ANTIBACTERIAL QUINOLINE DERIVATIVES

The present invention relates to novel substituted quinoline derivatives useful for the treatment of bacterial diseases, including but not limited to diseases caused by pathogenic mycobacteria such as *Mycobacterium tuberculosis, M. bovis, M. leprae, M. avium and M. marinum*, or pathogenic Staphylococci or Streptococci.

BACKGROUND OF THE INVENTION

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

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

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

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

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

The term “drug resistant” as used hereinbefore or hereinafter is a term well understood by the person skilled in microbiology. A drug resistant Mycobacterium is a Mycobacterium which is no longer susceptible to at least one previously effective drug; which has developed the ability to withstand antibiotic attack by at least one previously effective drug. A drug resistant strain may relay that ability to withstand to its progeny. Said resistance may be due to random genetic mutations in the bacterial cell that alters its sensitivity to a single drug or to different drugs.
MDR tuberculosis is a specific form of drug resistant tuberculosis due to a bacterium resistant to at least isoniazid and rifampicin (with or without resistance to other drugs), which are at present the two most powerful anti-TB drugs. Thus, whenever used hereinbefore or hereinafter “drug resistant” includes multi drug resistant.

Another factor in the control of the TB epidemic is the problem of latent TB. 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. 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. To control TB epidemic, the need is to discover new drugs that can kill dormant or latent 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. 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. 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. 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. These factors have been postulated to render these bacteria phenotypically tolerant to major anti-mycobacterial drugs.

In addition to the management of the TB epidemic, there is the emerging problem of resistance to first-line antibiotic agents. Some important examples include penicillin-resistant Streptococcus pneumoniae, vancomycin-resistant enterococci, methicillin-resistant Staphylococcus aureus, multi-resistant salmonellae.

The consequences of resistance to antibiotic agents are severe. Infections caused by resistant microbes fail to respond to treatment, resulting in prolonged illness and greater risk of death. Treatment failures also lead to longer periods of infectivity, which

increase the numbers of infected people moving in the community and thus exposing the general population to the risk of contracting a resistant strain infection. Hospitals are a critical component of the antimicrobial resistance problem worldwide. The combination of highly susceptible patients, intensive and prolonged antimicrobial use, and cross-infection has resulted in infections with highly resistant bacterial pathogens.

Self-medication with antimicrobials is another major factor contributing to resistance. Self-medicated antimicrobials may be unnecessary, are often inadequately dosed, or may not contain adequate amounts of active drug.

Patient compliance with recommended treatment is another major problem. Patients forget to take medication, interrupt their treatment when they begin to feel better, or may be unable to afford a full course, thereby creating an ideal environment for microbes to adapt rather than be killed.

Because of the emerging resistance to multiple antibiotics, physicians are confronted with infections for which there is no effective therapy. The morbidity, mortality, and financial costs of such infections impose an increasing burden for health care systems worldwide.

Therefore, there is a high need for new compounds to treat bacterial infections, especially mycobacterial infections including drug resistant and latent mycobacterial infections, and also other bacterial infections especially those caused by resistant bacterial strains.

WO2004/011436, WO2005/070924, WO2005/070430 and WO2005/075428 disclose certain substituted quinoline derivatives having activity against *Mycobacteria*, in particular against *Mycobacterium tuberculosis*. WO2005/117875 describes substituted quinoline derivatives having activity against resistant Mycobacterial strains. WO2006/067048 describes substituted quinoline derivatives having activity against latent tuberculosis. One particular compound of these substituted quinoline derivatives is described in Science (2005), 307, 223-227 and its mode of action is described in WO2006/035051.

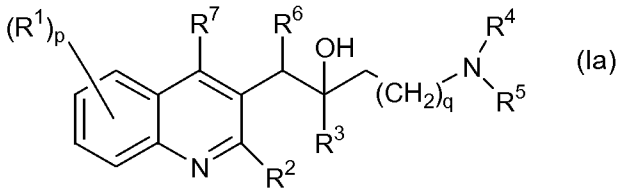
Other substituted quinolines are disclosed in US-5,965,572 (The United States of America) for treating antibiotic resistant infections and in WO00/34265 to inhibit the

growth of bacterial microorganisms.

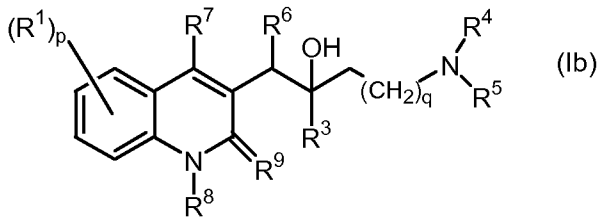
The purpose of the present invention is to provide novel compounds, in particular substituted quinoline derivatives, having the property of inhibiting bacterial growth especially of mycobacteria but also of other bacteria such as Streptococci and Staphylococci and the compounds are therefore useful for the treatment of bacterial diseases, particularly those diseases caused by pathogenic bacteria such as *Streptococcus pneumonia*, *Staphylococcus aureus* or *Mycobacterium tuberculosis* (including the latent disease and including drug resistant *M. tuberculosis* strains), *M. bovis, M. leprae, M. avium and M. marinum.*

SUMMARY OF THE INVENTION

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



(Ia)



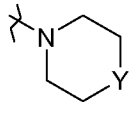
(Ib)

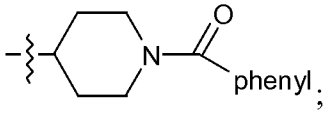
including any stereochemically isomeric form thereof, wherein

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

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

R^1 is alkenyl, alkynyl, -C=N-OR^{11}, amino, mono or di(alkyl)amino, aminoalkyl, mono or di(alkyl)aminoalkyl, alkylcarbonylaminoalkyl, aminocarbonyl, mono or di(alkyl)aminocarbonyl, arylcarbonyl, $R^{5a}R^{4a}$Nalkyl, $R^{5a}R^{4a}$N-, $R^{5a}R^{4a}$N-C(=O)-;

R^2 is hydrogen, alkyloxy, aryl, aryloxy, hydroxy, mercapto, alkyloxyalkyloxy, alkylthio, mono or di(alkyl)amino, pyrrolidino or a radical of formula  wherein Y is CH_2, O, S, NH or *N*-alkyl ;

R^3 is alkyl, arylalkyl, aryl-O-alkyl, aryl-alkyl-O-alkyl, aryl, Het, Het-alkyl, Het-O-alkyl, Het-alkyl-O-alkyl or ;

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, imidazolidinyl, pyridazinyl, pyrimidinyl, pyrazinyl, triazinyl, morpholinyl and thiomorpholinyl, each radical optionally substituted with alkyl, halo, haloalkyl, hydroxy, alkyloxy, amino, mono- or dialkylamino, alkylthio, alkyloxyalkyl, alkylthioalkyl and pyrimidinyl ;

R^{4a} and R^{5a} together with the nitrogen atom to which they are attached form a radical selected from the group consisting of pyrrolidino, piperidino, piperazino, morpholino, 4-thiomorpholino, 2,3-dihydroisoindol-1-yl, thiazolidin-3-yl, 1,2,3,6-tetrahydropyridyl, hexahydro-1*H*-azepinyl, hexahydro-1*H*-1,4-diazepinyl, hexahydro-1,4-oxazepinyl, 1,2,3,4-tetrahydroisoquinolin-2-yl, pyrrolinyl, pyrrolyl, imidazolidinyl, pyrazolidinyl, 2-imidazolinyl, 2-pyrazolinyl, imidazolyl, pyrazolyl, triazolyl, pyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl and triazinyl, each radical optionally substituted with 1, 2, 3 or 4 substituents, each substituent independently selected from alkyl, haloalkyl, halo, arylalkyl, hydroxy, alkyloxy, amino, mono- or dialkylamino, alkylthio, alkylthioalkyl, aryl, pyridyl or pyrimidinyl;

R^6 is $aryl^1$ or Het;

R^7 is hydrogen, halo, alkyl, aryl or Het;

R^8 is hydrogen or alkyl;

R^9 is oxo; or

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

R^{11} is hydrogen or alkyl;

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

aryl[1] is a homocycle selected from phenyl, naphthyl, acenaphthyl or tetrahydronaphthyl, each being optionally substituted with 1, 2 or 3 substituents, each substituent being independently selected from hydroxy, halo, cyano, nitro, amino, mono- or dialkylamino, alkyl, haloalkyl, alkyloxy, alkylthio, haloalkyloxy, carboxyl, alkyloxycarbonyl, aminocarbonyl, morpholinyl, Het or mono- or dialkylaminocarbonyl;

Het is a monocyclic heterocycle selected from *N*-phenoxypiperidinyl, piperidinyl, pyrrolyl, pyrazolyl, imidazolyl, furanyl, thienyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, pyridinyl, pyrimidinyl, pyrazinyl or pyridazinyl; or a bicyclic heterocycle selected from 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 being optionally substituted with 1, 2 or 3 substituents, each substituent independently selected from halo, hydroxy, alkyl or alkyloxy;

the *N*-oxides thereof, the pharmaceutically acceptable salts thereof or the solvates thereof.

Whenever used herein, the term "compounds of formula (Ia) or (Ib)" or "compounds according to the invention" is meant to also include their pharmaceutically acceptable salts or their *N*-oxide forms or their solvates.

The compounds of 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 definition of Het, 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 aryl, aryl[1] 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.

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

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. The pharmaceutically acceptable salts as mentioned hereinbefore or hereinafter are meant to also comprise the therapeutically active non-toxic metal or amine addition salt forms (base addition salt forms) which the compounds of formula (Ia) or (Ib) are able to form. Appropriate base addition 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, said acid or base addition salt forms can be converted into the free forms by treatment with an appropriate base or acid.

The term pharmaceutically acceptable salt also comprises the quaternary ammonium salts (quaternary amines) 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 C_{1-6}alkylhalide, arylC_{1-6}alkylhalide, C_{1-6}alkylcarbonylhalide, arylcarbonylhalide, HetC_{1-6}alkylhalide or Hetcarbonylhalide, e.g. methyliodide or benzyliodide. Preferably, Het represents a monocyclic heterocycle selected from furanyl or thienyl; or a bicyclic heterocycle selected from benzofuranyl or benzothienyl; each monocyclic and bicyclic heterocycle may optionally be substituted with 1, 2 or 3 substituents, each substituent independently selected from the group of halo, alkyl and aryl. Preferably, the quaternizing agent is C_{1-6}alkylhalide. Other reactants with good leaving groups may also be used, such as C_{1-6}alkyl trifluoromethanesulfonates, C_{1-6}alkyl methanesulfonates, and C_{1-6}alkyl *p*-toluenesulfonates. A quaternary amine has a positively charged nitrogen. Pharmaceutically acceptable counterions include chloro, bromo, iodo, trifluoroacetate, acetate, triflate, sulfate, sulfonate. Preferably, the counterion is iodo. The counterion of choice can be introduced using ion exchange resins.

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

In the framework of this application, a compound according to the invention is inherently intended to comprise all stereochemically isomeric forms thereof. 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 *N*-oxides, pharmaceutically acceptable 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. 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.

Of special interest are those compounds of formula (Ia) or (Ib) which are stereochemically pure.

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 (Ia) or (Ib) is for instance specified as (R,S), this means that the compound is substantially free of the (S,R) isomer.

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 compounds of either formula (Ia) and (Ib) may be synthesized in the form of mixtures, in particular 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 formula (Ia) or (Ib) are meant to comprise those compounds of formula (Ia) or (Ib) wherein e.g. an enol group is converted into a keto group (keto-enol tautomerism). Tautomeric forms of the compounds of formula (Ia) and (Ib) or of intermediates of the present invention are intended to be embraced by the ambit of this invention.

The *N*-oxide forms of the present compounds are meant to comprise the compounds of formula (Ia) or (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) or (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.

In the framework of this application, a compound according to the invention is inherently intended to comprise all isotopic combinations of its chemical elements. In the framework of this application, a chemical element, in particular when mentioned in relation to a compound according to formula (Ia) or (Ib), comprises all isotopes and

isotopic mixtures of this element, either naturally occuring or synthetically produced, either with natural abundance or in an isotopically enriched form. In particular, when hydrogen is mentioned, it is understood to refer to ^{1}H, ^{2}H, ^{3}H and mixtures thereof; when carbon is mentioned, it is understood to refer to ^{11}C, ^{12}C, ^{13}C, ^{14}C and mixtures thereof; when nitrogen is mentioned, it is understood to refer to ^{13}N, ^{14}N, ^{15}N and mixtures thereof; when oxygen is mentioned, it is understood to refer to ^{14}O, ^{15}O, ^{16}O, ^{17}O, ^{18}O and mixtures thereof; and when fluor is mentioned, it is understood to refer to ^{18}F, ^{19}F and mixtures thereof.

A compound according to the invention therefore inherently comprises a compound with one or more isotopes of one or more element, and mixtures thereof, including a radioactive compound, also called radiolabelled compound, wherein one or more non-radioactive atoms has been replaced by one of its radioactive isotopes. By the term "radiolabelled compound" is meant any compound according to formula (Ia) or (Ib), a pharmaceutically acceptable salt thereof or an *N*-oxide form thereof or a solvate thereof, which contains at least one radioactive atom. For example, a compound can be labelled with positron or with gamma emitting radioactive isotopes. For radioligand-binding techniques (membrane receptor assay), the ^{3}H-atom or the ^{125}I-atom is the atom of choice to be replaced. For imaging, the most commonly used positron emitting (PET) radioactive isotopes are ^{11}C, ^{18}F, ^{15}O and ^{13}N, all of which are accelerator produced and have half-lives of 20, 100, 2 and 10 minutes respectively. Since the half-lives of these radioactive isotopes are so short, it is only feasible to use them at institutions which have an accelerator on site for their production, thus limiting their use. The most widely used of these are ^{18}F, ^{99m}Tc, ^{201}Tl and ^{123}I. The handling of these radioactive isotopes, their production, isolation and incorporation in a molecule are known to the skilled person.

In particular, the radioactive atom is selected from the group of hydrogen, carbon, nitrogen, sulfur, oxygen and halogen. Preferably, the radioactive atom is selected from the group of hydrogen, carbon and halogen.

In particular, the radioactive isotope is selected from the group of ^{3}H, ^{11}C, ^{18}F, ^{122}I, ^{123}I, ^{125}I, ^{131}I, ^{75}Br, ^{76}Br, ^{77}Br and ^{82}Br. Preferably, the radioactive isotope is selected from the group of ^{3}H, ^{11}C and ^{18}F.

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

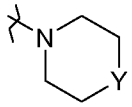
hydrocarbon radical having from 3 to 6 carbon atoms attached to a straight or branched saturated hydrocarbon radical having from 1 to 6 carbon atoms ; wherein each carbon atom can be optionally substituted with cyano, hydroxy, C_{1-6}alkyloxy or oxo.
Preferably alkyl is a straight or branched saturated hydrocarbon radical having from 1 to 6 carbon atoms ; or is a cyclic saturated hydrocarbon radical having from 3 to 6 carbon atoms ; wherein each carbon atom can be optionally substituted with hydroxyl or C_{1-6}alkyloxy.
Preferably, alkyl is methyl, ethyl or cyclohexylmethyl, more preferably methyl or ethyl.
An interesting embodiment of alkyl in all definitions used hereinbefore or hereinafter is C_{1-6}alkyl which represents 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. A preferred subgroup of C_{1-6}alkyl is C_{1-4}alkyl which represents 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.

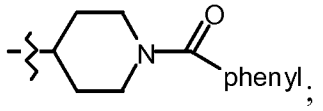
In the framework of this application C_{2-6}alkenyl is a straight or branched hydrocarbon radical having from 2 to 6 carbon atoms containing a double bond such as ethenyl, propenyl, butenyl, pentenyl, hexenyl and the like; C_{2-6}alkynyl is a straight or branched hydrocarbon radical having from 2 to 6 carbon atoms containing a triple bond such as ethynyl, propynyl, butynyl, pentynyl, hexynyl and the like; C_{3-6}cycloalkyl is a cyclic saturated hydrocarbon radical having from 3 to 6 carbon atoms and is generic to cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl

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 or 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 one or more carbon atoms are substituted with one or more halo atoms. Preferably, halo is bromo, fluoro or chloro; in particular chloro or bromo. 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 halo atom is attached to an alkyl or C_{1-6}alkyl group within the definition of haloalkyl or polyhaloC_{1-6}alkyl, they may be the same or different.

A first interesting embodiment relates to a compound of formula (Ia) or (Ib) or any subgroup thereof as mentioned hereinbefore as interesting embodiment wherein

R^1 is C_{2-6}alkenyl, C_{2-6}alkynyl, -C=N-OR^{11}, amino, mono or di(C_{1-6}alkyl)amino, aminoC_{1-6}alkyl, mono or di(C_{1-6}alkyl)aminoC_{1-6}alkyl, C_{1-6}alkylcarbonylaminoC_{1-6}alkyl, aminocarbonyl, mono or di(C_{1-6}alkyl)aminocarbonyl, arylcarbonyl, $R^{5a}R^{4a}$Nalkyl, $R^{5a}R^{4a}$N-, $R^{5a}R^{4a}$N-C(=O)-;

R^2 is hydrogen, C_{1-6}alkyloxy, aryl, aryloxy, hydroxy, mercapto, C_{1-6}alkyloxyC_{1-6}alkyloxy, C_{1-6}alkylthio, mono or di(C_{1-6}alkyl)amino, pyrrolidino or a radical of formula  wherein Y is CH_2, O, S, NH or *N*-C_{1-6}alkyl ;

R^3 is C_{1-6}alkyl, C_{3-6}cycloalkyl, arylC_{1-6}alkyl, aryl-O-C_{1-6}alkyl, arylC_{1-6}alkyl-O-C_{1-6}alkyl, aryl, Het, Het-C_{1-6}alkyl, Het-O-C_{1-6}alkyl or HetC_{1-6}alkyl-O-C_{1-6}alkyl, or ;

R^4 and R^5 each independently are hydrogen, C_{1-6}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, imidazolidinyl, pyridazinyl, pyrimidinyl, pyrazinyl, triazinyl, morpholinyl and thiomorpholinyl, each radical optionally substituted with C_{1-6}alkyl, halo, haloC_{1-6}alkyl, hydroxy, C_{1-6}alkyloxy, amino, mono- or di(C_{1-6}alkyl)amino, C_{1-6}alkylthio, C_{1-6}alkyloxyC_{1-6}alkyl, C_{1-6}alkylthioC_{1-6}alkyl and pyrimidinyl ;

R^{4a} and R^{5a} together with the nitrogen atom to which they are attached form a radical selected from the group consisting of pyrrolidino, piperidino, piperazino, morpholino, 4-thiomorpholino, 2,3-dihydroisoindol-1-yl, thiazolidin-3-yl, 1,2,3,6-tetrahydropyridyl, hexahydro-1*H*-azepinyl, hexahydro-1*H*-1,4-diazepinyl, hexahydro-1,4-oxazepinyl, 1,2,3,4-tetrahydroisoquinolin-2-yl, pyrrolinyl, pyrrolyl, imidazolidinyl, pyrazolidinyl, 2-imidazolinyl, 2-pyrazolinyl, imidazolyl, pyrazolyl, triazolyl, pyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl and triazinyl, each radical optionally substituted with 1, 2, 3 or 4 substituents, each

substituent independently selected from C_{1-6}alkyl, polyhaloC_{1-6}alkyl, halo, arylC_{1-6}alkyl, hydroxy, C_{1-6}alkyloxy, C_{1-6}alkyloxyC_{1-6}alkyl, amino, mono- or di(C_{1-6}alkyl)amino, C_{1-6}alkylthio, C_{1-6}alkyloxyC_{1-6}alkyl, C_{1-6}alkylthioC_{1-6}alkyl, aryl, pyridyl or pyrimidinyl;

R^6 is aryl[1] or Het;

R^7 is hydrogen, halo, C_{1-6}alkyl, aryl or Het;

R^8 is hydrogen or C_{1-6}alkyl;

R^9 is oxo; or

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

R^{11} is hydrogen or C_{1-6}alkyl;

aryl is a homocycle selected from phenyl, naphthyl, acenaphthyl or tetrahydronaphthyl, each being optionally substituted with 1, 2 or 3 substituents, each substituent being independently selected from 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, haloC_{1-6}alkyloxy, carboxyl, C_{1-6}alkyloxycarbonyl, aminocarbonyl, morpholinyl or mono- or di(C_{1-6}alkyl)aminocarbonyl;

aryl[1] is a homocycle selected from phenyl, naphthyl, acenaphthyl or tetrahydronaphthyl, each being optionally substituted with 1, 2 or 3 substituents, each substituent being independently selected from 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, C_{1-6}alkylthio, haloC_{1-6}alkyloxy, carboxyl, C_{1-6}alkyloxycarbonyl, aminocarbonyl, morpholinyl, Het or mono- or di(C_{1-6}alkyl)aminocarbonyl;

Het is a monocyclic heterocycle selected from *N*-phenoxypiperidinyl, piperidinyl, pyrrolyl, pyrazolyl, imidazolyl, furanyl, thienyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, pyridinyl, pyrimidinyl, pyrazinyl or pyridazinyl; or a bicyclic heterocycle selected from 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 being optionally substituted with 1, 2 or 3 substituents, each substituent independently selected from halo, hydroxy, C_{1-6}alkyl or C_{1-6}alkyloxy.

A second interesting embodiment relates to a compound of formula (Ia) or (Ib) or any subgroup thereof as mentioned hereinbefore as interesting embodiment wherein R^1 is C_{2-6}alkenyl, C_{2-6}alkynyl, -C=N-OR^{11}, amino, mono or di(C_{1-6}alkyl)amino, aminoC_{1-6}alkyl, mono or di(C_{1-6}alkyl)aminoC_{1-6}alkyl, C_{1-6}alkylcarbonylaminoC_{1-6}alkyl, aminocarbonyl, mono or di(C_{1-6}alkyl)aminocarbonyl, $R^{5a}R^{4a}$Nalkyl, $R^{5a}R^{4a}$N-, $R^{5a}R^{4a}$N-C(=O)-; in particular wherein R^1 is C_{2-6}alkenyl, C_{2-6}alkynyl, -C=N-OR^{11}, $R^{5a}R^{4a}$Nalkyl, $R^{5a}R^{4a}$N-, $R^{5a}R^{4a}$N-C(=O)-; even more in particular wherein R^1 is C_{2-6}alkenyl or -C=N-OR^{11}.

A third interesting embodiment relates to a compound of formula (Ia) or (Ib) or any subgroup thereof as mentioned hereinbefore as interesting embodiment wherein p is equal to 1.

A fourth interesting embodiment relates to a compound of formula (Ia) or (Ib) or any subgroup thereof as mentioned hereinbefore as interesting embodiment wherein R^2 is hydrogen, alkyloxy or alkylthio, in particular hydrogen, C_{1-6}alkyloxy or C_{1-6}alkylthio. More in particular, R^2 is C_{1-6}alkyloxy, preferably methyloxy.

A fifth interesting embodiment relates to a compound of formula (Ia) or (Ib) or any subgroup thereof as mentioned hereinbefore as interesting embodiment wherein R^3 is alkyl, arylalkyl, aryl, or Het; in particular C_{1-6}alkyl, arylC_{1-6}alkyl, aryl, or Het; more in particular C_{1-6}alkyl, optionally substituted phenyl, optionally substituted naphthyl, arylC_{1-6}alkyl wherein aryl represents optionally substituted phenyl or optionally substituted naphthyl, or Het; even more in particular optionally substituted phenyl, optionally substituted naphthyl, arylC_{1-6}alkyl wherein aryl represents optionally substituted phenyl or optionally substituted naphthyl; wherein the optional substituent is preferably halo, e.g. chloro. Preferably R^3 is phenyl; naphthyl; phenylC_{1-6}alkyl or naphthylC_{1-6}alkyl.

A sixth interesting embodiment relates to a compound of formula (Ia) or (Ib) or any subgroup thereof as mentioned hereinbefore as interesting embodiment wherein q is equal to 1, 2 or 3. More preferably, q is equal to 1 or 3.

A seventh interesting embodiment relates to a compound of formula (Ia) or (Ib) or any subgroup thereof as mentioned hereinbefore as interesting embodiment wherein R^4 and R^5 each independently represent hydrogen or C_{1-6}alkyl, in particular C_{1-6}alkyl, more in particular methyl or ethyl. Preferably R^4 and R^5 are methyl.

An eigth interesting embodiment relates to a compound of formula (Ia) or (Ib) or any subgroup thereof as mentioned hereinbefore as interesting embodiment wherein R^4 and R^5 together with the nitrogen atom to which they are attached form a radical selected from the group consisting of piperidino, piperazino, morpholino, imidazolyl, triazolyl, each of said rings optionally substituted with C_{1-6}alkyl; more in particular piperidino.

A ninth interesting embodiment relates to a compound of formula (Ia) or (Ib) or any subgroup thereof as mentioned hereinbefore as interesting embodiment wherein R^6 is phenyl optionally substituted with halo, cyano or C_{1-6}alkyloxy; in particular phenyl optionally substituted with halo.

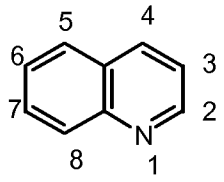
A tenth interesting embodiment relates to a compound of formula (Ia) or (Ib) or any subgroup thereof as mentioned hereinbefore as interesting embodiment wherein R^7 is hydrogen.

An eleventh interesting embodiment relates to a compound of formula (Ia) or (Ib) or any subgroup thereof as mentioned hereinbefore as interesting embodiment wherein the compound is a compound of formula (Ia).

A twelfth interesting embodiment relates to a compound of formula (Ia) or (Ib) or any subgroup thereof as mentioned hereinbefore as interesting embodiment wherein the compound is a compound of formula (Ib) and wherein R^8 is hydrogen and R^9 is oxo.

A thirteenth interesting embodiment relates to a compound of formula (Ia) or (Ib) or any subgroup thereof as mentioned hereinbefore as interesting embodiment wherein the compound is a compound of formula (Ib), in particular wherein R^8 is alkyl, more preferable C_{1-6}alkyl, e.g. methyl.

A fourteenth interesting embodiment relates to a compound of formula (Ia) or (Ib) or any subgroup thereof as mentioned hereinbefore as interesting embodiment wherein R^1 is placed in position 6 of the quinoline ring.
In the framework of this application, the quinoline ring of the compounds of formula (Ia) or (Ib) is numbered as follows :



A fourteenth interesting embodiment is a compound of formula (Ia) or (Ib) or any subgroup thereof as mentioned hereinbefore as interesting embodiment wherein aryl is naphthyl or phenyl, more preferably phenyl, each optionally substituted with one or two substituents selected from halo, for example chloro; cyano; alkyl for example methyl; or alkyloxy, for example methyloxy.

A fifteenth interesting embodiment is the use of a compound of formula (Ia) or (Ib) or any subgroup thereof as mentioned hereinbefore as interesting embodiment for the manufacture of a medicament for the treatment of a bacterial infection with a gram-positive and/or a gram-negative bacterium, preferably a bacterial infection with a gram-positive bacterium.

A sixteenth interesting embodiment is the use of a compound of formula (Ia) or (Ib) or any subgroup thereof as mentioned hereinbefore as interesting embodiment for the manufacture of a medicament for the treatment of a bacterial infection wherein the compound of formula (Ia) or (Ib) has a IC_{90} < 15 µl/ml against at least one bacterium, in particular a gram-positive bacterium; preferably a IC_{90} < 10 µl/ml; more preferably a IC_{90} < 5 µl/ml; the IC_{90} value being determined as described hereinafter.

A seventeenth interesting embodiment relates to a compound of formula (Ia) or any subgroup thereof as mentioned hereinbefore as interesting embodiment wherein one or more, preferably all, of the following definitions apply :

R^1 is C_{2-6}alkenyl, C_{2-6}alkynyl, -C=N-OR^{11}, amino, aminoC_{1-6}alkyl, mono or di(C_{1-6}alkyl)aminoC_{1-6}alkyl, C_{1-6}alkylcarbonylaminoC_{1-6}alkyl, mono or di(C_{1-6}alkyl)aminocarbonyl, arylcarbonyl, $R^{5a}R^{4a}$Nalkyl, $R^{5a}R^{4a}$N-, $R^{5a}R^{4a}$N-C(=O)-;

R^2 is alkyloxy, in particular C_{1-6}alkyloxy, preferably methyloxy;

R^3 is arylalkyl or aryl; in particular phenyl, naphthyl or phenylC_{1-6}alkyl optionally substituted with halo;

R^4 and R^5 are C_{1-6}alkyl; in particular methyl; or R^4 and R^5 together with the nitrogen atom to which they are attached form piperidino;

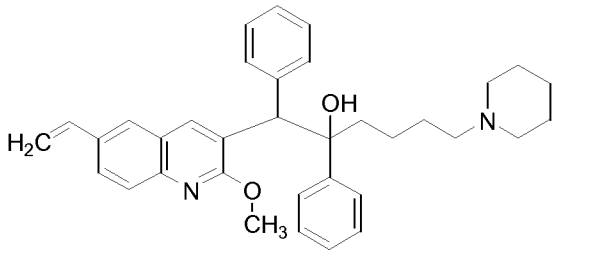
R^6 is phenyl optionally substituted with halo;

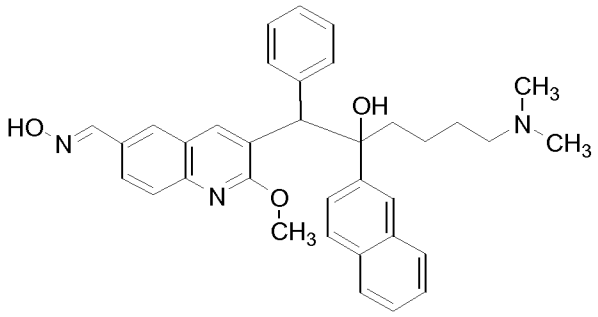
R^7 is hydrogen;

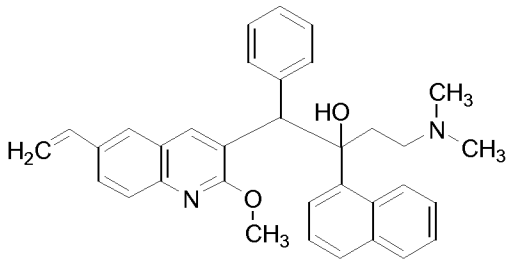
R^{11} is hydrogen or C_{1-4}alkyl; in particular hydrogen or methyl;
q is 1 or 3;
p is 1.

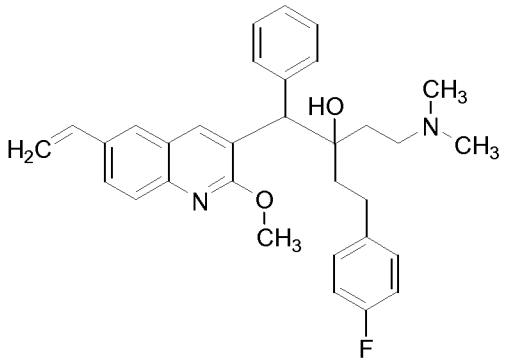
Preferably, in the compounds of formula (Ia) and (Ib) or any subgroup thereof as mentioned hereinbefore as interesting embodiment, the term "alkyl" represents C_{1-6}alkyl, more preferably C_{1-4}alkyl, and the term haloalkyl represents polyhaloC_{1-6}alkyl.

Most preferred compounds of formula (Ia) are compounds selected from









including any stereochemically isomeric form thereof,
a pharmaceutically acceptable salt thereof, a *N*-oxide form thereof or a solvate thereof.

In particular, preferred compounds of formula (Ia) are compounds 7, 33, 9 or 34 (see tables hereinafter); a pharmaceutically acceptable salt thereof, a *N*-oxide form thereof or a solvate thereof.

Preferably, the compound of formula (Ia) or (Ib) is a particular mixture of enantiomers (hereinafter indicated as a particular A or B diastereoisomer) and hence is substantially free of the other diastereoisomer(s)). In case the compound of formula (Ia) or (Ib) has two chiral centers, this means that the compound is a mixture, in particular a racemic mixture, of the (R,S) and (S,R) enantiomers or a mixture, in particular a racemic mixture, of the (R,R) and (S,S) enantiomer. Hereinafter, the mixtures, in particular the racemic mixtures, of 2 enantiomers are indicated as diastereoisomer A or B. Whether the racemic mixture is indicated as A or B depends on whether it is first isolated in the synthesis protocol (i.e. A) or second (i.e. B). More preferably, the compound of formula (Ia) or (Ib) is a particular enantiomer (substantially free of the other enantiomers). In case the compound of formula (Ia) or (Ib) has two chiral centers this means that the compound is the (R,S), (S,R), (R,R) or (S,S) enantiomer. Hereinafter, said particular enantiomers are indicated as A1, A2, B1 or B2. Whether the enantiomer is indicated as A1, A2, B1 or B2 depends on whether it is isolated first or second (1 or 2) in the synthesis protocol and whether it is separated from the A (A1, A2) or B (B1, B2) diastereoisomer.

PHARMACOLOGY

The compounds according to the invention have surprisingly been shown to be suitable for the treatment of a bacterial infection including a mycobacterial infection, particularly those diseases caused by pathogenic mycobacteria such as *Mycobacterium tuberculosis* (including the latent and drug resistant form thereof), *M. bovis*, *M. leprae*, *M. avium, M. leprae* and *M. marinum*. The present invention thus also relates to compounds of formula (Ia) or (Ib) as defined hereinabove, the pharmaceutically acceptable salts thereof or the *N*-oxide forms thereof or the solvates thereof, for use as a medicine, in particular for use as a medicine for the treatment of a bacterial infection including a mycobacterial infection.

Further, the present invention also relates to the use of a compound of formula (Ia) or (Ib), the pharmaceutically acceptable salts thereof or the *N*-oxide forms thereof or the

solvates thereof, as well as any of the pharmaceutical compositions thereof as described hereinafter for the manufacture of a medicament for the treatment of a bacterial infection including a mycobacterial infection.

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

In addition to their activity against mycobacteria, the compounds according to the invention are also active against other bacteria. In general, bacterial pathogens may be classified as either gram-positive or gram-negative pathogens. Antibiotic compounds with activity against both gram-positive and gram-negative pathogens are generally regarded as having a broad spectrum of activity. The compounds of the present invention are regarded as active against gram-positive and/or gram-negative bacterial pathogens, in particular against gram-positive bacterial pathogens. In particular, the present compounds are active against at least one gram-positive bacterium, preferably against several gram-positive bacteria, more preferably against one or more gram-positive bacteria and/or one or more gram-negative bacteria.

The present compounds have bactericidal or bacteriostatic activity.

Examples of gram-positive and gram-negative aerobic and anaerobic bacteria, include Staphylococci, for example *S. aureus*; Enterococci, for example *E. faecalis*; Streptococci, for example *S. pneumoniae*, *S. mutans*, *S. pyogens*; Bacilli, for example *Bacillus subtilis*; Listeria, for example *Listeria monocytogenes*; Haemophilus, for example *H. influenza*; Moraxella, for example *M. catarrhalis*; Pseudomonas, for example *Pseudomonas aeruginosa*; and Escherichia, for example *E. coli*. Gram-positive pathogens, for example Staphylococci, Enterococci and Streptococci are particularly important because of the development of resistant strains which are both difficult to treat and difficult to eradicate from for example a hospital environment once established. Examples of such strains are methicillin resistant *Staphylococcus aureus* (MRSA), methicillin resistant coagulase negative staphylococci (MRCNS), penicillin resistant *Streptococcus pneumoniae* and multiple resistant *Enterococcus faecium*.

The compounds of the present invention also show activity against resistant bacterial strains.

The compounds of the present invention are especially active against *Streptococcus pneumoniae* and *Staphylococcus aureus*, including resistant *Staphylococcus aureus* such as for example methicillin resistant *Staphylococcus aureus* (MRSA). The compounds of the present invention are in particular active against *Streptococcus pneumoniae.*

Therefore, the present invention also relates to the use of a compound of formula (Ia) or (Ib), the pharmaceutically acceptable salts thereof or the *N*-oxide forms thereof, as well as any of the pharmaceutical compositions thereof as described hereinafter for the manufacture of a medicament for the treatment of a bacterial infection including an infection caused by Staphylococci and/or Streptococci.

Accordingly, in another aspect, the invention provides a method of treating a patient suffering from, or at risk of, a bacterial infection, including an infection caused by Staphylococci and/or Streptococci, which comprises administering to the patient a therapeutically effective amount of a compound or pharmaceutical composition according to the invention.

Without being bound to any theory, it is taught that the activity of the present compounds lies in inhibition of the F1F0 ATP synthase, in particular the inhibition of the F0 complex of the F1F0 ATP synthase, more in particular the inhibition of subunit c of the F0 complex of the F1F0 ATP synthase, leading to killing of the bacteria by depletion of the cellular ATP levels of the bacteria. Therefore, in particular, the compounds of the present invention are active on those bacteria of which the viability depends on proper functioning of F1F0 ATP synthase.

Bacterial infections which may be treated by the present compounds include, for example, central nervous system infections, external ear infections, infections of the middle ear, such as acute otitis media, infections of the cranial sinuses, eye infections, infections of the oral cavity, such as infections of the teeth, gums and mucosa, upper respiratory tract infections, lower respiratory tract infections, genitourinary infections, gastrointestinal infections, gynaecological infections, septicemia, bone and joint infections, skin and skin structure infections, bacterial endocarditis, burns, antibacterial prophylaxis of surgery, and antibacterial prophylaxis in immunosuppressed patients, such as patients receiving cancer chemotherapy, or organ transplant patients.

Whenever used hereinbefore or hereinafter, that the compounds can treat a bacterial infection it is meant that the compounds can treat an infection with one or more bacterial strains.

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

Depending on the mode of administration, the pharmaceutical composition will preferably comprise from 0.05 to 99 % by weight, more preferably from 0.1 to 70 % by weight, even more preferably from 0.1 to 50 % by weight of the active ingredient(s), and, from 1 to 99.95 % by weight, more preferably from 30 to 99.9 % by weight, even

more preferably from 50 to 99.9 % by weight of a pharmaceutically acceptable carrier, all percentages being based on the total weight of the 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 gram, e.g. in the range from 10 to 50 mg/kg body weight.

Given the fact that the compounds of formula (Ia) or Formula (Ib) are active against bacterial infections, the present compounds may be combined with other antibacterial agents in order to effectively combat bacterial infections.

Therefore, the present invention also relates to a combination of (a) a compound according to the invention, and (b) one or more other antibacterial agents.

The present invention also relates to a combination of (a) a compound according to the invention, and (b) one or more other antibacterial agents, for use as a medicine.

The present invention also relates to the use of a combination or pharmaceutical composition as defined directly above for the treatment of a bacterial infection.

A pharmaceutical composition comprising a pharmaceutically acceptable carrier and, as active ingredient, a therapeutically effective amount of (a) a compound according to

the invention, and (b) one or more other antibacterial agents, is also comprised by the present invention.

The weight ratio of (a) the compound according to the invention and (b) the other antibacterial agent(s) when given as a combination may be determined by the person skilled in the art. Said ratio and the exact dosage and frequency of administration depends on the particular compound according to the invention and the other antibacterial agent(s) 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. A particular weight ratio for the present compound of formula (Ia) or (Ib) and another antibacterial agent may range from 1/10 to 10/1, more in particular from 1/5 to 5/1, even more in particular from 1/3 to 3/1.

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

The other antibacterial agents which may be combined with the compounds of formula (Ia) or (Ib) are for example antibacterial agents known in the art. The other antibacterial agents comprise antibiotics of the β-lactam group such as natural penicillins, semisynthetic penicillins, natural cephalosporins, semisynthetic cephalosporins, cephamycins, 1-oxacephems, clavulanic acids, penems, carbapenems, nocardicins, monobactams; tetracyclines, anhydrotetracyclines, anthracyclines; aminoglycosides; nucleosides such as *N*-nucleosides, C-nucleosides, carbocyclic nucleosides, blasticidin S; macrolides such as 12-membered ring macrolides, 14-membered ring macrolides, 16-membered ring macrolides; ansamycins; peptides such as bleomycins, gramicidins, polymyxins, bacitracins, large ring peptide antibiotics containing lactone linkages, actinomycins, amphomycin, capreomycin, distamycin,

enduracidins, mikamycin, neocarzinostatin, stendomycin, viomycin, virginiamycin; cycloheximide; cycloserine; variotin; sarkomycin A; novobiocin; griseofulvin; chloramphenicol; mitomycins; fumagillin; monensins; pyrrolnitrin; fosfomycin; fusidic acid; D-(*p*-hydroxyphenyl)glycine; D-phenylglycine; enediynes.

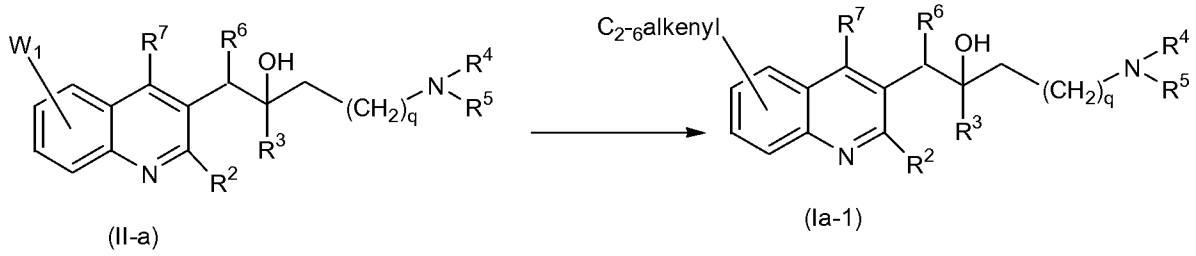
Specific antibiotics which may be combined with the present compounds of formula (Ia) or (Ib) are for example benzylpenicillin (potassium, procaine, benzathine), phenoxymethylpenicillin (potassium), phenethicillin potassium, propicillin, carbenicillin (disodium, phenyl sodium, indanyl sodium), sulbenicillin, ticarcillin disodium, methicillin sodium, oxacillin sodium, cloxacillin sodium, dicloxacillin, flucloxacillin, ampicillin, mezlocillin, piperacillin sodium, amoxicillin, ciclacillin, hectacillin, sulbactam sodium, talampicillin hydrochloride, bacampicillin hydrochloride, pivmecillinam, cephalexin, cefaclor, cephaloglycin, cefadroxil, cephradine, cefroxadine, cephapirin sodium, cephalothin sodium, cephacetrile sodium, cefsulodin sodium, cephaloridine, cefatrizine, cefoperazone sodium, cefamandole, vefotiam hydrochloride, cefazolin sodium, ceftizoxime sodium, cefotaxime sodium, cefmenoxime hydrochloride, cefuroxime, ceftriaxone sodium, ceftazidime, cefoxitin, cefmetazole, cefotetan, latamoxef, clavulanic acid, imipenem, aztreonam, tetracycline, chlortetracycline hydrochloride, demethylchlortetracycline, oxytetracycline, methacycline, doxycycline, rolitetracycline, minocycline, daunorubicin hydrochloride, doxorubicin, aclarubicin, kanamycin sulfate, bekanamycin, tobramycin, gentamycin sulfate, dibekacin, amikacin, micronomicin, ribostamycin, neomycin sulfate, paromomycin sulfate, streptomycin sulfate, dihydrostreptomycin, destomycin A, hygromycin B, apramycin, sisomicin, netilmicin sulfate, spectinomycin hydrochloride, astromicin sulfate, validamycin, kasugamycin, polyoxin, blasticidin S, erythromycin, erythromycin estolate, oleandomycin phosphate, tracetyloleandomycin, kitasamycin, josamycin, spiramycin, tylosin, ivermectin, midecamycin, bleomycin sulfate, peplomycin sulfate, gramicidin S, polymyxin B, bacitracin, colistin sulfate, colistinmethanesulfonate sodium, enramycin, mikamycin, virginiamycin, capreomycin sulfate, viomycin, enviomycin, vancomycin, actinomycin D, neocarzinostatin, bestatin, pepstatin, monensin, lasalocid, salinomycin, amphotericin B, nystatin, natamycin, trichomycin, mithramycin, lincomycin, clindamycin, clindamycin palmitate hydrochloride, flavophospholipol, cycloserine, pecilocin, griseofulvin, chloramphenicol, chloramphenicol palmitate, mitomycin C, pyrrolnitrin, fosfomycin, fusidic acid, bicozamycin, tiamulin, siccanin.

Other Mycobacterial agents which may be combined with the compounds of formula (Ia) or (Ib) are for example rifampicin (=rifampin); isoniazid; pyrazinamide; amikacin; ethionamide; ethambutol; streptomycin; para-aminosalicylic acid; cycloserine; capreomycin; kanamycin; thioacetazone; PA-824; quinolones/fluoroquinolones such as for example moxifloxacin, gatifloxacin, ofloxacin, ciprofloxacin, sparfloxacin; macrolides such as for example clarithromycin, clofazimine, amoxycillin with clavulanic acid; rifamycins; rifabutin; rifapentine; the compounds disclosed in WO2004/011436.

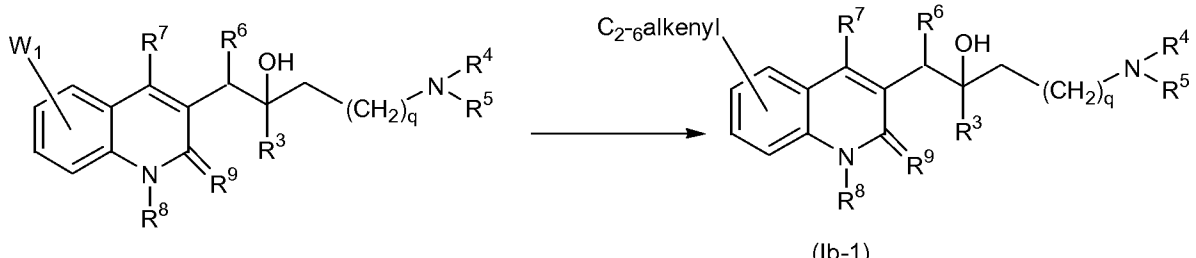
GENERAL PREPARATION

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

Compounds of formula (Ia) or (Ib) wherein R^1 represents C_{2-6}alkenyl, said compounds being represented by formula (Ia-1) or (Ib-1), can be prepared by reacting an intermediate of formula (II-a) or (II-b) wherein W_1 represents a suitable leaving group, such as for example halo, e.g. bromo and the like, with tributyl(C_{2-6}alkenyl)tin, such as for example tributyl(vinyl)tin, in the presence of a suitable catalyst, such as for example $Pd(PPh_3)_4$, in the presence of a suitable solvent, such as for example *N*,*N*-dimethylformamide. This reaction is preferably performed at elevated temperature.



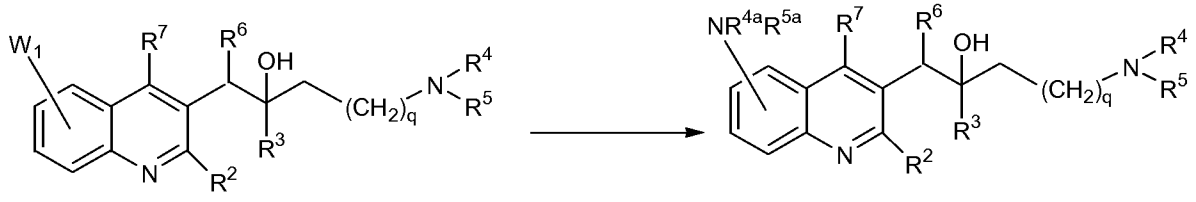
(II-a) (Ia-1)



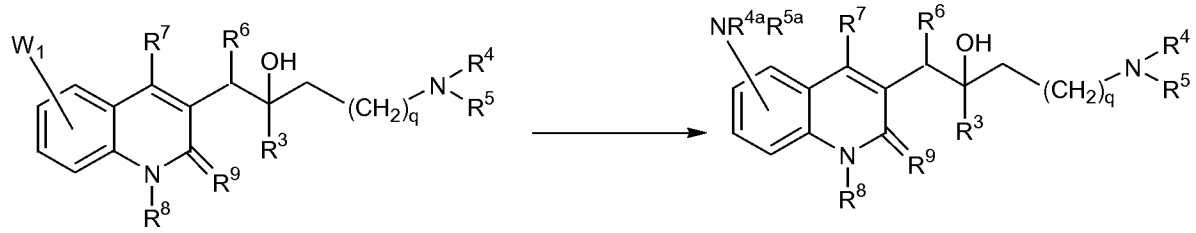
(II-b) (Ib-1)

Compounds of formula (Ia) or (Ib) wherein R^1 represents $R^{5a}R^{4a}N$-, said compounds being represented by formula (Ia-2) or (Ib-2), can be prepared from an intermediate of

formula (II-a) or (II-b) by reaction with $R^{5a}R^{4a}NH$ in the presence of a suitable catalyst, such as for example tris(dibenzylideneacetone)palladium, a suitable ligand, such as for example 2-(di-*t*-butylphosphino)biphenyl, a suitable base, such as for example sodium *t*-butoxide, and a suitable solvent, such as for example toluene.

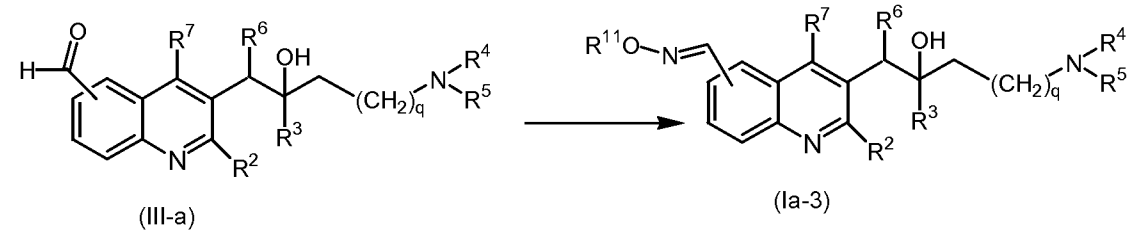


(II-a) (Ia-2)

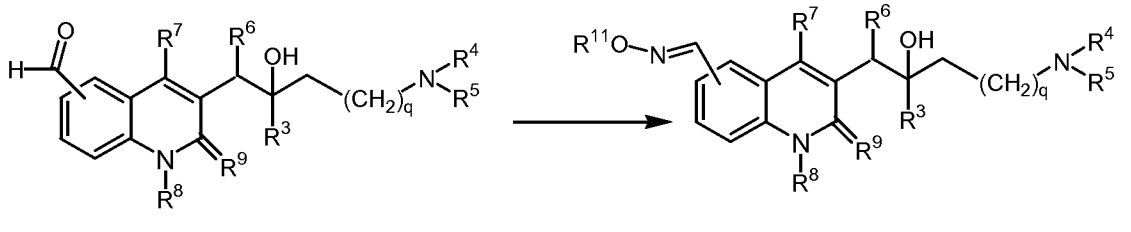


(II-b) (Ib-2)

Compounds of formula (Ia) or (Ib) wherein R^1 represents -C=N-OR^{11}, said compounds being represented by formula (Ia-3) or (Ib-3), can be prepared from an intermediate of formula (III-a) or (III-b) by reaction with hydroxylamine hydrochloride or C_{1-6}alkoxylamine hydrochloride in the presence of a suitable solvent, such as for example pyridine.



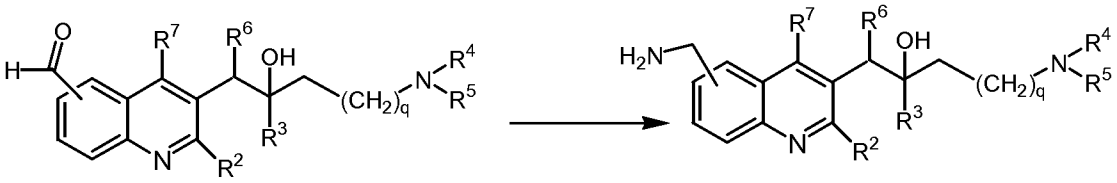
(III-a) (Ia-3)



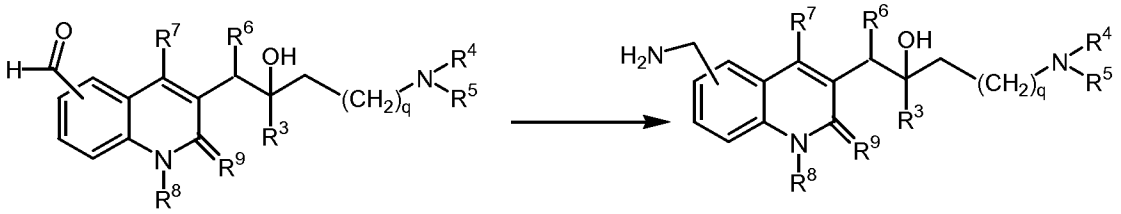
(III-b) (Ib-3)

Compounds of formula (Ia) or (Ib) wherein R^1 represents $-CH_2$-NH_2, said compounds being represented by formula (Ia-4) or (Ib-4), can be prepared from an intermediate of formula (III-a) or (III-b) by reduction in the presence of H_2, a suitable catalyst, such as

for example palladium on charcoal, and a suitable solvent, such as for example NH_3/alcohol, e.g. NH_3/methanol.

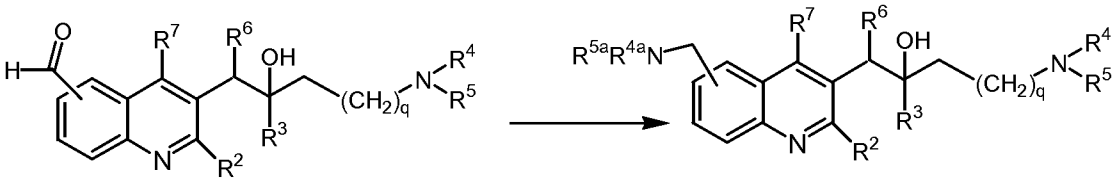


(III-a) (Ia-4)

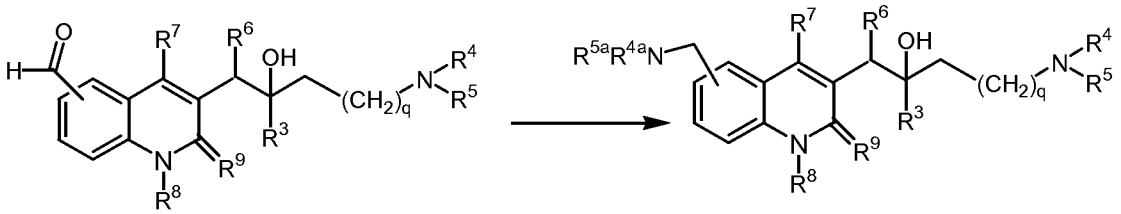


(III-b) (Ib-4)

Compounds of formula (Ia) or (Ib) wherein R^1 represents $R^{5a}R^{4a}N\text{-}CH_2\text{-}$, said compounds being represented by formula (Ia-5) or (Ib-5), can be prepared by reacting an intermediate of formula (III-a) or (III-b) with a suitable reagent of formula $R^{5a}R^{4a}N\text{-}H$ in the presence of a suitable reducing agent, such as for example BH_3CN, a suitable solvent, such as for example acetonitrile and tetrahydrofuran, and a suitable acid, such as for example acetic acid.



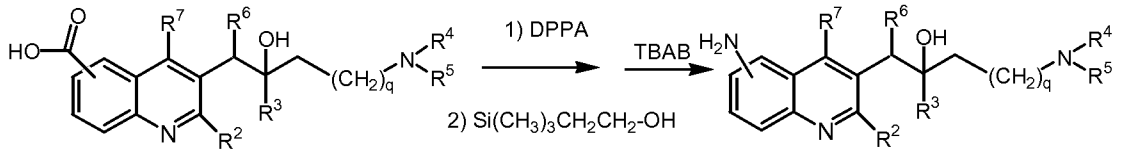
(III-a) (Ia-5)



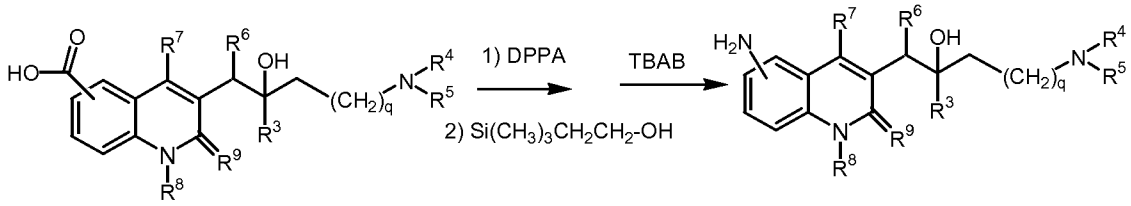
(III-b) (Ib-5)

Compounds of formula (Ia) or (Ib) wherein R^1 represents amino, said compounds being represented by formula (Ia-6) or (Ib-6), can be prepared by reacting an intermediate of formula (IV-a) or (IV-b) with a suitable azide, such as for example diphenylphosphorylazide (DPPA), and a suitable base, such as for example triethylamine, in a suitable solvent, such as for example toluene. The obtained product undergoes a modified Curtius reaction, and by adding trimethylsilylethanol a carbamate

intermediate is formed. In a next step, this intermediate is reacted with tetrabutylammonium bromide (TBAB) in a suitable solvent, such as for example tetrahydrofuran to obtain the amino derivative.

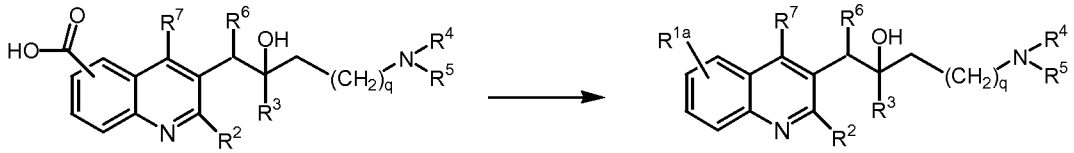


(IV-a) (Ia-6)

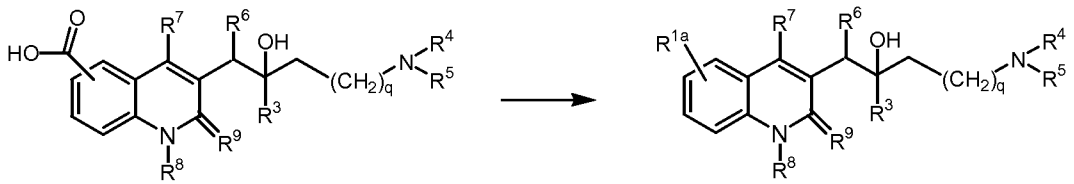


(IV-b) (Ib-6)

Compounds of formula (Ia) or (Ib) wherein R^1 represents aminocarbonyl, mono or di(alkyl)aminocarbonyl or $R^{5a}R^{4a}N$-C(=O)-, said R^1 being represented by R^{1a} and said compounds being represented by formula (Ia-7) or (Ib-7), can be prepared by reacting an intermediate of formula (IV-a) or (IV-b) with a suitable amine, a suitable coupling reagent, such as for example hydroxybenzotriazole, a suitable activating reagent such as a suitable carbodiimide, such as for example 1,1'-carbonyldiimidazole or *N,N'*-dicyclohexylcarbodiimide or 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide, a suitable base, such as for example triethylamine, and a suitable solvent, such as for example tetrahydrofuran and methylenechloride.



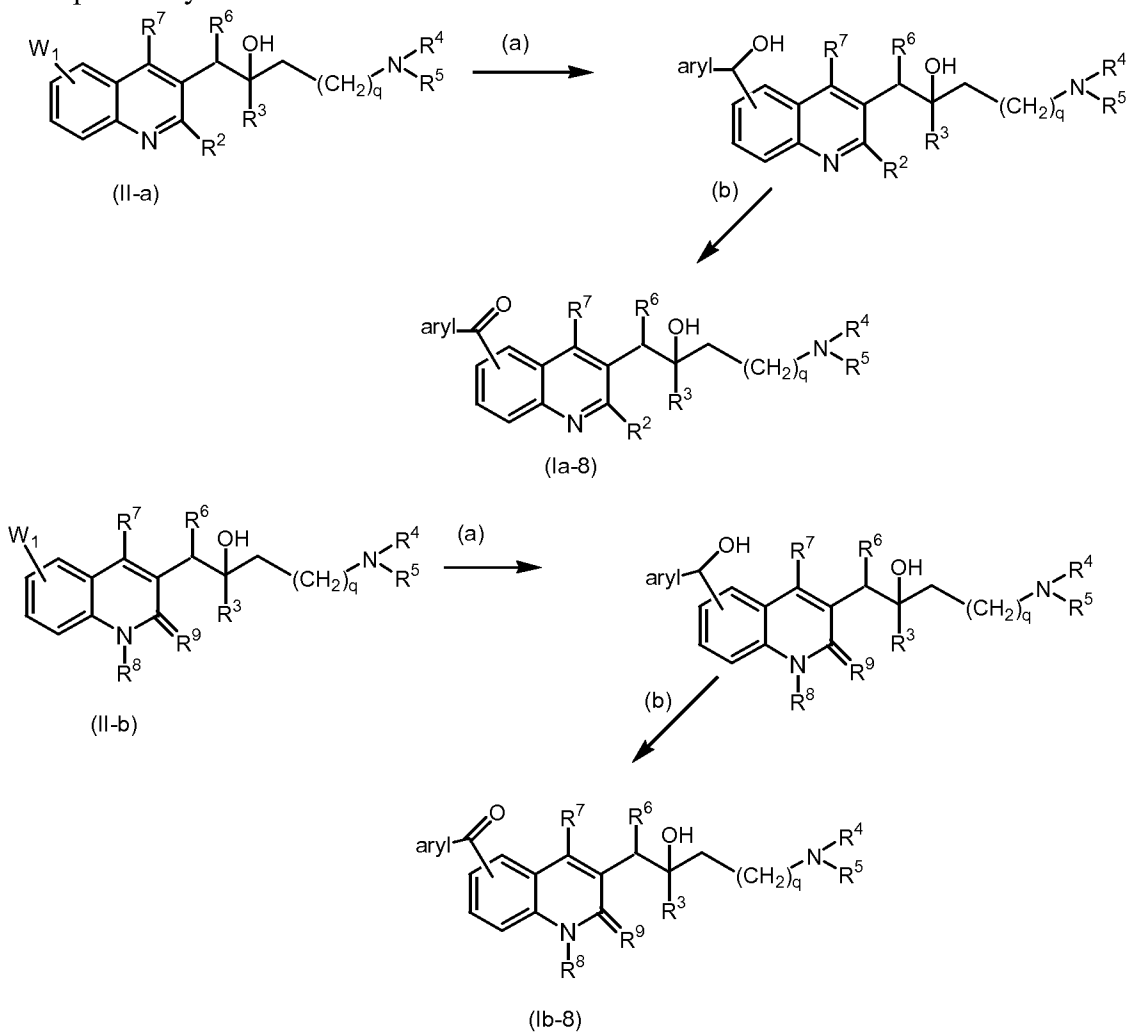
(IV-a) (Ia-7)



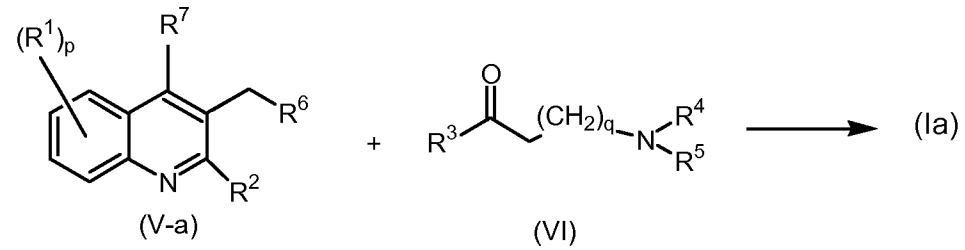
(IV-b) (Ib-7)

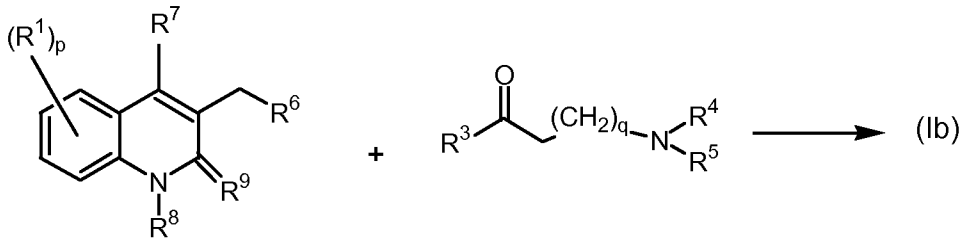
Compounds of formula (Ia) or (Ib) wherein R^1 represents arylcarbonyl, said compounds being represented by formula (Ia-8) or (Ib-8), can be prepared by reacting in a first step (a) an intermediate of formula (II-a) or (II-b) with a suitable arylaldehyde in the presence of *n*BuLi and a suitable solvent, such as for example tetrahydrofuran. This reaction is preferably performed at low temperature such as for example –70°C. In a

next step (b), the product obtained in step (a) is oxidized with a suitable oxidans, such as for example manganese oxide, in the presence of a suitable solvent, such as for example methylene chloride.



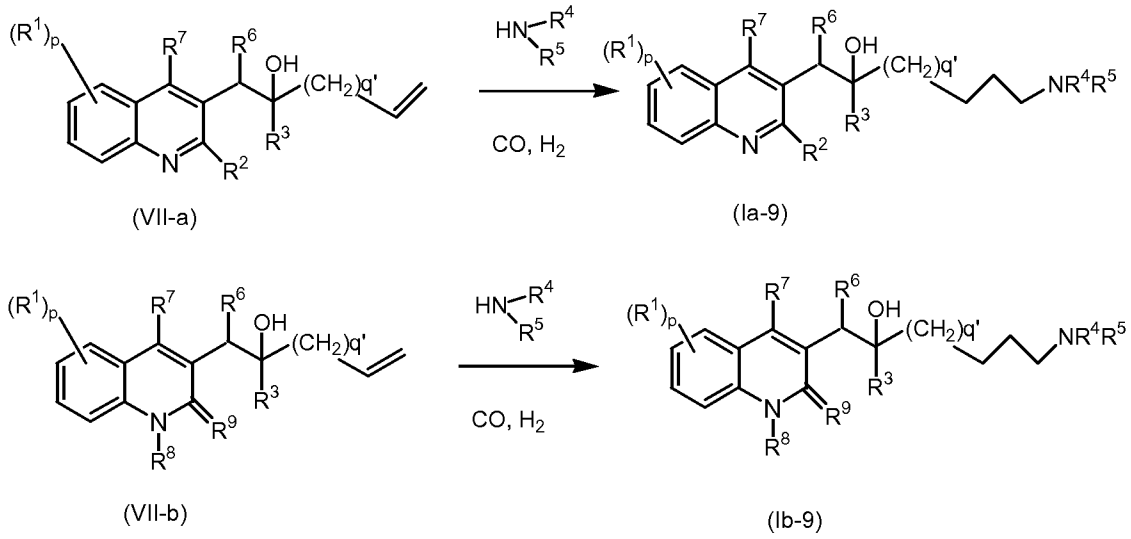
Compounds of formula (I-a) or (Ib) can also be prepared by reacting an intermediate of formula (V-a) or (V-b) with an intermediate of formula (VI) according to the following reaction scheme :





using *n*BuLi in a mixture of a suitable base, such as for example diisopropyl amine, and a suitable solvent, such as for example tetrahydrofuran, wherein all variables are defined as in formula (Ia) or (Ib). Stirring may enhance the rate of the reaction. The reaction may conveniently be carried out at a temperature ranging between –20 and –70 °C.

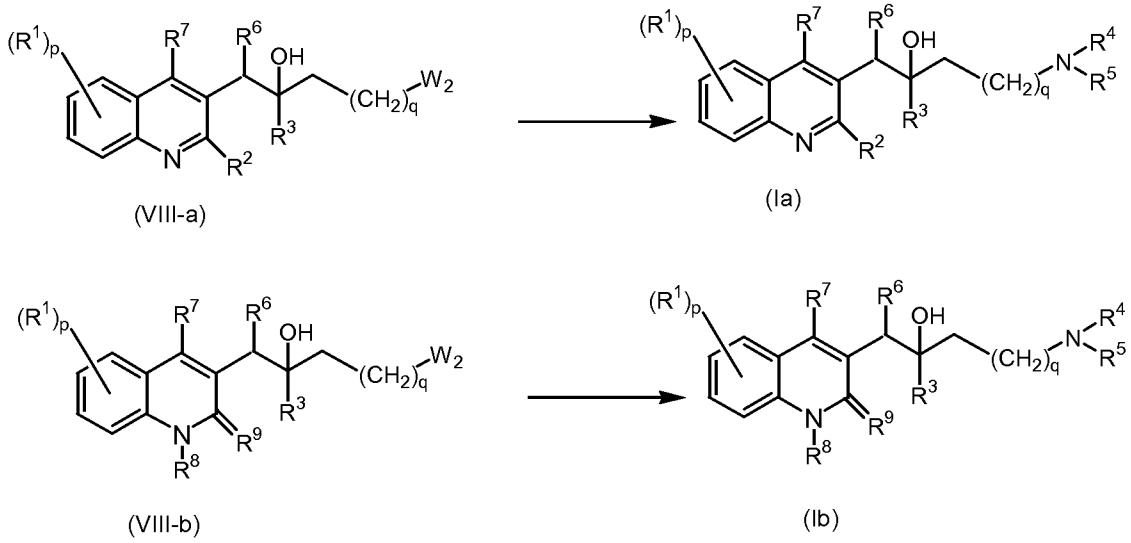
Compounds of formula (Ia) or (Ib) wherein q is equal to 2, 3 or 4, said compounds being represented by formula (Ia-9) or (Ib-9), can also be prepared by reacting an intermediate of formula (VII-a) or (VII-b) wherein q' is 0, 1 or 2, with a primary or secondary amine HNR^4R^5 in the presence of a suitable catalyst, such as for example $Rh(cod)_2BF_4$, optionally in the presence of a second catalyst (for the reduction), such as for example $Ir(cod)_2BF_4$, in the presence of a suitable ligand, such as for example Xantphos, in a suitable solvent, such as for example tetrahydrofuran and an alcohol, e.g. methanol, in the presence of CO and H_2 (under pressure) at elevated temperature. This reaction is preferably done for intermediates of formula (VII) wherein q' is 1.



(VII-a) (Ia-9)

(VII-b) (Ib-9)

Compounds of formula (Ia) or (Ib) can also be prepared by reacting an intermediate of formula (VIII-a) or (VIII-b) wherein W_2 represents a suitable leaving group, such as for example halo, e.g. chloro or bromo, with a suitable primary or secondary amine HNR^4R^5 optionally in the presence of a suitable solvent, such as for example acetonitrile.



(VIII-a) (Ia)

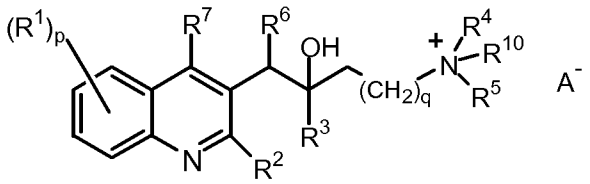
(VIII-b) (Ib)

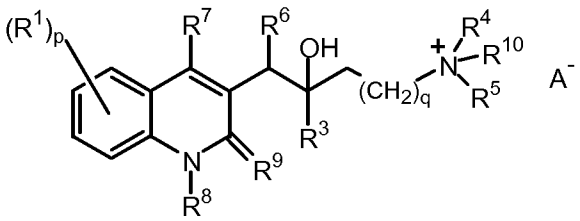
It is considered within the knowledge of the skilled man to explore the appropriate temperatures, dilutions, and reaction times in order to optimize the above reactions in order to obtain a desired compound.

The compounds of formula (Ia) or (Ib) may further be prepared by converting compounds of formula (Ia) or (Ib) into each other according to art-known group transformation reactions.

The compounds of formula (Ia) or (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) or (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. tert.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.

Compounds of formula (Ia) or (Ib) can also be converted into a quaternary amine by reaction with a suitable quaternizing agent, such as, for example, an optionally substituted C_{1-6}alkylhalide, arylC_{1-6}alkylhalide, C_{1-6}alkylcarbonylhalide, arylcarbonylhalide, Het^1C_{1-6}alkylhalide or Het^{1}carbonylhalide, e.g. methyliodide or benzyliodide, in the presence of a suitable solvent, such as for example acetone wherein Het^1 represents furanyl or thienyl; or a bicyclic heterocycle selected from benzofuranyl or benzothienyl; each monocyclic and bicyclic heterocycle may optionally be substituted with 1, 2 or 3 substituents, each substituent independently selected from the group of halo, C_{1-6}alkyl and aryl. Said quaternary amines are represented by the below formula wherein R^{10} represents C_{1-6}alkyl, C_{1-6}alkylcarbonyl, arylC_{1-6}alkyl, arylcarbonyl, Het^1C_{1-6}alkyl or Het^{1}carbonyl and wherein A^- represents a pharmaceutically acceptable counterion, such as for example iodide.





Compounds of formula (Ia) or (Ib) wherein R^6 represents phenyl substituted with halo, can be converted into a compound of formula (Ia) or (Ib) wherein R^6 represents phenyl substituted with Het, by reaction with Het-$B(OH)_2$ in the presence of a suitable catalyst, such as for example $Pd(PPh_3)_4$, in the presence of a suitable base, such as for example Na_2CO_3, and a suitable solvent, such as for example toluene or 1,2-dimethoxyethane (DME) and an alcohol, for example methanol.

Compounds of formula (Ia-4) or (Ib-4) can be converted into a compound of formula (Ia) or (Ib) wherein R^1 represents alkylcarbonylamino-CH_2-, by reaction with a suitable alkylcarbonyl chloride, in the presence of a suitable base, such as for example *N*,*N*-diethylethanamine, and a suitable solvent, such as for example methylene chloride.

Compounds of formula (Ia-4) or (Ib-4) can be converted into a compound of formula (Ia) or (Ib) wherein R^1 represents $-CH_2-N(C_{1-6}alkyl)_2$, by reaction with a suitable aldehyde or ketone reagent, such as for example paraformaldehyde or formaldehyde, in the presence of sodium cyanoborohydride, acetic acid and a suitable solvent, such as for example acetonitrile.

A compound of formula (Ia) wherein R^2 represents methoxy, can be converted into the corresponding compound of fomula (Ib) wherein R^8 is hydrogen and R^9 is oxo, by hydrolysis in the presence of a suitable acid, such as for example hydrochloric acid, and a suitable solvent, such as for example dioxane.

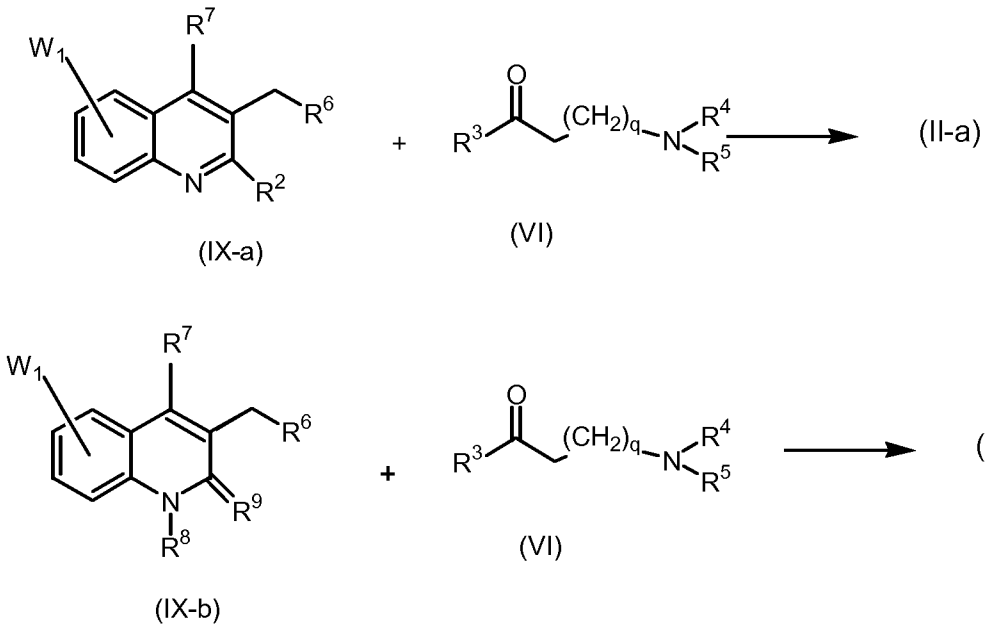
It is evident that in the foregoing and in the following reactions, the reaction products may be isolated from the reaction medium and, if necessary, further purified according to methodologies generally known in the art, such as extraction, crystallization and

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, chiral chromatography. Individual diastereoisomers or individual enantiomers can also be obtained by Supercritical Fluid Chromatography (SCF).

The starting materials and the intermediates are compounds that are either commercially available or may be prepared according to conventional reaction procedures generally known in the art. For example, the intermediates of formula (IIa) to (IId) can be prepared according to the methods described in WO2004/011436, WO2005/070924, WO2005/070430 or WO2005/075428, the contents of which are incorporated herein by reference.

In particular, intermediates of formula (II-a) or (II-b) can be prepared from an intermediate of formula (IX-a) or (IX-b) and an intermediate of formula (VI) according to the following reaction scheme (1) :

Scheme 1



using *n*BuLi in a mixture of a suitable base, such as for example diisopropyl amine, and a suitable solvent, such as for example tetrahydrofuran, wherein all variables are defined as in formula (Ia) or (Ib). Stirring may enhance the rate of the reaction. The reaction may conveniently be carried out at a temperature ranging between –20 and –70 °C.

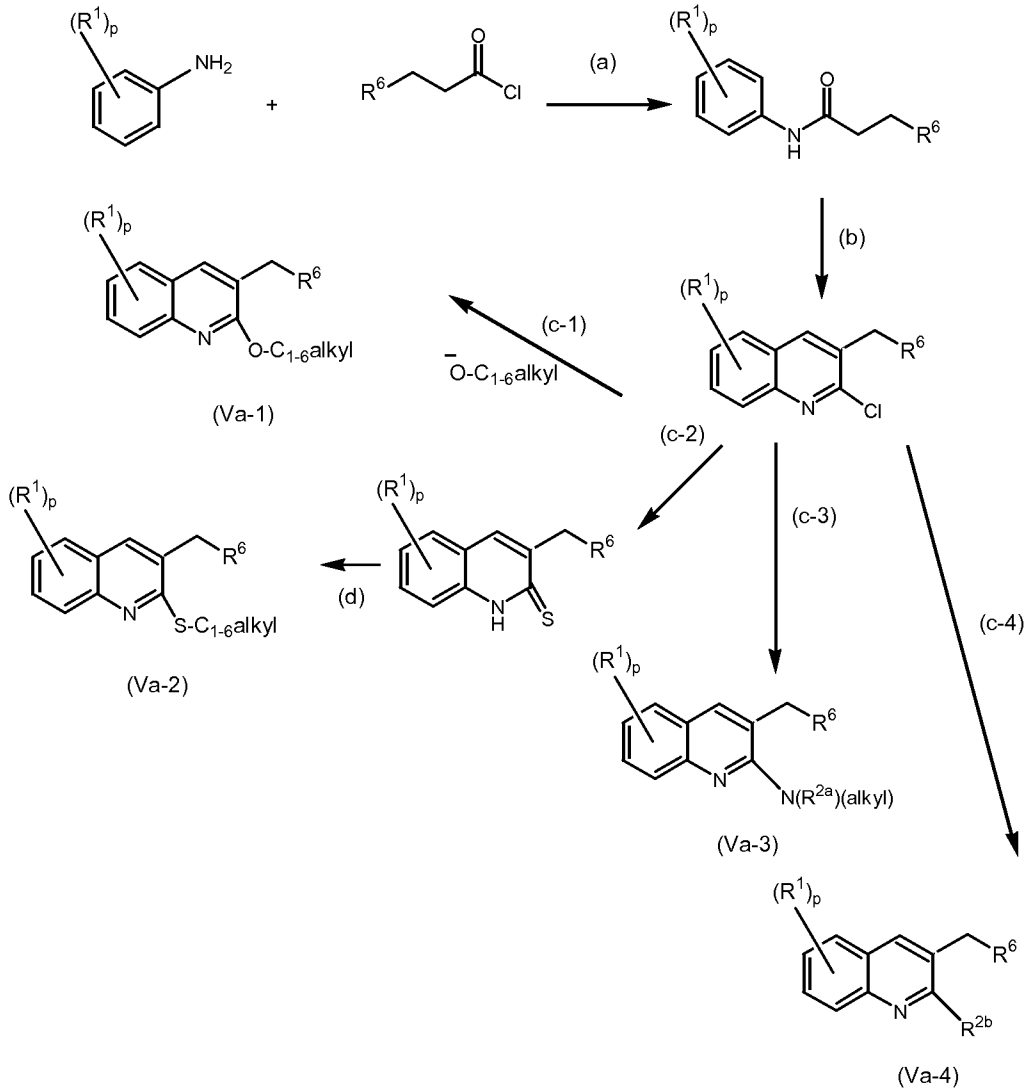
Intermediates of formula (III-a) or (III-b) can be prepared from an intermediate of

formula (II-a) or (II-b) by reaction with *N*,*N*-dimethylformamide in the presence of a suitable solvent, such as for example tetrahydrofuran. The reaction is preferably performed at low temperature, e.g. –70°C.

Intermediates of formula (IV-a) or (IV-b) can be prepared from an intermediate of formula (II-a) or (II-b) by reaction with CO_2 in the presence of *n*BuLi and a suitable solvent, such as for example tetrahydrofuran. The reaction is preferably performed at low temperature, e.g. –70°C.

Intermediates of formula (V-a) may be prepared according to the following reaction scheme (2):

Scheme 2

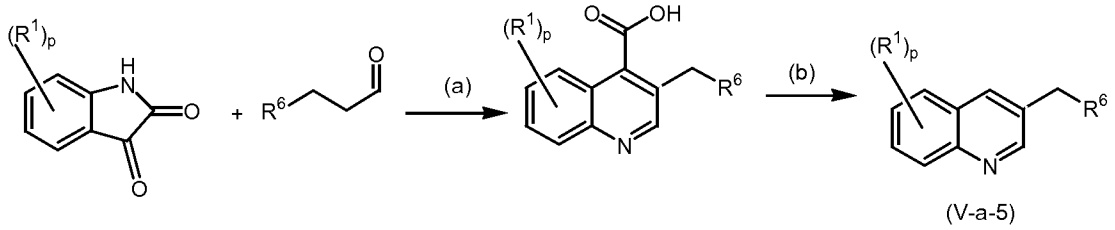


wherein all variables are defined as in formula (Ia). Reaction scheme (2) comprises

step (a) in which an appropriately substituted aniline is reacted with an appropriate acylchloride such as for example 3-phenylpropionyl chloride, 3-fluorobenzenepropionyl chloride or *p*-chlorobenzenepropionyl chloride, in the presence of a suitable base, such as triethylamine, and a suitable reaction-inert solvent, such as methylene chloride or ethylene dichloride. The reaction may conveniently be carried out at a temperature ranging between room temperature and reflux temperature. In a next step (b) the adduct obtained in step (a) is reacted with phosphoryl chloride ($POCl_3$) 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-1), a specific R^2-group, wherein R^2 is for example a C_{1-6}alkyloxy radical is introduced by reacting the intermediate compound obtained in step (b) with ^-O-C_{1-6}alkyl in the presence of a suitable solvent, such as for example HO-C_{1-6}alkyl. The intermediate obtained in step (b) can also be converted into an intermediate wherein R^2 is for example a C_{1-6}alkylthio radical by reaction with $S=C(NH_2)_2$ in the presence of a suitable solvent, such as for example an alcohol, e.g. ethanol, or an alcohol/water mixture, optionally in the presence of a suitable base, such as for example KOH, (see step (c-2)) followed by reaction with C_{1-6}alkyl-I in the presence of a suitable base, such as for example K_2CO_3 and a suitable solvent, such as for example 2-propanone (see step (d)). The intermediate obtained in step (b) can also be converted into an intermediate wherein R^2 is -N(R^{2a})(alkyl) wherein R^{2a} is hydrogen or alkyl, by reaction with a suitable salt of NH(R^{2a})(alkyl) in the presence of a suitable base, such as for example potassium carbonate, and a suitable solvent, such as for example acetonitrile (step (c-3)). The intermediate obtained in step (b) can also be converted into an intermediate wherein R^2 is C_{1-6}alkyloxyC_{1-6}alkyloxy optionally substituted with C_{1-6}alkyloxy, said R^2 being represented by R^{2b}, by reaction with C_{1-6}alkyloxyC_{1-6}yalkylOH optionally substituted with C_{1-6}alkyloxy, in the presence of NaH and a suitable solvent, such as for example tetrahydrofuran (step (c-4)).

Intermediates of formula (V-a) wherein R^2 and R^7 represent hydrogen , said intermediates being represented by formula (V-a-5), 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 an optionally substituted 3-phenylpropionaldehyde in the presence of a suitable base such as sodium hydroxide (Pfitzinger reaction), after which the 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.

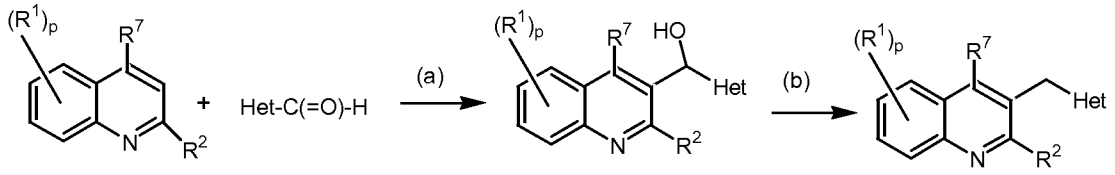
Scheme 3



(V-a-5)

Intermediates of formula (V-a) wherein R^6 represents Het, said intermediates being represented by formula (V-a-6), can be prepared according to the following reaction scheme 3a.

Scheme 3a

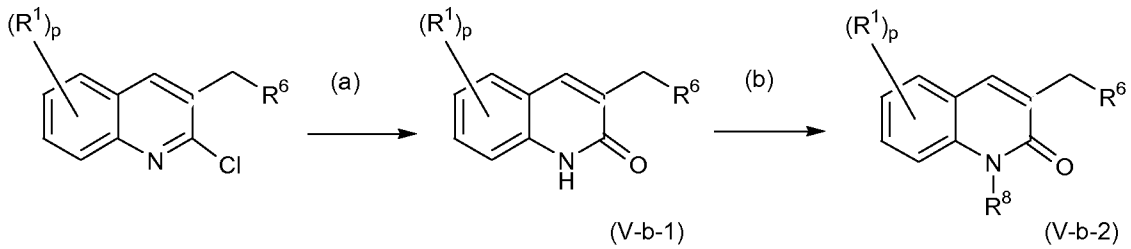


(V-a-6)

Reaction scheme (3a) comprises step (a) in which an appropriate quinoline moiety is reacted with Het-C(=O)-H using *n*BuLi in a mixture of a suitable base, such as for example 2,2,6,6-tetramethylpiperidine, and a suitable solvent, such as for example tetrahydrofuran. Stirring may enhance the rate of the reaction. The reaction may conveniently be carried out at a temperature ranging between –20 and –70 °C. In a next step (b), the product obtained in step (a) is converted in aan intermediate of formula (V-a-6) by reaction with a suitable acid, such as for example trifluoroacetic acid, and triisopropylsilane, in the presence of a suitable solvent, such as for example methylene chloride.

Intermediates of formula (V-b), in particular (V-b-1) or (V-b-2), can be prepared according to the following reaction scheme (4).

Scheme 4

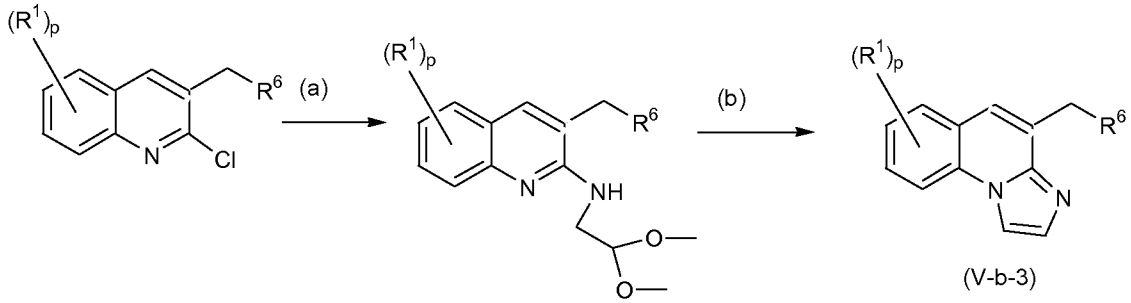


(V-b-1) (V-b-2)

Reaction scheme (4) comprises step (a) in which the quinoline moiety is converted in the quinolinone moiety by reaction with a suitable acid, such as for example hydrochloric acid. In a next step (b), a R^8 substituent is introduced by reacting the intermediate obtained in step (a) with a suitable alkylating agent, such as for example alkyliodide, e.g. methyliodide, in the presence of a suitable base, such as for example NaOH or benzyltriethylammonium chloride, a suitable solvent, such as for example tetrahydrofuran.

Intermediates of formula (V-b) wherein the R^8 and R^9 are taken together to form the radical –CH=CH-N=, said intermediates being represented by formula (V-b-3), can be prepared according to the following reaction scheme (5).

Scheme 5

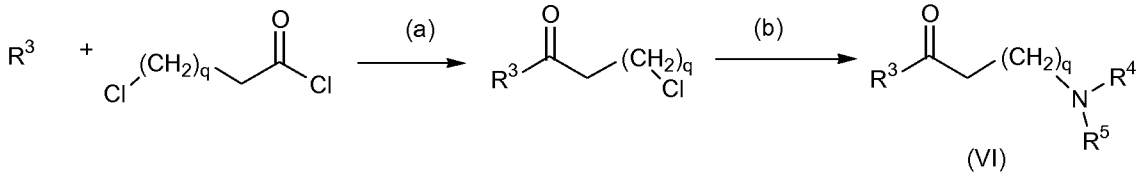


(V-b-3)

Reaction scheme (5) comprises step (a) in which the intermediate is reacted with NH_2-CH_2-$CH(OCH_3)_2$. In a next step (b), the fused imidazolyl moiety is formed by reaction with acetic acid in the presence of a suitable solvent, such as for example xylene.

The intermediates of formula (VI) are compounds that are either commercially available or may be prepared according to conventional reaction procedures generally known in the art. For example, intermediates of formula (VI) may be prepared according to the following reaction scheme (6):

Scheme 6

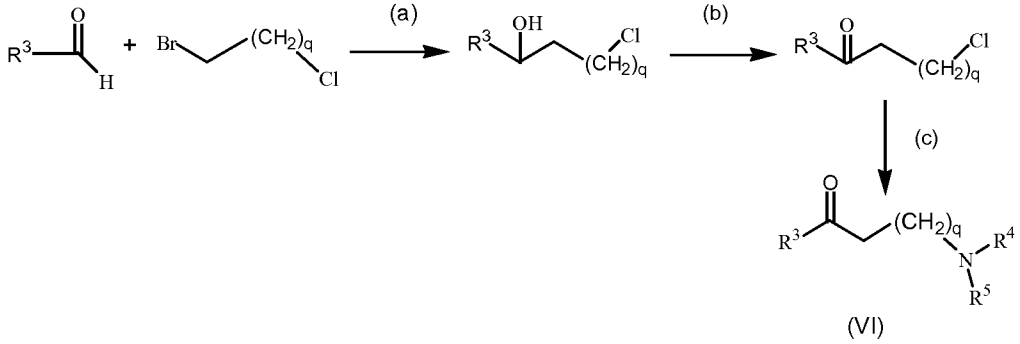


(VI)

Reaction scheme (6) comprises step (a) in which R^3, in particular an appropriately substituted aryl, more 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 obtained in step (a) with a primary or secondary amine (HNR^4R^5).

The intermediates of formula (VI) may also be prepared according to the following reaction Scheme (7) :

Scheme7



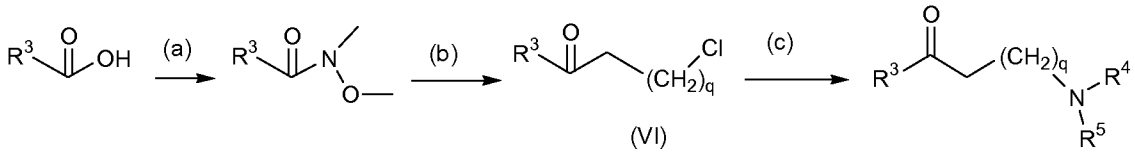
(VI)

Reaction scheme (7) comprises step (a) in which R^3-C(=O)-H, for instance an appropriately substituted arylcarboxaldehyde, more in particular an appropriately substituted phenyl or naphthylcarboxaldehyde, is reacted with an appropriate intermediate compound such as for example 1-bromo-4-chlorobutane, in the presence of Grignard reagent and a suitable solvent, such as for example diethyl ether, tetrahydrofuran. The reaction may conveniently be carried out at a low temperature for instance 5°C. In a next step (b), an oxidation is performed in the presence of Jones'reagent in a suitable solvent, such as for example acetone. In a next step (c), an amino group ($-NR_4R_5$) is introduced by reacting the intermediate compound obtained in step (b) with a primary or secondary amine HNR_4R_5 in the presence of a suitable

solvent, such as for example acetonitrile, and a suitable base, such as for example K_2CO_3.

Alternatively, intermediates of formula (VI) may be prepared according to the following reaction scheme (8):

Scheme 8

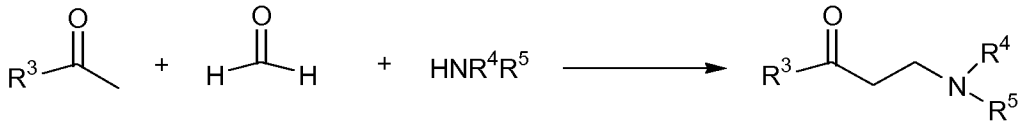


(VI)

Reaction scheme (8) comprises step (a) in which for instance a suitable acid is reacted with $NH(CH_3)(OCH_3)$ in the presence of 1,1'-carbonyldiimidazole and a suitable solvent, such as for example CH_2Cl_2. In a next step (b), the product obtained in step (a) is reacted with a suitable Grignard reagens, e.g. 4-chlorobutyl magnesium bromide, in the presence of a suitable solvent, such as for example tetrahydrofuran. In a next step (c), an amino group ($-NR_4R_5$) is introduced by reacting the intermediate obtained in step (b) with a primary or secondary amine HNR_4R_5 in the presence of a suitable solvent, such as for example acetonitrile, and a suitable base, such as for example K_2CO_3.

Alternatively, intermediates of formula (VI) wherein q is 1, said intermediates being represented by formula (VI-a), may be prepared according to the following reaction scheme (9):

Scheme 9



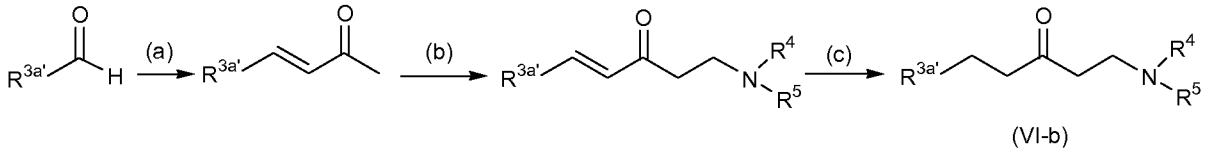
(VI-a)

Reaction scheme (9) comprises the step in which a suitable acetyl derivative of R^3 such as for example acetylcyclohexane, is reacted with paraformaldehyde and a suitable primary or secondary amine HNR^4R^5, preferably in its salt form, in the presence of a suitable acid, such as for example hydrochloric acid and the like, and a suitable solvent, such as for example an alcohol, e.g. ethanol.

Intermediates of formula (VI) wherein R^3 represents $R^{3a'}$-CH_2-CH_2- (which is possible for those intermediates of formula (VI) wherein R^3 represents alkyl, arylalkyl,

aryl-O-alkyl, aryl-alkyl-O-alkyl, Het-alkyl, Het-O-alkyl or Het-alkyl-O-alkyl and $R^{3a'}$ is the same as R^3 but with 2 carbon atoms less in the alkyl chain attached to the remainder of the molecule and wherein q represents 1, said intermediates being represented by formula (VI-b), can be prepared according to the following reaction scheme (10):

Scheme 10

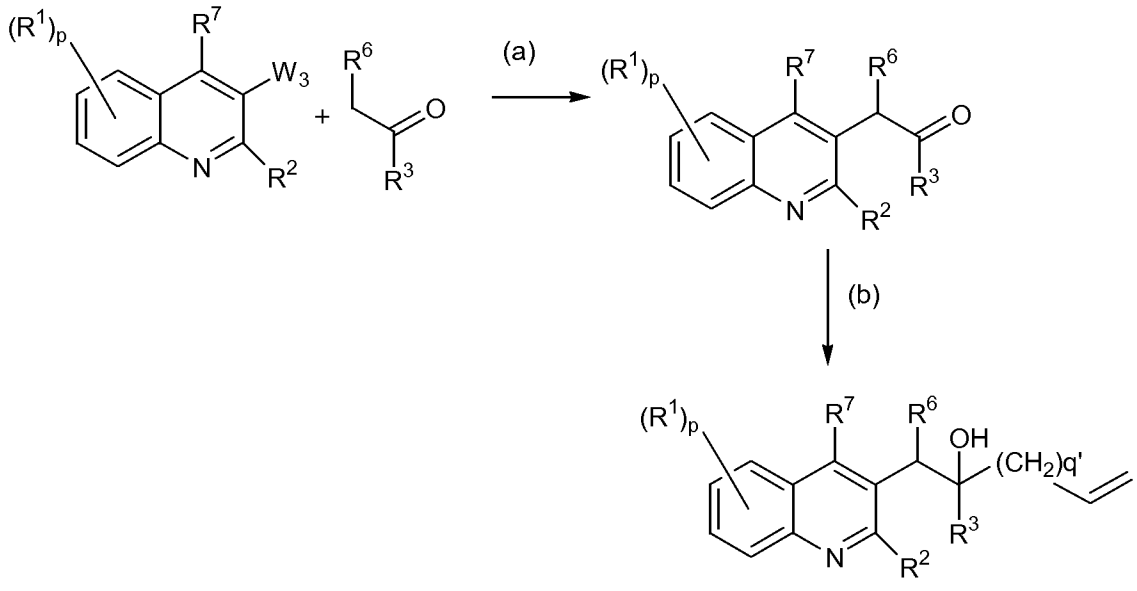


(VI-b)

Reaction scheme (10) comprises step (a) wherein a suitable aldehyde is reacted with acetone in the presence of a suitable base, such as for example sodium hydroxide. In a next step (b), the product obtained in step (a) is reacted with a primary or secondary amine HNR^4R^5 in the presence of $CH_2(=O)$, a suitable acid, such as for example hydrochloric acid and the like, and a suitable solvent, such as for example an alcohol, e.g. ethanol. In a next step (c), the product obtained in step (b) is hydrogenated (H_2) in the presence of a suitable catalyst, such as for example palladium on charcoal, and a suitable solvent, such as for example water and an alcohol, e.g. ethanol.

Intermediates of formula (VII-a) may be prepared according to the following reaction scheme (11):

Scheme 11



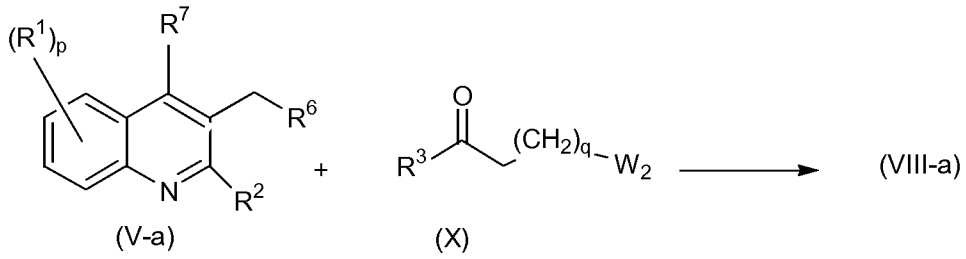
(VII-a)

Reaction scheme (11) comprises the step of reacting an appropriately substituted quinoline wherein W_2 represents a suitable leaving group, such as for example halo, e.g. bromo, with an appropriately substituted deoxybenzoin in the presence of a suitable catalyst, such as for example palladium diacetate, a suitable ligand, such as for example X-PHOS, a suitable base, such as for example cesium carbonate, a suitable solvent, such as for example xylene, under N_2 flow. In a next step (b), the product obtained in step (a) is reacted with a suitable Grignard reagens (e.g. CH_2=CH-$(CH_2)_q$-Mg-Br, such as for example allylmagnesium bromide, in a suitable solvent, such as for example tetrahydrofuran.

Intermediates of formula (VII-b) can be prepared accordingly.

Intermediates of formula (VIII-a) can be prepared according to the following reaction scheme (12):

Scheme 12



In reaction scheme (12), an intermediate of formula (V-a) is reacted with an intermediate of formula (X), for its synthesis reference is made to schemes 6, 7and 8, in the presence of *n*BuLi in a suitable solvent, such as for example tetrahydrofuran, and a suitable base, such as for example diisopropyl amine. Stirring may enhance the rate of the reaction. The reaction may conveniently be carried out at a temperature ranging between –20 and –70°C.

Intermediates of formula (VIII-b) can be prepared accordingly.

Intermediates of formula (IX-a) or (IX-b) can be prepared according to the reaction procedures described above for intermediates (V-a) or (V-b).

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

EXPERIMENTAL PART

Of some compounds or intermediates the absolute stereochemical configuration of the

Of some compounds or intermediates the absolute stereochemical configuration of the

stereogenic carbon atom(s) therein or the configuration at the double bond 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, NMR. It is considered to be within the knowledge of the skilled person to recognize the most appropriate method to determine the actual stereochemical configuration.

In case "A" and "B" are mixtures of stereochemically isomeric forms, in particular mixtures of enantiomers, 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, in particular said "A1", "A2" and "B1", "B2"enantiomeric forms, can be unambiguously characterized by a person skilled in the art, using art-known methods such as, for example, X-ray diffraction.

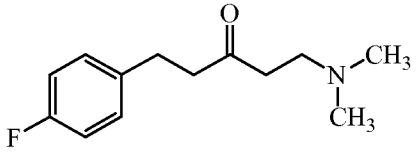
In some cases, when a final compound or an intermediate, indicated as a particular diastereoisomer or enantiomer, is converted into another final compound/intermediate, the latter may inherit the indication for diastereoisomer (A or B) or enantiomer (A1, A2, B1, B2) from the former.

Hereinafter "DMF" means *N*,*N*-dimethylformamide, "*i*PA" means isopropylamine, "THF" means tetrahydrofuran and "DIPE" means diisopropyl ether.

A. Preparation of the intermediate compounds

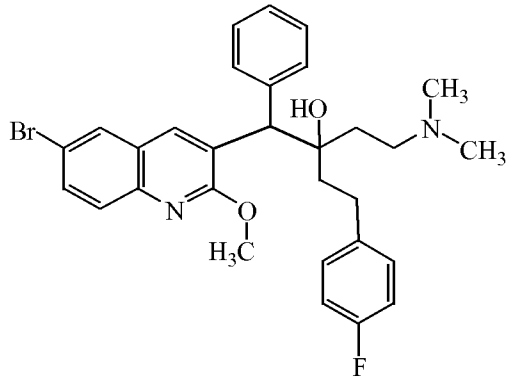
Example A1

a. Preparation of intermediate 18a



A mixture of 4-(4-fluorophenyl)-2-butanone (0.029 mol), formaldehyde (0.116 mol) and *N*-methylmethanamine (0.116 mol) in HCl conc. (1.4 ml) and ethanol (48 ml) was stirred and refluxed for 24 hours, then brought to room temperature. HCl 1N was added. The mixture was washed with diethyl ether, basified with K_2CO_3 2M and extracted with diethyl ether. 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: $CH_2Cl_2/CH_3OH/NH_4OH$ 95/5/0.1; 15-40µm). Two fractions were collected and the solvent was evaporated. Yield: 1.6 g of intermediate 18a (49 %).

b. Preparation of intermediate 1

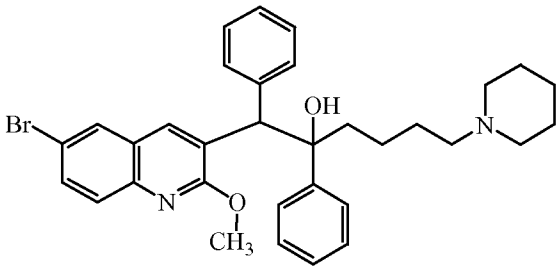


Intermediate 1 (dia A)
Intermediate 2 (dia B)

*n*BuLi 1.6M in hexane (0.0056 mol) was added dropwise at –20°C to a solution of *N*-(1-methylethyl)-2-propanamine (0.0564 mol) in THF (10 ml) under N_2 flow. The mixture was stirred at –20°C for 20 minutes, then cooled to –70°C. A solution of 6-bromo-2-methoxy-3-(phenylmethyl)-quinoline [654655-69-3] (intermediate compound 3 of WO 2004/011436) (0.0051 mol) in THF (20 ml) was added. The mixture was stirred at –70°C for 90 minutes. A solution of **intermediate 18a** (prepared according to A1.a) (0.0072 mol) in THF (18 ml) was added. The mixture was stirred at –70°C for 3 hours. H_2O was added at –30°C. The mixture was extracted with EtOAc. 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: $CH_2Cl_2/CH_3OH/NH_4OH$ 98.5/1.5/0.1; 15-40µm), then over kromasil (eluent: $CH_2Cl_2/CH_3OH/NH_4OH$ 99/1/0.1; 10µm). Two fractions were collected and the solvent was evaporated. Yield: 0.2 g of fraction 1 and 0.13 g of fraction 2. Both fractions were crystallized from DIPE. The precipitate was filtered off and dried.

Yield: 0.146 g of **intermediate 1** (5 %) (m.p. 148°C) and 0.076 g of **intermediate 2** (3 %) (m.p. 157°C).

c. Preparation of intermediate 14 and 15

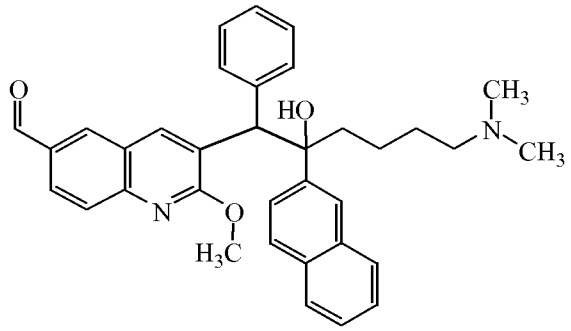


Intermediate 14 (dia A)
Intermediate 15 (dia B)

*n*BuLi 1.6M in hexane (0.0018 mol) was added dropwise at –20°C to a solution of diisopropylamine (0.0018 mol) in THF (4 ml) under N2 flow. The mixture was stirred at –20°C for 20 minutes, then cooled to –70°C. A solution of 6-bromo-2-methoxy-3-(phenylmethyl)-quinoline [654655-69-3], described in WO2004/011436 as intermediate 3 (of which the content is incorporated herein by reference) (0.0015 mol) in THF (5 ml) was added. The mixture was stirred at –70°C for 90 minutes. A solution of 1-phenyl-5-(1-piperidinyl)-1-pentanone (0.0018 mol) in THF (5 ml) was added. The mixture was stirred at –70°C for 90 minutes. H_2O was added. The mixture was extracted with EtOAc. The organic layer was washed with saturated aqueous NaCl, dried ($MgSO_4$), filtered and the solvent was evaporated. The residue (0.9 g) was purified by column chromatography over kromasil (eluent: $CH_2Cl_2/CH_3OH/NH_4OH$ 97/3/0.1; 10µm). Two fractions were collected and the solvent was evaporated. Yield: 0.085 g of **intermediate 14** (10 %; m.p. 129°C) and 0.133 g of a second fraction (15 %). This fraction was crystallized from DIPE. The precipitate was filtered off and dried at 60°C under vacuo. Yield: 0.05 g of **intermediate 15** (6 %; m.p. 166°C).

Example A2

a-1. Preparation of intermediate 4

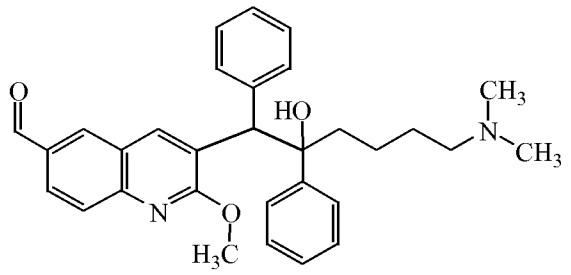


Intermediate 4 (dia A)
Intermediate 5 (dia B)

*n*BuLi 1.6 M in hexane (0.0071 mol) was added dropwise at –70°C to a solution of 25903852 compound 190 of WO2004/011436 (0.0028 mol) in THF (17 ml) under N_2 flow. The mixture was stirred at –70°C for 1 hours. A solution of *N,N*-dimethylformamide (0.014 mol) in THF (11 ml) was added at –70°C. The mixture was stirred at –70°C for 2 hours. H_2O was added. The mixture was extracted with EtOAc. The organic layer was washed with saturated aqueous NaCl, dried ($MgSO_4$), filtered and the solvent was evaporated. Yield: 1.45 g of **intermediate 4** (dia A). .

Intermediate 5 was prepared according to the same procedure as **intermediate 4,** but starting from compound 191of WO2004/011436. Yield: 0.92 g of **intermediate 5** (dia B).

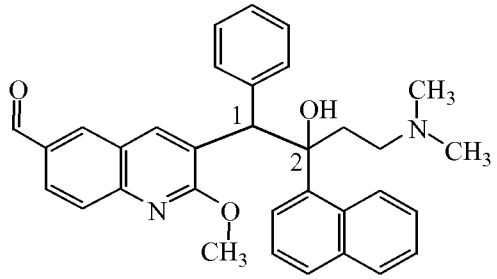
a-2. Preparation of intermediate 3



Intermediate 3 (dia B)

Intermediate 3 was prepared to the same procedure as **intermediate 4,** but starting from compound 66 of WO 2004/011436. The residue was crystallized from DIPE. Yield: 0.60 g of **intermediate 3** (69 %; dia B).

a-3. Preparation of intermediate 10, 11, 12 and 13



Intermediate 10 (dia A)
Intermediate 11 (dia B)
Intermediate 12 (A1)
Intermediate 13 (A2)

*n*BuLi (1.6M in hexanes, 14.1 ml, 0.0225 mol) was added dropwise at –70°C under nitrogen flow to a solution of compound 14 of WO2004/011436 (5.0g, 9.0 mmol) in THF (50 ml). The mixture was stirred for 90 minutes at –70°C then *N,N*-dimethylformamide (5.5 ml, 0.072 mol) was added. The resulting mixture was stirred for 2 hours at –70°C then water was added. The mixture was extracted with EtOAc. The organic layer was washed with water then brine, dried over $MgSO_4$, filtered and evaporated till dryness. The residue was crystallised from diisopropylether and methanol. Yield: 1.7 g of **intermediate 10** (38 %).

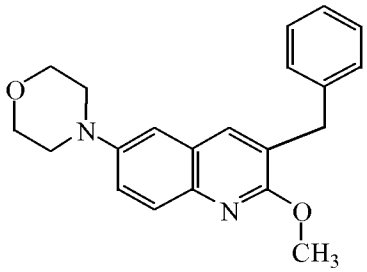
Intermediate 11 (dia B) was prepared according to **intermediate 10** but starting from compound 15 (B) of WO2004/011436). Yield: 1.0 g of **intermediate 11** (22%).

Intermediate 12 (A1; 1R,2S) was prepared according to **intermediate 10** but starting from compound 12 (A1; 1R,2S) of WO2004/011436). Yield: 3.8 g of **intermediate 12**.

Intermediate 13 (A2; 1S,2R) was prepared according to **intermediate 10** but starting from compound 13 (A2; 1S,2R) of WO2004/011436). Yield: 2 g of **intermediate 13**.

Example A3

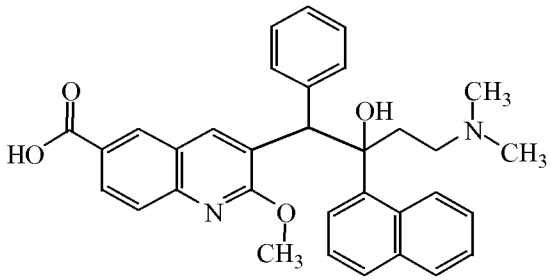
Preparation of intermediate 6



A solution of 6-bromo-2-methoxy-3-(phenylmethyl)-quinoline [654655-69-3], described as intermediate compound 3 in WO2004/011436 (2.0 g, 6.1 mmol), morpholine (0.644 ml, 7.3 mmol), tris(dibenzylideneacetone) palladium (0.28 g, 0.31 mmol), 2-(di-*t*-butylphosphino) biphenyl (0.18 g, 0.61 mmol) and sodium ter-butoxide (0.82 g, 8.54 mmol) in toluene (20 ml) was stirred at 80°C for 24 hours, then cooled down to room temperature and poured out into water. The organic layer was extracted with EtOAc, washed with water and brine, dried ($MgSO_4$), filtered, and the solvent was evaporated. The residue was purified by column chromatography over silica gel (15-40µm, 200g, Cyclohexane/EtOAc 80:20). Fractions were collected and the solvent was evaporated. Yield: 2.4 g of **intermediate 6** (yield: 78 %).

Example A4

a. Preparation of intermediate 7

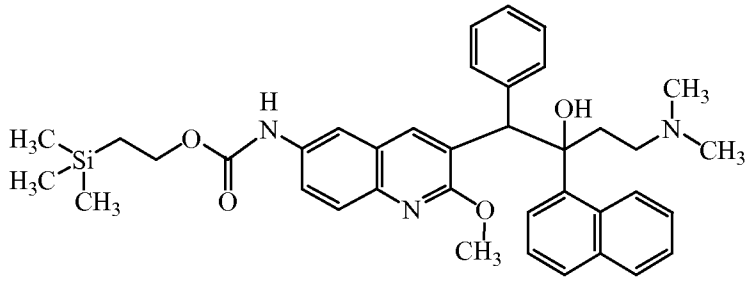


Intermediate 7 (dia A)

*n*BuLi (1.6M in hexanes, 14.1 ml, 0.0225 mol) was added dropwise at –70°C under nitrogen flow to a solution of compound 14 of WO2004/011436 (5.0 g, 9.0 mmol) in THF (5 0 ml). The mixture was stirred for 2 hours at –70°C then dry ice was added. The resulting mixture was stirred 1hour at –70°C then water was added. The precipitate was filtered off, washed with water, CH_3OH then CH_3CH_2OH and dried under vacuum. Yield: 0.8 g of **intermediate 7** (17 %).

A second fraction was obtained from the filtrate. Yield: 1.3 g of **intermediate 7** (28 %).

b. Preparation of intermediates 8 and 9



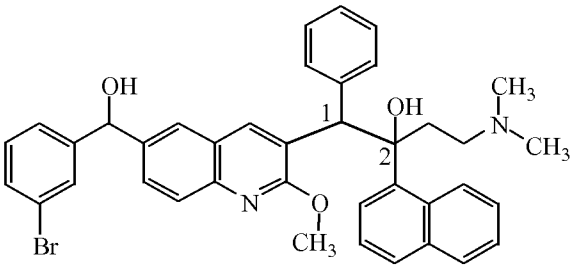
Intermediate 8 (dia A)
Intermediate 9 (dia B)

Diphenylphosphorylazide (DPPA, 0.454 ml, 2.11 mmol) was added to a solution of **intermediate 7** (prepared according to A4.a) (1.1 g, 2.11 mmol) and triethylamine (0.297 ml, 2.11 mmol) in toluene (20 ml) under nitrogen flow. The mixture was stirred at 80°C for 2 hours then 2-(trimethylsilyl)ethanol (0.61 ml, 4.2 mmol) was added. The solution was stirred 5 hours at 80°C then at room temperature overnight. The mixture was poured into water and extracted with EtOAc. The organic layer was washed with water then brine, dried over $MgSO_4$, filtered and evaporated till dryness. The residue (1.3 g) was purified by column chromatography over silica gel (SiO_2 15-40µm, eluent: $CH_2Cl_2/CH_3OH/NH_4OH$: 98/2/0.1). The pure fractions were collected and the solvent was evaporated. Yield: 0.46 g of **intermediate 8** (34 %).

Intermediate 9 (dia B) was prepared according the same procedure as **intermediate 8** (dia A), but starting from compound 15 of WO 2004/011436. Yield: 0.70 g of **intermediate 9** (52 %).

Example A5

a. Preparation of intermediate 16 and 17



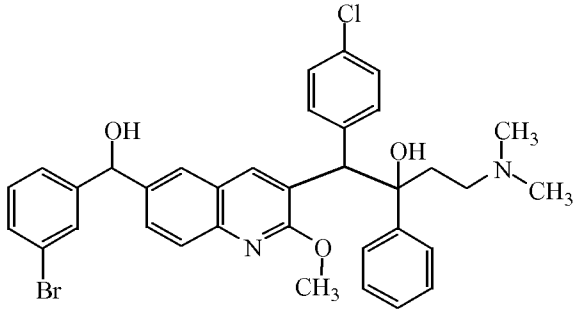
Intermediate 16 (A1)
Intermediate 17 (dia A)

*n*BuLi 1.6 M in hexane (0.563 ml, 0.90 mmol) was added drop wise to a solution of compound 12 of WO2004/011436 (0.25 g, 0.45 mmol) in THF (3 ml) cooled at –70°C

under N_2 atmosphere. The mixture was stirred for 1 hour at –70°C and then a solution of 3-bromobenzaldehyde (0.105 ml, 0.90 mmol) in THF (0.5 ml) was added slowly. The reaction mixture was stirred for 1 hour at –70°C, and then diluted with water at –40°C. The organic layer was extracted with ethyl acetate, and washed with brine. Next, the organic layer was dried ($MgSO_4$), filtered and concentrated. The crude product (0.34 g) was purified by chromatography over silica gel (15-40µm, 30 g, $CH_2Cl_2/CH_3OH/NH_4OH$ 97:3:0.1). Yield: 0.11 g of **intermediate 16** (37%; 1R,2S).

Intermediate 17 (dia A) was prepared according the same procedure as **intermediate 16,** but starting from compound 14 of WO2004/011436) Yield: 0.11 g of **intermediate 17** (34 %).

b. Preparation of intermediate 18



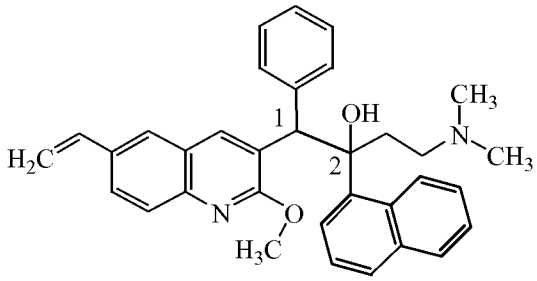
Intermediate 18 (dia B)

Accordingly, **intermediate 18** (dia B) was prepared according to the same procedure as **intermediate 16,** but starting from **compound 36** of WO2004/011436. Yield: 0.13 g of **intermediate 18** (36 %).

B. Preparation of the final compounds

Example B1

a. Preparation of compounds 8, 9 and 10



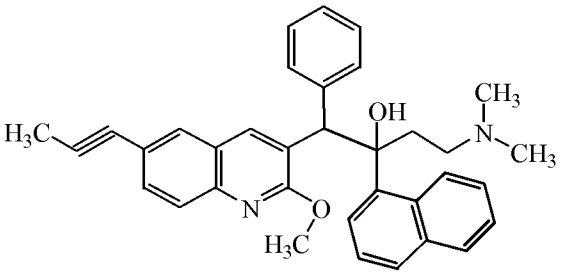
Compound 8 (dia A)
Compound 9 (A1)
Compound 10 (dia B)

A mixture of compound 14 of WO 2004/011436 (dia A, mixture of RS and SR;) (0.1 g, 0.18 mmol), tributylvinyltin (0.114 g, 0.36 mmol) and $PdCl_2(PPh_3)_2$ (0.013 g, 0.018 mmol) in *N,N*-dimethylformamide (3 ml) was heated in the microwave (80 °C, 10 minutes, 100 W). The mixture was cooled down, poured into an aqueous solution of KF (10 % w/w), extracted with EtOAc and filtered over a short pad of Celite. The organic layer was washed with water then brine and was dried over $MgSO_4$, filtered and evaporated till dryness. The residue (0.26 g) was purified by column chromatography over silica gel (eluent: CH_2Cl_2: 100 to $CH_2Cl_2/CH_3OH/NH_4OH$; 98/2/0.2). The pure fractions were collected and the solvent was evaporated. Yield: 0.018 g of **compound 8** (dia A; yield: 45 %, mp: 164 °C).

Compound 9 was prepared according to the same procedure, but starting from compound 12 of WO 2004/011436 (αS,βR; [843663-66-1]). Yield: 0.060 g of **compound 9** (A1; 1R,2S; yield: 45 %).

Compound 10 was prepared according to the same procedure, but starting from compound 15 of WO 2004/011436 (dia B, mixture of RR and SS). Yield: 0.055 g of **compound 10** (dia B; yield: 31 %, mp: 185 °C).

b. Preparation of compounds 13 and 14

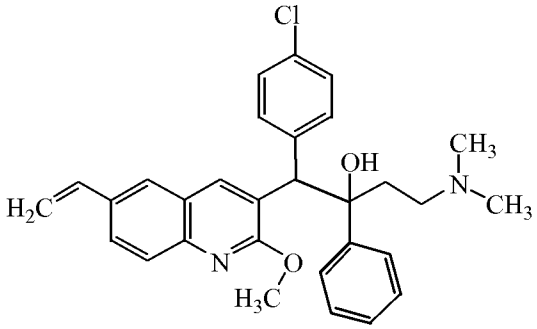


Compound 13 (dia A)
Compound 14 (dia B)

Compound 13 was prepared according to the procedure for compound 8, but using the appropriate alkyn reagens. Yield: 45 % (dia A; mp: 100 °C)

Compound 14 was prepared according to the procedure for compound 10, but using the appropriate alkyn reagens. Yield: 51 % (dia B; mp: 202 °C).

c. Preparation of compounds 1 and 2

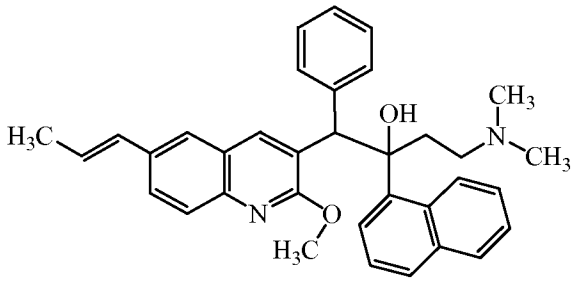


Compound 1 (dia A)
Compound 2 (dia B)

Compound 1 was prepared according to the procedure for compound 8, but starting from compound 37 of WO 2004/011436 (dia A). Yield: 25 % (dia A; m.p.: 184 °C).

Compound 2 was prepared according to the procedure for compound 10, but starting from compound 36 of WO 2004/011436 (dia B). Yield: 23 % (dia B; m.p.: 187 °C).

d. Preparation of compounds 11 and 12

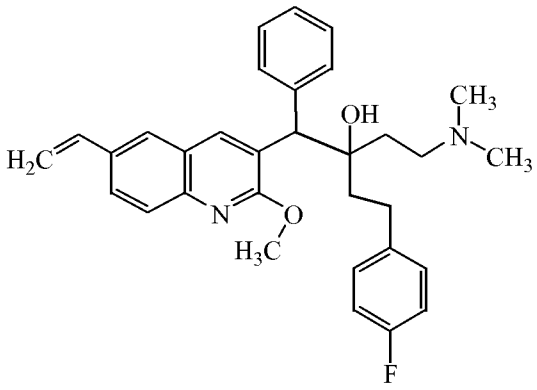


Compound 11 (dia A)
Compound 12 (dia B)

Compound 11 was prepared according to the procedure for compound 8. Yield: 65 % (dia A, (E); mp: 190 °C;)

Compound 12 was prepared according to the procedure for compound 10. Yield: 47 % (dia B, (E): mp: 189 °C).

e.Preparation of compounds 6 and 7



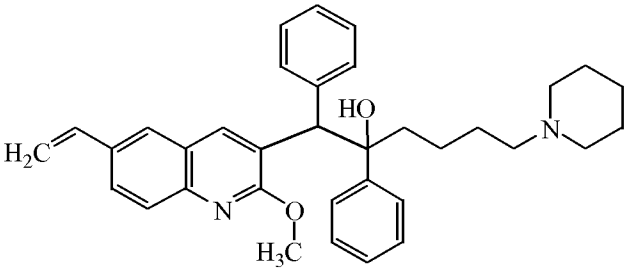
Compound 6 (dia A)
Compound 7 (dia B)

A solution of **intermediate 1** (0.2 g, 0.00036 mol), tributyl(vinyl)tin (0.21 ml, 0.000725 mol) and dichlorobis(triphenylphosphine)palladium (0.025 g, 0.000036 mol) in DMF (4 ml) was stirred for 10 minutes at 80°C in a microwave (100 W). Then an extra portion of tributyl(vinyl)tin (1 equivalent) and dichlorobis(triphenylphosphine)palladium (0.05 equivalent) were added and the mixture was stirred again for 10 minutes at 80°C in the microwave (100 W). Then the mixture was cooled to room temperature, poured out into a solution of KF 10 %, and diluted in EtOAc. The mixture was stirred for 1 hour at room temperature, filtered over Celite and washed with water. The organic layer was separated, washed with brine, dried over $MgSO_4$, filtered, and the solvent was evaporated. The residue was purified by column chromatography over silica gel (eluent: $CH_2Cl_2/CH_3OH/NH_4OH$; from

100/0/0 to 97/3/0.3; Sunfire 5 µm). The pure fractions were collected and the solvent was evaporated. Then the product was crystallized from DIPE. Yield: 0.067 g of **compound 6** (37 %; mp: 135 °C).

Accordingly **compound 7** was prepared according to the same procedure, but starting from **intermediate 2 (prepared according to A1.b)**. Yield: **Compound 7** (20 %; m.p: 156 °C).

f. Preparation of compounds 34 and 35



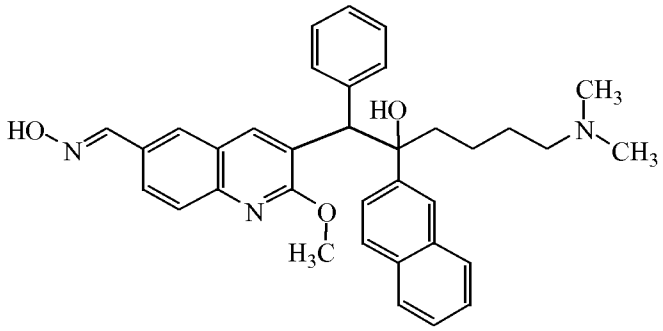
Compound 34 (dia A)
Compound 35 (dia B)

A mixture of **intermediate 14** (prepared according to A1.c) (0.35 mmol), tributyl(vinyl)tin (0.7 mmol) and $PdCl_2(PPh_3)_2$ (0.035 mmol) in *N,N*-dimethylformamide (4 ml) was heated under microwaves (80°C, 30', 100W). The mixture was cooled down and poured out into an aqueous solution of KF (10% w/w). EtOAc was added and the mixture was filtered over a short pad of celite. The filtrate was decanted and the organic layer was washed with water then brine, dried over $MgSO_4$, filtered and evaporated till dryness. The residue was purified by SFC (Pyridine column, eluent: CO_2/MeOH/isopropylamine: 80/20/0.5). The pure fractions were collected and the solvent was evaporated. Yield: 0.02 g of compound 34 (dia A; 11 %).

Compound 35 was prepared according to the procedure for **compound 34,** but starting from **intermediate 15** (prepared according to A1.c). Yield: 0.045 g of **compound 35** (dia B) (25 %).

Example B2

a. Preparation of compounds 32 and 33

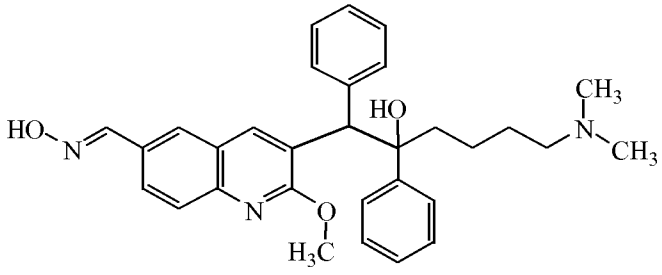


Compound 33 (dia A)
Compound 32 (dia B)

A solution of **intermediate 4** (prepared according to A2.a-1) (0.38 mmol) and hydroxylamine hydrochloride (0.57 mmol) in pyridine (2 ml) was stirred at room temperature for 18 hours. The mixture was poured out into water and extracted with EtOAc. The organic layer was separated, washed with brine, dried over $MgSO_4$, filtered and the solvent was evaporated. The residue (0.4 g) was purified by column chromatography over silica gel (eluent: $CH_2Cl_2/CH_3OH/NH_4OH$ 96/4/0.4 to 88/12/1.2; kromasil Si 5µm). The pure fractions were collected and the solvent was evaporated. Yield: 0.044 g **of compound 33** (21 %, m.p.180°C).

Compound 32 was prepared according to the same procedure, but starting from **intermediate 5** (prepared according to A2.a-1). Yield: 0.1 g of **compound 32** (dia B) 33 %.

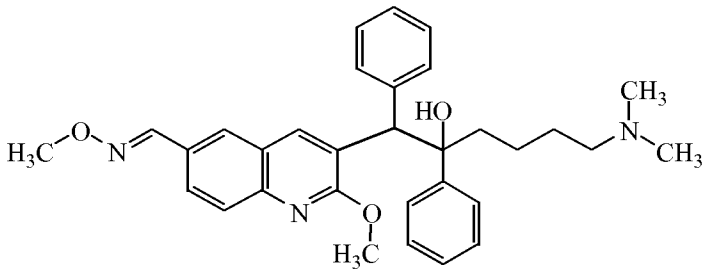
b. Preparation of compound 3



Compound 3 (dia B)

Compound 3 was prepared according to the procedure for compound 33, but starting from **intermediate 3** (prepared according to A2.a-2). Yield: 0.072 g of **compound 3** (dia B) 43 %.

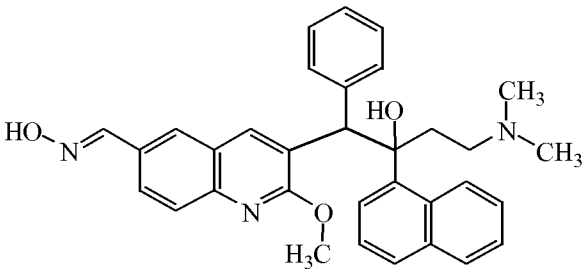
c. Preparation of compound 4



Compound 4 (dia B)

Compound 4 was prepared according to the procedure for compound 33, but starting from **intermediate 3** (prepared according to A2.a-1) and methoxylamine hydrochloride. Yield: 0.082 g of **compound 4** (dia B) 48 %.

d. Preparation of compounds 23 and 24

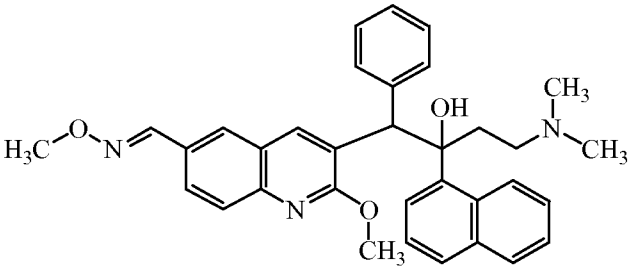


Compound 23 (dia A)
Compound 24 (dia B)

A mixture of **intermediate 10** (dia A) (prepared according to A2.a-3) (0.15 g, 0.297 mmol) and hydroxylamine hydrochloride (0.031 g, 0.446 mmol) in pyridine (2 ml) was stirred at room temperature overnight, poured into water and extracted with EtOAc. The organic layer was washed with water then brine, dried over $MgSO_4$, filtered and evaporated till dryness. The residue (0.17 g) was purified by column chromatography over silica gel (Sunfire 5µm, eluent: $CH_2Cl_2/CH_3OH/NH_4OH$: 99/1/0.1 to $CH_2Cl_2/CH_3OH/NH_4OH$: 94/6/0.5). The pure fractions were collected and the solvent was evaporated. Yield: 0.07 g of **compound 23** (46 %, m.p.=187°C).

Compound 24 (dia B) was prepared according to the same procedure as **compound 23,** but starting from **intermediate 11** (dia B) (prepared according to A2.a-3). Yield: 0.064 g of compound 24 (41 %, m.p. 167°C).

e. Preparation of compounds 25 and 26



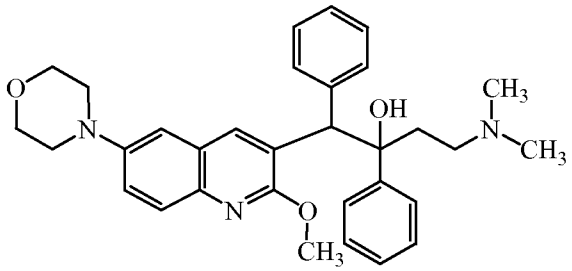
Compound 26 (dia A)
Compound 25 (dia B)

Compound 26 was prepared according to the procedure for **compound 23,** but starting from **intermediate 10** (prepared according to A2.a-3) and methoxylamine hydrochloride. Yield: 0.083 g of **compound 26** (dia A) (39 %; m.p.=170°C).

Compound 25 was prepared according to the procedure for **compound 23,** but starting from **intermediate 11** (prepared according to A2.a-3) and methoxylamine hydrochloride. Yield: 0.115 g of **compound 25** (dia B) (54 %; m.p.=228°C).

Example B3

a. Preparation of compounds 5 and 36

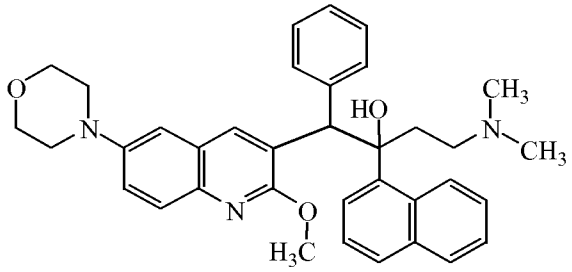


Compound 36 (dia A)
Compound 5 (dia B)

*n*BuLi 1.6M in hexane (2.24 ml, 3.60 mmol) was added slowly at –20°C under N_2 flow to a solution of diisopropylamine (0.503 ml, 3.60 mmol) in THF (8 ml). The mixture was stirred at –20°C for 20 minutes, and then cooled at –70°C. A solution of **intermediate 6** (prepared according to A3) (1.0 g, 3.0 mmol) in THF (10 ml) was added slowly. The mixture was stirred at –70°C for 1h30. A solution of 3-(dimethylamino)-1-phenyl-1-propanone (0.64 g, 3.6 mmol) in THF (7 ml) 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 over $MgSO_4$, filtered, and the solvent was evaporated. The residue (1.5 g) was purified by column chromatography over silica gel (SiO_2 15-40µm, eluent: $CH_2Cl_2/CH_3OH/NH_4OH$: 99/1/0.1). The pure fractions were collected and the solvent was evaporated. Products

were crystallized from methanol to afford 0.087 g of **compound 36** (6 %, m.p.=190°C) (dia A) and 0.088 g of **compound 5** (6 %, m.p.=140°C) (dia B).

b. Preparation of compound 30

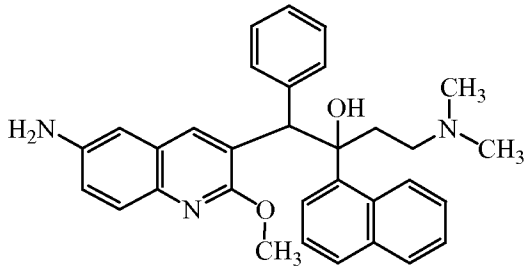


Compound 30 (dia B)

Compound 30 was prepared according to the procedure for **compound 5**, but starting from **intermediate 6** (prepared according to A3) and 3-(dimethylamino)-1-(1-naphthalenyl)-1-propanone as in procedure of compound 5. Yield: 0.087 g of **compound 30** (dia B) (5 %; m.p.=210°C).

Example B4

Preparation of compound 15 and 16



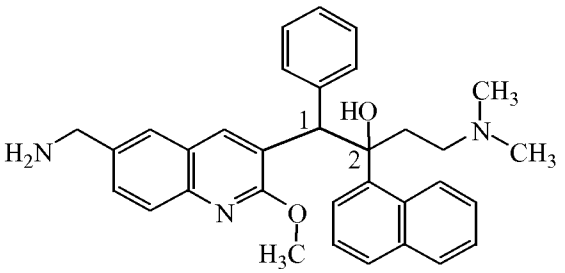
Compound 15 (dia A)
Compound 16 (dia B)

Tetrabutylammonium bromide (TBAB 1M in THF, 1.45 ml, 1.45 mmol) was added dropwise at 0°C to a solution of **intermediate 8** (prepared according to A4.b) (0.46 g, 0.72 mmol) in THF (5 ml). The mixture was stirred for 2 hours at room temperature then poured into $NaHCO_3$ 10% aqueous and extracted with EtOAc. The organic layer was washed with water then brine, dried over $MgSO_4$, filtered and evaporated till dryness. The residue (0.45 g) was purified by column chromatography over silica gel (Sunfire 5µm, eluent: $CH_2Cl_2/CH_3OH/NH_4OH$: 98/2/0.2). The pure fractions were collected and the solvent was evaporated. Yield: 0.014 g of **compound 15** (4 %, m.p. = 205°C).

Compound 16 was prepared according to the same procedure as **compound 15,** but starting from **intermediate 9** (prepared according to A4.b). Yield: 0.037 g of **compound 16** (7 %).

Example B5

Preparation of compound 17, 18, 19 and 20



Compound 17 (dia A)
Compound 20 (dia B)
Compound 18 (enantiomer A1)
Compound 19 (enantiomer A2)

A solution of **intermediate 13** (prepared according to A2.a-3) (enantio A2, 2.0 g, 3.96 mmol) in NH_3/MeOH (7N, 40 ml) was stirred at room temperature for 18 hours then Pd/C (10% dry, 2.0 g) was added. The resulting suspension was placed under 4 bars of H_2 and stirred for 24 hours. The mixture was filtered on a short pad of celite and the solvents were evaporated till dryness. The residue (2.0 g) was purified by column chromatography over silica gel (SiO_2 15-40µm, eluent: CH_2Cl_2/CH_3OH/NH_4OH: 93/7/0.5). The pure fractions were collected and the solvent was evaporated. Yield: 0.40 g of **compound 19** (**A2; 1S,2R**; 20 %).

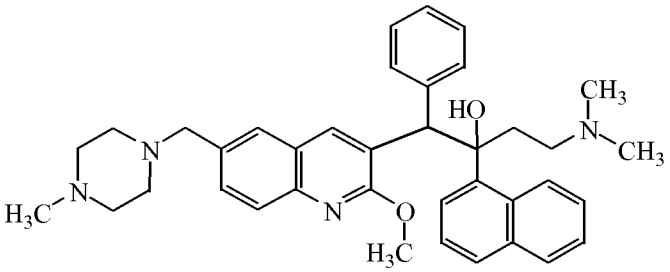
Compound 17 (dia A) was prepared according to the same as compound 19, but starting from **intermediate 10** (prepared according to A2.a-3). Yield: 0.083 g of **compound 17** (8 %, m.p.=180°C).

Compound 20 (dia B) was prepared according to the same procedure as compound 19, but starting from **intermediate 11** (prepared according to A2.a-3). Yield: 0.06 g of **compound 20** (20 %, m.p.=184°C).

Compound 18 (A1; 1R,S2) was prepared according to the same procedure as compound 19, but starting from **intermediate 12** (prepared according to A2.a-3). Yield: 0.73 g of **compound 18** (19 %).

Example B6

Preparation of compound 29

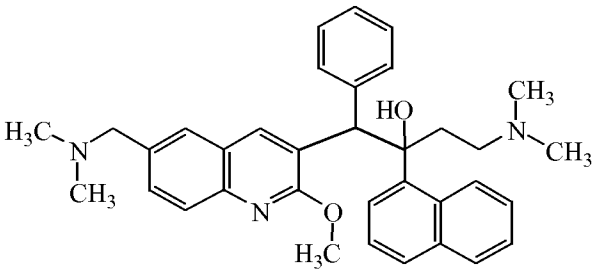


Compound 29 (dia A)

A mixture of **intermediate 10** (prepared according to A3.a-3) (dia A) (0.0002 mol) and methylpiperazine (0.0007 mol) in CH_3CN (3 ml), THF (3 ml) and AcOH (0.15 ml) was stirred at room temperature for 2 hours. BH_3CN (polymer support) (0.0003 mol), then CH_3CN (0.0003 mol) were added. The mixture was stirred at room temperature for 48 hours, poured out into H_2O and extracted with EtOAc. The organic layer was washed with saturated aqueous NaCl, dried ($MgSO_4$), filtered and the solvent was evaporated. The residue was purified by column chromatography over silica gel (eluent: $CH_2Cl_2/CH_3OH/NH_4OH$ 98/2/0.2 to 92/8/0.8; 5µm). The pure fractions were collected and the solvent was evaporated. Yield: 0.021 g of **compound 29** (12 %).

Example B7

Preparation of compound 21 and 22



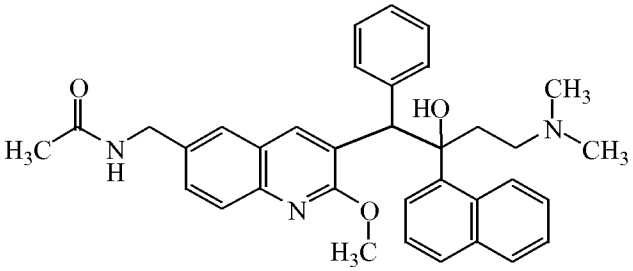
Compound 21 (dia A)
Compound 22 (dia B)

Sodium cyanoborohydride (0.056 g, 8.9 mmol) was added to a solution of **compound 17** (prepared according to B5) (0.15 g, 0.30 mmol), formaldehyde 30 % in water (0.24 ml, 3.0 mmol) and acetic acid (0.15 ml) in acetonitrile (3 ml). The reaction mixture was stirred at room temperature for 48 hours, and poured out into water. The organic layer was extracted with AcOEt and washed with brine, dried over $MgSO_4$, filtered and evaporated till dryness. The residue (0.18 g) was purified by column chromatography over silica gel (Sunfire 5µm, eluent: $CH_2Cl_2/CH_3OH/NH_4OH$: 98/2/0.2 to $CH_2Cl_2/CH_3OH/NH_4OH$: 94/6/0.6). The pure fractions were collected and the solvent was evaporated. Yield: 0.07 g of **compound 21** (44 %).

Compound 22 (dia B) was prepared according to same procedure for **compound 21,** but starting from **compound 20** (dia B) (prepared according to B5) . Yield: 0.063 g of **compound 22** (40 %).

Example B8

Preparation of compound 27

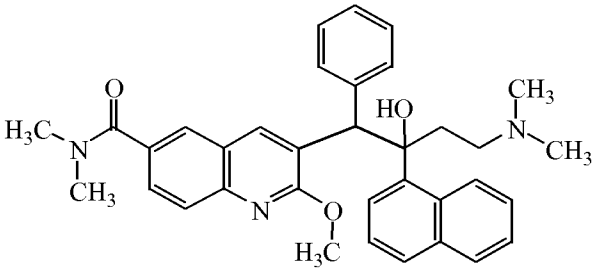


Compound 27 (dia B)

A solution of **compound 20** (prepared according to B5) (80 mg, 0.158 mmol), acetyl chloride (0.011 ml, 0.158 mmol) and triethylamine (0.024 ml, 0.174 mmol) in CH_2Cl_2 (5 ml) was stirred at room temperature for 24 hours. The mixture was poured into water and extracted with CH_2Cl_2. The organic layer was washed with water, dried over $MgSO_4$, filtered and evaporated till dryness. The residue (0.14 g) was purified by column chromatography over silica gel (Sunfire 5µm, eluent: $CH_2Cl_2/CH_3OH/NH_4OH$: 98/2/0.2 to $CH_2Cl_2/CH_3OH/NH_4OH$: 94/6/0.6). The pure fractions were collected and the solvent was evaporated. Yield: 0.084 g of **compound 27** (97 %, m.p.= 203°C).

Example B9

a. Preparation of compound 28

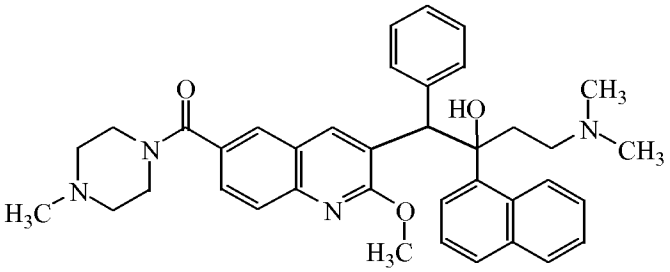


Compound 28 (dia A)

A solution of **intermediate 7** (prepared according to A4.a) (0.15 g, 0.288 mol), dimethylamine hydrochloride (0.047 g, 0.576 mol), hydroxybenzotriazole (0.047 g, 0.346 mol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (0.066 g, 0.346 mol), triethylamine (0.081 ml, 0.576 mol) in THF (2 ml) and CH_2Cl_2 (2 ml) was stirred at room temperature for 18 hours, and then poured out into water. The organic

layer was extracted with CH_2Cl_2 and washed with water, dried over $MgSO_4$, filtered and evaporated till dryness. The residue (0.15 g) was purified by column chromatography over silica gel (Kromasil 5µm, eluent: $CH_2Cl_2/CH_3OH/NH_4OH$: 99/1/0.1). The pure fractions were collected and the solvent was evaporated. Yield: 0.010 g of **compound 28** (64 %).

b. Preparation of compound 31

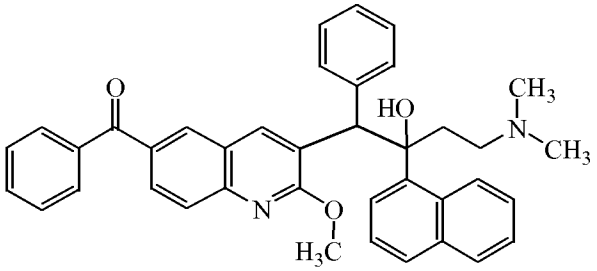


Compound 31 (dia A)

Compound 31 was prepared according to the procedure for **compound 28,** but starting from **intermediate 7** (prepared according to A4.a) and 1-methylpiperazine. Yield: 0.039 g of **compound 31** (dia A) (39 %; m.p.=195°C).

Example B10

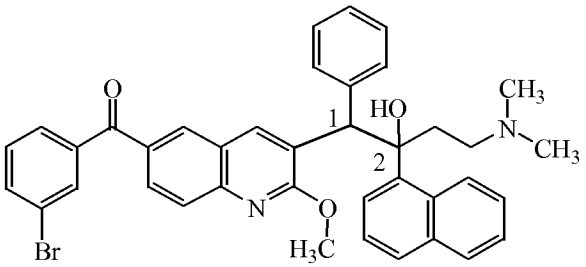
a. Preparation of compound 37



Compound 37 (dia A)

*n*BuLi 1.6 M in hexane (1.4 ml, 0.018 mol) was added to a solution of 6-bromo-α-[2-(dimethylamino)ethyl]-2-methoxy-α-1-naphthalenyl-β-phenyl-3-quinolineethanol (dia A, mixture of RS and SR; compound 14 of WO 2004/011436) (0.5 g, 0.009 mol) in THF (10 mol), cooled at –70°C under N_2 atmosphere. The mixture was stirred for 2 hours at –70°C, and then a solution of *N*-methyl-*N*-methoxybenzamide (0.3 g, 0.0018 mol) in THF (2.5 ml) was added drop wise. The reaction mixture was stirred at –70°C for 3 hours, and then diluted with water. The organic layer was dried ($MgSO_4$), filtered and concentrated. The crude product was purified by SFC chiral chromatography (ChiralPakADH 5µm, eluent: CO_2/MeOH 10/*i*PA: 92/8/0.5). Yield: 63 mg of **compound 37** (13 %).

b. Preparation of compound 38 and 39

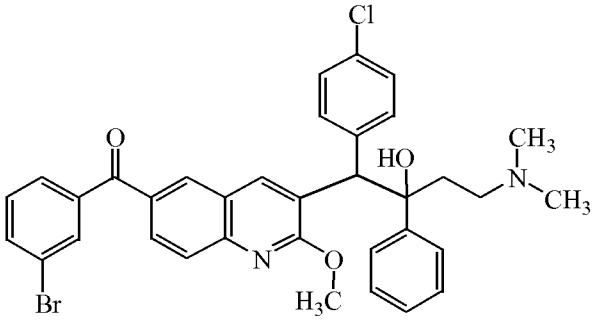


Compound 38 (A1)
Compound 39 (dia A)

Manganese oxide (0.11 g) was added portion wise to a solution of **intermediate 16** (prepared according to A5.a) (0.11 g, 0.166 mmol) in CH_2Cl_2 (5 ml), and the reaction mixture was stirred at room temperature for 5 hours. The resulting solution was filtered over celite, and washed with CH_2Cl_2. The filtrate was concentrated until dryness. The product was crystallized from 2-propanol. Yield: 82 mg of **compound 38** (A1; 1R,2S) (75 %, m.p. = 118 °C).

Compound 39 was prepared according to the procedure for **compound 38,** but starting from **intermediate 17** (prepared according to A5.a). Yield: 0.030 g of **compound 39** (dia A) (34 %).

c. Preparation of compound 40



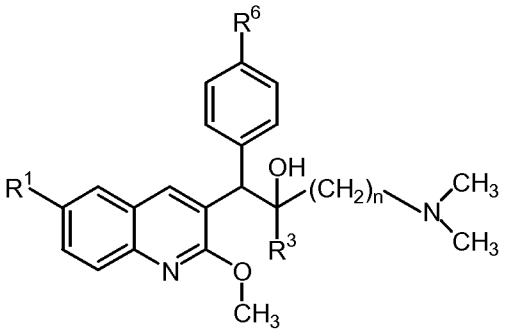
Compound 40 (dia B)

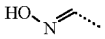
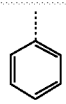
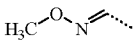
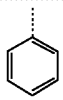
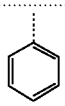
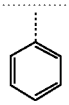
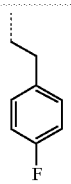
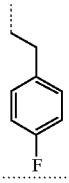
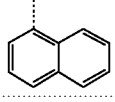
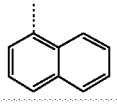
Compound 40 was prepared according to the procedure for **compound 38,** but starting from **intermediate 18** (prepared according to A5.b). Yield: 0.13 g of **compound 40** (dia B) (36 %; m.p.=185°C).

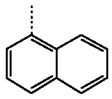
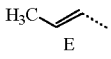
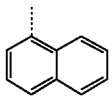
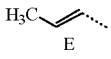
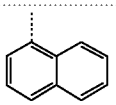
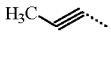
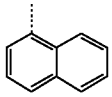
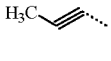
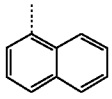
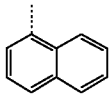
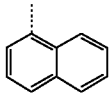
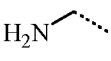
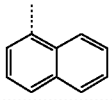
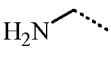
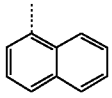
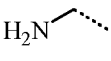
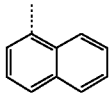
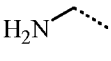
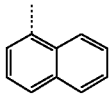
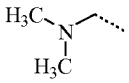
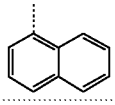
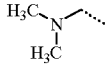
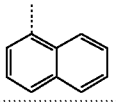
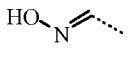
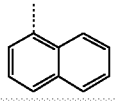
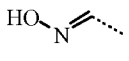
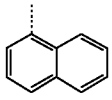
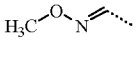
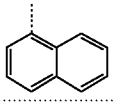
Tables 1 to 3 list compounds of formula (Ia) which were prepared according to one of the above procedures (Ex. No.).

For a number of compounds, melting points were obtained with a Kofler hot bench, consisting of a heated plate with linear temperature gradient, a sliding pointer and a temperature scale in degrees Celsius.

Table 1:



Comp nr.	Ex. nr.	R^1	R^3	R^6	n	Stereochemistry and melting points
1	B1.c			--Cl	2	dia A; 184 °C
2	B1.c			--Cl	2	dia B; 187 °C
3	B2.b			--H	4	dia B
4	B2.c			--H	4	dia B
36	B3.a			--H	2	dia A; 190 °C
5	B3.a			--H	2	dia B; 140 °C
6	B1.e			--H	2	dia A; 135 °C
7	B1.e			--H	2	dia B; 156 °C
8	B1.a			--H	2	dia A; 164 °C
9	B1.a			--H	2	A1; 1R,2S; 152 °C

Comp nr.	Ex. nr.	R^1	R^3	R^6	n	Stereochemistry and melting points
10	B1.a			--H	2	dia B; 185 °C
11	B1.d			--H	2	dia A; 190 °C
12	B1.d			--H	2	dia B; 189 °C
13	B1.b			--H	2	dia A; 100 °C
14	B1.b			--H	2	dia B; 202 °C
15	B4			--H	2	dia A; 205 °C
16	B4			--H	2	dia B
17	B5			--H	2	dia A; 180 °C
18	B5			--H	2	A1; 1R,2S
19	B5			--H	2	A2; 1S,2R
20	B5			--H	2	dia B; 184 °C
21	B7			--H	2	dia A
22	B7			--H	2	dia B
23	B2.d			--H	2	dia A; 187 °C
24	B2.d			--H	2	dia B; 167 °C
25	B2.e			--H	2	dia B; 228 °C

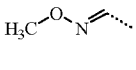
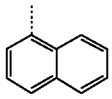
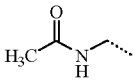
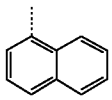
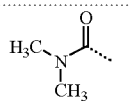
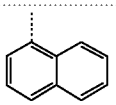
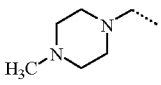
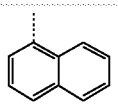
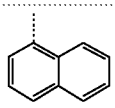
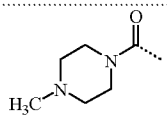
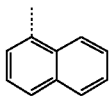
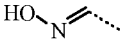
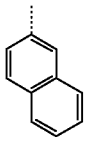
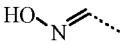
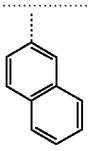
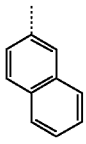
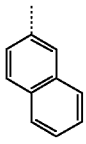
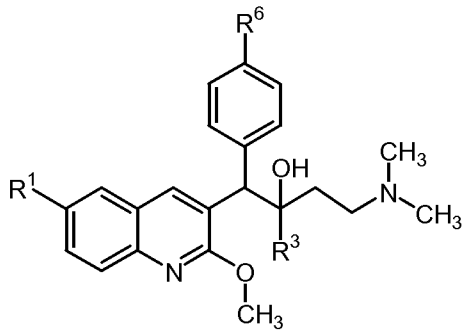
Comp nr.	Ex. nr.	R^1	R^3	R^6	n	Stereochemistry and melting points
26	B2.e			--H	2	dia A; 170 °C
27	B8			--H	2	dia B; 203 °C
28	B9.a			--H	2	dia A
29	B6			--H	2	dia A
30	B3.b			--H	2	dia B; 210 °C
31	B9.b			--H	2	dia A; 195 °C
32	B2.a			--H	4	dia B; 218 °C
33	B2.a			--H	4	dia A; 180 °C
41	B1.a			--H	4	dia B
42	B1.a			--H	4	dia A

Table 2:



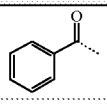
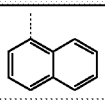
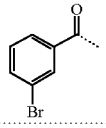
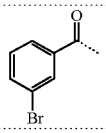
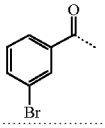
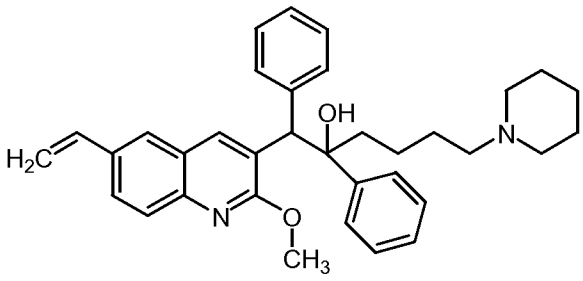
Comp. nr.	Ex. nr.	R^1	R^3	R^6	Stereochemistry and melting points
37	B10.a			--H	dia A; 202 °C
38	B10.b			--H	A1; 1R,2S; 118 °C
39	B10.b			--H	dia A; 170°C
40	B10.c			--Cl	dia B; 185°C

Table 3:



Comp. nr	Ex. nr.	Stereochemistry and melting points
34	B1.f	dia A
35	B1.f	dia B

C. Analytical methods

A. LCMS

The mass of some compounds was recorded with LCMS (liquid chromatography mass spectrometry). The methods used are described below.

General procedure A

The HPLC measurement was performed using an Alliance HT 2795 (Waters) system comprising a quaternary pump with degasser, an autosampler, a diode-array detector (DAD) and a column as specified in the respective methods below, the column is hold at a temperature of 30°C. Flow from the column was split to a MS spectrometer. The MS detector was configured with an electrospray ionization source. The capillary needle voltage was 3 kV and the source temperature was maintained at 100 °C on the LCT (Time of Flight Zspray™ mass spectrometer from Waters - for methods 1, 2, 3 and 4), and 3.15 kV at 110 °C on the ZQ™ (simple quadrupole Zspray™ mass spectrometer from Waters - for methods 5, 6 and 7). Nitrogen was used as the nebulizer gas. Data acquisition was performed with a Waters-Micromass MassLynx-Openlynx data system.

General procedure B

The LC measurement was performed using a UPLC (Ultra Performance Liquid Chromatography) Acquity (Waters) system comprising a binary pump with degasser, an autosampler, a diode-array detector (DAD) and a column as specified in the respective methods below, the column is hold at a temperature of 40°C. Flow from the column was brought to a MS detector. The MS detector was configured with an electrospray ionization source. The capillary needle voltage was 3 kV and the source temperature was maintained at 130 °C on the Quattro (triple quadrupole mass spectrometer from Waters). Nitrogen was used as the nebulizer gas. Data acquisition was performed with a Waters-Micromass MassLynx-Openlynx data system.

Method 1:

In addition to general procedure A: Reversed phase HPLC was carried out on a Kromasil C18 column (5 µm, 4.6 x 150 mm) with a flow rate of 1.0 ml/min. Three mobile phases (mobile phase A: 100 % 7 mM ammonium acetate; mobile phase B: 100 % acetonitrile; mobile phase C: 0.2 % formic acid + 99.8 % ultra-pure Water) were employed to run a gradient condition from 30 % A , 40 % B and 30 % C (hold for 1 minute) to 100 % B in 4 minutes, 100 % B for 5 minutes and reequilibrated with initial conditions for 3 minutes. An injection volume of 5 µl was used. Cone voltage was 20 V for positive ionization mode. Mass spectra were acquired by scanning from 100 to 900 in 0.8 seconds using an interscan delay of 0.08 seconds.

Method 2 :

In addition to general procedure A: Reversed phase HPLC was carried out on a Xterra-MS C18 column (5 µm, 4.6 x 150 mm) with a flow rate of 1.0 ml/min. Two mobile phases (mobile phase A: 100 % 7 mM ammonium acetate; mobile phase B: 100 % acetonitrile; were employed to run a gradient condition from 85 % A, 15 % B (hold for 3 minutes) to 20 % A, 80 % B in 5 minutes, hold at 20 % A and 80 % B for 6 minutes and reequilibrated with initial conditions for 3 minutes. An injection volume of 20 µl was used. Cone voltage was 20 V for positive ionization mode. Mass spectra were acquired by scanning from 100 to 900 in 0.8 seconds using an interscan delay of 0.08 seconds.

Method 3 :

In addition to general procedure A: Reversed phase HPLC was carried out on a Xterra-MS C18 column (5 µm, 4.6 x 150 mm) with a flow rate of 1.0 ml/min. Two mobile phases (mobile phase A: 100 % 7 mM ammonium acetate; mobile phase B: 100 % acetonitrile; were employed to run a gradient condition from 85 % A , 15 % B (hold for 3 minutes) to 20 % A, 80 % B in 5 minutes, hold at 20 % A and 80 % B for 6 minutes and reequilibrated with initial conditions for 3 minutes. An injection volume of 20 µl was used. Cone voltage was 20 V for positive ionization mode and 20 V for negative ionization mode. Mass spectra were acquired by scanning from 100 to 900 in 0.8 seconds using an interscan delay of 0.08 seconds.

Method 4 :

In addition to general procedure A: Reversed phase HPLC was carried out on a Kromasil C18 column (5 µm, 4.6 x 150 mm) with a flow rate of 1.0 ml/min. Three mobile phases (mobile phase A: 100 % 7 mM ammonium acetate; mobile phase B: 100 % acetonitrile; mobile phase C: 0.2 % formic acid + 99.8 % ultra-pure Water) were employed to run a gradient condition from 30 % A , 40 % B and 30 % C (hold for 1 minute) to 100 % B in 4 minutes, 100% B for 5 minutes and reequilibrated with initial conditions for 3 minutes. An injection volume of 5 µl was used. Cone voltage was 20 V for positive and negative ionization mode. Mass spectra were acquired by scanning from 100 to 900 in 0.8 seconds using an interscan delay of 0.08 seconds.

Method 5 :

In addition to general procedure A: Reversed phase HPLC was carried out on a Sunfire C18 column (3.5 µm, 4.6 x 100 mm) with an initial flow rate of 0.8 ml/min. Two mobile phases (mobile phase A: 35 % 6.5mM ammonium acetate + 30 % acetonitrile + 35 % formic acid (2 ml/l); mobile phase B: 100 % acetonitrile) were employed to run a gradient condition from 100 % A (hold for 1 minute) to 100% B in 4 minutes, hold at 100 % B at a flow rate of 1.2 ml/min for 4 minutes and reequilibrated with initial conditions for 3 minutes. An injection volume of 10 µl was used. Cone voltage was 20 V for positive and negative ionization mode. Mass spectra were acquired by scanning from 100 to 1000 in 0.4 seconds using an interscan delay of 0.3 seconds.

Method 6 :

In addition to general procedure A: Reversed phase HPLC was carried out on a Sunfire C18 column (3.5 µm, 4.6 x 100 mm) with an initial flow rate of 0.8 ml/min. Two mobile phases (mobile phase A: 35 % 6.5mM ammonium acetate + 30 % acetonitrile + 35 % formic acid (2 ml/l); mobile phase B: 100 % acetonitrile) were employed to run a gradient condition from 100 % A (hold for 1 minute) to 100% B in 4 minutes, hold at 100 % B at a flow rate of 1.2 ml/min for 4 minutes and reequilibrated with initial conditions for 3 minutes. An injection volume of 10 µl was used. Positive ionization mode was used with four different cone voltages (20,40,50,55 V). Mass spectra were acquired by scanning from 100 to 1000 in 0.4 seconds using an interscan delay of 0.1 seconds.

Method 7 :

In addition to general procedure A: Reversed phase HPLC was carried out on a Sunfire C18 column (3.5 µm, 4.6 x 100 mm) with an intial flow rate of 0.8 ml/min. Two mobile phases (mobile phase A: 25 % 7mM ammonium acetate + 50 % acetonitrile +25 % formic acid (2ml/l); mobile phase B: 100 % acetonitrile) were employed to run a gradient condition from 100 % A (hold for 1 minute) to 100 % B in 4 minutes, hold at 100 % B at a flow rate of 1.2 ml/min for 4 minutes and reequilibrated with initial conditions for 3 minutes). An injection volume of 10 µl was used. Cone voltage was 20 V for positive and negative ionization mode. Mass spectra were acquired by scanning from 100 to 1000 in 0.4 seconds using an interscan delay of 0.3 seconds.

Method 8 :

In addition to general procedure B: Reversed phase UPLC was carried out on a Waters Acquity bridged ethylsiloxane/silica hybrid (BEH) C18 column (1.7 µm, 2.1 x 100 mm) with a flow rate of 0.4 ml/min. Two mobile phases (mobile phase A: 100 % 7 mM ammonium acetate; mobile phase B: 100 % acetonitrile) were employed to run a gradient condition from 80 % A and 20 % B (hold for 0.5 minutes) to 10% A and 90 % B in 3.5 minutes, hold for 2 minutes and reequilibrated with initial conditions for 2 minutes. An injection volume of 2 µl was used. Cone voltages were 20, 30, 45, 60 V for positive ionization mode. Mass spectra were acquired by scanning from 100 to 1000 in 0.2 seconds using an interscan delay of 0.1 seconds.

When a compound is a mixture of isomers which give different peaks in the LCMS method , only the retention time of the main component is given in the LCMS table.

Table 4 : LCMS: (MH^+), protonated molecular ion (of the free base), and retention time (R_t, in minutes)

Comp.No.	LCMS method	(MH^+)	R_t (min)
1	6	487	4.98
2	6	487	4.87
3	5	498	4.21
4	5	512	4.83
5	6	512	4.25
6	6	499	4.93
7	6	499	4.92

Comp.No.	LCMS method	(MH^+)	R_t (min)
8	1	503	6.90
9	5	503	4.98
10	5	503	4.82
11	6	517	5.23
12	6	517	5.05
13	6	515	5.10
14	6	515	4.95
15	1	492	4.50
16	4	492	3.65
17	2	506	9.34
18	3	506	8.64
19	2	506	8.40
20	2	506	8.14
21	2	534	9.53
22	2	534	9.36
23	1	520	5.00
24	1	520	4.28
25	1	534	5.51
26	1	534	6.23
27	2	548	9.27
28	1	548	4.70
29	2	589	8.97
30	5	562	4.53
31	3	603	9.18
32	3	548	8.94
33	3	548	9.20
34	5	521	5.00
35	5	521	4.92
36	6	512	4.02
37	7	581	3.47
38	5	659	5.20
39	7	659	4.35
40	5	643	5.27
41	8	531	4.20

Comp.No.	LCMS method	(MH^+)	R_t (min)
42	8	531	4.29

B. Optical Rotation

The optical rotation was measured using a polarimeter. $[\alpha]_D^{20}$ indicates the optical rotation measured with light at the wavelength of the D-line of sodium (589 nm) at a temperature of 20°C. The cell pathlength is 1 dm. Behind the actual value the concentration and solvent of the solution which was used to measure the optical rotation are mentioned.

Table 5 : Optical rotation data

Comp. Nr.	$[\alpha]_D^{20}$	concentration	solvent
9	-221.34°	C = 0.328 w/v %	DMF
38	-206.95°	C = 0.518 w/v %	DMF

D. Pharmacological examples

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

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

The fluorescence was read in a computer-controlled fluorometer (Spectramax Gemini EM, Molecular Devices) at an excitation wavelength of 530 nm and an emission wavelength of 590 nm. The percentage growth inhibition achieved by the compounds was calculated according to standard methods and expressed as IC_{90} (µg/ml) which defines the 90 % inhibitory concentration for bacterial growth. See Table 6.

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

Flat-bottom, sterile 96-well plastic microtiter plates were filled with 180 µl of sterile deionized water, supplemented with 0.25 % BSA. Subsequently, stock solutions (7.8 x final test concentration) of compounds were added in 45 µl volumes to a series of duplicate wells in column 2 so as to allow evaluation of their effects on bacterial growth. Serial five-fold dilutions (45 µl in 180 µl) were made directly in the microtiter plates from column 2 to 11 using a customised robot system (Zymark Corp., Hopkinton, MA). Pipette tips were changed after every 3 dilutions to minimize pipetting errors with high hydrophobic compounds. Untreated control samples with (column 1) and without (column 12) inoculum were included in each microtiter plate. Approximately 250 CFU per well of bacteria inoculum, in a volume of 100 µl in 2.8x Mueller-Hinton broth medium, was added to the rows A to H, except column 12. The same volume of broth medium without inoculum was added to column 12 in row A to H. The cultures were incubated at 37°C for 48 hours in a humidified 5% CO_2 atmosphere (incubator with open air valve and continuous ventilation). At the end of incubation, two days after inoculation, the bacterial growth was quantitated fluorometrically. Therefore Alamar Blue (10x) was added to all wells in a volume of 20 µl and plates were incubated for another 2 hours at 50°C.

The fluorescence was read in a computer-controlled fluorometer (Cytofluor, Biosearch) at an excitation wavelength of 530 nm and an emission wavelength of 590 nm (gain 30). The percentage growth inhibition achieved by the compounds was calculated according to standard methods and expressed as IC_{90} (µg/ml) which defines the 90 % inhibitory concentration for bacterial growth. See Table 6.

D.3. In-vitro method for testing compounds for anti-bacterial activity against various non-mycobacterial strains

Preparation of bacterial suspensions for susceptibility testing:

The bacteria used in this study were grown overnight in flasks containing 100 ml Mueller-Hinton Broth (Becton Dickinson - cat. no. 275730) in sterile de-ionized water, with shaking, at 37 °C. Stocks (0.5 ml/tube) were stored at –70 °C until use. Bacteria titrations were performed in microtiter plates to detect the $TCID_{50}$, in which the TCID50 represents the dilution that gives rise to bacterial growth in 50 % of inoculated cultures.

In general, an inoculum level of approximately 100 $TCID_{50}$ was used for susceptibility testing.

Anti bacterial Susceptibility testing: IC_{90} determination

Microtitre plate assay

Flat-bottom, sterile 96-well plastic microtiter plates were filled with 180 µl of sterile deionized water, supplemented with 0.25 % BSA. Subsequently, stock solutions (7.8 x final test concentration) of compounds were added in 45 µl volumes in column 2. Serial five-fold dilutions (45 µl in 180 µl) were made directly in the microtiter plates from column 2 to reach column 11. Untreated control samples with (column 1) and without (column 12) inoculum were included in each microtiter plate. Depending on the bacteria type, approximately 10 to 60 CFU per well of bacteria inoculum (100 TCID50), in a volume of 100 µl in 2.8x Mueller-Hinton broth medium, was added to the rows A to H, except column 12. The same volume of broth medium without inoculum was added to column 12 in row A to H. The cultures were incubated at 37°C for 24 hours under a normal atmosphere (incubator with open air valve and continuous ventilation). At the end of incubation, one day after inoculation, the bacterial growth was quantitated fluorometrically. Therefore resazurin (0.6 mg/ml) was added in a volume of 20 µl to all wells 3 hours after inoculation, and the plates were re-incubated overnight. A change in colour from blue to pink indicated the growth of bacteria. The fluorescence was read in a computer-controlled fluorometer (Cytofluor Biosearch) at an excitation wavelength of 530 nm and an emission wavelength of 590 nm. The % growth inhibition achieved by the compounds was calculated according to standard methods. The IC_{90} (expressed in µg/ml) was defined as the 90 % inhibitory concentration for bacterial growth. The results are shown in Table 6.

Agar dilution method.

MIC_{99} values (the minimal concentration for obtaining 99 % inhibition of bacterial growth) can be determined by performing the standard Agar dilution method according to NCCLS standards* wherein the media used includes Mueller-Hinton agar.

* Clinical laboratory standard institute. 2005. Methods for dilution Antimicrobial susceptibility tests for bacteria that grows Aerobically: approved standard -sixth edition

Time kill assays

Bactericidal or bacteriostatic activity of the compounds may be determined in a time kill assay using the broth microdilution method *. In a time kill assay on *Staphylococcus aureus* and methicillin resistant *S. aureus* (MRSA), the starting inoculum of *S. aurues* and MRSA is 10^6 CFU / ml in Muller Hinton broth. The antibacterial compounds are used at the concentration of 0.1 to 10 times the MIC (i.e. IC_{90} as determined in microtitre plate assay). Wells receiving no antibacterial agent constitute the culture growth control. The plates containing the microorganism and the test compounds are incubated at 37 °C. After 0, 4, 24, and 48 hrs of incubation samples are removed for determination of viable counts by serial dilution (10^{-1} to 10^{-6}) in sterile PBS and plating (200 µl) on Mueller Hinton agar. The plates are incubated at 37 °C for 24 hrs and the number of colonies are determined. Killing curves can be constructed by plotting the log_{10}CFU per ml versus time. A bactericidal effect is commonly defined as 3-log_{10} decrease in number of CFU per ml as compared to untreated inoculum. The potential carryover effect of the drugs is removed by serial dilutions and counting the colonies at highest dilution used for plating.

* Zurenko,G.E. *et al.* In vitro activities of U-100592 and U-100766, novel oxazolidinone antibacterial agents. *Antimicrob. Agents Chemother.* **40**, 839-845 (1996).

Determination of cellular ATP levels

In order to analyse the change in the total cellular ATP concentration (using ATP bioluminescence Kit, Roche), assays are carried out by growing a culture of *S. aureus* (ATCC29213) stock in 100 ml Mueller Hinton flasks and incubate in a shaker-incubator for 24 hrs at 37 °C (300 rpm). Measure OD_{405} nm and calculate the CFU/ml. Dilute the cultures to 1 x 10^6 CFU/ml (final concentration for ATP measurement: 1 x 10^5 CFU/100 µl per well) and add test compound at 0.1 to 10 times the MIC (i.e. IC_{90} as determined in microtitre plate assay). Incubate these tubes for 0, 30 and 60 minutes at 300 rpm and 37°C. Use 0.6 ml bacterial suspension from the snap-cap tubes and add to a new 2 ml eppendorf tubes. Add 0.6 ml cell lysis reagent (Roche kit), vortex at max speed and incubate for 5 minutes at room temperature. Cool on ice. Let the

luminometer warm up to 30°C (Luminoskan Ascent Labsystems with injector). Fill one column (= 6 wells) with 100 µl of the same sample. Add 100 µl Luciferase reagent to each well by using the injector system. Measure the luminescence for 1 sec.

Table 6 : IC_{90} values (µg/ml).

Comp. Nr.	STA 1 B29213	SPN 1 6305	MTB 1 H37RV	MSM 1 ATCC607	EFA 29212	SPY 8668	PAE 27853	ECO 35218
29	9.3	10.5		2.6				
25	8.5	2.1	1.7	0.3	8.46	8.46	8.46	53.37
26	53.4	18.9	8.5	0.3	53.37	53.37	53.37	53.37
2	48.7	1.7		1.4	38.69	1.22		
1	48.7	1.7		0.0				
24	8.2	1.6		2.3				
23	6.5	0.3	7.3	0.3	18.44	8.24	8.24	51.97
21	10.7	13.4		0.7				
22	9.5	21.3		18.9				
13	51.5	0.3		0.003	51.47	51.47		
14	45.9	1.5		0.3	51.47	40.88		
12	51.7	0.7		0.3	51.67	51.67		
10	50.3	20.0		8.0				
8	50.3	2.0	3.6	0.0	50.27	50.27	44.8	50.27
9	50.3	0.3	0.2	0.003	50.27	50.27	50.27	50.27
30	44.6	14.1	8.9	0.1	44.62	44.62	22.36	56.17
11	51.7	1.8		0.01	51.67	51.67	51.67	
5	40.6	9.1		0.04	40.64	40.64		51.17
20	35.8	8.0		40.2				
17	8.0	8.0	3.6	0.4				
31	38.0	10.7	4.8	0.4				
19	8.0	1.8	8.0	1.6	40.17	8.01	8.01	40.17
18	8.0	3.6	1.6	0.4	17.94	6.37	8.01	8.01
27	34.6	8.7	21.8	4.4				
16	43.8	24.6	31.0	7.8				
15	7.8	7.8	1.6	0.3				
28	43.5	10.9	3.5	0.1				

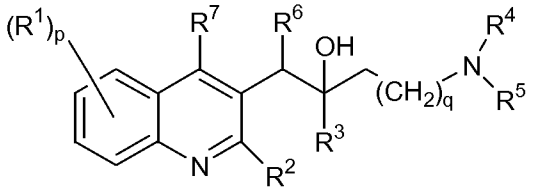
Comp. Nr.	STA 1 B29213	SPN 1 6305	MTB 1 H37RV	MSM 1 ATCC607	EFA 29212	SPY 8668	PAE 27853	ECO 35218
6	1.6	1.3		0.1				
7	1.6	1.3		1.3				
3	7.9	49.8		7.9				
32	1.7	10.9		7.7				
33	1.7	1.9		1.7				
34	1.7	2.1		1.7				
35	1.7	10.4		1.7				
4	8.1	10.2		1.6				
41	1.7	1.7		1.3				
42	1.7	1.7		1.5				
36	51.2	51.2		8.1	51.2	40.6		51.2

ECO 35218 means *Escherichia coli* (ATCC35218); EFA 29212 means *Enterococcus faecalis* (ATCC29212); PAE 27853 means *Pseudomonas aeruginosa* (ATCC27853); SPN 6305 means *Streptococcus pneumoniae* (ATCC6305); SPY 8668 means *Streptococcus pyogens* (ATCC8668); STA 29213 means *Staphylococcus aureus* (ATCC29213); MSM 607 means *M. Smegmatis* (ATCC607); MTB H37RV means *Mycobacterium tuberculosis* (strain H37RV);

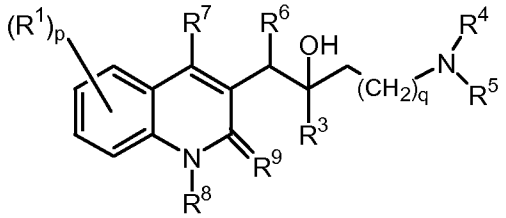
ATCC means American type tissue culture.

CLAIMS

1. A compound of formula (Ia) or (Ib)



(Ia)



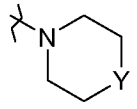
(Ib)

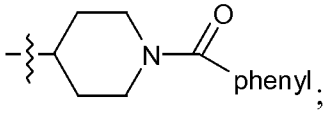
including any stereochemically isomeric form thereof, wherein

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

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

R^1 is alkenyl, alkynyl, -C=N-OR^{11}, amino, mono or di(alkyl)amino, aminoalkyl, mono or di(alkyl)aminoalkyl, alkylcarbonylaminoalkyl, aminocarbonyl, mono or di(alkyl)aminocarbonyl, arylcarbonyl, $R^{5a}R^{4a}$Nalkyl, $R^{5a}R^{4a}$N-, $R^{5a}R^{4a}$N-C(=O)-;

R^2 is hydrogen, alkyloxy, aryl, aryloxy, hydroxy, mercapto, alkyloxyalkyloxy, alkylthio, mono or di(alkyl)amino, pyrrolidino or a radical of formula  wherein Y is CH_2, O, S, NH or *N*-alkyl ;

R^3 is alkyl, arylalkyl, aryl-O-alkyl, aryl-alkyl-O-alkyl, aryl, Het, Het-alkyl, Het-O-alkyl, Het-alkyl-O-alkyl or ;

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, imidazolidinyl, pyridazinyl, pyrimidinyl, pyrazinyl, triazinyl, morpholinyl and thiomorpholinyl, each radical optionally substituted with alkyl, halo, haloalkyl, hydroxy, alkyloxy, amino, mono- or dialkylamino, alkylthio, alkyloxyalkyl, alkylthioalkyl and pyrimidinyl ;

R^{4a} and R^{5a} together with the nitrogen atom to which they are attached form a radical selected from the group consisting of pyrrolidino, piperidino,

piperazino, morpholino, 4-thiomorpholino, 2,3-dihydroisoindol-1-yl, thiazolidin-3-yl, 1,2,3,6-tetrahydropyridyl, hexahydro-1*H*-azepinyl, hexahydro-1*H*-1,4-diazepinyl, hexahydro-1,4-oxazepinyl, 1,2,3,4-tetrahydroisoquinolin-2-yl, pyrrolinyl, pyrrolyl, imidazolidinyl, pyrazolidinyl, 2-imidazolinyl, 2-pyrazolinyl, imidazolyl, pyrazolyl, triazolyl, pyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl and triazinyl, each radical optionally substituted with 1, 2, 3 or 4 substituents, each substituent independently selected from alkyl, haloalkyl, halo, arylalkyl, hydroxy, alkyloxy, amino, mono- or dialkylamino, alkylthio, alkylthioalkyl, aryl, pyridyl or pyrimidinyl;

R^6 is $aryl^1$ or Het;

R^7 is hydrogen, halo, alkyl, aryl or Het;

R^8 is hydrogen or alkyl;

R^9 is oxo; or

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

R^{11} is hydrogen or alkyl;

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

$aryl^1$ is a homocycle selected from phenyl, naphthyl, acenaphthyl or tetrahydronaphthyl, each being optionally substituted with 1, 2 or 3 substituents, each substituent being independently selected from hydroxy, halo, cyano, nitro, amino, mono- or dialkylamino, alkyl, haloalkyl, alkyloxy, alkylthio, haloalkyloxy, carboxyl, alkyloxycarbonyl, aminocarbonyl, morpholinyl, Het or mono- or dialkylaminocarbonyl;

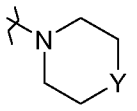
Het is a monocyclic heterocycle selected from *N*-phenoxypiperidinyl, piperidinyl, pyrrolyl, pyrazolyl, imidazolyl, furanyl, thienyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, pyridinyl, pyrimidinyl, pyrazinyl or pyridazinyl; or a bicyclic heterocycle selected from quinolinyl, quinoxalinyl, indolyl, benzimidazolyl, benzoxazolyl, benzisoxazolyl, benzothiazolyl, benzisothiazolyl, benzofuranyl, benzothienyl, 2,3-dihydrobenzo[1,4]dioxinyl or benzo[1,3]dioxolyl; each monocyclic and bicyclic heterocycle being optionally substituted with 1, 2 or 3

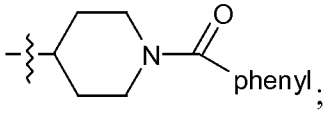
substituents, each substituent independently selected from halo, hydroxy, alkyl or alkyloxy;

a *N*-oxide thereof, a pharmaceutically acceptable salt thereof or a solvate thereof.

2. A compound according to claim 1 wherein

R^1 is C_{2-6}alkenyl, C_{2-6}alkynyl, -C=N-OR^{11}, amino, mono or di(C_{1-6}alkyl)amino, aminoC_{1-6}alkyl, mono or di(C_{1-6}alkyl)aminoC_{1-6}alkyl, C_{1-6}alkylcarbonylaminoC_{1-6}alkyl, aminocarbonyl, mono or di(C_{1-6}alkyl)aminocarbonyl, arylcarbonyl, $R^{5a}R^{4a}$Nalkyl, $R^{5a}R^{4a}$N-, $R^{5a}R^{4a}$N-C(=O)-;

R^2 is hydrogen, C_{1-6}alkyloxy, aryl, aryloxy, hydroxy, mercapto, C_{1-6}alkyloxyC_{1-6}alkyloxy, C_{1-6}alkylthio, mono or di(C_{1-6}alkyl)amino, pyrrolidino or a radical of formula  wherein Y is CH_2, O, S, NH or *N*-C_{1-6}alkyl ;

R^3 is C_{1-6}alkyl, C_{3-6}cycloalkyl, arylC_{1-6}alkyl, aryl-O-C_{1-6}alkyl, arylC_{1-6}alkyl-O-C_{1-6}alkyl, aryl, Het, Het-C_{1-6}alkyl, Het-O-C_{1-6}alkyl or HetC_{1-6}alkyl-O-C_{1-6}alkyl, or ;

R^4 and R^5 each independently are hydrogen, C_{1-6}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, imidazolidinyl, pyridazinyl, pyrimidinyl, pyrazinyl, triazinyl, morpholinyl and thiomorpholinyl, each radical optionally substituted with C_{1-6}alkyl, halo, haloC_{1-6}alkyl, hydroxy, C_{1-6}alkyloxy, amino, mono- or di(C_{1-6}alkyl)amino, C_{1-6}alkylthio, C_{1-6}alkyloxyC_{1-6}alkyl, C_{1-6}alkylthioC_{1-6}alkyl and pyrimidinyl ;

R^{4a} and R^{5a} together with the nitrogen atom to which they are attached form a radical selected from the group consisting of pyrrolidino, piperidino, piperazino, morpholino, 4-thiomorpholino, 2,3-dihydroisoindol-1-yl, thiazolidin-3-yl, 1,2,3,6-tetrahydropyridyl, hexahydro-1*H*-azepinyl, hexahydro-1*H*-1,4-diazepinyl, hexahydro-1,4-oxazepinyl, 1,2,3,4-tetrahydroisoquinolin-2-yl, pyrrolinyl, pyrrolyl, imidazolidinyl, pyrazolidinyl, 2-imidazolinyl, 2-pyrazolinyl, imidazolyl, pyrazolyl,

triazolyl, pyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl and triazinyl, each radical optionally substituted with 1, 2, 3 or 4 substituents, each substituent independently selected from C_{1-6}alkyl, polyhaloC_{1-6}alkyl, halo, arylC_{1-6}alkyl, hydroxy, C_{1-6}alkyloxy, C_{1-6}alkyloxyC_{1-6}alkyl, amino, mono- or di(C_{1-6}alkyl)amino, C_{1-6}alkylthio, C_{1-6}alkyloxyC_{1-6}alkyl, C_{1-6}alkylthioC_{1-6}alkyl, aryl, pyridyl or pyrimidinyl;

R^6 is aryl[1] or Het;

R^7 is hydrogen, halo, C_{1-6}alkyl, aryl or Het;

R^8 is hydrogen or C_{1-6}alkyl;

R^9 is oxo; or

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

R^{11} is hydrogen or C_{1-6}alkyl;

aryl is a homocycle selected from phenyl, naphthyl, acenaphthyl or tetrahydronaphthyl, each being optionally substituted with 1, 2 or 3 substituents, each substituent being independently selected from 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, haloC_{1-6}alkyloxy, carboxyl, C_{1-6}alkyloxycarbonyl, aminocarbonyl, morpholinyl or mono- or di(C_{1-6}alkyl)aminocarbonyl;

aryl[1] is a homocycle selected from phenyl, naphthyl, acenaphthyl or tetrahydronaphthyl, each being optionally substituted with 1, 2 or 3 substituents, each substituent being independently selected from 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, C_{1-6}alkylthio, haloC_{1-6}alkyloxy, carboxyl, C_{1-6}alkyloxycarbonyl, aminocarbonyl, morpholinyl, Het or mono- or di(C_{1-6}alkyl)aminocarbonyl;

Het is a monocyclic heterocycle selected from *N*-phenoxypiperidinyl, piperidinyl, pyrrolyl, pyrazolyl, imidazolyl, furanyl, thienyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, pyridinyl, pyrimidinyl, pyrazinyl or pyridazinyl; or a bicyclic heterocycle selected from 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 being optionally substituted with 1, 2 or 3 substituents, each substituent independently selected from halo, hydroxy, C_{1-6}alkyl or C_{1-6}alkyloxy.

3. A compound according to claim 1 or 2 wherein R^1 is C_{2-6}alkenyl, C_{2-6}alkynyl, -C=N-OR^{11}, amino, mono or di(C_{1-6}alkyl)amino, aminoC_{1-6}alkyl, mono or di(C_{1-6}alkyl)aminoC_{1-6}alkyl, C_{1-6}alkylcarbonylaminoC_{1-6}alkyl, aminocarbonyl, mono or di(C_{1-6}alkyl)aminocarbonyl, $R^{5a}R^{4a}$Nalkyl, $R^{5a}R^{4a}$N-, $R^{5a}R^{4a}$N-C(=O)-.

4. A compound according to claim 3 wherein R^1 is C_{2-6}alkenyl, C_{2-6}alkynyl, -C=N-OR^{11}, $R^{5a}R^{4a}$Nalkyl, $R^{5a}R^{4a}$N- or $R^{5a}R^{4a}$N-C(=O)-.

5. A compound according to claim 4 wherein R^1 is C_{2-6}alkenyl or -C=N-OR^{11}.

6. A compound according to any one of the preceding claims wherein p is equal to 1.

7. A compound according to any one of the preceding claims wherein R^2 is C_{1-6}alkyloxy.

8. A compound according to claim 7 wherein R^2 is methyloxy.

9. A compound according to any one of the preceding claims wherein R^3 is arylC_{1-6}alkyl or aryl.

10. A compound according to any one of the preceding claims wherein q is equal to 1 or 3.

11. A compound according to any one of the preceding claims wherein R^4 and R^5 represent C_{1-6}alkyl.

12. A compound according to any one of claims 1 to 10 wherein R^4 and R^5 are taken together with the nitrogen atom to which they are attached and form piperidino.

13. A compound according to any one of the preceding claims wherein R^6 is phenyl optionally substituted with halo.

14. A compound according to any one of the preceding claims wherein R^7 is hydrogen.

15. A compound according to any one of the preceding claims wherein the compound is a compound of formula (Ia).

16. A compound according to claim 1 wherein the compound is a compound of formula (Ia) and wherein R^1 is C_{2-6}alkenyl, C_{2-6}alkynyl, -C=N-OR^{11}, amino, aminoC_{1-6}alkyl, mono or di(C_{1-6}alkyl)aminoC_{1-6}alkyl, C_{1-6}alkylcarbonylaminoC_{1-6}alkyl, mono or di(C_{1-6}alkyl)aminocarbonyl, arylcarbonyl, $R^{5a}R^{4a}$Nalkyl, $R^{5a}R^{4a}$N-, $R^{5a}R^{4a}$N-C(=O)-; R^2 is alkyloxy; R^3 is arylalkyl or aryl; R^4 and R^5 are C_{1-6}alkyl; or R^4 and R^5 together with the nitrogen atom to which they are attached form piperidino; R^6 is phenyl optionally substituted with halo; R^7 is hydrogen; R^{11} is hydrogen or C_{1-4}alkyl; q is 1 or 3; p is 1.

17. A compound according to any one of the preceding claims for use as a medicine.

18. A compound according to any one of claims 1 to 16 for use as a medicine for the treatment of a bacterial infection including a mycobacterial infection.

19. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and, as active ingredient, a therapeutically effective amount of a compound as defined in any one of claims 1 to 16.

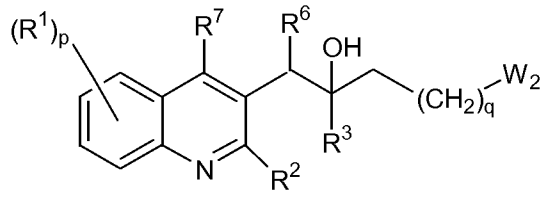
20. Use of a compound according to any one of claims 1 to 16 for the manufacture of a medicament for the treatment of a bacterial infection.

21. Use according to claim 20 wherein the bacterial infection is an infection with a gram-positive bacterium.

22. Use according to claim 21 wherein the gram-positive bacterium is Streptococcus pneumoniae.

23. Use according to claim 21 wherein the gram-positive bacterium is Staphylococcus aureus.

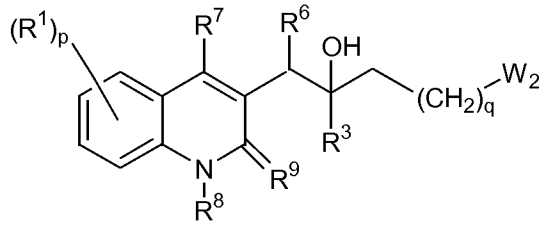
24. A compound of formula



(VIII-a)

wherein W_2 represents a suitable leaving group.

25. A compound of formula

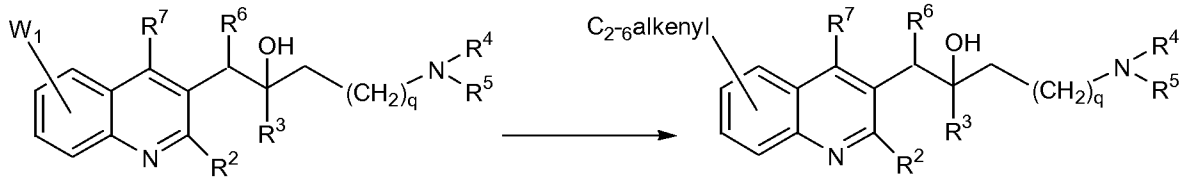


(VIII-b)

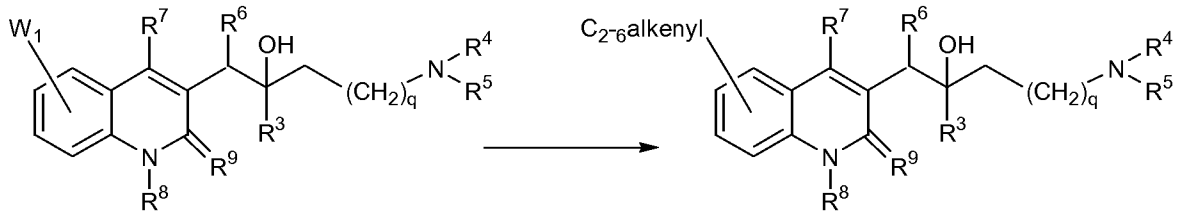
wherein W_2 represents a suitable leaving group.

26. A process to prepare a compound according to claim 1 characterized by

a) reacting an intermediate of formula (II-a) or (II-b) wherein W_1 represents a suitable leaving group, with tributyl(C_{2-6}alkenyl)tin in the presence of a suitable catalyst and a suitable solvent,



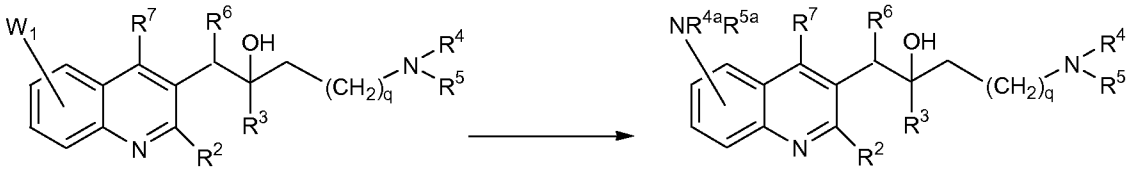
(II-a) (Ia-1)



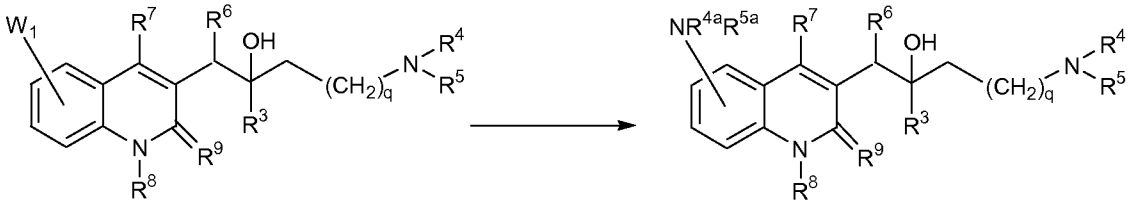
(II-b) (Ib-1)

wherein all variables are defined as in claim 1;

b) reacting an intermediate of formula (II-a) or (II-b) wherein W_1 represents a suitable leaving group with $R^{5a}R^{4a}NH$ in the presence of a suitable catalyst, a suitable ligand, a suitable base and a suitable solvent,



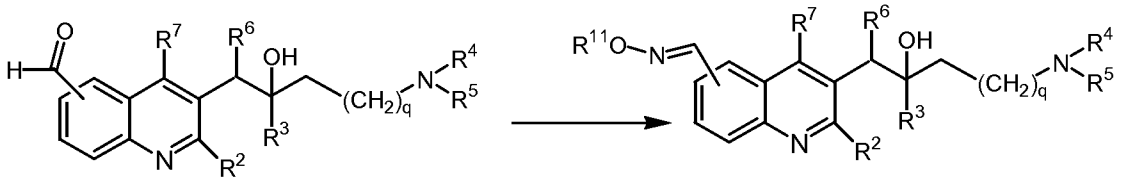
(II-a) (Ia-2)



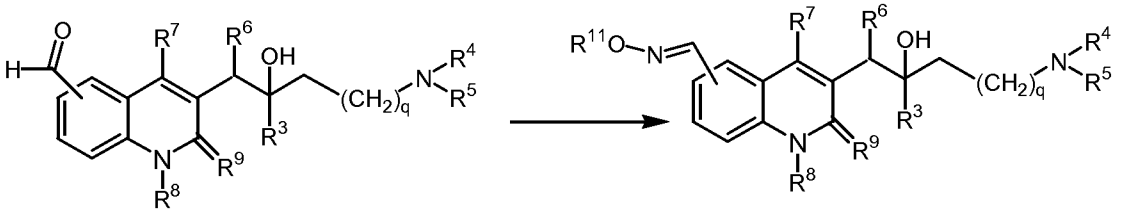
(II-b) (Ib-2)

wherein all variables are defined as in claim 1;

c) reacting an intermediate of formula (III-a) or (III-b) with hydroxylamine hydrochloride or C_{1-6}alkoxylamine hydrochloride in the presence of a suitable solvent,



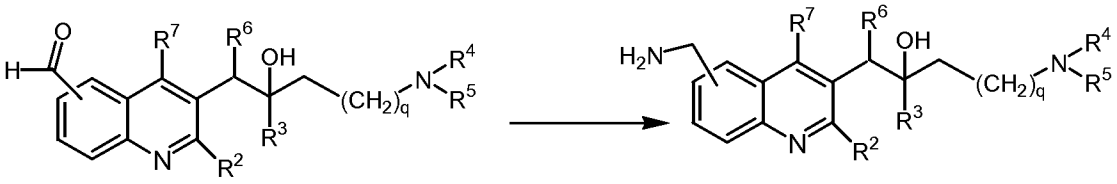
(III-a) (Ia-3)



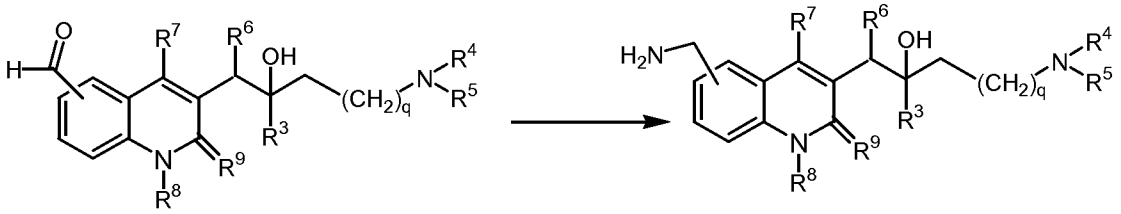
(III-b) (Ib-3)

wherein all variables are defined as in claim 1;

d) reducing an intermediate of formula (III-a) or (III-b) in the presence of H_2, a suitable catalyst, and a suitable solvent,



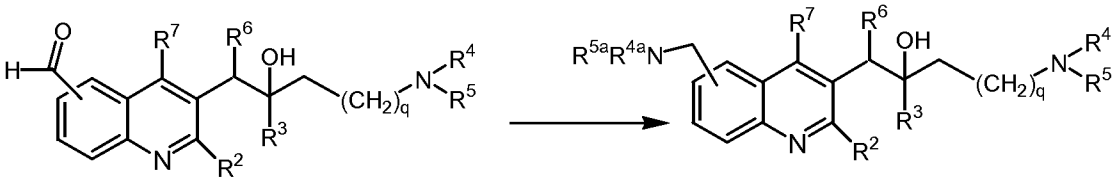
(III-a) (Ia-4)



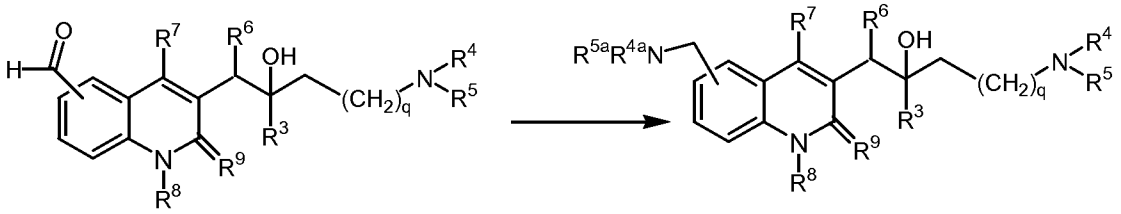
(III-b) (Ib-4)

wherein all variables are defined as in claim 1;

e) reacting an intermediate of formula (III-a) or (III-b) with a suitable reagent of formula $R^{5a}R^{4a}N$-H in the presence of a suitable reducing agent, a suitable solvent and a suitable acid,



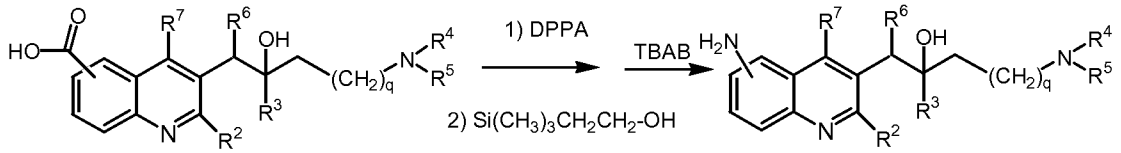
(III-a) (Ia-5)



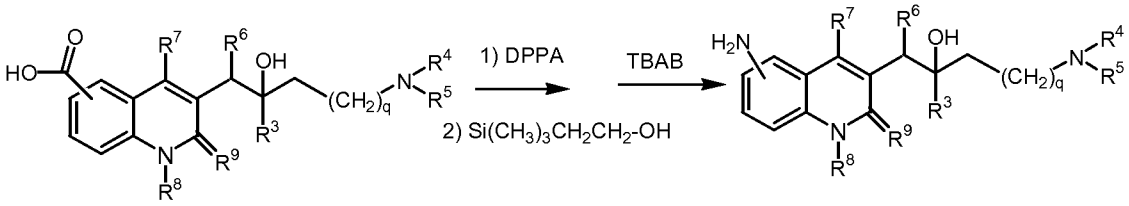
(III-b) (Ib-5)

wherein all variables are defined as in claim 1;

f) reacting an intermediate of formula (IV-a) or (IV-b) with diphenylphosphorylazide (DPPA) and a suitable base in a suitable solvent, followed by adding trimethylsilylethanol. The thus obtained product is further reacted with tetrabutylammonium bromide (TBAB) in a suitable solvent,



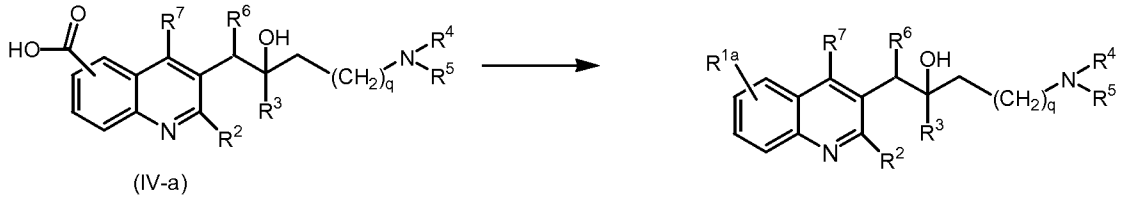
(IV-a) (Ia-6)



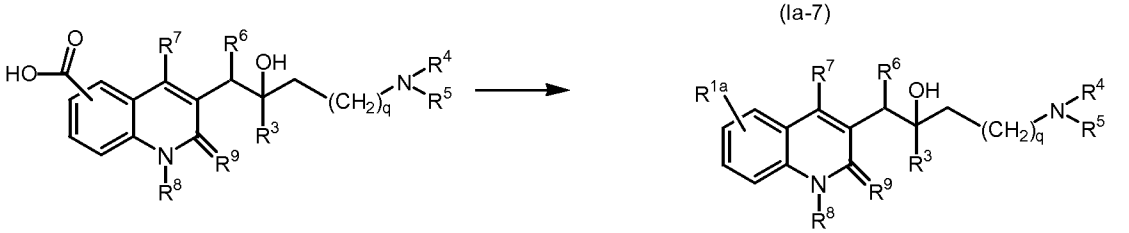
(IV-b) (Ib-6)

wherein all variables are defined as in claim 1;

g) reacting an intermediate of formula (IV-a) or (IV-b) with a suitable amine, hydroxybenzotriazole, 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide, a suitable base and a suitable solvent,



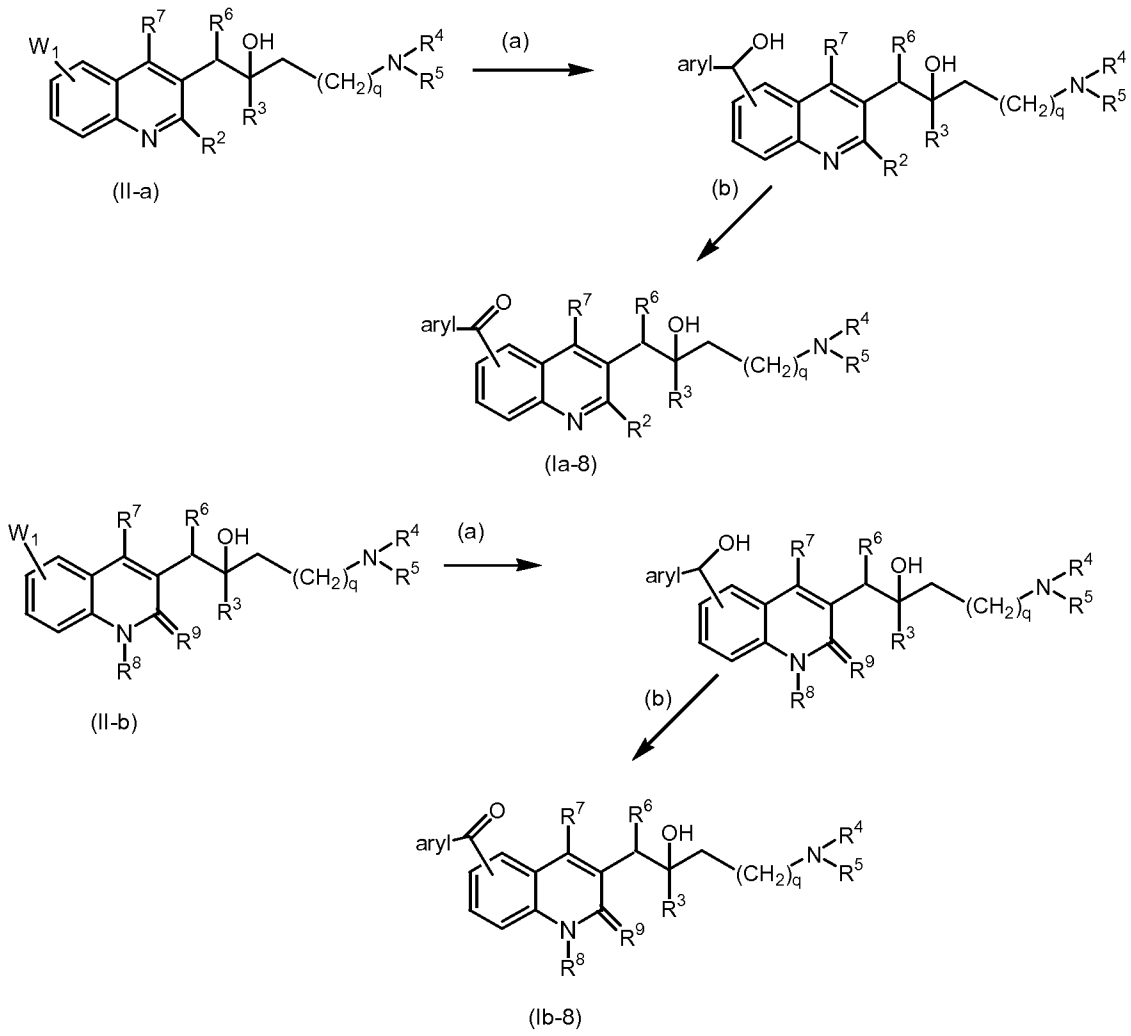
(IV-a) (Ia-7)



(IV-b) (Ib-7)

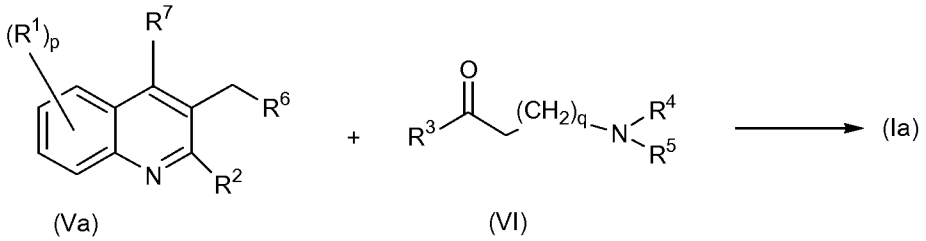
wherein R^{1a} represents aminocarbonyl, mono or di(alkyl)aminocarbonyl or $R^{5a}R^{4a}N$-C(=O)-, and wherein all other variables are defined as in claim 1;

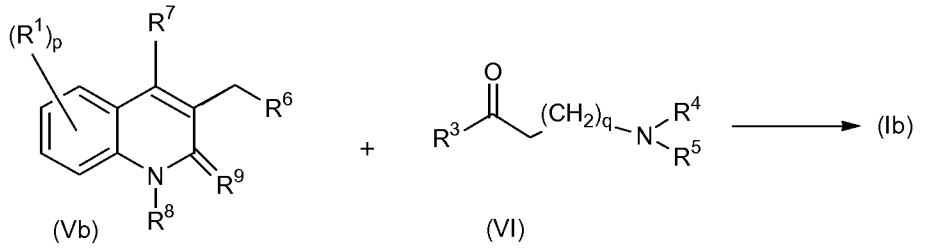
h) reacting in a first step (a) an intermediate of formula (II-a) or (II-b) with a suitable arylaldehyde in the presence of *n*BuLi and a suitable solvent, followed by oxidizing the product obtained in step (a) with a suitable oxidans in the presence of a suitable solvent,



wherein all variables are defined as in claim 1;

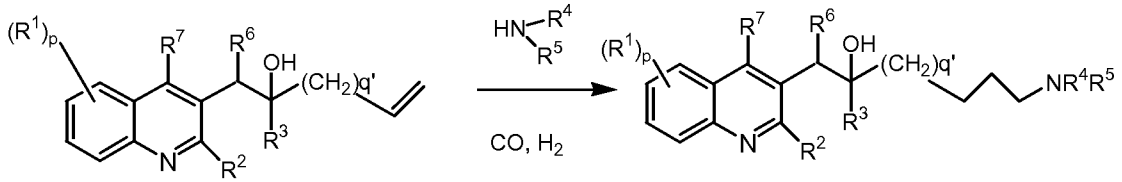
i) reacting an intermediate of formula (Va) or (Vb) with an intermediate of formula (VI) in the presence of *n*BuLi in a mixture of a suitable base and a suitable solvent,

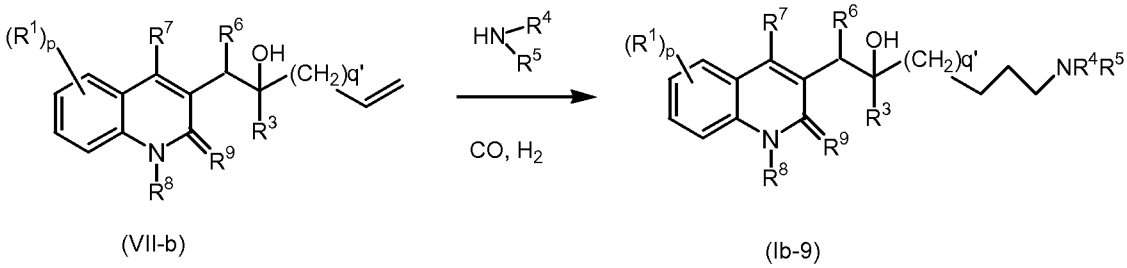




wherein all variables are defined as in claim 1;

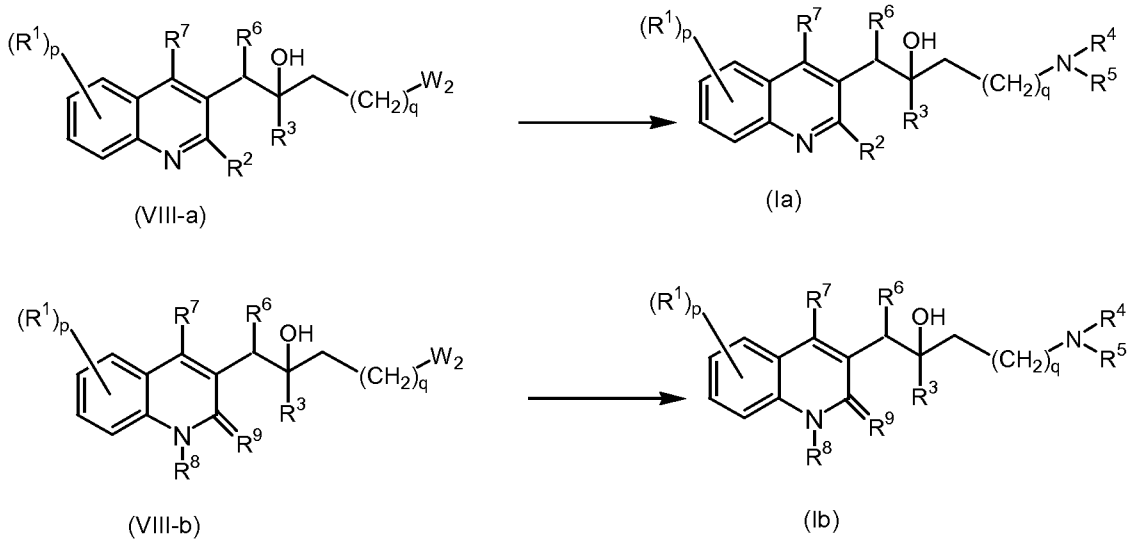
j) reacting an intermediate of formula (VII-a) or (VII-b) wherein q' is 0, 1 or 2, with a primary or secondary amine HNR^4R^5 in the presence of a suitable catalyst, optionally in the presence of a second catalyst (for the reduction), a suitable ligand and a suitable solvent, in the presence of CO and H_2 (under pressure)





wherein all variables are defined as in claim 1.

k) reacting an intermediate of formula (VIII-a) or (VIII-b) wherein W_2 represents a suitable leaving group, with a suitable primary or secondary amine HNR^4R^5 optionally in the presence of a suitable solvent



wherein all variables are defined as in claim 1.

or, if desired, converting compounds of formula (Ia) or (Ib) into each other following art-known transformations, and further, if desired, converting the compounds of formula (Ia) or (Ib), into a therapeutically active non-toxic acid addition salt by treatment with an acid, or into a therapeutically active non-toxic base addition salt by treatment with a base, or conversely, converting the acid addition salt form into the free base by treatment with alkali, or converting the base addition salt into the free acid by treatment with acid; and, if desired, preparing stereochemically isomeric forms, quaternary amines or *N*-oxide forms thereof.

27. A combination of (a) a compound according to any one of claims 1 to 16, and (b) one or more other antibacterial agents.

28. A product containing (a) a compound according to any one of claims 1 to 16, and (b) one or more other antibacterial agents, as a combined preparation for simultaneous, separate or sequential use in the treatment of a bacterial infection.