu\text{m}$ ). The pure fractions were collected and the solvent was evaporated. The residue was crystallized from diethyl ether. The precipitate was filtered off and dried. Yielding: 2.6g of final compound 9 (mp.  $204^{\circ}\text{C}$ ) (62%) as a pale yellow solid.

Example B5

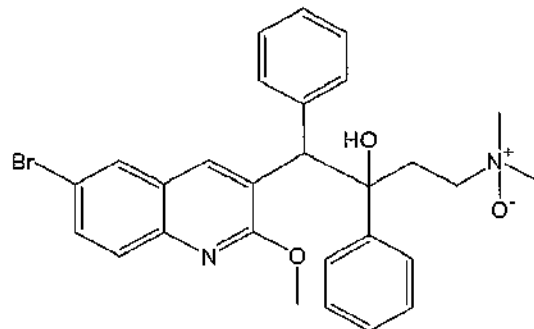
Preparation of final compound 10



CH<sub>3</sub>I (0.0033 mol) was added at room temperature to a solution of final compound 4 (prepared according to B1) (0.003 mol) in 2-propanone (15ml). The precipitate was filtered off and dried. Yielding: 1.2g of final compound 10 (mp. 198°C) (62%) as a pale yellow solid.

Example B6

Preparation of final compound 11

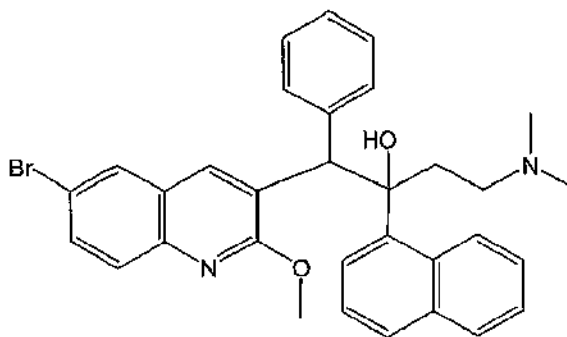


A solution of 3-chloroperoxybenzoic acid (0.0069 mol) in CH<sub>2</sub>Cl<sub>2</sub> (35ml) was added dropwise at room temperature to a solution of final compound 4 (prepared according to B1) (0.0069 mol) in CH<sub>2</sub>Cl<sub>2</sub> (35ml). The mixture was stirred at room temperature for 1 hour, washed with K<sub>2</sub>CO<sub>3</sub> 10%, dried (MgSO<sub>4</sub>), filtered and the solvent was evaporated. The residue was crystallized from diethyl ether. The precipitate was filtered off and dried. Yielding: 1.8g of final compound 11 (mp. 208°C) as a white solid.

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Example B7

Preparation of final compound 12, 13,  
14 and 15

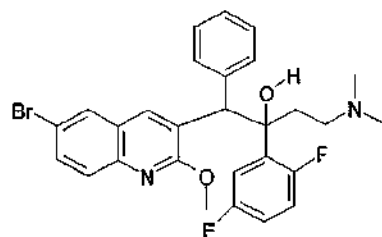


Compound 12 (A1)  
Compound 13 (A2)  
Compound 14 (A)  
Compound 15 (B)

nBuLi 1.6M (0.05 mol) was added slowly at -20°C under N<sub>2</sub> flow to a solution of *N*-(1-methylethyl)-2-propanamine (0.05 mol) in THF (80ml) . The mixture was stirred at -20°C for 15 minutes, then cooled to -70°C . A solution of intermediate compound 3  
5 (prepared according to A3) (0.046 mol) in THF (150ml) was added slowly . The mixture was stirred at -70°C for 30 minutes . A solution of 0.055 mol of 3-(dimethylamino)-1-(1-naphthyl)-1-propanone in THF (120ml) was added slowly . The mixture was stirred at -70°C for 3 hours, hydrolyzed at -30°C with ice water and extracted with EtOAc . The organic layer was separated, dried (MgSO<sub>4</sub>), filtered, and  
10 the solvent was evaporated . The residue (29g) was purified by column chromatography over silica gel (eluent: CH<sub>2</sub>Cl<sub>2</sub>/CH<sub>3</sub>OH/NH<sub>4</sub>OH; 99.5/0.5/0.1; 15-35µm) . Two fractions were collected and the solvent was evaporated . Yielding: 3g fraction 1 and 4.4g of fraction 2 . Fraction 1 and 2 were crystallized separately from DIPE . The precipitate was filtered off and dried, yielding: 2.2g of diastereoisomer A  
15 final compound 14 (Yield: 9%; mp.210°C) as a white solid and 4g of diastereoisomer B final compound 15 (Yield: 16%; mp.244°C) as a white solid . To obtain the corresponding enantiomers, diastereoisomer A (final compound 14) was purified by chiral chromatography over silica gel (eluent: hexane//EtOH; 99.95/0.05) . Two fractions were collected and the solvent was evaporated . Yielding: 0.233g of  
20 enantiomer A1 (final compound 12) (mp. 118°C) as a white solid and 0.287g of enantiomer A2 (final compound 13) (mp. 120°C) as a white solid.

**Example B8**

Preparation of final compounds 67,  
68, 110 and 111



compound 67(A)  
compound 68(B)

final compound 110

(A1)

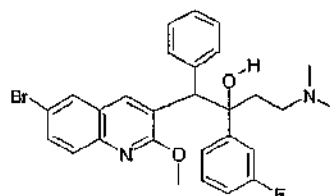
final compound 111

(A2)

nBuLi 1.6M (0.067 mol) was added slowly at  $-20^{\circ}\text{C}$  under  $\text{N}_2$  flow to a solution of *N*-(1-methylethyl)-2-propanamine (0.0104 mol) in THF (50ml). The mixture was cooled to  $-70^{\circ}\text{C}$ . A solution of intermediate compound 3 (prepared according to A3) (0.0087 mol) in THF (50ml) was added slowly. The mixture was stirred at  $-70^{\circ}\text{C}$  for 30 min. A solution of 3-(dimethylamino)-1-(2,5-difluorophenyl)-1-propanone (0.0122 mol) in THF (20ml) was added slowly. The mixture was stirred at  $-70^{\circ}\text{C}$  for 1 hour, then hydrolysed at  $-30^{\circ}\text{C}$  with ice water and extracted with EtOAc. The organic layer was separated, dried ( $\text{MgSO}_4$ ), filtered off and the solvent was evaporated. The residue (6.3g) was purified by column chromatography over silica gel (eluent:  $\text{CH}_2\text{Cl}_2/\text{CH}_3\text{OH}/\text{NH}_4\text{OH}$  98/2/0.2; 20-45 $\mu\text{m}$ ). Two pure fractions were collected and their solvents were evaporated. Fraction 1 (1,2g) was crystallized from  $\text{Et}_2\text{O}$ . The precipitate was filtered off and dried. Yield: 0.63g of diastereoisomer A (final compound 67)(mp.  $60^{\circ}\text{C}$ ; Y=13%) as a white solid. Fraction 2 (1g) was crystallized from diethylether. The precipitate was filtered off and dried. Yield: 0.64g of diastereoisomer B (final compound 68) (mp. $208^{\circ}\text{C}$ ; Y=14%). 0.63g of diastereoisomer A were purified by chiracel AD (eluent: heptane/*i*PrOH 99.95/0.05). Two fractions were collected corresponding to A1 enantiomer (final compound 110, 0.13g; mp  $167^{\circ}\text{C}$ ) as a white solid and the A2 enantiomer (final compound 111, 0.086g) as an oil.

Example B9

Preparation of final compound 38, 39,  
108 and 109



compound 38(A)  
compound 39(B)  
compound 108(A1)  
compound 109(A2)

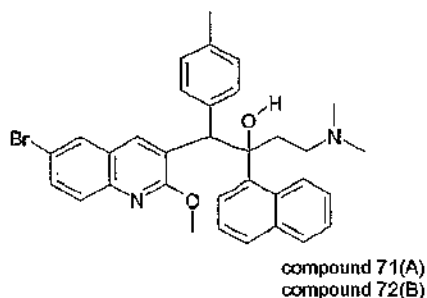
nBuLi 1.6M (0.04 mol) was added slowly at -20°C under N<sub>2</sub> flow to a solution of  
5 *N*-(1-methylethyl)-2-propanamine (0.04 mol) in THF (50ml) . The mixture was cooled  
to -70°C . A solution of intermediate compound 3 (prepared according to A3) (0.037  
mol) in THF (100ml) was added slowly . The mixture was stirred at -70°C for 30 min  
. A solution of 3-(dimethylamino)-1-(3-fluorophenyl)-1-propanone (0.044 mol) in  
THF (50ml) was added slowly . The mixture was stirred at -70°C for 1 hour, then  
10 hydrolyzed at -30°C with ice water and extracted with EtOAc . The organic layer was  
separated, dried (MgSO<sub>4</sub>), filtered and the solvent was evaporated . The residue (20g)  
was purified by column chromatography over silica gel (eluent:  
CH<sub>2</sub>Cl<sub>2</sub>/CH<sub>3</sub>OH/NH<sub>4</sub>OH 99.5/0.5/0.1; 15-40μm) . Three pure fractions were collected  
and their solvents were evaporated . Fraction 1 (2.8g) was crystallized from DIPE .  
15 The precipitate was filtered off and dried . Yielding: 1.45g (7%) of diastereoisomer A  
(final compound 38) (mp.198°C) as a white solid. Fraction 2 (3.4g) was crystallized  
from DIPE . The precipitate was filtered off and dried . Yielding: 1.55g (8%) of  
diastereoisomer B (final compound 39) (mp.207°C) as a white solid.  
Part of fraction of final compound 38 (1g) was separated into its enantiomers by chiral  
20 chromatography (eluent: hexane/2-propanol 99.9/0.1; column: CHIRACEL OD). Two  
pure fractions were collected and their solvents were evaporated. The residue was  
crystallized from pentane . The precipitate was filtered off and dried . Yield: 0.3g of  
enantiomer A1 (final compound 108) (mp. 160°C) as a white solid and 0.26g of  
enantiomer A2 (final compound 109) (mp. 156°C) as a white solid.

25

Example B10

Preparation of final compound 71 and

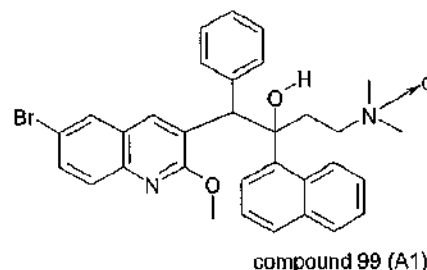
72



nBuLi 1.6M (0.0042 mol) was added slowly at  $-20^{\circ}\text{C}$  under  $\text{N}_2$  flow to a solution of *N*-(1-methylethyl)-2-propanamine (0.0042mol) in THF (20ml) . The mixture was cooled to  $-70^{\circ}\text{C}$  . A solution of intermediate compound 9 (prepared according to A1) (0.0038 mol) in THF (50ml) was added slowly . The mixture was stirred at  $-70^{\circ}\text{C}$  for 30 min . A solution of 3-(dimethylamino)-1-(1-naphthyl)-1-propanone (0.0059 mol) in THF (20ml) was added slowly . The mixture was stirred at  $-70^{\circ}\text{C}$  for 1 hour, then hydrolysed at  $-30^{\circ}\text{C}$  with ice water and extracted with EtOAc . The organic layer was separated, dried ( $\text{MgSO}_4$ ), filtered and the solvent was evaporated . The residue (2.2g) was purified by column chromatography over silica gel (eluent:  $\text{CH}_2\text{Cl}_2/\text{CH}_3\text{OH}/\text{NH}_4\text{OH}$  99/1/0.1; 15-40 $\mu\text{m}$ ) . Two pure fractions were collected and their solvents were evaporated. Fraction 1 (0.17g) was crystallized from  $\text{Et}_2\text{O}$  . The precipitate was filtered off and dried. Yield: 0.05g of diastereoisomer A (final compound 71)(mp.174 $^{\circ}\text{C}$ ; Yield= 3%) as a white solid. Fraction 2 (0.27g) was crystallized from diethyl ether. The precipitate was filtered off and dried . Yield: 0.053g of diastereoisomer B (final compound 72) (mp.178 $^{\circ}\text{C}$ ; Yield=4%) as a white solid.

20 Example B11

Preparation of final compound 99



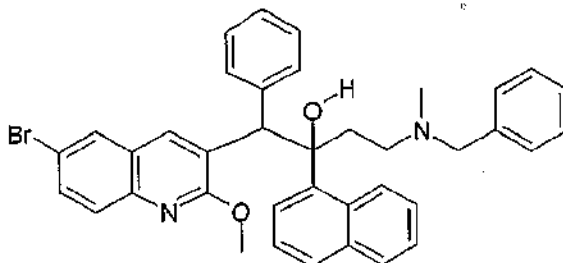
A solution of 3-chloroperoxybenzoic acid (0.0036 mol) in  $\text{CH}_2\text{Cl}_2$  (10ml) was added dropwise at room temperature to a solution of final compound 12 (enantiomer A1) (prepared according to B7) (0.0069 mol) in  $\text{CH}_2\text{Cl}_2$  (35ml) . The mixture was stirred at room temperature for 1 hour, washed with  $\text{K}_2\text{CO}_3$  10%, dried ( $\text{MgSO}_4$ ), filtered and the solvent was evaporated . The residue was crystallized from diethyl ether . The



precipitate was filtered off and dried . Yielding: 0.16g final compound 99 (mp. 218°C; Y=78%) as a white solid.

### Example B12

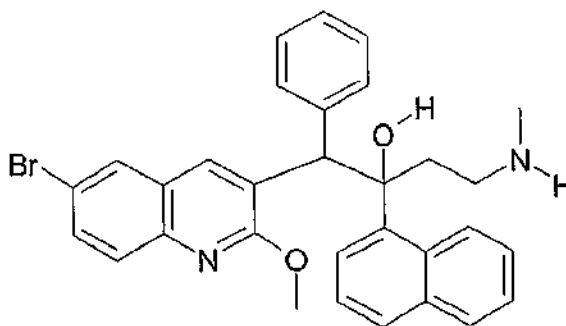
Preparation of final compound 110



- 5 nBuLi 1.6M (0.0075 mol) was added slowly at -20°C under N<sub>2</sub> flow to a solution of *N*-(1-methylethyl)-2-propanamine (0.0075 mol) in THF (30ml) . The mixture was cooled to -70°C . A solution of intermediate compound 3 (prepared according to A3) (0.0062 mol) in THF (20ml) was added slowly . The mixture was stirred at -70°C for 30 min . A solution of 0.0075 mol of intermediate compound 14 (prepared according to Example A9) in THF (10ml) was added slowly . The mixture was stirred at -70°C for 90 minutes, then hydrolysed at -30°C with ice water and extracted with EtOAc . The organic layer was separated, dried (MgSO<sub>4</sub>), filtered and the solvent was evaporated . The residue (3g) was purified by column chromatography over silica gel (eluent: Cyclohexane/EtOAc 90/10; 15-40µm) . The final compound 110 (1.5g ;
- 10
- 15 Yield=38%) was obtained as an oil.

### Example B13

Preparation of final compound 111 and 112



final compound 111 (A)

final compound 112 (B)

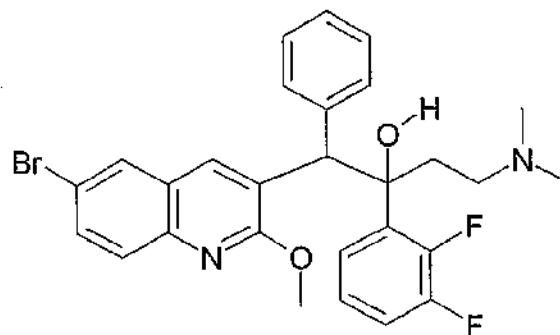
- 1-chloroethyl chloroformate (0.25ml, 0.0023mol) was added at room temperature under nitrogen to a solution of the derived 111 (1.5gr, 0.0023mol) in dichloromethane (30ml). The mixture was stirred at 80°C for 1 hour. The solvent was evaporated and the methanol (15ml) was added. The mixture was stirred and refluxed for 30 minutes. After evaporation, the residue (1.49gr) was purified by column chromatography over
- 20

silica gel (15-40 $\mu$ m). The first fraction collected was crystallized from DIPE to afford (0.168g; mp. 204°C; Yield=13%) final compound 111 as the A diastereoisomer. The second fraction collected was corresponded to final compound 112 as the B diastereoisomer (0.298g; mp.225°C; Yield=23%).

5

### Example B14

Preparation of final compounds 113 and 114



final compound 113

(A)

final compound 114

(B)

nBuLi 1.6M (3.5ml; 0.0056 mol) was added slowly at -20°C under N<sub>2</sub> flow to a solution of *N*-(1-methylethyl)-2-propanamine (770 $\mu$ l; 0.0055 mol) in THF (20ml) .

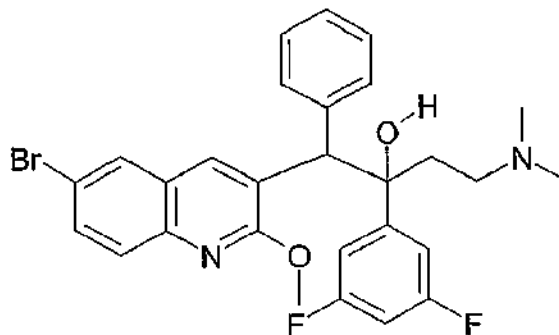
10 The mixture was cooled to -70°C . A solution of intermediate compound 3 (prepared according to A3) (1.5g ; 0.0047 mol) in THF (20ml) was added slowly . The mixture was stirred at -70°C for 30 min . A solution of intermediate compound 15 (1g ; 0.0047 mol) in THF (10ml) was added slowly . The mixture was stirred at -70°C for 3 hours, then hydrolysed at -30°C with ice water and extracted with EtOAc . The organic layer

15 was separated, dried (MgSO<sub>4</sub>), filtered off and the solvent was evaporated . The residue (2.8g) was purified by column chromatography over silica gel (eluent: CH<sub>2</sub>Cl<sub>2</sub>/CH<sub>3</sub>OH/NH<sub>4</sub>OH 99/1/0.1; 15-40 $\mu$ m) . Two pure fractions were collected and their solvents were evaporated . Fraction 1 (0.149g) was crystallized from DIPE to afford final compound 113 (0.14g; mp.185°C ;Yield= 6%) as a white powder.

20 Fraction 2 (0.14g) was crystallized from Et<sub>2</sub>O to afford final compound 114 (0.14g ; mp.210°C ;Yield= 6%) as a white powder.

Example B15

Preparation of final compounds 115,  
116, 117 and 118



final compound 115 (A diastereoisomer)

final compound 116 (B diastereoisomer)

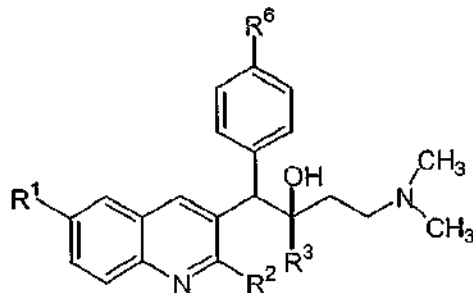
final compound 117 (A1 enantiomer)

final compound 118 (A2 enantiomer)

nBuLi 1.6M (4.6ml; 0.0074 mol) was added slowly at -20°C under N<sub>2</sub> flow to a solution of *N*-(1-methylethyl)-2-propanamine (1ml; 0.0071 mol) in THF (20ml). The mixture was cooled to -70°C. A solution of intermediate compound 15 (prepared according to A10) (2g; 0.0061 mol) in THF (10ml) was added slowly. The mixture was stirred at -70°C for 30 min. A solution of 3-(dimethylamino)-1-(3,5-difluorophenyl)-1-propanone (prepared according to A10) (2g; 0.0094 mol) in THF (15ml) was added slowly. The mixture was stirred at -70°C for 2 hours, then hydrolysed at -30°C with NH<sub>4</sub>Cl 10%aq and extracted with EtOAc. The organic layer was separated, dried (MgSO<sub>4</sub>), filtered off and the solvent was evaporated. The residue (4.5g) was purified by column chromatography over silica gel (eluent: CH<sub>2</sub>Cl<sub>2</sub>/iPrOH/NH<sub>4</sub>OH 99.5/0.5/0.05; 15-40μm). Two pure fractions were collected and their solvents were evaporated. Fraction 1 (0.67g; Yield=20%) was crystallized from DIPE to afford final compound 115 (0.29g; mp.192°C; Yield= 9%) as a white powder. Fraction 2 (0.46g) was crystallized from Et<sub>2</sub>O to afford final compound 116 (0.22g; mp. 224°C; Yield= 7%) as a white powder. From 0.1g of final compound 115, final compounds 116 and 117 (enantiomers) were separated over CHIRACEL OD (eluent: Heptane/iPrOH 99.9/0.1; 15-40μm). Two fractions were collected and crystallized from Et<sub>2</sub>O to afford final compound 116 (0.05g; mp.161°C; Yield=100%) as a white powder and final compound 117 (0.043g; mp158°C; Yield =98%) as a white powder.

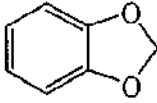
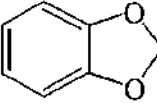
The following final compounds were prepared according to the methods described above :

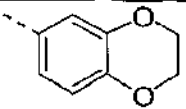
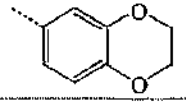
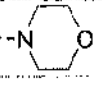
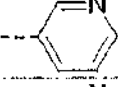
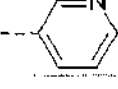
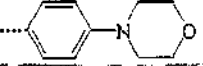
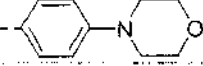
Table 1 :

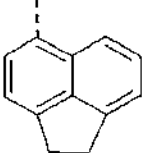
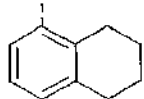







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| Comp. nr. | Ex. nr. | R <sup>1</sup>   | R <sup>2</sup>   | R <sup>3</sup> | R <sup>6</sup> | Stereochemistry and melting points |
|-----------|---------|------------------|------------------|----------------|----------------|------------------------------------|
| 1         | B1      | Br               | OCH <sub>3</sub> | phenyl         | H              | (A1); 194°C                        |
| 2         | B1      | Br               | OCH <sub>3</sub> | phenyl         | H              | (A2); 191°C                        |
| 3         | B1      | Br               | OCH <sub>3</sub> | phenyl         | H              | (A); 200°C                         |
| 4         | B1      | Br               | OCH <sub>3</sub> | phenyl         | H              | (B); 190°C                         |
| 16        | B1      | Br               | OCH <sub>3</sub> | 4-chlorophenyl | H              | (A); 200°C                         |
| 17        | B1      | Br               | OCH <sub>3</sub> | 4-chlorophenyl | H              | (B); 190°C                         |
| 20        | B1      | Br               | OCH <sub>3</sub> | 2-thienyl      | H              | (A); 96°C                          |
| 21        | B1      | Br               | OCH <sub>3</sub> | 2-thienyl      | H              | (B); 176°C                         |
| 22        | B1      | CH <sub>3</sub>  | OCH <sub>3</sub> | phenyl         | H              | (A); 148°C                         |
| 23        | B1      | CH <sub>3</sub>  | OCH <sub>3</sub> | phenyl         | H              | (B); 165°C                         |
| 24        | B1      | Br               | OCH <sub>3</sub> | 3-thienyl      | H              | (A); 162°C                         |
| 25        | B1      | Br               | OCH <sub>3</sub> | 3-thienyl      | H              | (B); 160°C                         |
| 26        | B1      | phenyl           | OCH <sub>3</sub> | phenyl         | H              | (A); 174°C                         |
| 27        | B1      | phenyl           | OCH <sub>3</sub> | phenyl         | H              | (B); 192°C                         |
| 28        | B1      | F                | OCH <sub>3</sub> | phenyl         | H              | (A); 190°C                         |
| 29        | B1      | F                | OCH <sub>3</sub> | phenyl         | H              | (B); 166°C                         |
| 30        | B1      | Cl               | OCH <sub>3</sub> | phenyl         | H              | (A); 170°C                         |
| 31        | B1      | Cl               | OCH <sub>3</sub> | phenyl         | H              | (B); 181°C                         |
| 32        | B1      | Br               | SCH <sub>3</sub> | phenyl         | H              | (A); 208°C                         |
| 33        | B1      | Br               | SCH <sub>3</sub> | phenyl         | H              | (B); 196°C                         |
| 34        | B1      | OCH <sub>3</sub> | OCH <sub>3</sub> | phenyl         | H              | (A); 165°C                         |
| 35        | B1      | OCH <sub>3</sub> | OCH <sub>3</sub> | phenyl         | H              | (B); 165°C                         |
| 36        | B1      | Br               | OCH <sub>3</sub> | phenyl         | Cl             | (A); 197°C                         |
| 37        | B1      | Br               | OCH <sub>3</sub> | phenyl         | Cl             | (B); 221°C                         |

| Comp. nr. | Ex. nr. | R <sup>1</sup> | R <sup>2</sup>                   | R <sup>3</sup>  | R <sup>6</sup>  | Stereochemistry and melting points |
|-----------|---------|----------------|----------------------------------|---|-----------------|------------------------------------|
| 38        | B9      | Br             | OCH <sub>3</sub>                 | 3-fluorophenyl  | H               | (A); 198°C                         |
| 39        | B9      | Br             | OCH <sub>3</sub>                 | 3-fluorophenyl  | H               | (B); 207°C                         |
| 108       | B9      | Br             | OCH <sub>3</sub>                 | 3-fluorophenyl  | H               | (A1); 160°C                        |
| 109       | B9      | Br             | OCH <sub>3</sub>                 | 3-fluorophenyl  | H               | (A2); 156°C                        |
| 40        | B1      | H              | OCH <sub>3</sub>                 | phenyl  | H               | (A); 152°C                         |
| 41        | B1      | H              | OCH <sub>3</sub>                 | phenyl  | H               | (B); 160°C                         |
| 42        | B1      | H              | OCH <sub>3</sub>                 | CH <sub>3</sub>   | H               | (A); 140°C                         |
| 43        | B1      | H              | OCH <sub>3</sub>                 | CH <sub>3</sub>   | H               | (B); 120°C                         |
| 59        | B1      | Br             | OH                               | phenyl  | H               | (A); >260°C                        |
| 60        | B1      | Br             | OH                               | phenyl  | H               | (B); 215°C                         |
| 5         | B2      | Br             | OCH <sub>2</sub> CH <sub>3</sub> | phenyl  | H               | (A); 162°C                         |
| 6         | B2      | Br             | OCH <sub>2</sub> CH <sub>3</sub> | phenyl  | H               | (B); 74°C                          |
| 7         | B3      | Br             | H                                | phenyl  | H               | (A); 98°C                          |
| 8         | B3      | Br             | H                                | phenyl  | H               | (B); 180°C                         |
| 12        | B7      | Br             | OCH <sub>3</sub>                 | 1-naphthyl  | H               | (A1); 118°C                        |
| 13        | B7      | Br             | OCH <sub>3</sub>                 | 1-naphthyl  | H               | (A2); 120°C                        |
| 14        | B7      | Br             | OCH <sub>3</sub>                 | 1-naphthyl  | H               | (A); 210°C                         |
| 15        | B7      | Br             | OCH <sub>3</sub>                 | 1-naphthyl  | H               | (B); 244°C                         |
| 45        | B7      | Br             | OCH <sub>3</sub>                 | 2-naphthyl  | H               | (A); 262°C                         |
| 46        | B7      | Br             | OCH <sub>3</sub>                 | 2-naphthyl  | H               | (B); 162°C                         |
| 67        | B8      | Br             | OCH <sub>3</sub>                 | 2,5-difluorophenyl  | H               | (A); 60°C                          |
| 68        | B8      | Br             | OCH <sub>3</sub>                 | 2,5-difluorophenyl  | H               | (B); 208°C                         |
| 110       | B8      | Br             | OCH <sub>3</sub>                 | 2,5-difluorophenyl  | H               | (A1); 167°C                        |
| 111       | B8      | Br             | OCH <sub>3</sub>                 | 2,5-difluorophenyl  | H               | (A2); oil                          |
| 69        | B1      | Br             | OCH <sub>3</sub>                 | 2-fluorophenyl  | H               | (A); oil                           |
| 70        | B1      | Br             | OCH <sub>3</sub>                 | 2-fluorophenyl  | H               | (B); oil                           |
| 71        | B1      | Br             | OCH <sub>3</sub>                 | 1-naphthyl  | CH <sub>3</sub> | (A); 174°C                         |
| 72        | B1      | Br             | OCH <sub>3</sub>                 | 1-naphthyl  | CH <sub>3</sub> | (B); 178°C                         |
| 73        | B1      | Br             | OCH <sub>3</sub>                 | 1-naphthyl  | Cl              | (B); 174°C                         |
| 74        | B1      | Br             | OCH <sub>3</sub>                 | 1-naphthyl  | Cl              | (A); 110°C                         |
| 75        | B1      | Br             | OCH <sub>3</sub>                 |  | H               | (A); 196°C                         |
| 76        | B1      | Br             | OCH <sub>3</sub>                 |  | H               | (B); 130°C                         |

| Comp. nr. | Ex. nr. | R <sup>1</sup>   | R <sup>2</sup>  | R <sup>3</sup>  | R <sup>6</sup> | Stereochemistry and melting points |
|-----------|---------|------------------|---|---|----------------|------------------------------------|
| 77        | B1      | Br               | OCH <sub>3</sub>  |    | H              | (A); 202°C                         |
| 78        | B1      | Br               | OCH <sub>3</sub>  |    | H              | (B); 202°C                         |
| 79        | B1      | Br               |  | 1-naphthyl  | H              | (A); >250°C                        |
| 80        | B1      | Br               | OCH <sub>3</sub>  | 4-cyanophenyl   | H              | (A); 224°C                         |
| 81        | B1      | Br               | OCH <sub>3</sub>  | 4-cyanophenyl   | H              | (B); 232°C                         |
| 82        | B1      | CH <sub>3</sub>  | OCH <sub>3</sub>  | 1-naphthyl  | H              | (A); 202°C                         |
| 83        | B1      | CH <sub>3</sub>  | OCH <sub>3</sub>  | 1-naphthyl  | H              | (B); 198°C                         |
| 84        | B1      | phenyl           | OCH <sub>3</sub>  | 1-naphthyl  | H              | (A); 248°C                         |
| 85        | B1      | phenyl           | OCH <sub>3</sub>  | 1-naphthyl  | H              | (B); 214°C                         |
| 86        | B1      | Br               | OCH <sub>3</sub>  |    | H              | (A); 184°C                         |
| 87        | B1      | Br               | OCH <sub>3</sub>  |   | H              | (B); 186°C                         |
| 88        | B1      | Br               | SCH <sub>3</sub>  | 1-naphthyl  | H              | (A); 240°C                         |
| 89        | B1      | Br               | OCH <sub>3</sub>  |  | H              | (A); 236°C                         |
| 90        | B1      | Br               | OCH <sub>3</sub>  |  | H              | (B); 206°C                         |
| 91        | B1      | H                | OCH <sub>3</sub>  | 1-naphthyl  | H              | (A); 178°C                         |
| 92        | B1      | H                | OCH <sub>3</sub>  | 1-naphthyl  | H              | (B); 160°C                         |
| 93        | B1      | H                | OCH <sub>3</sub>  | 3-fluorophenyl  | H              | (A); 178°C                         |
| 94        | B1      | H                | OCH <sub>3</sub>  | 3-fluorophenyl  | H              | (B); 182°C                         |
| 95        | B1      | Br               | OCH <sub>3</sub>  | 2-phenylethyl   | H              | (A); 178°C                         |
| 96        | B1      | Br               | OCH <sub>3</sub>  | 2-phenylethyl   | H              | (B); 146°C                         |
| 97        | B1      | OCH <sub>3</sub> | OCH <sub>3</sub>  | 1-naphthyl  | H              | (A); 168°C                         |
| 98        | B1      | OCH <sub>3</sub> | OCH <sub>3</sub>  | 1-naphthyl  | H              | (B); 154°C                         |
| 113       | B14     | Br               | OCH <sub>3</sub>  | 2,3-difluorophenyl  | H              | (A); 128°C                         |
| 114       | B14     | Br               | OCH <sub>3</sub>  | 2,3-difluorophenyl  | H              | (B); 213°C                         |
| 115       | B15     | Br               | OCH <sub>3</sub>  | 3,5-difluorophenyl  | H              | (A); 192°C                         |
| 116       | B15     | Br               | OCH <sub>3</sub>  | 3,5-difluorophenyl  | H              | (B); 224°C                         |
| 117       | B15     | Br               | OCH <sub>3</sub>  | 3,5-difluorophenyl  | H              | (A1); 161°C                        |
| 118       | B15     | Br               | OCH <sub>3</sub>  | 3,5-difluorophenyl  | H              | (A2); 158°C                        |
| 119       | B7      | Cl               | OCH <sub>3</sub>  | 1-naphthyl  | H              | (A); 212°C                         |
| 120       | B7      | Cl               | OCH <sub>3</sub>  | 1-naphthyl  | H              | (B); 236°C                         |

| Comp. nr. | Ex. nr. | R <sup>1</sup>  | R <sup>2</sup>  | R <sup>3</sup>  | R <sup>6</sup> | Stereochemistry and melting points |
|-----------|---------|---|---|---|----------------|------------------------------------|
| 122       | B7      | Br  | OCH <sub>3</sub>  |  | H              | (B); 227°C                         |
| 127       | B7      | Br  | OCH <sub>3</sub>  | 5-bromo-2-naphthyl  | H              | (A); 226°C                         |
| 130       | B7      | Br  | OCH <sub>3</sub>  | 5-bromo-2-naphthyl  | H              | (B); 220°C                         |
| 131       | B1      | Br  | OCH <sub>3</sub>  |  | H              | (A); 206°C                         |
| 134       | B9      | OCH <sub>3</sub>  | OCH <sub>3</sub>  | 3-fluorophenyl  | H              | (A); 172°C                         |
| 135       | B9      | OCH <sub>3</sub>  | OCH <sub>3</sub>  | 3-fluorophenyl  | H              | (B); 182°C                         |
| 143       | B7      | Br  | OCH <sub>3</sub>  | 3-bromo-1-naphthyl  | H              | (A); 234°C                         |
| 150       | B7      | Br  | OCH <sub>3</sub>  | 3-bromo-1-naphthyl  | H              | (B); 212°C                         |
| 159       | B8      | Br  | OCH <sub>3</sub>  | 2,5-difluorophenyl  | H              | (A1); 208°C                        |
| 160       | B8      | Br  | OCH <sub>3</sub>  | 2,5-difluorophenyl  | H              | (A2); 167°C                        |
| 162       | B7      | Br  | OCH <sub>3</sub>  | 6-methoxy-2-naphthyl  | H              | (A); 206°C                         |
| 163       | B7      | Br  | OCH <sub>3</sub>  | 6-methoxy-2-naphthyl  | H              | (B); 206°C                         |
| 164       | B9      | Br  |  | 3-fluorophenyl  | H              | (A); 118°C                         |
| 165       | B9      | Br  |  | 3-fluorophenyl  | H              | (B); oil                           |
| 167       | B8      | Br  | OCH <sub>3</sub>  | 2,6-difluorophenyl  | H              | (B); 180°C                         |
| 174       | B9      |  | OCH <sub>3</sub>  | 3-fluorophenyl  | H              | (A); 159°C                         |
| 175       | B9      |  | OCH <sub>3</sub>  | 3-fluorophenyl  | H              | (B); 196°C                         |
| 176       | B7      | Br  |  | 1-naphthyl  | H              | (A); oil                           |
| 179       | B9      | CN  | OCH <sub>3</sub>  | 3-fluorophenyl  | H              | (A); 213°C                         |
| 180       | B9      | CN  | OCH <sub>3</sub>  | 3-fluorophenyl  | H              | (B); 163°C                         |
| 181       | B9      | Br  | OCH <sub>3</sub>  | 4-fluorophenyl  | H              | (A); 198°C                         |
| 182       | B9      | Br  | OCH <sub>3</sub>  | 4-fluorophenyl  | H              | (B); 238°C                         |
| 183       | B1      | Br  | OCH <sub>3</sub>  | 3-trifluoro-methylphenyl  | H              | (A); 170°C                         |
| 188       | B1      | Br  | OCH <sub>3</sub>  | 1,4-pyrimidin-2-yl  | H              | (A); 110°C                         |

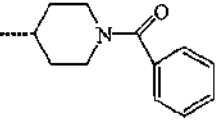
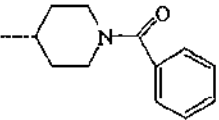
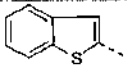
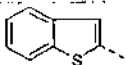
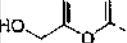
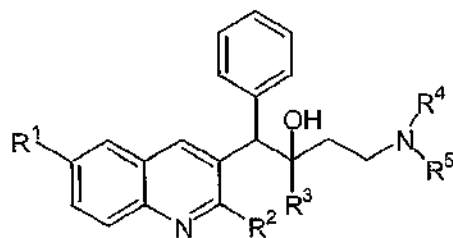
| Comp. nr. | Ex. nr. | R <sup>1</sup>  | R <sup>2</sup>   | R <sup>3</sup>  | R <sup>6</sup> | Stereochemistry and melting points |
|-----------|---------|---|------------------|---|----------------|------------------------------------|
| 189       | B1      | Br  | OCH <sub>3</sub> | 1,4-pyrimidin-2-yl  | H              | (B); 145°C                         |
| 195       | B15     | Br  | OCH <sub>3</sub> | 3,4-difluorophenyl  | H              | (A); 250°C                         |
| 196       | B15     | Br  | OCH <sub>3</sub> | 3,4-difluorophenyl  | H              | (B); 184°C                         |
| 201       | B1      | Br  | OCH <sub>3</sub> |  | H              | (A); 214°C                         |
| 202       | B1      | Br  | OCH <sub>3</sub> |  | H              | (B); 246°C                         |
| 203       | B9      |    | OCH <sub>3</sub> | 3-fluorophenyl  | H              | (A); 225°C                         |
| 204       | B9      |    | OCH <sub>3</sub> | 3-fluorophenyl  | H              | (B); 216°C                         |
| 205       | B7      | Br  | OCH <sub>3</sub> | 1-naphthyl  | F              | (A); 213°C                         |
| 206       | B7      | Br  | OCH <sub>3</sub> | 1-naphthyl  | F              | (B); 213°C                         |
| 207       | B15     | F   | OCH <sub>3</sub> | 3,5-difluorophenyl  | H              | (A); 232°C                         |
| 208       | B15     | F   | OCH <sub>3</sub> | 3,5-difluorophenyl  | H              | (B); 188°C                         |
| 212       | B7      |  | OCH <sub>3</sub> | 1-naphthyl  | H              | (B); 220°C                         |

Table 2:



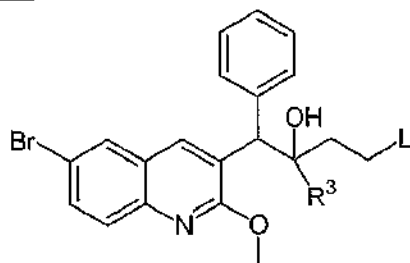
5

| Comp. nr. | Ex. nr. | R <sup>1</sup> | R <sup>2</sup>   | R <sup>3</sup> | R <sup>4</sup>                  | R <sup>5</sup>                  | Phys. data (salt/melting points) and stereochemistry |
|-----------|---------|----------------|------------------|----------------|---------------------------------|---------------------------------|--|
| 18        | B1      | Br             | OCH <sub>3</sub> | phenyl         | CH <sub>2</sub> CH <sub>3</sub> | CH <sub>2</sub> CH <sub>3</sub> | .ethanedioate (2:3); (A); 230°C                      |
| 19        | B1      | Br             | OCH <sub>3</sub> | phenyl         | CH <sub>2</sub> CH <sub>3</sub> | CH <sub>2</sub> CH <sub>3</sub> | .ethanedioate (2:3); (B);                            |

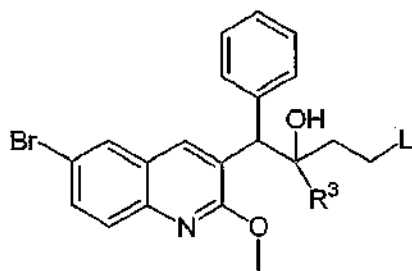


| Comp. nr. | Ex. nr. | R <sup>1</sup> | R <sup>2</sup>   | R <sup>3</sup> | R <sup>4</sup>  | R <sup>5</sup>                  | Phys.data<br>(salt/melting<br>points) and<br>stereo-<br>chemistry |
|-----------|---------|----------------|------------------|----------------|-----------------|---------------------------------|---|
|           |         |                |                  |                |                 |                                 | 150°C   |
| 44        | B4      | Br             | OCH <sub>3</sub> | phenyl         | H               | H                               | (A); 190°C  |
| 9         | B4      | Br             | OCH <sub>3</sub> | phenyl         | H               | H                               | (B); 204°C  |
| 141       | B7      | Br             | OCH <sub>3</sub> | 2-naphthyl     | CH <sub>3</sub> | CH <sub>2</sub> CH <sub>3</sub> | (A); 188°C  |
| 142       | B7      | Br             | OCH <sub>3</sub> | 2-naphthyl     | CH <sub>3</sub> | CH <sub>2</sub> CH <sub>3</sub> | (B); 202°C  |
| 230       | B12     | Br             | OCH <sub>3</sub> | 1-naphthyl     | CH <sub>3</sub> | benzyl                          | /oil  |
| 147       | B7      | Br             | OCH <sub>3</sub> | 1-naphthyl     | CH <sub>3</sub> | CH <sub>2</sub> CH <sub>3</sub> | (A); 168°C  |
| 148       | B7      | Br             | OCH <sub>3</sub> | 1-naphthyl     | CH <sub>3</sub> | CH <sub>2</sub> CH <sub>3</sub> | (B); 212°C  |
| 56        | B13     | Br             | OCH <sub>3</sub> | 1-naphthyl     | CH <sub>3</sub> | H                               | (A); 204°C  |
| 214       | B13     | Br             | OCH <sub>3</sub> | 1-naphthyl     | CH <sub>3</sub> | H                               | (B); 225°C  |

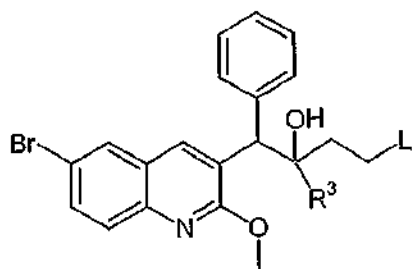
Table 3:



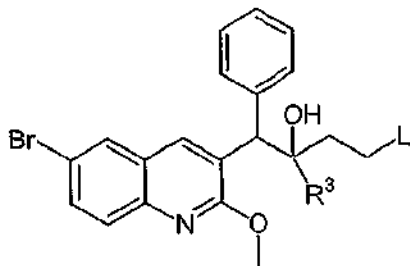
| Comp. nr. | Ex. nr. | R <sup>3</sup> | L                       | Stereochemistry<br>and melting<br>points |
|-----------|---------|----------------|-------------------------|--|
| 47        | B1      | phenyl         | 1-piperidinyl           | (A); 190°C                               |
| 48        | B1      | phenyl         | 1-piperidinyl           | (B); 210°C                               |
| 128       | B1      | 2-naphthyl     | 1-piperidinyl           | (A); 254°C                               |
| 129       | B1      | 2-naphthyl     | 1-piperidinyl           | (B); 212°C                               |
| 49        | B1      | phenyl         | 1-imidazolyl            | (A); 216°C                               |
| 50        | B1      | phenyl         | 1-imidazolyl            | (B); 230°C                               |
| 51        | B1      | phenyl         | 1-(4-methyl)piperazinyl | (A); 150°C                               |
| 52        | B1      | phenyl         | 1-(4-methyl)piperazinyl | (B); 230°C                               |
| 53        | B1      | phenyl         | 1-(1,2,4-triazolyl)     | (A); 180°C                               |



| Comp. nr. | Ex. nr. | R <sup>3</sup> | L                   | Stereochemistry and melting points |
|-----------|---------|----------------|---------------------|------------------------------------|
| 54        | B1      | phenyl         | 1-(1,2,4-triazolyl) | (B); 142°C                         |
| 55        | B1      | phenyl         | thiomorpholinyl     | (A); oil                           |
| 57        | B5      | phenyl         |                     | (A); 244°C                         |
| 10        | B5      | phenyl         |                     | (B); 198°C                         |
| 58        | B6      | phenyl         |                     | (A); 208°C                         |
| 11        | B6      | phenyl         |                     | (B); 208°C                         |
| 99        | B11     | 1-naphthyl     |                     | (A1); 218°C                        |
| 100       | B6      | 1-naphthyl     |                     | (A2); 218°C                        |
| 101       | B6      | 1-naphthyl     |                     | (B); 175°C                         |
| 102       | B5      | 1-naphthyl     |                     | (A2); 210°C                        |

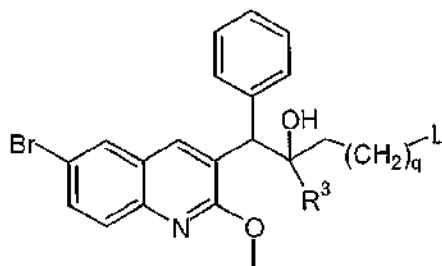


| Comp. nr. | Ex. nr. | R <sup>3</sup>     | L                   | Stereochemistry and melting points |
|-----------|---------|--------------------|---------------------|------------------------------------|
| 103       | B5      | 1-naphthyl         |                     | (B); >250°C                        |
| 121       | B5      | 1-naphthyl         |                     | (A1); 210°C                        |
| 123       | B1      | phenyl             | morpholinyl         | (A); 226°C                         |
| 124       | B1      | phenyl             | morpholinyl         | (B); 210°C                         |
| 136       | B7      | 2-naphthyl         | 4-methylpyrazinyl   | (A); 188°C                         |
| 137       | B7      | 2-naphthyl         | 4-methylpyrazinyl   | (B); 232°C                         |
| 139       | B7      | 2-naphthyl         | morpholinyl         | (A); 258°C                         |
| 140       | B7      | 2-naphthyl         | morpholinyl         | (B); 214°C                         |
| 144       | B7      | 2-naphthyl         | pyrrolidinyl        | (A); 238°C                         |
| 145       | B7      | 1-naphthyl         | 1-piperidinyl       | (A); 212°C                         |
| 146       | B7      | 1-naphthyl         | 1-piperidinyl       | (B); 220°C                         |
| 149       | B7      | 1-naphthyl         | 4-methylpyrazinyl   | (B); 232°C                         |
| 151       | B7      | 3-bromo-1-naphthyl | 4-methylpiperazinyl | (A); 178°C                         |
| 152       | B7      | 3-bromo-1-naphthyl | 4-methylpiperazinyl | (B); 226°C                         |
| 153       | B7      | 6-bromo-2-naphthyl | 4-methylpiperazinyl | (A); 208°C                         |
| 154       | B7      | 6-bromo-2-naphthyl | 4-methylpiperazinyl | (B); 254°C                         |
| 155       | B7      | 6-bromo-2-naphthyl | 1-piperidinyl       | (A); 224°C                         |
| 156       | B7      | 1-naphthyl         | 4-methylpiperazinyl | (A); 200°C                         |
| 157       | B7      | 6-bromo-2-naphthyl | 1-pyrrolidinyl      | (B); 220°C                         |
| 158       | B7      | 1-naphthyl         | morpholinyl         | (B); 272°C                         |
| 166       | B7      | 6-bromo-2-naphthyl | 1-piperidinyl       | (B); 218°C                         |
| 170       | B7      | 2-naphthyl         | 1-pyrrolidinyl      | (A); 238°C                         |
| 171       | B7      | 2-naphthyl         | 1-pyrrolidinyl      | (B); 218°C                         |

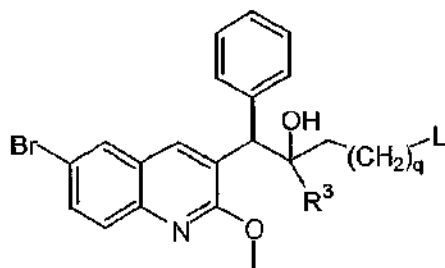


| Comp. nr. | Ex. nr. | R <sup>3</sup>     | L                  | Stereochemistry and melting points |
|-----------|---------|--------------------|--------------------|------------------------------------|
| 172       | B7      | 1-naphthyl         | 1,2,4-triazol-1-yl | /142°C                             |
| 173       | B7      | 1-naphthyl         | 1,2-imidazol-1-yl  | (A); 222°C                         |
| 177       | B7      | 6-bromo-2-naphthyl | morpholinyl        | (A); 242°C                         |
| 178       | B7      | 6-bromo-2-naphthyl | morpholinyl        | (B); 246°C                         |
| 187       | B7      | 1-naphthyl         | 1,2-imidazol-1-yl  | (B); 236°C                         |
| 200       | B7      | 2-naphthyl         |                    | (A); 254°C                         |
| 209       | B7      | 2-naphthyl         |                    | (B); 198°C                         |

Table 4:

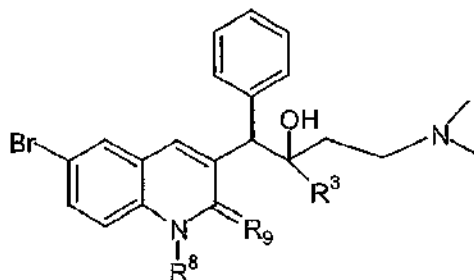


| Comp. nr. | Ex. nr. | R <sup>3</sup> | Q | L                                | Stereochemistry and melting points |
|-----------|---------|----------------|---|----------------------------------|------------------------------------|
| 61        | B1      | phenyl         | 0 | N(CH <sub>3</sub> ) <sub>2</sub> | (A); 220°C                         |
| 62        | B1      | phenyl         | 0 | N(CH <sub>3</sub> ) <sub>2</sub> | (B); 194°C                         |
| 63        | B1      | phenyl         | 2 | N(CH <sub>3</sub> ) <sub>2</sub> | (A); 150°C                         |
| 64        | B1      | phenyl         | 2 | N(CH <sub>3</sub> ) <sub>2</sub> | (B); 220°C                         |
| 125       | B7      | 2-naphthyl     | 2 | N(CH <sub>3</sub> ) <sub>2</sub> | (A); 229°C                         |
| 126       | B7      | 2-naphthyl     | 2 | N(CH <sub>3</sub> ) <sub>2</sub> | (B); 214°C                         |
| 65        | B1      | phenyl         | 3 | N(CH <sub>3</sub> ) <sub>2</sub> | (A); 130°C                         |

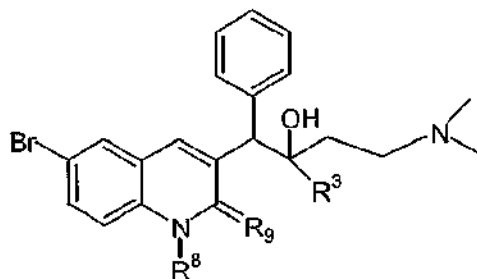


| Comp. nr. | Ex. nr. | R <sup>3</sup> | Q | L  | Stereochemistry and melting points |
|-----------|---------|----------------|---|--|------------------------------------|
| 66        | B1      | phenyl         | 3 | N(CH <sub>3</sub> ) <sub>2</sub>                 | (B); 170°C                         |
| 132       | B7      | 2-naphthyl     | 2 | pyrrolidinyl                                     | (A); 227°C                         |
| 133       | B7      | 2-naphthyl     | 2 | pyrrolidinyl                                     | (B); 222°C                         |
| 161       | B7      | 2-naphthyl     | 2 | morpholinyl                                      | (B); 234°C                         |
| 186       | B7      | 1-naphthyl     | 2 | N(CH <sub>3</sub> ) <sub>2</sub>                 | (A); 187°C                         |
| 190       | B7      | 2-naphthyl     | 3 | N(CH <sub>3</sub> ) <sub>2</sub>                 | (A); 170°C                         |
| 191       | B7      | 2-naphthyl     | 3 | N(CH <sub>3</sub> ) <sub>2</sub>                 | (B); 145°C                         |
| 192       | B7      | 2-naphthyl     | 2 | N(CH <sub>2</sub> CH <sub>3</sub> ) <sub>2</sub> | (A); 90°C                          |
| 193       | B7      | 2-naphthyl     | 2 | N(CH <sub>2</sub> CH <sub>3</sub> ) <sub>2</sub> | (B); 202°C                         |
| 194       | B7      | 1-naphthyl     | 2 | pyrrolidinyl                                     | (B); 206°C                         |
| 197       | B7      | 1-naphthyl     | 3 | N(CH <sub>3</sub> ) <sub>2</sub>                 | (A); 160°C                         |
| 198       | B7      | 2-naphthyl     | 2 | morpholinyl                                      | (A); 215°C                         |
| 199       | B7      | 1-naphthyl     | 2 | N(CH <sub>2</sub> CH <sub>3</sub> ) <sub>2</sub> | (A); 185°C                         |
| 210       | B7      | 1-naphthyl     | 2 | morpholinyl                                      | (B); 222°C                         |
| 211       | B7      | 1-naphthyl     | 2 | morpholinyl                                      | (A); 184°C                         |

Table 5:

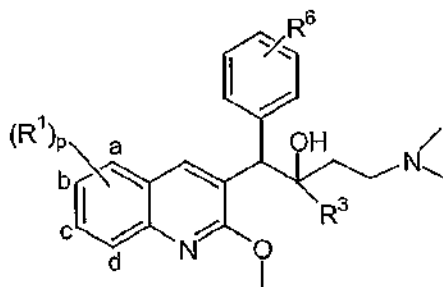




| Comp. nr. | Ex. nr. | R <sup>3</sup> | R <sup>8</sup> | R <sup>9</sup> | Stereochemistry and melting points |
|-----------|---------|----------------|----------------|----------------|------------------------------------|
| 104       | B1      | phenyl         |                | -CH=CH-N=      | (A); 170°C                         |
| 105       | B1      | phenyl         |                | -CH=CH-N=      | (B); 150°C                         |

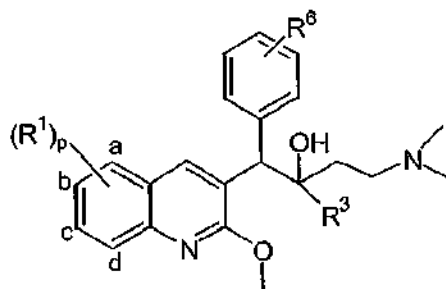


| Comp. nr. | Ex. nr. | R <sup>3</sup> | R <sup>8</sup>  | R <sup>9</sup> | Stereochemistry and melting points |
|-----------|---------|----------------|-----------------|----------------|------------------------------------|
| 106       | B1      | phenyl         | CH <sub>3</sub> | =O             | (A); 224°C                         |
| 107       | B1      | phenyl         | CH <sub>3</sub> | =O             | (B); 180°C                         |
| 138       | B7      | 1-naphthyl     | H               | =O             | (A1); >260°C                       |

Table 6:



| Comp. nr. | Ex. nr. | R <sup>1</sup> |    |                 |                 | R <sup>3</sup> | R <sup>6</sup>  | Stereochemistry and melting points |
|-----------|---------|----------------|----|-----------------|-----------------|----------------|---|------------------------------------|
|           |         | a              | b  | c               | d               |                |   |                                    |
| 215       | B9      | H              | Br | CH <sub>3</sub> | H               | 3-fluorophenyl | H   | (A); 197°C                         |
| 216       | B9      | H              | Br | CH <sub>3</sub> | H               | 3-fluorophenyl | H   | (B); 158°C                         |
| 217       | B7      | H              | H  | Br              | H               | 1-naphthyl     | H   | (A); 212°C                         |
| 218       | B7      | H              | H  | Br              | H               | 1-naphthyl     | H   | (B); 172°C                         |
| 219       | B9      | H              | Br | H               | CH <sub>3</sub> | 3-fluorophenyl | H   | (A); 220°C                         |
| 220       | B9      | H              | Br | H               | CH <sub>3</sub> | 3-fluorophenyl | H   | (B); 179°C                         |
| 221       | B7      | Br             | H  | H               | H               | 1-naphthyl     | H   | (A); 170°C                         |
| 224       | B7      | Br             | H  | H               | H               | 1-naphthyl     | H   | /205°C                             |
| 222       | B7      | H              | Br | H               | H               | 1-naphthyl     |  | (A); 155°C                         |
| 223       | B7      | H              | Br | H               | H               | 1-naphthyl     |  | (B); 205°C                         |



| Comp. nr. | Ex. nr. | R <sup>1</sup> |                 |                 |   | R <sup>3</sup>     | R <sup>6</sup> | Stereochemistry and melting points |
|-----------|---------|----------------|-----------------|-----------------|---|--------------------|----------------|------------------------------------|
|           |         | a              | b               | c               | d |                    |                |                                    |
| 225       | B7      | H              | Br              | CH <sub>3</sub> | H | 1-naphthyl         | H              | (A); 238°C                         |
| 226       | B7      | H              | Br              | CH <sub>3</sub> | H | 1-naphthyl         | H              | (B); 208°C                         |
| 227       | B15     | H              | Br              | CH <sub>3</sub> | H | 3,5-difluorophenyl | H              | (A); 195°C                         |
| 228       | B15     | H              | Br              | CH <sub>3</sub> | H | 3,5-difluorophenyl | H              | (B); 218°C                         |
| 229       | B7      | H              | CH <sub>3</sub> | CH <sub>3</sub> | H | 1-naphthyl         | H              | (A); 238°C                         |

### C. Pharmacological examples

#### C.1. In-vitro method for testing compounds against *M. tuberculosis*.

5

Flat-bottom, sterile 96-well plastic microtiter plates were filled with 100 µl of Middlebrook (1x) broth medium. Subsequently, stock solutions (10 x final test concentration) of compounds were added in 25 µl volumes to a series of duplicate wells in column 2 so as to allow evaluation of their effects on bacterial growth. Serial five-fold dilutions were made directly in the microtiter plates from column 2 to 11 using a customised robot system (Zymark Corp., Hopkinton, MA). Pipette tips were changed after every 3 dilutions to minimize pipetting errors with high hydrophobic compounds. Untreated control samples with (column 1) and without (column 12) inoculum were included in each microtiter plate. Approximately 5000 CFU per well of *Mycobacterium tuberculosis* (strain H37RV), in a volume of 100 µl in Middlebrook (1x) broth medium, was added to the rows A to H, except column 12. The same volume of broth medium without inoculum was added to column 12 in row A to H. The cultures were incubated at 37°C for 7 days in a humidified atmosphere (incubator with open air valve and continuous ventilation). One day before the end of incubation, 6 days after inoculation, Resazurin (1:5) was added to all wells in a volume of 20 µl and plates were incubated for another 24 hours at 37°C. On day 7 the bacterial growth was quantitated fluorometrically.

20

The fluorescence was read in a computer-controlled fluorometer (Spectramax Gemini EM, Molecular Devices) at an excitation wavelength of 530 nm and an emission wavelength of 590 nm. The percentage growth inhibition achieved by the compounds was calculated according to standard methods, and MIC data (representing IC<sub>90</sub>'s expressed in microgram/ml) were calculated. The results are shown in Table 5.

C.2. In-vitro method for testing compounds for anti-bacterial activity against strain M. Smegmatis ATCC607.

10 Flat-bottom, sterile 96-well plastic microtiter plates were filled with 180  $\mu$ l of sterile deionized water, supplemented with 0.25 % BSA. Subsequently, stock solutions (7.8 x final test concentration) of compounds were added in 45  $\mu$ l volumes to a series of duplicate wells in column 2 so as to allow evaluation of their effects on bacterial growth. Serial five-fold dilutions (45  $\mu$ l in 180  $\mu$ l) were made directly in the microtiter  
15 plates from column 2 to 11 using a customised robot system (Zymark Corp., Hopkinton, MA). Pipette tips were changed after every 3 dilutions to minimize pipetting errors with high hydrophobic compounds. Untreated control samples with (column 1) and without (column 12) inoculum were included in each microtiter plate. Approximately 250 CFU per well of bacteria inoculum, in a volume of 100  $\mu$ l in 2.8x  
20 Mueller-Hinton broth medium, was added to the rows A to H, except column 12. The same volume of broth medium without inoculum was added to column 12 in row A to H. The cultures were incubated at 37°C for 48 hours in a humidified 5% CO<sub>2</sub> atmosphere (incubator with open air valve and continuous ventilation). At the end of incubation, two days after inoculation, the bacterial growth was quantitated  
25 fluorometrically. Therefore Alamar Blue (10x) was added to all wells in a volume of 20  $\mu$ l and plates were incubated for another 2 hours at 50°C.

The fluorescence was read in a computer-controlled fluorometer (Cytofluor, Biosearch) at an excitation wavelength of 530 nm and an emission wavelength of 590 nm (gain  
30 30). The % growth inhibition achieved by the compounds was calculated according to standard methods. The pIC<sub>50</sub> was defined as the 50 % inhibitory concentration for bacterial growth. The results are shown in Table 5.



**Table 5 :** Results of an in vitro-screening of the compounds according to the invention for *M. tuberculosis* (MIC) and *M. smegmatis* (pIC<sub>50</sub>).

| Co.No. | MIC  | pIC <sub>50</sub> |
|--------|------|-------------------|
| 118    | 0.01 | 9.1               |
| 174    | 0.06 | 6.8               |
| 12     | 0.07 | 8.7               |
| 115    | 0.07 | 8.6               |
| 69     | 0.13 | 8.5               |
| 71     | 0.14 | 8.5               |
| 113    | 0.27 | 8.6               |
| 5      | 0.33 | 7.8               |
| 32     | 0.33 | 7.4               |
| 109    | 0.33 | 8.2               |
| 16     | 0.34 | 6.8               |
| 37     | 0.34 | 7.9               |
| 67     | 0.34 | 8.6               |
| 110    | 0.34 | 8.5               |
| 164    | 0.36 | 7.9               |
| 183    | 0.36 | 8.3               |
| 208    | 0.38 | 7.9               |
| 98     | 0.51 | 7.9               |
| 216    | 0.85 | 8.0               |
| 26     | 1.00 | 7.2               |
| 22     | 1.11 | 7.2               |
| 203    | 1.15 | 8.0               |
| 28     | 1.41 | 7.3               |
| 30     | 1.46 | 7.8               |
| 179    | 1.48 | 7.0               |
| 135    | 1.50 | 7.4               |
| 91     | 1.51 | 7.5               |
| 188    | 1.60 | 7.2               |
| 24     | 1.62 | 7.2               |
| 63     | 1.64 | 6.7               |
| 65     | 1.69 | 5.7               |
| 66     | 1.69 | 4.7               |
| 17     | 1.71 | 6.5               |
| 111    | 1.71 | 6.4               |
| 117    | 1.71 | 6.7               |
| 196    | 1.71 | 6.6               |
| 75     | 1.74 | 7.9               |
| 76     | 1.74 | 5.9               |
| 45     | 1.76 | 8.0               |
| 46     | 1.76 | 6.4               |

| Co.No. | MIC  | pIC <sub>50</sub> |
|--------|------|-------------------|
| 227    | 1.76 | 7.5               |
| 94     | 1.77 | 7.9               |
| 225    | 1.80 | 6.6               |
| 35     | 1.82 | 6.8               |
| 190    | 1.85 | 6.5               |
| 191    | 1.85 | 6.5               |
| 80     | 2.11 | 7.1               |
| 102    | 2.21 | 6.5               |
| 121    | 2.21 | 5.9               |
| 165    | 2.26 | 6.6               |
| 79     | 2.43 | 7.2               |
| 15     | 2.78 | 6.5               |
| 72     | 3.59 | 6.9               |
| 180    | 3.73 | 6.6               |
| 82     | 3.90 | 7.1               |
| 205    | 4.56 | 7.2               |
| 36     | 5.40 | 6.4               |
| 103    | 5.54 | 5.9               |
| 192    | 5.98 | 6.5               |
| 44     | 6.01 | 5.9               |
| 64     | 6.54 | 5.8               |
| 19     | 6.72 | 6.5               |
| 195    | 6.82 | 6.5               |
| 52     | 7.06 | 6.4               |
| 172    | 7.30 | 5.7               |
| 31     | 7.31 | 5.8               |
| 134    | 7.52 | 6.5               |
| 92     | 7.55 | 6.5               |
| 83     | 7.78 | 5.8               |
| 62     | 7.79 | 5.9               |
| 27     | 7.97 | 5.9               |
| 6      | 8.23 | 5.8               |
| 33     | 8.27 | 6.0               |
| 38     | 8.30 | 7.9               |
| 39     | 8.30 | 6.1               |
| 181    | 8.30 | 6.9               |
| 182    | 8.30 | 6.3               |
| 41     | 8.51 | 5.9               |
| 215    | 8.52 | 6.2               |
| 220    | 8.52 | 5.3               |
| 116    | 8.58 | 6.6               |
| 138    | 8.58 | 6.6               |
| 47     | 8.65 | 6.5               |
| 48     | 8.65 | 5.8               |
| 84     | 8.76 | 7.0               |

| Co.No. | MIC   | pIC <sub>50</sub> |
|--------|-------|-------------------|
| 85     | 8.76  | 5.9               |
| 23     | 8.79  | 6.4               |
| 14     | 8.80  | 6.8               |
| 218    | 8.80  | 6.6               |
| 228    | 8.80  | 5.1               |
| 77     | 8.93  | 7.2               |
| 141    | 9.03  | 7.3               |
| 142    | 9.03  | 6.2               |
| 226    | 9.03  | 5.5               |
| 99     | 9.06  | 7.9               |
| 101    | 9.06  | 5.8               |
| 212    | 9.08  | 6.0               |
| 206    | 9.09  | 6.5               |
| 204    | 9.14  | 5.4               |
| 197    | 9.25  | 6.6               |
| 162    | 9.28  | 7.0               |
| 193    | 9.47  | 5.6               |
| 176    | 9.50  | 6.8               |
| 156    | 9.68  | 5.3               |
| 201    | 9.77  | 5.7               |
| 175    | 10.19 | 6.5               |
| 119    | 10.20 | 7.8               |
| 10     | 10.26 | 5.6               |
| 18     | 10.60 | 6.7               |
| 152    | 10.93 | 5.8               |
| 147    | 11.36 | 7.4               |
| 151    | 13.76 | 5.0               |
| 86     | 16.02 | 6.9               |
| 21     | 16.17 | 5.4               |
| 58     | 16.49 | 6.8               |
| 136    | 16.81 | 6.2               |
| 95     | 16.87 | 6.9               |
| 125    | 18.01 | 4.4               |
| 97     | 20.17 | 5.9               |
| 25     | 20.36 | 5.2               |
| 96     | 21.24 | 6.2               |
| 40     | 21.38 | 4.7               |
| 73     | 23.49 | 8.0               |
| 8      | 23.83 | 5.7               |
| 127    | 25.26 | 6.9               |
| 189    | 25.43 | 5.5               |
| 57     | 25.77 | 5.4               |
| 222    | 30.35 | 8.0               |
| 93     | 35.31 | 4.8               |
| 9      | 37.92 | 4.5               |

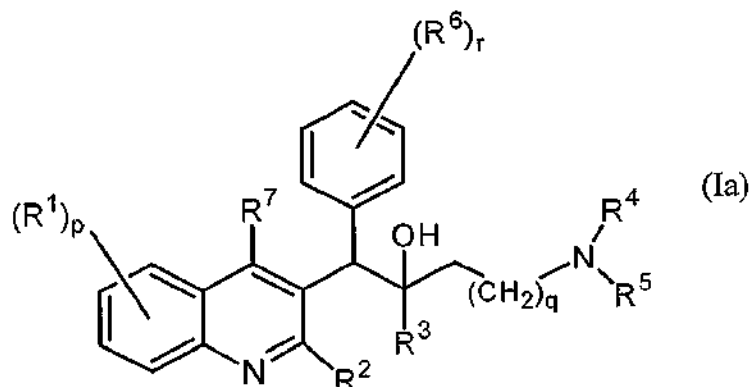
| Co.No. | MIC   | pIC <sub>50</sub> |
|--------|-------|-------------------|
| 61     | 39.04 | 4.5               |
| 229    | 40.09 | 7.1               |
| 87     | 40.23 | 5.0               |
| 120    | 40.60 | 5.9               |
| 20     | 40.63 | 5.9               |
| 11     | 41.42 | 4.6               |
| 81     | 42.14 | 5.4               |
| 137    | 42.23 | 4.6               |
| 219    | 42.69 | 5.8               |
| 56     | 43.01 | 7.2               |
| 114    | 43.01 | 5.9               |
| 167    | 43.01 | 5.5               |
| 13     | 44.13 | 6.7               |
| 107    | 44.13 | 5.8               |
| 217    | 44.13 | 6.9               |
| 221    | 44.13 | 6.5               |
| 224    | 44.13 | 4.9               |
| 42     | 44.34 | 6.3               |
| 43     | 44.34 | 4.4               |
| 131    | 44.45 | 6.9               |
| 29     | 44.46 | 5.9               |
| 78     | 44.76 | 5.8               |
| 55     | 44.77 | 5.1               |
| 88     | 45.40 | 6.8               |
| 100    | 45.40 | 7.1               |
| 34     | 45.66 | 5.1               |
| 170    | 46.19 | 5.6               |
| 171    | 46.19 | 4.3               |
| 163    | 46.51 | 5.9               |
| 129    | 47.31 | 4.7               |
| 132    | 47.31 | 4.4               |
| 194    | 47.31 | 4.9               |
| 199    | 47.47 | 6.5               |
| 7      | 47.54 | 4.6               |
| 207    | 48.05 | 5.2               |
| 149    | 48.50 | 5.1               |
| 202    | 48.98 | 4.8               |
| 130    | 50.32 | 5.3               |
| 143    | 50.39 | 6.9               |
| 70     | 52.35 | 5.8               |
| 144    | 52.46 | 7.0               |
| 157    | 52.46 | 5.6               |
| 49     | 52.85 | 5.4               |
| 50     | 52.85 | 5.0               |
| 53     | 52.94 | 5.1               |

| Co.No. | MIC   | pIC <sub>50</sub> |
|--------|-------|-------------------|
| 54     | 52.94 | 4.1               |
| 112    | 54.15 | 5.5               |
| 123    | 54.75 | 4.2               |
| 124    | 54.75 | 5.3               |
| 153    | 54.77 | 5.3               |
| 106    | 55.55 | 6.2               |
| 126    | 56.96 | 5.2               |
| 148    | 56.96 | 4.9               |
| 186    | 56.96 | 4.5               |
| 173    | 57.85 | 4.7               |
| 187    | 57.85 | 4.0               |
| 122    | 58.16 | 4.8               |
| 74     | 59.00 | 6.5               |
| 89     | 59.06 | 6.4               |
| 90     | 59.06 | 5.3               |
| 128    | 59.56 | 4.0               |
| 133    | 59.56 | 5.1               |
| 145    | 59.56 | 5.3               |
| 146    | 59.56 | 4.8               |
| 139    | 59.76 | 4.1               |
| 140    | 59.76 | 5.8               |
| 158    | 59.76 | 5.3               |
| 223    | 60.56 | 5.7               |
| 161    | 61.16 | 4.0               |
| 198    | 61.16 | 4.3               |
| 210    | 61.16 | 6.1               |
| 211    | 61.16 | 4.1               |
| 150    | 63.44 | 5.7               |
| 155    | 67.45 | 4.9               |
| 166    | 67.45 | 4.1               |
| 200    | 67.47 | 4.9               |
| 209    | 67.47 | 4.0               |
| 177    | 67.65 | 4.0               |
| 178    | 67.65 | 4.5               |
| 154    | 68.95 | 4.9               |
| 1      | n.d.  | 7.3               |
| 2      | n.d.  | 6.8               |
| 3      | n.d.  | 6.7               |
| 4      | n.d.  | 5.7               |
| 51     | n.d.  | 5.8               |
| 59     | n.d.  | 5.1               |
| 60     | n.d.  | 5.6               |
| 68     | n.d.  | 6.4               |
| 104    | n.d.  | 6.6               |
| 105    | n.d.  | 6.0               |

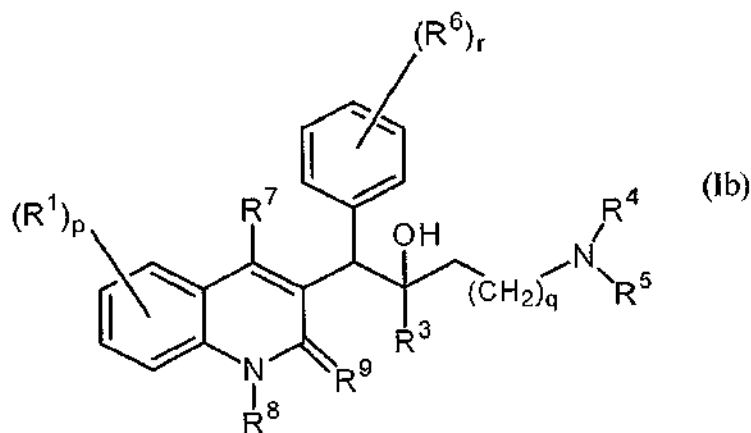
| Co.No. | MIC  | pIC <sub>50</sub> |
|--------|------|-------------------|
| 108    | n.d. | 7.0               |

## CLAIMS

1. A compound according to the general Formula (Ia) or the general Formula (Ib)



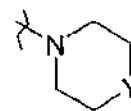
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the pharmaceutically acceptable acid or base addition salts thereof, the stereochemically isomeric forms thereof, the tautomeric forms thereof and the *N*-oxide forms thereof, wherein :

- 10  $R^1$  is hydrogen, halo, haloalkyl, cyano, hydroxy, Ar, Het, alkyl, alkyloxy, alkylthio, alkyloxyalkyl, alkylthioalkyl, Ar-alkyl or di(Ar)alkyl ;  
 $p$  is an integer equal to zero, 1, 2, 3 or 4 ;  
 $R^2$  is hydrogen, hydroxy, thio, alkyloxy, alkyloxyalkoxy, alkylthio, mono

or di(alkyl)amino or a radical of formula



wherein  $Y$  is  $CH_2$ ,

- 15  $R^3$  is alkyl, Ar, Ar-alkyl, Het or Het-alkyl;  
 $q$  is an integer equal to zero, 1, 2, 3 or 4 ;  
 $R^4$  and  $R^5$  each independently are hydrogen, alkyl or benzyl; or

- R<sup>4</sup> and R<sup>5</sup> together and including the N to which they are attached may form a radical selected from the group of pyrrolidinyl, 2H-pyrrolyl, 2-pyrrolinyl, 3-pyrrolinyl, pyrrolyl, imidazolidinyl, pyrazolidinyl, 2-imidazolynyl, 2-pyrazolinyl, imidazolyl, pyrazolyl, triazolyl, piperidinyl, pyridinyl, 5 piperazinyl, imidazolidinyl, pyridazinyl, pyrimidinyl, pyrazinyl, triazinyl, morpholinyl and thiomorpholinyl, optionally substituted with alkyl, halo, haloalkyl, hydroxy, alkyloxy, amino, mono- or dialkylamino, alkylthio, alkyloxyalkyl, alkylthioalkyl and pyrimidinyl ;
- R<sup>6</sup> is hydrogen, halo, haloalkyl, hydroxy, Ar, alkyl, alkyloxy, alkylthio, 10 alkyloxyalkyl, alkylthioalkyl, Ar-alkyl or di(Ar)alkyl ; or two vicinal R<sup>6</sup> radicals may be taken together to form a bivalent radical of formula =C-C=C=C- ;
- r is an integer equal to 0, 1, 2, 3, 4 or 5 ; and
- R<sup>7</sup> is hydrogen, alkyl, Ar or Het ;
- 15 R<sup>8</sup> is hydrogen or alkyl ;
- R<sup>9</sup> is oxo ; or
- R<sup>8</sup> and R<sup>9</sup> together form the radical =N-CH=CH- .
- alkyl is a straight or branched saturated hydrocarbon radical having from 1 to 6 carbon atoms ; or is a cyclic saturated hydrocarbon radical having from 3 to 6 20 carbon atoms ; or is a cyclic saturated hydrocarbon radical having from 3 to 6 carbon atoms attached to a straight or branched saturated hydrocarbon radical having from 1 to 6 carbon atoms ; wherein each carbon atom can be optionally substituted with halo, hydroxy, alkyloxy or oxo ;
- Ar is a homocycle selected from the group of phenyl, naphthyl, acenaphthyl, tetrahydronaphthyl, each optionally substituted with 1, 2 or 3 substituents, each 25 substituent independently selected from the group of hydroxy, halo, cyano, nitro, amino, mono- or dialkylamino, alkyl, haloalkyl, alkyloxy, haloalkyloxy, carboxyl, alkyloxycarbonyl, aminocarbonyl, morpholinyl and mono- or dialkylaminocarbonyl ;
- 30 Het is a monocyclic heterocycle selected from the group of N-phenoxy piperidinyl, pyrrolyl, pyrazolyl, imidazolyl, furanyl, thienyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, pyridinyl, pyrimidinyl, pyrazinyl and pyridazinyl; or a bicyclic heterocycle selected from the group of quinolinyl, quinoxalinyl, indolyl, benzimidazolyl, benzoxazolyl, benzisoxazolyl, benzothiazolyl, benzisothiazolyl, 35 benzofuranyl, benzothieryl, 2,3-dihydrobenzo[1,4]dioxinyl or benzo[1,3]dioxolyl ; each monocyclic and bicyclic heterocycle may optionally be substituted on a carbon atom with 1, 2 or 3 substituents selected from the group of halo, hydroxy, alkyl or alkyloxy ;



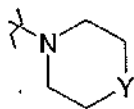
halo is a substituent selected from the group of fluoro, chloro, bromo and iodo and haloalkyl is a straight or branched saturated hydrocarbon radical having from 1 to 6 carbon atoms or a cyclic saturated hydrocarbon radical having from 3 to 6 carbon atoms, wherein one or more carbon atoms are substituted with one or more halo-atoms.

2. A compound according to claim 1, characterized in that

$R^1$  is hydrogen, halo, cyano, Ar, Het, alkyl, and alkyloxy ;

$p$  is an integer equal to zero, 1, 2, 3 or 4 ;

10  $R^2$  is hydrogen, hydroxy, alkyloxy, alkyloxyalkyloxy, alkylthio or a radical



of formula  $\text{C}_5\text{H}_9\text{NY}$  wherein Y is O ;

$R^3$  is alkyl, Ar, Ar-alkyl or Het ;

$q$  is an integer equal to zero, 1, 2, or 3 ;

$R^4$  and  $R^5$  each independently are hydrogen, alkyl or benzyl; or

15  $R^4$  and  $R^5$  together and including the N to which they are attached may form a radical selected from the group of pyrrolidinyl, imidazolyl, triazolyl, piperidinyl, piperazinyl, pyrazinyl, morpholinyl and thiomorpholinyl, optionally substituted with alkyl and pyrimidinyl ;

$R^6$  is hydrogen, halo or alkyl ; or

20 two vicinal  $R^6$  radicals may be taken together to form a bivalent radical of formula  $=\text{C}-\text{C}=\text{C}=\text{C}-$  ;

$r$  is an integer equal to 1 ; and

$R^7$  is hydrogen ;

$R^8$  is hydrogen or alkyl ;

25  $R^9$  is oxo ; or

$R^8$  and  $R^9$  together form the radical  $=\text{N}-\text{CH}=\text{CH}-$  .

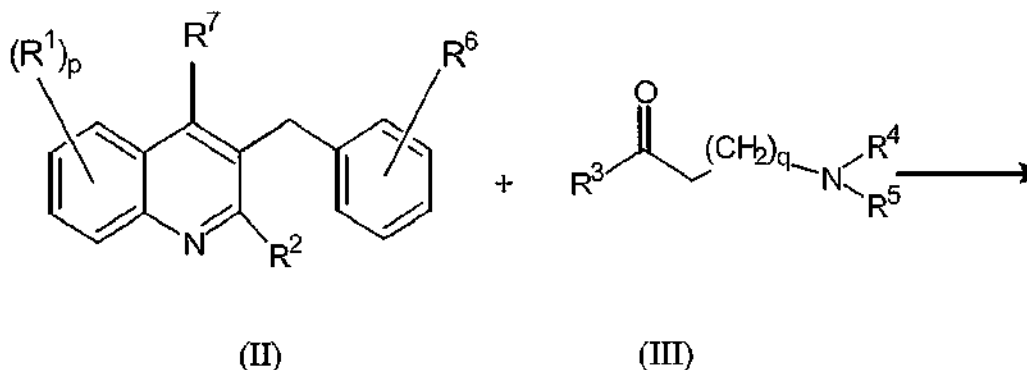
alkyl is a straight or branched saturated hydrocarbon radical having from 1 to 6 carbon atoms ; or is a cyclic saturated hydrocarbon radical having from 3 to 6 carbon atoms ; or is a cyclic saturated hydrocarbon radical having from 3 to 6 carbon atoms attached to a straight or branched saturated hydrocarbon radical having from 1 to 6 carbon atoms ; wherein each carbon atom can be optionally substituted with halo or hydroxy ;

Ar is a homocycle selected from the group of phenyl, naphthyl, acenaphthyl, tetrahydronaphthyl, each optionally substituted with 1, 2 or 3 substituents, each substituent independently selected from the group of halo, haloalkyl, cyano, alkyloxy and morpholinyl ;

- Het is a monocyclic heterocycle selected from the group of N-phenoxy piperidinyl, furanyl, thienyl, pyridinyl, pyrimidinyl ; or a bicyclic heterocycle selected from the group of benzothienyl, 2,3-dihydrobenzo[1,4]dioxinyl or benzo[1,3]-dioxolyl; each monocyclic and bicyclic heterocycle may optionally be substituted on a carbon atom with 1, 2 or 3 alkyl substituents ; and halo is a substituent selected from the group of fluoro, chloro and bromo.
3. A compound according to any one of claims 1 and 2, characterized in that, independently from each other, R<sup>1</sup> is hydrogen, halo, Ar, alkyl or alkyloxy, p = 1, R<sup>2</sup> is hydrogen, alkyloxy or alkylthio, R<sup>3</sup> is naphthyl, phenyl or thienyl, each optionally substituted with 1 or 2 substituents selected from the group of halo and haloalkyl, q = 0, 1, 2 or 3, R<sup>4</sup> and R<sup>5</sup> each independently are hydrogen or alkyl or R<sup>4</sup> and R<sup>5</sup> together and including the N to which they are attached form a radical selected from the group of imidazolyl, triazolyl, piperidinyl, piperazinyl and thiomorpholinyl, R<sup>6</sup> is hydrogen, alkyl or halo, r is equal to 0 or 1 and R<sup>7</sup> is hydrogen.
4. A compound according to claim 3, characterized in that, independently from each other, R<sup>1</sup> is bromo, R<sup>2</sup> is alkyloxy, R<sup>3</sup> is naphthyl or phenyl, q=1, R<sup>4</sup> and R<sup>5</sup> each independently are hydrogen, methyl or ethyl and R<sup>6</sup> is hydrogen.
5. A compound which is degraded in vivo to yield a compound according to any one of claims 1 to 4.
6. A compound according to claim 1, characterized in that the compound is :
- 1-(6-bromo-2-methoxy-quinolin-3-yl)-2-(3,5-difluoro-phenyl)-4-dimethylamino-1-phenyl-butan-2-ol ;
  - 1-(6-bromo-2-methoxy-quinolin-3-yl)-4-dimethylamino-2-naphthalen-1-yl-1-phenyl-butan-2-ol ;
  - 1-(6-bromo-2-methoxy-quinolin-3-yl)-2-(2,5-difluoro-phenyl)-4-dimethylamino-1-phenyl-butan-2-ol ;
  - 1-(6-bromo-2-methoxy-quinolin-3-yl)-2-(2,3-difluoro-phenyl)-4-dimethylamino-1-phenyl-butan-2-ol ;
  - 1-(6-bromo-2-methoxy-quinolin-3-yl)-4-dimethylamino-2-(2-fluoro-phenyl)-1-phenyl-butan-2-ol ;
  - 1-(6-bromo-2-methoxy-quinolin-3-yl)-4-dimethylamino-2-naphthalen-1-yl-1-p-tolyl-butan-2-ol ;
  - 1-(6-bromo-2-methoxy-quinolin-3-yl)-4-methylamino-2-naphthalen-1-yl-1-phenyl-butan-2-ol ; and

- o 1-(6-bromo-2-methoxy-quinolin-3-yl)-4-dimethylamino-2-(3-fluoro-phenyl)-1-phenyl-butan-2-ol,  
the pharmaceutically acceptable acid or base addition salts thereof, the stereochemically isomeric forms thereof, the tautomeric forms thereof and the *N*-oxide forms thereof.
7. A compound according to any one of claims 1 to 6 for use as a medicine.
8. A composition comprising a pharmaceutically acceptable carrier and, as active ingredient, a therapeutically effective amount of a compound as defined in any one of claims 1 to 7.
9. Use of a compound according to any one of claims 1 to 7 or a composition according to claim 8 for the manufacture of a medicament for the treatment of mycobacterial diseases.
10. Method of treating a patient suffering from, or at risk of, a mycobacterial disease, which comprises administering to the patient a therapeutically effective amount of a compound according to any one of claims 1 to 7 or pharmaceutical composition according to claim 8.
11. A process for preparing a compound according to any one of claims 1 to 7, characterized in that a compound of Formula (II) is reacted with a compound of Formula (III) according to the following reaction :

25



wherein  $R^1$ ,  $p$ ,  $R^2$ ,  $R^3$ ,  $q$ ,  $R^4$ ,  $R^5$ ,  $R^6$  and  $R^7$  are defined as in Formula (Ia).

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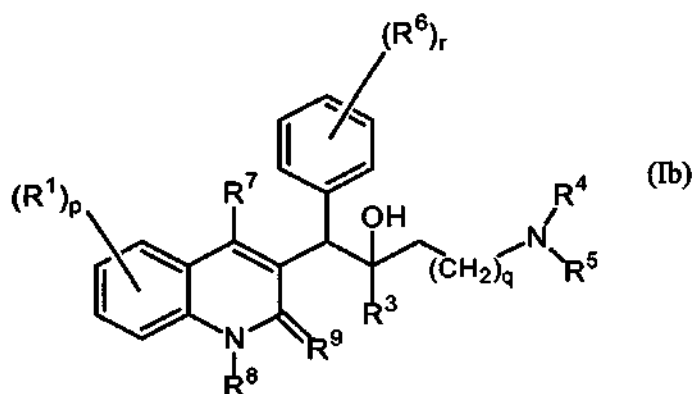
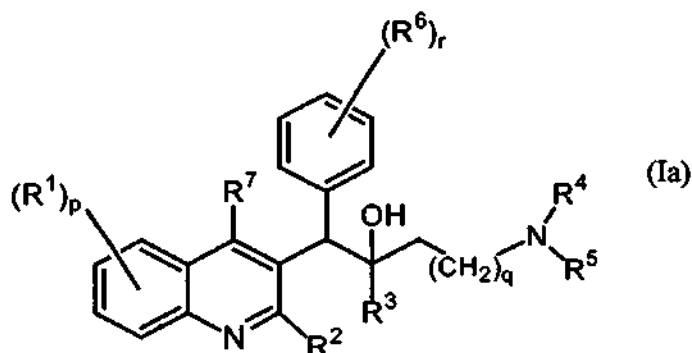
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- (71) Applicant (for all designated States except US):  
JANSSEN PHARMACEUTICA N.V. [BE/BE]; Turn-  
houtseweg 30, B-2340 Beerse (BE).
- (72) Inventors; and
- (75) Inventors/Applicants (for US only): ANDRIES, Koen-  
raad, Jozef, Lodewijk, Marcel [BE/BE]; c/o Janssen
- Pharmaceutica N.V., Turnhoutseweg 30, B-2340 Beerse  
(BE). VAN GESTEL, Jozef, Frans, Elisabetha [BE/BE];  
Renier Sniederspad 9, B-2350 Vosselaar (BE).
- (74) Common Representative: JANSSEN PHARMACEU-  
TICA N.V.; Turnhoutseweg 30, B-2340 Beerse (BE).
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(54) Title: USE OF SUBSTITUTED QUINOLINE DERIVATIVES FOR THE TREATMENT OF DRUG RESISTANT MYCOBACTERIAL DISEASES



(57) Abstract: The present invention relates to the use of a substituted quinoline derivative for the preparation of a medicament for the treatment of an infection with a drug resistant Mycobacterium strain wherein the substituted quinoline derivative is a compound according to Formula (Ia) or Formula (Ib) the pharmaceutically acceptable acid or base addition salts thereof, the stereochemically isomeric forms thereof, the tautomeric forms thereof and the *N*-oxide forms thereof. Also claimed is a composition comprising a pharmaceutically acceptable carrier and, as active ingredient, a therapeutically effective amount of the above compounds and one or more other antimycobacterial agents.

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## USE OF SUBSTITUTED QUINOLINE DERIVATIVES FOR THE TREATMENT OF DRUG RESISTANT MYCOBACTERIAL DISEASES

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5 The present invention relates to the use of substituted quinoline derivatives for  
inhibiting the growth of drug resistant *Mycobacterium* strains including growth  
inhibition of multi drug resistant *Mycobacterium* strains. The substituted quinoline  
derivatives can thus be used for the treatment or the prevention of Mycobacterial  
diseases caused by drug resistant, particularly multi drug resistant *Mycobacteria*. More  
10 in particular the present quinoline derivatives can be used for the treatment or the  
prevention of Mycobacterial diseases caused by drug resistant including multi drug  
resistant *Mycobacterium tuberculosis*. The present invention also relates to a  
combination of (a) a substituted quinoline derivative according to the present invention  
and (b) one or more other antimycobacterial agents.

15

### BACKGROUND OF THE INVENTION

*Mycobacterium tuberculosis* is the causative agent of tuberculosis (TB), a serious and  
potentially fatal infection with a world-wide distribution. Estimates from the World  
20 Health Organization indicate that more than 8 million people contract TB each year,  
and 2 million people die from tuberculosis yearly. In the last decade, TB cases have  
grown 20% worldwide with the highest burden in the most impoverished communities.  
If these trends continue, TB incidence will increase by 41% in the next twenty years.  
Fifty years since the introduction of an effective chemotherapy, TB remains after  
25 AIDS, the leading infectious cause of adult mortality in the world. Complicating the TB  
epidemic is the rising tide of multi-drug- resistant strains, and the deadly symbiosis  
with HIV. People who are HIV-positive and infected with TB are 30 times more likely  
to develop active TB than people who are HIV-negative and TB is responsible for the  
death of one out of every three people with HIV/AIDS worldwide

30

Existing approaches to treatment of tuberculosis all involve the combination of multiple  
agents . For example, the regimen recommended by the U.S. Public Health Service is a  
combination of isoniazid, rifampicin and pyrazinamide for two months, followed by  
isoniazid and rifampicin alone for a further four months. These drugs are continued for  
35 a further seven months in patients infected with HIV. For patients infected with multi-  
drug resistant strains of *M. tuberculosis*, agents such as ethambutol, streptomycin,  
kanamycin, amikacin, capreomycin, ethionamide, cycloserine, ciprofloxacin and

ofloxacin are added to the combination therapies. There exists no single agent that is effective in the clinical treatment of tuberculosis, nor any combination of agents that offers the possibility of therapy of less than six months' duration.

- 5 There is a high medical need for new drugs that improve current treatment by enabling regimens that facilitate patient and provider compliance. Shorter regimens and those that require less supervision are the best way to achieve this. Most of the benefit from treatment comes in the first 2 months, during the intensive, or bactericidal, phase when four drugs are given together; the bacterial burden is greatly reduced, and patients  
10 become noninfectious. The 4- to 6-month continuation, or sterilizing, phase is required to eliminate persisting bacilli and to minimize the risk of relapse. A potent sterilizing drug that shortens treatment to 2 months or less would be extremely beneficial. Drugs that facilitate compliance by requiring less intensive supervision also are needed. Obviously, a compound that reduces both the total length of treatment and the  
15 frequency of drug administration would provide the greatest benefit.

Complicating the TB epidemic is the increasing incidence of multi drug- resistant strains or MDR-TB. Up to four percent of all cases worldwide are considered MDR-TB - those resistant to the most effective drugs of the four-drug standard, isoniazid and  
20 rifampin. MDR-TB is lethal when untreated and can not be adequately treated through the standard therapy, so treatment requires up to 2 years of "second-line" drugs. These drugs are often toxic, expensive and marginally effective. In the absence of an effective therapy, infectious MDR-TB patients continue to spread the disease, producing new infections with MDR-TB strains. There is a high medical need for drugs which  
25 demonstrate activity against resistant and/or MDR strains.

The term "drug resistant" as used hereinbefore or hereinafter is a term well understood by the person skilled in microbiology. A drug resistant Mycobacterium is a  
30 Mycobacterium which is no longer susceptible to at least one previously effective drug; which has developed the ability to withstand antibiotic attack by at least one previously effective drug. A drug resistant strain may relay that ability to withstand to its progeny. Said resistance may be due to random genetic mutations in the bacterial cell that alters its sensitivity to a single drug or to different drugs.

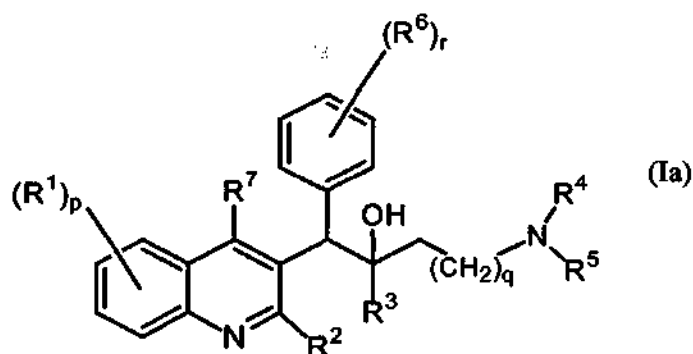
MDR tuberculosis is a specific form of drug resistant tuberculosis due to a bacterium  
35 resistant to at least isoniazid and rifampicin (with or without resistance to other drugs), which are at present the two most powerful anti-TB drugs. Thus, whenever used hereinbefore or hereinafter "drug resistant" includes multi drug resistant.

Unexpectedly, it has now been found that the substituted quinoline derivatives of the present invention are very useful for inhibiting growth of drug resistant, in particular multi drug resistant, Mycobacteria and therefore useful for the treatment of diseases caused by drug resistant, in particular multi drug resistant, Mycobacteria, particularly those diseases caused by drug resistant, in particular multi drug resistant, pathogenic *Mycobacterium (M.) tuberculosis*, *M. bovis*, *M. avium*, *M. fortuitum*, *M. leprae* and *M. marinum*, more particularly *Mycobacterium tuberculosis*.

The substituted quinoline derivatives relating to the present invention were already disclosed in WO 2004/011436. Said document discloses the antimycobacterial property of the substituted quinoline derivatives against sensitive, susceptible Mycobacterium strains but is silent on their activity against drug resistant, in particular multi drug resistant, Mycobacteria.

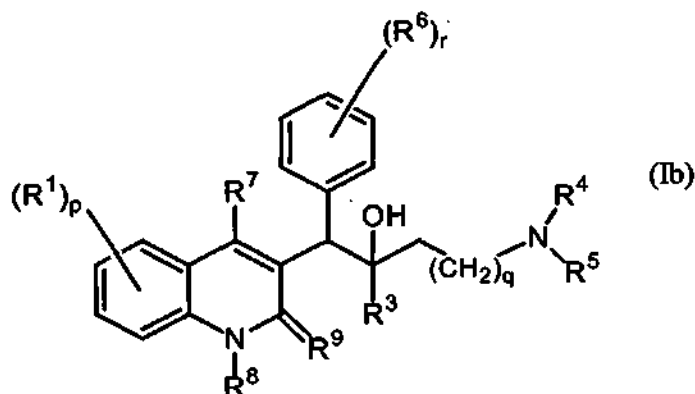
Thus, the present invention relates to the use of a substituted quinoline derivative for the preparation of a medicament for the treatment of a warm-blooded mammal infected with a drug resistant Mycobacterium strain wherein the substituted quinoline derivative is a compound according to Formula (Ia) or Formula (Ib)

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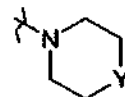
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a pharmaceutically acceptable acid or base addition salt thereof, a stereochemically isomeric form thereof, a tautomeric form thereof or a *N*-oxide form thereof, wherein :

- 5  $R^1$  is hydrogen, halo, haloalkyl, cyano, hydroxy, Ar, Het, alkyl, alkyloxy, alkylthio, alkyloxyalkyl, alkylthioalkyl, Ar-alkyl or di(Ar)alkyl ;  
 $p$  is an integer equal to 1, 2, 3 or 4 ;  
 $R^2$  is hydrogen, hydroxy, mercapto, alkyloxy, alkyloxyalkoxy, alkylthio,

mono or di(alkyl)amino or a radical of formula



wherein Y is

- 10  $R^3$  is alkyl, Ar, Ar-alkyl, Het or Het-alkyl;  
 $q$  is an integer equal to zero, 1, 2, 3 or 4 ;  
 $R^4$  and  $R^5$  each independently are hydrogen, alkyl or benzyl; or  
 $R^4$  and  $R^5$  together and including the N to which they are attached may form a radical  
 15 selected from the group of pyrrolidinyl, 2*H*-pyrrolyl, 2-pyrrolinyl, 3-pyrrolinyl, pyrrolyl, imidazolidinyl, pyrazolidinyl, 2-imidazolinyl, 2-pyrazolinyl, imidazolyl, pyrazolyl, triazolyl, piperidinyl, pyridinyl, piperazinyl, imidazolidinyl, pyridazinyl, pyrimidinyl, pyrazinyl, triazinyl, morpholinyl and thiomorpholinyl, optionally substituted with alkyl, halo, haloalkyl, hydroxy, alkyloxy, amino, mono- or dialkylamino, alkylthio, alkyloxyalkyl, alkylthioalkyl and pyrimidinyl ;  
 20  $R^6$  is hydrogen, halo, haloalkyl, hydroxy, Ar, alkyl, alkyloxy, alkylthio, alkyloxyalkyl, alkylthioalkyl, Ar-alkyl or di(Ar)alkyl ; or two vicinal  $R^6$  radicals may be taken together to form a bivalent radical of formula  
 $-\text{CH}=\text{CH}-\text{CH}=\text{CH}-$  ;  
 25  $r$  is an integer equal to 1, 2, 3, 4 or 5 ; and  
 $R^7$  is hydrogen, alkyl, Ar or Het ;

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R<sup>8</sup> is hydrogen or alkyl ;

R<sup>9</sup> is oxo ; or

R<sup>8</sup> and R<sup>9</sup> together form the radical =N-CH=CH-;

alkyl is a straight or branched saturated hydrocarbon radical having from 1 to 6 carbon atoms ; or is a cyclic saturated hydrocarbon radical having from 3 to 6 carbon atoms ; or is a cyclic saturated hydrocarbon radical having from 3 to 6 carbon atoms attached to a straight or branched saturated hydrocarbon radical having from 1 to 6 carbon atoms ; wherein each carbon atom can be optionally substituted with halo, hydroxy, alkyloxy or oxo ;

Ar is a homocycle selected from the group of phenyl, naphthyl, acenaphthyl, tetrahydronaphthyl, each optionally substituted with 1, 2 or 3 substituents, each substituent independently selected from the group of hydroxy, halo, cyano, nitro, amino, mono- or dialkylamino, alkyl, haloalkyl, alkyloxy, haloalkyloxy, carboxyl, alkyloxycarbonyl, aminocarbonyl, morpholinyl and mono- or dialkylaminocarbonyl ;

Het is a monocyclic heterocycle selected from the group of *N*-phenoxy piperidinyl, pyrrolyl, pyrazolyl, imidazolyl, furanyl, thienyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, pyridinyl, pyrimidinyl, pyrazinyl and pyridazinyl; or a bicyclic heterocycle selected from the group of quinolinyl, quinoxalinyl, indolyl, benzimidazolyl, benzoxazolyl, benzisoxazolyl, benzothiazolyl, benzisothiazolyl, benzofuranyl, benzothienyl, 2,3-dihydrobenzo[1,4]dioxinyl or benzo[1,3]dioxolyl ; each monocyclic and bicyclic heterocycle may optionally be substituted on a carbon atom with 1, 2 or 3 substituents selected from the group of halo, hydroxy, alkyl or alkyloxy ;

halo is a substituent selected from the group of fluoro, chloro, bromo and iodo and haloalkyl is a straight or branched saturated hydrocarbon radical having from 1 to 6 carbon atoms or a cyclic saturated hydrocarbon radical having from 3 to 6 carbon atoms, wherein one or more carbon atoms are substituted with one or more halo-atoms.

30

More in particular, the present invention relates to the use of a substituted quinoline derivative for the preparation of a medicament for the treatment of an infection with a drug resistant Mycobacterium strain wherein the substituted quinoline derivative is a compound according to Formula (Ia) or Formula (Ib).

35

The present invention also concerns a method of treating a patient suffering from , or at risk of, an infection with a drug resistant mycobacterial strain, which comprises

administering to the patient a therapeutically effective amount of a compound or pharmaceutical composition according to the invention.

5 The compounds according to Formula (Ia) and (Ib) are interrelated in that e.g. a compound according to Formula (Ib), with R<sup>9</sup> equal to oxo is the tautomeric equivalent of a compound according to Formula (Ia) with R<sup>2</sup> equal to hydroxy (keto-enol tautomerism).

10 In the framework of this application, alkyl is a straight or branched saturated hydrocarbon radical having from 1 to 6 carbon atoms ; or is a cyclic saturated hydrocarbon radical having from 3 to 6 carbon atoms ; or is a cyclic saturated hydrocarbon radical having from 3 to 6 carbon atoms attached to a straight or branched saturated hydrocarbon radical having from 1 to 6 carbon atoms ; wherein each carbon atom can be optionally substituted with halo, hydroxy, alkyloxy or oxo.  
15 Preferably, alkyl is methyl, ethyl or cyclohexylmethyl.

In the framework of this application, Ar is a homocycle selected from the group of phenyl, naphthyl, acenaphthyl, tetrahydronaphthyl, each optionally substituted with 1, 2 or 3 substituents, each substituent independently selected from the group of hydroxy,  
20 halo, cyano, nitro, amino, mono- or dialkylamino, alkyl, haloalkyl, alkyloxy, haloalkyloxy, carboxyl, alkyloxycarbonyl, aminocarbonyl, morpholinyl and mono- or dialkylaminocarbonyl. Preferably, Ar is naphthyl or phenyl, each optionally substituted with 1 or 2 halo substituents.

25 In the framework of this application, Het is a monocyclic heterocycle selected from the group of *N*-phenoxypiperidinyl, pyrrolyl, pyrazolyl, imidazolyl, furanyl, thienyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, pyridinyl, pyrimidinyl, pyrazinyl and pyridazinyl; or a bicyclic heterocycle selected from the group of quinolinyl, quinoxalinyl, indolyl, benzimidazolyl, benzoxazolyl, benzisoxazolyl, benzothiazolyl, benzisothiazolyl, benzofuranyl, benzothieryl, 2,3-dihydrobenzo[1,4]dioxinyl or benzo[1,3]dioxolyl ; each monocyclic and bicyclic heterocycle may optionally be substituted on a carbon atom with 1, 2 or 3 substituents selected from the group of halo,  
30 hydroxy, alkyl or alkyloxy. Preferably, Het is thienyl.

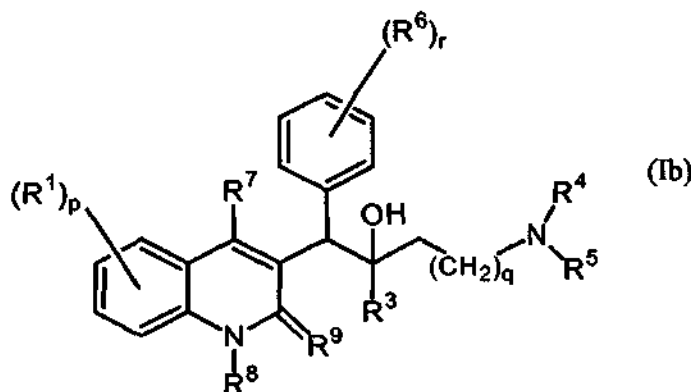
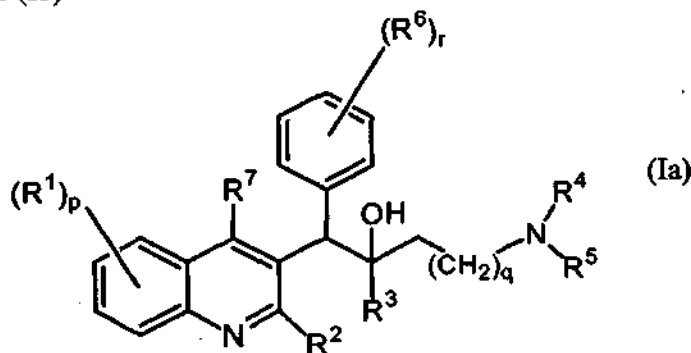
35 In the framework of this application, halo is a substituent selected from the group of fluoro, chloro, bromo and iodo and haloalkyl is a straight or branched saturated hydrocarbon radical having from 1 to 6 carbon atoms or a cyclic saturated hydrocarbon

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radical having from 3 to 6 carbon atoms, wherein one or more carbon atoms are substituted with one or more halo-atoms. Preferably, halo is bromo, fluoro or chloro and preferably, haloalkyl is trifluoromethyl. When alkyl is substituted with more than one halo atom, each halo atom may be the same or different.

5

Preferably, the invention relates to the use as defined hereinabove of compounds of Formula (Ia) or (Ib)



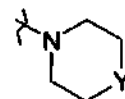
10 a pharmaceutically acceptable acid or base addition salt thereof, a stereochemically isomeric form thereof, a tautomeric form thereof or a *N*-oxide form thereof, wherein :

R<sup>1</sup> is hydrogen, halo, haloalkyl, cyano, hydroxy, Ar, Het, alkyl, alkyloxy, alkylthio, alkyloxyalkyl, alkylthioalkyl, Ar-alkyl or di(Ar)alkyl ;

p is an integer equal to 1, 2, 3 or 4 ;

15 R<sup>2</sup> is hydrogen, hydroxy, mercapto, alkyloxy, alkyloxyalkoxy, alkylthio,

mono or di(alkyl)amino or a radical of formula



wherein Y is

CH<sub>2</sub>, O, S, NH or N-alkyl ;

R<sup>3</sup> is alkyl, Ar, Ar-alkyl, Het or Het-alkyl;

- q is an integer equal to zero, 1, 2, 3 or 4 ;
- R<sup>4</sup> and R<sup>5</sup> each independently are hydrogen, alkyl or benzyl; or
- R<sup>4</sup> and R<sup>5</sup> together and including the N to which they are attached may form a radical selected from the group of pyrrolidinyl, 2*H*-pyrrolyl, 2-pyrrolinyl, 3-pyrrolinyl, pyrrolyl, imidazolidinyl, pyrazolidinyl, 2-imidazolinyl, 2-pyrazolinyl, imidazolyl, pyrazolyl, triazolyl, piperidinyl, pyridinyl, piperazinyl, imidazolidinyl, pyridazinyl, pyrimidinyl, pyrazinyl, triazinyl, morpholinyl and thiomorpholinyl, optionally substituted with alkyl, halo, haloalkyl, hydroxy, alkyloxy, amino, mono- or dialkylamino, alkylthio, alkyloxyalkyl, alkylthioalkyl and pyrimidinyl ;
- R<sup>6</sup> is hydrogen, halo, haloalkyl, hydroxy, Ar, alkyl, alkyloxy, alkylthio, alkyloxyalkyl, alkylthioalkyl, Ar-alkyl or di(Ar)alkyl ; or two vicinal R<sup>6</sup> radicals may be taken together to form a bivalent radical of formula =C-C=C-C- ;
- r is an integer equal to 1, 2, 3, 4 or 5 ; and
- R<sup>7</sup> is hydrogen, alkyl, Ar or Het ;
- R<sup>8</sup> is hydrogen or alkyl ;
- R<sup>9</sup> is oxo ; or
- R<sup>8</sup> and R<sup>9</sup> together form the radical =N-CH=CH-;
- alkyl is a straight or branched saturated hydrocarbon radical having from 1 to 6 carbon atoms ; or is a cyclic saturated hydrocarbon radical having from 3 to 6 carbon atoms ; or is a cyclic saturated hydrocarbon radical having from 3 to 6 carbon atoms attached to a straight or branched saturated hydrocarbon radical having from 1 to 6 carbon atoms ; wherein each carbon atom can be optionally substituted with halo, hydroxy, alkyloxy or oxo ;
- Ar is a homocycle selected from the group of phenyl, naphthyl, acenaphthyl, tetrahydronaphthyl, each optionally substituted with 1, 2 or 3 substituents, each substituent independently selected from the group of hydroxy, halo, cyano, nitro, amino, mono- or dialkylamino, alkyl, haloalkyl, alkyloxy, haloalkyloxy, carboxyl, alkyloxycarbonyl, aminocarbonyl, morpholinyl and mono- or dialkylaminocarbonyl ;
- Het is a monocyclic heterocycle selected from the group of *N*-phenoxy piperidinyl, pyrrolyl, pyrazolyl, imidazolyl, furanyl, thienyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, pyridinyl, pyrimidinyl, pyrazinyl and pyridazinyl; or a bicyclic heterocycle selected from the group of quinolinyl, quinoxalinyl, indolyl, benzimidazolyl, benzoxazolyl, benzisoxazolyl, benzothiazolyl, benzisothiazolyl, benzofuranyl, benzothienyl, 2,3-dihydrobenzo[1,4]dioxinyl or

benzo[1,3]dioxolyl ; each monocyclic and bicyclic heterocycle may optionally be substituted on a carbon atom with 1, 2 or 3 substituents selected from the group of halo, hydroxy, alkyl or alkyloxy ;

halo is a substituent selected from the group of fluoro, chloro, bromo and iodo and

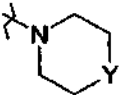
5 haloalkyl is a straight or branched saturated hydrocarbon radical having from 1 to 6 carbon atoms or a cyclic saturated hydrocarbon radical having from 3 to 6 carbon atoms, wherein one or more carbonatoms are substituted with one or more halo-atoms.

10 The invention also relates to the use as defined hereinabove of compounds of Formula (Ia) or (Ib) wherein

R<sup>1</sup> is hydrogen, halo, haloalkyl, cyano, hydroxy, Ar, Het, alkyl, alkyloxy, alkylthio, alkyloxyalkyl, alkylthioalkyl, Ar-alkyl or di(Ar)alkyl ;

p is an integer equal to 1, 2, 3 or 4 ;

15 R<sup>2</sup> is hydrogen, hydroxy, mercapto, alkyloxy, alkyloxyalkyloxy, alkylthio,

mono or di(alkyl)amino or a radical of formula  wherein Y is CH<sub>2</sub>, O, S, NH or N-alkyl ;

R<sup>3</sup> is alkyl, Ar, Ar-alkyl, Het or Het-alkyl;

q is an integer equal to zero, 1, 2, 3 or 4 ;

20 R<sup>4</sup> and R<sup>5</sup> each independently are hydrogen, alkyl or benzyl; or

R<sup>4</sup> and R<sup>5</sup> together and including the N to which they are attached may form a radical selected from the group of pyrrolidinyl, 2*H*-pyrrolyl, 2-pyrrolinyl, 3-pyrrolinyl, pyrrolyl, imidazolidinyl, pyrazolidinyl, 2-imidazoliny, 2-pyrazolinyl, imidazolyl, pyrazolyl, triazolyl, piperidinyl, pyridinyl, 25 piperazinyl, imidazolidinyl, pyridazinyl, pyrimidinyl, pyrazinyl, triazinyl, morpholinyl and thiomorpholinyl, optionally substituted with alkyl, halo, haloalkyl, hydroxy, alkyloxy, amino, mono- or dialkylamino, alkylthio, alkyloxyalkyl, alkylthioalkyl and pyrimidinyl ;

R<sup>6</sup> is hydrogen, halo, haloalkyl, hydroxy, Ar, alkyl, alkyloxy, alkylthio, 30 alkyloxyalkyl, alkylthioalkyl, Ar-alkyl or di(Ar)alkyl ;

r is an integer equal to 1, 2, 3, 4 or 5 ; and

R<sup>7</sup> is hydrogen, alkyl, Ar or Het ;

R<sup>8</sup> is hydrogen or alkyl ;

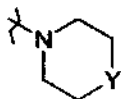
R<sup>9</sup> is oxo ; or

35 R<sup>8</sup> and R<sup>9</sup> together form the radical =N-CH=CH-;

- alkyl is a straight or branched saturated hydrocarbon radical having from 1 to 6 carbon atoms ; or is a cyclic saturated hydrocarbon radical having from 3 to 6 carbon atoms ; or is a cyclic saturated hydrocarbon radical having from 3 to 6 carbon atoms attached to a straight or branched saturated hydrocarbon radical having from 1 to 6 carbon atoms ; wherein each carbon atom can be optionally substituted with halo, hydroxy, alkyloxy or oxo ;
- Ar is a homocycle selected from the group of phenyl, naphthyl, acenaphthyl, tetrahydronaphthyl, each optionally substituted with 1, 2 or 3 substituents, each substituent independently selected from the group of hydroxy, halo, cyano, nitro, amino, mono- or dialkylamino, alkyl, haloalkyl, alkyloxy, haloalkyloxy, carboxyl, alkyloxy carbonyl, aminocarbonyl, morpholinyl and mono- or dialkylaminocarbonyl ;
- Het is a monocyclic heterocycle selected from the group of *N*-phenoxy piperidinyl, pyrrolyl, pyrazolyl, imidazolyl, furanyl, thienyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, pyridinyl, pyrimidinyl, pyrazinyl and pyridazinyl; or a bicyclic heterocycle selected from the group of quinolinyl, quinoxalinyl, indolyl, benzimidazolyl, benzoxazolyl, benzisoxazolyl, benzothiazolyl, benzisothiazolyl, benzofuranyl, benzothienyl, 2,3-dihydrobenzo[1,4]dioxinyl or benzo[1,3]dioxolyl ; each monocyclic and bicyclic heterocycle may optionally be substituted on a carbon atom with 1, 2 or 3 substituents selected from the group of halo, hydroxy, alkyl or alkyloxy ;
- halo is a substituent selected from the group of fluoro, chloro, bromo and iodo and haloalkyl is a straight or branched saturated hydrocarbon radical having from 1 to 6 carbon atoms or a cyclic saturated hydrocarbon radical having from 3 to 6 carbon atoms, wherein one or more carbon atoms are substituted with one or more halo-atoms.

The invention also relates to the use as defined hereinabove of compounds of Formula (Ia) or (Ib) wherein :

- 30  $R^1$  is hydrogen, halo, cyano, Ar, Het, alkyl, and alkyloxy ;  
 $p$  is an integer equal to zero, 1, 2, 3 or 4 ;  
 $R^2$  is hydrogen, hydroxy, alkyloxy, alkyloxyalkyloxy, alkylthio or a radical



of formula wherein Y is O ;

- $R^3$  is alkyl, Ar, Ar-alkyl or Het ;  
 35  $q$  is an integer equal to zero, 1, 2, or 3 ;

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- $R^4$  and  $R^5$  each independently are hydrogen, alkyl or benzyl; or  
 $R^4$  and  $R^5$  together and including the N to which they are attached may form a radical  
 selected from the group of pyrrolidinyl, imidazolyl, triazolyl,  
 piperidinyl, piperazinyl, pyrazinyl, morpholinyl and thiomorpholinyl,  
 optionally substituted with alkyl and pyrimidinyl ;  
 $R^6$  is hydrogen, halo or alkyl ; or  
 two vicinal  $R^6$  radicals may be taken together to form a bivalent radical of formula  
 $-\text{CH}=\text{CH}-\text{CH}=\text{CH}-$  ;  
 $r$  is an integer equal to 1 ; and  
 $R^7$  is hydrogen ;  
 $R^8$  is hydrogen or alkyl ;  
 $R^9$  is oxo ; or  
 $R^8$  and  $R^9$  together form the radical  $=\text{N}-\text{CH}=\text{CH}-$  .  
 alkyl is a straight or branched saturated hydrocarbon radical having from 1 to 6  
 carbon atoms ; or is a cyclic saturated hydrocarbon radical having from 3 to 6  
 carbon atoms ; or is a cyclic saturated hydrocarbon radical having from 3 to 6  
 carbon atoms attached to a straight or branched saturated hydrocarbon radical  
 having from 1 to 6 carbon atoms ; wherein each carbon atom can be optionally  
 substituted with halo or hydroxy ;  
 Ar is a homocycle selected from the group of phenyl, naphthyl, acenaphthyl,  
 tetrahydronaphthyl, each optionally substituted with 1, 2 or 3 substituents, each  
 substituent independently selected from the group of halo, haloalkyl, cyano,  
 alkyloxy and morpholinyl ;  
 Het is a monocyclic heterocycle selected from the group of *N*-phenoxypiperidinyl,  
 furanyl, thienyl, pyridinyl, pyrimidinyl ; or a bicyclic heterocycle selected from  
 the group of benzothienyl, 2,3-dihydrobenzo[1,4]dioxinyl or benzo[1,3]-  
 dioxolyl; each monocyclic and bicyclic heterocycle may optionally be  
 substituted on a carbon atom with 1, 2 or 3 alkyl substituents ; and  
 halo is a substituent selected from the group of fluoro, chloro and bromo.
- For compounds according to either Formula (Ia) and (Ib), preferably,  $R^1$  is hydrogen,  
 halo, Ar, alkyl or alkyloxy. More preferably,  $R^1$  is halo. Most preferably,  $R^1$  is bromo.
- Preferably,  $p$  is equal to 1.
- Preferably,  $R^2$  is hydrogen, alkyloxy or alkylthio. More preferably,  $R^2$  is alkyloxy, in  
 particular  $C_{1-4}$ alkyloxy. Most preferably,  $R^2$  is methyloxy.



C<sub>1-4</sub>alkyl is a straight or branched saturated hydrocarbon radical having from 1 to 4 carbon atoms such as for example methyl, ethyl, propyl, 2-methyl-ethyl and the like.

5 Preferably, R<sup>3</sup> is naphthyl, phenyl or thienyl, each optionally substituted with 1 or 2 substituents, that substituent preferably being a halo or haloalkyl, most preferably being a halo. More preferably, R<sup>3</sup> is naphthyl or phenyl, each optionally substituted with halo, preferably 3-fluoro. Even more preferably, R<sup>3</sup> is naphthyl or phenyl. Most preferably, R<sup>3</sup> is naphthyl.

10 Preferably, q is equal to zero, 1 or 2. More preferably, q is equal to 1.

Preferably, R<sup>4</sup> and R<sup>5</sup> each independently are hydrogen or alkyl, in particular hydrogen or C<sub>1-4</sub>alkyl, more in particular C<sub>1-4</sub>alkyl, more preferably hydrogen, methyl or ethyl, most preferably methyl.

15 C<sub>1-4</sub>alkyl is a straight or branched saturated hydrocarbon radical having from 1 to 4 carbon atoms such as for example methyl, ethyl, propyl, 2-methyl-ethyl and the like.

20 Preferably R<sup>4</sup> and R<sup>5</sup> together and including the N to which they are attached form a radical selected from the group of imidazolyl, triazolyl, piperidinyl, piperazinyl and thiomorpholinyl, optionally substituted with alkyl, halo, haloalkyl, hydroxy, alkyloxy, alkylthio, alkyloxyalkyl or alkylthioalkyl, preferably substituted with alkyl, most preferably substituted with methyl or ethyl.

25 Preferably, R<sup>6</sup> is hydrogen, alkyl or halo. Most preferably, R<sup>6</sup> is hydrogen. Preferably r is 0, 1 or 2.

Preferably, R<sup>7</sup> is hydrogen or methyl, more preferably hydrogen.

30 For compounds according to Formula (Ib) only, preferably, R<sup>8</sup> is alkyl, preferably methyl and R<sup>9</sup> is oxygen.

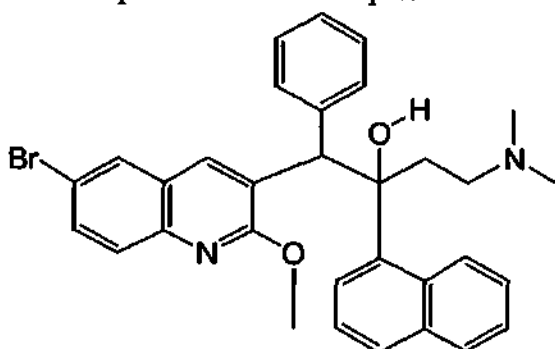
35 An interesting group of compounds are the compounds according to formula (Ia), the pharmaceutically acceptable acid or base addition salts thereof, the stereochemically isomeric forms thereof, the tautomeric forms thereof or the *N*-oxide forms thereof.

An interesting group of compounds are the compounds according to Formula (Ia), the pharmaceutically acceptable acid or base addition salts thereof, the stereochemically

- o 1-(6-bromo-2-methoxy-quinolin-3-yl)-4-dimethylamino-2-naphthalen-1-yl-1-phenyl-butan-2-ol corresponding to 6-bromo- $\alpha$ -[2-(dimethylamino)ethyl]-2-methoxy- $\alpha$ -1-naphthalenyl- $\beta$ -phenyl-3-quinolineethanol;  
 a pharmaceutically acceptable acid or base addition salt thereof, a stereochemically isomeric form thereof, a tautomeric form thereof or a *N*-oxide form thereof.

An alternative chemical name for 1-(6-bromo-2-methoxy-quinolin-3-yl)-4-dimethylamino-2-naphthalen-1-yl-1-phenyl-butan-2-ol is 6-bromo- $\alpha$ -[2-(dimethylamino)ethyl]-2-methoxy- $\alpha$ -1-naphthalenyl- $\beta$ -phenyl-3-quinolineethanol.

- 10 Said compound can also be represented as follows :



Most preferably, the compound is one of the following :

- 6-bromo- $\alpha$ -[2-(dimethylamino)ethyl]-2-methoxy- $\alpha$ -1-naphthalenyl- $\beta$ -phenyl-3-quinolineethanol, a pharmaceutically acceptable acid or base addition salt thereof, a stereochemically isomeric forms thereof, a tautomeric form thereof or a *N*-oxide form thereof; or  
 6-bromo- $\alpha$ -[2-(dimethylamino)ethyl]-2-methoxy- $\alpha$ -1-naphthalenyl- $\beta$ -phenyl-3-quinolineethanol, or a pharmaceutically acceptable acid addition salt thereof; or  
 6-bromo- $\alpha$ -[2-(dimethylamino)ethyl]-2-methoxy- $\alpha$ -1-naphthalenyl- $\beta$ -phenyl-3-quinolineethanol, or a stereochemically isomeric form thereof; or  
 6-bromo- $\alpha$ -[2-(dimethylamino)ethyl]-2-methoxy- $\alpha$ -1-naphthalenyl- $\beta$ -phenyl-3-quinolineethanol, or a *N*-oxide form thereof; or  
 ( $\alpha$ S,  $\beta$ R)-6-bromo- $\alpha$ -[2-(dimethylamino)ethyl]-2-methoxy- $\alpha$ -1-naphthalenyl- $\beta$ -phenyl-3-quinolineethanol, i.e. compound 12, or a pharmaceutically acceptable acid addition salt thereof; or  
 ( $\alpha$ S,  $\beta$ R)-6-bromo- $\alpha$ -[2-(dimethylamino)ethyl]-2-methoxy- $\alpha$ -1-naphthalenyl- $\beta$ -phenyl-3-quinolineethanol, i.e. compound 12.

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isomeric forms thereof, the tautomeric forms thereof or the *N*-oxide forms thereof, in which R<sup>1</sup> is hydrogen, halo, Ar, alkyl or alkyloxy, p = 1, R<sup>2</sup> is hydrogen, alkyloxy or alkylthio, R<sup>3</sup> is naphthyl, phenyl or thienyl, each optionally substituted with 1 or 2 substituents selected from the group of halo and haloalkyl, q = 0, 1, 2 or 3, R<sup>4</sup> and R<sup>5</sup> each independently are hydrogen or alkyl or R<sup>4</sup> and R<sup>5</sup> together and including the N to which they are attached form a radical selected from the group of imidazolyl, triazolyl, piperidinyl, piperazinyl and thiomorpholinyl, R<sup>6</sup> is hydrogen, alkyl or halo, r is equal to 0 or 1 and R<sup>7</sup> is hydrogen.

10 Preferable, the compound is :

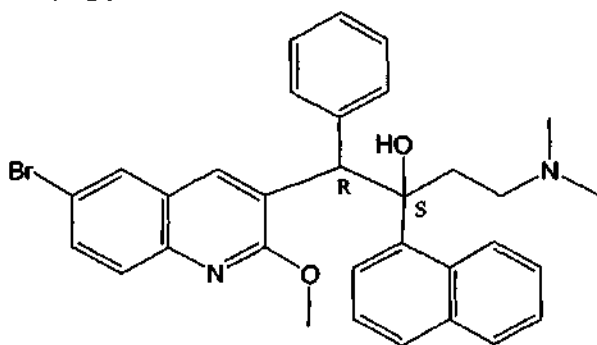
- 1-(6-bromo-2-methoxy-quinolin-3-yl)-2-(3,5-difluoro-phenyl)-4-dimethylamino-1-phenyl-butan-2-ol ;
- 1-(6-bromo-2-methoxy-quinolin-3-yl)-4-dimethylamino-2-naphthalen-1-yl-1-phenyl-butan-2-ol corresponding to 6-bromo- $\alpha$ -[2-(dimethylamino)ethyl]-2-methoxy- $\alpha$ -1-naphthalenyl- $\beta$ -phenyl-3-quinolineethanol;
- 15 ○ 1-(6-bromo-2-methoxy-quinolin-3-yl)-2-(2,5-difluoro-phenyl)-4-dimethylamino-1-phenyl-butan-2-ol ;
- 1-(6-bromo-2-methoxy-quinolin-3-yl)-2-(2,3-difluoro-phenyl)-4-dimethylamino-1-phenyl-butan-2-ol ;
- 20 ○ 1-(6-bromo-2-methoxy-quinolin-3-yl)-4-dimethylamino-2-(2-fluoro-phenyl)-1-phenyl-butan-2-ol ;
- 1-(6-bromo-2-methoxy-quinolin-3-yl)-4-dimethylamino-2-naphthalen-1-yl-1-p-tolyl-butan-2-ol ;
- 1-(6-bromo-2-methoxy-quinolin-3-yl)-4-methylamino-2-naphthalen-1-yl-1-phenyl-butan-2-ol ;
- 25 ○ 1-(6-bromo-2-methoxy-quinolin-3-yl)-4-dimethylamino-2-(3-fluoro-phenyl)-1-phenyl-butan-2-ol; and
- 1-(6-bromo-2-methoxy-quinolin-3-yl)-4-dimethylamino-2-phenyl-1-phenyl-butan-2-ol;
- 30 a pharmaceutically acceptable acid or base addition salt thereof, a stereochemically isomeric form thereof, a tautomeric form thereof or a *N*-oxide form thereof.

Even more preferably, the compound is

- 1-(6-bromo-2-methoxy-quinolin-3-yl)-4-dimethylamino-2-(3-fluoro-phenyl)-1-phenyl-butan-2-ol;
- 35 ○ 1-(6-bromo-2-methoxy-quinolin-3-yl)-4-dimethylamino-2-phenyl-1-phenyl-butan-2-ol;

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Thus, most preferably, the compound is ( $\alpha$ S,  $\beta$ R)-6-bromo- $\alpha$ -[2-(dimethylamino)ethyl]-2-methoxy- $\alpha$ -1-naphthalenyl- $\beta$ -phenyl-3-quinolineethanol which corresponds to (1R,2S)-1-(6-bromo-2-methoxy-quinolin-3-yl)-4-dimethylamino-2-naphthalen-1-yl-1-phenyl-butan-2-ol. Said compound can also be represented as follows :



The pharmaceutically acceptable acid addition salts are defined to comprise the therapeutically active non-toxic acid addition salt forms which the compounds according to either Formula (Ia) and (Ib) are able to form. Said acid addition salts can be obtained by treating the base form of the compounds according to either Formula (Ia) and (Ib) with appropriate acids, for example inorganic acids, for example hydrohalic acid, in particular hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid and phosphoric acid ; organic acids, for example acetic acid, hydroxyacetic acid, propanoic acid, lactic acid, pyruvic acid, oxalic acid, malonic acid, succinic acid, maleic acid, fumaric acid, malic acid, tartaric acid, citric acid, methanesulfonic acid, ethanesulfonic acid, benzenesulfonic acid, *p*-toluenesulfonic acid, cyclamic acid, salicylic acid, *p*-aminosalicylic acid and pamoic acid.

The compounds according to either Formula (Ia) and (Ib) containing acidic protons may also be converted into their therapeutically active non-toxic base addition salt forms by treatment with appropriate organic and inorganic bases. Appropriate base salts forms comprise, for example, the ammonium salts, the alkaline and earth alkaline metal salts, in particular lithium, sodium, potassium, magnesium and calcium salts, salts with organic bases, e.g. the benzathine, *N*-methyl-*D*-glucamine, hybramine salts, and salts with amino acids, for example arginine and lysine.

Conversely, said acid or base addition salt forms can be converted into the free forms by treatment with an appropriate base or acid.

30

The term addition salt as used in the framework of this application also comprises the solvates which the compounds according to either Formula (Ia) and (Ib) as well as the salts thereof, are able to form. Such solvates are, for example, hydrates and alcoholates.

5

The term "stereochemically isomeric forms" as used herein defines all possible isomeric forms which the compounds of either Formula (Ia) and (Ib) may possess. Unless otherwise mentioned or indicated, the chemical designation of compounds denotes the mixture of all possible stereochemically isomeric forms, said mixtures containing all diastereomers and enantiomers of the basic molecular structure. More in particular, stereogenic centers may have the R- or S-configuration; substituents on bivalent cyclic (partially) saturated radicals may have either the cis- or trans-configuration. Stereochemically isomeric forms of the compounds of either Formula (Ia) and (Ib) are obviously intended to be embraced within the scope of this invention.

10

Following CAS-nomenclature conventions, when two stereogenic centers of known absolute configuration are present in a molecule, an R or S descriptor is assigned (based on Cahn-Ingold-Prelog sequence rule) to the lowest-numbered chiral center, the reference center. The configuration of the second stereogenic center is indicated using relative descriptors  $[R^*,R^*]$  or  $[R^*,S^*]$ , where  $R^*$  is always specified as the reference center and  $[R^*,R^*]$  indicates centers with the same chirality and  $[R^*,S^*]$  indicates centers of unlike chirality. For example, if the lowest-numbered chiral center in the molecule has an S configuration and the second center is R, the stereo descriptor would be specified as  $S-[R^*,S^*]$ . If " $\alpha$ " and " $\beta$ " are used: the position of the highest priority substituent on the asymmetric carbon atom in the ring system having the lowest ring number, is arbitrarily always in the " $\alpha$ " position of the mean plane determined by the ring system. The position of the highest priority substituent on the other asymmetric carbon atom in the ring system relative to the position of the highest priority substituent on the reference atom is denominated " $\alpha$ ", if it is on the same side of the mean plane determined by the ring system, or " $\beta$ ", if it is on the other side of the mean plane determined by the ring system.

15

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Compounds of either Formula (Ia) and (Ib) and some of the intermediate compounds invariably have at least two stereogenic centers in their structure which may lead to at least 4 stereochemically different structures.

35

The tautomeric forms of the compounds of either Formula (Ia) and (Ib) are meant to comprise those compounds of either Formula (Ia) and (Ib) wherein e.g. an enol group is converted into a keto group (keto-enol tautomerism).

- 5 The *N*-oxide forms of the compounds according to either Formula (Ia) and (Ib) are meant to comprise those compounds of either Formula (Ia) and (Ib) wherein one or several tertiary nitrogen atoms are oxidized to the so-called *N*-oxide.

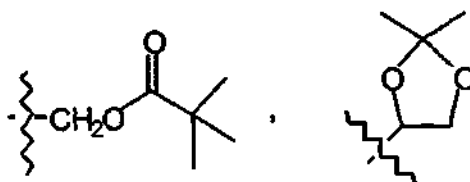
10 The compounds of either Formula (Ia) and (Ib) as prepared in the processes described below may be synthesized in the form of racemic mixtures of enantiomers which can be separated from one another following art-known resolution procedures. The racemic compounds of either Formula (Ia) and (Ib) may be converted into the corresponding diastereomeric salt forms by reaction with a suitable chiral acid. Said diastereomeric salt forms are subsequently separated, for example, by selective or  
15 fractional crystallization and the enantiomers are liberated therefrom by alkali. An alternative manner of separating the enantiomeric forms of the compounds of either Formula (Ia) and (Ib) involves liquid chromatography using a chiral stationary phase. Said pure stereochemically isomeric forms may also be derived from the corresponding pure stereochemically isomeric forms of the appropriate starting materials, provided  
20 that the reaction occurs stereospecifically. Preferably if a specific stereoisomer is desired, said compound will be synthesized by stereospecific methods of preparation. These methods will advantageously employ enantiomerically pure starting materials.

25 The invention also comprises derivative compounds (usually called "pro-drugs") of the pharmacologically-active compounds according to the invention, which are degraded *in vivo* to yield the compounds according to the invention. Pro-drugs are usually (but not always) of lower potency at the target receptor than the compounds to which they are degraded. Pro-drugs are particularly useful when the desired compound has chemical or physical properties that make its administration difficult or inefficient. For example,  
30 the desired compound may be only poorly soluble, it may be poorly transported across the mucosal epithelium, or it may have an undesirably short plasma half-life. Further discussion on pro-drugs may be found in Stella, V. J. *et al.*, "Prodrugs", *Drug Delivery Systems*, 1985, pp. 112-176, and *Drugs*, 1985, 29, pp. 455-473.

35 Pro-drugs forms of the pharmacologically-active compounds according to the invention will generally be compounds according to either Formula (Ia) and (Ib), the pharmaceutically acceptable acid or base addition salts thereof, the stereochemically

isomeric forms thereof, the tautomeric forms thereof and the *N*-oxide forms thereof, having an acid group which is esterified or amidated. Included in such esterified acid groups are groups of the formula  $-\text{COOR}^x$ , where  $\text{R}^x$  is a  $\text{C}_{1-6}$ alkyl, phenyl, benzyl or one of the following groups :

5



Amidated groups include groups of the formula  $-\text{CONR}^y\text{R}^z$ , wherein  $\text{R}^y$  is H,  $\text{C}_{1-6}$ alkyl, phenyl or benzyl and  $\text{R}^z$  is  $-\text{OH}$ , H,  $\text{C}_{1-6}$ alkyl, phenyl or benzyl.

- 10 Compounds according to the invention having an amino group may be derivatised with a ketone or an aldehyde such as formaldehyde to form a Mannich base. This base will hydrolyze with first order kinetics in aqueous solution.

15 An interesting embodiment of the present invention is the use of a substituted quinoline derivative according to Formula (Ia) or Formula (Ib), in particular ( $\alpha\text{S}$ ,  $\beta\text{R}$ )-6-bromo- $\alpha$ -[2-(dimethylamino)ethyl]-2-methoxy- $\alpha$ -1-naphthalenyl- $\beta$ -phenyl-3-quinolineethanol, for the preparation of a medicament for the treatment of an infection with a drug resistant Mycobacterium strain as defined hereinabove wherein the drug resistant Mycobacterium strain is a drug resistant *M. tuberculosis* strain.

20

A further interesting embodiment of the present invention is the use of a substituted quinoline derivative according to Formula (Ia) or Formula (Ib), in particular ( $\alpha\text{S}$ ,  $\beta\text{R}$ )-6-bromo- $\alpha$ -[2-(dimethylamino)ethyl]-2-methoxy- $\alpha$ -1-naphthalenyl- $\beta$ -phenyl-3-quinolineethanol, for the preparation of a medicament for the treatment of a human  
 25 infected with a drug resistant Mycobacterium strain, in particular a drug resistant *M. tuberculosis* strain.

30 Still a further interesting embodiment of the present invention is the use of a substituted quinoline derivative according to Formula (Ia) or Formula (Ib), in particular ( $\alpha\text{S}$ ,  $\beta\text{R}$ )-6-bromo- $\alpha$ -[2-(dimethylamino)ethyl]-2-methoxy- $\alpha$ -1-naphthalenyl- $\beta$ -phenyl-3-quinolineethanol, for the preparation of a medicament for the treatment of an infection with a multi drug resistant Mycobacterium strain, in particular a multi drug resistant *M. tuberculosis* strain, in particular for the preparation of a medicament for the treatment

of a mammal, including a human, infected with a multi drug resistant *Mycobacterium* strain, in particular a multi drug resistant *M. tuberculosis* strain.

As already stated above, the compounds of formula (Ia) and (Ib) can be used to treat drug resistant including multi drug resistant Mycobacterial diseases. The exact dosage and frequency of administration depends on the particular compound of formula (Ia) or (Ib) used, the particular condition being treated, the severity of the condition being treated, the age, weight and general physical condition of the particular patient as well as other medication the individual may be taking, as is well known to those skilled in the art. Furthermore, it is evident that said effective daily amount may be lowered or increased depending on the response of the treated subject and/or depending on the evaluation of the physician prescribing the compounds of the instant invention.

Given the fact that the compounds of formula (Ia) and (Ib) are active against drug resistant including multi drug resistant Mycobacterial strains, the present compounds may be combined with other antimycobacterial agents in order to effectively combat Mycobacterial diseases.

Therefore, the present invention also relates to a combination of (a) a compound of formula (Ia) or (Ib), in particular ( $\alpha$ S,  $\beta$ R)-6-bromo- $\alpha$ -[2-(dimethylamino)ethyl]-2-methoxy- $\alpha$ -1-naphthalenyl- $\beta$ -phenyl-3-quinolineethanol or a pharmaceutically acceptable acid addition salt thereof, and (b) one or more other antimycobacterial agents.

The present invention also relates to a combination of (a) a compound of formula (Ia) or (Ib), in particular ( $\alpha$ S,  $\beta$ R)-6-bromo- $\alpha$ -[2-(dimethylamino)ethyl]-2-methoxy- $\alpha$ -1-naphthalenyl- $\beta$ -phenyl-3-quinolineethanol or a pharmaceutically acceptable acid addition salt thereof, and (b) one or more other antimycobacterial agents for use as a medicine.

A pharmaceutical composition comprising a pharmaceutically acceptable carrier and, as active ingredient, a therapeutically effective amount of (a) a compound of formula (Ia) or (Ib), in particular ( $\alpha$ S,  $\beta$ R)-6-bromo- $\alpha$ -[2-(dimethylamino)ethyl]-2-methoxy- $\alpha$ -1-naphthalenyl- $\beta$ -phenyl-3-quinolineethanol or a pharmaceutically acceptable acid addition salt thereof, and (b) one or more other antimycobacterial agents, is also comprised by the present invention.



The present invention also relates to the use of a combination or pharmaceutical composition as defined above for the treatment of an infection with a drug resistant Mycobacterium strain, in particular a drug resistant *M tuberculosis* strain.

The above defined combination or pharmaceutical composition may also be used to  
5 treat an infection with a susceptible Mycobacterial strain, in particular a susceptible *M. tuberculosis* strain.

In the above defined combination or pharmaceutical composition, the compound of formula (Ia) or (Ib) is preferably a compound of formula (Ia).

10

The other Mycobacterial agents which may be combined with the compounds of formula (Ia) or (Ib) are for example rifampicin (=rifampin); isoniazid; pyrazinamide; amikacin; ethionamide; moxifloxacin; ethambutol; streptomycin; para-aminosalicylic acid; cycloserine; capreomycin; kanamycin; thioacetazone; PA-824;  
15 quinolones/fluoroquinolones such as for example ofloxacin, ciprofloxacin, sparfloxacin; macrolides such as for example clarithromycin, clofazimine, amoxicillin with clavulanic acid; rifamycins; rifabutin; rifapentine.

Preferably, the present compounds of formula (Ia) or (Ib), in particular ( $\alpha$ S,  $\beta$ R)-6-bromo- $\alpha$ -[2-(dimethylamino)ethyl]-2-methoxy- $\alpha$ -1-naphthalenyl- $\beta$ -phenyl-3-quinolineethanol, are combined with rifapentin and moxifloxacin.

Another interesting combination according to the present invention is a combination of  
25 (a) a compound of formula (Ia) or (Ib), in particular ( $\alpha$ S,  $\beta$ R)-6-bromo- $\alpha$ -[2-(dimethylamino)ethyl]-2-methoxy- $\alpha$ -1-naphthalenyl- $\beta$ -phenyl-3-quinolineethanol or a pharmaceutically acceptable acid addition salt thereof, and (b) one or more other antimycobacterial agents wherein said one or more other antimycobacterial agents comprise pyrazinamide. Thus, the present invention also relates to a combination of a compound of formula (Ia) or (Ib), in particular ( $\alpha$ S,  $\beta$ R)-6-bromo- $\alpha$ -[2-  
30 (dimethylamino)ethyl]-2-methoxy- $\alpha$ -1-naphthalenyl- $\beta$ -phenyl-3-quinolineethanol or a pharmaceutically acceptable acid addition salt thereof, and pyrazinamide and optionally one or more other antimycobacterial agents. Examples of such combinations are the combination of ( $\alpha$ S,  $\beta$ R)-6-bromo- $\alpha$ -[2-(dimethylamino)ethyl]-2-methoxy- $\alpha$ -1-naphthalenyl- $\beta$ -phenyl-3-quinolineethanol or a pharmaceutically acceptable acid addition salt thereof, and pyrazinamide;  
35 the combination of ( $\alpha$ S,  $\beta$ R)-6-bromo- $\alpha$ -[2-(dimethylamino)ethyl]-2-methoxy- $\alpha$ -1-naphthalenyl- $\beta$ -phenyl-3-quinolineethanol or a pharmaceutically acceptable acid addition salt thereof, pyrazinamide and rifapentin; the

combination of ( $\alpha$ S,  $\beta$ R)-6-bromo- $\alpha$ -[2-(dimethylamino)ethyl]-2-methoxy- $\alpha$ -1-naphthalenyl- $\beta$ -phenyl-3-quinolineethanol or a pharmaceutically acceptable acid addition salt thereof, pyrazinamide and isoniazid; the combination of ( $\alpha$ S,  $\beta$ R)-6-bromo- $\alpha$ -[2-(dimethylamino)ethyl]-2-methoxy- $\alpha$ -1-naphthalenyl- $\beta$ -phenyl-3-quinolineethanol or a pharmaceutically acceptable acid addition salt thereof,  
5 pyrazinamide and moxifloxacin; the combination of ( $\alpha$ S,  $\beta$ R)-6-bromo- $\alpha$ -[2-(dimethylamino)ethyl]-2-methoxy- $\alpha$ -1-naphthalenyl- $\beta$ -phenyl-3-quinolineethanol or a pharmaceutically acceptable acid addition salt thereof, pyrazinamide and rifampin. It has been found that a compound of formula (Ia) or (Ib), in particular ( $\alpha$ S,  $\beta$ R)-6-bromo- $\alpha$ -[2-(dimethylamino)ethyl]-2-methoxy- $\alpha$ -1-naphthalenyl- $\beta$ -phenyl-3-quinolineethanol or a pharmaceutically acceptable acid addition salt thereof, and  
10 pyrazinamide act synergistically.

Also interesting combinations are those combinations comprising a compound of  
15 formula (Ia) or (Ib), as described in Tables 11 and 12.

A pharmaceutical composition comprising a pharmaceutically acceptable carrier and, as active ingredient, a therapeutically effective amount of the active ingredients listed in the above combinations, is also comprised by the present invention.

20  
The present pharmaceutical composition may have various pharmaceutical forms for administration purposes. As appropriate compositions there may be cited all compositions usually employed for systemically administering drugs. To prepare the pharmaceutical compositions of this invention, an effective amount of the particular  
25 compounds, optionally in addition salt form, as the active ingredient is combined in intimate admixture with a pharmaceutically acceptable carrier, which carrier may take a wide variety of forms depending on the form of preparation desired for administration. These pharmaceutical compositions are desirable in unitary dosage form suitable, in particular, for administration orally or by parenteral injection. For example, in  
30 preparing the compositions in oral dosage form, any of the usual pharmaceutical media may be employed such as, for example, water, glycols, oils, alcohols and the like in the case of oral liquid preparations such as suspensions, syrups, elixirs, emulsions and solutions; or solid carriers such as starches, sugars, kaolin, diluents, lubricants, binders, disintegrating agents and the like in the case of powders, pills, capsules and tablets.  
35 Because of their ease in administration, tablets and capsules represent the most advantageous oral unit dosage forms in which case solid pharmaceutical carriers are obviously employed. For parenteral compositions, the carrier will usually comprise

sterile water, at least in large part, though other ingredients, for example, to aid solubility, may be included. Injectable solutions, for example, may be prepared in which the carrier comprises saline solution, glucose solution or a mixture of saline and glucose solution. Injectable suspensions may also be prepared in which case  
5 appropriate liquid carriers, suspending agents and the like may be employed. Also included are solid form preparations which are intended to be converted, shortly before use, to liquid form preparations.

Depending on the mode of administration, the pharmaceutical composition will  
10 preferably comprise from 0.05 to 99 % by weight, more preferably from 0.1 to 70 % by weight of the active ingredients, and, from 1 to 99.95 % by weight, more preferably from 30 to 99.9 weight % of a pharmaceutically acceptable carrier, all percentages being based on the total composition.

15 The weight to weight ratio's of the compound of formula (Ia) or (Ib) and (b) the other antimycobacterial agent(s) when given as a combination may be determined by the person skilled in the art. Said ratio and the exact dosage and frequency of administration depends on the particular compound of formula (Ia) or (Ib) and the other antimycobacterial agent(s) used, the particular condition being treated, the severity of  
20 the condition being treated, the age, weight and general physical condition of the particular patient as well as other medication the individual may be taking, as is well known to those skilled in the art. Furthermore, it is evident that said effective daily amount may be lowered or increased depending on the response of the treated subject and/or depending on the evaluation of the physician prescribing the compounds of the  
25 instant invention.

The compounds of formula (Ia) or (Ib) and the one or more other antimycobacterial agents may be combined in a single preparation or they may be formulated in separate preparations so that they can be administered simultaneously, separately or  
30 sequentially. Thus, the present invention also relates to a product containing (a) a compound of formula (Ia) or (Ib), and (b) one or more other antimycobacterial agents, as a combined preparation for simultaneous, separate or sequential use in the treatment of mycobacterial diseases.

35 The pharmaceutical composition may additionally contain various other ingredients known in the art, for example, a lubricant, stabilising agent, buffering agent,

emulsifying agent, viscosity-regulating agent, surfactant, preservative, flavouring or colorant.

It is especially advantageous to formulate the aforementioned pharmaceutical compositions in unit dosage form for ease of administration and uniformity of dosage. Unit dosage form as used herein refers to physically discrete units suitable as unitary dosages, each unit containing a predetermined quantity of active ingredient calculated to produce the desired therapeutic effect in association with the required pharmaceutical carrier. Examples of such unit dosage forms are tablets (including scored or coated tablets), capsules, pills, powder packets, wafers, suppositories, injectable solutions or suspensions and the like, and segregated multiples thereof. The daily dosage of the compound according to the invention will, of course, vary with the compound employed, the mode of administration, the treatment desired and the mycobacterial disease indicated. However, in general, satisfactory results will be obtained when the compound according to the invention is administered at a daily dosage not exceeding 1gram, e.g. in the range from 10 to 50 mg/kg body weight.

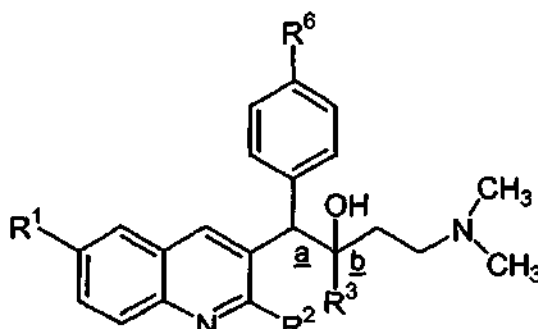
The compounds of formula (Ia) and (Ib) and their preparation is described in WO 2004/011436, which is incorporated herein by reference.

Of some compounds the absolute stereochemical configuration of the stereogenic carbon atom(s) therein was not experimentally determined. In those cases the stereochemically isomeric form which was first isolated is designated as "A" and the second as "B", without further reference to the actual stereochemical configuration. However, said "A" and "B" isomeric forms can be unambiguously characterized by a person skilled in the art, using art-known methods such as, for example, X-ray diffraction.

In case "A" and "B" are stereoisomeric mixtures, they can be further separated whereby the respective first fractions isolated are designated "A1" and "B1" and the second as "A2" and "B2", without further reference to the actual stereochemical configuration.

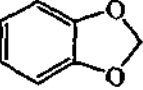
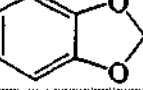
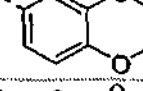
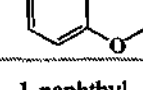

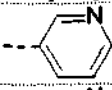
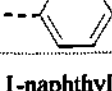
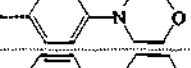
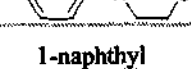
The following Tables list compounds of formula (Ia) and (Ib), which can all be prepared according to the methods described in WO 2004/011436.

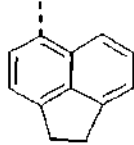
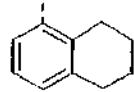





Table 1:



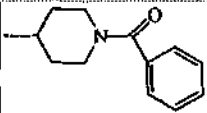
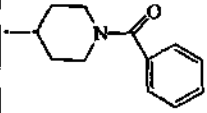
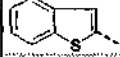
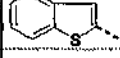
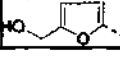
| Comp. nr. | Ex. nr. | R <sup>1</sup>   | R <sup>2</sup>   | R <sup>3</sup> | R <sup>6</sup> | Stereochemistry and melting points |
|-----------|---------|------------------|------------------|----------------|----------------|------------------------------------|
| 1         | B1      | Br               | OCH <sub>3</sub> | phenyl         | H              | (A1); 194°C                        |
| 2         | B1      | Br               | OCH <sub>3</sub> | phenyl         | H              | (A2); 191°C                        |
| 3         | B1      | Br               | OCH <sub>3</sub> | phenyl         | H              | (A); 200°C                         |
| 4         | B1      | Br               | OCH <sub>3</sub> | phenyl         | H              | (B); 190°C                         |
| 16        | B1      | Br               | OCH <sub>3</sub> | 4-chlorophenyl | H              | (A); 200°C                         |
| 17        | B1      | Br               | OCH <sub>3</sub> | 4-chlorophenyl | H              | (B); 190°C                         |
| 20        | B1      | Br               | OCH <sub>3</sub> | 2-thienyl      | H              | (A); 96°C                          |
| 21        | B1      | Br               | OCH <sub>3</sub> | 2-thienyl      | H              | (B); 176°C                         |
| 22        | B1      | CH <sub>3</sub>  | OCH <sub>3</sub> | phenyl         | H              | (A); 148°C                         |
| 23        | B1      | CH <sub>3</sub>  | OCH <sub>3</sub> | phenyl         | H              | (B); 165°C                         |
| 24        | B1      | Br               | OCH <sub>3</sub> | 3-thienyl      | H              | (A); 162°C                         |
| 25        | B1      | Br               | OCH <sub>3</sub> | 3-thienyl      | H              | (B); 160°C                         |
| 26        | B1      | phenyl           | OCH <sub>3</sub> | phenyl         | H              | (A); 174°C                         |
| 27        | B1      | phenyl           | OCH <sub>3</sub> | phenyl         | H              | (B); 192°C                         |
| 28        | B1      | F                | OCH <sub>3</sub> | phenyl         | H              | (A); 190°C                         |
| 29        | B1      | F                | OCH <sub>3</sub> | phenyl         | H              | (B); 166°C                         |
| 30        | B1      | Cl               | OCH <sub>3</sub> | phenyl         | H              | (A); 170°C                         |
| 31        | B1      | Cl               | OCH <sub>3</sub> | phenyl         | H              | (B); 181°C                         |
| 32        | B1      | Br               | SCH <sub>3</sub> | phenyl         | H              | (A); 208°C                         |
| 33        | B1      | Br               | SCH <sub>3</sub> | phenyl         | H              | (B); 196°C                         |
| 34        | B1      | OCH <sub>3</sub> | OCH <sub>3</sub> | phenyl         | H              | (A); 165°C                         |
| 35        | B1      | OCH <sub>3</sub> | OCH <sub>3</sub> | phenyl         | H              | (B); 165°C                         |
| 36        | B1      | Br               | OCH <sub>3</sub> | phenyl         | Cl             | (A); 197°C                         |
| 37        | B1      | Br               | OCH <sub>3</sub> | phenyl         | Cl             | (B); 221°C                         |
| 38        | B9      | Br               | OCH <sub>3</sub> | 3-fluorophenyl | H              | (A); 198°C                         |
| 39        | B9      | Br               | OCH <sub>3</sub> | 3-fluorophenyl | H              | (B); 207°C                         |

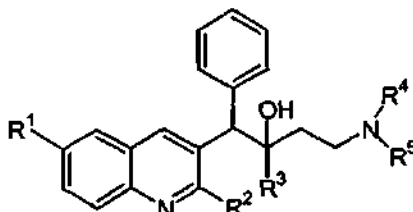
| Comp. nr. | Ex. nr. | R <sup>1</sup> | R <sup>2</sup>                   | R <sup>3</sup>     | R <sup>6</sup>  | Stereochemistry and melting points  |
|-----------|---------|----------------|----------------------------------|--------------------|-----------------|---|
| 108       | B9      | Br             | OCH <sub>3</sub>                 | 3-fluorophenyl     | H               | (A1); 160°C   |
| 109       | B9      | Br             | OCH <sub>3</sub>                 | 3-fluorophenyl     | H               | (A2); 156°C   |
| 40        | B1      | H              | OCH <sub>3</sub>                 | phenyl             | H               | (A); 152°C  |
| 41        | B1      | H              | OCH <sub>3</sub>                 | phenyl             | H               | (B); 160°C  |
| 42        | B1      | H              | OCH <sub>3</sub>                 | CH <sub>3</sub>    | H               | (A); 140°C  |
| 43        | B1      | H              | OCH <sub>3</sub>                 | CH <sub>3</sub>    | H               | (B); 120°C  |
| 59        | B1      | Br             | OH                               | phenyl             | H               | (A); >260°C   |
| 60        | B1      | Br             | OH                               | phenyl             | H               | (B); 215°C  |
| 5         | B2      | Br             | OCH <sub>2</sub> CH <sub>3</sub> | phenyl             | H               | (A); 162°C  |
| 6         | B2      | Br             | OCH <sub>2</sub> CH <sub>3</sub> | phenyl             | H               | (B); 74°C   |
| 7         | B3      | Br             | H                                | phenyl             | H               | (A); 98°C   |
| 8         | B3      | Br             | H                                | phenyl             | H               | (B); 180°C  |
| 12        | B7      | Br             | OCH <sub>3</sub>                 | 1-naphthyl         | H               | (A1); 118°C; <u>a</u> =R, <u>b</u> =S;<br>[alpha] <sub>D</sub> <sup>20</sup> = -166.98<br>(c=0.505g/100ml in DMF) |
| 13        | B7      | Br             | OCH <sub>3</sub>                 | 1-naphthyl         | H               | (A2); 120°C; <u>a</u> =S, <u>b</u> =R;<br>[alpha] <sub>D</sub> <sup>20</sup> = +167.60<br>(c=0.472g/100ml in DMF) |
| 14        | B7      | Br             | OCH <sub>3</sub>                 | 1-naphthyl         | H               | (A); 210°C  |
| 15        | B7      | Br             | OCH <sub>3</sub>                 | 1-naphthyl         | H               | (B); 244°C  |
| 45        | B7      | Br             | OCH <sub>3</sub>                 | 2-naphthyl         | H               | (A); 262°C  |
| 46        | B7      | Br             | OCH <sub>3</sub>                 | 2-naphthyl         | H               | (B); 162°C  |
| 67        | B8      | Br             | OCH <sub>3</sub>                 | 2,5-difluorophenyl | H               | (A); 60°C   |
| 68        | B8      | Br             | OCH <sub>3</sub>                 | 2,5-difluorophenyl | H               | (B); 208°C  |
| 110       | B8      | Br             | OCH <sub>3</sub>                 | 2,5-difluorophenyl | H               | (A1); 167°C   |
| 111       | B8      | Br             | OCH <sub>3</sub>                 | 2,5-difluorophenyl | H               | (A2); oil   |
| 69        | B1      | Br             | OCH <sub>3</sub>                 | 2-fluorophenyl     | H               | (A); oil  |
| 70        | B1      | Br             | OCH <sub>3</sub>                 | 2-fluorophenyl     | H               | (B); oil  |
| 71        | B1      | Br             | OCH <sub>3</sub>                 | 1-naphthyl         | CH <sub>3</sub> | (A); 174°C  |
| 72        | B1      | Br             | OCH <sub>3</sub>                 | 1-naphthyl         | CH <sub>3</sub> | (B); 178°C  |
| 73        | B1      | Br             | OCH <sub>3</sub>                 | 1-naphthyl         | Cl              | (B); 174°C  |
| 74        | B1      | Br             | OCH <sub>3</sub>                 | 1-naphthyl         | Cl              | (A); 110°C  |

| Comp. nr. | Ex. nr. | R <sup>1</sup>   | R <sup>2</sup>  | R <sup>3</sup>  | R <sup>6</sup> | Stereochemistry and melting points |
|-----------|---------|------------------|---|---|----------------|------------------------------------|
| 75        | B1      | Br               | OCH <sub>3</sub>  |    | H              | (A); 196°C                         |
| 76        | B1      | Br               | OCH <sub>3</sub>  |    | H              | (B); 130°C                         |
| 77        | B1      | Br               | OCH <sub>3</sub>  |    | H              | (A); 202°C                         |
| 78        | B1      | Br               | OCH <sub>3</sub>  |    | H              | (B); 202°C                         |
| 79        | B1      | Br               |  | 1-naphthyl  | H              | (A); >250°C                        |
| 80        | B1      | Br               | OCH <sub>3</sub>  | 4-cyanophenyl   | H              | (A); 224°C                         |
| 81        | B1      | Br               | OCH <sub>3</sub>  | 4-cyanophenyl   | H              | (B); 232°C                         |
| 82        | B1      | CH <sub>3</sub>  | OCH <sub>3</sub>  | 1-naphthyl  | H              | (A); 202°C                         |
| 83        | B1      | CH <sub>3</sub>  | OCH <sub>3</sub>  | 1-naphthyl  | H              | (B); 198°C                         |
| 84        | B1      | phenyl           | OCH <sub>3</sub>  | 1-naphthyl  | H              | (A); 248°C                         |
| 85        | B1      | phenyl           | OCH <sub>3</sub>  | 1-naphthyl  | H              | (B); 214°C                         |
| 86        | B1      | Br               | OCH <sub>3</sub>  |  | H              | (A); 184°C                         |
| 87        | B1      | Br               | OCH <sub>3</sub>  |  | H              | (B); 186°C                         |
| 88        | B1      | Br               | SCH <sub>3</sub>  | 1-naphthyl  | H              | (A); 240°C                         |
| 89        | B1      | Br               | OCH <sub>3</sub>  |  | H              | (A); 236°C                         |
| 90        | B1      | Br               | OCH <sub>3</sub>  |  | H              | (B); 206°C                         |
| 91        | B1      | H                | OCH <sub>3</sub>  | 1-naphthyl  | H              | (A); 178°C                         |
| 92        | B1      | H                | OCH <sub>3</sub>  | 1-naphthyl  | H              | (B); 160°C                         |
| 93        | B1      | H                | OCH <sub>3</sub>  | 3-fluorophenyl  | H              | (A); 178°C                         |
| 94        | B1      | H                | OCH <sub>3</sub>  | 3-fluorophenyl  | H              | (B); 182°C                         |
| 95        | B1      | Br               | OCH <sub>3</sub>  | 2-phenylethyl   | H              | (A); 178°C                         |
| 96        | B1      | Br               | OCH <sub>3</sub>  | 2-phenylethyl   | H              | (B); 146°C                         |
| 97        | B1      | OCH <sub>3</sub> | OCH <sub>3</sub>  | 1-naphthyl  | H              | (A); 168°C                         |
| 98        | B1      | OCH <sub>3</sub> | OCH <sub>3</sub>  | 1-naphthyl  | H              | (B); 154°C                         |
| 113       | B14     | Br               | OCH <sub>3</sub>  | 2,3-difluorophenyl  | H              | (A); 128°C                         |
| 114       | B14     | Br               | OCH <sub>3</sub>  | 2,3-difluorophenyl  | H              | (B); 213°C                         |

| Comp. nr. | Ex. nr. | R <sup>1</sup>  | R <sup>2</sup>  | R <sup>3</sup>   | R <sup>6</sup> | Stereochemistry and melting points |
|-----------|---------|---|---|--|----------------|------------------------------------|
| 115       | B15     | Br  | OCH <sub>3</sub>  | 3,5-difluorophenyl   | H              | (A); 192°C                         |
| 116       | B15     | Br  | OCH <sub>3</sub>  | 3,5-difluorophenyl   | H              | (B); 224°C                         |
| 117       | B15     | Br  | OCH <sub>3</sub>  | 3,5-difluorophenyl   | H              | (A1); 161°C                        |
| 118       | B15     | Br  | OCH <sub>3</sub>  | 3,5-difluorophenyl   | H              | (A2); 158°C                        |
| 119       | B7      | Cl  | OCH <sub>3</sub>  | 1-naphthyl   | H              | (A); 212°C                         |
| 120       | B7      | Cl  | OCH <sub>3</sub>  | 1-naphthyl   | H              | (B); 236°C                         |
| 122       | B7      | Br  | OCH <sub>3</sub>  |   | H              | (B); 227°C                         |
| 127       | B7      | Br  | OCH <sub>3</sub>  | 5-bromo-2-naphthyl   | H              | (A); 226°C                         |
| 130       | B7      | Br  | OCH <sub>3</sub>  | 5-bromo-2-naphthyl   | H              | (B); 220°C                         |
| 131       | B1      | Br  | OCH <sub>3</sub>  |  | H              | (A); 206°C                         |
| 134       | B9      | OCH <sub>3</sub>  | OCH <sub>3</sub>  | 3-fluorophenyl   | H              | (A); 172°C                         |
| 135       | B9      | OCH <sub>3</sub>  | OCH <sub>3</sub>  | 3-fluorophenyl   | H              | (B); 182°C                         |
| 143       | B7      | Br  | OCH <sub>3</sub>  | 3-bromo-1-naphthyl   | H              | (A); 234°C                         |
| 150       | B7      | Br  | OCH <sub>3</sub>  | 3-bromo-1-naphthyl   | H              | (B); 212°C                         |
| 159       | B8      | Br  | OCH <sub>3</sub>  | 2,5-difluorophenyl   | H              | (A1); 208°C                        |
| 160       | B8      | Br  | OCH <sub>3</sub>  | 2,5-difluorophenyl   | H              | (A2); 167°C                        |
| 162       | B7      | Br  | OCH <sub>3</sub>  | 6-methoxy-2-naphthyl   | H              | (A); 206°C                         |
| 163       | B7      | Br  | OCH <sub>3</sub>  | 6-methoxy-2-naphthyl   | H              | (B); 206°C                         |
| 164       | B9      | Br  |  | 3-fluorophenyl   | H              | (A); 118°C                         |
| 165       | B9      | Br  |  | 3-fluorophenyl   | H              | (B); oil                           |
| 167       | B8      | Br  | OCH <sub>3</sub>  | 2,6-difluorophenyl   | H              | (B); 180°C                         |
| 174       | B9      |  | OCH <sub>3</sub>  | 3-fluorophenyl   | H              | (A); 159°C                         |
| 175       | B9      |  | OCH <sub>3</sub>  | 3-fluorophenyl   | H              | (B); 196°C                         |
| 176       | B7      | Br  |  | 1-naphthyl   | H              | (A); oil                           |
| 179       | B9      | CN  | OCH <sub>3</sub>  | 3-fluorophenyl   | H              | (A); 213°C                         |

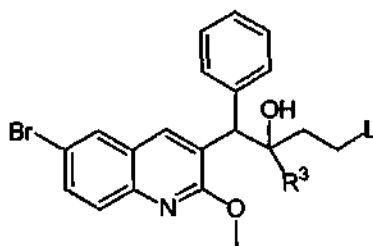


| Comp. nr. | Ex. nr. | R <sup>1</sup>  | R <sup>2</sup>   | R <sup>3</sup>   | R <sup>6</sup> | Stereochemistry and melting points |
|-----------|---------|---|------------------|--|----------------|------------------------------------|
| 180       | B9      | CN  | OCH <sub>3</sub> | 3-fluorophenyl   | H              | (B); 163°C                         |
| 181       | B9      | Br  | OCH <sub>3</sub> | 4-fluorophenyl   | H              | (A); 198°C                         |
| 182       | B9      | Br  | OCH <sub>3</sub> | 4-fluorophenyl   | H              | (B); 238°C                         |
| 183       | B1      | Br  | OCH <sub>3</sub> | 3-trifluoro-methylphenyl   | H              | (A); 170°C                         |
| 188       | B1      | Br  | OCH <sub>3</sub> | 1,4-pyrimidin-2-yl   | H              | (A); 110°C                         |
| 189       | B1      | Br  | OCH <sub>3</sub> | 1,4-pyrimidin-2-yl   | H              | (B); 145°C                         |
| 195       | B15     | Br  | OCH <sub>3</sub> | 3,4-difluorophenyl   | H              | (A); 250°C                         |
| 196       | B15     | Br  | OCH <sub>3</sub> | 3,4-difluorophenyl   | H              | (B); 184°C                         |
| 201       | B1      | Br  | OCH <sub>3</sub> |   | H              | (A); 214°C                         |
| 202       | B1      | Br  | OCH <sub>3</sub> |  | H              | (B); 246°C                         |
| 203       | B9      |  | OCH <sub>3</sub> | 3-fluorophenyl   | H              | (A); 225°C                         |
| 204       | B9      |  | OCH <sub>3</sub> | 3-fluorophenyl   | H              | (B); 216°C                         |
| 205       | B7      | Br  | OCH <sub>3</sub> | 1-naphthyl   | F              | (A); 213°C                         |
| 206       | B7      | Br  | OCH <sub>3</sub> | 1-naphthyl   | F              | (B); 213°C                         |
| 207       | B15     | F   | OCH <sub>3</sub> | 3,5-difluorophenyl   | H              | (A); 232°C                         |
| 208       | B15     | F   | OCH <sub>3</sub> | 3,5-difluorophenyl   | H              | (B); 188°C                         |
| 212       | B7      |  | OCH <sub>3</sub> | 1-naphthyl   | H              | (B); 220°C                         |

**Table 2:**

| Comp. nr. | Ex. nr. | R <sup>1</sup> | R <sup>2</sup>   | R <sup>3</sup> | R <sup>4</sup>                  | R <sup>5</sup>                  | Phys. data (salt/melting points) and stereo-chemistry |
|-----------|---------|----------------|------------------|----------------|---------------------------------|---------------------------------|---|
| 18        | B1      | Br             | OCH <sub>3</sub> | phenyl         | CH <sub>2</sub> CH <sub>3</sub> | CH <sub>2</sub> CH <sub>3</sub> | .ethanedioate (2:3); (A); 230°C                       |
| 19        | B1      | Br             | OCH <sub>3</sub> | phenyl         | CH <sub>2</sub> CH <sub>3</sub> | CH <sub>2</sub> CH <sub>3</sub> | .ethanedioate (2:3), (B); 150°C                       |
| 44        | B4      | Br             | OCH <sub>3</sub> | phenyl         | H                               | H                               | (A); 190°C  |
| 9         | B4      | Br             | OCH <sub>3</sub> | phenyl         | H                               | H                               | (B); 204°C  |
| 141       | B7      | Br             | OCH <sub>3</sub> | 2-naphthyl     | CH <sub>3</sub>                 | CH <sub>2</sub> CH <sub>3</sub> | (A); 188°C  |
| 142       | B7      | Br             | OCH <sub>3</sub> | 2-naphthyl     | CH <sub>3</sub>                 | CH <sub>2</sub> CH <sub>3</sub> | (B); 202°C  |
| 230       | B12     | Br             | OCH <sub>3</sub> | 1-naphthyl     | CH <sub>3</sub>                 | benzyl                          | /oil  |
| 147       | B7      | Br             | OCH <sub>3</sub> | 1-naphthyl     | CH <sub>3</sub>                 | CH <sub>2</sub> CH <sub>3</sub> | (A); 168°C  |
| 148       | B7      | Br             | OCH <sub>3</sub> | 1-naphthyl     | CH <sub>3</sub>                 | CH <sub>2</sub> CH <sub>3</sub> | (B); 212°C  |
| 56        | B13     | Br             | OCH <sub>3</sub> | 1-naphthyl     | CH <sub>3</sub>                 | H                               | (A); 204°C  |
| 214       | B13     | Br             | OCH <sub>3</sub> | 1-naphthyl     | CH <sub>3</sub>                 | H                               | (B); 225°C  |

Table 3:



| Comp nr. | Ex. nr. | R <sup>3</sup> | L                       | Stereochemistry and melting points |
|----------|---------|----------------|-------------------------|------------------------------------|
| 47       | B1      | phenyl         | 1-piperidinyl           | (A); 190°C                         |
| 48       | B1      | phenyl         | 1-piperidinyl           | (B); 210°C                         |
| 128      | B1      | 2-naphthyl     | 1-piperidinyl           | (A); 254°C                         |
| 129      | B1      | 2-naphthyl     | 1-piperidinyl           | (B); 212°C                         |
| 49       | B1      | phenyl         | 1-imidazolyl            | (A); 216°C                         |
| 50       | B1      | phenyl         | 1-imidazolyl            | (B); 230°C                         |
| 51       | B1      | phenyl         | 1-(4-methyl)piperazinyl | (A); 150°C                         |
| 52       | B1      | phenyl         | 1-(4-methyl)piperazinyl | (B); 230°C                         |
| 53       | B1      | phenyl         | 1-(1,2,4-triazolyl)     | (A); 180°C                         |
| 54       | B1      | phenyl         | 1-(1,2,4-triazolyl)     | (B); 142°C                         |
| 55       | B1      | phenyl         | thiomorpholinyl         | (A); oil                           |
| 57       | B5      | phenyl         |                         | (A); 244°C                         |
| 10       | B5      | phenyl         |                         | (B); 198°C                         |
| 58       | B6      | phenyl         |                         | (A); 208°C                         |
| 11       | B6      | phenyl         |                         | (B); 208°C                         |

| Comp<br>nr. | Ex.<br>nr. | R <sup>3</sup>     | L                   | Stereochemistry<br>and melting<br>points |
|-------------|------------|--------------------|---------------------|--|
| 99          | B11        | 1-naphthyl         |                     | (A1); 218°C                              |
| 100         | B6         | 1-naphthyl         |                     | (A2); 218°C                              |
| 101         | B6         | 1-naphthyl         |                     | (B); 175°C                               |
| 102         | B5         | 1-naphthyl         |                     | (A2); 210°C                              |
| 103         | B5         | 1-naphthyl         |                     | (B); >250°C                              |
| 121         | B5         | 1-naphthyl         |                     | (A1); 210°C                              |
| 123         | B1         | phenyl             | morpholinyl         | (A); 226°C                               |
| 124         | B1         | phenyl             | morpholinyl         | (B); 210°C                               |
| 136         | B7         | 2-naphthyl         | 4-methylpyrazinyl   | (A); 188°C                               |
| 137         | B7         | 2-naphthyl         | 4-methylpyrazinyl   | (B); 232°C                               |
| 139         | B7         | 2-naphthyl         | morpholinyl         | (A); 258°C                               |
| 140         | B7         | 2-naphthyl         | morpholinyl         | (B); 214°C                               |
| 144         | B7         | 2-naphthyl         | pyrrolidinyl        | (A); 238°C                               |
| 145         | B7         | 1-naphthyl         | 1-piperidinyl       | (A); 212°C                               |
| 146         | B7         | 1-naphthyl         | 1-piperidinyl       | (B); 220°C                               |
| 149         | B7         | 1-naphthyl         | 4-methylpyrazinyl   | (B); 232°C                               |
| 151         | B7         | 3-bromo-1-naphthyl | 4-methylpiperazinyl | (A); 178°C                               |
| 152         | B7         | 3-bromo-1-naphthyl | 4-methylpiperazinyl | (B); 226°C                               |
| 153         | B7         | 6-bromo-2-naphthyl | 4-methylpiperazinyl | (A); 208°C                               |
| 154         | B7         | 6-bromo-2-naphthyl | 4-methylpiperazinyl | (B); 254°C                               |

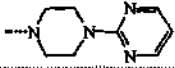
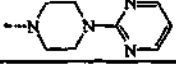
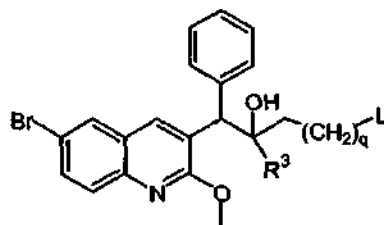
| Comp. nr. | Ex. nr. | R <sup>3</sup>     | L   | Stereochemistry and melting points |
|-----------|---------|--------------------|---|------------------------------------|
| 155       | B7      | 6-bromo-2-naphthyl | 1-piperidiny  | (A); 224°C                         |
| 156       | B7      | 1-naphthyl         | 4-methylpiperaziny  | (A); 200°C                         |
| 157       | B7      | 6-bromo-2-naphthyl | 1-pyrrolidiny   | (B); 220°C                         |
| 158       | B7      | 1-naphthyl         | morpholiny  | (B); 272°C                         |
| 166       | B7      | 6-bromo-2-naphthyl | 1-piperidiny  | (B); 218°C                         |
| 170       | B7      | 2-naphthyl         | 1-pyrrolidiny   | (A); 238°C                         |
| 171       | B7      | 2-naphthyl         | 1-pyrrolidiny   | (B); 218°C                         |
| 172       | B7      | 1-naphthyl         | 1,2,4-triazol-1-yl  | /142°C                             |
| 173       | B7      | 1-naphthyl         | 1,2-imidazol-1-yl   | (A); 222°C                         |
| 177       | B7      | 6-bromo-2-naphthyl | morpholiny  | (A); 242°C                         |
| 178       | B7      | 6-bromo-2-naphthyl | morpholiny  | (B); 246°C                         |
| 187       | B7      | 1-naphthyl         | 1,2-imidazol-1-yl   | (B); 236°C                         |
| 200       | B7      | 2-naphthyl         |   | (A); 254°C                         |
| 209       | B7      | 2-naphthyl         |  | (B); 198°C                         |

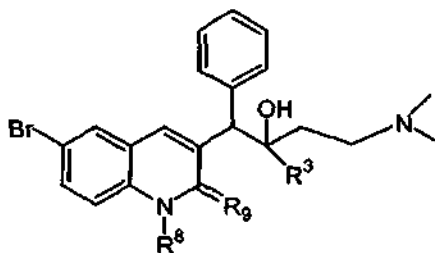
Table 4:



| Comp. nr. | Ex. nr. | R <sup>3</sup> | Q | L                                | Stereochemistry and melting points |
|-----------|---------|----------------|---|----------------------------------|------------------------------------|
| 61        | B1      | phenyl         | 0 | N(CH <sub>3</sub> ) <sub>2</sub> | (A); 220°C                         |
| 62        | B1      | phenyl         | 0 | N(CH <sub>3</sub> ) <sub>2</sub> | (B); 194°C                         |
| 63        | B1      | phenyl         | 2 | N(CH <sub>3</sub> ) <sub>2</sub> | (A); 150°C                         |
| 64        | B1      | phenyl         | 2 | N(CH <sub>3</sub> ) <sub>2</sub> | (B); 220°C                         |
| 125       | B7      | 2-naphthyl     | 2 | N(CH <sub>3</sub> ) <sub>2</sub> | (A); 229°C                         |
| 126       | B7      | 2-naphthyl     | 2 | N(CH <sub>3</sub> ) <sub>2</sub> | (B); 214°C                         |

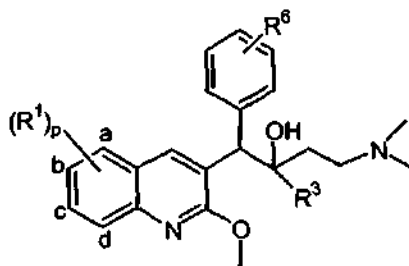
| Comp. nr. | Ex. nr. | R <sup>3</sup> | Q | L  | Stereochemistry and melting points |
|-----------|---------|----------------|---|--|------------------------------------|
| 65        | B1      | phenyl         | 3 | N(CH <sub>3</sub> ) <sub>2</sub>                 | (A); 130°C                         |
| 66        | B1      | phenyl         | 3 | N(CH <sub>3</sub> ) <sub>2</sub>                 | (B); 170°C                         |
| 132       | B7      | 2-naphthyl     | 2 | pyrrolidinyl                                     | (A); 227°C                         |
| 133       | B7      | 2-naphthyl     | 2 | pyrrolidinyl                                     | (B); 222°C                         |
| 161       | B7      | 2-naphthyl     | 2 | morpholinyl                                      | (B); 234°C                         |
| 186       | B7      | 1-naphthyl     | 2 | N(CH <sub>3</sub> ) <sub>2</sub>                 | (A); 187°C                         |
| 190       | B7      | 2-naphthyl     | 3 | N(CH <sub>3</sub> ) <sub>2</sub>                 | (A); 170°C                         |
| 191       | B7      | 2-naphthyl     | 3 | N(CH <sub>3</sub> ) <sub>2</sub>                 | (B); 145°C                         |
| 192       | B7      | 2-naphthyl     | 2 | N(CH <sub>2</sub> CH <sub>3</sub> ) <sub>2</sub> | (A); 90°C                          |
| 193       | B7      | 2-naphthyl     | 2 | N(CH <sub>2</sub> CH <sub>3</sub> ) <sub>2</sub> | (B); 202°C                         |
| 194       | B7      | 1-naphthyl     | 2 | pyrrolidinyl                                     | (B); 206°C                         |
| 197       | B7      | 1-naphthyl     | 3 | N(CH <sub>3</sub> ) <sub>2</sub>                 | (A); 160°C                         |
| 198       | B7      | 2-naphthyl     | 2 | morpholinyl                                      | (A); 215°C                         |
| 199       | B7      | 1-naphthyl     | 2 | N(CH <sub>2</sub> CH <sub>3</sub> ) <sub>2</sub> | (A); 185°C                         |
| 210       | B7      | 1-naphthyl     | 2 | morpholinyl                                      | (B); 222°C                         |
| 211       | B7      | 1-naphthyl     | 2 | morpholinyl                                      | (A); 184°C                         |



Table 5:



| Comp. nr. | Ex. nr. | R <sup>3</sup> | R <sup>8</sup>  | R <sup>9</sup> | Stereochemistry and melting points |
|-----------|---------|----------------|-----------------|----------------|------------------------------------|
| 104       | B1      | phenyl         | -CH=CH-N=       |                | (A); 170°C                         |
| 105       | B1      | phenyl         | -CH=CH-N=       |                | (B); 150°C                         |
| 106       | B1      | phenyl         | CH <sub>3</sub> | =O             | (A); 224°C                         |
| 107       | B1      | phenyl         | CH <sub>3</sub> | =O             | (B); 180°C                         |
| 138       | B7      | 1-naphthyl     | H               | =O             | (A1); >260°C                       |

Table 6:



| Comp<br>nr. | Ex.<br>nr. | R <sup>1</sup> |                 |                 |                 | R <sup>3</sup>     | R <sup>6</sup>  | Stereochemistry<br>and melting<br>points |
|-------------|------------|----------------|-----------------|-----------------|-----------------|--------------------|---|--|
|             |            | a              | b               | c               | d               |                    |   |  |
| 215         | B9         | H              | Br              | CH <sub>3</sub> | H               | 3-fluorophenyl     | H   | (A); 197°C                               |
| 216         | B9         | H              | Br              | CH <sub>3</sub> | H               | 3-fluorophenyl     | H   | (B); 158°C                               |
| 217         | B7         | H              | H               | Br              | H               | 1-naphthyl         | H   | (A); 212°C                               |
| 218         | B7         | H              | H               | Br              | H               | 1-naphthyl         | H   | (B); 172°C                               |
| 219         | B9         | H              | Br              | H               | CH <sub>3</sub> | 3-fluorophenyl     | H   | (A); 220°C                               |
| 220         | B9         | H              | Br              | H               | CH <sub>3</sub> | 3-fluorophenyl     | H   | (B); 179°C                               |
| 221         | B7         | Br             | H               | H               | H               | 1-naphthyl         | H   | (A); 170°C                               |
| 224         | B7         | Br             | H               | H               | H               | 1-naphthyl         | H   | 205°C                                    |
| 222         | B7         | H              | Br              | H               | H               | 1-naphthyl         |  | (A); 155°C                               |
| 223         | B7         | H              | Br              | H               | H               | 1-naphthyl         |  | (B); 205°C                               |
| 225         | B7         | H              | Br              | CH <sub>3</sub> | H               | 1-naphthyl         | H   | (A); 238°C                               |
| 226         | B7         | H              | Br              | CH <sub>3</sub> | H               | 1-naphthyl         | H   | (B); 208°C                               |
| 227         | B15        | H              | Br              | CH <sub>3</sub> | H               | 3,5-difluorophenyl | H   | (A); 195°C                               |
| 228         | B15        | H              | Br              | CH <sub>3</sub> | H               | 3,5-difluorophenyl | H   | (B); 218°C                               |
| 229         | B7         | H              | CH <sub>3</sub> | CH <sub>3</sub> | H               | 1-naphthyl         | H   | (A); 238°C                               |

Pharmacological examples*In-vitro method for testing compounds against resistant Mycobacteria strains.*

The *in vitro* activity has been assessed by the determination of the minimal inhibitory concentration (MIC : MIC will be the lowest drug concentration inhibiting more than  
5 99 % of the bacterial growth on control medium without antibiotic) in solid medium.

For the *in vitro* test, the following medium was used : 10 % Oleic acid Albumin Dextrose Catalase (OADC)-enriched 7H11 medium.

As inoculum was used: two appropriate dilutions of 10 % OADC-enriched 7H9 broth  
10 culture aged of 3 to 14 days depending on the mycobacterial species (final inocula = about  $10^2$  and  $10^4$  cfu (colony forming units))

The incubations were done at 30°C or 37°C for 3 to 42 days depending on the mycobacterial species.

15 Tables 7 and 8 list the MICs (mg/L) against different clinical isolates of resistant Mycobacterium strains. Tables 9 and 10 list the MICs (mg/L) against different clinical isolates of Mycobacterium strains resistant to fluoroquinolones.

In the Tables rifampin and ofloxacin are also included as reference.

20 Table 7 :

| Strains  | Rifampin | Compound 12 | Compound 109 | Compound 2 |
|--|----------|-------------|--------------|------------|
| <i>M.tuberculosis</i><br>isoniazid-resistant<br>low level  | 0.5      | 0.06        | 0.12         | 0.25       |
| <i>M.tuberculosis</i><br>isoniazid-resistant<br>high level | 0.5      | ≤ 0.01      | 0.03         | ≤ 0.01     |
| <i>M.tuberculosis</i><br>rifampin-resistant                | >256     | 0.06        | 0.12         | 0.06       |



**Table 8:**

| Strains   | Rifampin | Compound 12 |
|---|----------|-------------|
| <i>M.tuberculosis</i><br>isoniazid-resistant High<br>Level                                | 0.25     | 0.01        |
| <i>M.tuberculosis</i><br>isoniazid-resistant high<br>level                                | 0.5      | 0.06        |
| <i>M.tuberculosis</i><br>isoniazid-resistant high<br>level                                | 0.12     | 0.03        |
| <i>M.tuberculosis</i><br>isoniazid-resistant high<br>level                                | ≤ 0.06   | 0.01        |
| <i>M.tuberculosis</i><br>isoniazid-Resistant high<br>level and streptomycin-<br>resistant | 0.25     | 0.01        |
| <i>M. tuberculosis</i><br>rifampin-resistant  | 256      | 0.03        |
| <i>M.tuberculosis</i><br>rifampin-resistant   | 16       | 0.03        |
| <i>M.tuberculosis</i><br>rifampin-resistant   | 256      | 0.01        |
| <i>M.tuberculosis</i><br>streptomycin-resistant   | 0.5      | 0.01        |
| <i>M.tuberculosis</i><br>ethambutol-resistant   | 0.25     | 0.01        |
| <i>M.tuberculosis</i><br>pyrazinamide-resistant   | 0.5      | 0.03        |

Table 9 :

| Strains               | Rifampin | Compound 12 | Ofloxacin                 |
|-----------------------|----------|-------------|---------------------------|
| <i>M.tuberculosis</i> | 1        | 0.06        | 8 (Ala83Val<br>Ser84Pro)* |
| <i>M.tuberculosis</i> | 2        | 0.12        | 32 (Asp87Gly)*            |
| <i>M.avium</i>        | 16       | 0.007       | 128 (Ala83Val)*           |

\* The indications between parentheses indicate the mutations in the protein responsible for ofloxacin resistance

5

Table 10 :

| Strains            | Rifampin | Compound 12 | Ofloxacin                        |
|--------------------|----------|-------------|----------------------------------|
| <i>M.smegmatis</i> | 64       | 0.01        | 8 (Asp87Gly)*                    |
| <i>M.smegmatis</i> | 64       | 0.01        | 32 (Ala 83 Val<br>and Asp87Gly)* |
| <i>M.smegmatis</i> | 64       | 0.01        | 32 (Ala83Val and<br>Asp87Gly)*   |
| <i>M.smegmatis</i> | 128      | 0.007       | 2 (Ala83Val)*                    |
| <i>M.smegmatis</i> | ND       | 0.003       | 32 (Asp87Gly)*                   |
| <i>M.fortuitum</i> | 128      | 0.01        | 1                                |
| <i>M.fortuitum</i> | 128      | 0.007       | 1 (Ser84Pro)*                    |
| <i>M.fortuitum</i> | >64      | 0.01        | 1.5 (Asp87Gly)*                  |

\* The indications between parentheses indicate the mutations in the protein responsible for ofloxacin resistance.

10

From these results it can be concluded that the present compounds are highly active against drug resistant Mycobacterium strains. There is no evidence of cross-resistance with antituberculosis drugs : isoniazid, rifampin, streptomycin, ethambutol and pyrazinamide.

In the same manner, there is no evidence of cross-resistance with fluoroquinolones.

5

Compound 12 was also tested against 2 multi-drug resistant *M. tuberculosis* strains, i.e. a strain resistant to isoniazid 10 mg/L and rifampin and a strain resistant to isoniazid 0.2 mg/L and rifampin. The MIC obtained for compound 12 for both strains is 0.03mg/L.

10

*In vivo method for testing combinations against M.tuberculosis infected mice.*

Four weeks old Swiss female mice were infected intravenously with  $5 \times 10^6$  CFU of *M.tuberculosis* H37Rv strain. On D1 and D14 following the infection, ten mice were sacrificed to determine the baseline values of spleen weight and CFU counts in the spleens and the lungs after inoculation and at the beginning of treatment. The remaining mice were allocated to the following treatment groups : an untreated control group for survival monitoring, two positive control groups, one with a regimen for susceptible tuberculosis treated with 2 months of isoniazid 25 mg/kg, rifampin 10 mg/kg, pyrazinamide 150 mg/kg daily, and the other with a regimen for multi drug resistant tuberculosis treated with 2 months of daily amikacin 150 mg/kg, ethionamide 50 mg/kg, moxifloxacin 100 mg/kg and pyrazinamide 150 mg/kg. Three negative control groups were treated for 2 months with one of the following drugs, rifampin 10 mg/kg daily, moxifloxacin 100 mg/kg daily and compound 12 25 mg/kg daily. All the tested regimens either for susceptible tuberculosis or for MDR tuberculosis are summarized in table 11. All the groups contained ten mice and were treated during 8 weeks from D14 to D70 five days a week. The parameters used for assessing the severity of infection and the effectiveness of treatments were : survival rate, spleen weight, gross lung lesions and CFU counts in the spleens and in the lungs.

30 Survival rate : The untreated mice began to die by day 21 after infection and all the mice were dead by day 28 of infection. All the treatments were able to prevent the mortality of mice and few mice died because of accident of gavage.

**Table 11. Experimental design**

|    | Dates of sacrifices                             |           |           | Total mice |            |
|----|---|-----------|-----------|------------|------------|
|    | D-13  | D0        | 1month    | 2 month    |            |
| 5  |   |           |           |            |            |
|    | <u>Controls</u>                                 |           |           |            |            |
|    | Untreated                                       | 10        | 10        | 10         | 30         |
|    | 2 Rifampicin                                    |           |           | 10         | 10         |
| 10 | 2 Moxifloxacin                                  |           |           | 10         | 10         |
|    | 2 compound 12                                   |           |           | 20*        | 10         |
|    | <u>Positive Controls</u>                        |           |           |            |            |
|    | 2 RMP+INH+PZA                                   |           |           | 10         | 10         |
|    | 2 AMIK+ETHIO+MXFX+PZA                           |           |           | 10         | 10         |
| 15 | <u>Tested regimens (Susceptible TB regimen)</u> |           |           |            |            |
|    | 2 RMP+INH                                       |           |           | 10         | 10         |
|    | 2 RMP+ compound 12                              |           |           | 10         | 10         |
|    | 2 INH+ compound 12                              |           |           | 10         | 10         |
| 20 | 2 RMP+INH+ compound 12                          |           |           | 10         | 10         |
|    | 2 INH+PZA+ compound 12                          |           |           | 10         | 10         |
|    | 2 RMP+PZA+ compound 12                          |           |           | 10         | 10         |
|    | 2 RMP+INH+PZA+ compound 12                      |           |           | 10         | 10         |
| 25 | <u>Tested regimens (Resistant TB regimen)</u>   |           |           |            |            |
|    | 2 AMIK+ETHIO+PZA                                |           |           | 10         | 10         |
|    | 2 AMIK+ETHIO +PZA+ compound 12                  |           |           | 10         | 10         |
|    | 2 AMIK+MXFX+PZA                                 |           |           | 10         | 10         |
|    | 2 AMIK +MXFX+PZA+ compound 12                   |           |           | 10         | 10         |
| 30 | 2 AMIK+ETHIO+MXFX+PZA+ compound 12              |           |           | 10         | 10         |
|    | <b>Total</b>                                    | <b>10</b> | <b>10</b> | <b>190</b> | <b>170</b> |
|    |   |           |           |            | <b>380</b> |

Dosages :

35 Rifampicin (RMP)= 10 mg/kg, Isoniazid (INH) = 25 mg/kg,  
 Pyrazinamide (PZA) = 150 mg/kg, Amikacin (AMIK) = 150 mg/kg,  
 Ethionamide (ETHIO) = 50 mg/kg, Moxifloxacin (MXFX) = 100 mg/kg,  
 compound 12 = 25 mg/kg \*: for serum dosage

The following Table shows the results of the 2 month experiment.

**Table 12. Mean spleen weight and number of CFU per spleen and lung of *M.tuberculosis*-infected mice and treated with various treatments for 2 months.**

| Group <sup>a</sup> | No. mice | Spleen weight<br>(mg) | Mean CFU (log <sub>10</sub> ) per |           |
|--------------------|----------|-----------------------|-----------------------------------|-----------|
|                    |          |                       | Spleen                            | Lung      |
| Pretreatment       | 10       | 631±121               | 6.40±0.30                         | 6.94±0.51 |
| R 10 mg/kg         | 9        | 391±70                | 2.75±0.34                         | 1.89±0.50 |
| M 100 mg/kg        | 10       | 400±99                | 3.53±0.34                         | 2.89±0.57 |
| J 25 mg/kg         | 8        | 248±47                | 1.24±0.50                         | 0.22±0.32 |
| RHZ                | 10       | 326±78                | 1.91±0.52                         | 0.97±0.61 |
| AEtZM              | 10       | 331±86                | 1.60±0.38                         | 0.10±0.09 |
| RH                 | 10       | 400±100               | 2.49±0.42                         | 1.09±0.36 |
| RJ                 | 9        | 304±61                | 2.06±0.61                         | 1.63±0.77 |
| HJ                 | 8        | 293±56                | 1.27±0.31                         | 0.36±0.40 |
| RHJ                | 9        | 297±74                | 0.64±0.63                         | 0.19±0.36 |
| HZJ                | 7        | 257±40                | 0.07±0                            | 0.07±0    |
| RZJ                | 9        | 281±56                | 0.07±0                            | 0.07±0    |
| RHZJ               | 10       | 265±47                | 0.12±0.15                         | 0.07±0    |
| AEtZ               | 10       | 344±46                | 2.75±0.25                         | 1.20±0.26 |
| AEtZJ              | 9        | 331±86                | 0.10±0.10                         | 0.07±0    |
| AMZ                | 10       | 287±31                | 1.89±0.51                         | 0.75±0.55 |
| AMZJ               | 8        | 296±63                | 0.07±0                            | 0.07±0    |
| AEtMZJ             | 8        | 285±53                | 0.07±0                            | 0.07±0    |

<sup>a</sup>: Except the pretreatment values were obtained from mice sacrificed on day 14 after inoculation, the remaining results were obtained from mice sacrificed on day 42 after inoculation. Treatment began on day 14, and was administered five time weekly for four weeks. Isoniazid (H), rifampin (R), moxifloxacin (M), pyrazinamide (Z), compound 12 (J), amikacin (A), ethionamide (Et).

*In vitro testing of susceptibility to compound 12 of fully susceptible and multi drug resistant M.tuberculosis strains in solid medium assay.*

The susceptibility to compound 12 of 73 *M. tuberculosis* strains was tested in a solid medium assay (agar plates). The panel of strains included strains (41) fully susceptible to standard anti-tuberculosis drugs as well as multi drug resistant (MDR) strains (32).  
5 i.e. strains resistant to at least rifampin and isoniazid.

Agar plates were welded with solutions containing compound 12 in a concentration ranging from 0.002 mg/L to 0.256 mg/L (8 different concentrations tested). *M. tuberculosis* isolates were then plated on each agar plate and the plates were sealed and  
10 incubated at 36°C for 3 weeks.

Isolate growth was analyzed 3 weeks following plate inoculation and an isolate's MIC was defined as the first concentration at which no growth was observed.

For all the tested strains, no growth was seen at concentrations higher than 0.064 mg/L, the majority of strains showed an MIC of 0.032 mg/L.

15 No difference in MIC was seen between fully susceptible and MDR *M. tuberculosis* strains.

*In vivo testing of susceptibility of M tuberculosis to compound 12 in combination with other antimycobacterial agents.*

20 Swiss mice were inoculated intravenously with  $10^6$  log colony forming units (CFU) of strain H37Rv. Compound 12 (J) was administrated by gavage 5 days/week (once a day treatment group) or once a week from day 14 to day 70 after inoculation, in monotherapy or in association with isoniazid (H), rifampin (R), pyrazinamide (Z), or moxifloxacin (M). The lung CFU was determined after 1 or 2 months of treatment.

25 The results are gathered in Tables 13 and 14.

**Table 13 : Results for once-a-day group after 1 and 2 months**

|     | CFU    |          | % positive mice | Decrease 1mo | Decrease 2mo |
|-----|--------|----------|-----------------|--------------|--------------|
|     | 1month | 2 months | 2nd month       | vs D0        | vs D0        |
| D0  | 7.23   |          |                 |              |              |
| R   | 6.01   | 4.07     | 10/10           | -1.22        | -3.16        |
| H   | 4.89   | 4.72     | 10/10           | -2.34        | -2.51        |
| Z   | 6.17   | 6.43     | 7/7             | -1.06        | -0.8         |
| M   | 5.51   | 4.3      | 10/10           | -1.72        | -2.93        |
| J   | 4.14   | 2.28     | 8/10            | -3.09        | -4.95        |
| RH  | 5.07   | 3.12     | 10/10           | -2.16        | -4.11        |
| RZ  | 5.38   | 1.91     | 8/10            | -1.85        | -5.32        |
| HZ  | 5.47   | 3.93     | 10/10           | -1.76        | -3.3         |
| RM  | 5.52   | 3.13     | 8/10            | -1.71        | -4.1         |
| JR  | 4.67   | 1.89     | 7/10            | -2.56        | -5.34        |
| JH  | 3.75   | 1.91     | 8/10            | -3.48        | -5.32        |
| JZ  | 1.61   | 0        | 0/10            | -5.62        | -7.23        |
| JM  | 4.61   | 2.13     | 7/9             | -2.62        | -5.1         |
| RHZ | 3.87   | 2.22     | 9/9             | -3.36        | -5.01        |
| RMZ | 4.59   | 1.36     | 8/10            | -2.64        | -5.87        |
| JHZ | 1.71   | 0.18     | 2/9             | -5.52        | -7.05        |
| JHR | 4.37   | 1.15     | 8/10            | -2.86        | -6.08        |
| JMR | 4.42   | 1.37     | 8/9             | -2.81        | -5.86        |
| JRZ | 2.31   | 0.07     | 3/10            | -4.92        | -7.16        |
| JMZ | 1.44   | 0.03     | 2/9             | -5.79        | -7.2         |

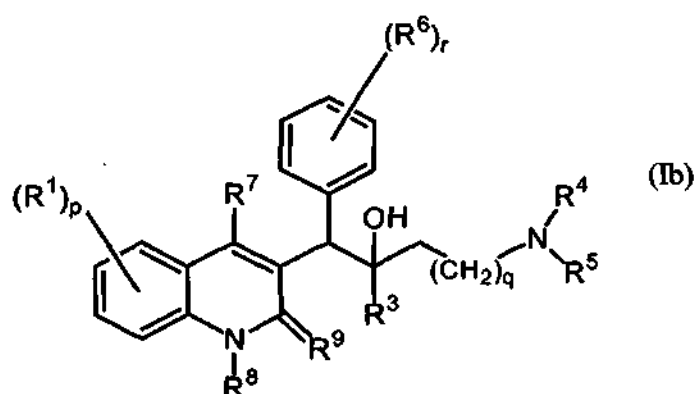
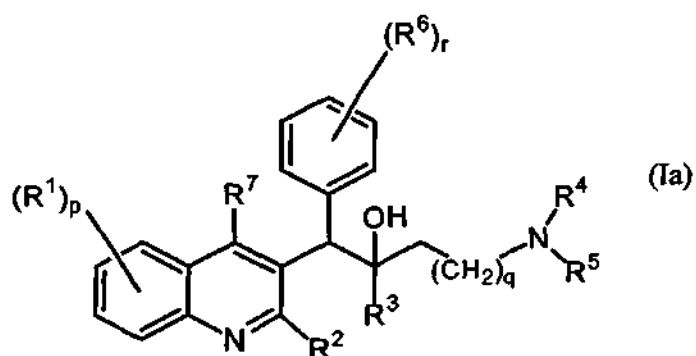
**Table 14 : Results for once-a-week group after 2 months**

|     | lung CFU*   | % positive mice |
|-----|-------------|-----------------|
| D0  | 7.23        |                 |
| J   | 1,99+/-0,75 | 9/9             |
| M   | 6,44+/-0,5  | 7/7             |
| P   | 3,26+/-0,58 | 10/10           |
| JP  | 1,63+/-0,92 | 8/9             |
| JPM | 1,85+/-0,7  | 10/10           |
| JPH | 1,48+/-0,79 | 10/10           |
| JPZ | 0,23+/-0,72 | 1/10            |



## CLAIMS

1. Use of a substituted quinoline derivative for the preparation of a medicament for the treatment of an infection with a drug resistant Mycobacterium strain wherein the substituted quinoline derivative is a compound according to Formula (Ia) or Formula (Ib)

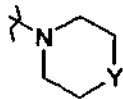


10

a pharmaceutically acceptable acid or base addition salt thereof, a stereochemically isomeric form thereof, a tautomeric form thereof or a *N*-oxide form thereof, wherein :

- 15  $R^1$  is hydrogen, halo, haloalkyl, cyano, hydroxy, Ar, Het, alkyl, alkyloxy, alkylthio, alkyloxyalkyl, alkylthioalkyl, Ar-alkyl or di(Ar)alkyl ;
- $p$  is an integer equal to 1, 2, 3 or 4 ;

R<sup>2</sup> is hydrogen, hydroxy, mercapto, alkyloxy, alkyloxyalkyloxy, alkylthio, mono or di(alkyl)amino or a radical of formula



wherein Y is CH<sub>2</sub>, O, S, NH or N-alkyl ;

R<sup>3</sup> is alkyl, Ar, Ar-alkyl, Het or Het-alkyl;

5 q is an integer equal to zero, 1, 2, 3 or 4 ;

R<sup>4</sup> and R<sup>5</sup> each independently are hydrogen, alkyl or benzyl; or

R<sup>4</sup> and R<sup>5</sup> together and including the N to which they are attached may form a radical selected from the group of pyrrolidinyl, 2*H*-pyrrolyl, 2-pyrrolinyl, 3-pyrrolinyl, pyrrolyl, imidazolidinyl, pyrazolidinyl, 2-imidazolinyll, 2-pyrazolinyl, imidazolyl, pyrazolyl, triazolyl, piperidinyl, pyridinyl, piperazinyl, imidazolidinyl, pyridazinyl, pyrimidinyl, pyrazinyl, triazinyl, morpholinyl and thiomorpholinyl, optionally substituted with alkyl, halo, haloalkyl, hydroxy, alkyloxy, amino, mono- or dialkylamino, alkylthio, alkyloxyalkyl, alkylthioalkyl and pyrimidinyl ;

R<sup>6</sup> is hydrogen, halo, haloalkyl, hydroxy, Ar, alkyl, alkyloxy, alkylthio, alkyloxyalkyl, alkylthioalkyl, Ar-alkyl or di(Ar)alkyl ; or

two vicinal R<sup>6</sup> radicals may be taken together to form a bivalent radical of formula -CH=CH-CH=CH- ;

20 r is an integer equal to 1, 2, 3, 4 or 5 ; and

R<sup>7</sup> is hydrogen, alkyl, Ar or Het ;

R<sup>8</sup> is hydrogen or alkyl ;

R<sup>9</sup> is oxo ; or

R<sup>8</sup> and R<sup>9</sup> together form the radical =N-CH=CH-;

25 alkyl is a straight or branched saturated hydrocarbon radical having from 1 to 6 carbon atoms ; or is a cyclic saturated hydrocarbon radical having from 3 to 6 carbon atoms ; or is a cyclic saturated hydrocarbon radical having from 3 to 6 carbon atoms attached to a straight or branched saturated hydrocarbon radical having from 1 to 6 carbon atoms ; wherein each carbon atom can be optionally substituted with halo, hydroxy, alkyloxy or oxo ;

30 Ar is a homocycle selected from the group of phenyl, naphthyl, acenaphthyl, tetrahydronaphthyl, each optionally substituted with 1, 2 or 3 substituents, each substituent independently selected from the group of hydroxy, halo, cyano, nitro, amino, mono- or dialkylamino, alkyl,

35

- haloalkyl, alkyloxy, haloalkyloxy, carboxyl, alkyloxycarbonyl, aminocarbonyl, morpholinyl and mono- or dialkylaminocarbonyl ;
- Het is a monocyclic heterocycle selected from the group of *N*-phenoxy piperidinyl, pyrrolyl, pyrazolyl, imidazolyl, furanyl, thienyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, pyridinyl, pyrimidinyl, pyrazinyl and pyridazinyl; or a bicyclic heterocycle selected from the group of quinolinyl, quinoxalinyl, indolyl, benzimidazolyl, benzoxazolyl, benzisoxazolyl, benzothiazolyl, benzisothiazolyl, benzofuranyl, benzothieryl, 2,3-dihydrobenzo[1,4]dioxinyl or benzo[1,3]dioxolyl ; each monocyclic and bicyclic heterocycle may optionally be substituted on a carbon atom with 1, 2 or 3 substituents selected from the group of halo, hydroxy, alkyl or alkyloxy ;
- halo is a substituent selected from the group of fluoro, chloro, bromo and iodo and
- haloalkyl is a straight or branched saturated hydrocarbon radical having from 1 to 6 carbon atoms or a cyclic saturated hydrocarbon radical having from 3 to 6 carbon atoms, wherein one or more carbon atoms are substituted with one or more halo-atoms.
2. Use according to claim 1 wherein R<sup>6</sup> in Formula (Ia) or (Ib) is hydrogen, halo, haloalkyl, hydroxy, Ar, alkyl, alkyloxy, alkylthio, alkyloxyalkyl, alkylthioalkyl, Ar-alkyl or di(Ar)alkyl.
  3. Use according to claim 1 or 2 wherein in Formula (Ia) or (Ib) R<sup>1</sup> is halo.
  4. Use according to any one of the preceding claims wherein in Formula (Ia) or (Ib) p is equal to 1.
  5. Use according to any one of the preceding claims wherein in Formula (Ia) or (Ib) R<sup>2</sup> is alkyloxy.
  6. Use according to any one of the preceding claims wherein in Formula (Ia) or (Ib) R<sup>3</sup> is naphthyl or phenyl, each optionally substituted with halo.
  7. Use according to claim 6 wherein R<sup>3</sup> is naphthyl.

8. Use according to any one of the preceding claims wherein in Formula (Ia) or (Ib)  $q$  is equal to 1.
9. Use according to any one of the preceding claims wherein in Formula (Ia) or (Ib)  $R^4$  and  $R^5$  each independently are hydrogen or alkyl.
10. Use according to claim 9 wherein  $R^4$  and  $R^5$  each independently are  $C_{1-4}$ alkyl.
11. Use according to any one of the preceding claims wherein in Formula (Ia) or (Ib)  $R^6$  is hydrogen.
12. Use according to any one of the preceding claims wherein in Formula (Ia) or (Ib)  $R^7$  is hydrogen.
13. Use according to claim 1, characterized in that the compound is selected from the group consisting of :
- 1-(6-bromo-2-methoxy-quinolin-3-yl)-2-(3,5-difluoro-phenyl)-4-dimethylamino-1-phenyl-butan-2-ol ;
  - 1-(6-bromo-2-methoxy-quinolin-3-yl)-4-dimethylamino-2-naphthalen-1-yl-1-phenyl-butan-2-ol ;
  - 1-(6-bromo-2-methoxy-quinolin-3-yl)-2-(2,5-difluoro-phenyl)-4-dimethylamino-1-phenyl-butan-2-ol ;
  - 1-(6-bromo-2-methoxy-quinolin-3-yl)-2-(2,3-difluoro-phenyl)-4-dimethylamino-1-phenyl-butan-2-ol ;
  - 1-(6-bromo-2-methoxy-quinolin-3-yl)-4-dimethylamino-2-(2-fluoro-phenyl)-1-phenyl-butan-2-ol ;
  - 1-(6-bromo-2-methoxy-quinolin-3-yl)-4-dimethylamino-2-naphthalen-1-yl-1-p-tolyl-butan-2-ol ;
  - 1-(6-bromo-2-methoxy-quinolin-3-yl)-4-methylamino-2-naphthalen-1-yl-1-phenyl-butan-2-ol ;
  - 1-(6-bromo-2-methoxy-quinolin-3-yl)-4-dimethylamino-2-(3-fluoro-phenyl)-1-phenyl-butan-2-ol; and
  - 1-(6-bromo-2-methoxy-quinolin-3-yl)-4-dimethylamino-2-phenyl-1-phenyl-butan-2-ol;
- a pharmaceutically acceptable acid or base addition salt thereof, a stereochemically isomeric form thereof, a tautomeric form thereof or a *N*-oxide form thereof.

14. Use according to claim 13 wherein the compound is selected from the group consisting of
- 1-(6-bromo-2-methoxy-quinolin-3-yl)-4-dimethylamino-2-(3-fluoro-phenyl)-1-phenyl-butan-2-ol;
  - 5 ○ 1-(6-bromo-2-methoxy-quinolin-3-yl)-4-dimethylamino-2-phenyl-1-phenyl-butan-2-ol;
  - 1-(6-bromo-2-methoxy-quinolin-3-yl)-4-dimethylamino-2-naphthalen-1-yl-1-phenyl-butan-2-ol ;
- a pharmaceutically acceptable acid or base addition salt thereof, a stereochemically isomeric form thereof, a tautomeric form thereof or a *N*-oxide form thereof.
- 10
15. Use according to claim 1 wherein the compound is 6-bromo- $\alpha$ -[2-(dimethylamino)ethyl]-2-methoxy- $\alpha$ -1-naphthalenyl- $\beta$ -phenyl-3-quinolineethanol, a pharmaceutically acceptable acid or base addition salt thereof, a stereochemically isomeric forms thereof, a tautomeric form thereof or a *N*-oxide form thereof.
- 15
16. Use according to claim 15 wherein the compound is 6-bromo- $\alpha$ -[2-(dimethylamino)ethyl]-2-methoxy- $\alpha$ -1-naphthalenyl- $\beta$ -phenyl-3-quinolineethanol, or a pharmaceutically acceptable acid addition salt thereof.
- 20
17. Use according to claim 15 wherein the compound is 6-bromo- $\alpha$ -[2-(dimethylamino)ethyl]-2-methoxy- $\alpha$ -1-naphthalenyl- $\beta$ -phenyl-3-quinolineethanol, or a stereochemically isomeric form thereof.
- 25
18. Use according to claim 15 wherein the compound is 6-bromo- $\alpha$ -[2-(dimethylamino)ethyl]-2-methoxy- $\alpha$ -1-naphthalenyl- $\beta$ -phenyl-3-quinolineethanol, or a *N*-oxide form thereof.
- 30
19. Use according to claim 15 wherein the compound is ( $\alpha$ S,  $\beta$ R)-6-bromo- $\alpha$ -[2-(dimethylamino)ethyl]-2-methoxy- $\alpha$ -1-naphthalenyl- $\beta$ -phenyl-3-quinolineethanol, or a pharmaceutically acceptable acid addition salt thereof.
- 35
20. Use according to claim 19 wherein the compound is ( $\alpha$ S,  $\beta$ R)-6-bromo- $\alpha$ -[2-(dimethylamino)ethyl]-2-methoxy- $\alpha$ -1-naphthalenyl- $\beta$ -phenyl-3-quinolineethanol.

21. Use according to any one of the preceding claim wherein the drug resistant Mycobacterium strain is multi drug resistant.
22. Use according to any one of the preceding claims wherein the Mycobacterium strain is a Mycobacterium tuberculosis strain.
23. A combination of (a) a compound of formula (Ia) or (Ib) as defined in any one of claims 1 to 20 and (b) one or more other antimycobacterial agents.
24. A combination of (a) a compound of formula (Ia) or (Ib) as defined in any one of claims 1 to 20 and (b) one or more other antimycobacterial agents for use as a medicine.
25. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and, as active ingredient, a therapeutically effective amount of (a) a compound of formula (Ia) or (Ib) as defined in any one of claims 1 to 20 and (b) one or more other antimycobacterial agents.
26. A product containing (a) a compound of formula (Ia) or (Ib) as defined in any one of claims 1 to 20, and (b) one or more other antimycobacterial agents, as a combined preparation for simultaneous, separate or sequential use in the treatment of mycobacterial diseases.
27. A combination, a pharmaceutical composition or a product as claimed in any one of claims 23 to 26 wherein the one or more other antimycobacterial agents comprise pyrazinamide.
28. A combination, a pharmaceutical composition or a product as claimed in any one of claims 23 to 27 wherein the compound of formula (Ia) or (Ib) is ( $\alpha$ S,  $\beta$ R)-6-bromo- $\alpha$ -[2-(dimethylamino)ethyl]-2-methoxy- $\alpha$ -1-naphthalenyl- $\beta$ -phenyl-3-quinolineethanol or a pharmaceutically acceptable acid addition salt thereof.
29. A combination, a pharmaceutical composition or a product as claimed in any one of claims 23 to 28 wherein the compound of formula (Ia) or (Ib) is ( $\alpha$ S,  $\beta$ R)-6-bromo- $\alpha$ -[2-(dimethylamino)ethyl]-2-methoxy- $\alpha$ -1-naphthalenyl- $\beta$ -phenyl-3-quinolineethanol.

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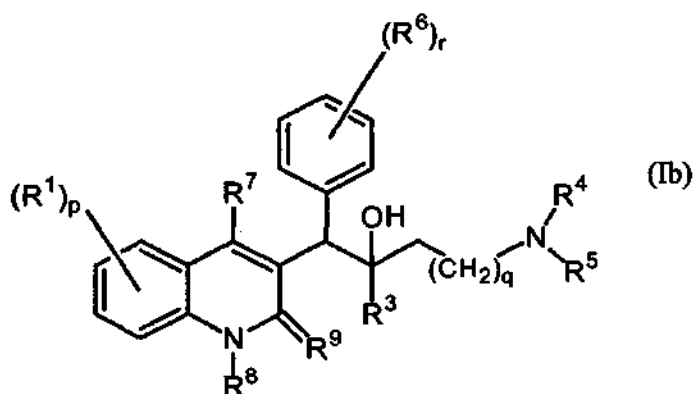
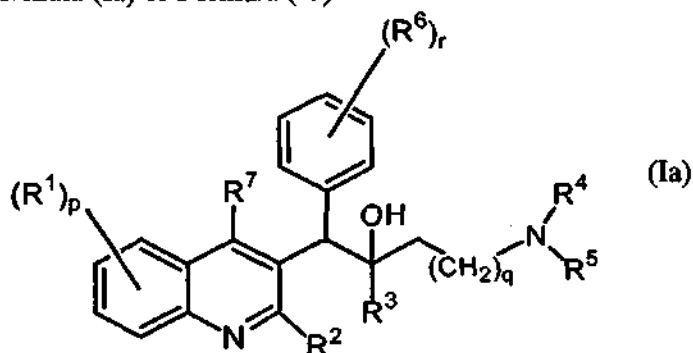
30. Use of a combination, a pharmaceutical composition or a product as claimed in any one of claims 23 to 29 for the treatment of an infection with a drug resistant Mycobacterium strain.
- 5 31. Use according to claim 30 wherein the drug resistant Mycobacterium strain is a drug resistant *M. tuberculosis* strain.

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## ABSTRACT

USE OF SUBSTITUTED QUINOLINE DERIVATIVES FOR THE TREATMENT  
OF DRUG RESISTANT MYCOBACTERIAL DISEASES

- 5 The present invention relates to the use of a substituted quinoline derivative for the preparation of a medicament for the treatment of an infection with a drug resistant Mycobacterium strain wherein the substituted quinoline derivative is a compound according to Formula (Ia) or Formula (Ib)



- 10 the pharmaceutically acceptable acid or base addition salts thereof, the stereochemically isomeric forms thereof, the tautomeric forms thereof and the *N*-oxide forms thereof. Also claimed is a composition comprising a pharmaceutically acceptable carrier and, as active ingredient, a therapeutically effective amount of the above compounds and one or more other antimycobacterial agents.



INTERNATIONAL SEARCH REPORT

International Application No  
PCT/EP2005/052371

|   |  |  |
|---|--|--|
| <b>A. CLASSIFICATION OF SUBJECT MATTER</b><br>IPC 7 A61K31/47 A61P31/06   |  |  |
| According to International Patent Classification (IPC) or to both national classification and IPC   |  |  |
| <b>B. FIELDS SEARCHED</b>   |  |  |
| Minimum documentation searched (classification system followed by classification symbols)<br>IPC 7 A61K A61P  |  |  |
| Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched   |  |  |
| Electronic data base consulted during the international search (name of data base and, where practical, search terms used)<br>EPO-Internal, WPI Data, PAJ, BIOSIS, EMBASE, CHEM ABS Data  |  |  |
| <b>C. DOCUMENTS CONSIDERED TO BE RELEVANT</b>   |  |  |
| Category *  | Citation of document, with indication, where appropriate, of the relevant passages   | Relevant to claim No.  |
| A   | WO 2004/011436 A (JANSSEN PHARMACEUTICA NV<br>; VAN GESTEL JOZEF FRANS ELISABE (BE);<br>POIGNE) 5 February 2004 (2004-02-05)<br>cited in the application<br>the whole document |  |
| <input type="checkbox"/> Further documents are listed in the continuation of box C.   |  |  |
| <input checked="" type="checkbox"/> Patent family members are listed in annex.  |  |  |
| * Special categories of cited documents :   |  |  |
| *A* document defining the general state of the art which is not considered to be of particular relevance<br>*E* earlier document but published on or after the international filing date<br>*L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)<br>*O* document referring to an oral disclosure, use, exhibition or other means<br>*P* document published prior to the international filing date but later than the priority date claimed   |  |  |
| *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention<br>*X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone<br>*Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.<br>*&* document member of the same patent family |  |  |
| Date of the actual completion of the international search<br><br>30 August 2005   |  | Date of mailing of the international search report<br><br>06/09/2005 |
| Name and mailing address of the ISA<br>European Patent Office, P.B. 5818 Patentlaan 2<br>NL - 2280 HV Rijswijk<br>Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,<br>Fax: (+31-70) 340-3016  |  | Authorized officer<br><br>Friederich, M                              |

# INTERNATIONAL SEARCH REPORT

International application No.  
PCT/EP2005/052371

## Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1.  Claims Nos.: —  
because they relate to subject matter not required to be searched by this Authority, namely:  
Although claims 30 and 31 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2.  Claims Nos.:  
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3.  Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1.  As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2.  As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3.  As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4.  No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- The additional search fees were accompanied by the applicant's protest.  
 No protest accompanied the payment of additional search fees.

## INTERNATIONAL SEARCH REPORT

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|---|---------------------|----------------------------|---------------------|
| WO 2004011436 A                           | 05-02-2004          | AU 2003262529 A1           | 16-02-2004          |
|   |                     | CA 2493225 A1              | 05-02-2004          |
|   |                     | WO 2004011436 A1           | 05-02-2004          |
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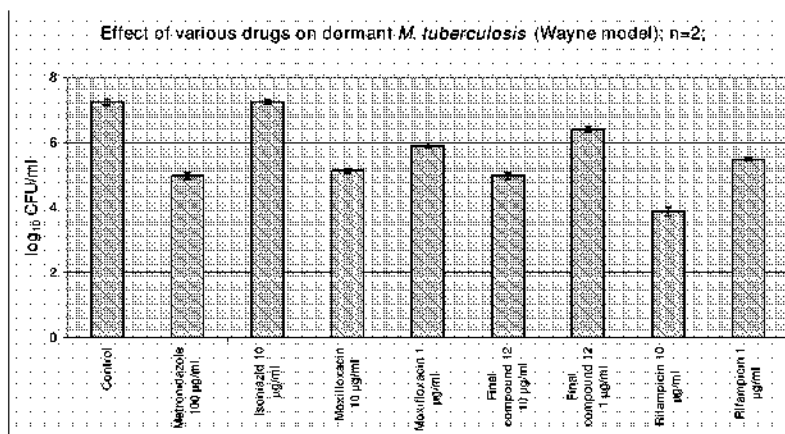
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- (71) Applicant (for all designated States except US):  
JANSSEN PHARMACEUTICA N.V. [BE/BE]; Turnhoutseweg 30, B-2340 Beerse (BE).
- (72) Inventors; and
- (75) Inventors/Applicants (for US only): ANDRIES, Koenraad, Jozef, Lodewijk, Marcel [BE/BE]; c/o Janssen Pharmaceutica N.V., Turnhoutseweg 30, B-2340 Beerse (BE). KOUL, Anil [IN/BE]; c/o Janssen Pharmaceutica N.V., Turnhoutseweg 30, B-2340 Beerse (BE).
- (74) Common Representative: JANSSEN PHARMACEUTICA N.V.; Turnhoutseweg 30, B-2340 Beerse (BE).
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- Declarations under Rule 4.17:**
- as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))
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[Continued on next page]

(54) Title: QUINOLINE DERIVATIVES FOR THE TREATMENT OF LATENT TUBERCULOSIS



(57) Abstract: Use of a compound of formula (Ia) or (Ib) for the manufacture of a medicament for the 5 treatment of latent tuberculosis, wherein the compound of formula (Ia) or (Ib) is a pharmaceutically acceptable salt, a quaternary amine, a N-oxide, a tautomeric form or a stereochemically isomeric form thereof wherein R<sup>1</sup> is hydrogen, halo, haloalkyl, cyano, hydroxy, Ar, Het, alkyl, alkyloxy, alkylthio, alkyloxyalkyl, alkylthioalkyl, Ar-alkyl or di(Ar)alkyl; p is 1, 2, 3 or 4; R<sup>2</sup> is hydrogen, hydroxy, mercapto, alkyloxy, alkyloxyalkoxy, alkylthio, mono or di(alkyl)amino or a radical of formula (II); R<sup>3</sup> is alkyl, Ar, Ar-alkyl, Het or Het-alkyl; q is zero, 1, 2, 3 or 4; R<sup>4</sup> and R<sup>5</sup> each independently are hydrogen, alkyl or benzyl; or R<sup>4</sup> and R<sup>5</sup> may be taken together including the N to which they are attached; R<sup>6</sup> is hydrogen, halo, haloalkyl, hydroxy, Ar, alkyl, alkyloxy, alkylthio, alkyloxyalkyl, alkylthioalkyl, Ar-alkyl or di(Ar)alkyl; or two vicinal R<sup>6</sup> radicals may be taken together to form a bivalent radical -CH=CH-CH=CH-; r is 1, 2, 3, 4 or 5; R<sup>7</sup> is hydrogen, alkyl, Ar or Het; R<sup>8</sup> is hydrogen or alkyl; R<sup>9</sup> is oxo; or R<sup>8</sup> and R<sup>9</sup> together form the radical =N-CH=CH-

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## QUINOLINE DERIVATIVES FOR THE TREATMENT OF LATENT TUBERCULOSIS

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The present invention relates to the use of a compound of formula (Ia) or (Ib) for  
5 treating latent tuberculosis.

### BACKGROUND OF THE INVENTION

*Mycobacterium tuberculosis* results in more than 2 million deaths per year and is the  
10 leading cause of mortality in people infected with HIV<sup>1</sup>. In spite of decades of tuberculosis (TB) control programs, about 2 billion people are infected by *M. tuberculosis*, though asymptotically. About 10% of these individuals are at risk of developing active TB during their lifespan<sup>2</sup>. The global epidemic of TB is fuelled by infection of HIV patients with TB and rise of multi-drug resistant TB strains  
15 (MDR-TB). The reactivation of latent TB is a high risk factor for disease development and accounts for 32% deaths in HIV infected individuals<sup>1</sup>. To control TB epidemic, the need is to discover new drugs that can kill dormant or latent TB bacilli. The dormant TB can get reactivated to cause disease by several factors like suppression of host immunity by use of immunosuppressive agents like antibodies against tumor necrosis  
20 factor  $\alpha$  or interferon- $\gamma$ . In case of HIV positive patients the only prophylactic treatment available for latent TB is two- three months regimens of rifampicin, pyrazinamide<sup>3,4</sup>. The efficacy of the treatment regime is still not clear and furthermore the length of the treatments is an important constrain in resource-limited environments. Hence there is a drastic need to identify new drugs, which can act as  
25 chemoprophylactic agents for individuals harboring latent TB bacilli. The tubercle bacilli enter healthy individuals by inhalation; they are phagocytosed by the alveolar macrophages of the lungs. This leads to potent immune response and formation of granulomas, which consist of macrophages infected with *M. tuberculosis* surrounded by T cells. After a period of 6-8 weeks the host immune response cause  
30 death of infected cells by necrosis and accumulation of caseous material with certain extracellular bacilli, surrounded by macrophages, epitheloid cells and layers of lymphoid tissue at the periphery<sup>5</sup>. In case of healthy individuals, most of the mycobacteria are killed in these environments but a small proportion of bacilli still survive and are thought to exist in a non-replicating, hypometabolic state and are  
35 tolerant to killing by anti-TB drugs like isoniazid<sup>6</sup>. These bacilli can remain in the altered physiological environments even for individual's lifetime without showing any clinical symptoms of disease. However, in 10% of the cases these latent bacilli may

reactivate to cause disease. One of the hypothesis about development of these persistent bacteria is patho-physiological environment in human lesions namely, reduced oxygen tension, nutrient limitation, and acidic pH<sup>7</sup>. These factors have been postulated to render these bacteria phenotypically tolerant to major anti-mycobacterial drugs<sup>7</sup>.

WO 2004/011436 describes substituted quinoline derivatives useful for the treatment of mycobacterial diseases. Said document discloses the antimycobacterial property of the substituted quinoline derivatives against sensitive, susceptible *Mycobacterium* strains but is silent on their activity against latent, dormant, persistent mycobacteria.

We have now found that the compounds of WO 2004/011436, in particular the compounds of formula (Ia) and (Ib) as defined hereinbelow, have sterilizing properties; are effective in killing dormant, latent, persistent mycobacteria, in particular *Mycobacterium tuberculosis*, and can consequently be used to treat latent TB. They will therefore greatly enhance the arsenal to fight TB.

#### DESCRIPTION OF THE FIGURES

Figure 1 : The effect of various drugs on dormant *M. bovis* assayed by Luciferase counts (RLU : relative luminescence units) (the bacteria were suspended in drug free medium for 5 days after 7 days of anaerobiosis).

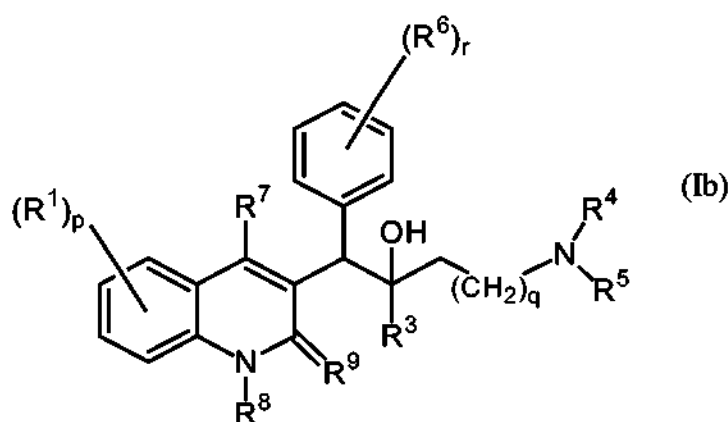
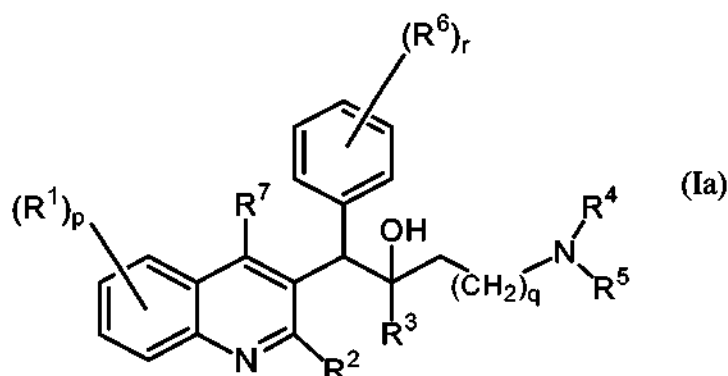
Figure 2A) : The effect of various drugs on dormant *M. bovis* (CFU : colony forming units) (CFU determined 2 days after anaerobiosis, are reported).

Figure 2B) : The effect of various drugs on dormant *M. bovis* (CFU : colony forming units) (CFU determined 5 days after anaerobiosis, are reported).

Figure 3 : The effect of various drugs on dormant *M. tuberculosis* (Wayne model)

#### INVENTION

Thus, the present invention relates to the use of a compound of formula (Ia) or (Ib) for the manufacture of a medicament for the treatment of latent tuberculosis, wherein the compound of formula (Ia) or (Ib) is



a pharmaceutically acceptable acid or base addition salt thereof, a quaternary amine thereof, a *N*-oxide thereof, a tautomeric form thereof or a stereochemically isomeric form thereof wherein

5  $R^1$  is hydrogen, halo, haloalkyl, cyano, hydroxy, Ar, Het, alkyl, alkyloxy, alkylthio, alkyloxyalkyl, alkylthioalkyl, Ar-alkyl or di(Ar)alkyl ;

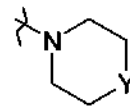
$p$  is an integer equal to 1, 2, 3 or 4 ;

$R^2$  is hydrogen, hydroxy, mercapto, alkyloxy, alkyloxyalkyloxy, alkylthio,

10  $R^3$  is alkyl, Ar, Ar-alkyl, Het or Het-alkyl ;  
 $q$  is an integer equal to zero, 1, 2, 3 or 4 ;

$R^4$  and  $R^5$  each independently are hydrogen, alkyl or benzyl; or

15  $R^4$  and  $R^5$  together and including the N to which they are attached may form a radical selected from the group of pyrrolidinyl, 2-pyrrolinyl, 3-pyrrolinyl, pyrrolyl, imidazolidinyl, pyrazolidinyl, 2-imidazoliny, 2-pyrazolinyl, imidazolyl, pyrazolyl, triazolyl, piperidinyl, pyridinyl, piperazinyl,



wherein Y is



- pyridazinyl, pyrimidinyl, pyrazinyl, triazinyl, morpholinyl and thiomorpholinyl, each of said ring systems optionally substituted with alkyl, halo, haloalkyl, hydroxy, alkyloxy, amino, mono- or dialkylamino, alkylthio, alkyloxyalkyl, alkylthioalkyl and pyrimidinyl ;
- 5  $R^6$  is hydrogen, halo, haloalkyl, hydroxy, Ar, alkyl, alkyloxy, alkylthio, alkyloxyalkyl, alkylthioalkyl, Ar-alkyl or di(Ar)alkyl ; or two vicinal  $R^6$  radicals may be taken together to form a bivalent radical of formula  $-CH=CH-CH=CH-$  ;
- $r$  is an integer equal to 1, 2, 3, 4 or 5 ;
- 10  $R^7$  is hydrogen, alkyl, Ar or Het ;
- $R^8$  is hydrogen or alkyl ;
- $R^9$  is oxo ; or
- $R^8$  and  $R^9$  together form the radical  $=N-CH=CH-$ ;
- alkyl is a straight or branched saturated hydrocarbon radical having from 1 to 6
- 15 carbon atoms ; or is a cyclic saturated hydrocarbon radical having from 3 to 6 carbon atoms ; or is a cyclic saturated hydrocarbon radical having from 3 to 6 carbon atoms attached to a straight or branched saturated hydrocarbon radical having from 1 to 6 carbon atoms ; wherein each carbon atom can be optionally substituted with halo, hydroxy, alkyloxy or oxo ;
- 20 Ar is a homocycle selected from the group of phenyl, naphthyl, acenaphthyl, tetrahydronaphthyl, each homocycle optionally substituted with 1, 2 or 3 substituents, each substituent independently selected from the group of hydroxy, halo, cyano, nitro, amino, mono- or dialkylamino, alkyl, haloalkyl, alkyloxy, haloalkyloxy, carboxyl, alkyloxycarbonyl, aminocarbonyl, morpholinyl and
- 25 mono- or dialkylaminocarbonyl ;
- Het is a monocyclic heterocycle selected from the group of *N*-phenoxy piperidinyl, piperidinyl, pyrrolyl, pyrazolyl, imidazolyl, furanyl, thienyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, pyridinyl, pyrimidinyl, pyrazinyl and pyridazinyl; or a bicyclic heterocycle selected from the group of quinolinyl,
- 30 quinoxalinyl, indolyl, benzimidazolyl, benzoxazolyl, benzisoxazolyl, benzothiazolyl, benzisothiazolyl, benzofuranyl, benzothienyl, 2,3-dihydrobenzo[1,4]dioxinyl or benzo[1,3]dioxolyl ; each monocyclic and bicyclic heterocycle may optionally be substituted with 1, 2 or 3 substituents selected from the group of halo, hydroxy, alkyl, alkyloxy, or Ar-carbonyl;
- 35 halo is a substituent selected from the group of fluoro, chloro, bromo and iodo; and haloalkyl is a straight or branched saturated hydrocarbon radical having from 1 to 6 carbon atoms or a cyclic saturated hydrocarbon radical having from 3

to 6 carbon atoms, wherein one or more carbon atoms are substituted with one or more halo-atoms.

The present invention also relates to a method of treating a patient, including a human, with latent TB, which comprises administering to the patient a therapeutically effective amount of a compound according to the invention.

The compounds according to formula (Ia) and (Ib) are interrelated in that e.g. a compound according to formula (Ib), with R<sup>9</sup> equal to oxo is the tautomeric equivalent of a compound according to formula (Ia) with R<sup>2</sup> equal to hydroxy (keto-enol tautomerism).

In the framework of this application, alkyl is a straight or branched saturated hydrocarbon radical having from 1 to 6 carbon atoms ; or is a cyclic saturated hydrocarbon radical having from 3 to 6 carbon atoms ; or is a cyclic saturated hydrocarbon radical having from 3 to 6 carbon atoms attached to a straight or branched saturated hydrocarbon radical having from 1 to 6 carbon atoms ; wherein each carbon atom can be optionally substituted with halo, hydroxy, alkyloxy or oxo. Preferably, alkyl is methyl, ethyl or cyclohexylmethyl.

In the framework of this application, Ar is a homocycle selected from the group of phenyl, naphthyl, acenaphthyl, tetrahydronaphthyl, each optionally substituted with 1, 2 or 3 substituents, each substituent independently selected from the group of hydroxy, halo, cyano, nitro, amino, mono- or dialkylamino, alkyl, haloalkyl, alkyloxy, haloalkyloxy, carboxyl, alkyloxycarbonyl, aminocarbonyl, morpholinyl and mono- or dialkylaminocarbonyl. Preferably, Ar is naphthyl or phenyl, each optionally substituted with 1 or 2 halo substituents.

In the framework of this application, Het is a monocyclic heterocycle selected from the group of *N*-phenoxypiperidinyl, piperidinyl, pyrrolyl, pyrazolyl, imidazolyl, furanyl, thienyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, pyridinyl, pyrimidinyl, pyrazinyl and pyridazinyl; or a bicyclic heterocycle selected from the group of quinolinyl, quinoxalinyl, indolyl, benzimidazolyl, benzoxazolyl, benzisoxazolyl, benzothiazolyl, benzisothiazolyl, benzofuranyl, benzothienyl, 2,3-dihydrobenzo[1,4]dioxinyl or benzo[1,3]dioxolyl ; each monocyclic and bicyclic heterocycle may optionally be substituted with 1, 2 or 3 substituents selected from the group of halo, hydroxy, alkyl, alkyloxy or Ar-carbonyl. Preferably, Het is thienyl.

In the framework of this application, halo is a substituent selected from the group of fluoro, chloro, bromo and iodo and haloalkyl is a straight or branched saturated hydrocarbon radical having from 1 to 6 carbon atoms or a cyclic saturated hydrocarbon radical having from 3 to 6 carbon atoms, wherein one or more carbon atoms are substituted with one or more halo-atoms. Preferably, halo is bromo, fluoro or chloro and preferably, haloalkyl is polyhaloC<sub>1-6</sub>alkyl which is defined as mono- or polyhalosubstituted C<sub>1-6</sub>alkyl, for example, methyl with one or more fluoro atoms, for example, difluoromethyl or trifluoromethyl, 1,1-difluoro-ethyl and the like. In case more than one halogen atoms are attached to an alkyl group within the definition of polyhaloC<sub>1-6</sub>alkyl, they may be the same or different. C<sub>1-6</sub>alkyl is a straight or branched saturated hydrocarbon radical having from 1 to 6 carbon atoms such as for example methyl, ethyl, propyl, 2-methyl-ethyl, pentyl, hexyl and the like.

In the definition of Het, or when R<sup>4</sup> and R<sup>5</sup> are taken together, it is meant to include all the possible isomeric forms of the heterocycles, for instance, pyrrolyl comprises 1*H*-pyrrolyl and 2*H*-pyrrolyl.

The Ar or Het listed in the definitions of the substituents of the compounds of formula (Ia) or (Ib) (see for instance R<sup>3</sup>) as mentioned hereinbefore or hereinafter may be attached to the remainder of the molecule of formula (Ia) or (Ib) through any ring carbon or heteroatom as appropriate, if not otherwise specified. Thus, for example, when Het is imidazolyl, it may be 1-imidazolyl, 2-imidazolyl, 4-imidazolyl and the like.

Lines drawn from substituents into ring systems indicate that the bond may be attached to any of the suitable ring atoms.

When two vicinal R<sup>6</sup> radicals are taken together to form a bivalent radical of formula -CH=CH-CH=CH-, this means that the two vicinal R<sup>6</sup> radicals form together with the phenyl ring to which they are attached a naphthyl.

For therapeutic use, salts of the compounds of formula (Ia) or (Ib) are those wherein the counterion is pharmaceutically acceptable. However, salts of acids and bases which are non-pharmaceutically acceptable may also find use, for example, in the preparation or purification of a pharmaceutically acceptable compound. All salts, whether

pharmaceutically acceptable or not, are included within the ambit of the present invention.

The pharmaceutically acceptable addition salts as mentioned hereinabove or hereinafter  
5 are meant to comprise the therapeutically active non-toxic acid addition salt forms  
which the compounds of formula (Ia) or (Ib) are able to form. The latter can  
conveniently be obtained by treating the base form with such appropriate acids as  
inorganic acids, for example, hydrohalic acids, e.g. hydrochloric, hydrobromic and the  
like; sulfuric acid; nitric acid; phosphoric acid and the like; or organic acids, for  
10 example, acetic, propanoic, hydroxyacetic, 2-hydroxypropanoic, 2-oxopropanoic,  
oxalic, malonic, succinic, maleic, fumaric, malic, tartaric, 2-hydroxy-1,2,3-  
propanetricarboxylic, methanesulfonic, ethanesulfonic, benzenesulfonic, 4-methyl-  
benzenesulfonic, cyclohexanesulfamic, 2-hydroxybenzoic, 4-amino-2-hydroxybenzoic  
and the like acids. Conversely the salt form can be converted by treatment with alkali  
15 into the free base form.

The compounds of formula (Ia) or (Ib) containing acidic protons may be converted into  
their therapeutically active non-toxic metal or amine addition salt forms by treatment  
with appropriate organic and inorganic bases. Appropriate base salt forms comprise, for  
20 example, the ammonium salts, the alkali and earth alkaline metal salts, e.g. the lithium,  
sodium, potassium, magnesium, calcium salts and the like, salts with organic bases, e.g.  
primary, secondary and tertiary aliphatic and aromatic amines such as methylamine,  
ethylamine, propylamine, isopropylamine, the four butylamine isomers,  
dimethylamine, diethylamine, diethanolamine, dipropylamine, diisopropylamine,  
25 di-*n*-butylamine, pyrrolidine, piperidine, morpholine, trimethylamine, triethylamine,  
tripropylamine, quinuclidine, pyridine, quinoline and isoquinoline, the benzathine,  
*N*-methyl-D-glucamine, 2-amino-2-(hydroxymethyl)-1,3-propanediol, hydrabamine  
salts, and salts with amino acids such as, for example, arginine, lysine and the like.  
Conversely the salt form can be converted by treatment with acid into the free acid  
30 form.

The term addition salt also comprises the hydrates and solvent addition forms which the  
compounds of formula (Ia) or (Ib) are able to form. Examples of such forms are e.g.  
hydrates, alcoholates and the like.

35 The term "quaternary amine" as used hereinbefore defines the quaternary ammonium  
salts which the compounds of formula (Ia) or (Ib) are able to form by reaction between  
a basic nitrogen of a compound of formula (Ia) or (Ib) and an appropriate quaternizing

agent, such as, for example, an optionally substituted alkylhalide, arylhalide, alkylcarbonylhalide, arylcarbonylhalide, or arylalkylhalide, e.g. methyl iodide or benzyl iodide. Other reactants with good leaving groups may also be used, such as

5 *p*-toluenesulfonates. A quaternary amine has a positively charged nitrogen. Pharmaceutically acceptable counterions include chloro, bromo, iodo, trifluoroacetate, acetate, triflate, sulfate, sulfonate. The counterion of choice can be introduced using ion exchange resins.

10 Compounds of either formula (Ia) and (Ib) and some of the intermediate compounds invariably have at least two stereogenic centers in their structure which may lead to at least 4 stereochemically different structures.

The term "stereochemically isomeric forms" as used hereinbefore or hereinafter defines  
15 all the possible stereoisomeric forms which the compounds of formula (Ia) and (Ib), and their quaternary amines, *N*-oxides, addition salts or physiologically functional derivatives may possess. Unless otherwise mentioned or indicated, the chemical designation of compounds denotes the mixture of all possible stereochemically isomeric forms, said mixtures containing all diastereomers and enantiomers of the basic  
20 molecular structure.

In particular, stereogenic centers may have the *R*- or *S*-configuration; substituents on bivalent cyclic (partially) saturated radicals may have either the *cis*- or *trans*-  
configuration. Compounds encompassing double bonds can have an *E* (entgegen) or *Z* (zusammen) -stereochemistry at said double bond. The terms *cis*, *trans*, *R*, *S*, *E* and *Z*  
25 are well known to a person skilled in the art.

Stereochemically isomeric forms of the compounds of formula (Ia) and (Ib) are obviously intended to be embraced within the scope of this invention.

Following CAS-nomenclature conventions, when two stereogenic centers of known  
30 absolute configuration are present in a molecule, an *R* or *S* descriptor is assigned (based on Cahn-Ingold-Prelog sequence rule) to the lowest-numbered chiral center, the reference center. The configuration of the second stereogenic center is indicated using relative descriptors [*R*\*,*R*\*] or [*R*\*,*S*\*], where *R*\* is always specified as the reference center and [*R*\*,*R*\*] indicates centers with the same chirality and [*R*\*,*S*\*] indicates  
35 centers of unlike chirality. For example, if the lowest-numbered chiral center in the molecule has an *S* configuration and the second center is *R*, the stereo descriptor would be specified as *S*-[*R*\*,*S*\*]. If "α" and "β" are used : the position of the highest priority

substituent on the asymmetric carbon atom in the ring system having the lowest ring number, is arbitrarily always in the "α" position of the mean plane determined by the ring system. The position of the highest priority substituent on the other asymmetric carbon atom in the ring system relative to the position of the highest priority substituent on the reference atom is denominated "α", if it is on the same side of the mean plane  
5 determined by the ring system, or "β", if it is on the other side of the mean plane determined by the ring system.

When a specific stereoisomeric form is indicated, this means that said form is  
10 substantially free, *i.e.* associated with less than 50 %, preferably less than 20 %, more preferably less than 10%, even more preferably less than 5%, further preferably less than 2% and most preferably less than 1% of the other isomer(s). Thus, when a compound of formula (I) is for instance specified as (αS, βR), this means that the compound is substantially free of the (αR, β S) isomer.

15 The compounds of either formula (Ia) and (Ib) may be synthesized in the form of racemic mixtures of enantiomers which can be separated from one another following art-known resolution procedures. The racemic compounds of either formula (Ia) and (Ib) may be converted into the corresponding diastereomeric salt forms by reaction  
20 with a suitable chiral acid. Said diastereomeric salt forms are subsequently separated, for example, by selective or fractional crystallization and the enantiomers are liberated therefrom by alkali. An alternative manner of separating the enantiomeric forms of the compounds of either formula (Ia) and (Ib) involves liquid chromatography using a chiral stationary phase. Said pure stereochemically isomeric forms may also be derived  
25 from the corresponding pure stereochemically isomeric forms of the appropriate starting materials, provided that the reaction occurs stereospecifically. Preferably if a specific stereoisomer is desired, said compound will be synthesized by stereospecific methods of preparation. These methods will advantageously employ enantiomerically pure starting materials.

30 The tautomeric forms of the compounds of either formula (Ia) and (Ib) are meant to comprise those compounds of either formula (Ia) and (Ib) wherein e.g. an enol group is converted into a keto group (keto-enol tautomerism).

35 The *N*-oxide forms of the compounds according to either formula (Ia) and (Ib) are meant to comprise those compounds of either formula (Ia) and (Ib) wherein one or several tertiary nitrogen atoms are oxidized to the so-called *N*-oxide.

The compounds of formula (Ia) and (Ib) may be converted to the corresponding *N*-oxide forms following art-known procedures for converting a trivalent nitrogen into its *N*-oxide form. Said *N*-oxidation reaction may generally be carried out by reacting the starting material of formula (Ia) and (Ib) with an appropriate organic or inorganic peroxide. Appropriate inorganic peroxides comprise, for example, hydrogen peroxide, alkali metal or earth alkaline metal peroxides, e.g. sodium peroxide, potassium peroxide; appropriate organic peroxides may comprise peroxy acids such as, for example, benzenecarboperoxoic acid or halo substituted benzenecarboperoxoic acid, e.g. 3-chlorobenzenecarboperoxoic acid, peroxyalkanoic acids, e.g. peroxyacetic acid, alkyhydroperoxides, e.g. *t*.butyl hydro-peroxide. Suitable solvents are, for example, water, lower alcohols, e.g. ethanol and the like, hydrocarbons, e.g. toluene, ketones, e.g. 2-butanone, halogenated hydrocarbons, e.g. dichloromethane, and mixtures of such solvents.

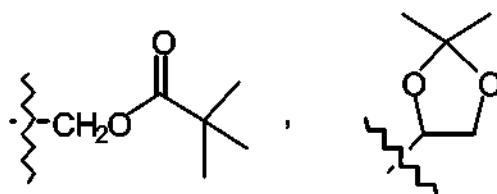
15

The invention also comprises derivative compounds (usually called "pro-drugs") of the pharmacologically-active compounds according to the invention, which are degraded *in vivo* to yield the compounds according to the invention. Pro-drugs are usually (but not always) of lower potency at the target receptor than the compounds to which they are degraded. Pro-drugs are particularly useful when the desired compound has chemical or physical properties that make its administration difficult or inefficient. For example, the desired compound may be only poorly soluble, it may be poorly transported across the mucosal epithelium, or it may have an undesirably short plasma half-life. Further discussion on pro-drugs may be found in Stella, V. J. *et al.*, "Prodrugs", *Drug Delivery Systems*, 1985, pp. 112-176, and *Drugs*, 1985, **29**, pp. 455-473.

25

Pro-drug forms of the pharmacologically-active compounds according to the invention will generally be compounds according to either formula (Ia) and (Ib), the pharmaceutically acceptable acid or base addition salts thereof, the quaternary amines thereof, the stereochemically isomeric forms thereof, the tautomeric forms thereof and the *N*-oxide forms thereof, having an acid group which is esterified or amidated. Included in such esterified acid groups are groups of the formula  $-\text{COOR}^x$ , where  $\text{R}^x$  is a  $\text{C}_{1-6}$ alkyl, phenyl, benzyl or one of the following groups :

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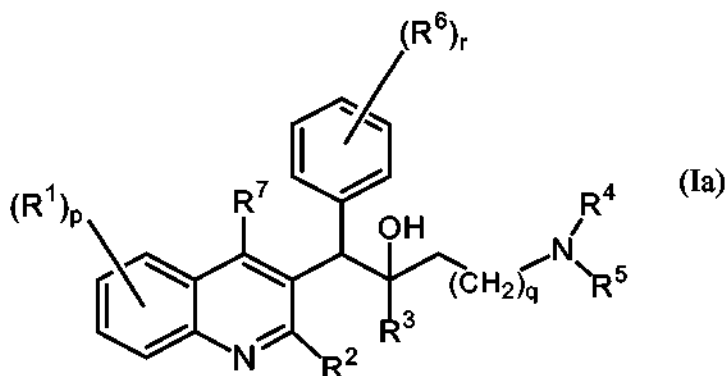


Amidated groups include groups of the formula – CONR<sup>y</sup>R<sup>z</sup>, wherein R<sup>y</sup> is H, C<sub>1-6</sub>alkyl, phenyl or benzyl and R<sup>z</sup> is –OH, H, C<sub>1-6</sub>alkyl, phenyl or benzyl.

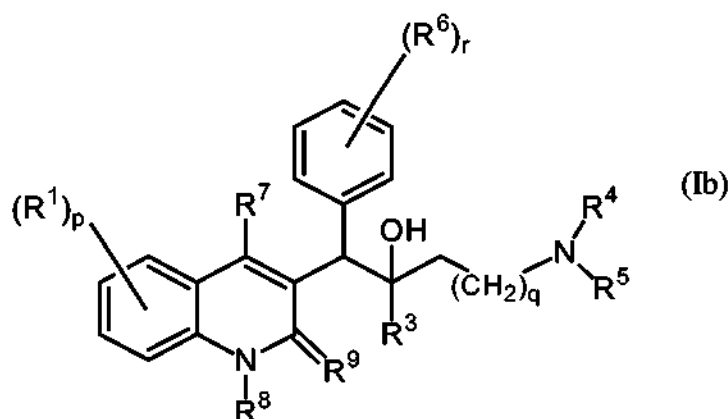
- 5 Compounds according to the invention having an amino group may be derivatised with a ketone or an aldehyde such as formaldehyde to form a Mannich base. This base will hydrolyze with first order kinetics in aqueous solution.

Whenever used herein, the term "compounds of formula (Ia) or (Ib)" is meant to also  
 10 include their pharmaceutically acceptable acid or base addition salts, their quaternary amines, their *N*-oxide forms, their tautomeric forms or their stereochemically isomeric forms. Of special interest are those compounds of formula (Ia) or (Ib) which are stereochemically pure.

- 15 A first interesting embodiment of the present invention relates to the use as defined hereinbefore of compounds of formula (Ia) or (Ib), wherein the compound of formula (Ia) or (Ib) is



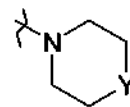




a pharmaceutically acceptable acid or base addition salt thereof, a *N*-oxide thereof, a tautomeric form thereof or a stereochemically isomeric form thereof wherein

- $R^1$  is hydrogen, halo, haloalkyl, cyano, hydroxy, Ar, Het, alkyl, alkyloxy, alkylthio, alkyloxyalkyl, alkylthioalkyl, Ar-alkyl or di(Ar)alkyl ;
- $p$  is an integer equal to 1, 2, 3 or 4 ;
- $R^2$  is hydrogen, hydroxy, mercapto, alkyloxy, alkyloxyalkyloxy, alkylthio,

mono or di(alkyl)amino or a radical of formula



wherein Y is

- $R^3$  is alkyl, Ar, Ar-alkyl, Het or Het-alkyl;
- $q$  is an integer equal to zero, 1, 2, 3 or 4 ;
- $R^4$  and  $R^5$  each independently are hydrogen, alkyl or benzyl; or
- $R^4$  and  $R^5$  together and including the N to which they are attached may form a radical selected from the group of pyrrolidinyl, 2-pyrrolinyl, 3-pyrrolinyl, pyrrolyl, imidazolidinyl, pyrazolidinyl, 2-imidazoliny, 2-pyrazoliny, imidazolyl, pyrazolyl, triazolyl, piperidinyl, pyridinyl, piperazinyl, pyridazinyl, pyrimidinyl, pyrazinyl, triazinyl, morpholinyl and thiomorpholinyl, each of said ring systems optionally substituted with alkyl, halo, haloalkyl, hydroxy, alkyloxy, amino, mono- or dialkylamino, alkylthio, alkyloxyalkyl, alkylthioalkyl and pyrimidinyl ;
- $R^6$  is hydrogen, halo, haloalkyl, hydroxy, Ar, alkyl, alkyloxy, alkylthio, alkyloxyalkyl, alkylthioalkyl, Ar-alkyl or di(Ar)alkyl ; or
- two vicinal  $R^6$  radicals may be taken together to form a bivalent radical of formula  $-\text{CH}=\text{CH}-\text{CH}=\text{CH}-$  ;
- $r$  is an integer equal to 1, 2, 3, 4 or 5 ;
- $R^7$  is hydrogen, alkyl, Ar or Het ;

R<sup>8</sup> is hydrogen or alkyl ;

R<sup>9</sup> is oxo ; or

R<sup>8</sup> and R<sup>9</sup> together form the radical =N-CH=CH-;

alkyl is a straight or branched saturated hydrocarbon radical having from 1 to 6  
5 carbon atoms ; or is a cyclic saturated hydrocarbon radical having from 3 to 6  
carbon atoms ; or is a cyclic saturated hydrocarbon radical having from 3 to 6  
carbon atoms attached to a straight or branched saturated hydrocarbon radical  
having from 1 to 6 carbon atoms ; wherein each carbon atom can be optionally  
substituted with halo, hydroxy, alkyloxy or oxo ;

10 Ar is a homocycle selected from the group of phenyl, naphthyl, acenaphthyl,  
tetrahydronaphthyl, each homocycle optionally substituted with 1, 2 or 3  
substituents, each substituent independently selected from the group of hydroxy,  
halo, cyano, nitro, amino, mono- or dialkylamino, alkyl, haloalkyl, alkyloxy,  
haloalkyloxy, carboxyl, alkyloxycarbonyl, aminocarbonyl, morpholinyl and  
15 mono- or dialkylaminocarbonyl ;

Het is a monocyclic heterocycle selected from the group of *N*-phenoxy piperidinyl,  
piperidinyl, pyrrolyl, pyrazolyl, imidazolyl, furanyl, thienyl, oxazolyl,  
isoxazolyl, thiazolyl, isothiazolyl, pyridinyl, pyrimidinyl, pyrazinyl and  
pyridazinyl; or a bicyclic heterocycle selected from the group of quinolinyl,  
20 quinoxalinyl, indolyl, benzimidazolyl, benzoxazolyl, benzisoxazolyl,  
benzothiazolyl, benzisothiazolyl, benzofuranyl, benzothienyl, 2,3-  
dihydrobenzo[1,4]dioxinyl or benzo[1,3]dioxolyl ; each monocyclic and  
bicyclic heterocycle may optionally be substituted with 1, 2 or 3 substituents  
selected from the group of halo, hydroxy, alkyl, alkyloxy, or Ar-carbonyl;

25 halo is a substituent selected from the group of fluoro, chloro, bromo and iodo; and

haloalkyl is a straight or branched saturated hydrocarbon radical having from 1 to  
6 carbon atoms or a cyclic saturated hydrocarbon radical having from 3  
to 6 carbon atoms, wherein one or more carbon atoms are substituted  
with one or more halo-atoms.

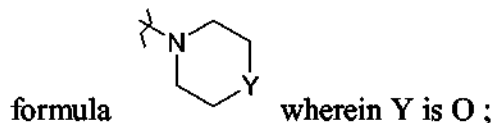
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A second interesting embodiment of the present invention relates to the use as defined  
hereinbefore of compounds of formula (Ia) or (Ib) or any subgroup thereof as  
mentioned hereinbefore as interesting embodiment wherein

R<sup>1</sup> is hydrogen, halo, cyano, Ar, Het, alkyl, and alkyloxy ;

35 p is an integer equal to 1, 2, 3 or 4 ; in particular 1 or 2;

$R^2$  is hydrogen, hydroxy, alkyloxy, alkyloxyalkyloxy, alkylthio or a radical of



$R^3$  is alkyl, Ar, Ar-alkyl or Het ;

q is an integer equal to zero, 1, 2, or 3 ;

5  $R^4$  and  $R^5$  each independently are hydrogen, alkyl or benzyl; or

$R^4$  and  $R^5$  together and including the N to which they are attached may form a radical selected from the group of pyrrolidinyl, imidazolyl, triazolyl, piperidinyl, piperazinyl, pyrazinyl, morpholinyl and thiomorpholinyl, each ring system optionally substituted with alkyl or pyrimidinyl ;

10  $R^6$  is hydrogen, halo or alkyl ; or

two vicinal  $R^6$  radicals may be taken together to form a bivalent radical of formula  
-CH=CH-CH=CH- ;

r is an integer equal to 1 ;

$R^7$  is hydrogen ;

15  $R^8$  is hydrogen or alkyl ;

$R^9$  is oxo ; or

$R^8$  and  $R^9$  together form the radical =N-CH=CH-;

alkyl is a straight or branched saturated hydrocarbon radical having from 1 to 6

20 carbon atoms ; or is a cyclic saturated hydrocarbon radical having from 3 to 6 carbon atoms ; or is a cyclic saturated hydrocarbon radical having from 3 to 6 carbon atoms attached to a straight or branched saturated hydrocarbon radical having from 1 to 6 carbon atoms ; wherein each carbon atom can be optionally substituted with halo or hydroxy ;

25 Ar is a homocycle selected from the group of phenyl, naphthyl, acenaphthyl, tetrahydronaphthyl, each homocycle optionally substituted with 1, 2 or 3 substituents, each substituent independently selected from the group of halo, haloalkyl, cyano, alkyloxy and morpholinyl ;

30 Het is a monocyclic heterocycle selected from the group of *N*-phenoxy piperidinyl, piperidinyl, furanyl, thienyl, pyridinyl, pyrimidinyl ; or a bicyclic heterocycle selected from the group of benzothienyl, 2,3-dihydrobenzo[1,4]dioxinyl or benzo[1,3]dioxolyl; each monocyclic and bicyclic heterocycle may optionally be substituted with 1, 2 or 3 alkyl or Ar-carbonyl substituents ; and

halo is a substituent selected from the group of fluoro, chloro and bromo.

In a third interesting embodiment the compounds of formula (Ia) or (Ib) or any subgroup thereof as mentioned hereinbefore as interesting embodiment are those compounds according to either formula (Ia) and (Ib) wherein  $R^1$  is hydrogen, halo, Ar, alkyl or alkyloxy; preferably,  $R^1$  is halo; more preferably,  $R^1$  is bromo.

5

In a fourth interesting embodiment the compounds of formula (Ia) or (Ib) or any subgroup thereof as mentioned hereinbefore as interesting embodiment are those compounds according to either formula (Ia) and (Ib) wherein p is equal to 1 and  $R^1$  is different from hydrogen.

10

In a fifth interesting embodiment the compounds of formula (Ia) or (Ib) or any subgroup thereof as mentioned hereinbefore as interesting embodiment are those compounds according to either formula (Ia) and (Ib) wherein  $R^2$  is hydrogen, alkyloxy or alkylthio; preferably,  $R^2$  is alkyloxy, in particular  $C_{1-4}$ alkyloxy; more preferably,  $R^2$  is methyloxy.

15

$C_{1-4}$ alkyl is a straight or branched saturated hydrocarbon radical having from 1 to 4 carbon atoms such as for example methyl, ethyl, propyl, 2-methyl-ethyl and the like.

In a sixth interesting embodiment the compounds of formula (Ia) or (Ib) or any subgroup thereof as mentioned hereinbefore as interesting embodiment are those compounds according to either formula (Ia) and (Ib) wherein  $R^3$  is naphthyl, phenyl or thienyl, each optionally substituted with 1 or 2 substituents, that substituent preferably being a halo or haloalkyl, most preferably being a halo; preferably,  $R^3$  is naphthyl or phenyl, each optionally substituted with halo, preferably 3-fluoro; more preferably,  $R^3$  is naphthyl or phenyl; most preferably,  $R^3$  is naphthyl.

20

In a seventh interesting embodiment the compounds of formula (Ia) or (Ib) or any subgroup thereof as mentioned hereinbefore as interesting embodiment are those compounds according to either formula (Ia) and (Ib) wherein q is equal to zero, 1 or 2; preferably, q is equal to 1.

30

In an eighth interesting embodiment the compounds of formula (Ia) or (Ib) or any subgroup thereof as mentioned hereinbefore as interesting embodiment are those compounds according to either formula (Ia) and (Ib) wherein  $R^4$  and  $R^5$  each independently are hydrogen or alkyl, in particular hydrogen or  $C_{1-4}$ alkyl, more in particular  $C_{1-4}$ alkyl; preferably hydrogen, methyl or ethyl; most preferably methyl.

35

C<sub>1-4</sub>alkyl is a straight or branched saturated hydrocarbon radical having from 1 to 4 carbon atoms such as for example methyl, ethyl, propyl, 2-methyl-ethyl and the like.

In a ninth interesting embodiment the compounds of formula (Ia) or (Ib) or any  
5 subgroup thereof as mentioned hereinbefore as interesting embodiment are those  
compounds according to either formula (Ia) and (Ib) wherein R<sup>4</sup> and R<sup>5</sup> together and  
including the N to which they are attached form a radical selected from the group of  
imidazolyl, triazolyl, piperidinyl, piperazinyl and thiomorpholinyl, optionally  
10 substituted with alkyl, halo, haloalkyl, hydroxy, alkyloxy, alkylthio, alkyloxyalkyl or  
alkylthioalkyl, preferably substituted with alkyl, most preferably substituted with  
methyl or ethyl.

In a tenth interesting embodiment the compounds of formula (Ia) or (Ib) or any  
subgroup thereof as mentioned hereinbefore as interesting embodiment are those  
15 compounds according to either formula (Ia) and (Ib) wherein R<sup>6</sup> is hydrogen, alkyl or  
halo; preferably, R<sup>6</sup> is hydrogen.

In an eleventh interesting embodiment the compounds of formula (Ia) or (Ib) or any  
subgroup thereof as mentioned hereinbefore as interesting embodiment are those  
20 compounds according to either formula (Ia) and (Ib) wherein r is 1 or 2.

In a twelfth interesting embodiment the compounds of formula (Ia) or (Ib) or any  
subgroup thereof as mentioned hereinbefore as interesting embodiment are those  
compounds according to either formula (Ia) and (Ib) wherein R<sup>7</sup> is hydrogen or methyl;  
25 preferably R<sup>7</sup> is hydrogen.

In a thirteenth interesting embodiment the compounds of formula (Ia) or (Ib) or any  
subgroup thereof as mentioned hereinbefore as interesting embodiment are those  
compounds according to either formula (Ia) and (Ib) wherein, for compounds according  
30 to Formula (Ib) only, R<sup>8</sup> is alkyl, preferably methyl, and R<sup>9</sup> is oxygen.

In a fourteenth interesting embodiment the compounds of formula (Ia) or (Ib) or any  
subgroup thereof as mentioned hereinbefore as interesting embodiment are those  
compounds according to either formula (Ia) and (Ib) wherein the compound is a  
35 compound according to formula (Ia), a pharmaceutically acceptable acid or base  
addition salt thereof, a quaternary amine thereof, a *N*-oxide thereof, a tautomeric form  
thereof or a stereochemically isomeric form thereof.

A fifteenth interesting embodiment of the compounds of formula (Ia) or (Ib) are the compounds according to formula (Ia), the pharmaceutically acceptable acid or base addition salts thereof, the quaternary amines thereof, the stereochemically isomeric forms thereof, the tautomeric forms thereof or the *N*-oxide forms thereof, in which R<sup>1</sup> is hydrogen, halo, Ar, alkyl or alkyloxy; p = 1; R<sup>2</sup> is hydrogen, alkyloxy or alkylthio; R<sup>3</sup> is naphthyl, phenyl or thienyl, each optionally substituted with 1 or 2 substituents selected from the group of halo and haloalkyl; q = 0, 1, 2 or 3; R<sup>4</sup> and R<sup>5</sup> each independently are hydrogen or alkyl or R<sup>4</sup> and R<sup>5</sup> together and including the N to which they are attached form a radical selected from the group of imidazolyl, triazolyl, piperidinyl, piperazinyl and thiomorpholinyl; R<sup>6</sup> is hydrogen, alkyl or halo; r is equal to 1 and R<sup>7</sup> is hydrogen.

A sixteenth interesting embodiment of the compounds of formula (Ia) or (Ib) are the compounds of formula (Ia) or (Ib) or any subgroup thereof as mentioned hereinbefore as interesting embodiment or the pharmaceutically acceptable acid or base addition salts thereof.

A seventeenth interesting embodiment of the compounds of formula (Ia) or (Ib) are the compounds of formula (Ia) or (Ib) or any subgroup thereof as mentioned hereinbefore as interesting embodiment or the quaternary amines thereof.

An eighteenth interesting embodiment of the compounds of formula (Ia) or (Ib) are the compounds of formula (Ia) or (Ib) or any subgroup thereof as mentioned hereinbefore as interesting embodiment or the *N*-oxides thereof.

A nineteenth interesting embodiment of the compounds of formula (Ia) or (Ib) are the compounds of formula (Ia) or (Ib) or any subgroup thereof as mentioned hereinbefore as interesting embodiment or the stereochemically isomeric forms thereof.

A twentieth interesting embodiment of the compounds of formula (Ia) or (Ib) are the compounds of formula (Ia) or (Ib) or any subgroup thereof as mentioned hereinbefore as interesting embodiment.

Preferably, in the compounds of formula (Ia) and (Ib) or any subgroup thereof as mentioned hereinbefore as interesting embodiment, the term "alkyl" represents C<sub>1-6</sub>alkyl wherein C<sub>1-6</sub>alkyl is a straight or branched saturated hydrocarbon radical having

from 1 to 6 carbon atoms such as for example methyl, ethyl, propyl, 2-methyl-ethyl, pentyl, hexyl and the like.

Preferably, in the compounds of formula (Ia) and (Ib) or any subgroup thereof as mentioned hereinbefore as interesting embodiment, the term "haloalkyl" represents polyhaloC<sub>1-6</sub>alkyl which is defined as mono- or polyhalosubstituted C<sub>1-6</sub>alkyl, for example, methyl with one or more fluoro atoms, for example, difluoromethyl or trifluoromethyl, 1,1-difluoro-ethyl and the like. In case more than one halogen atoms are attached to an alkyl group within the definition of polyhaloC<sub>1-6</sub>alkyl, they may be the same or different. C<sub>1-6</sub>alkyl is a straight or branched saturated hydrocarbon radical having from 1 to 6 carbon atoms such as for example methyl, ethyl, propyl, 2-methyl-ethyl, pentyl, hexyl and the like.

Preferably, the compound is selected from :

- 1-(6-bromo-2-methoxy-quinolin-3-yl)-2-(3,5-difluoro-phenyl)-4-dimethylamino-1-phenyl-butan-2-ol ;
- 1-(6-bromo-2-methoxy-quinolin-3-yl)-4-dimethylamino-2-naphthalen-1-yl-1-phenyl-butan-2-ol corresponding to 6-bromo- $\alpha$ -[2-(dimethylamino)ethyl]-2-methoxy- $\alpha$ -1-naphthalenyl- $\beta$ -phenyl-3-quinolineethanol;
- 1-(6-bromo-2-methoxy-quinolin-3-yl)-2-(2,5-difluoro-phenyl)-4-dimethylamino-1-phenyl-butan-2-ol ;
- 1-(6-bromo-2-methoxy-quinolin-3-yl)-2-(2,3-difluoro-phenyl)-4-dimethylamino-1-phenyl-butan-2-ol ;
- 1-(6-bromo-2-methoxy-quinolin-3-yl)-4-dimethylamino-2-(2-fluoro-phenyl)-1-phenyl-butan-2-ol ;
- 1-(6-bromo-2-methoxy-quinolin-3-yl)-4-dimethylamino-2-naphthalen-1-yl-1-*p*-tolyl-butan-2-ol ;
- 1-(6-bromo-2-methoxy-quinolin-3-yl)-4-methylamino-2-naphthalen-1-yl-1-phenyl-butan-2-ol ;
- 1-(6-bromo-2-methoxy-quinolin-3-yl)-4-dimethylamino-2-(3-fluoro-phenyl)-1-phenyl-butan-2-ol; and
- 1-(6-bromo-2-methoxy-quinolin-3-yl)-4-dimethylamino-2-phenyl-1-phenyl-butan-2-ol;

a pharmaceutically acceptable acid or base addition salt thereof, a *N*-oxide thereof, a tautomeric form thereof or a stereochemically isomeric form thereof.

More preferably, the compound is

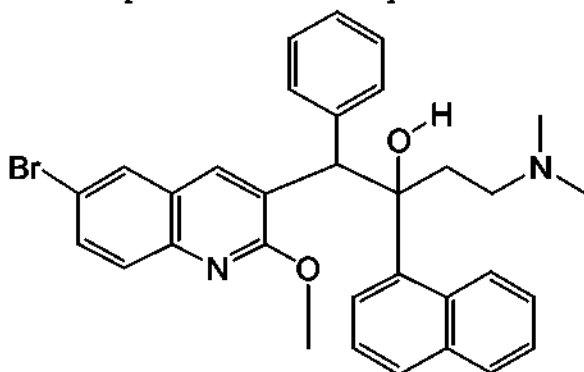
- 1-(6-bromo-2-methoxy-quinolin-3-yl)-2-(2,3-difluoro-phenyl)-4-dimethylamino-1-phenyl-butan-2-ol ; or
  - 1-(6-bromo-2-methoxy-quinolin-3-yl)-4-dimethylamino-2-naphthalen-1-yl-1-phenyl-butan-2-ol corresponding to 6-bromo- $\alpha$ -[2-(dimethylamino)ethyl]-2-methoxy- $\alpha$ -1-naphthalenyl- $\beta$ -phenyl-3-quinolineethanol;
- 5 a pharmaceutically acceptable acid or base addition salt thereof, a *N*-oxide thereof, a tautomeric form thereof or a stereochemically isomeric form thereof.

Even more preferably, the compound is 1-(6-bromo-2-methoxy-quinolin-3-yl)-4-dimethylamino-2-naphthalen-1-yl-1-phenyl-butan-2-ol,

10 a pharmaceutically acceptable acid or base addition salt thereof, a *N*-oxide thereof, or a stereochemically isomeric form thereof.

An alternative chemical name for 1-(6-bromo-2-methoxy-quinolin-3-yl)-4-dimethylamino-2-naphthalen-1-yl-1-phenyl-butan-2-ol is 6-bromo- $\alpha$ -[2-

15 (dimethylamino)ethyl]-2-methoxy- $\alpha$ -1-naphthalenyl- $\beta$ -phenyl-3-quinolineethanol. Said compound can also be represented as follows :



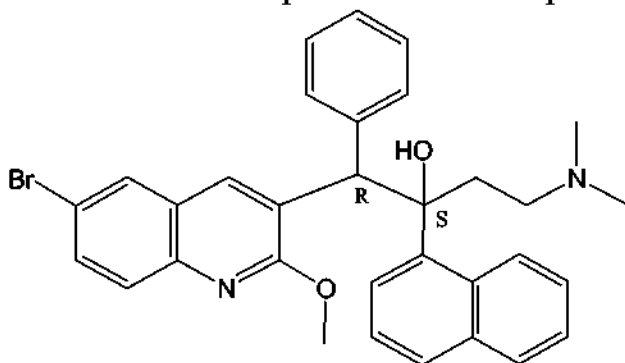
- 20 Further preferably, the compound is one of the following :
- 6-bromo- $\alpha$ -[2-(dimethylamino)ethyl]-2-methoxy- $\alpha$ -1-naphthalenyl- $\beta$ -phenyl-3-quinolineethanol, or a pharmaceutically acceptable acid addition salt thereof; or
  - 6-bromo- $\alpha$ -[2-(dimethylamino)ethyl]-2-methoxy- $\alpha$ -1-naphthalenyl- $\beta$ -phenyl-3-quinolineethanol, or a stereochemically isomeric form thereof; or
  - 25 6-bromo- $\alpha$ -[2-(dimethylamino)ethyl]-2-methoxy- $\alpha$ -1-naphthalenyl- $\beta$ -phenyl-3-quinolineethanol, or a *N*-oxide form thereof; or
  - a mixture, in particular a racemic mixture, of ( $\alpha$ S,  $\beta$ R)-6-bromo- $\alpha$ -[2-(dimethylamino)ethyl]-2-methoxy- $\alpha$ -1-naphthalenyl- $\beta$ -phenyl-3-quinolineethanol and ( $\alpha$ R,  $\beta$ S)-6-bromo- $\alpha$ -[2-(dimethylamino)ethyl]-2-methoxy- $\alpha$ -1-naphthalenyl- $\beta$ -



phenyl-3-quinolineethanol, or a pharmaceutically acceptable acid addition salt thereof, or a stereochemically isomeric forms thereof; i.e. compound 14 (diastereoisomer A); or ( $\alpha$ S,  $\beta$ R)-6-bromo- $\alpha$ -[2-(dimethylamino)ethyl]-2-methoxy- $\alpha$ -1-naphthalenyl- $\beta$ -phenyl-3-quinolineethanol, i.e. compound 12, or a pharmaceutically acceptable acid addition salt thereof; or

5 ( $\alpha$ S,  $\beta$ R)-6-bromo- $\alpha$ -[2-(dimethylamino)ethyl]-2-methoxy- $\alpha$ -1-naphthalenyl- $\beta$ -phenyl-3-quinolineethanol, i.e. compound 12.

The most preferred compound is ( $\alpha$ S,  $\beta$ R)-6-bromo- $\alpha$ -[2-(dimethylamino)ethyl]-2-methoxy- $\alpha$ -1-naphthalenyl- $\beta$ -phenyl-3-quinolineethanol which corresponds to (1R,2S)-1-(6-bromo-2-methoxy-quinolin-3-yl)-4-dimethylamino-2-naphthalen-1-yl-1-phenylbutan-2-ol. Said compound can also be represented as follows :



15 Another interesting group of compounds is the following : compounds 12, 71, 174, 75, 172, 79 and 125 as described hereinafter in Tables 1 to 6; in particular compounds 12, 71, 174, 75, 172 and 79 or compounds 12, 71, 75, 172 and 125; more in particular compounds 12, 71, 174 and 75 or compounds 12, 71, 75 and 172; even more in particular compounds 12, 71 and 174 or compounds 12, 71 and 75; a pharmaceutically

20 acceptable acid or base addition salt thereof, a *N*-oxide thereof, a tautomeric form thereof or a stereochemically isomeric form thereof.

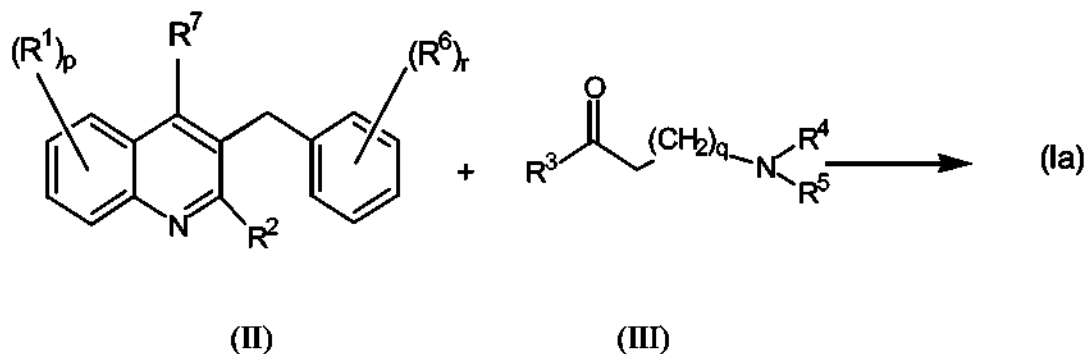
The compounds of formula (Ia) and (Ib) can be prepared according to the methods described in WO 2004/011436, which is incorporated herein by reference.

25 In general, the compounds according to the invention can be prepared by a succession of steps, each of which is known to the skilled person.

In particular, the compounds according to formula (Ia) can be prepared by reacting an intermediate compound of formula (II) with an intermediate compound of formula (III) according to the following reaction scheme (1) :

30

Scheme 1



5 using BuLi in a mixture of diisopropyl amine and tetrahydrofuran, and wherein all variables are defined as in formula (Ia). Stirring may enhance the rate of the reaction. The reaction may conveniently be carried out at a temperature ranging between  $-20$  and  $-70$  °C.

The same reaction procedure can be used to synthesize compounds of formula (Ib).

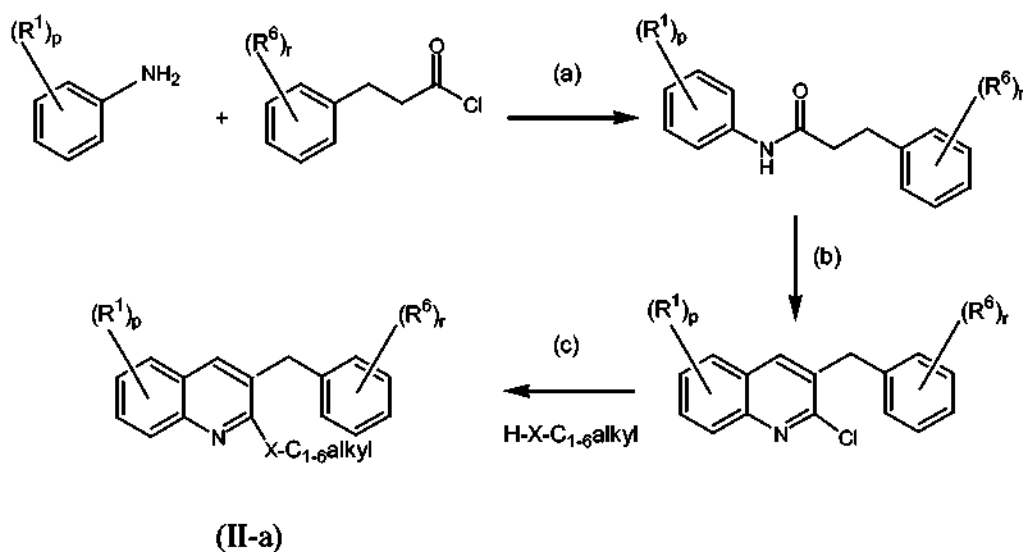
10

The starting materials and the intermediate compounds of formula (II) and (III) are compounds that are either commercially available or may be prepared according to conventional reaction procedures generally known in the art. For example, intermediate compounds of formula (II-a) may be prepared according to the following

15

reaction scheme (2):

Scheme 2



wherein all variables are defined as in formula (Ia). Reaction scheme (2) comprises step (a) in which an appropriately substituted aniline is reacted with an appropriate acylchloride such as 3-phenylpropionyl chloride, 3-fluorobenzenepropanoyl chloride or *p*-chlorobenzenepropanoyl chloride, in the presence of a suitable base, such as triethylamine and a suitable reaction-inert solvent, such as methylene chloride or ethylene dichloride. The reaction may conveniently be carried out at a temperature ranging between room temperature and reflux temperature. In a next step (b) the adduct obtained in step (a) is reacted with phosphoryl chloride (POCl<sub>3</sub>) in the presence of *N,N*-dimethylformamide (Vilsmeier-Haack formylation followed by cyclization).

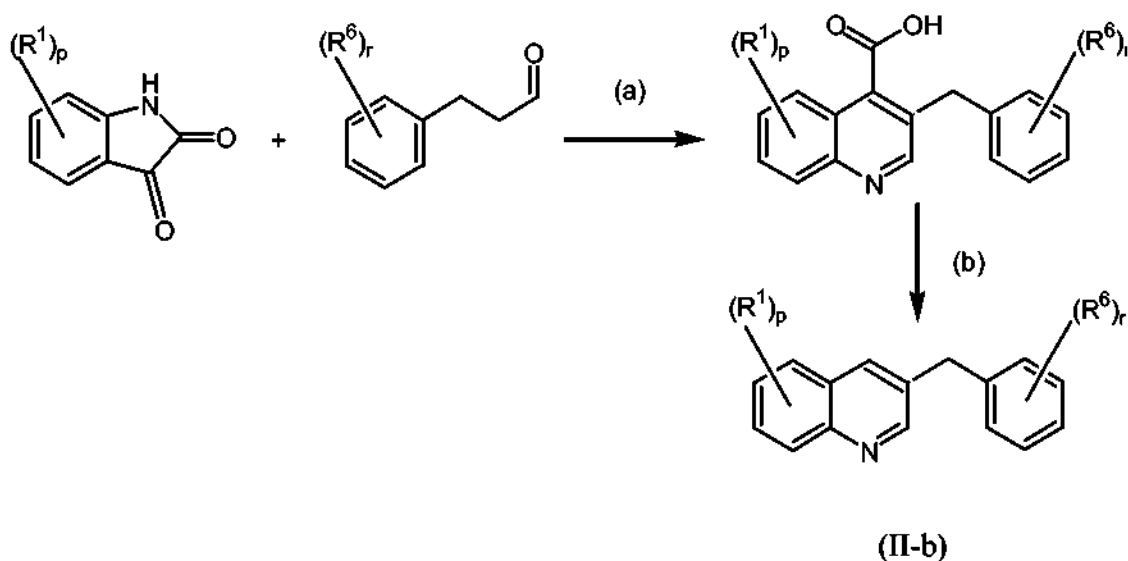
10 The reaction may conveniently be carried out at a temperature ranging between room temperature and reflux temperature. In a next step (c) a specific R<sup>2</sup>-group, wherein R<sup>2</sup> is for example an C<sub>1-6</sub>alkoxy or C<sub>1-6</sub>alkylthio radical is introduced by reacting the intermediate compound obtained in step (b) with a compound H-X-C<sub>1-6</sub>alkyl wherein X is S or O.

15

Intermediate compounds according to formula (II-b) may be prepared according to the following reaction scheme (3), wherein in a first step (a) a substituted indole-2,3-dione is reacted with a substituted 3-phenylpropionaldehyde in the presence of a suitable base such as sodium hydroxide (Pfitzinger reaction), after which the resulting carboxylic acid compound is decarboxylated in a next step (b) at high temperature in the presence of a suitable reaction-inert solvent such as diphenylether.

20

Scheme 3

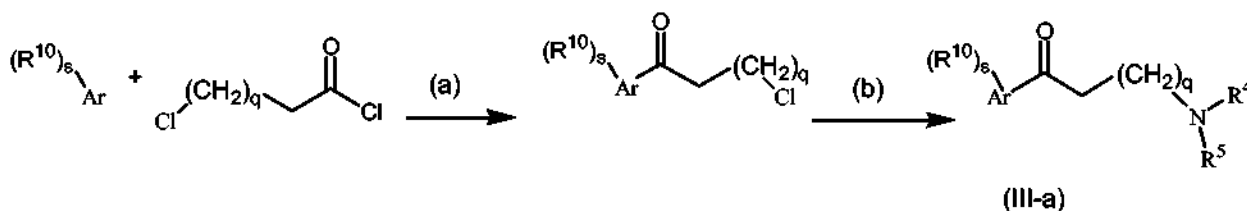


25

It is evident that in the foregoing and in the following reactions, the reaction products may be isolated from the reaction medium and, if necessary, further purified according to methodologies generally known in the art, such as extraction, crystallization and chromatography. It is further evident that reaction products that exist in more than one enantiomeric form, may be isolated from their mixture by known techniques, in particular preparative chromatography, such as preparative HPLC. Typically, compounds of formula (I) may be separated into their isomeric forms.

The intermediate compounds of formula (III) are compounds that are either commercially available or may be prepared according to conventional reaction procedures generally known in the art. For example, intermediate compounds of formula (III-a) in which  $R^3$  is Ar substituted with  $s$  substituents  $R^{10}$ , wherein each  $R^{10}$  is independently selected from the group of hydroxy, halo, cyano, nitro, amino, mono- or di( $C_{1-6}$ alkyl)amino,  $C_{1-6}$ alkyl, polyhalo $C_{1-6}$ alkyl,  $C_{1-6}$ alkyloxy, polyhalo $C_{1-6}$ alkyloxy, carboxyl,  $C_{1-6}$ alkyloxycarbonyl, aminocarbonyl, morpholinyl and mono- or di( $C_{1-6}$ alkyl)aminocarbonyl and  $s$  is an integer equal to zero, 1, 2 or 3, may be prepared according to the following reaction scheme (4):

Scheme 4



Reaction scheme (4) comprises step (a) in which an appropriately substituted Ar, in particular an appropriately substituted phenyl, is reacted by Friedel-Craft reaction with an appropriate acylchloride such as 3-chloropropionyl chloride or 4-chlorobutyryl chloride, in the presence of a suitable Lewis acid, such as for example  $AlCl_3$ ,  $FeCl_3$ ,  $SnCl_4$ ,  $TiCl_4$  or  $ZnCl_2$  and a suitable reaction-inert solvent, such as methylene chloride or ethylene dichloride. The reaction may conveniently be carried out at a temperature ranging between room temperature and reflux temperature. In a next step (b) an amino group ( $-NR^4R^5$ ) is introduced by reacting the intermediate compound obtained in step (a) with an appropriate primary or secondary amine.

As for the interpretation of the present invention, latent TB, dormant TB or persistent TB are the same (TB stands for tuberculosis).

As already stated above, the compounds of formula (Ia) and (Ib) can be used to treat latent TB. The exact dosage and frequency of administration of the present compounds depends on the particular compound of formula (Ia) and (Ib) used, the particular  
5 condition being treated, the severity of the condition being treated, the age, weight, gender, diet, time of administration and general physical condition of the particular patient, the mode of administration as well as other medication the individual may be taking, as is well known to those skilled in the art. Furthermore, it is evident that the effective daily amount may be lowered or increased depending on the response of the  
10 treated subject and/or depending on the evaluation of the physician prescribing the compounds of the instant invention.

The compounds of the present invention may be administered in a pharmaceutically acceptable form optionally in a pharmaceutically acceptable carrier.

15

The pharmaceutical compositions may have various pharmaceutical forms for administration purposes. As appropriate compositions there may be cited all compositions usually employed for systemically administering drugs. To prepare the pharmaceutical compositions, an effective amount of the particular compounds,  
20 optionally in addition salt form, as the active ingredient is combined in intimate admixture with a pharmaceutically acceptable carrier, which carrier may take a wide variety of forms depending on the form of preparation desired for administration. These pharmaceutical compositions are desirable in unitary dosage form suitable, in particular, for administration orally or by parenteral injection. For example, in  
25 preparing the compositions in oral dosage form, any of the usual pharmaceutical media may be employed such as, for example, water, glycols, oils, alcohols and the like in the case of oral liquid preparations such as suspensions, syrups, elixirs, emulsions and solutions; or solid carriers such as starches, sugars, kaolin, diluents, lubricants, binders, disintegrating agents and the like in the case of powders, pills, capsules and tablets.  
30 Because of their ease in administration, tablets and capsules represent the most advantageous oral unit dosage forms in which case solid pharmaceutical carriers are obviously employed. For parenteral compositions, the carrier will usually comprise sterile water, at least in large part, though other ingredients, for example, to aid solubility, may be included. Injectable solutions, for example, may be prepared in  
35 which the carrier comprises saline solution, glucose solution or a mixture of saline and glucose solution. Injectable suspensions may also be prepared in which case appropriate liquid carriers, suspending agents and the like may be employed. Also

included are solid form preparations which are intended to be converted, shortly before use, to liquid form preparations.

Depending on the mode of administration, the pharmaceutical composition will preferably comprise from 0.05 to 99 % by weight, more preferably from 0.1 to 70 % by weight of the active ingredient, and, from 1 to 99.95 % by weight, more preferably from 30 to 99.9 weight % of a pharmaceutically acceptable carrier, all percentages being based on the total composition.

The pharmaceutical composition may additionally contain various other ingredients known in the art, for example, a lubricant, stabilising agent, buffering agent, emulsifying agent, viscosity-regulating agent, surfactant, preservative, flavouring or colorant.

It is especially advantageous to formulate the aforementioned pharmaceutical compositions in unit dosage form for ease of administration and uniformity of dosage. Unit dosage form as used herein refers to physically discrete units suitable as unitary dosages, each unit containing a predetermined quantity of active ingredient calculated to produce the desired therapeutic effect in association with the required pharmaceutical carrier. Examples of such unit dosage forms are tablets (including scored or coated tablets), capsules, pills, powder packets, wafers, suppositories, injectable solutions or suspensions and the like, and segregated multiples thereof. The daily dosage of the compound according to the invention will, of course, vary with the compound employed, the mode of administration, the treatment desired and the mycobacterial disease indicated. However, in general, satisfactory results will be obtained when the compound according to the invention is administered at a daily dosage not exceeding 1 or 2 gram, e.g. in the range from 10 to 50 mg/kg body weight.

#### EXPERIMENTAL PART

As already stated above, the compounds of formula (Ia) and (Ib) and their preparation is described in WO 2004/011436, which is incorporated herein by reference.

Of some compounds the absolute stereochemical configuration of the stereogenic carbon atom(s) therein was not experimentally determined. In those cases the stereochemically isomeric form which was first isolated is designated as "A" and the second as "B", without further reference to the actual stereochemical configuration. However, said "A" and "B" isomeric forms can be unambiguously characterized by a

person skilled in the art, using art-known methods such as, for example, X-ray diffraction.

In case "A" and "B" are stereoisomeric mixtures, they can be further separated whereby the respective first fractions isolated are designated "A1" respectively "B1" and the second as "A2" respectively "B2", without further reference to the actual  
5 stereochemical configuration. However, said "A1, A2" and "B1, B2" isomeric forms can be unambiguously characterized by a person skilled in the art, using art-known methods such as, for example, X-ray diffraction.

10 The present compounds (see Tables 1 to 6) are numbered in conformity with the compounds of WO 2004/011436 and can be prepared according to the methods described in WO 2004/011436. The Ex. Nr. in the below Tables refer to the Example numbers of WO 2004/011436 indicating according to which procedure the compounds can be prepared.

15

In particular, the preparation of compounds 12, 13, 12a, 13a, 14 and 15 are described below in detail.

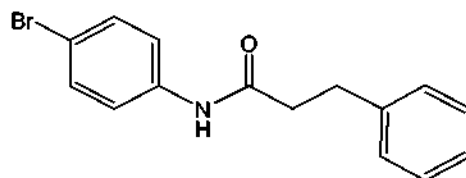
Hereinafter, "DMF" is defined as *N,N*-dimethylformamide, "THF" is defined as tetrahydrofuran, "DIPE" is defined as diisopropylether.

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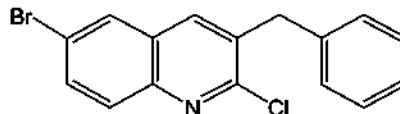
#### Preparation of the intermediate compounds

##### Example A1

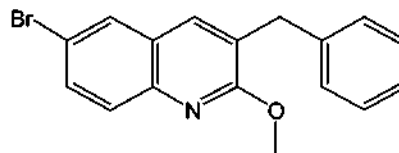
Preparation of intermediate compound 1



Benzenepropanoylchloride (0.488 mol) was added dropwise at room temperature to a solution of 4-bromobenzenamine (0.407 mol) in Et<sub>3</sub>N (70ml) and CH<sub>2</sub>Cl<sub>2</sub> (700ml) and the mixture was stirred at room temperature overnight. The mixture was poured out  
25 into water and concentrated NH<sub>4</sub>OH, and extracted with CH<sub>2</sub>Cl<sub>2</sub>. The organic layer was dried (MgSO<sub>4</sub>), filtered, and the solvent was evaporated. The residue was crystallized from diethyl ether. The residue (119.67g) was taken up in CH<sub>2</sub>Cl<sub>2</sub> and washed with HCl 1N. The organic layer was dried (MgSO<sub>4</sub>), filtered, and the solvent  
30 was evaporated. Yield: 107.67g of intermediate compound 1.

**Example A2****Preparation of intermediate compound 2**

The reaction was carried out twice .  $\text{POCl}_3$  (1.225 mol) was added dropwise at  $10^\circ\text{C}$  to *N,N*-dimethylformamide (DMF) (0.525 mol) . Then intermediate compound 1 (prepared according A1) (0.175 mol) was added at room temperature . The mixture was stirred overnight at  $80^\circ\text{C}$ , poured out on ice and extracted with  $\text{CH}_2\text{Cl}_2$  . The organic layer was dried ( $\text{MgSO}_4$ ), filtered, and the solvent was evaporated . The product was used without further purification. Yield : 77.62g of intermediate compound 2 (67%).

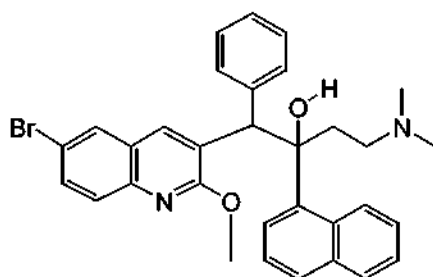
10 **Example A3****Preparation of intermediate compound 3**

A mixture of intermediate compound 2 (prepared according to A2) (0.233 mol) in  $\text{CH}_3\text{ONa}$  (30%) in methanol (222.32 ml) and methanol (776ml) was stirred and refluxed overnight, then poured out on ice and extracted with  $\text{CH}_2\text{Cl}_2$  . The organic layer was separated, dried ( $\text{MgSO}_4$ ), filtered and the solvent was evaporated . The residue was purified by column chromatography over silica gel (eluent:  $\text{CH}_2\text{Cl}_2$ /cyclohexane 20/80 and then 100/0; 20-45 $\mu\text{m}$ ). The pure fractions were collected and the solvent was evaporated . Yield : 25g of intermediate compound 3 (Yield=33%; mp. $84^\circ\text{C}$ ) as a white powder .

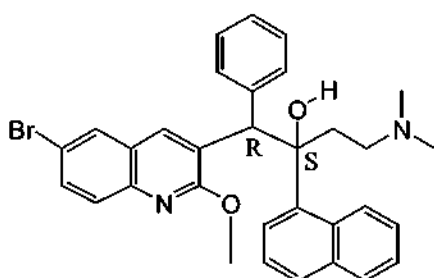
20 **Preparation of final compounds 12, 13, 12a, 13a, 14 and 15**

Preparation of final compounds 12,  
13, 12a, 13a, 14 and 15



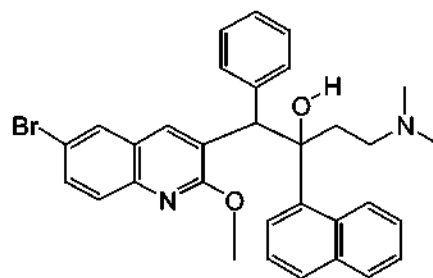


Compound 14 (A)  
Compound 15 (B)



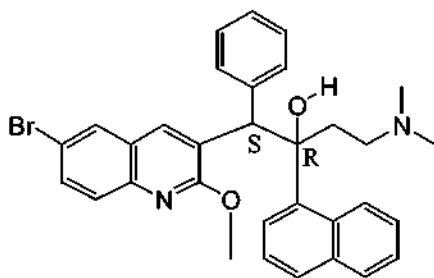
Compound 12 (A1)

$[\alpha]_D^{20} = -166.98$  (c=0.505g/100ml in DMF)



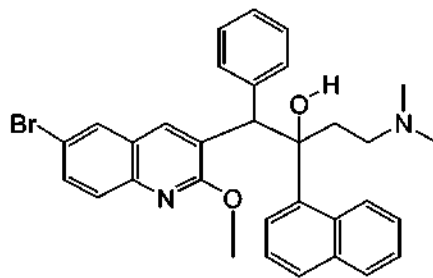
Compound 12a (B1)

$[\alpha]_D^{20} = -42.56$  (c=0.336g/100ml in DMF)



Compound 13 (A2)

$[\alpha]_D^{20} = +167.60$  (c=0.472g/100ml in DMF)



Compound 13a (B2)

$[\alpha]_D^{20} = +43.55$  (c=0.349g/100ml in DMF)

- nBuLi 1.6M (0.05 mol) was added slowly at  $-20^{\circ}\text{C}$  under  $\text{N}_2$  flow to a solution of *N*-(1-methylethyl)-2-propanamine (0.05 mol) in tetrahydrofuran (THF) (80ml) . The mixture was stirred at  $-20^{\circ}\text{C}$  for 15 minutes, then cooled to  $-70^{\circ}\text{C}$  . A solution of intermediate compound 3 (prepared according to A3 described above) (0.046 mol) in THF (150ml) was added slowly . The mixture was stirred at  $-70^{\circ}\text{C}$  for 30 minutes . A solution of 0.055 mol of 3-(dimethylamino)-1-(1-naphthyl)-1-propanone in THF (120ml) was added slowly . The mixture was stirred at  $-70^{\circ}\text{C}$  for 3 hours, hydrolyzed at  $-30^{\circ}\text{C}$  with ice water and extracted with EtOAc . The organic layer was separated, dried ( $\text{MgSO}_4$ ), filtered, and the solvent was evaporated . The residue (29g) was purified by column chromatography over silica gel (eluent:  $\text{CH}_2\text{Cl}_2/\text{CH}_3\text{OH}/\text{NH}_4\text{OH}$ ; 99.5/0.5/0.1; 15-35 $\mu\text{m}$ ) . Two fractions were collected and the solvent was evaporated,

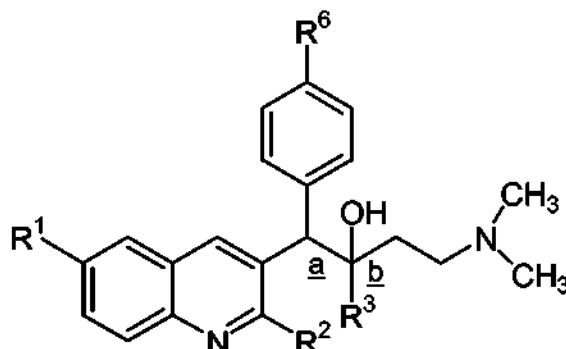
yielding 3g of fraction 1 and 4.4g of fraction 2 . Fraction 1 and 2 were crystallized separately from DIPE . The precipitate was filtered off and dried, yielding 2.2g of diastereoisomer A, i.e. final compound 14 (Yield: 9%; mp.210°C) as a white solid and 4g of diastereoisomer B, i.e. final compound 15 (Yield: 16%; mp.244°C) as a white solid . To obtain the corresponding enantiomers, diastereoisomer A (final compound 14) was purified by chiral chromatography over silica gel (chiralpack AD) (eluent: hexane/EtOH; 99.95/0.05) . Two fractions were collected and the solvent was evaporated . Yield: 0.233g of enantiomer A1 (final compound 12) (mp. 118°C,  $[\alpha]_D^{20} = -166.98^\circ$  (c = 0.505 g/100 ml in DMF)) as a white solid and 0.287g of enantiomer A2 (final compound 13) (mp. 120°C,  $[\alpha]_D^{20} = +167.60^\circ$  (c = 0.472 g/100 ml in DMF)) as a white solid. Enantiomer A1 was crystallised from EtOH to give a white solid: mp. 184°C,  $[\alpha]_D^{20} = -188.71^\circ$ (c= 0.621 g/100ml in DMF). Crystallization of enantiomer A2 from EtOH gave a solid with mp. of 175°C.

0.2g of diastereoisomer B (final compound 15) was purified by chiral chromatography over silica gel (chiralpack AD) (eluent: EtOH/iPrOH/*N*-ethyl-ethanamine; 50/50/0.1). Two fractions were collected and the solvent was evaporated . Yield: 78.2mg of enantiomer B1 and 78.8mg of enantiomer B2. Enantiomer B1 was purified by column chromatography over silica gel (eluent: CH<sub>2</sub>Cl<sub>2</sub>/CH<sub>3</sub>OH/NH<sub>4</sub>OH; 99/1/0.1; 15-40µm). One fraction was collected and the solvent was evaporated . Yield: 57mg of enantiomer B1 (final compound 12a) ( $[\alpha]_D^{20} = -42.56^\circ$  (c = 0.336 g/100 ml in DMF)). Enantiomer B2 was purified by column chromatography over silica gel (eluent: CH<sub>2</sub>Cl<sub>2</sub>/CH<sub>3</sub>OH/NH<sub>4</sub>OH; 99/1/0.1; 15-40µm). One fraction was collected and the solvent was evaporated . Yield: 53mg of enantiomer B2 (final compound 13a) ( $[\alpha]_D^{20} = + 43.55^\circ$  (c = 0.349 g/100 ml in DMF)).

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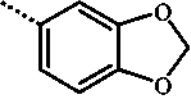
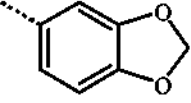
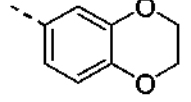
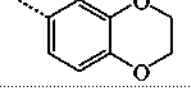

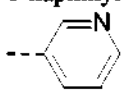
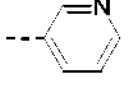
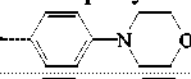
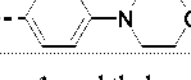
Tables 1 to 6 list compounds of formula (Ia) and (Ib).

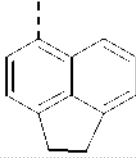
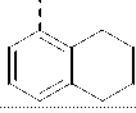



Table 1 :



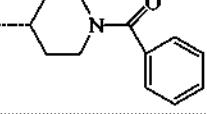
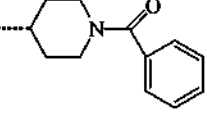





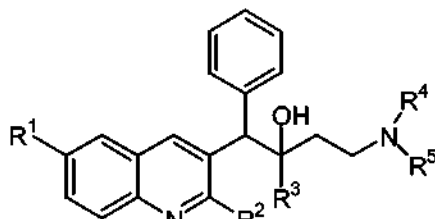
| Comp. nr. | Ex. nr. | R <sup>1</sup>   | R <sup>2</sup>   | R <sup>3</sup> | R <sup>6</sup> | Stereochemistry and melting points |
|-----------|---------|------------------|------------------|----------------|----------------|------------------------------------|
| 1         | B1      | Br               | OCH <sub>3</sub> | phenyl         | H              | (A1); 194°C                        |
| 2         | B1      | Br               | OCH <sub>3</sub> | phenyl         | H              | (A2); 191°C                        |
| 3         | B1      | Br               | OCH <sub>3</sub> | phenyl         | H              | (A); 200°C                         |
| 4         | B1      | Br               | OCH <sub>3</sub> | phenyl         | H              | (B); 190°C                         |
| 16        | B1      | Br               | OCH <sub>3</sub> | 4-chlorophenyl | H              | (A); 200°C                         |
| 17        | B1      | Br               | OCH <sub>3</sub> | 4-chlorophenyl | H              | (B); 190°C                         |
| 20        | B1      | Br               | OCH <sub>3</sub> | 2-thienyl      | H              | (A); 96°C                          |
| 21        | B1      | Br               | OCH <sub>3</sub> | 2-thienyl      | H              | (B); 176°C                         |
| 22        | B1      | CH <sub>3</sub>  | OCH <sub>3</sub> | phenyl         | H              | (A); 148°C                         |
| 23        | B1      | CH <sub>3</sub>  | OCH <sub>3</sub> | phenyl         | H              | (B); 165°C                         |
| 24        | B1      | Br               | OCH <sub>3</sub> | 3-thienyl      | H              | (A); 162°C                         |
| 25        | B1      | Br               | OCH <sub>3</sub> | 3-thienyl      | H              | (B); 160°C                         |
| 26        | B1      | phenyl           | OCH <sub>3</sub> | phenyl         | H              | (A); 174°C                         |
| 27        | B1      | phenyl           | OCH <sub>3</sub> | phenyl         | H              | (B); 192°C                         |
| 28        | B1      | F                | OCH <sub>3</sub> | phenyl         | H              | (A); 190°C                         |
| 29        | B1      | F                | OCH <sub>3</sub> | phenyl         | H              | (B); 166°C                         |
| 30        | B1      | Cl               | OCH <sub>3</sub> | phenyl         | H              | (A); 170°C                         |
| 31        | B1      | Cl               | OCH <sub>3</sub> | phenyl         | H              | (B); 181°C                         |
| 32        | B1      | Br               | SCH <sub>3</sub> | phenyl         | H              | (A); 208°C                         |
| 33        | B1      | Br               | SCH <sub>3</sub> | phenyl         | H              | (B); 196°C                         |
| 34        | B1      | OCH <sub>3</sub> | OCH <sub>3</sub> | phenyl         | H              | (A); 165°C                         |
| 35        | B1      | OCH <sub>3</sub> | OCH <sub>3</sub> | phenyl         | H              | (B); 165°C                         |
| 36        | B1      | Br               | OCH <sub>3</sub> | phenyl         | Cl             | (A); 197°C                         |
| 37        | B1      | Br               | OCH <sub>3</sub> | phenyl         | Cl             | (B); 221°C                         |
| 38        | B9      | Br               | OCH <sub>3</sub> | 3-fluorophenyl | H              | (A); 198°C                         |
| 39        | B9      | Br               | OCH <sub>3</sub> | 3-fluorophenyl | H              | (B); 207°C                         |

| Comp. nr. | Ex. nr. | R <sup>1</sup> | R <sup>2</sup>                   | R <sup>3</sup>     | R <sup>6</sup> | Stereochemistry and melting points  |
|-----------|---------|----------------|----------------------------------|--------------------|----------------|---|
| 108       | B9      | Br             | OCH <sub>3</sub>                 | 3-fluorophenyl     | H              | (A1); 160°C   |
| 109       | B9      | Br             | OCH <sub>3</sub>                 | 3-fluorophenyl     | H              | (A2); 156°C   |
| 40        | B1      | H              | OCH <sub>3</sub>                 | phenyl             | H              | (A); 152°C  |
| 41        | B1      | H              | OCH <sub>3</sub>                 | phenyl             | H              | (B); 160°C  |
| 42        | B1      | H              | OCH <sub>3</sub>                 | CH <sub>3</sub>    | H              | (A); 140°C  |
| 43        | B1      | H              | OCH <sub>3</sub>                 | CH <sub>3</sub>    | H              | (B); 120°C  |
| 59        | B1      | Br             | OH                               | phenyl             | H              | (A); >260°C   |
| 60        | B1      | Br             | OH                               | phenyl             | H              | (B); 215°C  |
| 5         | B2      | Br             | OCH <sub>2</sub> CH <sub>3</sub> | phenyl             | H              | (A); 162°C  |
| 6         | B2      | Br             | OCH <sub>2</sub> CH <sub>3</sub> | phenyl             | H              | (B); 74°C   |
| 7         | B3      | Br             | H                                | phenyl             | H              | (A); 98°C   |
| 8         | B3      | Br             | H                                | phenyl             | H              | (B); 180°C  |
| 12        | B7      | Br             | OCH <sub>3</sub>                 | 1-naphthyl         | H              | (A1); 118°C (foam); $\underline{a}=\underline{R}$ , $\underline{b}=\underline{S}$ ;<br>[ $\alpha$ ] <sub>D</sub> <sup>20</sup> = -166.98<br>(c=0.505g/100ml in DMF) |
| 13        | B7      | Br             | OCH <sub>3</sub>                 | 1-naphthyl         | H              | (A2); 120°C (foam); $\underline{a}=\underline{S}$ , $\underline{b}=\underline{R}$ ;<br>[ $\alpha$ ] <sub>D</sub> <sup>20</sup> = +167.60<br>(c=0.472g/100ml in DMF) |
| 12a       | B7      | Br             | OCH <sub>3</sub>                 | 1-naphthyl         | H              | (B1); [ $\alpha$ ] <sub>D</sub> <sup>20</sup> = -42.56 (c = 0.336<br>g/100 ml in DMF)   |
| 13a       | B7      | Br             | OCH <sub>3</sub>                 | 1-naphthyl         | H              | (B2); [ $\alpha$ ] <sub>D</sub> <sup>20</sup> = +43.55 (c = 0.349<br>g/100 ml in DMF)   |
| 14        | B7      | Br             | OCH <sub>3</sub>                 | 1-naphthyl         | H              | (A); 210°C  |
| 15        | B7      | Br             | OCH <sub>3</sub>                 | 1-naphthyl         | H              | (B); 244°C  |
| 45        | B7      | Br             | OCH <sub>3</sub>                 | 2-naphthyl         | H              | (A); 262°C  |
| 46        | B7      | Br             | OCH <sub>3</sub>                 | 2-naphthyl         | H              | (B); 162°C  |
| 67        | B8      | Br             | OCH <sub>3</sub>                 | 2,5-difluorophenyl | H              | (A); 60°C   |
| 68        | B8      | Br             | OCH <sub>3</sub>                 | 2,5-difluorophenyl | H              | (B); 208°C  |
| 110       | B8      | Br             | OCH <sub>3</sub>                 | 2,5-difluorophenyl | H              | (A1); 167°C   |
| 111       | B8      | Br             | OCH <sub>3</sub>                 | 2,5-difluorophenyl | H              | (A2); oil   |
| 69        | B1      | Br             | OCH <sub>3</sub>                 | 2-fluorophenyl     | H              | (A); oil  |
| 70        | B1      | Br             | OCH <sub>3</sub>                 | 2-fluorophenyl     | H              | (B); oil  |

| Comp. nr. | Ex. nr. | R <sup>1</sup>  | R <sup>2</sup>   | R <sup>3</sup>  | R <sup>6</sup>  | Stereochemistry and melting points |
|-----------|---------|-----------------|--|---|-----------------|------------------------------------|
| 71        | B1      | Br              | OCH <sub>3</sub>   | 1-naphthyl  | CH <sub>3</sub> | (A); 174°C                         |
| 72        | B1      | Br              | OCH <sub>3</sub>   | 1-naphthyl  | CH <sub>3</sub> | (B); 178°C                         |
| 73        | B1      | Br              | OCH <sub>3</sub>   | 1-naphthyl  | Cl              | (B); 174°C                         |
| 74        | B1      | Br              | OCH <sub>3</sub>   | 1-naphthyl  | Cl              | (A); 110°C                         |
| 75        | B1      | Br              | OCH <sub>3</sub>   |    | H               | (A); 196°C                         |
| 76        | B1      | Br              | OCH <sub>3</sub>   |    | H               | (B); 130°C                         |
| 77        | B1      | Br              | OCH <sub>3</sub>   |    | H               | (A); 202°C                         |
| 78        | B1      | Br              | OCH <sub>3</sub>   |   | H               | (B); 202°C                         |
| 79        | B1      | Br              |  | 1-naphthyl  | H               | (A); >250°C                        |
| 80        | B1      | Br              | OCH <sub>3</sub>   | 4-cyanophenyl   | H               | (A); 224°C                         |
| 81        | B1      | Br              | OCH <sub>3</sub>   | 4-cyanophenyl   | H               | (B); 232°C                         |
| 82        | B1      | CH <sub>3</sub> | OCH <sub>3</sub>   | 1-naphthyl  | H               | (A); 202°C                         |
| 83        | B1      | CH <sub>3</sub> | OCH <sub>3</sub>   | 1-naphthyl  | H               | (B); 198°C                         |
| 84        | B1      | phenyl          | OCH <sub>3</sub>   | 1-naphthyl  | H               | (A); 248°C                         |
| 85        | B1      | phenyl          | OCH <sub>3</sub>   | 1-naphthyl  | H               | (B); 214°C                         |
| 86        | B1      | Br              | OCH <sub>3</sub>   |  | H               | (A); 184°C                         |
| 87        | B1      | Br              | OCH <sub>3</sub>   |  | H               | (B); 186°C                         |
| 88        | B1      | Br              | SCH <sub>3</sub>   | 1-naphthyl  | H               | (A); 240°C                         |
| 89        | B1      | Br              | OCH <sub>3</sub>   |  | H               | (A); 236°C                         |
| 90        | B1      | Br              | OCH <sub>3</sub>   |  | H               | (B); 206°C                         |
| 91        | B1      | H               | OCH <sub>3</sub>   | 1-naphthyl  | H               | (A); 178°C                         |
| 92        | B1      | H               | OCH <sub>3</sub>   | 1-naphthyl  | H               | (B); 160°C                         |
| 93        | B1      | H               | OCH <sub>3</sub>   | 3-fluorophenyl  | H               | (A); 178°C                         |
| 94        | B1      | H               | OCH <sub>3</sub>   | 3-fluorophenyl  | H               | (B); 182°C                         |
| 95        | B1      | Br              | OCH <sub>3</sub>   | 2-phenylethyl   | H               | (A); 178°C                         |
| 96        | B1      | Br              | OCH <sub>3</sub>   | 2-phenylethyl   | H               | (B); 146°C                         |

| Comp. nr. | Ex. nr. | R <sup>1</sup>  | R <sup>2</sup>  | R <sup>3</sup>  | R <sup>6</sup> | Stereochemistry and melting points |
|-----------|---------|---|---|---|----------------|------------------------------------|
| 97        | B1      | OCH <sub>3</sub>  | OCH <sub>3</sub>  | 1-naphthyl  | H              | (A); 168°C                         |
| 98        | B1      | OCH <sub>3</sub>  | OCH <sub>3</sub>  | 1-naphthyl  | H              | (B); 154°C                         |
| 113       | B14     | Br  | OCH <sub>3</sub>  | 2,3-difluorophenyl  | H              | (A); 128°C                         |
| 114       | B14     | Br  | OCH <sub>3</sub>  | 2,3-difluorophenyl  | H              | (B); 213°C                         |
| 115       | B15     | Br  | OCH <sub>3</sub>  | 3,5-difluorophenyl  | H              | (A); 192°C                         |
| 116       | B15     | Br  | OCH <sub>3</sub>  | 3,5-difluorophenyl  | H              | (B); 224°C                         |
| 117       | B15     | Br  | OCH <sub>3</sub>  | 3,5-difluorophenyl  | H              | (A1); 161°C                        |
| 118       | B15     | Br  | OCH <sub>3</sub>  | 3,5-difluorophenyl  | H              | (A2); 158°C                        |
| 119       | B7      | Cl  | OCH <sub>3</sub>  | 1-naphthyl  | H              | (A); 212°C                         |
| 120       | B7      | Cl  | OCH <sub>3</sub>  | 1-naphthyl  | H              | (B); 236°C                         |
| 122       | B7      | Br  | OCH <sub>3</sub>  |   | H              | (B); 227°C                         |
| 127       | B7      | Br  | OCH <sub>3</sub>  | 5-bromo-2-naphthyl  | H              | (A); 226°C                         |
| 130       | B7      | Br  | OCH <sub>3</sub>  | 5-bromo-2-naphthyl  | H              | (B); 220°C                         |
| 131       | B1      | Br  | OCH <sub>3</sub>  |  | H              | (A); 206°C                         |
| 134       | B9      | OCH <sub>3</sub>  | OCH <sub>3</sub>  | 3-fluorophenyl  | H              | (A); 172°C                         |
| 135       | B9      | OCH <sub>3</sub>  | OCH <sub>3</sub>  | 3-fluorophenyl  | H              | (B); 182°C                         |
| 143       | B7      | Br  | OCH <sub>3</sub>  | 3-bromo-1-naphthyl  | H              | (A); 234°C                         |
| 150       | B7      | Br  | OCH <sub>3</sub>  | 3-bromo-1-naphthyl  | H              | (B); 212°C                         |
| 159       | B8      | Br  | OCH <sub>3</sub>  | 2,5-difluorophenyl  | H              | (A1); 208°C                        |
| 160       | B8      | Br  | OCH <sub>3</sub>  | 2,5-difluorophenyl  | H              | (A2); 167°C                        |
| 162       | B7      | Br  | OCH <sub>3</sub>  | 6-methoxy-2-naphthyl  | H              | (A); 206°C                         |
| 163       | B7      | Br  | OCH <sub>3</sub>  | 6-methoxy-2-naphthyl  | H              | (B); 206°C                         |
| 164       | B9      | Br  |  | 3-fluorophenyl  | H              | (A); 118°C                         |
| 165       | B9      | Br  |  | 3-fluorophenyl  | H              | (B); oil                           |
| 167       | B8      | Br  | OCH <sub>3</sub>  | 2,6-difluorophenyl  | H              | (B); 180°C                         |
| 174       | B9      |  | OCH <sub>3</sub>  | 3-fluorophenyl  | H              | (A); 159°C                         |

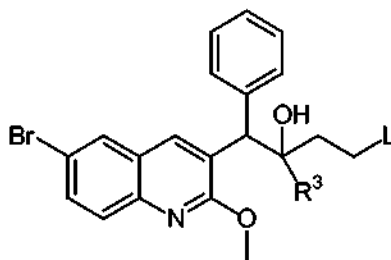
| Comp. nr. | Ex. nr. | R <sup>1</sup>  | R <sup>2</sup>  | R <sup>3</sup>  | R <sup>6</sup> | Stereochemistry and melting points |
|-----------|---------|---|---|---|----------------|------------------------------------|
| 175       | B9      |    | OCH <sub>3</sub>  | 3-fluorophenyl  | H              | (B); 196°C                         |
| 176       | B7      | Br  |  | 1-naphthyl  | H              | (A); oil                           |
| 179       | B9      | CN  | OCH <sub>3</sub>  | 3-fluorophenyl  | H              | (A); 213°C                         |
| 180       | B9      | CN  | OCH <sub>3</sub>  | 3-fluorophenyl  | H              | (B); 163°C                         |
| 181       | B9      | Br  | OCH <sub>3</sub>  | 4-fluorophenyl  | H              | (A); 198°C                         |
| 182       | B9      | Br  | OCH <sub>3</sub>  | 4-fluorophenyl  | H              | (B); 238°C                         |
| 183       | B1      | Br  | OCH <sub>3</sub>  | 3-trifluoro-methylphenyl  | H              | (A); 170°C                         |
| 188       | B1      | Br  | OCH <sub>3</sub>  | 1,4-pyrimidin-2-yl  | H              | (A); 110°C                         |
| 189       | B1      | Br  | OCH <sub>3</sub>  | 1,4-pyrimidin-2-yl  | H              | (B); 145°C                         |
| 195       | B15     | Br  | OCH <sub>3</sub>  | 3,4-difluorophenyl  | H              | (A); 250°C                         |
| 196       | B15     | Br  | OCH <sub>3</sub>  | 3,4-difluorophenyl  | H              | (B); 184°C                         |
| 201       | B1      | Br  | OCH <sub>3</sub>  |  | H              | (A); 214°C                         |
| 202       | B1      | Br  | OCH <sub>3</sub>  |  | H              | (B); 246°C                         |
| 203       | B9      |  | OCH <sub>3</sub>  | 3-fluorophenyl  | H              | (A); 225°C                         |
| 204       | B9      |  | OCH <sub>3</sub>  | 3-fluorophenyl  | H              | (B); 216°C                         |
| 205       | B7      | Br  | OCH <sub>3</sub>  | 1-naphthyl  | F              | (A); 213°C                         |
| 206       | B7      | Br  | OCH <sub>3</sub>  | 1-naphthyl  | F              | (B); 213°C                         |
| 207       | B15     | F   | OCH <sub>3</sub>  | 3,5-difluorophenyl  | H              | (A); 232°C                         |
| 208       | B15     | F   | OCH <sub>3</sub>  | 3,5-difluorophenyl  | H              | (B); 188°C                         |
| 212       | B7      |  | OCH <sub>3</sub>  | 1-naphthyl  | H              | (B); 220°C                         |

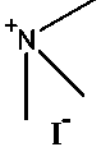
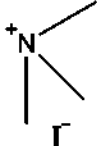
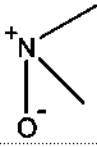
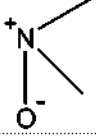
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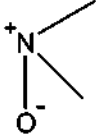
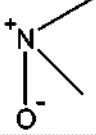
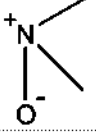
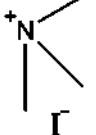
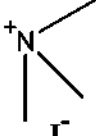
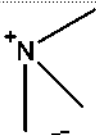
| Comp. nr. | Ex. nr. | R <sup>1</sup> | R <sup>2</sup>   | R <sup>3</sup> | R <sup>4</sup>                  | R <sup>5</sup>                  | Phys.data (salt/melting points) and stereo-chemistry |
|-----------|---------|----------------|------------------|----------------|---------------------------------|---------------------------------|--|
| 18        | B1      | Br             | OCH <sub>3</sub> | phenyl         | CH <sub>2</sub> CH <sub>3</sub> | CH <sub>2</sub> CH <sub>3</sub> | .ethanedioate (2:3); (A); 230°C                      |
| 19        | B1      | Br             | OCH <sub>3</sub> | phenyl         | CH <sub>2</sub> CH <sub>3</sub> | CH <sub>2</sub> CH <sub>3</sub> | .ethanedioate (2:3), (B); 150°C                      |
| 44        | B4      | Br             | OCH <sub>3</sub> | phenyl         | H                               | H                               | (A); 190°C   |
| 9         | B4      | Br             | OCH <sub>3</sub> | phenyl         | H                               | H                               | (B); 204°C   |
| 141       | B7      | Br             | OCH <sub>3</sub> | 2-naphthyl     | CH <sub>3</sub>                 | CH <sub>2</sub> CH <sub>3</sub> | (A); 188°C   |
| 142       | B7      | Br             | OCH <sub>3</sub> | 2-naphthyl     | CH <sub>3</sub>                 | CH <sub>2</sub> CH <sub>3</sub> | (B); 202°C   |
| 230       | B12     | Br             | OCH <sub>3</sub> | 1-naphthyl     | CH <sub>3</sub>                 | benzyl                          | /oil   |
| 147       | B7      | Br             | OCH <sub>3</sub> | 1-naphthyl     | CH <sub>3</sub>                 | CH <sub>2</sub> CH <sub>3</sub> | (A); 168°C   |
| 148       | B7      | Br             | OCH <sub>3</sub> | 1-naphthyl     | CH <sub>3</sub>                 | CH <sub>2</sub> CH <sub>3</sub> | (B); 212°C   |
| 56        | B13     | Br             | OCH <sub>3</sub> | 1-naphthyl     | CH <sub>3</sub>                 | H                               | (A); 204°C   |
| 214       | B13     | Br             | OCH <sub>3</sub> | 1-naphthyl     | CH <sub>3</sub>                 | H                               | (B); 225°C   |



Table 3:



| Comp. nr. | Ex. nr. | R <sup>3</sup> | L   | Stereochemistry and melting points |
|-----------|---------|----------------|---|------------------------------------|
| 47        | B1      | phenyl         | 1-piperidinyl   | (A); 190°C                         |
| 48        | B1      | phenyl         | 1-piperidinyl   | (B); 210°C                         |
| 128       | B1      | 2-naphthyl     | 1-piperidinyl   | (A); 254°C                         |
| 129       | B1      | 2-naphthyl     | 1-piperidinyl   | (B); 212°C                         |
| 49        | B1      | phenyl         | 1-imidazolyl  | (A); 216°C                         |
| 50        | B1      | phenyl         | 1-imidazolyl  | (B); 230°C                         |
| 51        | B1      | phenyl         | 1-(4-methyl)piperazinyl   | (A); 150°C                         |
| 52        | B1      | phenyl         | 1-(4-methyl)piperazinyl   | (B); 230°C                         |
| 53        | B1      | phenyl         | 1-(1,2,4-triazolyl)   | (A); 180°C                         |
| 54        | B1      | phenyl         | 1-(1,2,4-triazolyl)   | (B); 142°C                         |
| 55        | B1      | phenyl         | thiomorpholinyl   | (A); oil                           |
| 57        | B5      | phenyl         |  | (A); 244°C                         |
| 10        | B5      | phenyl         |  | (B); 198°C                         |
| 58        | B6      | phenyl         |  | (A); 208°C                         |
| 11        | B6      | phenyl         |  | (B); 208°C                         |

| Comp. nr. | Ex. nr. | R <sup>3</sup>     | L   | Stereochemistry and melting points |
|-----------|---------|--------------------|---|------------------------------------|
| 99        | B11     | 1-naphthyl         |    | (A1); 218°C                        |
| 100       | B6      | 1-naphthyl         |    | (A2); 218°C                        |
| 101       | B6      | 1-naphthyl         |    | (B); 175°C                         |
| 102       | B5      | 1-naphthyl         |   | (A2); 210°C                        |
| 103       | B5      | 1-naphthyl         |  | (B); >250°C                        |
| 121       | B5      | 1-naphthyl         |  | (A1); 210°C                        |
| 123       | B1      | phenyl             | morpholinyl   | (A); 226°C                         |
| 124       | B1      | phenyl             | morpholinyl   | (B); 210°C                         |
| 136       | B7      | 2-naphthyl         | 4-methylpyrazinyl   | (A); 188°C                         |
| 137       | B7      | 2-naphthyl         | 4-methylpyrazinyl   | (B); 232°C                         |
| 139       | B7      | 2-naphthyl         | morpholinyl   | (A); 258°C                         |
| 140       | B7      | 2-naphthyl         | morpholinyl   | (B); 214°C                         |
| 144       | B7      | 2-naphthyl         | pyrrolidinyl  | (A); 238°C                         |
| 145       | B7      | 1-naphthyl         | 1-piperidinyl   | (A); 212°C                         |
| 146       | B7      | 1-naphthyl         | 1-piperidinyl   | (B); 220°C                         |
| 149       | B7      | 1-naphthyl         | 4-methylpyrazinyl   | (B); 232°C                         |
| 151       | B7      | 3-bromo-1-naphthyl | 4-methylpiperazinyl   | (A); 178°C                         |
| 152       | B7      | 3-bromo-1-naphthyl | 4-methylpiperazinyl   | (B); 226°C                         |
| 153       | B7      | 6-bromo-2-naphthyl | 4-methylpiperazinyl   | (A); 208°C                         |
| 154       | B7      | 6-bromo-2-naphthyl | 4-methylpiperazinyl   | (B); 254°C                         |

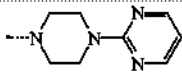
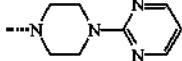
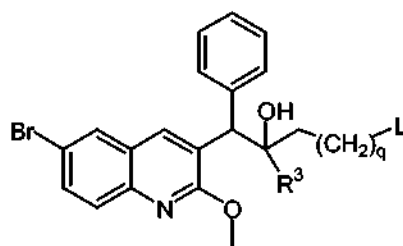
| Comp. nr. | Ex. nr. | R <sup>3</sup>     | L   | Stereochemistry and melting points |
|-----------|---------|--------------------|---|------------------------------------|
| 155       | B7      | 6-bromo-2-naphthyl | 1-piperidinyl   | (A); 224°C                         |
| 156       | B7      | 1-naphthyl         | 4-methylpiperazinyl   | (A); 200°C                         |
| 157       | B7      | 6-bromo-2-naphthyl | 1-pyrrolidinyl  | (B); 220°C                         |
| 158       | B7      | 1-naphthyl         | morpholinyl   | (B); 272°C                         |
| 166       | B7      | 6-bromo-2-naphthyl | 1-piperidinyl   | (B); 218°C                         |
| 170       | B7      | 2-naphthyl         | 1-pyrrolidinyl  | (A); 238°C                         |
| 171       | B7      | 2-naphthyl         | 1-pyrrolidinyl  | (B); 218°C                         |
| 172       | B7      | 1-naphthyl         | 1,2,4-triazol-1-yl  | /142°C                             |
| 173       | B7      | 1-naphthyl         | 1,2-imidazol-1-yl   | (A); 222°C                         |
| 177       | B7      | 6-bromo-2-naphthyl | morpholinyl   | (A); 242°C                         |
| 178       | B7      | 6-bromo-2-naphthyl | morpholinyl   | (B); 246°C                         |
| 187       | B7      | 1-naphthyl         | 1,2-imidazol-1-yl   | (B); 236°C                         |
| 200       | B7      | 2-naphthyl         |  | (A); 254°C                         |
| 209       | B7      | 2-naphthyl         |  | (B); 198°C                         |

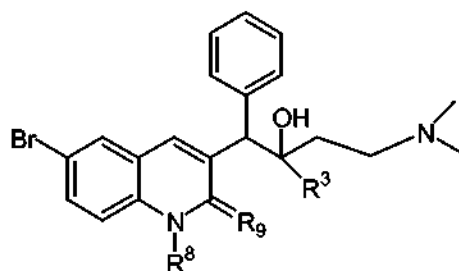
Table 4:



| Comp. nr. | Ex. nr. | R <sup>3</sup> | Q | L                                | Stereochemistry and melting points |
|-----------|---------|----------------|---|----------------------------------|------------------------------------|
| 61        | B1      | phenyl         | 0 | N(CH <sub>3</sub> ) <sub>2</sub> | (A); 220°C                         |
| 62        | B1      | phenyl         | 0 | N(CH <sub>3</sub> ) <sub>2</sub> | (B); 194°C                         |
| 63        | B1      | phenyl         | 2 | N(CH <sub>3</sub> ) <sub>2</sub> | (A); 150°C                         |
| 64        | B1      | phenyl         | 2 | N(CH <sub>3</sub> ) <sub>2</sub> | (B); 220°C                         |
| 125       | B7      | 2-naphthyl     | 2 | N(CH <sub>3</sub> ) <sub>2</sub> | (A); 229°C                         |
| 126       | B7      | 2-naphthyl     | 2 | N(CH <sub>3</sub> ) <sub>2</sub> | (B); 214°C                         |

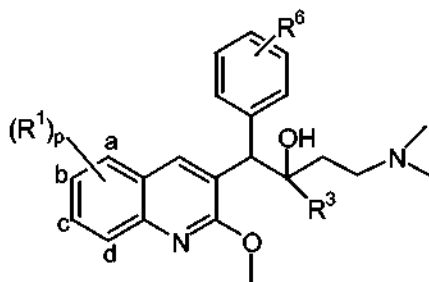
| Comp. nr. | Ex. nr. | R <sup>3</sup> | Q | L  | Stereochemistry and melting points |
|-----------|---------|----------------|---|--|------------------------------------|
| 65        | B1      | phenyl         | 3 | N(CH <sub>3</sub> ) <sub>2</sub>                 | (A); 130°C                         |
| 66        | B1      | phenyl         | 3 | N(CH <sub>3</sub> ) <sub>2</sub>                 | (B); 170°C                         |
| 132       | B7      | 2-naphthyl     | 2 | pyrrolidinyl                                     | (A); 227°C                         |
| 133       | B7      | 2-naphthyl     | 2 | pyrrolidinyl                                     | (B); 222°C                         |
| 161       | B7      | 2-naphthyl     | 2 | morpholinyl                                      | (B); 234°C                         |
| 186       | B7      | 1-naphthyl     | 2 | N(CH <sub>3</sub> ) <sub>2</sub>                 | (A); 187°C                         |
| 190       | B7      | 2-naphthyl     | 3 | N(CH <sub>3</sub> ) <sub>2</sub>                 | (A); 170°C                         |
| 191       | B7      | 2-naphthyl     | 3 | N(CH <sub>3</sub> ) <sub>2</sub>                 | (B); 145°C                         |
| 192       | B7      | 2-naphthyl     | 2 | N(CH <sub>2</sub> CH <sub>3</sub> ) <sub>2</sub> | (A); 90°C                          |
| 193       | B7      | 2-naphthyl     | 2 | N(CH <sub>2</sub> CH <sub>3</sub> ) <sub>2</sub> | (B); 202°C                         |
| 194       | B7      | 1-naphthyl     | 2 | pyrrolidinyl                                     | (B); 206°C                         |
| 197       | B7      | 1-naphthyl     | 3 | N(CH <sub>3</sub> ) <sub>2</sub>                 | (A); 160°C                         |
| 198       | B7      | 2-naphthyl     | 2 | morpholinyl                                      | (A); 215°C                         |
| 199       | B7      | 1-naphthyl     | 2 | N(CH <sub>2</sub> CH <sub>3</sub> ) <sub>2</sub> | (A); 185°C                         |
| 210       | B7      | 1-naphthyl     | 2 | morpholinyl                                      | (B); 222°C                         |
| 211       | B7      | 1-naphthyl     | 2 | morpholinyl                                      | (A); 184°C                         |



Table 5:



| Comp. nr. | Ex. nr. | R <sup>3</sup> | R <sup>8</sup>  | R <sup>9</sup> | Stereochemistry and melting points |
|-----------|---------|----------------|-----------------|----------------|------------------------------------|
| 104       | B1      | phenyl         | -CH=CH-N=       |                | (A); 170°C                         |
| 105       | B1      | phenyl         | -CH=CH-N=       |                | (B); 150°C                         |
| 106       | B1      | phenyl         | CH <sub>3</sub> | =O             | (A); 224°C                         |
| 107       | B1      | phenyl         | CH <sub>3</sub> | =O             | (B); 180°C                         |
| 138       | B7      | 1-naphthyl     | H               | =O             | (A1); >260°C                       |

Table 6:



| Comp. nr. | Ex. nr. | R <sup>1</sup> |                 |                 |                 | R <sup>3</sup>     | R <sup>6</sup>  | Stereochemistry and melting points |
|-----------|---------|----------------|-----------------|-----------------|-----------------|--------------------|---|------------------------------------|
|           |         | a              | b               | c               | d               |                    |   |                                    |
| 215       | B9      | H              | Br              | CH <sub>3</sub> | H               | 3-fluorophenyl     | H   | (A); 197°C                         |
| 216       | B9      | H              | Br              | CH <sub>3</sub> | H               | 3-fluorophenyl     | H   | (B); 158°C                         |
| 217       | B7      | H              | H               | Br              | H               | 1-naphthyl         | H   | (A); 212°C                         |
| 218       | B7      | H              | H               | Br              | H               | 1-naphthyl         | H   | (B); 172°C                         |
| 219       | B9      | H              | Br              | H               | CH <sub>3</sub> | 3-fluorophenyl     | H   | (A); 220°C                         |
| 220       | B9      | H              | Br              | H               | CH <sub>3</sub> | 3-fluorophenyl     | H   | (B); 179°C                         |
| 221       | B7      | Br             | H               | H               | H               | 1-naphthyl         | H   | (A); 170°C                         |
| 224       | B7      | Br             | H               | H               | H               | 1-naphthyl         | H   | /205°C                             |
| 222       | B7      | H              | Br              | H               | H               | 1-naphthyl         |  | (A); 155°C                         |
| 223       | B7      | H              | Br              | H               | H               | 1-naphthyl         |  | (B); 205°C                         |
| 225       | B7      | H              | Br              | CH <sub>3</sub> | H               | 1-naphthyl         | H   | (A); 238°C                         |
| 226       | B7      | H              | Br              | CH <sub>3</sub> | H               | 1-naphthyl         | H   | (B); 208°C                         |
| 227       | B15     | H              | Br              | CH <sub>3</sub> | H               | 3,5-difluorophenyl | H   | (A); 195°C                         |
| 228       | B15     | H              | Br              | CH <sub>3</sub> | H               | 3,5-difluorophenyl | H   | (B); 218°C                         |
| 229       | B7      | H              | CH <sub>3</sub> | CH <sub>3</sub> | H               | 1-naphthyl         | H   | (A); 238°C                         |

## PHARMACOLOGICAL PART

**A. Study of the effect of final compound 12 in killing dormant *Mycobacterium bovis*****Bacterial strains and Culture medium**

- 5 *Mycobacterium bovis* BCG were obtained from Tibotec Virco (TB0087- (Belgium). *M. bovis* BCG, expressing the luciferase gene on plasmid pSMT1 (a kind gift from Dr. Kris Huygen at Pasteur Institute, Brussels<sup>8</sup>) were cultured in Middlebrook 7H9 medium (Difco, BD271310) with 0.05% Tween-80 (Sigma) in log phase for a period of 3-4 days before start of the experiment.
- 10 To prepare growth medium with supplements: dissolve 4.7 g of the Middlebrook powder in 895 ml distilled water and add 5 ml Glycerol, 200 µl Tween 80 and autoclave at 121°C for 15 minutes. Aseptically add 100 ml Middlebrook OADC enrichment to the medium when cooled to 45 °C. Store at 4°C for maximum 1 month. Pre-incubate all media 2 days at 37°C to check for contamination. Add 50 µg/ml
- 15 hygromycin for strain *M. bovis* BCG expressing the luciferase gene (BCG-pSMT1).

**I. Study with *Mycobacterium bovis* BCG****Dormancy assay**

- 500 µl of *Mycobacterium bovis* BCG stock was added to 100 ml Middlebrook 7H9
- 20 broth with supplements in a 250 ml sterile Duran bottle with a magnetic stirring rod. Incubation was done on an electric magnetic stirrer for 7 days at 37 °C (500 rpm). 5 ml aliquots of log phase culture ( $OD_{600nm}=0.5$  to 0.8) were transferred into 15 ml screw capped falcon tubes. Various drugs were added to the individual tubes to a final concentration of 10 µg/ml. After the addition of the drugs, all tube were closed loosely
- 25 and placed inside an anaerobic jar (BBL). Anaerobic gas generation envelopes were used to get anaerobic conditions in the jar and anaerobic strips to monitor the anaerobic conditions. The addition of the individual drugs and the start of the anaerobiosis within the jar was done extremely quickly as previously described<sup>9</sup>. The jar was incubated for 7 days at 37 °C.

**30 CFU assay**

- After 7 days of anaerobiosis, the dormant cultures were collected by low speed centrifugation (2000 rpm for 10 minutes). The cells were washed twice with 7H9 medium so as to remove the drugs and resuspended in drug free medium. The CFU of the treated and untreated cultures were determined by plating at day 0, 2, and day 5 to
- 35 evaluate the bactericidal activity.

## II. Study with *M. bovis* BCG, expressing the luciferase gene on plasmid pSMT1

### Dormancy assay

500  $\mu$ l of *Mycobacterium bovis* BCG luciferase (pSMT1) stock was added to 100 ml Middlebrook 7H9 broth with supplements in a 250 ml sterile Duran bottle with a magnetic stirring rod. Incubation was done on an electric magnetic stirrer for 7 days at 37 °C (500 rpm). 5 ml aliquots of log phase culture ( $OD_{600nm} = 0.5$  to 0.8) were transferred into 15 ml screw capped falcon tubes. Various drugs were added to the individual tubes to a final concentration of 10  $\mu$ g/ml. After addition of the drugs, all tube were closed loosely and placed very quickly inside an anaerobic jar (BBL) as previously described<sup>9</sup>. Anaerobic gas generation envelopes were used to get anaerobic conditions in the jar and anaerobic strips to monitor the anaerobic conditions. The jar was incubated for 7 days at 37 °C.

### Luciferase assay

After 7 days of anaerobiosis, the dormant cultures were collected by low speed centrifugation (2000 rpm for 10 minutes). The cells were washed twice with 7H9 medium so as to remove the drugs and resuspended in drug free medium. After washing, 250  $\mu$ l of the dormant *M. bovis* BCG luciferase (pSMT1) was added to 5 different microplates (day 0 to day 5). Every sample was diluted in microplates (5-fold dilutions) in medium and incubated again for 37 °C from 0 to 5 days. 40  $\mu$ l of samples and dilutions were added to 140  $\mu$ l PBS. 20  $\mu$ l luciferase substrate (1% n-decyl aldehyde in ethanol) was added. The luminescence was measured for 10 seconds to follow the growth of the viable bacteria on every day from 0 to 5 days (Use Luminoskan Ascent Labsystems with injector).

### Experimental organization:

| Sample number | Strain M.Bovis | Sample/compound   | microgram/ml |
|---------------|----------------|-------------------|--------------|
| 1-2           | BCG            | Control           |              |
| 3             | BCG            | Metronidazole     | 10           |
| 4             | BCG            | Isoniazid         | 10           |
| 5-6           | BCG            | Final compound 12 | 10           |
| 7-8           | BCG            | Final compound 12 | 1            |
| 9-10          | BCG            | Final compound 12 | 0.1          |
| 11-12         | BCG/pSMT1      | Control           |              |
| 13            | BCG/pSMT1      | Metronidazole     | 10           |
| 14            | BCG/pSMT1      | Isoniazid         | 10           |
| 15-16         | BCG/pSMT1      | Final compound 12 | 10           |

| Sample number | Strain M.Bovis | Sample/compound   | microgram/ml |
|---------------|----------------|-------------------|--------------|
| 17-18         | BCG/pSMT1      | Final compound 12 | 1            |
| 19-20         | BCG/pSMT1      | Final compound 12 | 0.1          |

### **Results and Discussion**

An *in vitro* dormancy model of dormancy was developed based on Wayne's method of creating dormant bacteria by oxygen depletion<sup>9,10</sup>. In Wayne's model as mycobacteria settle down to the bottom of the flask they generate an oxygen gradient creating anaerobic conditions at the bottom of the flask. This transition to low oxygen concentrations causes mycobacteria to become dormant and that leads to upregulated expression of several genes including isocitrate lyase and glycine dehydrogenase<sup>7</sup>. These enzymes are responsible for production of energy in absence of oxygen and the terminal electron acceptors are nitrate, sulfates etc as compared to molecular oxygen in case of aerobic respiration. The energy of reduced substrates generates a electron chemical gradient.

In this experiment, an adaptation of Wayne's model was used in the experimental set up involving the use of gaspak anaerobic jars in which oxygen is depleted in the chamber by means of a chemical reaction<sup>9</sup>. Gaspak jars are fitted with a lid containing a catalyst. A Gaspak foil envelope containing substances that generate hydrogen and CO<sub>2</sub> is placed in the jar with the bacterial cultures. The envelope is opened, and 10 ml of tap water is pipetted into it. When the jar is closed (the lid is clamped down tightly), the hydrogen given off combines with oxygen, through the mediation of the catalyst, to form water. This leads to the gradual depletion of the oxygen present in the chamber and as such creates the oxygen gradient. Furthermore, an indicator strip in the jar contains methylene blue, which turns colourless in the absence of oxygen. The colour change in the indicator strip signifies that the proper atmospheric condition has been achieved.

For rapid analysis of the effect of the compound on the dormant bacteria, *M. bovis* BCG transformed with the luciferase construct was used. *M. bovis* BCG has been used in earlier experiments as a surrogate to mimic dormancy in mycobacteria in general and *M. tuberculosis* in particular<sup>11,12</sup>. Luciferase reporter strains have been used quite often to access the viability of the bacteria<sup>13,14</sup>. The *M. bovis* BCG is transformed with the reporter plasmid pSMT1, which is a shuttle vector containing the origin of replication of *E.coli* and mycobacteria<sup>8</sup>. The luminescent genes from *Vibrio harveyi* (lux A and B) are under control of BCG hsp60 promoter and produce light in presence of ATP or Flavin mononucleotide (FMNH<sub>2</sub>). Dead cells are not able to produce these cofactors, thus corresponding to decline in luminescence.



The activity of final compound 12 in this dormancy assay was analysed as well as the activity of other drugs including metronidazole and Isoniazid. Dormant bacteria are not killed by Isoniazid and to some extent are also resistant to rifampicin but are susceptible to killing by metronidazole, an antibiotic for anaerobic pathogens<sup>15,16</sup>.

5 Isoniazid acts as an early bactericidal agent and its activity is limited to killing of replicating bacilli but does not have a significant sterilizing activity on dormant bacilli<sup>17</sup>.

After 7 days of anaerobiosis, the bacteria were suspended in drug free medium for 5 days and the effect of different compounds on bacterial viability was assayed by

10 Luciferase counts. As shown in Figure 1, Isoniazid had no effect on these dormant bacteria and these bacteria had almost similar growth characteristics as compared to control, demonstrating the dormant or non-replicating status of the cultured bacilli. In contrast, metronidazole was clearly effective in killing the dormant bacilli over a period of time with reduction of 2 log<sub>10</sub> as compared to control. Final compound 12 affects the  
15 survival of the dormant bacteria in concentration dependent manner. At 10 µg/ml concentration of final compound 12 there was approximately 4-log<sub>10</sub> reduction in bacterial survival as compared to untreated control. At 0.1 and 1 µg/ml of the compound the corresponding killing of dormant bacteria was about 0.5 log<sub>10</sub> and 2 log<sub>10</sub> respectively.

20 To correlate the effects of final compound 12 on bacteria killing in terms relative luminescence units (RLU/ml) versus colony forming units (CFU/ml), bacterial counts were also measured on 7H10 plates. A similar ratio of RLU units with the CFU counts was observed after plating the day 2 and day 4 samples on 7H10 plates. The reduction in CFU counts compared with that of untreated control showed that final compound 12  
25 at 10 µg/ml, 1 µg/ml and 0.1 µg/ml reduced the viability by approximately 4, 2.3, and 0.5 log<sub>10</sub> at day 2 and about 6, 4.7 and 1.1 log<sub>10</sub> at day 5 respectively. Fig 2 (A and B) reports CFU data. A close correlation was observed between luminescence and the CFU during various stages of the experiment. Interestingly there was marked reduction in RLUs at time point 0 as compared to CFU counts, primarily because ATP  
30 concentration within these cells is very low, which has been shown to be the characteristics of the metabolic state of the dormant bacilli<sup>8</sup>.

The activity of final compound 12 on dormant (non-multiplying) mycobacteria is an extremely important finding, as it will help in the fight against tuberculosis by eradicating the disease in individuals who are at risk of developing TB.

35

**B. Study of the effect of present compounds in killing dormant *Mycobacterium tuberculosis* according to the Wayne dormancy model\***

**Bacterial strain and Culture medium**

*Mycobacterium tuberculosis* (H37RV) was cultured in Middlebrook medium with  
5 0.05% Tween.

To prepare Middlebrook 7H9 Broth (1X) (BD 271310) with supplements :dissolve 4.7 g of the Middlebrook powder in 895 ml distilled water and add 5 ml Glycerol, 200 µl Tween 80 and autoclave at 121 °C for 15 minutes. Aseptically add 100 ml Middlebrook OADC Enrichment (BD 211886) to the medium when cooled to 45 °C.  
10 Store at 4 °C for maximum 1 month. Pre-incubate all media 2 days at 37 °C to check for contamination.

\* Wayne L.G. et al.; Infection and Immunity 64 (6), 2062-2069 (1996)

15 **Study with *Mycobacterium tuberculosis* (H37RV)**

**Dormancy assay**

1000 µl of *Mycobacterium tuberculosis* stock (previous culture) was added to 100 ml Middlebrook 7H9 broth with supplements in a 250 ml sterile Duran bottle with a magnetic stirring rod. Incubation was done on an electric magnetic stirrer for 7 days at  
20 37 °C (500 rpm). 17 ml aliquots of log phase culture (calculated OD<sub>600nm</sub> = 0.01) were transferred into 25 ml tubes. The tubes were tightly closed with caps with rubber septa and incubated on a magnetic stirring plate to create anaerobiosis by oxygen depletion. Stirring in the tubes was achieved with 8 mm teflon stirring bar. The tubes were incubated for 22 days at 37 °C in an incubator on a magnetic stirring plate (120 rpm)  
25 until anaerobiosis (methylene blue (1.5 mg/liter) is turned to colourless). After 14 days various drugs (final concentration of 100, 10, 1 and 0.1 µg/ml) were added to the individual tubes. Metronidazole was added as control to kill the dormant bacteria (added at start). Isoniazid was added as control to show that it does not have any effect on growth and viability of dormant bacteria.

30

**CFU assay**

After 22 days, the cultures were collected by low speed centrifugation (2000 rpm for 10 minutes). The cells were washed twice with drug free medium and the cells were resuspended in drug-free medium and incubated. The reduction in CFU compared to  
35 untreated control cultures, was determined by plating after anaerobiosis to evaluate the bactericidal activity.

**Experimental organization**

| Sample number | Sample / Compound | $\mu\text{g} / \text{ml}$ |
|---------------|-------------------|---------------------------|
| 1 - 2         | Control           | -                         |
| 3 - 4         | Metronidazole     | 100                       |
| 5 - 6         | Isoniazid         | 10                        |
| 7 - 8         | Moxifloxacin      | 10                        |
| 9 - 10        |                   | 1                         |
| 11 - 12       | Final compound 12 | 10                        |
| 13 - 14       |                   | 1                         |
| 15 - 16       | Rifampicin        | 10                        |
| 17 - 18       |                   | 1                         |

**Results and Discussion:**

The effect of the final compound 12 on dormant bacteria is demonstrated (see Fig. 3) using the Wayne dormancy model. As already indicated above, it is an *in vitro* oxygen depletion model, which triggers a dormancy response in the bacteria<sup>18-23</sup>. In Wayne model, cultures of the bacterium are subjected to the gradual oxygen depletion by incubation in stirred sealed tubes. With slow shift of the aerobic growing bacteria to anaerobic conditions, the culture is more capable to adapt and survive the anaerobiosis by shifting down to a state of anaerobic persistence. Wayne model is a well-characterized *in vitro* model for dormancy.

At 10 $\mu\text{g}/\text{ml}$  concentration of final compound 12, more than 2 log<sub>10</sub> reduction of the dormant bacteria was observed as also seen in case of moxifloxacin and rifampin. At 1 $\mu\text{g}/\text{ml}$  concentration, 1.41 log<sub>10</sub> reduction was observed for compound 12.

Compounds 71, 75, 172 and 125 were also tested in the same test. At 10 $\mu\text{g}/\text{ml}$  concentration, more than 2 log<sub>10</sub> reduction of the dormant bacteria was observed for compound 71; 1.14 log<sub>10</sub> reduction was observed for compound 75; 0.98 log<sub>10</sub> reduction was observed for compound 172; 0.23 log<sub>10</sub> reduction was observed for compound 125. At 1 $\mu\text{g}/\text{ml}$  concentration, 1.55 log<sub>10</sub> reduction was observed for compound 71; 0.87 log<sub>10</sub> reduction was observed for compound 75; 0.29 log<sub>10</sub> reduction was observed for compound 172.

Isoniazid did not have any effect on dormant bacteria while the control compound, metronidazole showed good efficacy.

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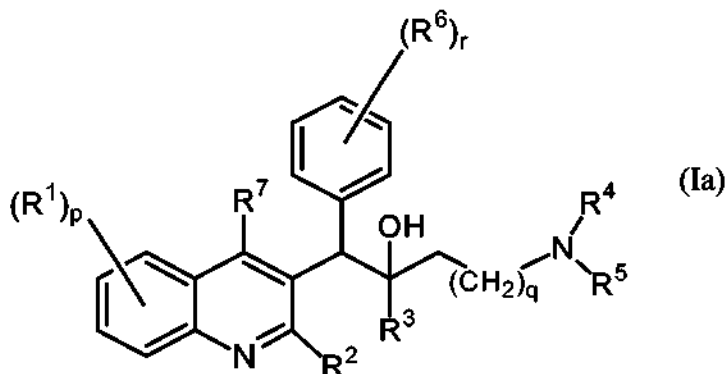
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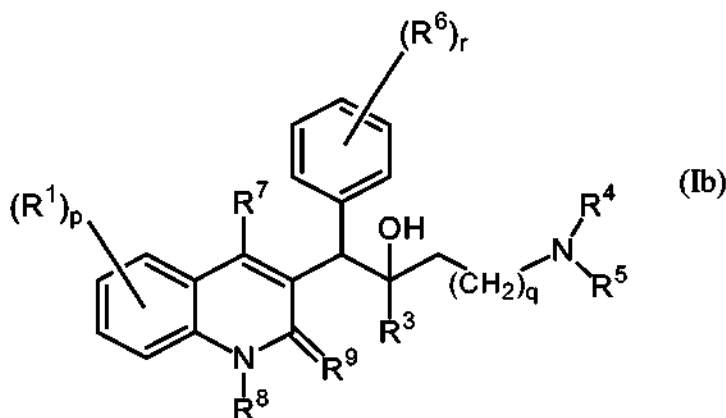
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**Claims**

1. Use of a compound of formula (Ia) or (Ib) for the manufacture of a medicament for the treatment of latent tuberculosis, wherein the compound of formula (Ia) or (Ib) is

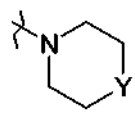


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a pharmaceutically acceptable acid or base addition salt thereof, a quaternary amine thereof, a *N*-oxide thereof, a tautomeric form thereof or a stereochemically isomeric form thereof wherein

- 10  $R^1$  is hydrogen, halo, haloalkyl, cyano, hydroxy, Ar, Het, alkyl, alkyloxy, alkylthio, alkyloxyalkyl, alkylthioalkyl, Ar-alkyl or di(Ar)alkyl ;
- $p$  is an integer equal to 1, 2, 3 or 4 ;
- $R^2$  is hydrogen, hydroxy, mercapto, alkyloxy, alkyloxyalkyloxy, alkylthio,

mono or di(alkyl)amino or a radical of formula  wherein Y is  $CH_2$ , O, S, NH or *N*-alkyl ;

- 15  $R^3$  is alkyl, Ar, Ar-alkyl, Het or Het-alkyl;
- $q$  is an integer equal to zero, 1, 2, 3 or 4 ;
- $R^4$  and  $R^5$  each independently are hydrogen, alkyl or benzyl; or

- R<sup>4</sup> and R<sup>5</sup> together and including the N to which they are attached may form a radical selected from the group of pyrrolidinyl, 2-pyrrolinyl, 3-pyrrolinyl, pyrrolyl, imidazolidinyl, pyrazolidinyl, 2-imidazoliny, 2-pyrazolinyl, imidazolyl, pyrazolyl, triazolyl, piperidinyl, pyridinyl, piperazinyl, pyridazinyl, pyrimidinyl, pyrazinyl, triazinyl, morpholinyl and thiomorpholinyl, each of said ring systems optionally substituted with alkyl, halo, haloalkyl, hydroxy, alkyloxy, amino, mono- or dialkylamino, alkylthio, alkyloxyalkyl, alkylthioalkyl and pyrimidinyl ;
- R<sup>6</sup> is hydrogen, halo, haloalkyl, hydroxy, Ar, alkyl, alkyloxy, alkylthio, alkyloxyalkyl, alkylthioalkyl, Ar-alkyl or di(Ar)alkyl ; or two vicinal R<sup>6</sup> radicals may be taken together to form a bivalent radical of formula -CH=CH-CH=CH- ;
- r is an integer equal to 1, 2, 3, 4 or 5 ;
- R<sup>7</sup> is hydrogen, alkyl, Ar or Het ;
- R<sup>8</sup> is hydrogen or alkyl ;
- R<sup>9</sup> is oxo ; or
- R<sup>8</sup> and R<sup>9</sup> together form the radical =N-CH=CH-;
- alkyl is a straight or branched saturated hydrocarbon radical having from 1 to 6 carbon atoms ; or is a cyclic saturated hydrocarbon radical having from 3 to 6 carbon atoms ; or is a cyclic saturated hydrocarbon radical having from 3 to 6 carbon atoms attached to a straight or branched saturated hydrocarbon radical having from 1 to 6 carbon atoms ; wherein each carbon atom can be optionally substituted with halo, hydroxy, alkyloxy or oxo ;
- Ar is a homocycle selected from the group of phenyl, naphthyl, acenaphthyl, tetrahydronaphthyl, each homocycle optionally substituted with 1, 2 or 3 substituents, each substituent independently selected from the group of hydroxy, halo, cyano, nitro, amino, mono- or dialkylamino, alkyl, haloalkyl, alkyloxy, haloalkyloxy, carboxyl, alkyloxycarbonyl, aminocarbonyl, morpholinyl and mono- or dialkylaminocarbonyl ;
- Het is a monocyclic heterocycle selected from the group of *N*-phenoxy piperidinyl, piperidinyl, pyrrolyl, pyrazolyl, imidazolyl, furanyl, thienyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, pyridinyl, pyrimidinyl, pyrazinyl and pyridazinyl; or a bicyclic heterocycle selected from the group of quinolinyl, quinoxalinyl, indolyl, benzimidazolyl, benzoxazolyl, benzisoxazolyl, benzothiazolyl, benzisothiazolyl, benzofuranyl, benzothienyl, 2,3-dihydrobenzo[1,4]dioxinyl or benzo[1,3]dioxolyl ; each monocyclic and



bicyclic heterocycle may optionally be substituted with 1, 2 or 3 substituents selected from the group of halo, hydroxy, alkyl, alkyloxy or Ar-carbonyl;

halo is a substituent selected from the group of fluoro, chloro, bromo and iodo; and

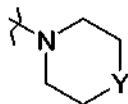
haloalkyl is a straight or branched saturated hydrocarbon radical having from 1 to 6 carbon atoms or a cyclic saturated hydrocarbon radical having from 3 to 6 carbon atoms, wherein one or more carbon atoms are substituted with one or more halo-atoms.

2. Use according to claim 1 wherein

10  $R^1$  is hydrogen, halo, cyano, Ar, Het, alkyl, and alkyloxy ;

p is an integer equal to 1 or 2;

$R^2$  is hydrogen, hydroxy, alkyloxy, alkyloxyalkyloxy, alkylthio or a radical



of formula wherein Y is O;

$R^3$  is alkyl, Ar, Ar-alkyl or Het ;

15 q is an integer equal to zero, 1, 2, or 3 ;

$R^4$  and  $R^5$  each independently are hydrogen, alkyl or benzyl; or

$R^4$  and  $R^5$  together and including the N to which they are attached may form a radical selected from the group of pyrrolidinyl, imidazolyl, triazolyl, piperidinyl, piperazinyl, pyrazinyl, morpholinyl and thiomorpholinyl, each ring system optionally substituted with alkyl or pyrimidinyl ;

20  $R^6$  is hydrogen, halo or alkyl ; or

two vicinal  $R^6$  radicals may be taken together to form a bivalent radical of formula  $-\text{CH}=\text{CH}-\text{CH}=\text{CH}-$  ;

r is an integer equal to 1 ;

25  $R^7$  is hydrogen ;

$R^8$  is hydrogen or alkyl ;

$R^9$  is oxo ; or

$R^8$  and  $R^9$  together form the radical  $=\text{N}-\text{CH}=\text{CH}-$ ;

alkyl is a straight or branched saturated hydrocarbon radical having from 1 to 6 carbon atoms ; or is a cyclic saturated hydrocarbon radical having from 3 to 6 carbon atoms ; or is a a cyclic saturated hydrocarbon radical having from 3 to 6 carbon atoms attached to a straight or branched saturated hydrocarbon radical having from 1 to 6 carbon atoms ; wherein each carbon atom can be optionally substituted with halo or hydroxy ;

- Ar is a homocycle selected from the group of phenyl, naphthyl, acenaphthyl, tetrahydronaphthyl, each homocycle optionally substituted with 1, 2 or 3 substituents, each substituent independently selected from the group of halo, haloalkyl, cyano, alkyloxy and morpholinyl ;
- 5 Het is a monocyclic heterocycle selected from the group of *N*-phenoxypiperidinyl, piperidinyl, furanyl, thienyl, pyridinyl, pyrimidinyl ; or a bicyclic heterocycle selected from the group of benzothienyl, 2,3-dihydrobenzo[1,4]dioxinyl or benzo[1,3]dioxolyl; each monocyclic and bicyclic heterocycle may optionally be substituted with 1, 2 or 3 alkyl or Ar-carbonyl substituents ; and
- 10 halo is a substituent selected from the group of fluoro, chloro and bromo.
3. Use according to claim 1 or 2 wherein in formula (Ia) or (Ib) R<sup>1</sup> is hydrogen, halo, Ar, alkyl or alkyloxy.
- 15 4. Use according to claim 3 wherein R<sup>1</sup> is halo.
5. Use according to any one of the preceding claims wherein in formula (Ia) or (Ib) p is equal to 1.
- 20 6. Use according to any one of the preceding claims wherein in formula (Ia) or (Ib) R<sup>2</sup> is hydrogen, alkyloxy or alkylthio.
7. Use according to claim 6 wherein R<sup>2</sup> is alkyloxy.
- 25 8. Use according to any one of the preceding claims wherein in formula (Ia) or (Ib) R<sup>3</sup> is naphthyl, phenyl or thienyl, each optionally substituted with 1 or 2 substituents selected from the group of halo and haloalkyl.
9. Use according to claim 8 wherein R<sup>3</sup> is naphthyl.
- 30 10. Use according to any one of the preceding claims wherein in formula (Ia) or (Ib) q is equal to 1.
- 35 11. Use according to any one of the preceding claims wherein in formula (Ia) or (Ib) R<sup>4</sup> and R<sup>5</sup> each independently are hydrogen or alkyl or R<sup>4</sup> and R<sup>5</sup> together and including the N to which they are attached form a radical selected from the group of imidazolyl, triazolyl, piperidinyl, piperazinyl and thiomorpholinyl.

12. Use according to claim 11 wherein in formula (Ia) or (Ib) R<sup>4</sup> and R<sup>5</sup> each independently are hydrogen or alkyl.
- 5 13. Use according to claim 12 wherein R<sup>4</sup> and R<sup>5</sup> are C<sub>1-4</sub>alkyl.
14. Use according to any one of the preceding claims wherein in formula (Ia) or (Ib) R<sup>6</sup> is hydrogen, alkyl or halo.
- 10 15. Use according to claim 14 wherein R<sup>6</sup> is hydrogen.
16. Use according to any one of the preceding claims wherein in formula (Ia) or (Ib) r is equal to 1.
- 15 17. Use according to any one of the preceding claims wherein in formula (Ia) or (Ib) R<sup>7</sup> is hydrogen.
18. Use according to claim 1 wherein in formula (Ia) or (Ib) R<sup>1</sup> is hydrogen, halo, Ar, alkyl or alkyloxy; p = 1; R<sup>2</sup> is hydrogen, alkyloxy or alkylthio; R<sup>3</sup> is naphthyl, phenyl or thienyl, each optionally substituted with 1 or 2 substituents selected from the group of halo and haloalkyl; q = 0, 1, 2 or 3; R<sup>4</sup> and R<sup>5</sup> each independently are hydrogen or alkyl or R<sup>4</sup> and R<sup>5</sup> together and including the N to which they are attached form a radical selected from the group of imidazolyl, triazolyl, piperidinyl, piperazinyl and thiomorpholinyl; R<sup>6</sup> is hydrogen, alkyl or halo; r is equal to 1 and R<sup>7</sup> is hydrogen.
- 20
- 25
19. Use according to any one of the preceding claims wherein alkyl represents C<sub>1-6</sub>alkyl.
- 30 20. Use according to any one of the preceding claims wherein haloalkyl represents polyhaloC<sub>1-6</sub>alkyl.
21. Use according to claim 1, characterized in that the compound is selected from the group consisting of :
- 35     ○ 1-(6-bromo-2-methoxy-quinolin-3-yl)-2-(3,5-difluoro-phenyl)-4-dimethylamino-1-phenyl-butan-2-ol ;

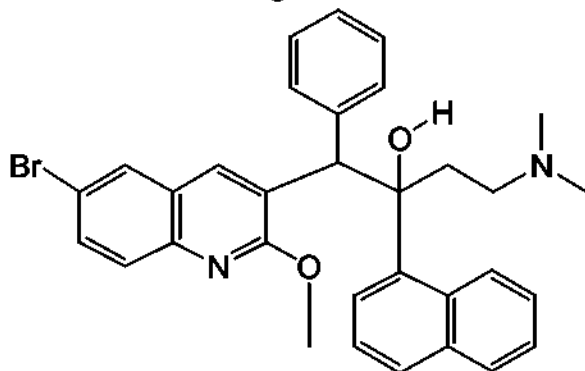
- 1-(6-bromo-2-methoxy-quinolin-3-yl)-4-dimethylamino-2-naphthalen-1-yl-1-phenyl-butan-2-ol ;
- 1-(6-bromo-2-methoxy-quinolin-3-yl)-2-(2,5-difluoro-phenyl)-4-dimethylamino-1-phenyl-butan-2-ol ;
- 5 ○ 1-(6-bromo-2-methoxy-quinolin-3-yl)-2-(2,3-difluoro-phenyl)-4-dimethylamino-1-phenyl-butan-2-ol ;
- 1-(6-bromo-2-methoxy-quinolin-3-yl)-4-dimethylamino-2-(2-fluoro-phenyl)-1-phenyl-butan-2-ol ;
- 1-(6-bromo-2-methoxy-quinolin-3-yl)-4-dimethylamino-2-naphthalen-1-yl-1-*p*-tolyl-butan-2-ol ;
- 10 ○ 1-(6-bromo-2-methoxy-quinolin-3-yl)-4-methylamino-2-naphthalen-1-yl-1-phenyl-butan-2-ol ;
- 1-(6-bromo-2-methoxy-quinolin-3-yl)-4-dimethylamino-2-(3-fluoro-phenyl)-1-phenyl-butan-2-ol; and
- 15 ○ 1-(6-bromo-2-methoxy-quinolin-3-yl)-4-dimethylamino-2-phenyl-1-phenyl-butan-2-ol;

a pharmaceutically acceptable acid or base addition salt thereof, a *N*-oxide thereof, a tautomeric form thereof or a stereochemically isomeric form thereof.

- 20 22. Use according to claim 1 wherein the compound is selected from the group consisting of
- 1-(6-bromo-2-methoxy-quinolin-3-yl)-2-(2,3-difluoro-phenyl)-4-dimethylamino-1-phenyl-butan-2-ol ;
  - 1-(6-bromo-2-methoxy-quinolin-3-yl)-4-dimethylamino-2-naphthalen-1-yl-1-phenyl-butan-2-ol;

25 a pharmaceutically acceptable acid or base addition salt thereof, a *N*-oxide thereof, a tautomeric form thereof or a stereochemically isomeric form thereof.

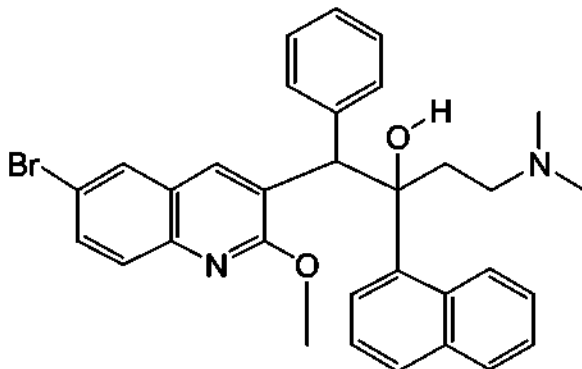
23. Use according to claim 1 wherein the compound is



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a pharmaceutically acceptable acid or base addition salt thereof, a *N*-oxide thereof, or a stereochemically isomeric form thereof.

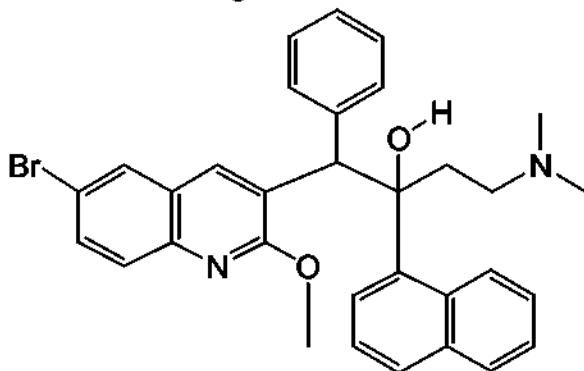
24. Use according to claim 23 wherein the compound is



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or a pharmaceutically acceptable acid addition salt thereof.

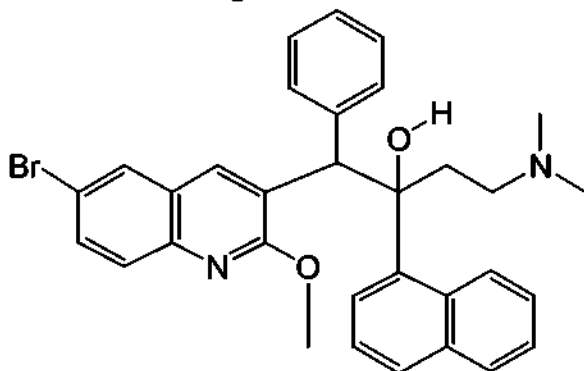
25. Use according to claim 23 wherein the compound is



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or a stereochemically isomeric form thereof.

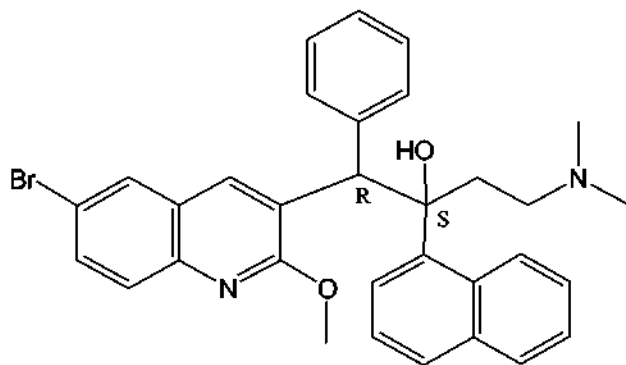
26. Use according to claim 23 wherein the compound is



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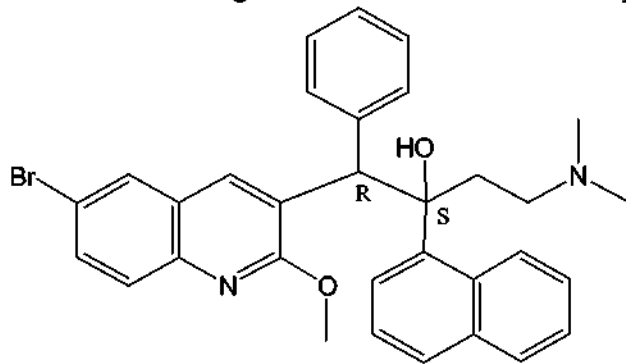
or a *N*-oxide form thereof.

27. Use according to claim 23 wherein the compound is



or a pharmaceutically acceptable acid addition salt thereof.

28. Use according to claim 27 wherein the compound is



5

10

FIGURE 1

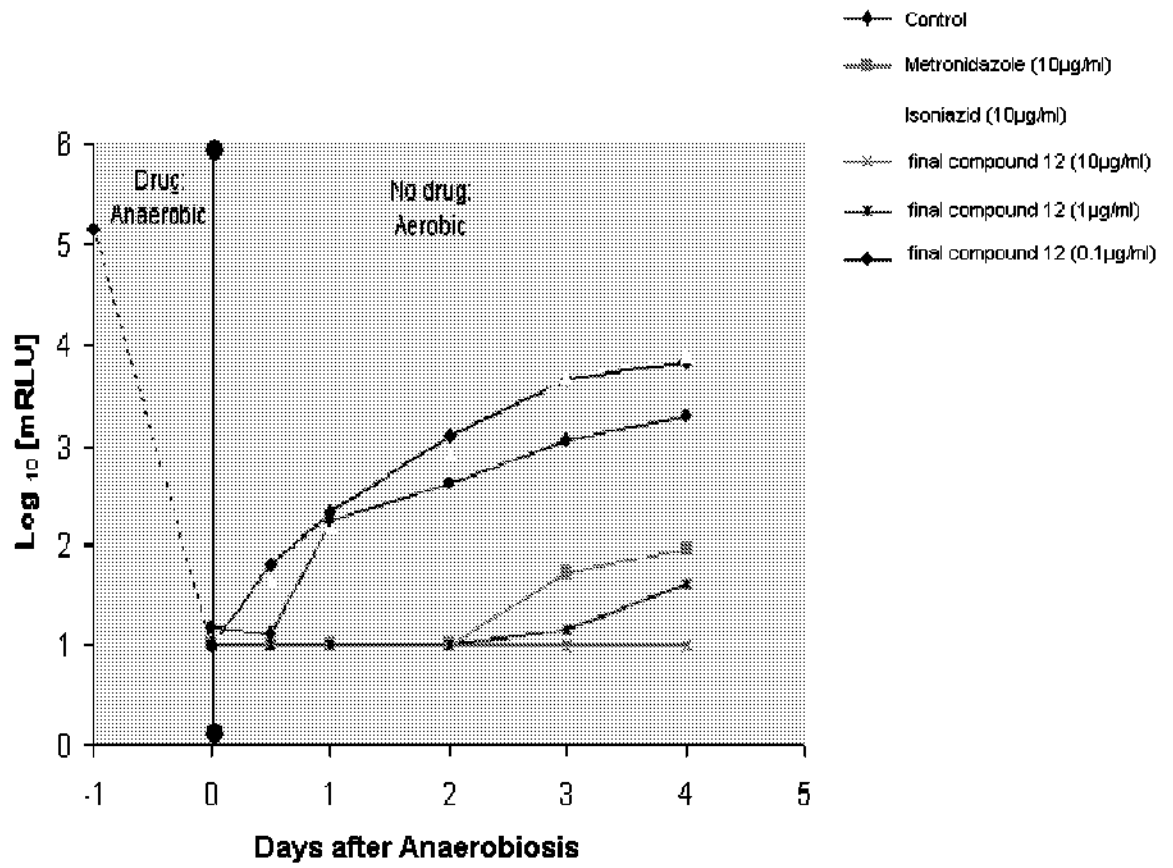
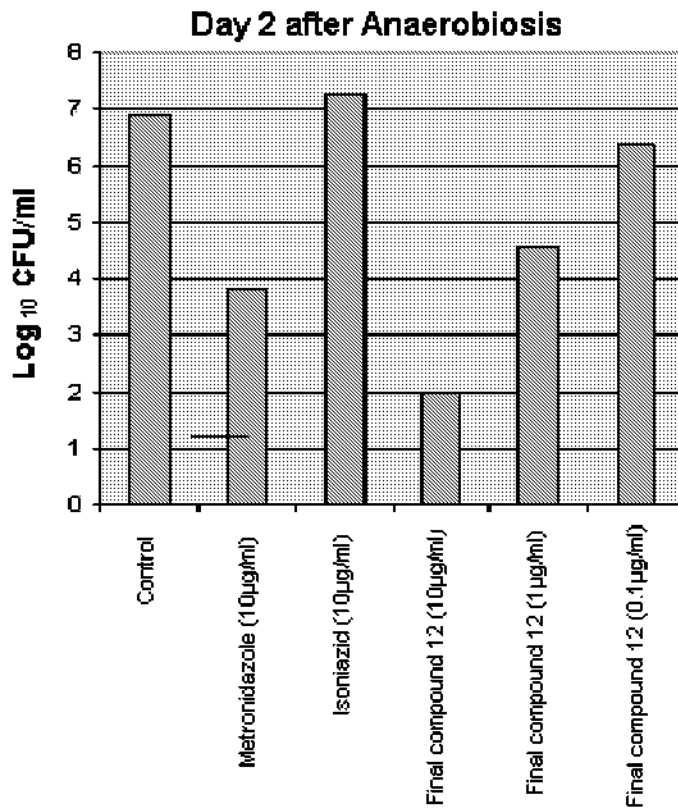
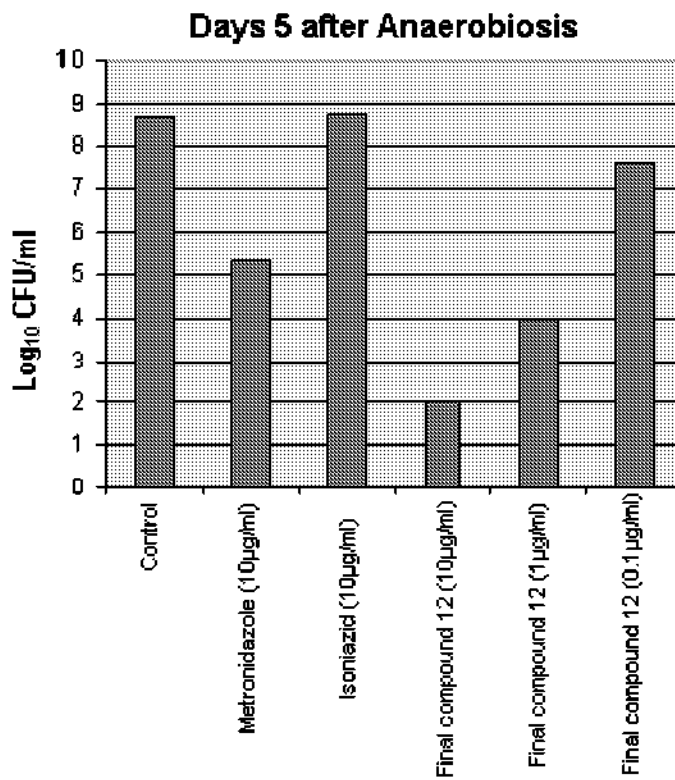


FIGURE 2

A)



B)





Effect of various drugs on dormant *M. tuberculosis* (Wayne model); n=2;

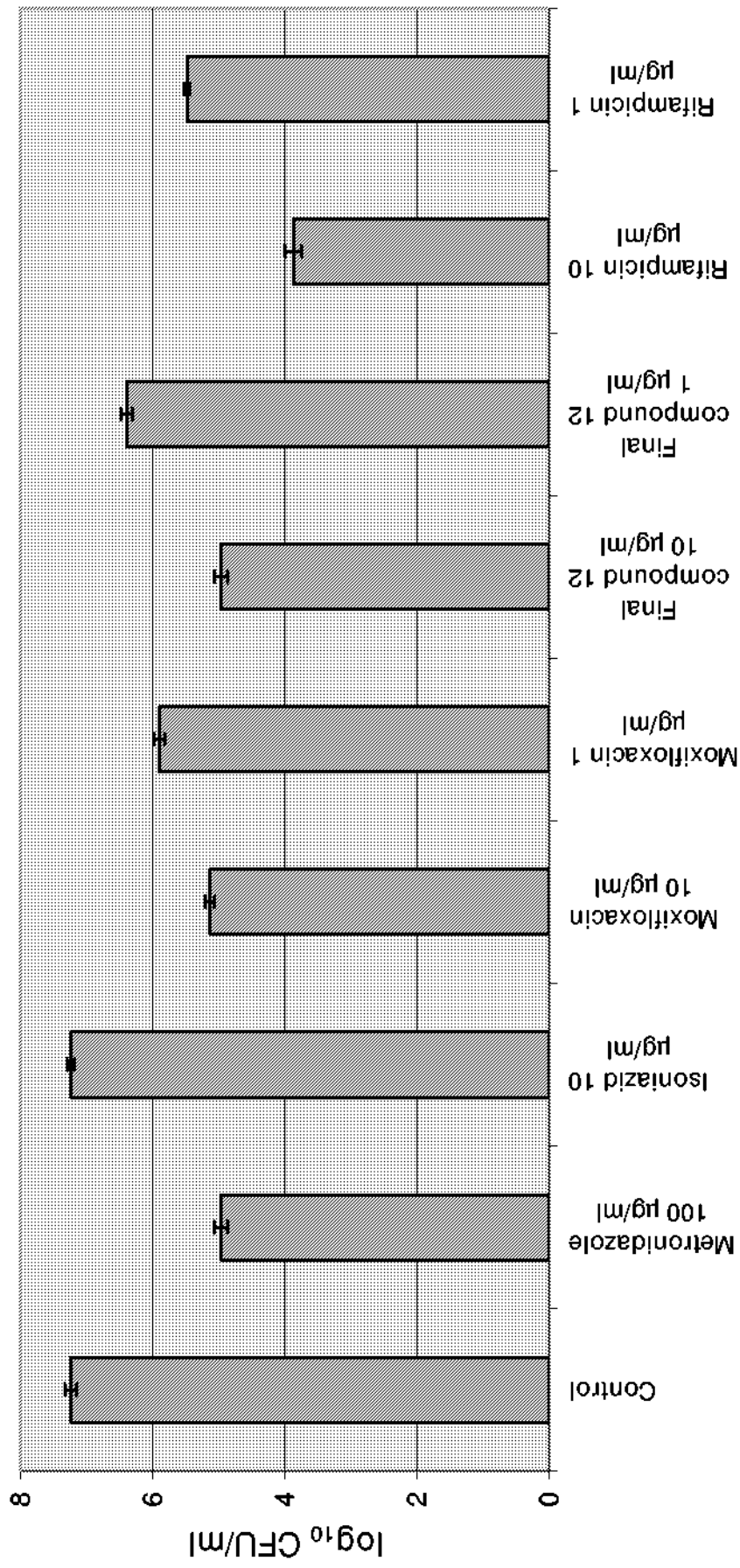


FIGURE 3

## INTERNATIONAL SEARCH REPORT

International application No  
PCT/EP2005/056594A. CLASSIFICATION OF SUBJECT MATTER  
A61K31/47 A61K31/4704 A61P31/06

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)  
A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ, BIOSIS, EMBASE, CHEM ABS Data

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages  | Relevant to claim No. |
|-----------|---|-----------------------|
| A         | WO 2004/011436 A (JANSSEN PHARMACEUTICA N.V; VAN GESTEL, JOZEF, FRANS, ELISABETHA; GUILL) 5 February 2004 (2004-02-05)<br>cited in the application<br>the whole document  | 1-28                  |
| A         | -----<br>NUERMBERGER ERIC ET AL: "Latent tuberculosis infection."<br>SEMINARS IN RESPIRATORY AND CRITICAL CARE MEDICINE. JUN 2004,<br>vol. 25, no. 3, June 2004 (2004-06), pages 317-336, XP009061348<br>ISSN: 1069-3424<br>the whole document<br>-----<br>-/-- | 1-28                  |

 Further documents are listed in the continuation of Box C. See patent family annex.

## \* Special categories of cited documents:

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- \*X\* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
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- \*&\* document member of the same patent family

Date of the actual completion of the international search

15 February 2006

Date of mailing of the international search report

23/02/2006

Name and mailing address of the ISA/

European Patent Office, P.B. 5818 Patentlaan 2  
NL - 2280 HV Rijswijk  
Tel: (+31-70) 340-2040, Tx. 31 651 epo nl,  
Fax: (+31-70) 340-3016

Authorized officer

Paul Soto, R

## INTERNATIONAL SEARCH REPORT

International application No  
PCT/EP2005/056594

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages   | Relevant to claim No. |
|-----------|--|-----------------------|
| A,P       | ANDRIES K ET AL: "A DIARYLQUINOLINE DRUG ACTIVE ON THE ATP SYNTHASE OF MYCOBACTERIUM TUBERCULOSIS" SCIENCE, AMERICAN ASSOCIATION FOR THE ADVANCEMENT OF SCIENCE,, US, vol. 307, 14 January 2005 (2005-01-14), pages 223-227, XP002358962 ISSN: 0036-8075 the whole document<br>----- | 1-28                  |

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No  
PCT/EP2005/056594

| Patent document cited in search report |   | Publication date |    | Patent family member(s) | Publication date |
|--|---|------------------|----|-------------------------|------------------|
| WO 2004011436                          | A | 05-02-2004       | AU | 2003262529 A1           | 16-02-2004       |
|  |   |                  | CA | 2493225 A1              | 05-02-2004       |
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|  |   |                  | EP | 1527050 A1              | 04-05-2005       |
|  |   |                  | NZ | 538391 A                | 28-10-2005       |

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- (21) **International Application Number:**  
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- (22) **International Filing Date:**  
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- (25) **Filing Language:** English
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- (30) **Priority Data:**
- |                   |                               |    |
|-------------------|-------------------------------|----|
| PI20043578        | 2 September 2004 (02.09.2004) | MY |
| PCT/EP2004/052028 |                               |    |
|                   | 3 September 2004 (03.09.2004) | EP |
| 05101447.0        | 25 February 2005 (25.02.2005) | EP |
- (71) **Applicants (for all designated States except US):** JANSSEN PHARMACEUTICA N.V. [BE/BE]; Turnhoutseweg 30, B-2340 Beerse (BE). TIBOTEC PHARMACEUTICALS LTD. [IE/IE]; Little Island, Co Cork (IE).
- (72) **Inventors; and**
- (75) **Inventors/Applicants (for US only):** STEVENS, Paul, Theodoor, Agnes [BE/BE]; c/o Janssen Pharmaceutica N.V., Turnhoutseweg 30, B-2340 Beerse (BE). PEETERS, Jozef [BE/BE]; c/o Janssen Pharmaceutica N.V., Turnhoutseweg 30, B-2340 Beerse (BE). VANDECRUYS, Roger, Petrus, Gerebern [BE/BE]; c/o Janssen Pharmaceutica N.V., Turnhoutseweg 30, B-2340 Beerse (BE). STAPPERS, Alfred, Elisabeth [BE/BE]; c/o Janssen Pharmaceutica N.V., Turnhoutseweg 30, B-2340 Beerse (BE).
- (74) **Common Representative:** JANSSEN PHARMACEUTICA N.V.; Turnhoutseweg 30, B-2340 Beerse (BE).
- (81) **Designated States (unless otherwise indicated, for every kind of national protection available):** AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.
- (84) **Designated States (unless otherwise indicated, for every kind of regional protection available):** ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).
- Published:**  
— with international search report
- For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.*

(54) **Title:** FURAMATE OF 4-(4-(4-(2-CYANOETHENYL)-2,6-DIMETHYLPHENYL)AMINO)-2-PYRIMIDINYL)AMINO)BENZONITRILE(57) **Abstract:** The present invention relates to the fumarate salt of 4-[[4-[[4-(2-cyanoethenyl)-2,6-dimethylphenyl]amino]-2-pyrimidinyl]amino]benzonitrile, pharmaceutical compositions comprising as active ingredient said salt and to processes for their preparation.

WO 2006/024667 A1

FURAMATE OF 4-((4-((4-(2-CYANOETHENYL)-2,6-DIMETHYLPHENYL) AMINO)-2-PYRIMIDINYL) AMINO) BENZONITRILE

---

5 The present invention relates to the fumarate salt of 4-[[4-[[4-(2-cyanoethenyl)-2,6-dimethylphenyl]amino]-2-pyrimidinyl]amino]benzonnitrile, pharmaceutical compositions comprising said fumarate salt, to the preparation of the salt and the pharmaceutical compositions.

10 WO 03/16306 discloses HIV replication inhibiting pyrimidine derivatives among which 4-[[4-[[4-(2-cyanoethenyl)-2,6-dimethylphenyl]amino]-2-pyrimidinyl]amino]-benzonnitrile and the pharmaceutically acceptable salts thereof.

WO 04/0162581 disclose processes to prepare 4-[[4-[[4-(2-cyanoethenyl)-2,6-dimethylphenyl]amino]-2-pyrimidinyl]amino]benzonnitrile.

15

4-[[4-[[4-(2-cyanoethenyl)-2,6-dimethylphenyl]amino]-2-pyrimidinyl]amino]-benzonnitrile, in particular the E-isomer, has excellent HIV replication inhibiting activity against the wild type of HIV as well as drug and multi drug resistant strains of HIV (i.e. strains which have become resistant to art-known drug(s)). The compound has thus  
20 potential to be a good candidate for the development of a medicament for the treatment of HIV infection.

High pharmacological activity, a good pharmacological profile is however not the only factor which determines the drugability of a compound.

25 A good drug candidate should preferably also be stable chemically as well as physically; should have an acceptable toxicity profile; should have an acceptable bioavailability.

The bioavailability of the compound influences the dose of the compound required for  
30 administration in order to reach a therapeutically effective concentration of the compound in the patient. Compounds having a low bioavailability need to be administered in higher doses compared to compounds having a higher bioavailability. Possible consequences of the need for higher doses may comprise : an increased risk to adverse effects; an increase in the size of the dosage form; an increase in the frequency  
35 of administration. These factors may influence adherence to antiretroviral therapy.

Therapy adherence is one of the most important factors influencing the effectiveness of HIV treatment. Increase in dosing frequency and increase in pill size may lead to reduced therapy adherence and hence reduced therapy effectiveness.

- 5 Therefore, when designing a medicament for HIV treatment it is preferable to have an active compound with an acceptable bioavailability.

The bioavailability of a compound intended to be administered orally, is dependent on the compounds solubility in water as well as the compounds permeability (its ability to  
10 be absorbed across the intestinal membrane).

A scientific framework for classifying drug substances based on their aqueous solubility and intestinal permeability is the Biopharmaceutics Classification System or BCS. According to the BCS, drug substances are classified as follows:

- 15                   Class 1: High Solubility - High Permeability  
                    Class 2: Low Solubility - High Permeability  
                    Class 3: High Solubility - Low Permeability  
                    Class 4: Low Solubility - Low Permeability

- 20 Compounds with a low solubility or a low permeability (class 2 to 4) may suffer from a low bioavailability when administered orally.

Free base 4-[[4-[[4-(2-cyanoethenyl)-2,6-dimethylphenyl]amino]-2-pyrimidinyl]-  
amino]benzotrile can be classified as a BCS class 2 compound and has thus a low  
25 solubility in water. 4-[[4-[[4-(2-cyanoethenyl)-2,6-dimethylphenyl]amino]-2-  
pyrimidinyl]amino]benzotrile does not only exhibit a low solubility in water, but also  
in an acidic environment. Consequently, when administered orally in a conventional  
solid dosage form, a low bioavailability may be expected.

- 30 When confronted with a BCS class 2 compound intended for oral administration, a person skilled in pharmaceutical technology would turn to exploring possibilities for improving the compound's solubility, for instance by preparing an appropriate salt.

This route was also followed for 4-[[4-[[4-(2-cyanoethenyl)-2,6-dimethylphenyl]-amino]-2-pyrimidinyl]amino]benzonitrile.

The prepared salts appeared to have only a slight improved solubility in water and in HCl. The prepared salts still belong to BCS class 2. Thus, also for the prepared salts a  
5 low bioavailability could be expected.

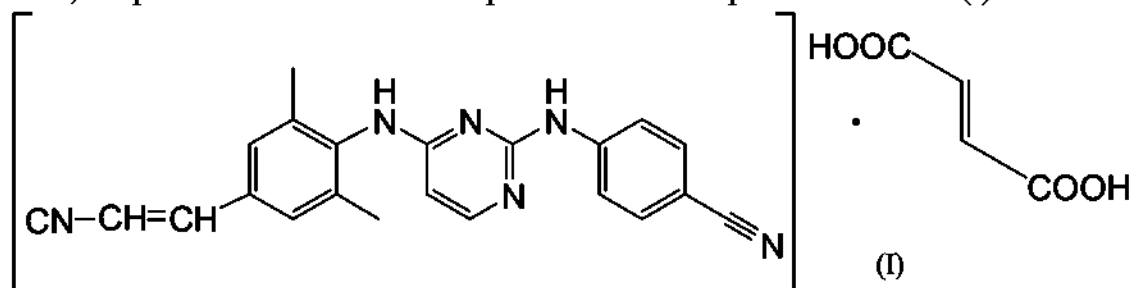
Unexpectedly, it has now been found that the fumarate salt (trans  
CH(COOH)=CH(COOH)) of 4-[[4-[[4-(2-cyanoethenyl)-2,6-dimethylphenyl]amino]-2-  
pyrimidinyl]amino]benzonitrile, in particular its E-isomer, has a significant improved  
10 *in vivo* bioavailability compared to the free base. In fact, the present salt administered  
as a solid dosage form has an *in vivo* bioavailability which is comparable with the  
bioavailability of the free base administered as an oral PEG 400 solution.  
Because of the increased bioavailability *in vivo*, the fumarate salt may be formulated  
without the need of complex formulation techniques.

15

The fumarate salt of the present invention was also found to be non-hygroscopic and to  
be chemically and physically stable in different conditions of humidity and  
temperatures.

20 Therefore, the present invention relates to a compound of formula (I), i.e. the fumarate  
(trans CH(COOH)=CH(COOH)) salt of 4-[[4-[[4-(2-cyanoethenyl)-2,6-dimethyl-  
phenyl]amino]-2-pyrimidinyl]amino]benzonitrile, a *N*-oxide or a stereochemically  
isomeric form thereof.

25 Thus, the present invention relates in particular to a compound of formula (I)



a *N*-oxide or a stereochemically isomeric form thereof.

The *N*-oxide forms of the present compound of formula (I) are meant to comprise the  
30 compounds of formula (I) wherein one or several tertiary nitrogen atoms are oxidized  
to the so-called *N*-oxide.



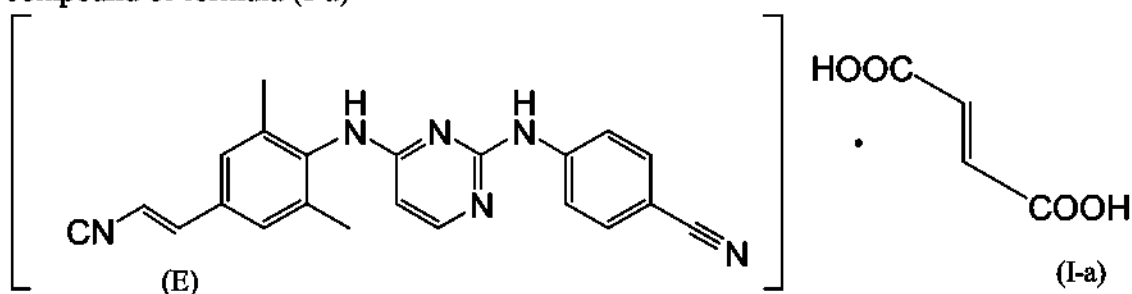
The term "stereochemically isomeric forms" as used hereinbefore defines all the possible stereoisomeric forms which the compound of formula (I), and the *N*-oxides, or quaternary amines may possess. Unless otherwise mentioned or indicated, the chemical designation of the compound denotes the mixture of all possible

5 stereochemically isomeric forms as well as each of the individual isomeric forms of formula (I) and the *N*-oxides, solvates or quaternary amines substantially free of the other isomers. Stereochemically isomeric forms of the compound of formula (I) are obviously intended to be embraced within the scope of this invention.

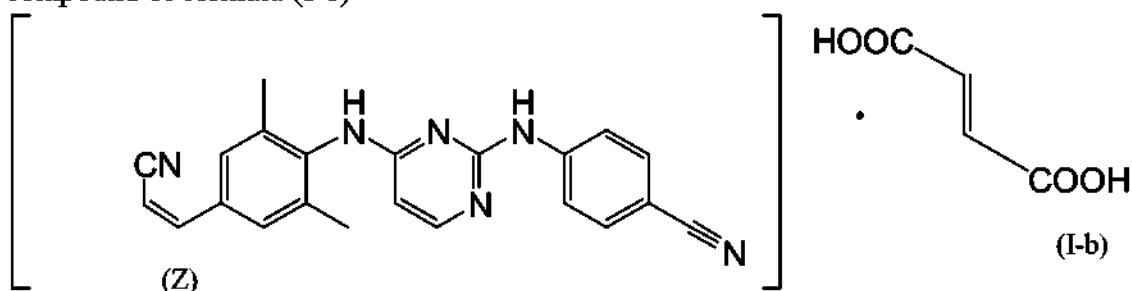
- 10 The compound of formula (I) may exist in 2 stereochemical configurations at the double bond of the cyanoethenyl chain, i.e. the E (Entgegen) configuration (E-isomer) and the Z (Zusammen) configuration (Z isomer).

The terms E and Z are well known to a person skilled in the art.

- 15 A particular embodiment of the compound of formula (I) is the E-isomer, i.e. a compound of formula (I-a)



- 20 Another particular embodiment of the compound of formula (I) is the Z-isomer, i.e. a compound of formula (I-b)



- Whenever reference is made herein to the E-isomer, the pure E-isomer or any isomeric mixture of the E- and the Z-isomers wherein the E-isomer is predominantly present is meant, i.e. an isomeric mixture containing more than 50% or in particular more than
- 25 80% of the E-isomer, or even more in particular more than 90% of the E-isomer. Of particular interest is the E-isomer substantially free of the Z-isomer. Substantially free

in this context refers to E-Z-mixtures with no or almost no Z-isomer, e.g. isomeric mixtures containing as much as 90%, in particular 95% or even 98% or 99% of the E-isomer.

- 5 Whenever reference is made herein to the Z-isomer, the pure Z-isomer or any isomeric mixture of the Z- and the E-isomers wherein the Z-isomer is predominantly present is meant, i.e. an isomeric mixture containing more than 50% or in particular more than 80% of the Z-isomer, or even more in particular more than 90% of the Z-isomer. Of particular interest is the Z-isomer substantially free of the E-isomer. Substantially free
- 10 in this context refers to E-Z-mixtures with no or almost no E-isomer, e.g. isomeric mixtures containing as much as 90%, in particular 95% or even 98% or 99% of the Z-isomer.

- Polymorphic forms of the present salts also fall within the ambit of the present
- 15 invention.

- Polymorphic forms of pharmaceutical compounds may be of interest to those involved in the development of a suitable dosage form because if the polymorphic form is not held constant during clinical and stability studies, the exact dosage used or measured
- 20 may not be comparable from one lot to the next. Once a pharmaceutical compound is produced for use, it is important to recognize the polymorphic form delivered in each dosage form to assure that the production process use the same form and that the same amount of drug is included in each dosage. Therefore, it is imperative to assure that either a single polymorphic form or some known combination of polymorphic forms is
- 25 present. In addition, certain polymorphic forms may exhibit enhanced thermodynamic stability and may be more suitable than other polymorphic forms for inclusion in pharmaceutical formulations. As used herein, a polymorphic form of a compound of the invention is the same chemical entity, but in a different crystalline arrangement.

- 30 Solvent addition forms (solvates) which the salts of the present invention are able to form also fall within the ambit of the present invention. Examples of such forms are e.g. hydrates, alcoholates and the like. Solvates are herein also referred to as pseudopolymorphic forms. Preferred is an anhydric salt.

- 35 Whenever used hereinafter, the term "compound of formula (I), (I-a) or (I-b)" is meant to also include the N-oxide forms, the stereochemically isomeric forms and the polymorphic or pseudopolymorphic forms. Of special interest is a stereochemically

pure form of a compound of formula (I). A preferred compound of formula (I) is a compound of formula (I-a).

5 The compounds of formula (I), (I-a) or (I-b) can be prepared by reacting the corresponding free base with fumaric acid in the presence of a suitable solvent, such as for example a suitable acid, e.g. acetic acid.

10 The compounds of formula (I), (I-a) or (I-b) have antiretroviral activity. They are able to inhibit the replication of HIV, in particular HIV-1. HIV (Human Immunodeficiency Virus) is the aetiological agent of Acquired Immune Deficiency Syndrome (AIDS) in humans. The HIV virus preferentially infects human T-4 cells and destroys them or changes their normal function, particularly the coordination of the immune system. As a result, an infected patient has an ever decreasing number of T-4 cells, which moreover behave abnormally. Hence, the immunological defense system is unable to  
15 combat infections and neoplasms and the HIV infected subject usually dies by opportunistic infections such as pneumonia, or by cancers. Other conditions associated with HIV infection include thrombocytopaenia, Kaposi's sarcoma and infection of the central nervous system characterized by progressive demyelination, resulting in dementia and symptoms such as, progressive dysarthria, ataxia and disorientation. HIV  
20 infection further has also been associated with peripheral neuropathy, progressive generalized lymphadenopathy (PGL) and AIDS-related complex (ARC).

The present compounds also show activity against drug and multidrug resistant HIV strains, in particular drug and multidrug resistant HIV-1 strains, more in particular the  
25 present compounds show activity against HIV strains, especially HIV-1 strains, that have acquired resistance to one or more art-known non-nucleoside reverse transcriptase inhibitors. Art-known non-nucleoside reverse transcriptase inhibitors are those non-nucleoside reverse transcriptase inhibitors other than the present compounds and in particular commercial non-nucleoside reverse transcriptase inhibitors.

30 The HIV replication inhibiting activity of 4-[[4-[[4-(2-cyanoethenyl)-2,6-dimethylphenyl]amino]-2-pyrimidinyl]amino]benzotrile is described in WO 03/16306, which is incorporated herein by reference.

35 Due to their antiretroviral properties, particularly their anti-HIV properties, especially their HIV-1 replication inhibiting activity, the present compounds are useful in the treatment of individuals infected by HIV and for the prophylaxis of these infections. In

general, the compounds of the present invention may be useful in the treatment of warm-blooded mammals infected with viruses whose existence is mediated by, or depends upon, the enzyme reverse transcriptase. Conditions which may be prevented or treated with the compounds of the present invention, especially conditions associated with HIV and other pathogenic retroviruses, include AIDS, AIDS-related complex (ARC), progressive generalized lymphadenopathy (PGL), as well as chronic Central Nervous System diseases caused by retroviruses, such as, for example HIV mediated dementia and multiple sclerosis

Therefore, the compounds of formula (I), (I-a) or (I-b) can be used as a medicine.

10

The compounds of the present invention may therefore be used as medicines against above-mentioned conditions. Said use as a medicine or method of treatment comprises the administration to HIV-infected subjects of an amount effective to combat the conditions associated with HIV and other pathogenic retroviruses, especially HIV-1. In particular, the present compounds may be used in the manufacture of a medicament for the treatment or the prevention of HIV infection, preferably for the treatment of HIV infection.

15

In view of the utility of the present compounds, there is also provided a method of treating mammals, including humans, suffering from or a method of preventing warm-blooded mammals, including humans, to suffer from viral infections, especially HIV infections. Said method comprises the administration, preferably oral administration, of an effective amount of a salt of the present invention to mammals including humans.

20

Due to the higher bioavailability of the present compounds compared to the corresponding free base, therapeutic effective plasma levels may be obtained by administering a pharmaceutical composition comprising a lower amount of the salt compared to what would be needed of the corresponding free base.

25

Therefore, the size of the pharmaceutical composition may be reduced or the frequency of dosing may be reduced.

30

Thus, the present invention also relates to a pharmaceutical composition comprising a pharmaceutically acceptable carrier and as active ingredient a therapeutically effective amount of a compound of formula (I), (I-a) or (I-b).

35

In particular, the present invention also relates to a pharmaceutical composition comprising a pharmaceutically acceptable carrier and as active ingredient a

therapeutically effective amount of a compound of formula (I), (I-a) or (I-b) provided that the composition does not contain one or more nucleoside reverse transcriptase inhibitors and/or one or more nucleotide reverse transcriptase inhibitors.

- 5 The present compounds of formula (I), (I-a) or (I-b) may be formulated into various pharmaceutical compositions for administration purposes. As appropriate compositions there may be cited all compositions usually employed for systemically administering drugs. To prepare the pharmaceutical compositions of this invention, an effective amount of the compound of formula (I), (I-a) or (I-b) as the active ingredient is
- 10 combined in intimate admixture with a pharmaceutically acceptable carrier, which carrier may take a wide variety of forms depending on the form of preparation desired for administration. These pharmaceutical compositions are desirable in unitary dosage form suitable, particularly, for administration orally. For example, in preparing the compositions in oral dosage form, any of the usual pharmaceutical media may be
- 15 employed such as, for example, water, glycols, oils, alcohols and the like in the case of oral liquid preparations such as suspensions, syrups, elixirs, emulsions and solutions; or solid carriers such as starches, sugars, kaolin, diluents, lubricants, binders, disintegrating agents and the like in the case of powders, pills, capsules, and tablets. Because of their ease in administration, tablets and capsules represent the most
- 20 advantageous oral unit dosage forms, in which case solid pharmaceutical carriers are obviously employed. For parenteral compositions, the carrier will usually comprise sterile water, at least in large part, though other ingredients, for example, to aid solubility, may be included. Injectable solutions, for example, may be prepared in which the carrier comprises saline solution, glucose solution or a mixture of saline and
- 25 glucose solution. Injectable suspensions may also be prepared in which case appropriate liquid carriers, suspending agents and the like may be employed. Also included are solid form preparations, which are intended to be converted, shortly before use, to liquid form preparations. In the compositions suitable for percutaneous administration, the carrier optionally comprises a penetration enhancing agent and/or a
- 30 suitable wetting agent, optionally combined with suitable additives of any nature in minor proportions, which additives do not introduce a significant deleterious effect on the skin. Said additives may facilitate the administration to the skin and/or may be helpful for preparing the desired compositions. These compositions may be administered in various ways, e.g., as a transdermal patch, as a spot-on, as an ointment.
- 35 The salts of the present invention may also be administered via inhalation or insufflation by means of methods and formulations employed in the art for administration via this way. Thus, in general the salts of the present invention may be

administered to the lungs in the form of a solution, a suspension or a dry powder. Any system developed for the delivery of solutions, suspensions or dry powders via oral or nasal inhalation or insufflation are suitable for the administration of the present compounds.

5 The compounds of the present invention may also be topically administered in the form of drops, in particular eye drops. Said eye drops may be in the form of a solution or a suspension. Any system developed for the delivery of solutions or suspensions as eye drops are suitable for the administration of the present compounds.

10 WO 2004/069812 which is incorporated herein by reference, describes the ability of pyrimidine derivatives among which 4-[[4-[[4-(2-cyanoethenyl)-2,6-dimethylphenyl]-amino]-2-pyrimidinyl]amino]benzotrile and pharmaceutically acceptable salts thereof, to prevent HIV infection via sexual intercourse or related intimate contact between partners. Therefore, the present invention also relates to a pharmaceutical  
15 composition in a form adapted to be applied to a site where sexual intercourse or related intimate contact can take place, such as the genitals, rectum, mouth, hands, lower abdomen, upper thighs, especially the vagina and mouth, comprising a pharmaceutically acceptable carrier and as active ingredient an effective amount of a compound of formula (I), (I-a) or (I-b). In particular, the present invention also relates  
20 to a pharmaceutical composition in a form adapted to be applied to a site where sexual intercourse or related intimate contact can take place, such as the genitals, rectum, mouth, hands, lower abdomen, upper thighs, especially the vagina and mouth, comprising a pharmaceutically acceptable carrier and as active ingredient an effective amount of a compound of formula (I), (I-a) or (I-b) provided that the composition does  
25 not contain one or more nucleoside reverse transcriptase inhibitors and/or one or more nucleotide reverse transcriptase inhibitors. As appropriate special adapted compositions there may be cited all compositions usually employed for being applied to the vagina, rectum, mouth and skin such as for example gels, jellies, creams, ointments, films, sponges, foams, intravaginal rings, cervical caps, suppositories for  
30 rectal or vaginal application, vaginal or rectal or buccal tablets, mouthwashes. To prepare such pharmaceutical compositions, an effective amount of the active ingredient is combined in intimate admixture with a pharmaceutically acceptable carrier, which carrier may take a wide variety of forms depending on the form of administration. In order to increase the residence time of such pharmaceutical composition at the site of  
35 administration, it may be advantageous to include in the composition a bioadhesive, in particular a bioadhesive polymer. A bioadhesive may be defined as a material that

adheres to a live biological surface such as for example a mucus membrane or skin tissue.

Thus, the present invention also relates to a pharmaceutical composition comprising a  
5 pharmaceutically acceptable carrier and as active ingredient an effective amount of a  
compound of formula (I), (I-a) or (I-b) characterized in that the pharmaceutical  
composition is bioadhesive to the site of application. In particular, the present  
invention also relates to a pharmaceutical composition comprising a pharmaceutically  
10 acceptable carrier and as active ingredient an effective amount of a compound of  
formula (I), (I-a) or (I-b) characterized in that the pharmaceutical composition is  
bioadhesive to the site of application provided that the composition does not contain  
one or more nucleoside reverse transcriptase inhibitors and/or one or more nucleotide  
reverse transcriptase inhibitors. Preferably, the site of application is the vagina, rectum,  
mouth or skin, most preferred is the vagina.

15 It is especially advantageous to formulate the aforementioned pharmaceutical  
compositions in unit dosage form for ease of administration and uniformity of dosage.  
Unit dosage form as used herein refers to physically discrete units suitable as unitary  
dosages, each unit containing a predetermined quantity of active ingredient calculated  
20 to produce the desired therapeutic effect in association with the required  
pharmaceutical carrier. Examples of such unit dosage forms are tablets (including  
scored or coated tablets), capsules, pills, powder packets, wafers, suppositories,  
injectable solutions or suspensions and the like, and segregated multiples thereof.

25 The exact dosage and frequency of administration depends on the particular condition  
being treated, the severity of the condition being treated, the age, weight, sex, extent of  
disorder and general physical condition of the particular patient as well as other  
medication the individual may be taking, as is well known to those skilled in the art.  
Furthermore, it is evident that said effective daily amount may be lowered or increased  
30 depending on the response of the treated subject and/or depending on the evaluation of  
the physician prescribing the compounds of the instant invention.

The pharmaceutical compositions of the present invention can be administered at any  
time of the day independently of the food taken in by the subject. Preferably, the  
35 present compositions are administered to fed subjects.

An interesting embodiment of the present invention concerns an oral pharmaceutical composition, i.e. a pharmaceutical composition suitable for oral administration, comprising a pharmaceutically acceptable carrier and as active ingredient a therapeutically effective amount of a compound of formula (I), (I-a) or (I-b); in

5 particular a pharmaceutical composition suitable for oral administration, comprising a pharmaceutically acceptable carrier and as active ingredient a therapeutically effective amount of a compound of formula (I), (I-a) or (I-b) provided that the composition does not contain one or more nucleoside reverse transcriptase inhibitors and/or one or more nucleotide reverse transcriptase inhibitors.

10

In particular, the oral pharmaceutical composition is a solid oral pharmaceutical composition, more in particular a tablet or a capsule, even more in particular a tablet. A tablet according to the present invention may be formulated as a once daily tablet.

15 Preferably, the pharmaceutical compositions of the present invention contain those quantities of a compound of formula (I), (I-a) or (I-b) equivalent to from about 5 to about 500 mg of the corresponding free base 4-[[4-[[4-(2-cyanoethenyl)-2,6-dimethylphenyl]amino]-2-pyrimidinyl]amino]benzotrile, its E or Z isomer, more preferably from about 10 mg to about 250 mg of the corresponding free base, even  
20 more preferably from about 20 mg to about 200 mg of the corresponding free base. Preferably, the present pharmaceutical compositions contain those quantities of a compound of formula (I), (I-a) or (I-b) equivalent to 25 mg, 50 mg, 75 mg, 100 mg or 150 mg of the corresponding free base (base equivalent).

25 As used hereinbefore or hereinafter, the term "about" in relation to a numerical value x means, for example,  $x \pm 10\%$ .

The particle size of the compound of formula (I), (I-a) or (I-b) preferably is less than 50  $\mu\text{m}$ , more preferably less than 25  $\mu\text{m}$ , even more preferably less than 20  $\mu\text{m}$ . Further  
30 preferred is a particle size of about 15  $\mu\text{m}$  or less, or about 12  $\mu\text{m}$  or less, or about 10  $\mu\text{m}$  or less, or about 5  $\mu\text{m}$  or less. Most preferably, the particle size ranges between about 0.2 and about 15  $\mu\text{m}$  or between about 0.2 and about 10  $\mu\text{m}$ .

The pharmaceutical compositions of the present invention preferably comprise a  
35 wetting agent.



As for the wetting agent in the compositions of the invention, there may be used any of the physiologically tolerable wetting agent suitable for use in a pharmaceutical composition.

- 5 It is well-known in the art that a wetting agent is an amphiphilic compound; it contains polar, hydrophilic moieties as well as non-polar, hydrophobic moieties.

The terms "hydrophilic" or "hydrophobic" are relative terms.

- 10 The relative hydrophilicity or hydrophobicity of a wetting agent may be expressed by its hydrophilic-lipophilic balance value ("HLB value). Wetting agents with a lower HLB value are categorized as being "hydrophobic" wetting agents whereas wetting agents with a higher HLB value are categorized as being "hydrophilic" wetting agents. As a rule of thumb, wetting agents having a HLB value greater than about 10 are  
15 generally considered as being hydrophilic wetting agents; wetting agents having a HLB value lower than about 10 are generally considered as being hydrophobic wetting agents.

The present compositions preferably comprise a hydrophilic wetting agent.

- 20 It should be appreciated that the HLB value of a wetting agent is only a rough guide to indicate the hydrophilicity/hydrophobicity of a wetting agent. The HLB value of a particular wetting agent may vary depending upon the method used to determine the HLB value; may vary depending on its commercial source; is subject to batch to batch variability. A person skilled in the art can readily identify hydrophilic wetting agents  
25 suitable for use in the pharmaceutical compositions of the present invention.

The wetting agent of the present invention can be an anionic, a cationic, a zwitterionic or a non-ionic wetting agent, the latter being preferred. The wetting agent of the present invention can also be a mixture of two or more wetting agents.

- 30 Suitable wetting agents for use in the compositions of the present invention are listed below. It should be emphasized that said list of wetting agents is only illustrative, representative and not exhaustive. Thus the invention is not limited to the wetting agents listed below. In the present compositions, also mixtures of wetting agents may  
35 be used.

Suitable wetting agents which may be used in the present invention comprise :

- a) Polyethylene glycol fatty acid monoesters comprising esters of lauric acid, oleic acid, stearic acid, ricinoic acid and the like with PEG 6, 7, 8, 9, 10, 12, 15, 20, 25, 30, 32, 40, 45, 50, 55, 100, 200, 300, 400, 600 and the like, for instance PEG-6 laurate or stearate, PEG-7 oleate or laurate, PEG-8 laurate or oleate or stearate, PEG-9 oleate or stearate, PEG-10 laurate or oleate or stearate, PEG-12 laurate or oleate or stearate or ricinoleate, PEG-15 stearate or oleate, PEG-20 laurate or oleate or stearate, PEG-25 stearate, PEG-32 laurate or oleate or stearate, PEG-30 stearate, PEG-40 laurate or oleate or stearate, PEG-45 stearate, PEG-50 stearate, PEG-55 stearate, PEG-100 oleate or stearate, PEG-200 oleate, PEG-400 oleate, PEG-600 oleate; (the wetting agents belonging to this group are for instance known as Cithrol, Algon, Kessco, Lauridac, Mapeg, Cremophor, Emulgante, Nikkol, Myrj, Crodet, Albunol, Lactomul)
- b) Polyethylene glycol fatty acid diesters comprising diesters of lauric acid, stearic acid, palmitic acid, oleic acid and the like with PEG-8, 10, 12, 20, 32, 400 and the like, for instance PEG-8 dilaurate or distearate, PEG-10 dipalmitate, PEG-12 dilaurate or distearate or dioleate, PEG-20 dilaurate or distearate or dioleate, PEG-32 dilaurate or distearate or dioleate, PEG-400 dioleate or distearate; (the wetting agents belonging to this group are for instance known as Mapeg, Polyalso, Kessco, Cithrol)
- c) Polyethylene glycol fatty acid mono- and diester mixtures such as for example PEG 4-150 mono and dilaurate, PEG 4-150 mono and dioleate, PEG 4-150 mono and distearate and the like; (the wetting agents belonging to this group are for instance known as Kessco)
- d) Polyethylene glycol glycerol fatty acid esters such as for instance PEG-20 glyceryl laurate or glyceryl stearate or glyceryl oleate, PEG-30 glyceryl laurate or glyceryl oleate, PEG-15 glyceryl laurate, PEG-40 glyceryl laurate and the like; (the wetting agents belonging to this group are for instance known as Tagat, Glycerox L, Capmul)
- e) Alcohol-oil transesterification products comprising esters of alcohols or polyalcohols such as glycerol, propylene glycol, ethylene glycol, polyethylene glycol, sorbitol, pentaerythritol and the like with natural and/or hydrogenated oils or oil-soluble vitamins such as castor oil, hydrogenated castor oil, vitamin A, vitamin D, vitamin E, vitamin K, an edible vegetable oil e.g. corn oil, olive oil, peanut oil, palm kernel oil, apricot kernel oil, almond oil and the like, such as PEG-20 castor oil or hydrogenated castor oil or corn glycerides or almond glycerides, PEG-23 castor oil, PEG-25 hydrogenated castor oil or trioleate, PEG-35 castor oil, PEG-30 castor oil or hydrogenated castor oil, PEG-38 castor oil, PEG-40 castor oil or hydrogenated castor oil or palm kernel oil, PEG-45 hydrogenated castor oil, PEG-50 castor oil or hydrogenated castor oil, PEG-56 castor oil, PEG-60 castor oil or hydrogenated castor oil or corn glycerides or almond glycerides, PEG-80 hydrogenated castor oil, PEG-100

- castor oil or hydrogenated castor oil, PEG-200 castor oil, PEG-8 caprylic/capric glycerides, PEG-6 caprylic/capric glycerides, lauroyl macrogol-32 glyceride, stearyl macrogol glyceride, tocopheryl PEG-1000 succinate (TPGS); (the wetting agents belonging to this group are for instance known as Emalex, Cremophor, Emulgante, Eumulgin, Nikkol, Thornley, Simulsol, Cerex, Crovol, Labrasol, Softigen, Gelucire, Vitamin E TPGS),
- 5 f) polyglycerized fatty acids comprising polyglycerol esters of fatty acids such as for instance polyglyceryl-10 laurate or oleate or stearate, polyglyceryl-10 mono and dioleate, polyglyceryl polyricinoleate and the like; (the wetting agents belonging to this group are for instance known as Nikkol Decaglyn, Caprol or Polymuls)
- 10 g) Sterol derivatives comprising polyethylene glycol derivatives of sterol such as PEG-24 cholesterol ether, PEG-30 cholestanol, PEG-25 phyto sterol, PEG-30 soya sterol and the like; (the wetting agents belonging to this group are for instance known as Solulan™ or Nikkol BPSH)
- 15 h) Polyethylene glycol sorbitan fatty acid esters such as for example PEG-10 sorbitan laurate, PEG-20 sorbitan monolaurate or sorbitan tristearate or sorbitan monooleate or sorbitan trioleate or sorbitan monoisostearate or sorbitan monopalmitate or sorbitan monostearate, PEG-4 sorbitan monolaurate, PEG-5 sorbitan monooleate, PEG-6 sorbitan monooleate or sorbitan monolaurate or sorbitan monostearate, PEG-8 sorbitan monostearate, PEG-30 sorbitan tetraoleate, PEG-40 sorbitan oleate or sorbitan tetraoleate, PEG-60 sorbitan tetrastearate, PEG-80 sorbitan monolaurate, PEG sorbitol hexaoleate (Atlas G-1086) and the like; (the wetting agents belonging to this group are for instance known as Liposorb, Tween, Dacol MSS, Nikkol, Emalex, Atlas)
- 20 i) Polyethylene glycol alkyl ethers such as for instance PEG-10 oleyl ether or cetyl ether or stearyl ether, PEG-20 oleyl ether or cetyl ether or stearyl ether, PEG-9 lauryl ether, PEG-23 lauryl ether (laureth-23), PEG-100 stearyl ether and the like; (the wetting agents belonging to this group are for instance known as Volpo, Brij)
- 25 j) Sugar esters such as for instance sucrose distearate/monostearate, sucrose monostearate or monopalmitate or monolaurate and the like; (the wetting agents belonging to this group are for instance known as Sucro ester, Crodesta, Saccharose monolaurate)
- 30 k) Polyethylene glycol alkyl phenols such as for instance PEG-10-100 nonyl phenol (Triton X series), PEG-15-100 oyl phenol ether (Triton N series) and the like;
- l) Polyoxyethylene-polyoxypropylene block copolymers (poloxamers) such as for instance poloxamer 108, poloxamer 188, poloxamer 237, poloxamer 288 and the like; (the wetting agents belonging to this group are for instance known as Synperonic PE, Pluronic, Emkalyx, Lutrol™, Supronic, Monolan, Pluracare, Plurodac)
- 35

m) ionic wetting agents including cationic, anionic and zwitterionic surfactans such as the fatty acid salts e.g. sodium oleate, sodium lauryl sulfate, sodium lauryl sarcosinate, sodium dioctyl sulfosuccinate, sodium myristate, sodium palmitate, sodium state, sodium ricinoleate and the like; such as bile salts e.g. sodium cholate, sodium taurocholate, sodium glycocholate and the like; such as phospholipids e.g. egg/soy lecithin, hydroxylated lecithin, lysophosphatidylcholine, phosphatidylcholine, phosphatidyl ethanolamine, phosphatidyl glycerol, phosphatidyl serine and the like; such as phosphoric acid esters e.g. diethanolammonium polyoxyethylene-10 oleyl ether phosphate, esterification products of fatty alcohols or fatty alcohol ethoxylates with phosphoric acid or anhydride; such as carboxylates e.g. succinylated monoglycerides, sodium stearyl fumarate, stearyl propylene glycol hydrogen succinate, mono/diacetylated tartaric acid esters of mono-and diglycerides, citric acid esters of mono-and diglycerides, glyceryl-lacto esters of fatty acids, lactic esters of fatty acids, calcium/sodium stearyl-2-lactylate, calcium/sodium stearyl lactylate, alginate salts, propylene glycol alginate, ether carboxylates and the like; such as sulfates and sulfonates e.g. ethoxylated alkyl sulfates, alkyl benzene sulfates, alpha-olefin sulfonates, acyl isethionates, acyl taurates, alkyl glyceryl ether sulfonates, octyl sulfosuccinate disodium, disodium undecyleneamido-MEA-sulfosuccinate and the like; such as cationic wetting agents e.g. hexadecyl triammonium bromide, decyl trimethyl ammonium bromide, cetyl trimethyl ammonium bromide, dodecyl ammonium chloride, alkyl benzyldimethylammonium salts, diisobutyl phenoxyethoxydimethyl benzylammonium salts, alkylpyridinium salts, betaines (lauryl betaine), ethoxylated amines (polyoxyethylene-15 coconut amine) and the like.

When in the above list of suitable wetting agents, different possibilities are listed such as for example PEG-20 oleyl ether or cetyl ether or stearyl ether, this means that PEG-20 oleyl ether and PEG-20 cetyl ether and PEG-20 stearyl ether are intended. Thus for instance PEG-20 castor oil or hydrogenated castor oil or corn glycerides or almond glycerides has to be read as PEG-20 castor oil and PEG-20 hydrogenated castor oil and PEG-20 corn glycerides and PEG-20 almond glycerides.

Preferred wetting agents in the present compositions are sodium lauryl sulfate, sodium dioctyl sulfosuccinate, or those wetting agents belonging to the group of the polyethylene glycol sorbitan fatty acid esters, such as wetting agents known as Tween, e.g. Tween 20, 60, 80. Most preferred, the wetting agent is Tween 20.

In the compositions of the invention, the wetting agent is preferably present at a

concentration from about 0.01 to about 5% by weight relative to the total weight of the composition, preferably from about 0.1 to about 3 % by weight, more preferably from about 0.1 to about 1 % by weight.

The quantity of wetting agent used in the present compositions may depend on the amount of the compound of formula (I), (I-a) or (I-b) present in the composition or on the particle size of the compound of formula (I), (I-a) or (I-b). A higher amount or a smaller particle size may require more wetting agent.

In case of a solid oral pharmaceutical composition according to the present invention, such as a tablet or a capsule, the composition may also further contain an organic polymer.

The organic polymer may be used as a binder during the manufacture of the composition.

The organic polymer used in the compositions of the invention may be any of the physiologically tolerable water soluble synthetic, semi-synthetic or non-synthetic organic polymers.

Thus for example the polymer may be a natural polymer such as a polysaccharide or polypeptide or a derivative thereof, or a synthetic polymer such as a polyalkylene oxide (e.g. PEG), polyacrylate, polyvinylpyrrolidone, etc. Mixed polymers, e.g. block copolymers and glycopeptides may of course also be used.

The polymer conveniently has a molecular weight in the range 500D to 2 MD, and conveniently has an apparent viscosity of 1 to 15,000 mPa.s when in a 2% aqueous solution at 20°C. For example, the water-soluble polymer can be selected from the group comprising

- alkylcelluloses such as methylcellulose,
- hydroxyalkylcelluloses such as hydroxymethylcellulose, hydroxyethylcellulose, hydroxypropylcellulose and hydroxybutylcellulose,
- hydroxyalkyl alkylcelluloses such as hydroxyethyl methylcellulose and hydroxypropyl methylcellulose,
- carboxyalkylcelluloses such as carboxymethylcellulose,
- alkali metal salts of carboxyalkylcelluloses such as sodium carboxymethylcellulose,
- carboxyalkylalkylcelluloses such as carboxymethylethylcellulose,
- carboxyalkylcellulose esters,

- starches,
- pectins such as sodium carboxymethylamylopectin,
- chitin derivatives such as chitosan,
- heparin and heparinoids,
- 5 - polysaccharides such as alginic acid, alkali metal and ammonium salts thereof, carrageenans, galactomannans, tragacanth, agar-agar, gum arabic, guar gum and xanthan gum,
- polyacrylic acids and the salts thereof,
- polymethacrylic acids and the salts thereof, methacrylate copolymers,
- 10 - polyvinylalcohol,
- polyvinylpyrrolidone, copolymers of polyvinylpyrrolidone with vinyl acetate,
- polyalkylene oxides such as polyethylene oxide and polypropylene oxide and copolymers of ethylene oxide and propylene oxide, e.g. poloxamers and poloxamines.

15

Non-enumerated polymers which are pharmaceutically acceptable and have appropriate physico-chemical properties as defined hereinbefore are equally suited for preparing compositions according to the present invention.

- 20 Preferably the organic polymer is starch, polyvinylpyrrolidone or a cellulose ether, e.g. PVP K29-32, PVP K90, methyl cellulose, hydroxypropylcellulose, hydroxyethyl methylcellulose, or hydroxypropyl methylcellulose (HPMC).

Said HPMC contains sufficient hydroxypropyl and methoxy groups to render it water-  
25 soluble. HPMC having a methoxy degree of substitution from about 0.8 to about 2.5 and a hydroxypropyl molar substitution from about 0.05 to about 3.0 are generally water-soluble. Methoxy degree of substitution refers to the average number of methyl ether groups present per anhydroglucose unit of the cellulose molecule. Hydroxypropyl molar substitution refers to the average number of moles of propylene oxide  
30 which have reacted with each anhydroglucose unit of the cellulose molecule. A preferred HPMC is hypromellose 2910 15 mPa.s or hypromellose 2910 5mPa.s, especially hypromellose 2910 15 mPa.s. Hydroxypropyl methylcellulose is the United States Adopted Name for hypromellose (see Martindale, The Extra Pharmacopoeia, 29th edition, page 1435). In the four digit number "2910", the first two digits represent  
35 the approximate percentage of methoxyl groups and the third and fourth digits the approximate percentage composition of hydroxypropoxyl groups ;

15 mPa.s or 5 mPa.s is a value indicative of the apparent viscosity of a 2 % aqueous solution at 20°C.

In the compositions of the invention the organic polymer may conveniently be present  
5 up to about 10% by weight, preferably from about 0.1 to about 5%, more preferably  
from about 0.5 to about 3% by weight (relative to the total weight of the composition).

In case of a solid oral pharmaceutical composition according to the present invention,  
such as a tablet or a capsule, the composition may also further contain a diluent and/or  
10 a glidant.

Pharmaceutical acceptable diluents comprise calcium carbonate, dibasic calcium  
phosphate, dibasic calcium phosphate dihydrate, tribasic calcium phosphate, calcium  
sulfate, microcrystalline cellulose including silicified microcrystalline cellulose,  
15 powdered cellulose, dextrates, dextrin, dextrose excipient, fructose, kaolin, lactitol,  
lactose anhydrous, lactose monohydrate, mannitol, sorbitol, starch, pregelatinized  
starch, sodium chloride, sucrose, compressible sugar, confectioner's sugar, a spray-  
dried mixture of lactose monohydrate and microcrystalline cellulose (75:25),  
commercially available as Microcelac<sup>®</sup>, a co-processed spray-dried mixture of  
20 microcrystalline cellulose and colloidal silicon dioxide (98:2), commercially available  
as Prosolv<sup>®</sup>. Preferred is lactose monohydrate, microcrystalline cellulose or silicified  
microcrystalline cellulose.

Pharmaceutically acceptable glidants comprise talc, colloidal silicon dioxide, starch.  
25 magnesium stearate. Preferred is colloidal silicon dioxide.

In case of a tablet, the composition may also further comprise a disintegrant and a  
lubricant.

30 Pharmaceutically acceptable disintegrants comprise starch, ion exchange resins, e.g.  
Amberlite, cross-linked polyvinylpyrrolidone, modified cellulose gum, e.g.  
croscarmellose sodium (e.g. Ac-di-Sol<sup>®</sup>), sodium starch glycollate, sodium  
carboxymethylcellulose, sodium dodecyl sulphate, modified corn starch,  
microcrystalline cellulose, magnesium aluminium silicate, alginic acid, alginate,  
35 powdered cellulose.

Pharmaceutically acceptable lubricants comprise magnesium stearate, calcium stearate, stearic acid, talc, polyethylene glycol, sodium lauryl sulfate, magnesium lauryl sulphate.

- 5     Tablets of the present invention may in addition include other optional excipients such as, for example, flavors, sweeteners and colors.

Solid pharmaceutical compositions according to the present invention may comprise by weight based on the total weight of the composition :

- 10    (a) from 5 to 50% of a compound of formula (I), (I-a) or (I-b);  
      (b) from 0.01 to 5% of a wetting agent;  
      (c) from 40 to 92% of a diluent;  
      (d) from 0.1 to 5% of a glidant.

- 15    Tablets according to the present invention may comprise by weight based on the total weight of the tablet core :

- (a) from 5 to 50% of a compound of formula (I), (I-a) or (I-b);  
      (b) from 0.01 to 5% of a wetting agent;  
      (c) from 40 to 92% of a diluent;  
20    (d) from 0 to 10% of a polymer;  
      (e) from 2 to 10% of a disintegrant;  
      (f) from 0.1 to 5% of a glidant;  
      (g) from 0.1 to 1.5% of a lubricant.

- 25    Tablets of the present invention may optionally be film-coated following art-known coating procedures. Film-coated tablets are easier to swallow than uncoated tablet cores, are usually easier to distinguish from other tablets - in particular when the film-coat contains a dye or a pigment -, may have reduced tackiness, and may furthermore have an improved stability (increased shelf-life), e.g. because the coating may protect  
30    the active ingredient from the influence of light. Preferably, the film coat is an immediate release coat. Film coatings may comprise a film-forming polymer and optionally a plasticizer or a pigment. An example of a suitable film-forming polymer is hydroxypropyl methylcellulose, and an example of a suitable plasticizer is polyethyleneglycol, e.g. macrogol 3000 or 6000, or triacetin. Commercially available  
35    suitable coatings for pharmaceutical tablets are well-known to a person skilled in the art. Preferably, the film coating is a non-transparent film coating. An example of a suitable coating is Opadry<sup>®</sup>, in particular coating powder Opadry<sup>®</sup> II White.



Tablets of the present invention can be prepared by direct compression or wet granulation.

- 5 Therefore, the present invention is also concerned with a process of preparing a tablet comprising a compound of formula (I), (I-a) or (I-b) comprising the steps of :
- (i) dry blending the active ingredient, the disintegrant and the optional glidant with the diluent;
  - (ii) optionally mixing the lubricant with the mixture obtained in step (i);
  - 10 (iii) compressing the mixture obtained in step (i) or in step (ii) in the dry state into a tablet; and
  - (iv) optionally film-coating the tablet obtained in step (iii).

- The present invention is also concerned with a process of preparing a tablet comprising
- 15 a compound of formula (I), (I-a) or (I-b) comprising the steps of :
- (i) dry blending the active ingredient and part of the diluent;
  - (ii) preparing a binder solution by dissolving the binder and the wetting agent in the binder solution solvent;
  - (iii) spraying the binder solution obtained in step (ii) on the mixture obtained in step (i);
  - 20 (iv) drying the wet powder obtained in step (iii) followed by sieving and optionally mixing;
  - (v) mixing the remaining part of the diluent, the disintegrant and the optional glidant in the mixture obtained in step (iv);
  - (vi) optionally adding the lubricant to the mixture obtained in step (v);
  - 25 (vii) compressing the mixture obtained in step (vi) into a tablet;
  - (viii) optionally film-coating the tablet obtained in step (vii).

A person skilled in the art will recognize the most appropriate equipment to be used for the above-described processes.

- 30 The above general route of preparing tablets of the present invention may be modified by a person skilled in the art by for instance adding certain ingredients at other stages than indicated above.

- The present compound of formula (I), (I-a) or (I-b) can be used alone or in combination
- 35 with other therapeutic agents, such as anti-virals, antibiotics, immunomodulators or vaccines for the treatment of viral infections. They may also be used alone or in combination with other prophylactic agents for the prevention of viral infections. The

present compounds may be used in vaccines and methods for protecting individuals against viral infections over an extended period of time. The compounds may be employed in such vaccines either alone or together with other anti-viral agents in a manner consistent with the conventional utilization of reverse transcriptase inhibitors in vaccines. Thus, the present compounds may be combined with pharmaceutically acceptable adjuvants conventionally employed in vaccines and administered in prophylactically effective amounts to protect individuals over an extended period of time against HIV infection.

Also, the combination of an antiretroviral compound and a compound of formula (I), (I-a) or (I-b) can be used as a medicine. Thus, the present invention also relates to a product containing (a) a compound of formula (I), (I-a) or (I-b), and (b) one or more other antiretroviral compounds, as a combined preparation for simultaneous, separate or sequential use in anti-HIV treatment. In particular, the invention also relates to a product containing (a) a compound of formula (I), (I-a) or (I-b), and (b) one or more other antiretroviral compounds, as a combined preparation for simultaneous, separate or sequential use in anti-HIV treatment provided that the one or more other antiretroviral compounds are other than nucleoside reverse transcriptase inhibitors and/or nucleotide reverse transcriptase inhibitors. The different drugs may be combined in a single preparation together with pharmaceutically acceptable carriers. Thus, the present invention also relates to a pharmaceutical composition comprising a pharmaceutically acceptable carrier and (a) a therapeutically effective amount of a compound of formula (I), (I-a) or (I-b) and (b) one or more other antiretroviral agents.

Said other antiretroviral compounds may be known antiretroviral compounds such as suramine, pentamidine, thymopentin, castanospermine, dextran (dextran sulfate), foscarnet-sodium (trisodium phosphono formate); nucleoside reverse transcriptase inhibitors, e.g. zidovudine (3'-azido-3'-deoxythymidine, AZT), didanosine (2',3'-dideoxyinosine; ddI), zalcitabine (dideoxycytidine, ddC) or lamivudine (2'-3'-dideoxy-3'-thiacytidine, 3TC), stavudine (2',3'-didehydro-3'-deoxythymidine, d4T), abacavir, abacavir sulfate, emtricitabine ((-) FTC), racemic FTC and the like; non-nucleoside reverse transcriptase inhibitors such as nevirapine (11-cyclopropyl-5,11-dihydro-4-methyl-6H-dipyrido-[3,2-b : 2',3'-e][1,4]diazepin-6-one), efavirenz, delavirdine, TMC-120, TMC-125 and the like; compounds of the TIBO (tetrahydroimidazo[4,5,1-jk][1,4]benzodiazepine-2(1H)-one and thione)-type e.g. (S)-8-chloro-4,5,6,7-tetrahydro-5-methyl-6-(3-methyl-2-butenyl)imidazo-[4,5,1-jk][1,4]benzodiazepine-2(1H)-thione; compounds of the  $\alpha$ -APA ( $\alpha$ -anilino

phenyl acetamide) type e.g.  $\alpha$ -[(2-nitrophenyl)amino]-2,6-dichlorobenzene-acetamide and the like; inhibitors of trans-activating proteins, such as TAT-inhibitors, e.g. RO-5-3335, or REV inhibitors, and the like; protease inhibitors e.g. indinavir, ritonavir, saquinavir, lopinavir (ABT-378), nelfinavir, amprenavir, TMC-114, BMS-232632, 5 VX-175 and the like; fusion inhibitors, e.g. T-20, T-1249 and the like; CXCR4 receptor antagonists, e.g. AMD-3100 and the like; inhibitors of the viral integrase; nucleotide-like reverse transcriptase inhibitors, e.g. tenofovir, tenofovir diphosphate, tenofovir disoproxil fumarate and the like; ribonucleotide reductase inhibitors, e.g. hydroxyurea and the like; CCR5 antagonists, e.g. ancriviroc, aplaviroc hydrochloride, vicriviroc.

10

By administering the compounds of the present invention with other anti-viral agents which target different events in the viral life cycle, the therapeutic effect of these compounds can be potentiated. Combination therapies as described above exert a synergistic effect in inhibiting HIV replication because each component of the 15 combination acts on a different site of HIV replication. The use of such combinations may reduce the dosage of a given conventional anti-retroviral agent which would be required for a desired therapeutic or prophylactic effect as compared to when that agent is administered as a monotherapy. These combinations may reduce or eliminate the side effects of conventional single anti-retroviral therapy while not interfering with the 20 anti-viral activity of the agents. These combinations reduce potential of resistance to single agent therapies, while minimizing any associated toxicity. These combinations may also increase the efficacy of the conventional agent without increasing the associated toxicity.

25 The compounds of the present invention may also be administered in combination with immunomodulating agents, e.g. levamisole, bropridine, anti-human alpha interferon antibody, interferon alpha, interleukin 2, methionine enkephalin, diethyldithiocarbamate, tumor necrosis factor, naltrexone and the like; antibiotics, e.g. pentamidine isethionate and the like; cholinergic agents, e.g. tacrine, rivastigmine, 30 donepezil, galantamine and the like; NMDA channel blockers, e.g. memantine to prevent or combat infection and diseases or symptoms of diseases associated with HIV infections, such as AIDS and ARC, e.g. dementia.

Although the present invention focuses on the use of the present compounds for 35 preventing or treating HIV infections, the present compounds may also be used as inhibitory agents for other viruses which depend on similar reverse transcriptases for obligatory events in their life cycle.

**Experimental part****A. Synthesis of the compound of formula (I-a)**

5 One mol of (E) 4-[[4-[[4-(2-cyanoethenyl)-2,6-dimethylphenyl]amino]-2-pyrimidinyl]amino]benzotrile free base was dissolved in acetic acid (2L/mol at 80-100°C). 1.2 mol of fumaric acid was added.

At 60-70 °C, water (2L/mol) was added portionwise.

The mixture was stirred overnight at room temperature.

10 The precipitate was filtered , washed twice with water and dried in vacuo at 50 °C, yielding 90 % of a compound of formula (I-a).

**B. Solubility data**

15 Table 1 lists solubility data of free base (E) 4-[[4-[[4-(2-cyanoethenyl)-2,6-dimethylphenyl]amino]-2-pyrimidinyl]amino]benzotrile and of the compound of formula (I-a).

**Table 1 :**

| Compound                  | Concentration in mg/ml |            |         |
|---------------------------|------------------------|------------|---------|
|                           | Water                  | 0.01 N HCl | PEG 400 |
| Free base (E-isomer)      | 0.00002                | 0.019      | 40      |
| Compound of formula (I-a) | 0.0009                 | 0.013      |         |

20

The free base as well as the fumarate salt have a poor solubility in water as well as in 0.01 N HCl. Free base and fumarate salt may be classified as BCS class 2 compounds. The solubility of the free base is significantly increased in PEG 400.

25 **C. Stability data**

a) Chemical stability

Compound (I-a) was stored under different conditions of humidity and temperature. After storage, the salt was analyzed by High Performance Liquid Chromatography (HPLC) for percentage of impurities.

30

The results are gathered in Table 2 below. It can be concluded that the compound of formula (I-a) is chemically stable.

**Table 2:**

5

| Storage condition | Sum of impurities % (% , w/w) |         |         |
|-------------------|-------------------------------|---------|---------|
|                   | 1 week                        | 4 weeks | 8 weeks |
| Reference         | 0.58                          | -       | -       |
| 40°C/75% RH       | -                             | 0.62    | 0.61    |
| 50°C/air          | -                             | 0.62    | 0.61    |
| RT/<5% RH         | -                             | 0.61    | 0.62    |
| RT/56% RH         | -                             | 0.58    | 0.64    |
| RT/75% RH         | -                             | 0.59    | 0.65    |

**Explanatory note:** - = not tested  
 RT = room temperature  
 RH = Relative Humidity

10 The compound of formula (I-a) was also found to be not hygroscopic.

**b) Physical stability**

The stability of the crystal structure of the compound of formula (I-a) was studied after storage for a period of six weeks under different conditions of humidity and temperature. The same conditions as described in Table 2 were applied.

15

After storage the compound was analyzed with infrared spectroscopy.

No changes in crystal structure were observed, indicating that the compound is crystallographically stable.

20

**D. Tablet formulations**

Tablet compositions illustrating the present invention are :

25 **Composition 1a**

*Tablet core :*

Compound of formula (I-a) 32.9 mg (i.e. 25 mg base equivalent)

Lactose monohydrate 236.6 mg

|   |                            |         |
|---|----------------------------|---------|
|   | Hypromellose 2910 15mPa.s  | 5.6 mg  |
|   | Polysorbate 20             | 1.4 mg  |
|   | Microcrystalline cellulose | 52.5 mg |
|   | Croscarmellose sodium      | 17.5 mg |
| 5 | Colloidal silicon dioxide  | 1.05 mg |
|   | Magnesium stearate         | 2.45 mg |

*Tablet film coat*

|    |                                 |       |
|----|---------------------------------|-------|
|    | Coating powder Opadry® II White | 14 mg |
| 10 | Purified water*                 | 80 µl |

Composition 1b*Tablet core :*

|    |                            |                                      |
|----|----------------------------|--------------------------------------|
|    | Compound of formula (I-a)  | 32.9 mg (i.e. 25 mg base equivalent) |
| 15 | Lactose monohydrate        | 46.85 mg                             |
|    | Hypromellose 2910 5mPa.s   | 1.40 mg                              |
|    | Polysorbate 20             | 0.35 mg                              |
|    | Microcrystalline cellulose | 13.125 mg                            |
|    | Croscarmellose sodium      | 4.375 mg                             |
| 20 | Magnesium stearate         | 1.00 mg                              |

*Tablet film coat*

|  |                                 |      |
|--|---------------------------------|------|
|  | Coating powder Opadry® II White | 4 mg |
|  | Purified water*                 | q.s. |

25

Composition 1c*Tablet core :*

|    |                                       |                                      |
|----|---------------------------------------|--------------------------------------|
|    | Compound of formula (I-a)             | 32.9 mg (i.e. 25 mg base equivalent) |
|    | Lactose monohydrate                   | 51.57 mg                             |
| 30 | Hypromellose 2910 5mPa.s              | 1.75 mg                              |
|    | Polysorbate 20                        | 0.35 mg                              |
|    | Silicified microcrystalline cellulose | 16.83 mg                             |
|    | Croscarmellose sodium                 | 5.5 mg                               |
|    | Magnesium stearate                    | 1.10 mg                              |

35

*Tablet film coat*

|                                 |        |
|---------------------------------|--------|
| Coating powder Opadry® II White | 4.4 mg |
| Purified water*                 | q.s.   |

5 Composition 1d*Tablet core :*

|                                       |                                      |
|---------------------------------------|--------------------------------------|
| Compound of formula (I-a)             | 32.9 mg (i.e. 25 mg base equivalent) |
| Lactose monohydrate                   | 49.745 mg                            |
| Polyvinylpyrrolidone                  | 3.25 mg                              |
| 10 Polysorbate 20                     | 0.35 mg                              |
| Silicified microcrystalline cellulose | 16.605 mg                            |
| Croscarmellose sodium                 | 6.05 mg                              |
| Magnesium stearate                    | 1.10 mg                              |

15 *Tablet film coat*

|                                 |        |
|---------------------------------|--------|
| Coating powder Opadry® II White | 4.4 mg |
| Purified water*                 | q.s.   |

Composition 2a20 *Tablet core :*

|                               |                                      |
|-------------------------------|--------------------------------------|
| Compound of formula (I-a)     | 110 mg (i.e. 100 mg base equivalent) |
| Lactose monohydrate           | 137.8 mg                             |
| Hypromellose 2910 15mPa.s     | 5.6 mg                               |
| Polysorbate 20                | 1.4 mg                               |
| 25 Microcrystalline cellulose | 52.5 mg                              |
| Croscarmellose sodium         | 17.5 mg                              |
| Colloidal silicon dioxide     | 1.05 mg                              |
| Magnesium stearate            | 2.45 mg                              |

30 *Tablet film coat*

|                                 |       |
|---------------------------------|-------|
| Coating powder Opadry® II White | 14 mg |
| Purified water*                 | 80 µl |

Composition 2b35 *Tablet core :*

|                           |  |
|---------------------------|--|
| Compound of formula (I-a) | 131.7 mg (i.e. 100 mg base equivalent) |
| Lactose monohydrate       | 187.3 mg                               |

|   |                            |         |
|---|----------------------------|---------|
|   | Hypromellose 2910 5mPa.s   | 5.6 mg  |
|   | Polysorbate 20             | 1.4 mg  |
|   | Microcrystalline cellulose | 52.5 mg |
|   | Croscarmellose sodium      | 17.5 mg |
| 5 | Magnesium stearate         | 4.00 mg |

*Tablet film coat*

|  |                                 |       |
|--|---------------------------------|-------|
|  | Coating powder Opadry® II White | 16 mg |
|  | Purified water*                 | q.s.  |

10

Composition 2c*Tablet core :*

|    |                                       |  |
|----|---------------------------------------|--|
|    | Compound of formula (I-a)             | 131.7 mg (i.e. 100 mg base equivalent) |
|    | Lactose monohydrate                   | 206.18 mg                              |
| 15 | Hypromellose 2910 5mPa.s              | 7.00 mg                                |
|    | Polysorbate 20                        | 1.4 mg                                 |
|    | Silicified microcrystalline cellulose | 67.32 mg                               |
|    | Croscarmellose sodium                 | 22.00 mg                               |
|    | Magnesium stearate                    | 4.40 mg                                |

20

*Tablet film coat*

|  |                                 |         |
|--|---------------------------------|---------|
|  | Coating powder Opadry® II White | 17.6 mg |
|  | Purified water*                 | q.s.    |

25 Composition 2d*Tablet core :*

|    |                                       |  |
|----|---------------------------------------|--|
|    | Compound of formula (I-a)             | 131.7 mg (i.e. 100 mg base equivalent) |
|    | Lactose monohydrate                   | 198.88 mg                              |
|    | Polyvinylpyrrolidone                  | 13.00 mg                               |
| 30 | Polysorbate 20                        | 1.4 mg                                 |
|    | Silicified microcrystalline cellulose | 66.42 mg                               |
|    | Croscarmellose sodium                 | 24.2 mg                                |
|    | Magnesium stearate                    | 4.40 mg                                |

35 *Tablet film coat*

|  |                                 |         |
|--|---------------------------------|---------|
|  | Coating powder Opadry® II White | 17.6 mg |
|  | Purified water*                 | q.s.    |



**Composition 3a***Tablet core :*

|    |                            |                                      |
|----|----------------------------|--------------------------------------|
|    | Compound of formula (I-a)  | 65.8 mg (i.e. 50 mg base equivalent) |
| 5  | Lactose monohydrate        | 203.7 mg                             |
|    | Hypromellose 2910 15mPa.s  | 5.6 mg                               |
|    | Polysorbate 20             | 1.4 mg                               |
|    | Microcrystalline cellulose | 52.5 mg                              |
|    | Croscarmellose sodium      | 17.5 mg                              |
| 10 | Colloidal silicon dioxide  | 1.05 mg                              |
|    | Magnesium stearate         | 2.45 mg                              |

*Tablet film coat*

|    |                                 |       |
|----|---------------------------------|-------|
|    | Coating powder Opadry® II White | 14 mg |
| 15 | Purified water*                 | 80 µl |

**Composition 3b***Tablet core :*

|    |                            |                                      |
|----|----------------------------|--------------------------------------|
|    | Compound of formula (I-a)  | 65.8 mg (i.e. 50 mg base equivalent) |
| 20 | Lactose monohydrate        | 93.7 mg                              |
|    | Hypromellose 2910 5mPa.s   | 2.80 mg                              |
|    | Polysorbate 20             | 0.70 mg                              |
|    | Microcrystalline cellulose | 26.25 mg                             |
|    | Croscarmellose sodium      | 8.75 mg                              |
| 25 | Magnesium stearate         | 2.00 mg                              |

*Tablet film coat*

|  |                                 |         |
|--|---------------------------------|---------|
|  | Coating powder Opadry® II White | 8.00 mg |
|  | Purified water*                 | q.s.    |

30

**Composition 3c***Tablet core :*

|    |                                       |                                      |
|----|---------------------------------------|--------------------------------------|
|    | Compound of formula (I-a)             | 65.8 mg (i.e. 50 mg base equivalent) |
|    | Lactose monohydrate                   | 103.14 mg                            |
| 35 | Hypromellose 2910 5mPa.s              | 3.50 mg                              |
|    | Polysorbate 20                        | 0.70 mg                              |
|    | Silicified microcrystalline cellulose | 33.66 mg                             |

|                       |         |
|-----------------------|---------|
| Croscarmellose sodium | 11.0 mg |
| Magnesium stearate    | 2.20 mg |

*Tablet film coat*

|   |                                 |         |
|---|---------------------------------|---------|
| 5 | Coating powder Opadry® II White | 8.80 mg |
|   | Purified water*                 | q.s.    |

Composition 3d*Tablet core :*

|    |                                       |                                      |
|----|---------------------------------------|--------------------------------------|
| 10 | Compound of formula (I-a)             | 65.8 mg (i.e. 50 mg base equivalent) |
|    | Lactose monohydrate                   | 99.49 mg                             |
|    | Polyvinylpyrrolidone                  | 6.50 mg                              |
|    | Polysorbate 20                        | 0.70 mg                              |
|    | Silicified microcrystalline cellulose | 33.21 mg                             |
| 15 | Croscarmellose sodium                 | 12.1 mg                              |
|    | Magnesium stearate                    | 2.20 mg                              |

*Tablet film coat*

|    |                                 |         |
|----|---------------------------------|---------|
|    | Coating powder Opadry® II White | 8.80 mg |
| 20 | Purified water*                 | q.s.    |

Composition 4*Tablet core :*

|    |                                       |                                      |
|----|---------------------------------------|--------------------------------------|
|    | Compound of formula (I-a)             | 98.7 mg (i.e. 75 mg base equivalent) |
| 25 | Lactose monohydrate                   | 149.235 mg                           |
|    | Polyvinylpyrrolidone                  | 9.75 mg                              |
|    | Polysorbate 20                        | 1.05 mg                              |
|    | Silicified microcrystalline cellulose | 49.815 mg                            |
|    | Croscarmellose sodium                 | 18.15 mg                             |
| 30 | Magnesium stearate                    | 3.30 mg                              |

*Tablet film coat*

|  |                                 |         |
|--|---------------------------------|---------|
|  | Coating powder Opadry® II White | 13.2 mg |
|  | Purified water*                 | q.s.    |

Composition 5a*Tablet core :*

|   |                                       |  |
|---|---------------------------------------|--|
|   | Compound of formula (I-a)             | 197.4 mg (i.e. 150 mg base equivalent) |
|   | Lactose monohydrate                   | 298.47 mg                              |
| 5 | Polyvinylpyrrolidone                  | 19.5 mg                                |
|   | Polysorbate 20                        | 2.1 mg                                 |
|   | Silicified microcrystalline cellulose | 99.63 mg                               |
|   | Croscarmellose sodium                 | 36.30 mg                               |
|   | Magnesium stearate                    | 6.6 mg                                 |

10

*Tablet film coat*

|  |                                 |          |
|--|---------------------------------|----------|
|  | Coating powder Opadry® II White | 19.80 mg |
|  | Purified water*                 | q.s.     |

15 Composition 5b*Tablet core :*

|    |                                       |  |
|----|---------------------------------------|--|
|    | Compound of formula (I-a)             | 197.4 mg (i.e. 150 mg base equivalent) |
|    | Lactose monohydrate                   | 309.42 mg                              |
|    | Hypromellose 2910 5 mPa.s             | 10.5 mg                                |
| 20 | Polysorbate 20                        | 2.1 mg                                 |
|    | Silicified microcrystalline cellulose | 100.98 mg                              |
|    | Croscarmellose sodium                 | 33.00 mg                               |
|    | Magnesium stearate                    | 6.6 mg                                 |

25 *Tablet film coat*

|  |                                 |          |
|--|---------------------------------|----------|
|  | Coating powder Opadry® II White | 19.80 mg |
|  | Purified water*                 | q.s.     |

\* not present in final tablet

30

The above tablets are prepared by dissolving hypromellose or polyvinylpyrrolidone and polysorbate 20 in purified water (q.s.) followed by spraying said solution on fluidized powder consisting of a mixture of Form A and lactose monohydrate. The obtained granulate is dried, sieved and mixed with microcrystalline cellulose or silicified microcrystalline cellulose, croscarmellose sodium and optionally colloidal silicon dioxide. After addition of Magnesium stearate, the powder mixture is compressed into

35

tablets followed by film coating the tablets with a suspension of Coating powder Opadry® II White in purified water.

In the above compositions, microcrystalline cellulose is preferably Avicel® PH101,  
5 croscarmellose sodium is preferably Ac-Di-Sol®; silicified microcrystalline cellulose is preferably Prosolv®HD90; polyvinylpyrrolidone is preferably PVP K29-32.

#### **E. In vivo bioavailability study**

The *in vivo* bioavailability of the compound of formula (I-a) was studied in male beagle  
10 dogs.

The formulations used for oral administration were :

- a PEG 400 solution of (E) 4-[[4-[[4-(2-cyanoethenyl)-2,6-dimethylphenyl]amino]-2-pyrimidinyl]amino]benzotrile free base (25 mg/ml) (group I);
- 15 - a capsule (size 0; red cap-red body) containing a mixture consisting of 32.9 mg of compound of formula (I) (i.e. 25 mg base equivalent); 300 mg lactose DC (direct compression); 0.59 mg of silicon dioxide; 0.59 mg of sodium lauryl sulphate (group II);

The formulations of group II were orally administered at a dose level of 5 mg base  
20 equivalent/kg. The formulations were prepared based on previously determined body weights of the animals. The exact administered dose was calculated using the body weights just before dosing and amounted on average to 5 mg base equivalent/kg.

The reference PEG400 formulation (group I) was administered orally via gavage by use  
25 of a stomach tube at a daily volume of 0.2 ml/kg body weight. The stomach tube was flushed with 2 ml of PEG400 per dog, followed by the placement of a syringe of 10 ml filled with air on the stomach tube. The tube was removed after a pause of 10 to 15 seconds.

30 The reference PEG400 solution (group I) and the compound of formula (I-a) (group II) were dosed according to a cross-over design. The first group of 2 dogs was dosed with the reference formulation of group I at 5 mg eq./kg (0.2 ml/kg) and the second group of 2 dogs was dosed with the fumarate salt formulation of group II at 5 mg basd eq./kg (2 capsules/dog). After a washout-period of 14 days, the first group of dogs was dosed  
35 with the fumarate salt (group II) and the second group with the reference formulation (group I).

Blood samples (3 ml on EDTA) were taken from a jugular vein at 0 (= predose), 0.5, 1, 2, 4, 6, 8, 24, 32, 48, 72 and 96 hours after dosing on day 0 and day 14.

Immediately after blood sampling, blood samples were shielded from light.

Blood samples were centrifuged at room temperature at 1900 x g for about 10 minutes to allow plasma separation. Plasma was separated, transferred into a second tube, and frozen within two hours of blood sampling.

Plasma samples were analysed individually for (E)-4-[[4-[[4-(2-cyanoethenyl)-2,6-dimethylphenyl]amino]-2-pyrimidinyl]amino]benzotrile by means of a validated LC-MS/MS method.

LC-MS/MS analysis was carried out on an API-3000 system (Applied Biosystems), which was coupled to an HPLC-system (Agilent).

Individual plasma concentration-time profiles were subjected to a non-compartmental pharmacokinetic analysis using WinNonlin software (WinNonlin Release 4.0.1a Enterprise, Pharsight Corporation, Mountain View, California, U.S.A.). Peak plasma concentrations ( $C_{max}$ ) and corresponding peak times ( $T_{max}$ ) were calculated. The area under the plasma concentration-time curve ( $AUC_{0-t}$ ) was calculated using the linear up/log down trapezoidal rule. The  $AUC_{0-\infty}$  was calculated as the sum of  $AUC_{0-96h}$  and  $C_{96h}/\beta$ , with  $\beta$ , the elimination rate constant, determined by log-linear regression of the terminal plasma concentration-time data. Mean plasma concentrations and mean pharmacokinetic parameters were calculated per formulation.

Mean plasma concentrations and basic pharmacokinetic parameters of group I and II are given in Table 3.

**Table 3:** Mean ( $\pm$  S.D) plasma concentrations together with some basic pharmacokinetic parameters of (E)-4-[[4-[[4-(2-cyanoethenyl)-2,6-dimethylphenyl]amino]-2-pyrimidinyl]amino]benzotrile in male beagle dogs after oral administration of formulation of group I and II dosed at 5 mg base eq./kg.

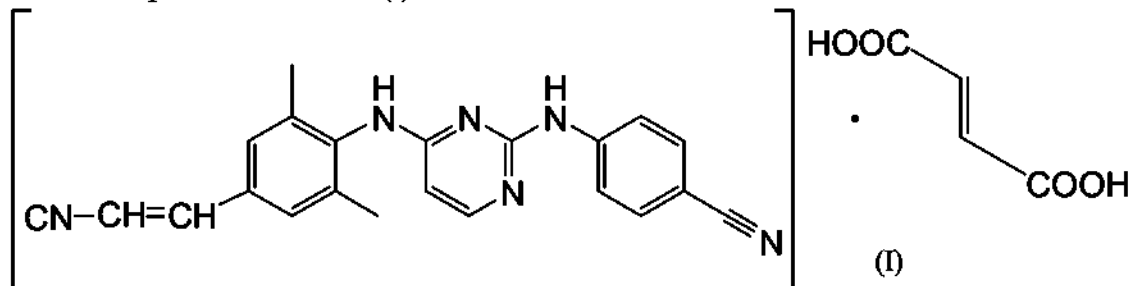
| Time (h) | Group I |       |     | Group II |       |      |
|----------|---------|-------|-----|----------|-------|------|
| 0        | <1.0    |       |     | <1.0     |       |      |
| 0.5      | 104     | $\pm$ | 79  | 5.64     | $\pm$ | 2.76 |
| 1        | 258     | $\pm$ | 79  | 108      | $\pm$ | 75   |
| 2        | 478     | $\pm$ | 83  | 362      | $\pm$ | 132  |
| 4        | 462     | $\pm$ | 155 | 372      | $\pm$ | 121  |

| Time (h)                             | Group I |   |      | Group II |   |      |
|--------------------------------------|---------|---|------|----------|---|------|
| <b>6</b>                             | 354     | ± | 111  | 346      | ± | 141  |
| <b>8</b>                             | 256     | ± | 117  | 247      | ± | 94   |
| <b>24</b>                            | 179     | ± | 106  | 187      | ± | 50   |
| <b>32</b>                            | 150     | ± | 89   | 163      | ± | 66   |
| <b>48</b>                            | 79.4    | ± | 49.1 | 89.2     | ± | 39.7 |
| <b>72</b>                            | 42.5    | ± | 25.1 | 50.9     | ± | 29.7 |
| <b>96</b>                            | 21.6    | ± | 15.6 | 25.0     | ± | 12.6 |
| <b>C<sub>max</sub></b> (ng/ml)       | 523     | ± | 104  | 417      | ± | 125  |
| <b>T<sub>max</sub></b> (h)           | 3.0     | ± | 1.2  | 4.0      | ± | 2.3  |
| <b>AUC<sub>0-72</sub></b> (ng.h/ml)  | 11497   | ± | 5437 | 11527    | ± | 2896 |
| <b>AUC<sub>0-inf</sub></b> (ng.h/ml) | 12299   | ± | 5906 | 12489    | ± | 3405 |

Based on the AUC-values, the fumarate salt capsule formulation seems bioequivalent to the reference PEG400 solution of (E)-4-[[4-[[4-(2-cyanoethyl)-2,6-dimethylphenyl]amino]-2-pyrimidinyl]amino]benzotrile.

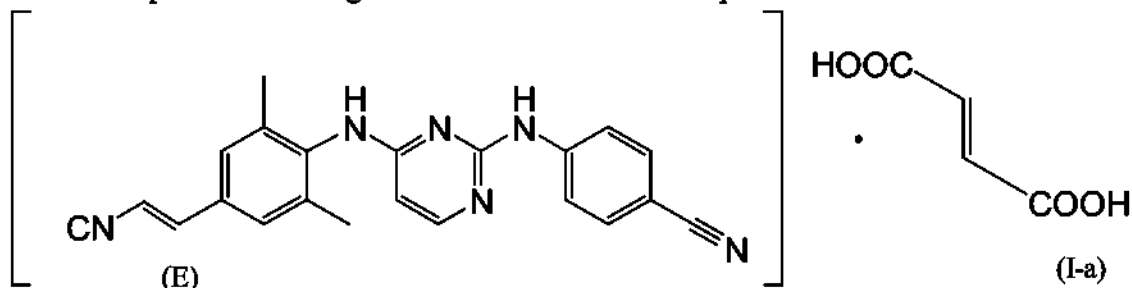
Claims

1. A compound of formula (I)



5 a *N*-oxide or a stereochemically isomeric form thereof.

2. A compound according to claim 1 wherein the compound is



10 3. A compound according to claim 1 or 2 for use as a medicine.

4. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and as active ingredient a therapeutically effective amount of a compound as claimed in claim 1 or 2.

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5. A pharmaceutical composition according to claim 4 wherein the composition is suitable for oral administration.

20

6. A pharmaceutical composition according to claim 4 or 5 wherein the composition is a solid composition.

7. A pharmaceutical composition according to any one of claims 4 to 6 further comprising a wetting agent.

25

8. A pharmaceutical composition according to claim 7 wherein the wetting agent is Tween.

9. A pharmaceutical composition according to any one of claims 4 to 8 wherein the composition is in the form of a tablet.
10. A pharmaceutical composition according to claim 9 which is film-coated.
- 5
11. A pharmaceutical composition according to any one of claims 4 to 10 having the following composition
- (a) from 5 to 50% of active ingredient;
  - (b) from 0.01 to 5 % of a wetting agent;
  - 10 (c) from 40 to 92% of a diluent;
  - (d) from 0 to 10 % of a polymer;
  - (e) from 2 to 10 % of a disintegrant;
  - (f) from 0.1 to 5% of a glidant;
  - (g) from 0.1 to 1.5 % of a lubricant.
- 15
12. A process for preparing a pharmaceutical composition according to any one of claims 4 to 11 comprising the following steps :
- (i) dry blending the active ingredient and part of the diluent;
  - (ii) preparing a binder solution by dissolving the binder and the wetting agent in  
20 the binder solution solvent;
  - (iii) spraying the binder solution obtained in step (ii) on the mixture obtained in step (i);
  - (iv) drying the wet powder obtained in step (iii) followed by sieving and optionally mixing;
  - 25 (v) mixing the remaining part of the diluent, the disintegrant and the optional glidant in the mixture obtained in step (iv);
  - (vi) optionally adding the lubricant to the mixture obtained in step (v);
  - (vii) compressing the mixture obtained in step (vi) into a tablet;
  - (viii) optionally film-coating the tablet obtained in step (vii).
- 30
13. Use of a compound as claimed in claim 1 or 2 for the manufacture of a medicament for the treatment or the prevention of HIV infection.
- 35
14. Process for the preparation of a compound of formula (I) or (I-a) as claimed in claim 1 or 2 characterized by reacting the corresponding free base with fumaric acid in the presence of a suitable acid.



15. Process according to claim 14 wherein the suitable acid is acetic acid.

**INTERNATIONAL SEARCH REPORT**

International Application No  
PCT/EP2005/054341

**A. CLASSIFICATION OF SUBJECT MATTER**  
A61P31/18      A61K31/505

According to International Patent Classification (IPC) or to both national classification and IPC

**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)  
A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the International search (name of data base and, where practical, search terms used)  
EPO-Internal, WPI Data, CHEM ABS Data, PAJ, EMBASE, MEDLINE, SCISEARCH, BIOSIS

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

| Category * | Citation of document, with indication, where appropriate, of the relevant passages  | Relevant to claim No. |
|------------|---|-----------------------|
| X          | WO 2004/016581 A (JANSSEN PHARMACEUTICA N.V; SCHILS, DIDIER, PHILIPPE, ROBERT; WILLEMS,) 26 February 2004 (2004-02-26)<br>page 4, paragraph 3<br>page 15, paragraph 5             | 1-15                  |
| X          | WO 03/016306 A (JANSSEN PHARMACEUTICA N.V; GUILLEMONT, JEROME, EMILE, GEORGES; PALANDJ) 27 February 2003 (2003-02-27)<br>example B1<br>page 1, paragraph 1<br>page 8, paragraph 5 | 1-15                  |
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Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

\* Special categories of cited documents :

- \*A\* document defining the general state of the art which is not considered to be of particular relevance
- \*E\* earlier document but published on or after the international filing date
- \*L\* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- \*O\* document referring to an oral disclosure, use, exhibition or other means
- \*P\* document published prior to the international filing date but later than the priority date claimed

- \*T\* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- \*X\* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- \*Y\* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- \*Z\* document member of the same patent family

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|---|--|
| Date of the actual completion of the international search<br><br>13 December 2005 | Date of mailing of the international search report<br><br>22/12/2005 |
|---|--|

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| Name and mailing address of the ISA<br>European Patent Office, P.B. 5818 Patentlaan 2<br>NL - 2280 HV Rijswijk<br>Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,<br>Fax: (+31-70) 340-3016 | Authorized officer<br><br>Strack, E |
|--|-------------------------------------|

# INTERNATIONAL SEARCH REPORT

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|  |   |                  | NO 20040633             | A 12-03-2004     |
|  |   |                  | NZ 530951               | A 28-10-2005     |
|  |   |                  | US 2004198739           | A1 07-10-2004    |
|  |   |                  | WO 2005021001           | A                |



(12) **United States Patent**  
**Young et al.**

(10) **Patent No.: US 6,534,508 B2**  
(45) **Date of Patent: \*Mar. 18, 2003**

(54) **METHODS AND COMPOSITIONS FOR TREATING INFECTION USING OPTICALLY PURE (S)-LOMEFLOXACIN**

(75) Inventors: **James W. Young**, Palo Alto, CA (US);  
**A. K. Gunnar Aberg**, Westborough, MA (US)

(73) Assignee: **Sepracor Inc.**, Marlborough, MA (US)

(\* ) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 3 days.

This patent is subject to a terminal disclaimer.

(21) Appl. No.: **09/996,822**

(22) Filed: **Nov. 30, 2001**

(65) **Prior Publication Data**

US 2002/0061894 A1 May 23, 2002

**Related U.S. Application Data**

(63) Continuation of application No. 09/794,006, filed on Feb. 28, 2001, now Pat. No. 6,337,339, which is a continuation of application No. 09/332,197, filed on Jun. 14, 1998, now Pat. No. 6,274,595, which is a continuation of application No. 08/455,471, filed on May 31, 1995, now Pat. No. 6,075,024, and a continuation-in-part of application No. 08/285,610, filed on Aug. 3, 1994, now abandoned, which is a continuation of application No. 07/981,469, filed on Nov. 25, 1992, now abandoned, which is a continuation-in-part of application No. 07/799,243, filed on Nov. 27, 1991, now abandoned.

(51) **Int. Cl.**<sup>7</sup> ..... **A61K 31/495**; A61K 31/50;  
A61K 31/47  
(52) **U.S. Cl.** ..... **514/254**; 514/312  
(58) **Field of Search** ..... 514/312, 254

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Primary Examiner—Russell Travers  
(74) Attorney, Agent, or Firm—Pennie & Edmonds LLP

(57) **ABSTRACT**

Methods and compositions are disclosed utilizing the optically pure (S)-isomer of lomefloxacin to treat bacterial infection. In particular, this compound is a potent drug for the treatment of Mycobacteria infection.

**14 Claims, No Drawings**

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## METHODS AND COMPOSITIONS FOR TREATING INFECTION USING OPTICALLY PURE (S)-LOMEFLOXACIN

The application is continuation of application Ser. No. 09/794,006, filed Feb. 28, 2001, now U.S. Pat. No. 6,337,339, which is a continuation of application Ser. No. 09/332,197, filed Jun. 14, 1998, now U.S. Pat. No. 6,274,595, which is a continuation of application Ser. No. 08/455,471, filed May 31, 1995, now U.S. Pat. No. 6,075,024 and a continuation-in-part of application Ser. No. 08/285,610, filed Aug. 3, 1994, now abandoned; which is a continuation of application Ser. No. 07/981,469, filed Nov. 25, 1992, now abandoned, which is a continuation-in-part of application Ser. No. 07/799,243, filed Nov. 27, 1991, now abandoned.

### FIELD OF THE INVENTION

This invention relates to novel compositions of matter containing optically pure (S)-lomefloxacin. These compositions possess potent activity in treating various infections while avoiding adverse effects associated with racemic lomefloxacin including but not limited to headache, stomach discomfort, gastrointestinal disorders, hypoglycemia, renal and hepatic dysfunction, allergic reactions and respiratory distress, and arthropathy, such as cartilage lesions and erosion and abnormalities in bone growth in immature patients. Additionally, these novel compositions of matter containing optically pure (S)-lomefloxacin are useful in treating infection in those patients with impaired renal function. Also disclosed are methods for treating the above-described conditions in a human while avoiding adverse effects that are associated with the racemic mixture of lomefloxacin, by administering the (S)-isomer of lomefloxacin to said human.

### BACKGROUND OF THE INVENTION

#### Steric Relationship and Drug Action

Many organic compounds exist in optically active forms, i.e., they have the ability to rotate the plane of plane-polarized light. In describing an optically active compound, the prefixes D and L or R and S are used to denote the absolute configuration of the molecule about its chiral center(s). The prefixes d and l or (+) and (-) are employed to designate the sign of rotation of plane-polarized light by the compound, with (-) or l meaning that the compound is levorotatory. A compound prefixed with (+) or d is dextrorotatory. For a given chemical structure, these compounds, called stereoisomers, are identical except that they are mirror images of one another. A specific stereoisomer may also be referred to as an enantiomer, and a mixture of such isomers is often called an enantiomeric mixture. A 50:50 mixture of enantiomers is referred to as a racemic mixture.

Stereochemical purity is of importance in the field of pharmaceuticals, where 12 of the 20 most prescribed drugs exhibit chirality. A case in point is provided by the L-form of the  $\beta$ -adrenergic blocking agent, propranolol, which is known to be 100 times more potent than the D-enantiomer.

Furthermore, optical purity is important since certain isomers may actually be deleterious rather than simply inert. For example, it has been suggested that the D-enantiomer of thalidomide was a safe and effective sedative when prescribed for the control of morning sickness during pregnancy, and that the corresponding L-enantiomer was a potent teratogen.

#### Racemic Lomefloxacin

Lomefloxacin is described in U.S. Pat. No. 4,528,287 and Japan Patent Publication No. 64979 (1985). Lomefloxacin is

currently available commercially in the United States as MAXAQUIN® as well as in Argentina, Japan, Mexico and certain countries in Asia and Eastern Europe, as the racemic mixture, i.e., it is a 1:1 mixture of optical isomers. It is the optically pure, or substantially optically pure (S)-isomer of lomefloxacin, which is the subject of the present invention, hereinafter referred to as (S)-lomefloxacin.

Racemic lomefloxacin, having the chemical name 1-ethyl-6,8-difluoro-1,4-dihydro-7-(3-methyl-piperazinyl)-4-oxo-3-quinolinecarboxylic acid, belongs to the quinoline class of antibiotics. The quinoline antibiotics, in general, exhibit a broad spectrum of antibacterial action, demonstrating effectiveness against both Gram-positive and Gram-negative bacterial strains. Quinoline antibiotics have been shown to be effective in treating infections of the respiratory, genito-urinary, and gastrointestinal tracts. They have also demonstrated utility in the treatment of patients with cystic fibrosis and pulmonary infections. Effectiveness has also been demonstrated in the treatment of intra-abdominal, bone and joint, skin, soft-tissue, pelvic, and eye, ear, nose, and throat infections.

Examples of Gram-positive bacteria include but are not limited to *Streptococcus*, *Staphylococcus*, *Mycobacteria*, *Listeriaceae*, *Bacillus* and *Nocardia*. A number of Gram-positive bacteria cause respiratory tract infections including, but not limited to, *Streptococcus pneumoniae* and *Mycobacteria*. The majority of clinically diagnosed cases of pneumonia are caused by *Streptococcus pneumoniae*. However, recently there has been an increase in the number of pneumonias caused by *Mycobacteria*. Three different species of *Mycobacteria*, *Mycobacteria tuberculosis* (*M. tuberculosis*), *Mycobacteria bovis* (*M. bovis*), and *Mycobacteria africanum* (*M. africanum*) can cause a disease state commonly known as tuberculosis. Tuberculosis is a highly contagious disease which is most commonly transmitted by aerosolized respiratory secretions. While infection usually begins in the lungs, mycobacteria can easily spread to other organs as well, including eyes, intestine, pericardium, peritoneum, bone and joints, urinary tract, and lymphatic system. See The Merck Manual, 16th ed., pp. 131-146, Merck Sharpe & Dohme.

In addition to *M. tuberculosis*, *M. bovis*, and *M. africanum*, other species of *Mycobacteria* include *M. chelonae*, *M. Marinum*, *M. avium* and *M. kansasii*.

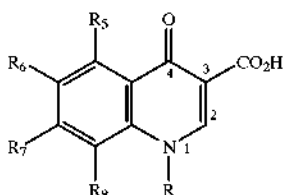
The quinoline antibiotics derive their activity through inhibition of the bacterial enzyme, DNA gyrase, which is responsible for catalyzing the bacterial DNA supercoiling necessary to pack DNA filaments into bacterial cells. This inhibition causes irreversible chromosome damage leading to bacterial cell death. The selectivity of quinoline antibiotics for bacterial cells is the result of the supercoiling mechanism in eukariotic cells being mediated by a different set of enzymes not susceptible to quinoline inhibition. Quinoline antibiotics are also thought to interfere with proper bacterial cell membrane function, also contributing to cell death.

The first quinoline antibiotic to be commercialized, nalidixic acid, was discovered following the observation that the structurally similar 6-chloro-1H-ethyl-4-oxoquinolone-3-carboxylic acid, a minor by-product of the commercial production of the antimalarial agent chloroquine, exhibited weak antibacterial action. Since the discovery of nalidixic acid, some 7,000 analogues belonging to approximately 16 different ring systems have been synthesized and tested for antibacterial action. From this data, a comprehensive structure/activity relationship has been elucidated.

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Structural activity studies have demonstrated that substitution at position 1 and a carbonyl substitution at position 4 on the quinoline ring appear to be required for antimicrobial activity. No substitution at position 2 and a carboxyl function at position 3 also appear to be required for activity. The only exception appears to be a thiazolidone ring fused at positions 2 and 3. Depending on modification, the presence of additional fused rings, as well as various ring substitutions can be either beneficial or detrimental to activity.

FIG. 1



Racemic lomefloxacin exhibits a broad spectrum of antibacterial action, demonstrating effectiveness against both Gram-positive and Gram-negative bacterial strains. Lomefloxacin has shown to be more effective against Gram-negative bacteria. In particular, lomefloxacin has shown excellent bacteriocidal activity against strains of Enterobacteriaceae, *Haemophilus influenzae*, *Neisseria gonorrhoeae*, *Branhamella catarrhalis*, *L. pneumophila*, and good-to-moderate activity against strains of Acinetobacter, *Pseudomonas aeruginosa*, *Staphylococcus aureus* and *Staphylococcus epidermidis*, but poor activity against *Pseudomonas cepacia*. There is only a low propensity for bacteria to develop a resistance to lomefloxacin by spontaneous mutation. However, development of resistance is facilitated when bacteria are exposed to sub-inhibitory concentrations of the antibiotic.

Lomefloxacin has an average elimination half-life of approximately 8 hours with peak plasma concentrations occurring at approximately 1 hour after oral dosing in humans. Its long half-life and dose proportionality have led to introduction of lomefloxacin as the first, once-daily 4-quinolone antibiotic.

Furthermore, unlike ciprofloxacin, lomefloxacin does not interfere with the metabolism of theophylline. Likewise, co-administration of ranitidine with lomefloxacin has no effect on lomefloxacin's pharmacokinetics. However, co-administration of sucralfate with lomefloxacin, presumably through aluminum complexation, does reduce the absorption of the antibiotic. In patients with reduced renal function, lomefloxacin exhibits reduced renal clearance, with a consequential prolongation of the half-life by up to 24 hours. Antibacterial levels of lomefloxacin are therefore maintained in patients with reduced renal function for up to five days.

Little is known about the pharmacology of the individual isomers of lomefloxacin. The pure enantiomer form of ofloxacin, a related quinolone antibiotic, has been studied (Antimicrob. Agents Chemother., 1988, 32(9), 1336-1340). The (S)-isomer of ofloxacin has been reported to be twice as potent a bactericide as the racemate against a variety of Gram-positive and Gram-negative pathogens.

The racemic mixture of lomefloxacin is presently used primarily as an antibiotic agent for treatment of infection of the upper respiratory and urinary tracts. Viral infections of the respiratory tract are acute illnesses with local and systemic manifestations. Coryza (common cold), pharyngitis,

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laryngitis (including croup), and tracheobronchitis are common respiratory syndromes. See, for example, Merck Manual 5th Ed., p. 169, Merck, Sharpe & Dohme Research Laboratories (1987). Bacterial infections of the lower urinary tract are very common. The majority of urinary tract infections are caused by Gram-negative bacteria. Organisms gaining access to the urethra may colonize on the periurethral glands and produce acute and chronic infection. This condition is termed urethritis. Infections of the prostate gland give rise to the condition prostatitis. Enteric, Gram-negative organisms are the most common cause of prostate infection. Merck Manual 5th Ed., p. 1610, Merck, Sharpe & Dohme Research Laboratories (1987).

Additionally, racemic lomefloxacin has also been used in treating enteritis, sexually transmitted diseases, obstetric and gynecological infections, surgical infections, skin, soft tissue and joint infections, otorhinolaryngologic infections and ophthalmological infections.

Lomefloxacin has been shown to have activity against *Mycobacteria tuberculosis*, the most common causative agent of the tuberculosis disease. (Piersimoni et al., 1992, "In Vitro Activity of the New Quinolone Lomefloxacin against *Mycobacterium tuberculosis*," Am. Rev. Respir. Dis. 146:1445-1447). Piersimoni et al. compared the inhibitory effect of ofloxacin, ciprofloxacin, and lomefloxacin against 79 strains of *M. tuberculosis* which were susceptible to conventional drug therapy and 11 strains of *M. tuberculosis* which were resistant to conventional drug therapy. Their data showed that the MIC50 and MIC90 of lomefloxacin in the 79 susceptible strains were, respectively, 0.96 µg/ml and 1.02 µg/ml with a range of 0.5 to 2.0 µg/ml. The MIC50 and MIC90 of lomefloxacin in the 11 resistant strains were, respectively, 1.0 µg/ml and 1.1 µg/ml. Piersimoni et al. concluded that lomefloxacin, orally administered once daily could achieve adequate serum levels to inhibit *M. tuberculosis*.

Although lomefloxacin and quinolone antibiotics have several advantages, they also have disadvantages, namely, adverse effects. The adverse effects of quinolone antibiotics in general include arthropathy, headache, stomach discomfort, gastrointestinal disorders, hypoglycemia, renal and hepatic dysfunction, allergic reactions and respiratory distress, and central nervous system effects including convulsions, increased intracranial pressure, and toxic psychoses. The adverse effects of lomefloxacin, in particular, include but are not limited to headache, stomach discomfort, gastrointestinal disorders, dizziness, phototoxicity, and arthropathy, such as cartilage lesions and erosion and abnormalities in bone growth in immature patients. Thus, it would be particularly desirable to find a compound with the advantages of the racemic mixture of lomefloxacin which would not have the aforementioned disadvantages.

#### SUMMARY OF THE INVENTION

It has now been discovered that the optically pure (S)-isomer of lomefloxacin is effective in treating infection in a human. Further, it has also been discovered that the optically pure (S)-isomer of lomefloxacin is effective in treating infection in a human while avoiding adverse effects associated with the administration of racemic lomefloxacin, including but not limited to headache, stomach discomfort, gastrointestinal disorders, hypoglycemia, renal and hepatic dysfunction, allergic reactions and respiratory distress, and arthropathy, such as cartilage lesions and erosion and abnormalities in bone growth in immature patients. The present invention also includes methods for treating the above-

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described conditions in a human while avoiding the adverse effects that are associated with the racemic mixture of lomefloxacin, by administering the optically pure (S)-isomer of lomefloxacin to said human.

#### DETAILED DESCRIPTION OF THE INVENTION

The present invention is a method of treating infection in a human which comprises administering to the human, an amount of (S)-lomefloxacin, or a pharmaceutically acceptable thereof, substantially free of its (R)-stereoisomer, said amount being sufficient to alleviate infection.

The present invention encompasses a method of treating infection in a human while avoiding the concomitant liability of adverse effects associated with the administration of racemic lomefloxacin, which comprises administering to said human, an amount of (S)-lomefloxacin, or a pharmaceutically acceptable salt thereof, substantially free of its (R)-stereoisomer, said amount being sufficient to alleviate infection, but insufficient to cause said adverse effects associated with administration of racemic lomefloxacin.

The present invention also encompasses an antibiotic composition for treating infection in a human which comprises, an amount of (S)-lomefloxacin or a pharmaceutically acceptable salt thereof, substantially free of its (R)-stereoisomer, said amount being sufficient to alleviate said infection but insufficient to cause adverse effects associated with lomefloxacin.

The available racemic mixture of lomefloxacin (i.e., a 1:1 mixture of the two enantiomers) possesses antibiotic activity, and provides therapy and a reduction of symptoms in a variety of conditions and disorders related to bacterial infection; however, this racemic mixture, while offering the expectation of efficacy, causes adverse effects. Utilizing the substantially optically pure (S)-isomer of lomefloxacin results in clearer dose-related definitions of efficacy, diminished adverse effects, and accordingly, an improved therapeutic index. It is therefore, more desirable to use the (S)-isomer of lomefloxacin.

The term "adverse effects" includes, but is not limited to headache, stomach discomfort, gastrointestinal disorders, hypoglycemia, renal and hepatic dysfunction, allergic reactions, nausea, photosensitivity (phototoxicity), dizziness, diarrhea, respiratory distress, and arthropathy, such as cartilage lesions and erosion and abnormalities in bone growth in immature patients. (See Physician's Desk Reference, 1994, p. 2216.)

The term "substantially free of its (R)-stereoisomer" as used herein means that the composition contains a greater proportion of the (S)-isomer of lomefloxacin in relation to the (R)-isomer of lomefloxacin. In a preferred embodiment the term "substantially free of its (R)-isomer" as used herein means that the composition contains at least 90% by weight of (S)-lomefloxacin, and 10% by weight or less of (R)-lomefloxacin. These percentages are based on the total amount of lomefloxacin present in the composition. In the most preferred embodiment the term "substantially free of the (R)-stereoisomer" means that the composition contains at least 99% by weight (S)-lomefloxacin, and 1% or less of (R)-lomefloxacin. In another preferred embodiment, the term "substantially free of its (R)-stereoisomer" as used herein means that the composition contains 100% by weight of (S)-lomefloxacin. The terms "substantially optically pure (S)-isomer of lomefloxacin" and "optically pure (S)-isomer of lomefloxacin" are also encompassed by the above-described amounts.

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The term "amount sufficient to alleviate infection" as used herein means an amount which eliminates or inhibits the growth of foreign microorganisms that are harmful to the normal functioning of the host organism, particularly humans.

It has unexpectedly been discovered that (S)-lomefloxacin is more active than (R,S)- or (R)-lomefloxacin in inhibiting certain species of Mycobacteria, including but not limited to *M. tuberculosis*, *M. chelonae* and *M. marinum*. It has further been discovered that (S)-lomefloxacin is more active than (R)-lomefloxacin in inhibiting *M. avium* and *M. kansasii*.

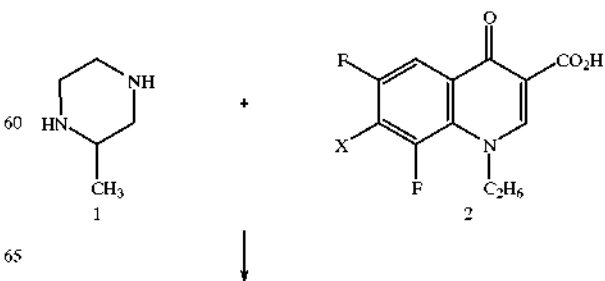
In a specific embodiment of the present invention, an effective amount of (S)-lomefloxacin is used to treat an individual infected with Mycobacteria; said effective amount being sufficient to reduce the infection. In an preferred embodiment, the Mycobacteria is selected from a group consisting of *M. tuberculosis*, *M. chelonae*, *M. marinum*, *M. avium* and *M. kansasii*.

Thus, the present invention encompasses an improved method of treating infection in a human or animal, caused by mycobacteria which comprises administering an effective amount of S-lomefloxacin, substantially free of its R-stereoisomer. In addition, the invention encompasses the treatment of mycobacteria infection in a human by administering an effective amount of S-lomefloxacin, substantially free of its R-stereoisomer alone or in combination with another therapeutic agent, such as an antiviral or another antibiotic. Suitable antivirals or antibiotics are known to those skilled in the art and include but are not limited to AZT, acyclovir, gancyclovir, ribavirin; and penicillin, cephalixm, amikacin, gentamycin, ethanbutil, rifampacin, erythromycin, and tetracycline.

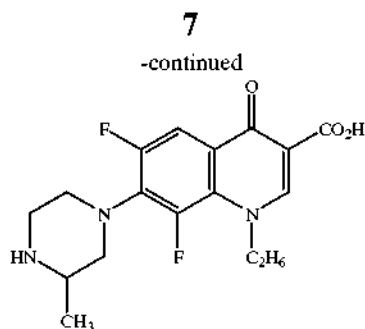
As a result of the increased activity of S-lomefloxacin over that of the racemate or R-lomefloxacin in the treatment of certain bacterial infections, the effective dose may be lower than the doses described herein, e.g., from about 50 mg to 400 mg per day; preferably 50 mg to 200 mg per day. However, the doses described further herein may also be used if desired or necessary for a particular patient.

The chemical synthesis of the racemic mixture of lomefloxacin can be performed by the method described in U.S. Pat. No. 4,528,287. The method involves the reaction of 1,4-dihydro-4-oxoquinoline-3-carboxylic acid 2 (where X=Cl or F) with piperazine 1. The preparation of the type 2 compounds has previously been described in Japanese Patent Publication No. 141286/1978, Japanese Patent Publication No. 47658/1980 and Japanese Patent Publication No. 30964/1981.

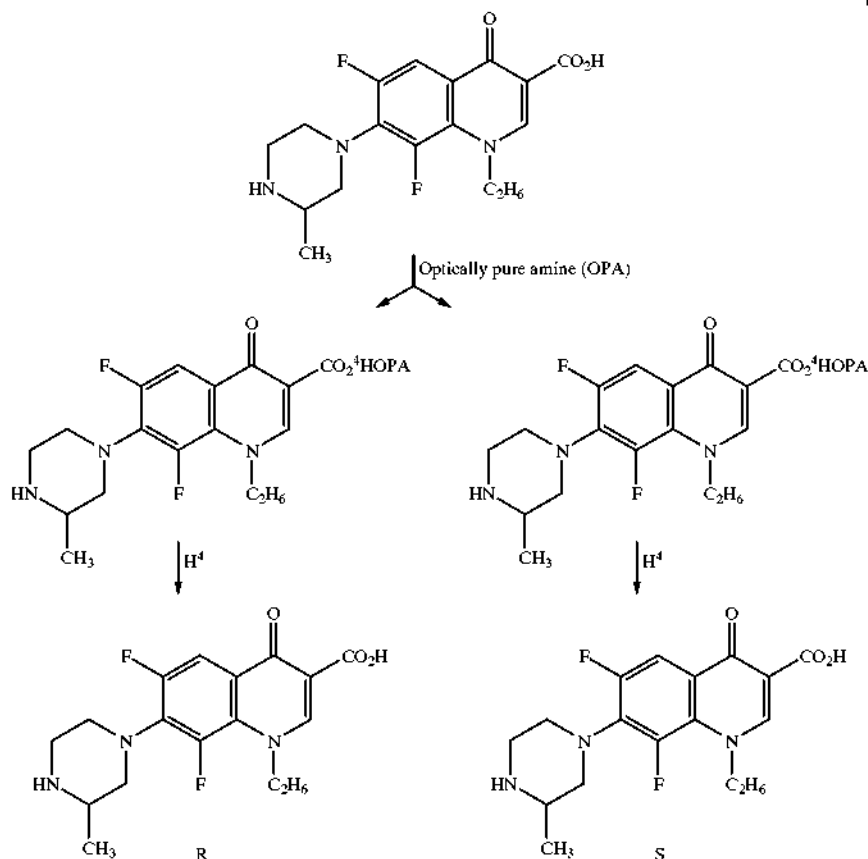
FIG. 2







Furthermore, the (S)-isomer of lomefloxacin may be obtained by resolution of the mixture of enantiomers of lomefloxacin using conventional means such as an optically active resolving acid; see, for example "Stereochemistry of Carbon Compounds," by D. L. Eliel (McGraw Hill 1962) and Lochmuller, C. H. et al., *J. Chromatogr.* 113:(3) 283-302 (1975). (S)-Lomefloxacin can be prepared from the racemate through the diastereomeric crystallization scheme shown below:



Racemic lomefloxacin is treated with an optically pure base (an amine is shown above) to give a pair of diastereomeric salts. The difference in solubility between the two diastereomers allows one to be selectively crystallized from the solvent while the other remains in solution. Crystals of the single diastereomer are then separated from the other diastereomer by filtration. Once separated, the diastereomers can be converted back to the original enantiomers by treatment with acid.

The magnitude of a prophylactic or therapeutic dose of (S)-lomefloxacin in the acute or chronic management of disease will vary with the severity of the condition to be treated and the route of administration. The dose, and perhaps the dose frequency, will also vary according to the age, body weight, and response of the individual patient. In general, the total daily dose ranges, for the conditions described herein, is from about 100 mg to about 400 mg. However, the dosage may be as high as about 800 mg. Preferably, a daily dose range should be between about 100 mg to about 200 mg. In managing the patient, the therapy should be initiated at a lower dose, perhaps about 100 mg to about 200 mg and increased up to about 400 mg or higher depending on the patient's global response. It is further recommended that children, patients over age 65, and those with impaired renal or hepatic function, initially receive low doses. Those dosages should also be titrated based on global response and blood level. In some cases, it may be necessary to use dosages outside these ranges.

The term, "an amount sufficient to alleviate infection but insufficient to cause said adverse effects," is encompassed by the above described dosage amounts and dose frequency schedule.

The term, "method of treating infection" as used herein, includes but is not limited to infections such as urinary tract infection, upper and lower respiratory tract infection, sexually transmitted infection, ophthalmological infection, gastrointestinal infections such as those caused by *H. pylori* and any other infections which may arise in cells or tissues of a human and which require treatment with antibiotics. Such infection may be caused by either Gram-positive or Gram-negative bacteria. The Gram-negative bacteria include but

are not limited to *Escherichia*, *Haemophilus*, *Klebsiella*, *Proteus*, *Moraxella*, *Citrobacter*, *Enterobacter*, *Pseudomonas*, *Salmonella*, *Shigella*, *Yersinia*, *Campylobacter*, *Neisseriaceae* and *Serratia*. The Gram-positive bacteria include but are not limited to *Staphylococcus*, *Streptococcus*, *Bacillus* and *Mycobacteria*.

The present inventors have shown that optically pure (S)-lomefloxacin unexpectedly has an even lower MIC<sub>50</sub> and a lower range MIC<sub>50</sub> than that for either (R)- or racemic lomefloxacin for *Mycobacteria tuberculosis* and a lower MIC<sub>50</sub> than R-lomefloxacin for *Mycobacteria kansasii* and *Mycobacteria avium*. (See *infra*, Example 6).

Any suitable route of administration may be employed for providing the patient with an effective dosage of (S)-lomefloxacin. For example, oral, rectal, parenteral, transdermal, subcutaneous, intramuscular, and the like may be employed as appropriate. Dosage forms include tablets, coated tablets, troches, dispersions, suspensions, solutions, caplets, capsules, patches, and the like.

The pharmaceutical compositions of the present invention comprise (S)-lomefloxacin as active ingredient, or a pharmaceutically acceptable salt thereof, and may also contain a pharmaceutically acceptable carrier, and optionally, other therapeutic ingredients. (S)-lomefloxacin hydrochloride is a pharmaceutically acceptable salt of (S)-lomefloxacin. The most preferred pharmaceutically acceptable salt of (S)-lomefloxacin is the monohydrochloride salt.

The term "pharmaceutically acceptable salts" refers to salts prepared from pharmaceutically acceptable non-toxic acids or bases including inorganic acids and bases and organic acids and bases.

Since the compound of the present invention is both basic and acidic, salts may be prepared from pharmaceutically acceptable non-toxic acids or bases including inorganic and organic acids or inorganic and organic bases. Such salts may contain any of the following anions: acetate, benzenesulfonate, benzoate, camphorsulfonate, citrate, fumarate, gluconate, hydrobromide, hydrochloride, lactate, maleate, mandelate, mucate, nitrate, pamoate, phosphate, succinate, sulfate, tartrate and the like. Particularly preferred are benzenesulfonate, hydrobromate, hydrochloride and sulfate. Such salts may also contain the following cations: aluminum, calcium, lithium, magnesium, potassium, sodium, zinc, benzathine, chlorprocaine, choline, diethanolamine, ethylenediamine, meglumine, and procaine.

The compositions include compositions suitable for oral, rectal and parenteral (including subcutaneous, intramuscular, and intravenous) administration, although the most suitable route in any given case will depend on the nature and severity of the condition being treated. The most preferred route of the present invention is the oral route. The compositions may be conveniently presented in unit dosage form, and prepared by any of the methods well known in the art of pharmacy.

In the case where an oral composition is employed, a suitable dosage range for use is, e.g., from about 100 mg to about 400 mg total daily dose, given as a once daily administration in the morning or in divided doses if required. Preferably, a dose of 400 mg is given as a once daily administration. More preferably, a dose range of between about 100 mg to about 200 mg is given as a once daily administration or in divided doses if required. Patients may be upwardly titrated from below to within this dose range to a satisfactory control of symptoms.

In practical use, (S)-lomefloxacin can be combined as the active ingredient in intimate admixture with a pharmaceu-

tical carrier according to conventional pharmaceutical compounding techniques. The carrier may take a wide variety of forms depending on the form of the preparation desired for administration, e.g., oral or parenteral (including intravenous injections or infusions). In preparing the compositions for oral dosage form any of the usual pharmaceutical media may be employed. Usual pharmaceutical media includes, for example, water, glycols, oils, alcohols, flavoring agents, preservatives, coloring agents, and the like in the case of oral liquid preparations (such as for example, suspensions, solutions, and elixirs); aerosols; or carriers such as starches, sugars, microcrystalline cellulose, diluents, granulating agents, lubricants, binders, disintegrating agents and the like, in the case of oral solid preparations (such as for example, powders, capsules, and tablets) with the oral solid preparations being preferred over the oral liquid preparations. The most preferred oral solid preparation is tablets.

Because of their ease of administration, tablets and capsules represent the most advantageous oral dosage unit form, in which case solid pharmaceutical carriers are employed. If desired, tablets may be coated by standard aqueous or nonaqueous techniques. The parenteral dosage form can consist of a sterile solution of the active ingredient, either in its free or salt form, in physiological buffer or sterile water.

In addition to the common dosage forms set out above, the compounds of the present invention may also be administered by controlled release means and/or delivery devices such as those described in U.S. Pat. Nos.: 3,845,770; 3,916,899; 3,536,809; 3,598,123; 3,630,200; 4,008,719; 4,687,660 and 4,769,207, the disclosures of which are hereby incorporated by reference.

Pharmaceutical compositions of the present invention suitable for oral administration may be presented as discrete units such as capsules, cachets, or tablets, or aerosols sprays, each containing a predetermined amount of the active ingredient, as a powder or granules, or as a solution or a suspension in an aqueous liquid, a non-aqueous liquid, an oil-in-water emulsion, or a water-in-oil liquid emulsion. Such compositions may be prepared by any of the methods of pharmacy, but all methods include the step of bringing into association the active ingredient with the carrier which constitutes one or more necessary ingredients. In general, the compositions are prepared by uniformly and intimately admixing the active ingredient with liquid carriers or finely divided solid carriers or both, and then, if necessary, shaping the product into the desired presentation.

For example, a tablet may be prepared by compression or molding, optionally, with one or more accessory ingredients. Compressed tablets may be prepared by compressing in a suitable machine the active ingredient in a free-flowing form such as powder or granules, optionally mixed with a binder, lubricant, inert diluent, surface active or dispersing agent. Molded tablets may be made by molding in a suitable machine, a mixture of the powdered compound moistened with an inert liquid diluent. Desirably, each tablet contains from about 100 mg to about 200 mg of the active ingredient, and each cachet or capsule contains from about 100 mg to about 200 mg of the active ingredient, (S)-lomefloxacin. Most preferably, the tablet, cachet or capsule contains either one of two dosages, about 100 mg or about 200 mg of the active ingredient.

The invention is further defined by reference to the following examples describing in detail, the preparation of the compound, and the compositions of the present invention. It will be apparent to those skilled in the art, that many modifications, both to materials, and methods, may be practiced without departing from the purpose and interest of this invention.

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## EXAMPLES

## Example 1

## Oral Formulation

Capsules:

| Formula   | Quantity per Capsule<br>in mg. |     |
|---|--------------------------------|-----|
| Active Ingredient<br>(S)-lomefloxacin hydrochloride | 100                            | 200 |
| Lactose   | 349                            | 349 |
| Corn Starch   | 50                             | 50  |
| Magnesium Stearate                                  | 1.0                            | 1.0 |
| Compression Weight                                  | 500                            | 500 |

The active ingredient, (S)-lomefloxacin, lactose, and corn starch are blended until uniform. The magnesium stearate is then blended into the resulting powder. The resulting mixture is encapsulated into suitably sized two-piece hard gelatin capsules.

## Example 2

## Oral Formulation

Tablets

| Formula   | Quantity per Capsule<br>in mg. |     |
|---|--------------------------------|-----|
| Active Ingredient<br>(S)-lomefloxacin hydrochloride | 100                            | 200 |
| Lactose BP  | 309                            | 209 |
| Starch BP   | 60                             | 60  |
| Pregelatinized Maize Starch BP                      | 30                             | 30  |
| Magnesium Stearate                                  | 1                              | 1   |
| Compression Weight                                  | 500                            | 500 |

The active ingredient is sieved through a suitable sieve and blended with lactose, starch, and pregelatinized maize starch. Suitable volumes of purified water are added and the powders are granulated. After drying, the granules are screened and blended with the magnesium stearate. The granules are then compressed into tablets using punches.

Tablets of other strengths may be prepared by altering the ratio of active ingredient to lactose or the compression weight and using punches to suit.

## Example 3

## Intravenous Formulation

| Formula   | Quantity per 100 ml |
|---|---------------------|
| Active Ingredient<br>(S)-lomefloxacin hydrochloride | 20 ml               |
| Sterile Water                                       | 100 ml              |

Intravenous infusion solutions of (S)-lomefloxacin may also be prepared with Sodium Chloride Injection USP 0.9% or Dextrose Injection USP 5%.

## Example 4

The anti-bacterial activity of (S)-lomefloxacin towards specific microorganisms is assessed by determination of the

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minimal inhibitory concentration (MIC) of the compound that prevents growth of that microorganism under assay conditions.

Cultures of various Gram-negative and Gram-positive bacteria, including obligate anaerobes, are grown in various standard media suited to the particular microorganism of interest. [See, for example, Sato, K. et al., *Antimicrob. Agents and Chemotherapy*, 22 (4): 548-553 (1982).] Isolates are grown overnight at 37° C. and adjusted to the density of a 0.5 McFarland standard (i.e., about 10<sup>8</sup> cFu/mL), and then diluted to 10<sup>-2</sup>. One loopful of cells (5 μL) of each diluted culture (approximately 1000 cells) is then inoculated onto 10-mL drug-containing agar layers in Petri dishes using a multi-point inoculator. Following inoculation, agar plates are incubated for 18 hours at 37° C. in air with the exception of the obligate anaerobes, which are incubated in an atmosphere containing 10% CO<sub>2</sub>. The MIC is defined as the lowest concentration of (S)-lomefloxacin that completely prevents the visible growth of the inoculum on the surface of the (S)-lomefloxacin-containing medium.

Testing for quinolone-induced arthropathy can be accomplished by administering the quinolone at a suitable dose, on a once-daily basis, to 3-4 month old, skeletally immature Beagle dogs, for 1, 2, 5, or 7 days. A placebo is given to a second group of Beagle dogs to act as a control. A scoring technique that includes lesion size and histologic features is used to determine the progression of the lesions.

## Example 5

## Test of Hepatotoxicity

## Microsomal Preparation

Hepatic microsomes are prepared from human liver. Tissue is thawed and then homogenized in 0.15 M KCl in a Polytron homogenizer. The homogenate is centrifuged and the pellet is resuspended and homogenized in 0.15 M KCl. Aliquots are frozen and stored at -70° C.

## Lymphocyte Preparation

Human lymphocytes are aseptically isolated from fresh, heparinized human blood. Blood is diluted with Eagle's minimal essential medium and layered on Ficoll-Paque. The samples are centrifuged, and lymphocytes are then removed from the aqueous-Ficoll interface and suspended in medium (15 Mm 4-(2-hydroxyethyl)-1-piperazine ethane sulfonic acid [HEPES], pH 7.4). The cells are then centrifuged, washed once in the HEPES medium, and resuspended.

## Incubation Conditions and Cytotoxic Assay

Cytotoxicity is assessed by the conversion of MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide) to a purple formazan. The conversion of MTT to dye is done in multiwell plates.

After preparation, hepatic microsomes or lymphocytes are incubated alone or with the test compound in a concentration range from 1 to 400 μM at 37° C. in a humidified incubator. After incubation, the microsomes/cells are washed with 5% albumin in HEPES buffered medium and resuspended. The microsomes/cells are then incubated at 37° C. in a humidified incubator. After the incubation, 125 μg of MTT is added to each well. The plates are incubated at 37° C. and centrifuged. After centrifugation, 100 μL of isopropanol is added and, after incubation, the optical density is determined using an automated plate-reader.

## Example 6

## Susceptibility of Pathogenic Mycobacteria to Lomefloxacin(LM) and its Optically Active Isomers

## Introduction

In this study, the in vitro activities of LM, R-LM and S-LM against 31 clinical isolates of pathogenic mycobacteria and 4 control strains were tested and compared.

Methods

LM, R-LM, and S-LM were synthesized at Sepracor Inc. Drugs were dissolved in distilled water and kept in a -70° C. freezer. Clinical isolates were obtained from the blood or sputum of patients with mycobacterial infection. Control strains include H37RV (ATCC 27294), H37Ra (ATCC 25177), *M. marinum* (ATCC 927) and *M. avium* 101.

A broth microdilution method was used. An aliquot of a suspension of mycobacteria was inoculated into 7H9 broth at a ratio of 1:20 and incubated overnight or up to two weeks, depending on the species. The cultures were then adjusted to optical density of No. 0.5 McFarland standard. Inocula were prepared in 7H9 broth at PH 6.7 and incubated at 30° C. (*M. marinum*) or 37° C. (all other species) in ambient atmosphere. The final concentration of mycobacteria in each microplate well was 1x10<sup>5</sup> cfu/ml. The range of concentrations of drugs used was: 0.125-32.0 µg/mL.

MIC's were determined after 4 days (*M. chelonae*), 7 days (*M. avium*, *M. marinum*, *M. kansasii*) and 14 days (*M. tuberculosis*) of incubation. The endpoint for susceptibility/resistance was set at 4.0 µg/ml. Each organism-drug concentration combination was performed in the duplicate and each experiment was repeated three times.

TABLE 1

| Strains (n)                          | Susceptibility (µg/mL) |      |        |
|--------------------------------------|------------------------|------|--------|
|                                      | LM                     | R-LM | S-LM   |
| <u><i>M. tuberculosis</i> (12)</u>   |                        |      |        |
| Range                                | 0.5-2                  | 1-4  | 0.25-1 |
| MIC50                                | 1                      | 2    | 0.5    |
| MIC90                                | 2                      | 4    | 1      |
| <u><i>M. avium</i> (11)</u>          |                        |      |        |
| Range                                | 4-16                   | 4-32 | 2-16   |
| MIC50                                | 8                      | 16   | 8      |
| MIC90                                | 16                     | 32   | 16     |
| <u><i>M. kansasii</i> (10)</u>       |                        |      |        |
| Range                                | 1-2                    | 2-4  | 1-2    |
| MIC50                                | 1                      | 2    | 1      |
| MIC90                                | 2                      | 4    | 2      |
| <u><i>N. chelonae</i> C315 (1)</u>   |                        |      |        |
| MIC                                  | 4                      | 4    | 2      |
| <u><i>N. marinum</i> ATCC927 (1)</u> |                        |      |        |
| MIC                                  | 4                      | 4    | 2      |

Results

This study demonstrates that the MIC90 of LM, R-LM, and S-LM to *M. tuberculosis* and *M. kansasii* are all lower than the endpoint for susceptibility (4.0 µg/ml) and the reported Cmax of LM (Table 1). For *M. tuberculosis* isolates, S-LM had the lowest MIC90 (1.0 µg/ml), micro-broth method, with the former having the higher MIC result (ICAAC, New Orleans, 1993; Abstract No. 1584).

Conclusions

1. LM and its isomers have significant activity against clinical strains of *M. tuberculosis*, *M. kansasii*, *M. chelonae* C 315 and *M. marinum* ATCC 9271.

2. The relative antimycobacterial activities against *M. tuberculosis* are unexpectedly (S)-LM>LM>(R)-LM and against *M. kansasii* are unexpectedly (S)-LM=LM>(R)-LM.

3. For *M. kansasii*, (S)-LM and LM unexpectedly had the same MIC90 of 2.0 µg/ml, but (R)-LM had an MIC of 4.0 µg/ml. All three compounds have much higher MIC90 than the susceptibility endpoint for *M. avium*. For *M. chelonae* C315 and *M. marinum* ATCC 927, the MIC50 of both LM and (R)-LM was 4.0 µg/ml, but that of (S)-LM was 2.0 µg/ml.

It may be apparent to those skilled in the art that modifications and variations of the present invention are possible in light of the above disclosure. It is understood that such modifications are within the spirit and scope of the invention, which is defined by the appended claims.

What is claimed is:

1. A method for treating microbial infection in a human, which comprises administering to said human a therapeutically effective amount of (S)-lomefloxacin, or a pharmaceutically acceptable salt thereof, substantially free of its (R)-stereoisomer.

2. The method of claim 1, wherein the (S)-lomefloxacin is administered parenterally, transdermally, or orally.

3. The method of claim 2, wherein (S)-lomefloxacin is administered orally as a tablet or a capsule.

4. The method of claim 1, wherein the amount of (S)-lomefloxacin administered is from about 50 mg to about 800 mg.

5. The method of claim 4, wherein the amount of (S)-lomefloxacin administered is from about 50 mg to about 400 mg.

6. The method of claim 5, wherein the amount administered is from about 50 mg to about 200 mg.

7. The method of claim 1, wherein the (S)-lomefloxacin, or a pharmaceutically acceptable salt thereof, is greater than approximately 90% by weight of the total weight of lomefloxacin.

8. The method of claim 1, wherein the amount of (S)-lomefloxacin, or a pharmaceutically acceptable salt thereof, substantially free of its (R)-stereoisomer, is administered together with a pharmaceutically acceptable carrier.

9. The method of claim 1, wherein (S)-lomefloxacin, substantially free of its (R) isomer, is administered as a hydrochloride salt.

10. The method of claim 1, wherein said infection is selected from the group consisting of urinary tract infections, upper and lower respiratory tract infections, sexually transmitted infections, ophthalmological infections, gastrointestinal infections, bone infections, and lymph node infections.

11. The method of claim 1, wherein the microbial infection is caused by gram-negative bacteria.

12. The method of claim 11, wherein the gram-negative bacteria is one or more of *Escherichia*, *Haemophilus*, *Klebsiella*, *Proteus*, *Moraxella*, *Citrobacter*, *Enterobacter*, *Pseudomonas*, *Salmonella*, *Shigella*, *Yersinia*, *Camplobacter*, *Neisseriaceae*, or *Serratia*.

13. The method of claim 1, wherein the microbial infection is caused by gram-positive bacteria.

14. The method of claim 13, wherein the gram-positive bacteria is one or more of *Staphylococcus*, *Streptococcus*, and *Bacillus*.

\* \* \* \* \*

**THE PATENTS ACT 1970**

**(AMENDED BY THE PATENTS ACT 2005)**

**AND**

**THE PATENT RULES , 2003**

**(AMENDED BY THE PATENT RULES 2006 )**

**In the matter of Patent application No.**

**314/MUM/2008 Application Date 13/02/2008**

**AND**

**In the matter of Section (14)**

**& (15)of the Patents Act**

**RAJEEV M. HUZURBAZAR.....The Applicant**

**Present: RAJEEV M. HUZURBAZAR.**

## DECISION

The instant Patent Application filed as ORDINARY APPLICATION filed on 13/02/2008 entitled 'ORAL FOOD SUPPLEMENT POWDER FOR DIARRHOEA IN PAEDIATRICS' . The initially filed claims in its Complete Specification were examined in accordance with the Patents Act 1970 and consequently numbers of objections comprising of both formal and technical were conveyed by the Patent office, Mumbai to the applicant as per First Examination Report dated 28<sup>th</sup> April 2010 which is the part of file of the instant case. The main technical objections were u/s 10(4) & u/s 3(e) of the Patents Act..

The initially filed set of claims are stated as follows:

1 .An Oral Food Supplement compositon, for Diarrhea for paediatric patients, comprising,

|                    |             |
|--------------------|-------------|
| Mixed Fruit Powder | 1 to 50%    |
| Potato Powder      | 15 to 30 %  |
| Rice Powder        | 11 to 15 %  |
| Soyabean Powder    | 1.5 to 10 % |
| Sago Powder        | .5 to 10 %  |
| Lentil Powder      | 1 to 5 %    |
| Tur Powder         | 1 to 5 %    |

2. A process of making the food supplement composition as claimed in claim 1, where in the all the powder are spray Dried, Powder are weighed and added to mixer and process is continued for 30 min. mixing mass is then transferred to stainless steel vessel , powder is then transferred to filling machine and packed in containers.

The applicants had filed their reply to the First Examination Report (FER ) 11<sup>th</sup> January 2011 ie within the prescribed period enclosing therewith the desired Forms, revised retyped papers etc. They simultaneously made some rewording of the said claims . The said reply & the set of claims is also part of file of the instant case . Further Second Examination Report has been issued by the office maintaining the main requirements which has been replied by the applicant.

The last date to put the application in order for grant has been expired on 28/04/2011 . As the Patent office was still not satisfied with the said compliance, the above objections were maintained & stated that the revised set of claims are not allowable under section 3(e) of the Act. For the sake of natural justice the applicant has been offered an hearing on 04/07/2011.

The main requirements of the First Examination Report (FER ) the claims fall within the scope of section 3(e) of the Act.

Applicant Sri Rajeev Huzurbazar appeared for hearing before me on 04/07/2011.

The set of claims on record are stated as follows.

1. An Oral Food Supplement composition, for Diarrhea for paediatric patients, comprising ,

|                             |             |
|-----------------------------|-------------|
| Apple, Banana, Guava Powder | 1 to 50%    |
| Potato Powder               | 15 to 30 %  |
| Rice Powder                 | 11 to 15 %  |
| Soyabean Powder             | 1.5 to 10 % |
| Sago Powder                 | 0.5 to 10 % |
| Lentil Powder               | 1 to 5 %    |
| Tur Powder                  | 1 to 5 %    |

2. An Oral Food Supplement composition has combine / synergistic effect as given in next pages. Chart presentation of Various combination is given from page one to four along with synergistic effect of Oral Food Composition on first page .

The applicant submitted that the present Invention relate to application of Oral Food Supplement Powder in case of diarrhea in pediatric patient. Diarrhea is too frequent passage of poorly formed stools i.e passage of excessive water in faces. Diarrheal diseases constitute a major cause of morbidity and mortality worldwide. More than five million children under age of five years die every year of diarrhea. Diarrhea has been shown to have significant impact on. nutrition. Child with multiple episodes of diarrhea suffers most severely from protein energy malnutrition . A considerable quantity of nutrients is lost in diarrheal stool. Protein energy malnutrition develops. A vicious cycle of diarrhea-malnutrition-diarrhea sets in. Significant death occur as a result of malnutrition, unnecessary starvation, consequent series of diarrhea. Pediatric diarrheal patients by administering an effective daily amount of Food Supplement Powder of composition comprising mixture of Mixed Fruit Powder, Rice, Potato, Soyabean, Sago, when given in definite proportion and dose with other drugs controls the diarrhea , formation of normal stool very fast as compared to drugs given alone to



paediatric patients.. Food Supplement powder not only reduces the fluidity and frequency of loose stool which is necessary to alter the picture of diarrhea , but also prevents malnutrition. The formulation may be available in biscuit form.

The applicant merely repeated the same thing which they have submitted during the reply to the FER that the claims has been revised & it meets the requirement of Section 3(e) & it is a synergistic composition & not a admixture. The Applicant stated that they submitted the clinical data while filing reply to first examination report & further data in view of their reply to hearing . They stated that it is not the individual effect of the ingredients but due to the combined effect of all the ingredients that they are using in the food supplement composition & that help to control the diarrhea . They stated that if using the hundred percent of one the ingredient in the composition it has a adverse effect on body & not effective to control diarrhea. Further , they stated that indifferent proportion of different ingredients will also not give result & will not be effective in controlling diarrhea.

So , they requested you to waive the objection.

The above submission to the hearing is also part of the instant case. Their submissions have been considered carefully but it does not fulfill the requirement of Section 3(e) of the Act .

I had gone through the specification & their submission .The instant application relates to an oral food supplement in the form of compositon, for controlling diarrhea particularly for paediatric patients, infants & babies. It comprising mainly different fruit powder, potato powder ,rice powder,soyabeen powder,sago powder ,lentil powder ,tur dal powder in a proportion mentioned in the specification & claimed in the claims.

**Section 3(e) of the Act says "*...a substance obtained by a mere admixture resulting only in the aggregation of the properties of the components thereof or a process for producing such substance.*"**

So, the question of synergism are matters of scientific facts which are required to be embodied in the specification so that the said characteristics are apparent from the specification.

Claims as stated above of the applicant claimed a composition comprising fruit powder, potato powder ,rice powder,soyabean powder, sago powder,lentil powder ,tur dal powder in a different proportion . The composition claimed by the applicant is a mere admixture of above mentioned ingredients without showing any synergism. The combination does not result in any enhanced additive effect. There is not a single example in the entire specification which demonstrates that the said combination provides surprising results apart from being a mere collocation of the properties of the individual ingredients. What applicant claiming as a synergy has not been demonstrated at all in the complete specification . What applicant tries to show in the form of clinical data & other data at the time filing reply to the first examination report & reply to the hearing has not filed as a part of description in the specification.

So, it is pertinent to mention here that , at the time of filing of instant application for patent no where mentioned in the specification that how the components or ingredients of the composition act together and is responsible for controlling the diarrhea. No comparative results/data on the controlling in respect diarrhea of the claimed composition is disclosed. A mere statement at the time of hearing & filing reply on enhanced property

of the composition regarding controlling diarrhea in absence of experimental/technical evidences in the specification itself is not credible. The specification is silent on unexpected effect/synergism of the claimed composition. The question of efficacy and or synergism are matters of scientific facts which are required to be embodied in the specification so that the said characteristics are apparent from the specification. The applicant vaguely claimed that the composition is a synergistic composition but no support in this regard was provided in the specification . Actually applicant has to study the ingredients used in the composition individually and need to see whether these ingredients possess property towards controlling the diarrhea individually & how effective in controlling diarrhea when these have mixed together in particular proportion. So, the applicant failed to demonstrate the data of individual ingredients and when these have mixed together, need to be mentioned in the description of specification.

In the absence of such evidence, it is evident that the claims cannot be patented under Section 3(e) of the Act and ought to be rejected.

It is not uncommon for the effect of two or more chemicals/ingredients on an organism to be greater than the effect of each chemical/ingredient individually, or the sum of the individual effects. The presence of different ingredient together enhances the effects of the composition as a whole. This is called a synergistic effect or synergy .The applicant has to define the a synergy ie how different entities cooperate advantageously for a final outcome shall be defined in the specification which applicant failed to define.

In the absence of synergism between the defined components , which applicant failed, the claimed composition of the alleged application is considered mere admixture as defined under clause (e) of Section 3 of the Act.

So, considering the clause (e) of Section 3 of the Act & in the absence of synergistic data in the specification as stated above, the composition claimed herein in claims is a mere admixture.

Further the revised set of claims which applicant has filed after the hearing, claim 2 is not the same claim which applicant has filed at the time of filing of the application. What applicant claimed in the initially filed set of claims in claim 2 is process of making the composition. However, it has been converted to the product claim & now claiming composition with synergistic effect which they have not demonstrated in the specification and claimed in such a way that it lacks clarity. Further, applicant has added the matter regarding the fruit powder. They are now claiming fruit powder used in the composition is made from fruits apple, banana & guava are not fully supported by the description of the initially filed specification. Applicant has carried out the voluntary amendments without following the prescribed procedure under the Act. Though applicant has explained in their submission of first examination report regarding the steps used for making the composition, they have not taken the care to explain these each of the steps in the complete specification filed initially. So, the complete specification does not meet the requirement of 10 (4) of the Patents Act, 1970.

As per Section 10 (4) of the Patents Act every complete specification shall –

- a) fully & particularly describe the invention & its operation or use & the method by which it is to be performed ;
- b) disclose the best method of performing the the invention which is known to the applicant & for which he is entitled to claim the protection ; and
- c) end with a claim or claims defining the scope of the invention for which protection is claimed ;
- d) be accompanied by an abstract to provide the technical information on the invention .

The Complete Specification describing the invention is a techno-legal document. It should disclose the invention completely to meet the requirement of the Patents Act and should also enable a person possessing average skill in the art to work the invention without assistance of the patentee . This is possible when the complete specification describes the invention fully and particularly and describes its operation and/or method by which it is to be performed. It is also essential that the best method for performing the invention, which is known to the applicant is disclosed in the Complete Specification . The complete specification must describe an embodiment of the invention claimed in claims & that description must be sufficient to enable those in the industry concerned to carry it into effect without their to making further invention. The ordinary skilled person in the art must be able to perform the invention which satisfies the requirement of disclosure. Further as stated above, applicant failed to demonstrate the synergy with required data in the specification.

Having considered all the circumstances, reply , submission made by the agent for the applicant, I hereby refuse the application on the grounds as stated above.

Accordingly the instant Patent Application No. 314/MUM/2008 is refused u/s 15 of the Patents Act 1970.

Dated: 05.10.2012.

(A. T.PATRE)

Place: Mumbai

Asstt. Controller of Patents & Designs



E-Mail: [chennai-patent@nic.in](mailto:chennai-patent@nic.in)  
Website: [www.ipindia.nic.in](http://www.ipindia.nic.in)  
Telefax: 2250 2066

GOVERNMENT OF INDIA  
**PATENT OFFICE**  
INTELLECTUAL PROPERTY BUILDING  
G.S.T ROAD, GUINDY  
CHENNAI - 600 032

Telephone: 2250 2081  
2250 2082  
2250 2083  
2250 2084

No. POC/DECISION/SEC.15 /2012/

Dated: 09/10/2012

To

**Depenning & Depenning**  
**31 South Bank Road**  
**Chennai 600 028**

**Sub:Patent Application No. 3725/Chenp/2006- Reg.**

Sir,

The above referred patent application filed by you has been refused U/S 15 of Patents Act, 1970 for not meeting requirements of Act. A copy of the order is enclosed herewith.

Thanking you,

Yours faithfully,

  
(PRIYADHARSINI RAJANBABU)

**Asst. Controller of Patents & Designs.**

Encl: Copy of decision.

**THE PATENTS ACT, 1970  
&  
THE PATENTS RULES, 2003**

**In the matter of Application for Patent bearing the number as  
3725/CHENP/2006  
Filed by NOVARTIS AG**

**And**

**In the matter of Section 15 of the Patents  
Act, 1970**

## ORDER

1. A PCT national phase application for patent titled "AN ETHANOL FREE PHARMACEUTICAL COMPOSITION COMPRISING PIMECROLIMUS" was filed by NOVARTIS AG on 09.10.2006 at Patent office Chennai.

2. The said application was the national phase application of PCT international application PCT/EP05/03669 filed on 07.04.2005, which claimed priority from GB application 04-08070.1 and GB 0408076.8. A request for examination for this application was filed on 13.03.2008.

3. A FER was sent on 02.09.11, a reply was refiled on 29.05.12. Again a second examination report sent on 28.06.2012, a reply was refiled on 2.08.2012. As on the last date for putting the application in order for grant, the application was found to be not complying with certain requirements of act. Accordingly a hearing notice was issued with the following objections:

- a. Objection no.5 of FER, dated 2 September 2011 and Objection no.01 of Examination report dated 28 June 2012 stands maintained.
- b. Claims 1-2[amended] do not meet the requirements of Section 10(5)(c) of the Patents Act, 1970 ; as claims are not succinct.

4. Hearing has been fixed on 24/08/12 at 11.00Am. Agent for the applicant attended the hearing. And they refiled the documents on 31/08/12.



5. Objection number 5 of FER dated 2<sup>nd</sup> sep 2011 talks about section 3(e) of the patents act 1970 and objection no.1 of examination report dated 28<sup>th</sup> june 2012 speaks about novelty and inventive step.

6. Amended claims 1 and 2 are not allowable U/S 3(e) and 10(5)(c) of the patents act 1970.

### Amended claims

1. A pharmaceutical foam composition substantially free of ethanol and comprising pimecrolimus in a carrier vehicle comprising a mixture of oily solvents amounting to at least 40% of the total weight of the composition and consisting of

- i. Hexylene glycol in the range of 1% to 10%
- ii. Optionally Oleyl alcohol in the range of 1% to 20% and
- iii. Dimethylisobornyl diacetate in the range of 35% to 90% and medium chain triglycerides in the range of 5% to 20% and additionally:
- iv. Hydroxypropyl cellulose and /or stearyl alcohol in the range of 0.1% to 5%
- v. p-hydroxybenzoic acid ester with ethyleneglycol phenylether in the range of 0.1% to 0.5% and
- vi. glyceryl monostearate in the range of 1% to 3% and non-ionic sugar esters and butane/propane 80/20 as propellant gas for foaming.

2. A pharmaceutical foam composition substantially free of ethanol and comprising pimecrolimus in a carrier vehicle comprising a mixture of oily

solvents amounting to at least 40% of the total weight of the composition and consisting of

- i. Hexylene glycol in the range of 2% to 20%
- ii. medium chain triglycerides in the range of 50% to 80% and optionally Dimethyl lisorbide in the range of 0% to 20% and additionally:
- iii. Water in an amount less than 25%
- iv. polyvinylpyrrolidone and stearyl alcohol in the range of 1% to 10%
- v. p-hydroxybenzoic acid ester with ethyleneglycol phenylether in the range of 0.1% to 0.5% and
- vi. glyceryl monostearate in the range of 1% to 3% and lecithin; and butane/propane 80/20 as propellant gas for foaming.

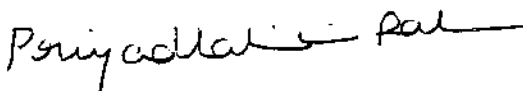
7. Amended claims is now limited to pharmaceutical foam composition with specific ingredients based on the formulation described in examples 1, 2 and 3. The pharmaceutical form of the present invention shows improved penetration properties and is particularly convenient in terms of ease of administration and patient compliance. Hence objection no.1 of examination report dated 28<sup>th</sup> Jun '12 is waived.

8. Claims 1 and 2 are not succinct and it doesn't fall under single inventive concept, because the components range and components as claimed in claim 1 and claim 2 are different. And hence they are not allowable u/s 10(5) (c) of the patents act 1970.

9. Applicant doesn't provide any supportive experimental data or comparative examples highlighting the surprising and or synergistic effect of the claimed formulation over the prior art compositions. Instead, examples 1, 2 and 3 provide only the amount of individual components in grams.

10. Hence in view of the above findings I hereby conclude that the application do not meet the requirements of section 3(e) and 10(5) (c) of the Patent Act. Therefore I refuse the application for patent 3725/CHENP/2006 U/S 15 of the Patents Act, 1970.

Dated 9<sup>th</sup> October, 2012

  
(PRIYADHARSINI RAJANBABU)  
Assistant controller of Patents & Designs.