QUINOLINE DERIVATIVES FOR THE TREATMENT OF LATENT TUBERCULOSIS

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

BACKGROUND OF THE INVENTION

Mycobacterium tuberculosis results in more than 2 million deaths per year and is the leading cause of mortality in people infected with HIV[1]. In spite of decades of tuberculosis (TB) control programs, about 2 billion people are infected by *M. tuberculosis*, though asymptomatically. About 10% of these individuals are at risk of developing active TB during their lifespan [2]. The global epidemic of TB is fuelled by infection of HIV patients with TB and rise of multi-drug resistant TB strains (MDR-TB). The reactivation of latent TB is a high risk factor for disease development and accounts for 32% deaths in HIV infected individuals[1]. 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 factor α or interferon-γ. In case of HIV positive patients the only prophylactic treatment available for latent TB is two- three months regimens of rifampicin, pyrazinamide [3,4]. 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 chemoprophylatic 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 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[5]. 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 tolerant to killing by anti-TB drugs like isoniazid[6]. 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[7]. These factors have been postulated to render these bacteria phenotypically tolerant to major anti-mycobacterial drugs[7].

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).

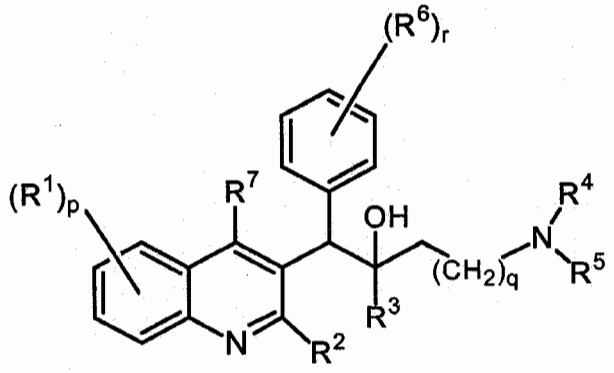
Figure 2A) : The effect of various drugs on dormant *M. bovis* (CFU : colony forming units) (CFU determined 2 days after anaerobiosis, are reported).

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

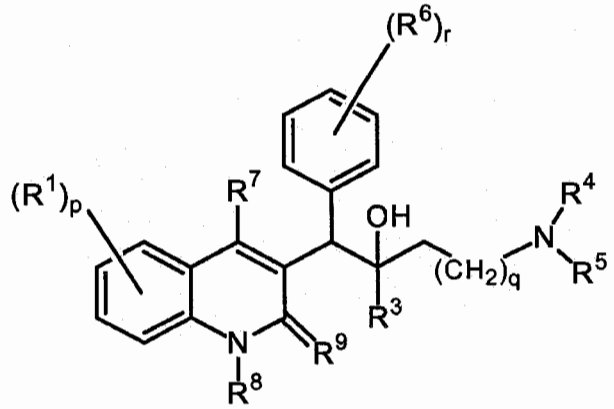
Figure 3 : The effect of various drugs on dormant *M. tuberculosis* (Wayne model)

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



(Ia)

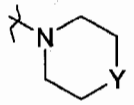


(Ib)

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

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 ;

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-imidazolinyl, 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^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 ;

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 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*-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;

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^9 equal to oxo is the tautomeric equivalent of a compound according to formula (Ia) with R^2 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_{1-6}alkyl which is defined as mono- or polyhalosubstituted C_{1-6}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_{1-6}alkyl, they may be the same or different. C_{1-6}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^4 and R^5 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^3) 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^6 radicals are taken together to form a bivalent radical of formula –CH=CH-CH=CH-, this means that the two vicinal R^6 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 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 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 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 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, 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 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.

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. methyliodide or benzyliodide. Other reactants with good leaving groups may also be used, such as alkyl trifluoromethanesulfonates, alkyl methanesulfonates, and alkyl *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.

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 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 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 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 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 "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 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 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.

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 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 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.

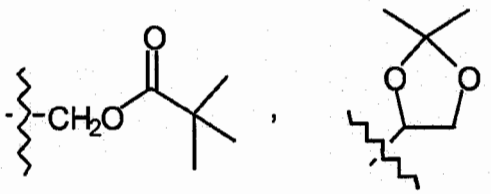
The tautomeric forms of the compounds of either formula (Ia) and (Ib) are meant to comprise those compounds of either formula (Ia) and (Ib) wherein e.g. an enol group is converted into a keto group (keto-enol tautomerism).

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, peroxoalkanoic acids, e.g. peroxoacetic acid, alkylhydroperoxides, 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.

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-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 $-COOR^x$, where R^x is a C_{1-6}alkyl, phenyl, benzyl or one of the following groups :

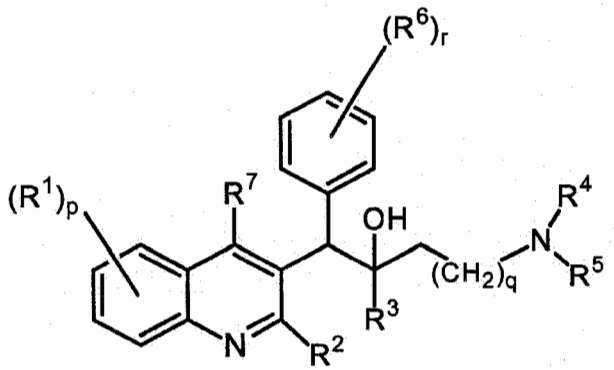


Amidated groups include groups of the formula – $CONR^yR^z$, wherein R^y is H, C_{1-6}alkyl, phenyl or benzyl and R^z is –OH, H, C_{1-6}alkyl, phenyl or benzyl.

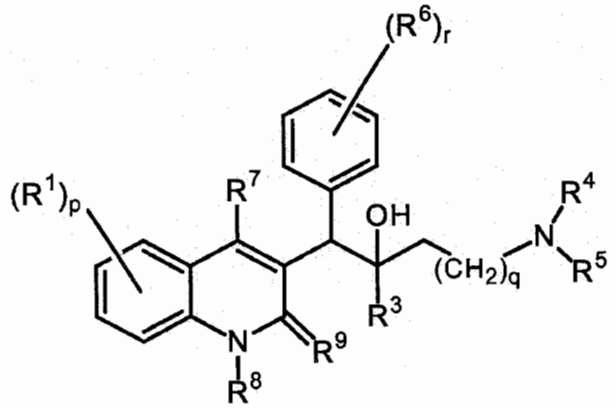
Compounds according to the invention having an amino group may be derivatised with a ketone or an aldehyde such as formaldehyde to form a Mannich base. This base will hydrolyze with first order kinetics in aqueous solution.

Whenever used herein, the term "compounds of formula (Ia) or (Ib)" is meant to also 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.

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



(Ia)

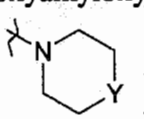


(Ib)

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 CH_2, 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

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-imidazolinyl, 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^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- ;

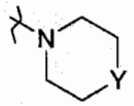
r is an integer equal to 1, 2, 3, 4 or 5 ;

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 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*-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;
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.

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

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 ;

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 ;

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 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 ;

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

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.

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.

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.
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.

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.

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.

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 ninth 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 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.

In a tenth 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^6 is hydrogen, alkyl or halo; preferably, R^6 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 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^7 is hydrogen or methyl; preferably R^7 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 to Formula (Ib) only, R^8 is alkyl, preferably methyl, and R^9 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 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^1 is hydrogen, halo, Ar, alkyl or alkyloxy; p = 1; R^2 is hydrogen, alkyloxy or alkylthio; R^3 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^4 and R^5 each independently are hydrogen or alkyl or 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, piperidinyl, piperazinyl and thiomorpholinyl; R^6 is hydrogen, alkyl or halo; r is equal to 1 and R^7 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_{1-6}alkyl wherein C_{1-6}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_{1-6}alkyl which is defined as mono- or polyhalosubstituted C_{1-6}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_{1-6}alkyl, they may be the same or different. C_{1-6}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-α-[2-(dimethylamino)ethyl]-2-methoxy-α-1-naphthalenyl-β-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.

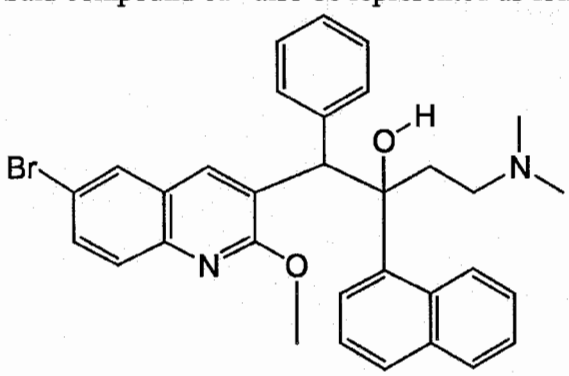
More preferably, the compound is

- 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-α-[2-(dimethylamino)ethyl]-2-methoxy-α-1-naphthalenyl-β-phenyl-3-quinolineethanol;

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

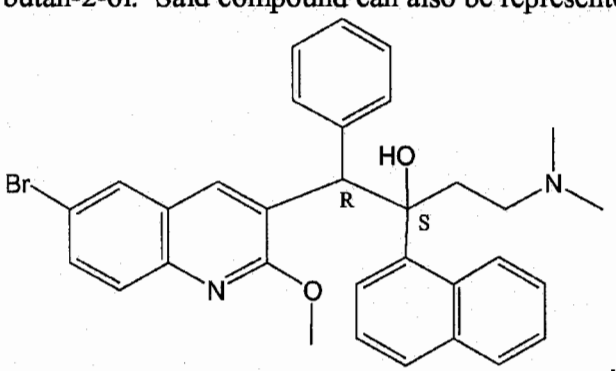
An alternative chemical name for 1-(6-bromo-2-methoxy-quinolin-3-yl)-4-dimethylamino-2-naphthalen-1-yl-1-phenyl-butan-2-ol is 6-bromo-α-[2-(dimethylamino)ethyl]-2-methoxy-α-1-naphthalenyl-β-phenyl-3-quinolineethanol. Said compound can also be represented as follows :



Further preferably, the compound is one of the following :
6-bromo-α-[2-(dimethylamino)ethyl]-2-methoxy-α-1-naphthalenyl-β-phenyl-3-quinolineethanol, or a pharmaceutically acceptable acid addition salt thereof; or
6-bromo-α-[2-(dimethylamino)ethyl]-2-methoxy-α-1-naphthalenyl-β-phenyl-3-quinolineethanol, or a stereochemically isomeric form thereof; or
6-bromo-α-[2-(dimethylamino)ethyl]-2-methoxy-α-1-naphthalenyl-β-phenyl-3-quinolineethanol, or a *N*-oxide form thereof; or
a mixture, in particular a racemic mixture, of (αS, βR)-6-bromo-α-[2-(dimethylamino)ethyl]-2-methoxy-α-1-naphthalenyl-β-phenyl-3-quinolineethanol and (αR, β S)-6-bromo-α-[2-(dimethylamino)ethyl]-2-methoxy-α-1-naphthalenyl-β-

phenyl-3-quinolineethanol, or a pharmaceutically acceptable acid addition salt thereof, or a stereochemically isomeric forms thereof; i.e. compound 14 (diastereoisomer A); or (αS, βR)-6-bromo-α-[2-(dimethylamino)ethyl]-2-methoxy-α-1-naphthalenyl-β-phenyl-3-quinolineethanol, i.e. compound 12, or a pharmaceutically acceptable acid addition salt thereof; or
(αS, βR)-6-bromo-α-[2-(dimethylamino)ethyl]-2-methoxy-α-1-naphthalenyl-β-phenyl-3-quinolineethanol, i.e. compound 12.

The most preferred compound is (αS, βR)-6-bromo-α-[2-(dimethylamino)ethyl]-2-methoxy-α-1-naphthalenyl-β-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 :

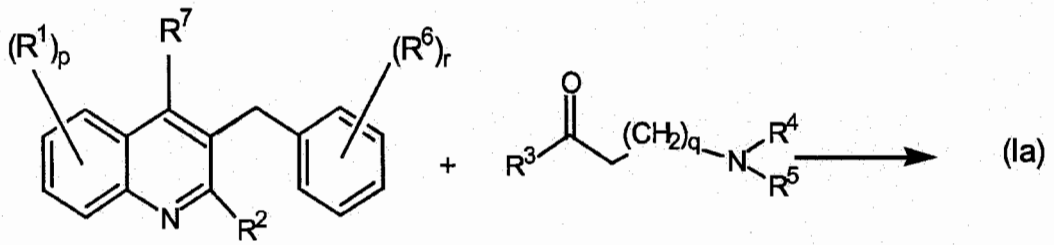


Another interesting group of compounds is the following : compounds 12, 71, 174, 75, 172, 79 and 125 as described hereinafter in Tables 1 to 6; in particular compounds 12, 71, 174, 75, 172 and 79 or compounds 12, 71, 75, 172 and 125; more in particular compounds 12, 71, 174 and 75 or compounds 12, 71,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

Scheme 1



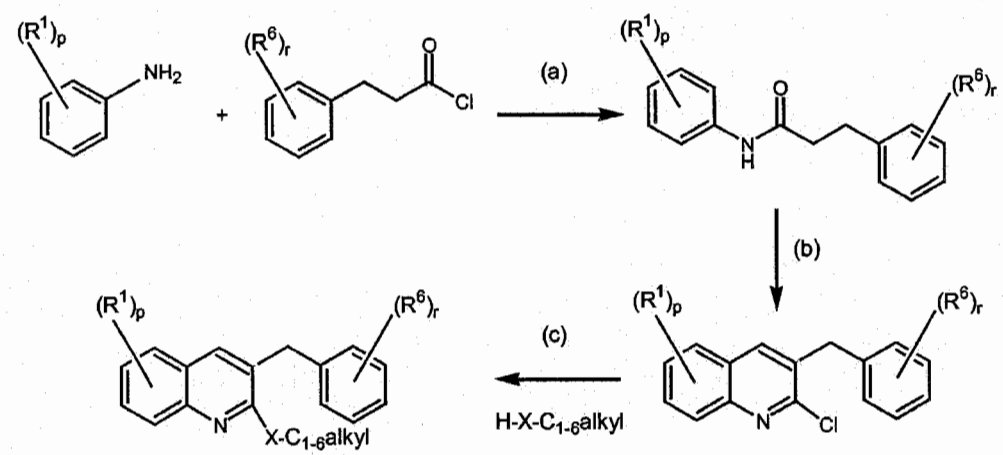
(II) (III)

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).

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 reaction scheme (2):

Scheme 2

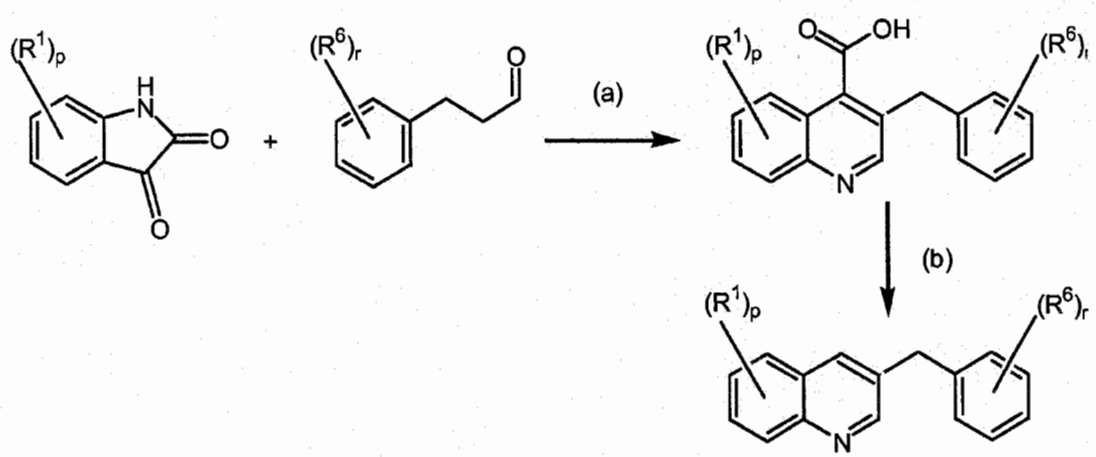


(II-a)

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 ($POCl_3$) 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 R^2-group, wherein R^2 is for example an C_{1-6}alkyloxy or C_{1-6}alkylthio radical is introduced by reacting the intermediate compound obtained in step (b) with a compound H-X-C_{1-6}alkyl wherein X is S or O.

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.

Scheme 3

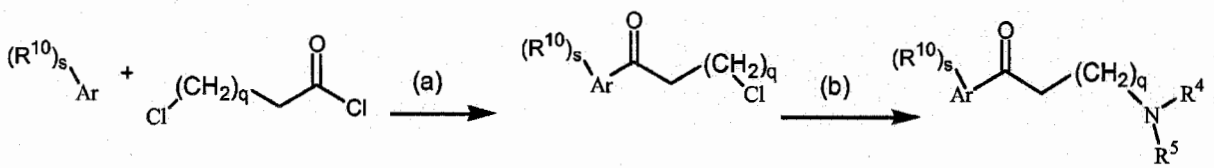


(II-b)

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, polyhaloC_{1-6}alkyl, C_{1-6}alkyloxy, polyhaloC_{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



(III-a)

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 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 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.

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, 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 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 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 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.

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.

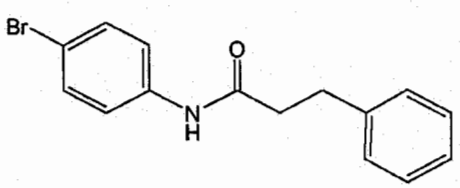
In particular, the preparation of compounds 12, 13, 12a, 13a, 14 and 15 are described below in detail.

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

Preparation of the intermediate compounds

Example A1

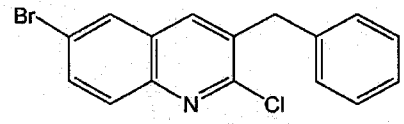
Preparation of intermediate compound 1



Benzenepropanoylchloride (0.488 mol) was added dropwise at room temperature to a solution of 4-bromobenzenamine (0.407 mol) in Et_3N (70ml) and CH_2Cl_2 (700ml) and the mixture was stirred at room temperature overnight. The mixture was poured out into water and concentrated NH_4OH, and extracted with CH_2Cl_2 . The organic layer was dried ($MgSO_4$), filtered, and the solvent was evaporated . The residue was crystallized from diethyl ether . The residue (119.67g) was taken up in CH_2Cl_2 and washed with HCl 1N . The organic layer was dried ($MgSO_4$), filtered, and the solvent was evaporated. Yield: 107.67g of intermediate compound 1.

Example A2

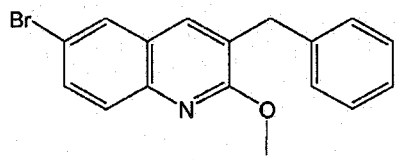
Preparation of intermediate compound 2



The reaction was carried out twice . $POCl_3$ (1.225 mol) was added dropwise at 10°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°C, poured out on ice and extracted with CH_2Cl_2 . The organic layer was dried ($MgSO_4$), filtered, and the solvent was evaporated . The product was used without further purification. Yield : 77.62g of intermediate compound 2 (67%).

Example A3

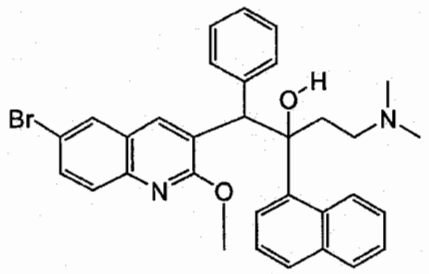
Preparation of intermediate compound 3



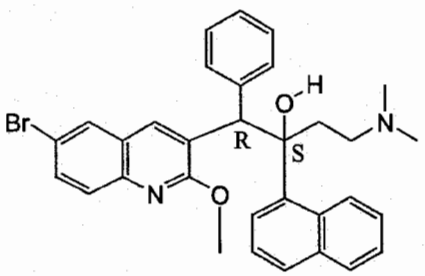
A mixture of intermediate compound 2 (prepared according to A2) (0.233 mol) in CH_3ONa (30%) in methanol (222.32 ml) and methanol (776ml) was stirred and refluxed overnight, then poured out on ice and extracted with CH_2Cl_2 . The organic layer was separated, dried ($MgSO_4$), filtered and the solvent was evaporated . The residue was purified by column chromatography over silica gel (eluent: CH_2Cl_2/cyclohexane 20/80 and then 100/0; 20-45µm). The pure fractions were collected and the solvent was evaporated . Yield : 25g of intermediate compound 3 (Yield=33%; mp.84°C) as a white powder .

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

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

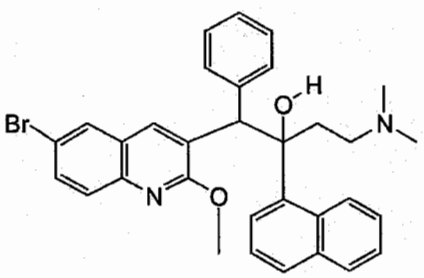


Compound 14 (A)
Compound 15 (B)



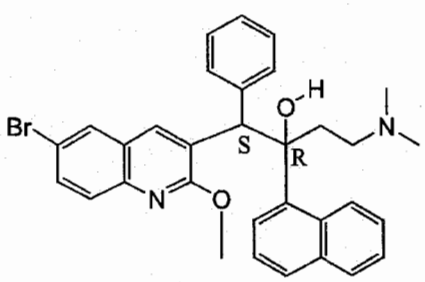
Compound 12 (A1)

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



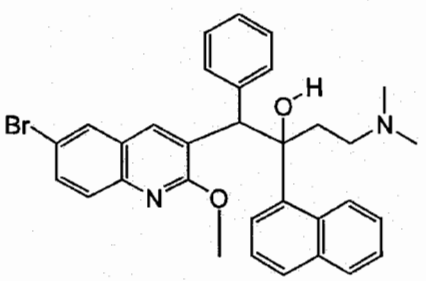
Compound 12a (B1)

$[alpha]_D^{20}$ = -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)

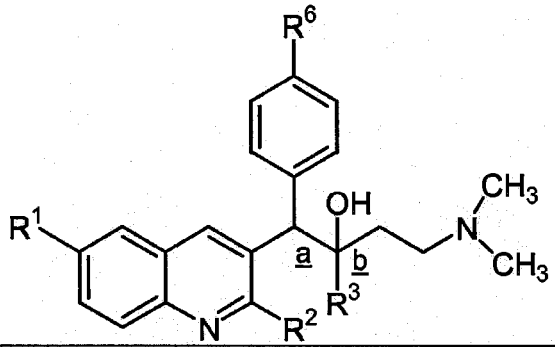
nBuLi 1.6M (0.05 mol) was added slowly at -20°C under N_2 flow to a solution of *N*-(1-methylethyl)-2-propanamine (0.05 mol) in tetrahydrofuran (THF) (80ml) . The mixture was stirred at -20°C for 15 minutes, then cooled to -70°C . A solution of intermediate compound 3 (prepared according to A3 described above) (0.046 mol) in THF (150ml) was added slowly . The mixture was stirred at -70°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 ($MgSO_4$), filtered, and the solvent was evaporated . The residue (29g) was purified by column chromatography over silica gel (eluent: $CH_2Cl_2/CH_3OH/NH_4OH$; 99.5/0.5/0.1; 15-35µm) . 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° (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° (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°(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: $CH_2Cl_2/CH_3OH/NH_4OH$; 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° (c = 0.336 g/100 ml in DMF)). Enantiomer B2 was purified by column chromatography over silica gel (eluent: $CH_2Cl_2/CH_3OH/NH_4OH$; 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° (c = 0.349 g/100 ml in DMF)).

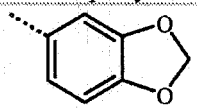
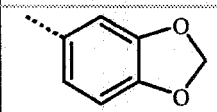
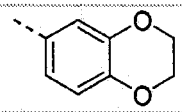
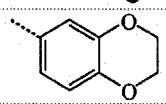
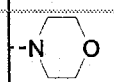
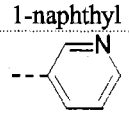
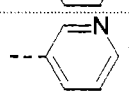
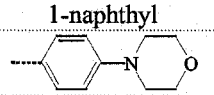
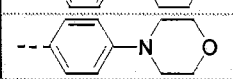
Tables 1 to 6 list compounds of formula (Ia) and (Ib).

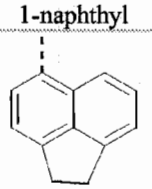
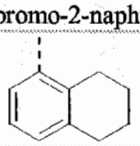
Table 1 :



Comp. nr.	Ex. nr.	R^1	R^2	R^3	R^6	Stereochemistry and melting points
1	B1	Br	OCH_3	phenyl	H	(A1); 194°C
2	B1	Br	OCH_3	phenyl	H	(A2); 191°C
3	B1	Br	OCH_3	phenyl	H	(A); 200°C
4	B1	Br	OCH_3	phenyl	H	(B); 190°C
16	B1	Br	OCH_3	4-chlorophenyl	H	(A); 200°C
17	B1	Br	OCH_3	4-chlorophenyl	H	(B); 190°C
20	B1	Br	OCH_3	2-thienyl	H	(A); 96°C
21	B1	Br	OCH_3	2-thienyl	H	(B); 176°C
22	B1	CH_3	OCH_3	phenyl	H	(A); 148°C
23	B1	CH_3	OCH_3	phenyl	H	(B); 165°C
24	B1	Br	OCH_3	3-thienyl	H	(A); 162°C
25	B1	Br	OCH_3	3-thienyl	H	(B); 160°C
26	B1	phenyl	OCH_3	phenyl	H	(A); 174°C
27	B1	phenyl	OCH_3	phenyl	H	(B); 192°C
28	B1	F	OCH_3	phenyl	H	(A); 190°C
29	B1	F	OCH_3	phenyl	H	(B); 166°C
30	B1	Cl	OCH_3	phenyl	H	(A); 170°C
31	B1	Cl	OCH_3	phenyl	H	(B); 181°C
32	B1	Br	SCH_3	phenyl	H	(A); 208°C
33	B1	Br	SCH_3	phenyl	H	(B); 196°C
34	B1	OCH_3	OCH_3	phenyl	H	(A); 165°C
35	B1	OCH_3	OCH_3	phenyl	H	(B); 165°C
36	B1	Br	OCH_3	phenyl	Cl	(A); 197°C
37	B1	Br	OCH_3	phenyl	Cl	(B); 221°C
38	B9	Br	OCH_3	3-fluorophenyl	H	(A); 198°C
39	B9	Br	OCH_3	3-fluorophenyl	H	(B); 207°C

Comp. nr.	Ex. nr.	R^1	R^2	R^3	R^6	Stereochemistry and melting points
108	B9	Br	OCH_3	3-fluorophenyl	H	(A1); 160°C
109	B9	Br	OCH_3	3-fluorophenyl	H	(A2); 156°C
40	B1	H	OCH_3	phenyl	H	(A); 152°C
41	B1	H	OCH_3	phenyl	H	(B); 160°C
42	B1	H	OCH_3	CH_3	H	(A); 140°C
43	B1	H	OCH_3	CH_3	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_2CH_3	phenyl	H	(A); 162°C
6	B2	Br	OCH_2CH_3	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_3	1-naphthyl	H	(A1); 118°C (foam); a=R, b=S; $[alpha]_D^{20} = -166.98$ (c=0.505g/100ml in DMF)
13	B7	Br	OCH_3	1-naphthyl	H	(A2); 120°C (foam); a=S; b=R; $[alpha]_D^{20} = +167.60$ (c=0.472g/100ml in DMF)
12a	B7	Br	OCH_3	1-naphthyl	H	(B1); $[\alpha]_D^{20}$ =-42.56 (c = 0.336 g/100 ml in DMF)
13a	B7	Br	OCH_3	1-naphthyl	H	(B2); $[\alpha]_D^{20}$ =+43.55 (c = 0.349 g/100 ml in DMF)
14	B7	Br	OCH_3	1-naphthyl	H	(A); 210°C
15	B7	Br	OCH_3	1-naphthyl	H	(B); 244°C
45	B7	Br	OCH_3	2-naphthyl	H	(A); 262°C
46	B7	Br	OCH_3	2-naphthyl	H	(B); 162°C
67	B8	Br	OCH_3	2,5-difluorophenyl	H	(A); 60°C
68	B8	Br	OCH_3	2,5-difluorophenyl	H	(B); 208°C
110	B8	Br	OCH_3	2,5-difluorophenyl	H	(A1); 167°C
111	B8	Br	OCH_3	2,5-difluorophenyl	H	(A2); oil
69	B1	Br	OCH_3	2-fluorophenyl	H	(A); oil
70	B1	Br	OCH_3	2-fluorophenyl	H	(B); oil

Comp. nr.	Ex. nr.	R^1	R^2	R^3	R^6	Stereochemistry and melting points
71	B1	Br	OCH_3	1-naphthyl	CH_3	(A); 174°C
72	B1	Br	OCH_3	1-naphthyl	CH_3	(B); 178°C
73	B1	Br	OCH_3	1-naphthyl	Cl	(B); 174°C
74	B1	Br	OCH_3	1-naphthyl	Cl	(A); 110°C
75	B1	Br	OCH_3		H	(A); 196°C
76	B1	Br	OCH_3		H	(B); 130°C
77	B1	Br	OCH_3		H	(A); 202°C
78	B1	Br	OCH_3		H	(B); 202°C
79	B1	Br		1-naphthyl	H	(A); >250°C
80	B1	Br	OCH_3	4-cyanophenyl	H	(A); 224°C
81	B1	Br	OCH_3	4-cyanophenyl	H	(B); 232°C
82	B1	CH_3	OCH_3	1-naphthyl	H	(A); 202°C
83	B1	CH_3	OCH_3	1-naphthyl	H	(B); 198°C
84	B1	phenyl	OCH_3	1-naphthyl	H	(A); 248°C
85	B1	phenyl	OCH_3	1-naphthyl	H	(B); 214°C
86	B1	Br	OCH_3		H	(A); 184°C
87	B1	Br	OCH_3		H	(B); 186°C
88	B1	Br	SCH_3	1-naphthyl	H	(A); 240°C
89	B1	Br	OCH_3		H	(A); 236°C
90	B1	Br	OCH_3		H	(B); 206°C
91	B1	H	OCH_3	1-naphthyl	H	(A); 178°C
92	B1	H	OCH_3	1-naphthyl	H	(B); 160°C
93	B1	H	OCH_3	3-fluorophenyl	H	(A); 178°C
94	B1	H	OCH_3	3-fluorophenyl	H	(B); 182°C
95	B1	Br	OCH_3	2-phenylethyl	H	(A); 178°C
96	B1	Br	OCH_3	2-phenylethyl	H	(B); 146°C

Comp. nr.	Ex. nr.	R^1	R^2	R^3	R^6	Stereochemistry and melting points
97	B1	OCH_3	OCH_3	1-naphthyl	H	(A); 168°C
98	B1	OCH_3	OCH_3	1-naphthyl	H	(B); 154°C
113	B14	Br	OCH_3	2,3-difluorophenyl	H	(A); 128°C
114	B14	Br	OCH_3	2,3-difluorophenyl	H	(B); 213°C
115	B15	Br	OCH_3	3,5-difluorophenyl	H	(A); 192°C
116	B15	Br	OCH_3	3,5-difluorophenyl	H	(B); 224°C
117	B15	Br	OCH_3	3,5-difluorophenyl	H	(A1); 161°C
118	B15	Br	OCH_3	3,5-difluorophenyl	H	(A2); 158°C
119	B7	Cl	OCH_3	1-naphthyl	H	(A); 212°C
120	B7	Cl	OCH_3	1-naphthyl	H	(B); 236°C
122	B7	Br	OCH_3		H	(B); 227°C
127	B7	Br	OCH_3	5-bromo-2-naphthyl	H	(A); 226°C
130	B7	Br	OCH_3	5-bromo-2-naphthyl	H	(B); 220°C
131	B1	Br	OCH_3		H	(A); 206°C
134	B9	OCH_3	OCH_3	3-fluorophenyl	H	(A); 172°C
135	B9	OCH_3	OCH_3	3-fluorophenyl	H	(B); 182°C
143	B7	Br	OCH_3	3-bromo-1-naphthyl	H	(A); 234°C
150	B7	Br	OCH_3	3-bromo-1-naphthyl	H	(B); 212°C
159	B8	Br	OCH_3	2,5-difluorophenyl	H	(A1); 208°C
160	B8	Br	OCH_3	2,5-difluorophenyl	H	(A2); 167°C
162	B7	Br	OCH_3	6-methoxy-2-naphthyl	H	(A); 206°C
163	B7	Br	OCH_3	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_3	2,6-difluorophenyl	H	(B); 180°C
174	B9		OCH_3	3-fluorophenyl	H	(A); 159°C

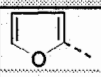
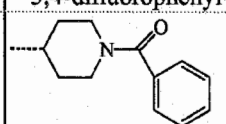
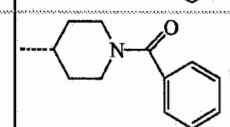
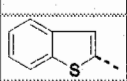
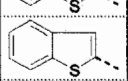
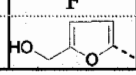
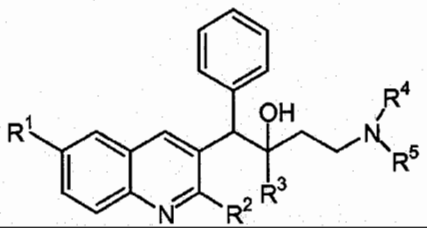
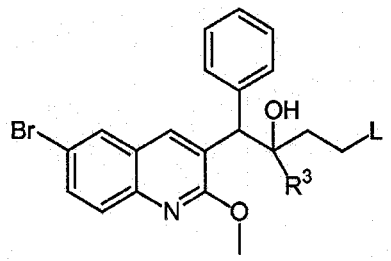
Comp. nr.	Ex. nr.	R^1	R^2	R^3	R^6	Stereochemistry and melting points
175	B9		OCH_3	3-fluorophenyl	H	(B); 196°C
176	B7	Br		1-naphthyl	H	(A); oil
179	B9	CN	OCH_3	3-fluorophenyl	H	(A); 213°C
180	B9	CN	OCH_3	3-fluorophenyl	H	(B); 163°C
181	B9	Br	OCH_3	4-fluorophenyl	H	(A); 198°C
182	B9	Br	OCH_3	4-fluorophenyl	H	(B); 238°C
183	B1	Br	OCH_3	3-trifluoro-methylphenyl	H	(A); 170°C
188	B1	Br	OCH_3	1,4-pyrimidin-2-yl	H	(A); 110°C
189	B1	Br	OCH_3	1,4-pyrimidin-2-yl	H	(B); 145°C
195	B15	Br	OCH_3	3,4-difluorophenyl	H	(A); 250°C
196	B15	Br	OCH_3	3,4-difluorophenyl	H	(B); 184°C
201	B1	Br	OCH_3		H	(A); 214°C
202	B1	Br	OCH_3		H	(B); 246°C
203	B9		OCH_3	3-fluorophenyl	H	(A); 225°C
204	B9		OCH_3	3-fluorophenyl	H	(B); 216°C
205	B7	Br	OCH_3	1-naphthyl	F	(A); 213°C
206	B7	Br	OCH_3	1-naphthyl	F	(B); 213°C
207	B15	F	OCH_3	3,5-difluorophenyl	H	(A); 232°C
208	B15	F	OCH_3	3,5-difluorophenyl	H	(B); 188°C
212	B7		OCH_3	1-naphthyl	H	(B); 220°C

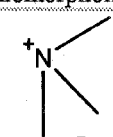
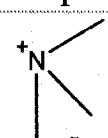
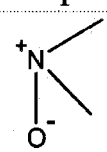
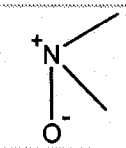
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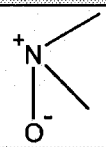
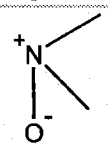
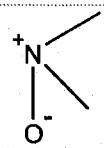
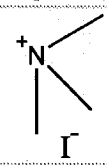
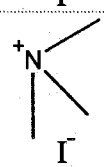
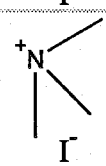


Comp. nr.	Ex. nr.	R^1	R^2	R^3	R^4	R^5	Phys.data (salt/melting points) and stereo-chemistry
18	B1	Br	OCH_3	phenyl	CH_2CH_3	CH_2CH_3	.ethanedioate (2:3); (A); 230°C
19	B1	Br	OCH_3	phenyl	CH_2CH_3	CH_2CH_3	.ethanedioate (2:3), (B); 150°C
44	B4	Br	OCH_3	phenyl	H	H	(A); 190°C
9	B4	Br	OCH_3	phenyl	H	H	(B); 204°C
141	B7	Br	OCH_3	2-naphthyl	CH_3	CH_2CH_3	(A); 188°C
142	B7	Br	OCH_3	2-naphthyl	CH_3	CH_2CH_3	(B); 202°C
230	B12	Br	OCH_3	1-naphthyl	CH_3	benzyl	/oil
147	B7	Br	OCH_3	1-naphthyl	CH_3	CH_2CH_3	(A); 168°C
148	B7	Br	OCH_3	1-naphthyl	CH_3	CH_2CH_3	(B); 212°C
56	B13	Br	OCH_3	1-naphthyl	CH_3	H	(A); 204°C
214	B13	Br	OCH_3	1-naphthyl	CH_3	H	(B); 225°C

Table 3:



Comp nr.	Ex. nr.	R^3	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^3	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

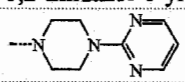
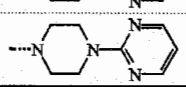
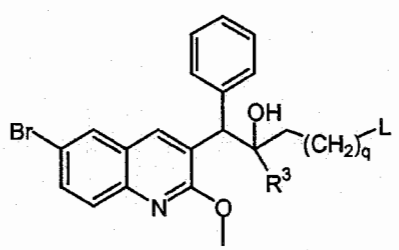
Comp nr.	Ex. nr.	R^3	L	Stereochemistry and melting points
155	B7	6-bromo-2-naphthyl	1-piperidinyl	(A); 224°C
156	B7	1-naphthyl	4-methylpiperazinyl	(A); 200°C
157	B7	6-bromo-2-naphthyl	1-pyrrolidinyl	(B); 220°C
158	B7	1-naphthyl	morpholinyl	(B); 272°C
166	B7	6-bromo-2-naphthyl	1-piperidinyl	(B); 218°C
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

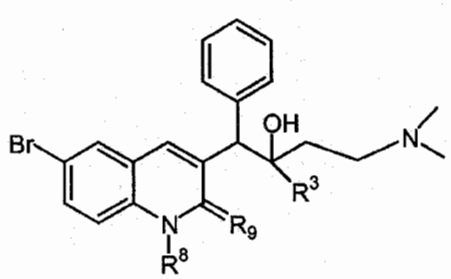
Table 4:



Comp. nr.	Ex. nr.	R^3	Q	L	Stereochemistry and melting points
61	B1	phenyl	0	$N(CH_3)_2$	(A); 220°C
62	B1	phenyl	0	$N(CH_3)_2$	(B); 194°C
63	B1	phenyl	2	$N(CH_3)_2$	(A); 150°C
64	B1	phenyl	2	$N(CH_3)_2$	(B); 220°C
125	B7	2-naphthyl	2	$N(CH_3)_2$	(A); 229°C
126	B7	2-naphthyl	2	$N(CH_3)_2$	(B); 214°C

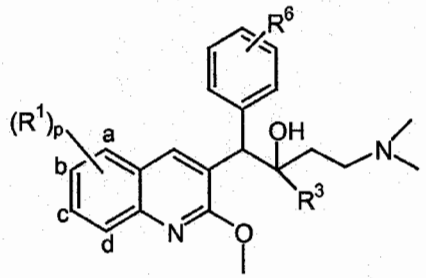
Comp. nr.	Ex. nr.	R^3	Q	L	Stereochemistry and melting points
65	B1	phenyl	3	$N(CH_3)_2$	(A); 130°C
66	B1	phenyl	3	$N(CH_3)_2$	(B); 170°C
132	B7	2-naphthyl	2	pyrrolidinyl	(A); 227°C
133	B7	2-naphthyl	2	pyrrolidinyl	(B); 222°C
161	B7	2-naphthyl	2	morpholinyl	(B); 234°C
186	B7	1-naphthyl	2	$N(CH_3)_2$	(A); 187°C
190	B7	2-naphthyl	3	$N(CH_3)_2$	(A); 170°C
191	B7	2-naphthyl	3	$N(CH_3)_2$	(B); 145°C
192	B7	2-naphthyl	2	$N(CH_2CH_3)_2$	(A); 90°C
193	B7	2-naphthyl	2	$N(CH_2CH_3)_2$	(B); 202°C
194	B7	1-naphthyl	2	pyrrolidinyl	(B); 206°C
197	B7	1-naphthyl	3	$N(CH_3)_2$	(A); 160°C
198	B7	2-naphthyl	2	morpholinyl	(A); 215°C
199	B7	1-naphthyl	2	$N(CH_2CH_3)_2$	(A); 185°C
210	B7	1-naphthyl	2	morpholinyl	(B); 222°C
211	B7	1-naphthyl	2	morpholinyl	(A); 184°C

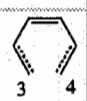
Table 5:



Comp nr.	Ex. nr.	R^3	R^8	R^9	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_3	=O	(A); 224°C
107	B1	phenyl	CH_3	=O	(B); 180°C
138	B7	1-naphthyl	H	=O	(A1); >260°C

Table 6:



Comp nr.	Ex. nr.	R^1				R^3	R^6	Sterechemistry and melting points
		a	b	c	d			
215	B9	H	Br	CH_3	H	3-fluorophenyl	H	(A); 197°C
216	B9	H	Br	CH_3	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_3	3-fluorophenyl	H	(A); 220°C
220	B9	H	Br	H	CH_3	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_3	H	1-naphthyl	H	(A); 238°C
226	B7	H	Br	CH_3	H	1-naphthyl	H	(B); 208°C
227	B15	H	Br	CH_3	H	3,5-difluorophenyl	H	(A); 195°C
228	B15	H	Br	CH_3	H	3,5-difluorophenyl	H	(B); 218°C
229	B7	H	CH_3	CH_3	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

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, Brussles[8]) 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.

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 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 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 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[9]. The jar was incubated for 7 days at 37 °C.

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 evaluate the bactericidal activity.

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

Dormancy assay

500 µl 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 µg/ml. After addition of the drugs, all tube were closed loosely and placed very quickly inside an anaerobic jar (BBL) as previously described[9]. 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 µl 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 µl of samples and dilutions were added to 140 µl PBS. 20 µl 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 [9,10]. 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[7]. 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[9]. Gaspak jars are fitted with a lid containing a catalyst. A Gaspak foil envelope containing substances that generate hydrogen and CO_2 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[11,12]. Luciferase reporter strains have been used quite often to access the viability of the bacteria [13,14]. 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[8]. The luminescent genes from *Vibro harveyi* (lux A and B) are under control of BCG hsp60 promoter and produce light in presence of ATP or Flavin mononucleotide ($FMNH_2$). 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 [15,16]. 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 [17].

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 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 $\log_{10}$ as compared to control. Final compound 12 affects the survival of the dormant bacteria in concentration dependent manner. At 10 µg/ml concentration of final compound 12 there was approximately 4-$\log_{10}$ 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 $\log_{10}$ and 2 $\log_{10}$ respectively.

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 at 10 µg/ml, 1 µg/ml and 0.1 µg/ml reduced the viability by approximately 4, 2.3, and 0.5 $\log_{10}$ at day 2 and about 6, 4.7 and 1.1 $\log_{10}$ 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 concentration within these cells is very low, which has been shown to be the characteristics of the metabolic state of the dormant bacilli[8] .

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.

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 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. 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)

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 37 °C (500 rpm). 17 ml aliquots of log phase culture (calculated OD_{600nm} = 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) 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.

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 untreated control cultures, was determined by plating after anaerobiosis to evaluate the bactericidal activity.

Experimental organization

Sample number	Sample / Compound	µg / 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[18-23]. 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 10µg/ml concentration of final compound 12, more than 2 $\log_{10}$ reduction of the dormant bacteria was observed as also seen in case of moxifloxacin and rifampin. At 1µg/ml concentration, 1.41 $\log_{10}$ reduction was observed for compound 12.

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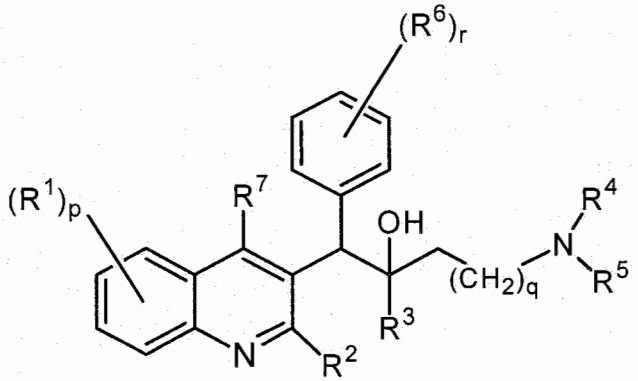
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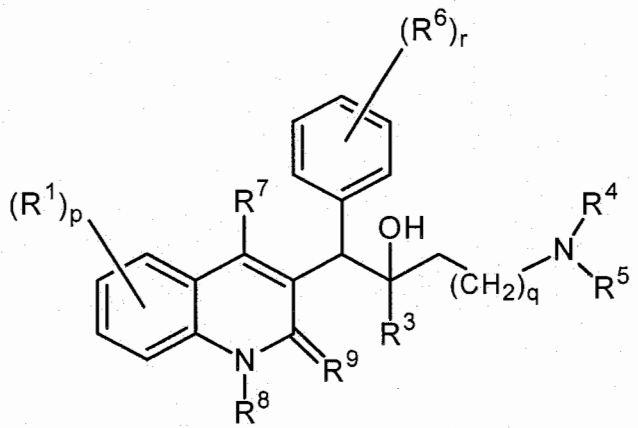
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Claims

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



(Ia)

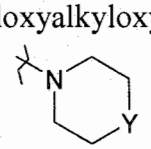


(Ib)

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

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 ;

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-imidazolinyl, 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^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 ;

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 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*-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;

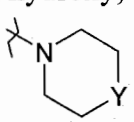
halo is a substituent selected from the group of fluoro, chloro, bromo and iodo; and

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^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 ;

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 ;

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 ;

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 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 ;

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

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^1 is hydrogen, halo, Ar, alkyl or alkyloxy.

4. Use according to claim 3 wherein R^1 is halo.

5. Use according to any one of the preceding claims wherein in formula (Ia) or (Ib) p is equal to 1.

6. Use according to any one of the preceding claims wherein in formula (Ia) or (Ib) R^2 is hydrogen, alkyloxy or alkylthio.

7. Use according to claim 6 wherein R^2 is alkyloxy.

8. Use according to any one of the preceding claims wherein in formula (Ia) or (Ib) R^3 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^3 is naphthyl.

10. Use according to any one of the preceding claims wherein in formula (Ia) or (Ib) q is equal to 1.

11. 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 or 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, piperidinyl, piperazinyl and thiomorpholinyl.

12. Use according to claim 11 wherein in formula (Ia) or (Ib) R^4 and R^5 each independently are hydrogen or alkyl.

13. Use according to claim 12 wherein R^4 and R^5 are C_{1-4}alkyl.

14. Use according to any one of the preceding claims wherein in formula (Ia) or (Ib) R^6 is hydrogen, alkyl or halo.

15. Use according to claim 14 wherein R^6 is hydrogen.

16. Use according to any one of the preceding claims wherein in formula (Ia) or (Ib) r is equal to 1.

17. Use according to any one of the preceding claims wherein in formula (Ia) or (Ib) R^7 is hydrogen.

18. Use according to claim 1 wherein in formula (Ia) or (Ib) R^1 is hydrogen, halo, Ar, alkyl or alkyloxy; p = 1; R^2 is hydrogen, alkyloxy or alkylthio; R^3 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^4 and R^5 each independently are hydrogen or alkyl or 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, piperidinyl, piperazinyl and thiomorpholinyl; R^6 is hydrogen, alkyl or halo; r is equal to 1 and R^7 is hydrogen.

19. Use according to any one of the preceding claims wherein alkyl represents C_{1-6}alkyl.

20. Use according to any one of the preceding claims wherein haloalkyl represents polyhaloC_{1-6}alkyl.

21. 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;

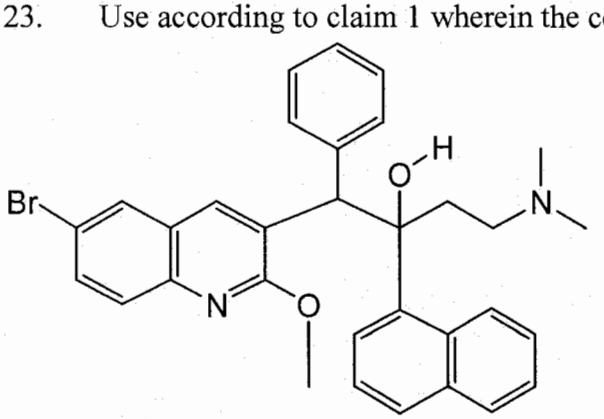
a pharmaceutically acceptable acid or base addition salt thereof, a *N*-oxide thereof, or a stereochemically isomeric form thereof.

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;

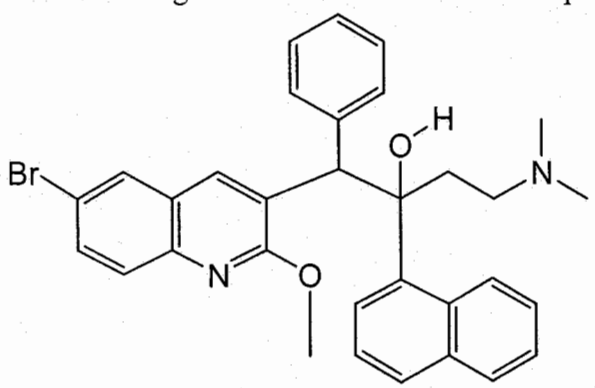
a pharmaceutically acceptable acid or base addition salt thereof, a *N*-oxide thereof, or a stereochemically isomeric form thereof.

23. Use according to claim 1 wherein the compound is



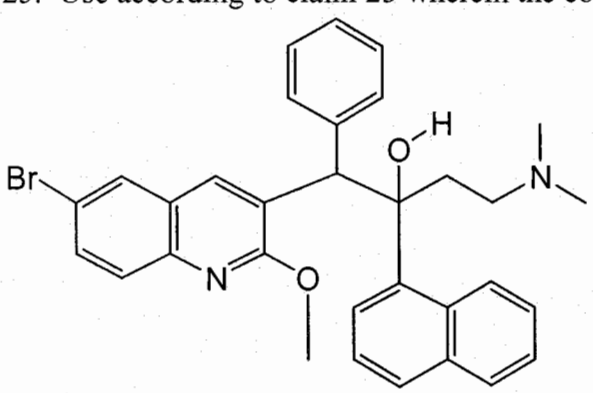
a pharmaceutically acceptable acid or base addition salt thereof, a *N*-oxide thereof, or a stereochemically isomeric form thereof.

24. Use according to claim 23 wherein the compound is



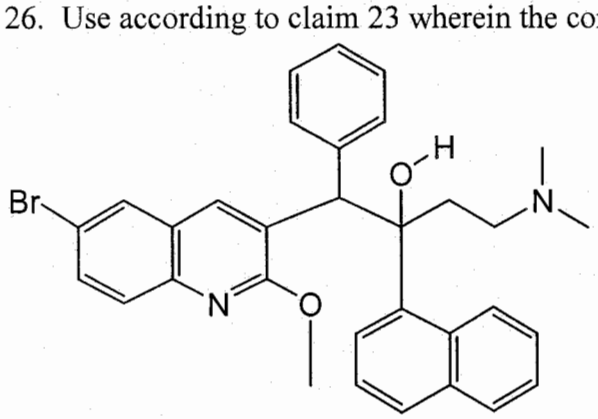
or a pharmaceutically acceptable acid addition salt thereof.

25. Use according to claim 23 wherein the compound is



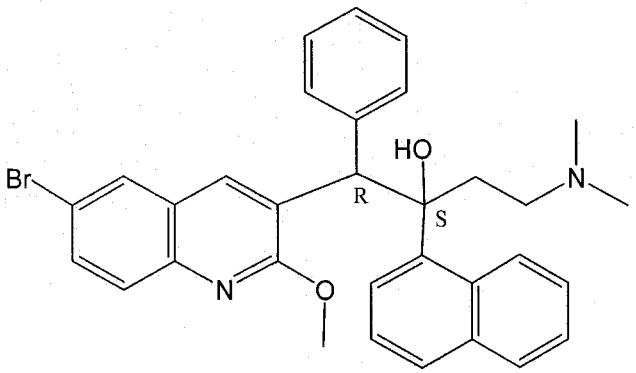
or a stereochemically isomeric form thereof.

26. Use according to claim 23 wherein the compound is



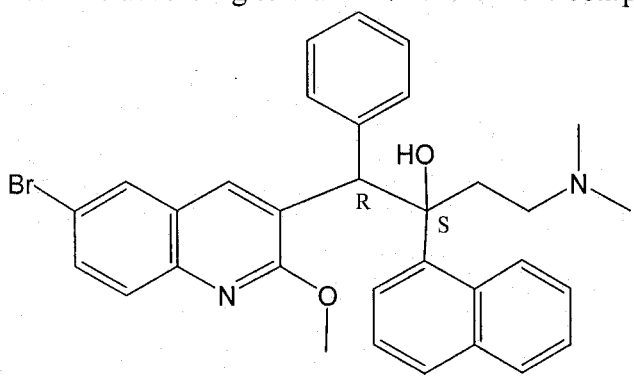
or a *N*-oxide form thereof.

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



29. Use according to any one of claims 1 to 20 wherein the compound is a compound according to formula (Ia).