QUINOLINE DERIVATIVES AS ANTIBACTERIAL AGENTS

The present invention relates to the use of quinoline derivatives for the manufacture of a medicament for the treatment of a bacterial infection.

Resistance to first-line antibiotic agents is an emerging problem. 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 for the treatment of infections caused by resistant strains.

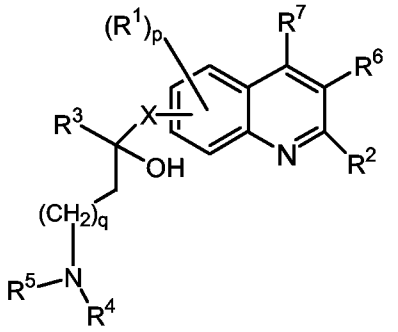
Substituted quinolines were already disclosed in US 5,965,572 (The United States of America) for treating antibiotic resistant infections and in WO 00/34265 to inhibit the growth of bacterial microorganisms.

WO 2004/011436, WO2005/070924, WO2005/070430 and WO2005/075428 disclose substituted quinoline derivatives having activity against Mycobacteria, in particular against *Mycobacterium tuberculosis*. One particular compound of these substituted quinoline derivatives is described in Science (2005), 307, 223-227.

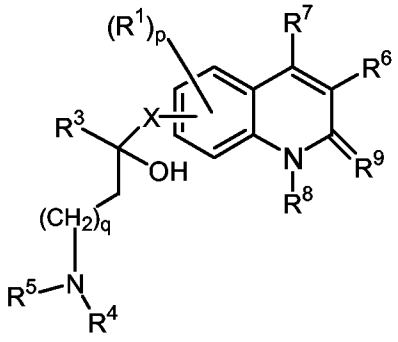
None of these publications disclose the use of the present substituted quinoline derivatives according to this invention.

SUMMARY OF THE INVENTION

The present invention relates to the use of a compound for the manufacture of a medicament for the treatment of a bacterial infection, said compound being a compound of Formula (Ia) and (Ib)



(Ia)

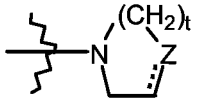
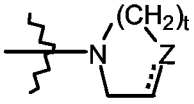


(Ib)

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

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

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

R^2 is hydrogen; alkyl; hydroxy; mercapto; alkyloxy optionally substituted with amino or mono or di(alkyl)amino or a radical of formula  wherein Z is CH_2, CH-R^{10}, O, S, N-R^{10} and t is an integer equal to 1 or 2 and the dotted line represents an optional bond; alkyloxyalkyloxy; alkylthio; mono or di(alkyl)amino wherein alkyl may optionally be substituted with one or two substituents each independently be selected from alkyloxy or Ar or Het or morpholinyl or 2-oxopyrrolidinyl; Ar; Het or a radical of formula  wherein Z is CH_2, CH-R^{10}, O, S, N-R^{10} ; t is an integer equal to 1 or 2; and the dotted line represents an optional bond;

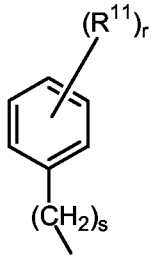
R^3 is alkyl, Ar, Ar-alkyl, Het or Het-alkyl;

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

X is a direct bond or CH_2;

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, pyrazolidinyl, 2-imidazolinyl, 2-pyrazolinyl, imidazolyl, pyrazolyl, triazolyl, piperidinyl, pyridinyl, piperazinyl, imidazolidinyl, pyridazinyl, pyrimidinyl, pyrazinyl, triazinyl, morpholinyl and thiomorpholinyl, each of said rings optionally being substituted with alkyl, halo, haloalkyl, hydroxy, alkyloxy, amino, mono- or dialkylamino, alkylthio, alkyloxyalkyl, alkylthioalkyl or pyrimidinyl;

R^6 is hydrogen or a radical of formula  wherein s is an integer equal to zero, 1, 2, 3 or 4; r is an integer equal to 1, 2, 3, 4 or 5 ; and R^{11} is hydrogen, halo, haloalkyl, hydroxy, Ar, alkyl, alkyloxy, alkylthio, alkyloxyalkyl, alkylthioalkyl, Ar-alkyl or di(Ar)alkyl ; or two vicinal R^{11} radicals may be taken together to form together with the phenyl ring to which they are attached a naphthyl;

R^7 is hydrogen, alkyl, Ar or Het;

R^8 is hydrogen or alkyl ;

R^9 is oxo ; or

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

R^{10} is hydrogen, alkyl, hydroxyl, aminocarbonyl, mono-or di(alkyl)aminocarbonyl, Ar, Het, alkyl substituted with one or two Het, alkyl substituted with one or two Ar, Het-C(=O)-, Ar-C(=O)-;

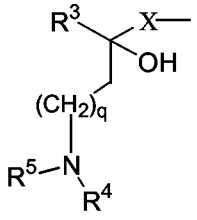
alkyl is a straight or branched saturated hydrocarbon radical having from 1 to 6 carbon atoms ; or is a cyclic saturated hydrocarbon radical having from 3 to 6 carbon atoms ; or is a cyclic saturated hydrocarbon radical having from 3 to 6 carbon atoms attached to a straight or branched saturated hydrocarbon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

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

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

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

haloalkyl is a straight or branched saturated hydrocarbon radical having from 1 to 6 carbon atoms or a cyclic saturated hydrocarbon radical having from 3 to 6 carbon atoms 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;

provided that when R^7 is hydrogen then the  radical may also be placed in position 4 of the quinoline ring; and
provided that the bacterial infection is other than a Mycobacterial infection.

The present invention also relates to a method of treating a bacterial infection provided that the bacterial infection is other than a Mycobacterial infection, in a mammal, in particular a warm-blooded mammal, more in particular a human, comprising administering an effective amount of a compound of the invention to the mammal.

The compounds according to Formula (Ia) and (Ib) are interrelated in that e.g. a compound according to Formula (Ib), with R^8 equal to oxo is the tautomeric equivalent of a compound according to Formula (Ia) with R^2 equal to hydroxy (keto-enol tautomerism).

DETAILED DESCRIPTION

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

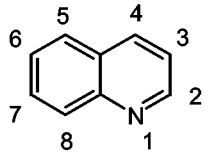
In the framework of this application, Ar is a homocycle selected from the group of phenyl, naphthyl, acenaphthyl, tetrahydronaphthyl, each optionally substituted with 1, 2 or 3 substituents, each substituent independently selected from the group of hydroxy,

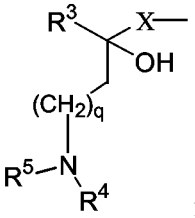
halo, cyano, nitro, amino, mono- or dialkylamino, alkyl, haloalkyl, alkyloxy, haloalkyloxy, carboxyl, alkyloxycarbonyl, aminocarbonyl, morpholinyl and mono- or dialkylaminocarbonyl. Preferably, Ar is naphthyl or phenyl, each optionally substituted with 1 or 2 halo substituents.

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

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 and preferably, haloalkyl is polyhaloC_{1-6}alkyl which is defined as mono- or polyhalosubstituted C_{1-6}alkyl, for example, methyl with one or more fluoro atoms, for example, difluoromethyl or trifluoromethyl, 1,1-difluoro-ethyl and the like. In case more than one halo atom is attached to an alkyl group within the definition of haloalkyl or polyhaloC_{1-6}alkyl, they may be the same or different.

In the framework of this application, the quinoline ring of the compounds of Formula (Ia) or (Ib) is numbered as follows:





The radical may be placed on any available position of the quinoline moiety.

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

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

The pharmaceutically acceptable acid addition salts are defined to comprise the therapeutically active non-toxic acid addition salt forms which the compounds according to either Formula (Ia) or (Ib) are able to form. Said acid addition salts can be obtained by treating the base form of the compounds according to either Formula (Ia) or (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 according to either Formula (Ia) or (Ib) containing acidic protons may also be converted into their therapeutically active non-toxic base addition salt forms by treatment with appropriate organic and inorganic bases. Appropriate base salts forms comprise, for example, the ammonium salts, the alkaline and earth alkaline metal salts, in particular lithium, sodium, potassium, magnesium and calcium salts, salts with

organic bases, e.g. the benzathine, *N*-methyl-D-glucamine, hybramine salts, and salts with amino acids, for example arginine and lysine.

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

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

The term "quaternary amine" as used hereinbefore defines the quaternary ammonium salts which the compounds of formula (I) are able to form by reaction between a basic nitrogen of a compound of formula (I) and an appropriate quaternizing agent, such as, for example, an optionally substituted alkylhalide, arylalkylhalide, alkylcarbonylhalide, Arcarbonylhalide, Hetalkylhalide 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 Ar. Preferably, the quaternizing agent is alkylhalide. Other reactants with good leaving groups may also be used, such as alkyl trifluoromethanesulfonates, alkyl methanesulfonates, and alkyl p-toluenesulfonates. A quaternary amine has a positively charged nitrogen. Pharmaceutically acceptable counterions include chloro, bromo, iodo, trifluoroacetate, acetate, triflate, sulfate, sulfonate. Preferably, the counterion is iodo. The counterion of choice can be introduced using ion exchange resins.

Compounds of either Formula (Ia) or (Ib) and some of the intermediate compounds invariably have at least one stereogenic center in their structure which may lead to at least 2 stereochemically different structures.

The term "stereochemically isomeric forms" as used herein defines all possible isomeric forms which the compounds of either Formula (Ia) or (Ib) may possess. Unless otherwise mentioned or indicated, the chemical designation of compounds denotes the mixture of all possible stereochemically isomeric forms, said mixtures containing all diastereomers and enantiomers of the basic molecular structure . More in

particular, stereogenic centers may have the R- or S-configuration; substituents on bivalent cyclic (partially) saturated radicals may have either the cis- or trans-configuration. Stereochemically isomeric forms of the compounds of either Formula (Ia) or (Ib) are obviously intended to be embraced within the scope of this invention.

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

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

The compounds of either Formula (Ia) and (Ib) may be synthesized in the form of racemic mixtures of enantiomers which can be separated from one another following art-known resolution procedures. The racemic compounds of either Formula (Ia) and (Ib) may be converted into the corresponding diastereomeric salt forms by reaction with a suitable chiral acid. Said diastereomeric salt forms are subsequently separated, for example, by selective or fractional crystallization and the enantiomers are liberated therefrom by alkali. An alternative manner of separating the enantiomeric forms of the compounds of either Formula (Ia) and (Ib) involves liquid chromatography using a

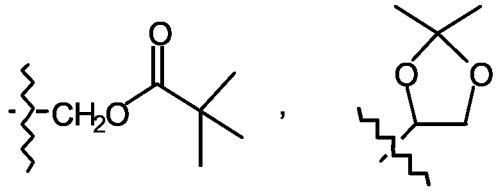
chiral stationary phase. Said pure stereochemically isomeric forms may also be derived from the corresponding pure stereochemically isomeric forms of the appropriate starting materials, provided that the reaction occurs stereospecifically. Preferably if a specific stereoisomer is desired, said compound will be synthesized by stereospecific methods of preparation. These methods will advantageously employ enantiomerically pure starting materials.

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

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

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

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



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

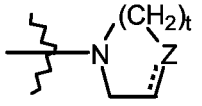
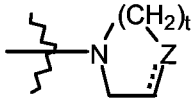
Compounds according to the invention having an amino group may be derivatised with a ketone or an aldehyde such as formaldehyde to form a Mannich base. This base will hydrolyze with first order kinetics in aqueous solution.

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

An interesting embodiment of the present invention relates to those compounds of Formula (Ia) or (Ib), the pharmaceutically acceptable acid or base addition salts thereof, the quaternary amines thereof, the stereochemically isomeric forms thereof, the tautomeric forms thereof and the *N*-oxide forms thereof, wherein

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

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

R^2 is hydrogen; alkyl; hydroxy; mercapto; alkyloxy optionally substituted with amino or mono or di(alkyl)amino or a radical of formula  wherein Z is CH_2, CH-R^{10}, O, S, N-R^{10} and t is an integer equal to1 or 2 and the dotted line represents an optional bond; alkyloxyalkyloxy; alkylthio; mono or di(alkyl)amino wherein alkyl may optionally be substituted with one or two substituents each independently be selected from alkyloxy or Ar or Het or morpholinyl or 2-oxopyrrolidinyl; Het or a radical of formula  wherein Z is CH_2, CH-R^{10}, O, S, N-R^{10} ; t is an integer equal to 1 or 2; and the dotted line represents an optional bond;

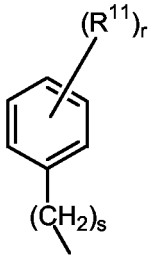
R^3 is alkyl, Ar, Ar-alkyl, Het or Het-alkyl;

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

X is a direct bond;

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, pyrazolidinyl, 2-imidazolinyl, 2-pyrazolinyl, imidazolyl, pyrazolyl, triazolyl, piperidinyl, pyridinyl, piperazinyl, imidazolidinyl, pyridazinyl, pyrimidinyl, pyrazinyl, triazinyl, morpholinyl and thiomorpholinyl, each of said rings optionally being substituted with alkyl, halo, haloalkyl, hydroxy, alkyloxy, amino, mono- or dialkylamino, alkylthio, alkyloxyalkyl, alkylthioalkyl and pyrimidinyl ;

R^6 is a radical of formula  wherein s is an integer equal to zero, 1, 2, 3 or 4; r is an integer equal to 1, 2, 3, 4 or 5 ; and R^{11} is hydrogen, halo, haloalkyl, hydroxy, Ar, alkyl, alkyloxy, alkylthio, alkyloxyalkyl, alkylthioalkyl, Ar-alkyl or di(Ar)alkyl ; or two vicinal R^{11} radicals may be taken together to form together with the phenyl ring to which they are attached a naphthyl;

R^7 is hydrogen, alkyl, Ar or Het ;

R^8 is hydrogen or alkyl ;

R^9 is oxo ; or

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

R^{10} is hydrogen, alkyl, aminocarbonyl, mono-or di(alkyl)aminocarbonyl, Ar, Het, alkyl substituted with one or two Het, alkyl substituted with one or two Ar, Het-C(=O)- ;

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 hydroxy, alkyloxy or oxo;

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

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

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

haloalkyl is a straight or branched saturated hydrocarbon radical having from 1 to 6 carbon atoms or a cyclic saturated hydrocarbon radical having from 3 to 6 carbon atoms 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, the invention relates to a compound of Formula (Ia) or (Ib) or any subgroup thereof as mentioned hereinbefore as interesting embodiment wherein R^{11} is hydrogen, halo, haloalkyl, hydroxy, Ar, alkyl, alkyloxy, alkylthio, alkyloxyalkyl, alkylthioalkyl, Ar-alkyl or di(Ar)alkyl.

Preferably, the invention relates to a compound of Formula (Ia) or (Ib) or any subgroup thereof as mentioned hereinbefore as interesting embodiment wherein when R^6 is other than hydrogen then R^7 is hydrogen and when R^7 is other than hydrogen then R^6 is hydrogen.

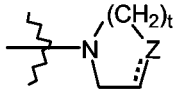
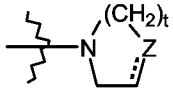
Preferably, the invention relates to a compound of Formula (Ia) or (Ib) or any subgroup thereof as mentioned hereinbefore as interesting embodiment wherein R^6 is other than hydrogen and R^7 is hydrogen.

Preferably, the invention relates to a compound of Formula (Ia) or (Ib) or any subgroup thereof as mentioned hereinbefore as interesting embodiment wherein R^7 is other than hydrogen and R^6 is hydrogen.

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

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

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

R^2 is hydrogen; alkyl; hydroxy; alkyloxy optionally substituted with amino or mono or di(alkyl)amino or a radical of formula  wherein Z is CH_2, CH-R^{10}, O, S, N-R^{10} and t is an integer equal to 1 or 2 and the dotted line represents an optional bond; alkyloxyalkyloxy; alkylthio; mono or di(alkyl)amino; Ar; Het or a radical of formula  wherein Z is CH_2, CH-R^{10}, O, S, N-R^{10} ; t is an integer equal to 1 or 2; and the dotted line represents an optional bond;

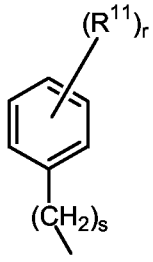
R^3 is alkyl, Ar, Ar-alkyl or Het ;

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

X is a direct bond or CH_2;

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

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

R^6 is hydrogen or a radical of formula  wherein s is an integer equal zero, 1, 2, 3 or 4; r is an integer equal to 1, 2, 3, 4 or 5 ; and R^{11} is hydrogen, halo, or alkyl; or two vicinal R^{11} radicals may be taken together to form together with the phenyl ring to which they are attached a naphthyl; preferably R^{11} is hydrogen, halo, or alkyl;

r is an integer equal to 1 ;

R^7 is hydrogen or Ar;

R^8 is hydrogen or alkyl ;

R^9 is oxo ; or

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

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 hydroxy;

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

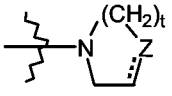
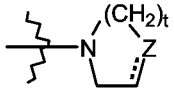
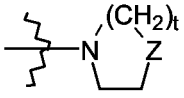
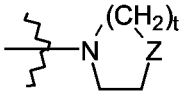
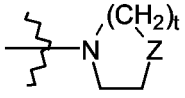
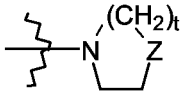
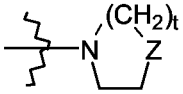
Het is a monocyclic heterocycle selected from the group of N-phenoxypiperidinyl, pyrrolyl, pyrazolyl, imidazolyl, furanyl, thienyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, triazolyl, pyridinyl, pyrimidinyl, pyrazinyl and pyridazinyl; or a bicyclic heterocycle selected from the group of quinolinyl,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

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

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, the invention relates to a compound of Formula (Ia) or (Ib) or any subgroup thereof as mentioned hereinbefore as interesting embodiment wherein R^1 is hydrogen, halo, Ar, Het, alkyl or alkyloxy. More preferably, R^1 is hydrogen, halo, alkyl or Het. Even more in particular R^1 is hydrogen, halo or Het. Most preferably, R^1 is halo, in particular bromo.

Preferably, the invention 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.

Preferably, the invention relates to a compound of Formula (Ia) or (Ib) or any subgroup thereof as mentioned hereinbefore as interesting embodiment wherein R^2 is hydrogen; alkyl; alkyloxy optionally substituted with amino or mono or di(alkyl)amino or a radical of formula  wherein Z is CH_2, CH-R^{10}, O, S, N-R^{10} and t is an integer equal to 1 or 2 and the dotted line represents an optional bond; mono or di(alkyl)amino wherein alkyl may optionally be substituted with one or two substituents each independently be selected from alkyloxy or Ar; Ar; Het or a radical of formula  wherein Z is CH_2, CH-R^{10}, O, S, N-R^{10} ; t is an integer equal to 1 or 2; and the dotted line represents an optional bond. More preferably, R^2 is alkyloxy; Het; Ar; alkyl; mono or di(alkyl)amino wherein alkyl may optionally be substituted with one or two substituents each independently be selected from alkyloxy or Ar; a radical of formula  wherein Z is CH_2, CH-R^{10}, O, N-R^{10} ; t is an integer equal to 1 or 2; alkyloxy substituted with amino or mono or di(alkyl)amino or a radical of formula  wherein Z is CH_2, CH-R^{10}, O, N-R^{10} and t is an integer equal to 1 or 2. Even more preferably, R^2 is alkyloxy; Het; Ar; mono or di(alkyl)amino wherein alkyl may optionally be substituted with one or two Ar substituents; a radical of formula  wherein Z is N-R^{10} ; t is an integer equal to 2; alkyloxy substituted with amino or mono or di(alkyl)amino or a radical of formula  wherein Z is CH_2 and t is an integer equal to 2. Most preferably, R^2 is alkyloxy, e.g. methyloxy; Het or a radical of formula  wherein Z is CH_2, CH-R^{10}, O, N-R^{10} and t is 1 or 2; in particular R^2 is alkyloxy.

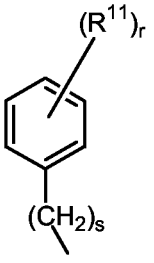
Preferably, the invention relates to a compound of Formula (Ia) or (Ib) or any subgroup thereof as mentioned hereinbefore as interesting embodiment wherein R^3 is naphthyl, phenyl or Het, each optionally substituted with 1 or 2 substituents, that substituent preferably being a halo or haloalkyl, most preferably being a halo. More preferably, R^3

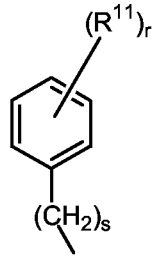
is naphthyl, phenyl, 3,5-dihalophenyl, 1,6-dihalophenyl, thienyl, furanyl, benzofuranyl, pyridyl. Even more preferably R^3 is naphthyl, phenyl, 3,5-dihalophenyl, thienyl, furanyl or benzofuranyl. Most preferably, R^3 is optionally substituted phenyl, e.g. 3,5-dihalophenyl, or naphthyl.

Preferably, the invention relates to a compound of Formula (Ia) or (Ib) or any subgroup thereof as mentioned hereinbefore as interesting embodiment wherein q is equal to zero, 1 or 2. More preferably, q is equal to 1.

Preferably, the invention 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 are hydrogen or alkyl, more preferably hydrogen, methyl or ethyl, most preferably methyl.

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

Preferably, the invention relates to a compound of Formula (Ia) or (Ib) or any subgroup thereof as mentioned hereinbefore as interesting embodiment wherein R^6 is hydrogen or a radical of formula  wherein s is an integer equal to zero, 1 or 2, preferably zero or 1; r is an integer equal to 1 or 2, preferably 1; and R^{11} is hydrogen, halo, or alkyl, preferably hydrogen or alkyl. More preferably, R^6 is a radical of formula



. Most preferably, R^6 is benzyl or phenyl. Preferably r is 1 and R^{11} is hydrogen.

Preferably, the invention relates to a compound of Formula (Ia) or (Ib) or any subgroup thereof as mentioned hereinbefore as interesting embodiment wherein R^7 is hydrogen, alkyl or Ar. More preferably hydrogen or Ar, in particular hydrogen or phenyl. Most preferably R^7 is hydrogen.

For compounds according to Formula (Ib) only, preferably, the invention relates to a compound of Formula (Ib) or any subgroup thereof as mentioned hereinbefore as interesting embodiment wherein R^8 is alkyl or hydrogen, preferably hydrogen, and R^9 is oxygen.

Preferably, the invention relates to a compound of Formula (Ia) or (Ib) or any subgroup thereof as mentioned hereinbefore as interesting embodiment wherein R^{10} is hydrogen, alkyl, hydroxyl, alkyl substituted with one or two Het, alkyl substituted with one or two Ar, Het-C(=O)-. More preferably, R^{10} is alkyl or Ar. Most preferably R^{10} is hydroxyl, Het, alkyl substituted with one Het, alkyl substituted with one Ar.

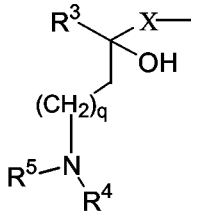
Preferably, the compounds of the present invention or any subgroup thereof as mentioned hereinbefore as interesting embodiment are compounds according to Formula (Ia), the pharmaceutically acceptable acid or base addition salts thereof, the quaternary amines thereof, the stereochemically isomeric forms thereof, the tautomeric forms thereof or the *N*-oxide forms thereof.

Preferably, the invention relates to a compound of Formula (Ia) or (Ib) or any subgroup thereof as mentioned hereinbefore as interesting embodiment wherein X is a direct bond.

Preferably, the invention relates to a compound of Formula (Ia) or (Ib) or any subgroup thereof as mentioned hereinbefore as interesting embodiment wherein X is CH_2.

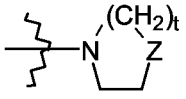
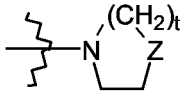
Preferably, the invention relates to a compound of Formula (Ia) or (Ib) or any subgroup thereof as mentioned hereinbefore as interesting embodiment wherein R^3 is other than unsubstituted phenyl when R^2 is Het.

Preferably, the invention relates to a compound of Formula (Ia) or (Ib) or any subgroup thereof as mentioned hereinbefore as interesting embodiment wherein the

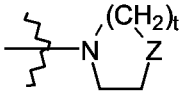
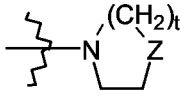


radical is placed in position 4, 5 or 8, in particular 8.

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

Also an interesting group of compounds are those compounds according to Formula (Ia) or (Ib), preferably (Ia), the pharmaceutically acceptable acid or base addition salts thereof, the quaternary amines thereof, the stereochemically isomeric forms thereof, the tautomeric forms thereof or the *N*-oxide forms thereof, wherein R^1 is hydrogen, halo, alkyl or Het, wherein Het is preferably pyridyl; R^2 is alkyl, alkyloxy optionally substituted with mono or di(alkyl)amino or a radical of formula  wherein Z is CH_2, CH-R^{10}, O, N-R^{10}, preferably Z is CH_2, t is an integer equal to 1 or 2, and R^{10} is hydrogen, alkyl, hydroxyl, alkyl substituted with one or two Het, alkyl substituted with one or two Ar, Het-C(=O)-, preferably R^{10} is hydrogen; Ar; Het; a radical of formula  wherein Z is CH_2, CH-R^{10}, O, N-R^{10} , t is an integer equal to 1 or 2, wherein R^{10} is hydrogen, alkyl, hydroxyl, alkyl substituted with one or two Het, alkyl substituted with one or two Ar, Het-C(=O)-; R^3 is Ar, preferably phenyl or

naphthyl, or Het, preferably thienyl, furanyl, pyridyl, benzofuranyl ,each of said Ar or Het optionally substituted with 1 or 2 substituents that substituent preferably being a halo; R^4 and R^5 are each alkyl, preferably methyl; R^6 is hydrogen, phenyl, benzyl or 4-methylbenzyl; R^7 is hydrogen or phenyl; R^8 is hydrogen; R^9 is oxo.

In particular, compounds according to Formula (Ia) or (Ib), preferably (Ia), the pharmaceutically acceptable acid or base addition salts thereof, the quaternary amines thereof, the stereochemically isomeric forms thereof, the tautomeric forms thereof or the *N*-oxide forms thereof, wherein R^1 is hydrogen, halo or Het, wherein Het is preferably pyridyl; R^2 is alkyloxy optionally substituted with mono or di(alkyl)amino or a radical of formula  wherein Z is CH_2, t is an integer equal to 2; mono or di(alkyl)amino wherein alkyl is optionally substituted with one or two Ar; a radical of formula  wherein Z is N-R^{10}, t is an integer equal to 2; or Het; R^3 is Ar, preferably phenyl or naphthyl, or Het, preferably thienyl, furanyl, or benzofuranyl ,each of said Ar or Het optionally substituted with 1 or 2 substituents that substituent preferably being a halo; R^4 and R^5 are each alkyl, preferably methyl; R^6 is hydrogen, phenyl or benzyl, in particular phenyl or benzyl; R^7 is hydrogen.

An 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 an infection with a gram-positive and/or a gram-negative bacterium.

An 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 an infection with a gram-positive bacterium.

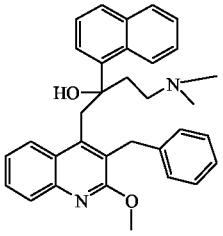
An interesting embodiment is the use of the compounds of Formula (Ia) or (Ib) or any subgroup thereof as mentioned hereinbefore as interesting embodiment for the manufacture of a medicament for the treatment of an infection with a gram-negative bacterium.

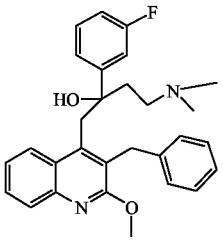
An interesting embodiment is the use of a compound of Formula (Ia) or (Ib) or any subgroup thereof as mentioned hereinbefore as interesting embodiment for the

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.

Preferred compounds of the present invention are compounds 64, 8, 46, 12, 10, 24, 9, 13, 22, 33, 20, 65, 19, 59, 54, 26, 66, 67, 49, 48, 70, 71, 21, 6, 45, 2, 5, 4, 1, 3 as described hereinafter in the experimental part, a pharmaceutically acceptable acid or base addition salt thereof, a quaternary amine thereof, a stereochemically isomeric form thereof, a tautomeric form thereof or a *N*-oxide form thereof.

The present invention also relates to the following compounds :





,

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

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, 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. Also intermediates of formula (II) wherein W_1 represents halo, show antibacterial activity.

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 *Staphylococcus aureus*, including resistant *Staphylococcus aureus* such as for example methicillin resistant *Staphylococcus aureus* (MRSA), and *Streptococcus pneumoniae*.

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. 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.

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.
Whenever used hereinbefore or hereinafter, that the bacterial infection is other than a Mycobacterial infection it is meant that the bacterial infection is other than an infection with one or more Mycobacteria strains.

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

The compound of the present invention may be administered in a pharmaceutically acceptable form optionally in a pharmaceutically acceptable carrier. The compounds and compositions comprising the compounds can be administered by routes such as topically, locally or systemically. Systemic application includes any method of introducing the compound into the tissues of the body, e.g., intrathecal, epidural, intramuscular, transdermal, intravenous, intraperitoneal, subcutaneous, sublingual, rectal, and oral administration. The specific dosage of antibacterial to be administered, as well as the duration of treatment, may be adjusted as needed.

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, gynecological 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.

Given the fact that the compounds of Formula (Ia) or (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 of Formula (Ia) or (Ib), and (b) one or more other antibacterial agents provided that the one or more other antibacterial agents are other than antimycobacterial agents.

The present invention also relates to a combination of (a) a compound of Formula (Ia) or (Ib), and (b) one or more other antibacterial agents provided that the one or more other antibacterial agents are other than antimycobacterial agents, for use as a medicine.

A pharmaceutical composition comprising a pharmaceutically acceptable carrier and, as active ingredient, a therapeutically effective amount of (a) a compound of Formula (Ia) or (Ib), and (b) one or more other antibacterial agents provided that the one or more other antibacterial agents are other than antimycobacterial agents, is also comprised by the present invention.

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

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

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

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

The weight to weight ratio's of the compound of Formula (Ia) or (Ib) 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 of Formula (Ia) or (Ib) 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.

The compounds of Formula (Ia) or (Ib) 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 of Formula (Ia) or (Ib), and (b) one or more other antibacterial agents provided that the one or more other antibacterial agents are other than antimycobacterial agents, as a combined preparation for simultaneous, separate or sequential use in the treatment of a bacterial infection.

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 bacterial disease indicated.

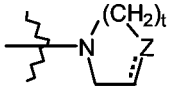
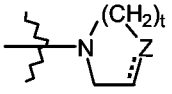
The other antibacterial agents which may be combined with the compounds of formula (I) are antibacterial agents known in the art. The other antibacterial agents comprise antibiotics of the β-lactam group such as natural penicillins, semisynthetic penicillins, natural cephalosporins, semisynthetic cephalosporins, 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,

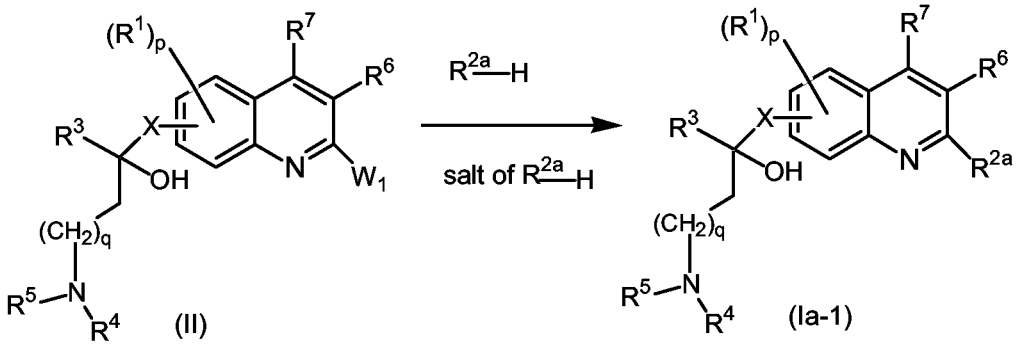
cefmetazole, cefotetan, latamoxef, clavulanic acid, imipenem, aztreonam, tetracycline, chlortetracycline hydrochloride, demethylchlortetracycline, oxytetracycline, methacycline, doxycycline, rolitetracycline, minocycline, daunorubicin hydrochloride, doxorubicin, aclarubicin, kanamycin sulfate, bekanamycin, 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.

GENERAL PREPARATION

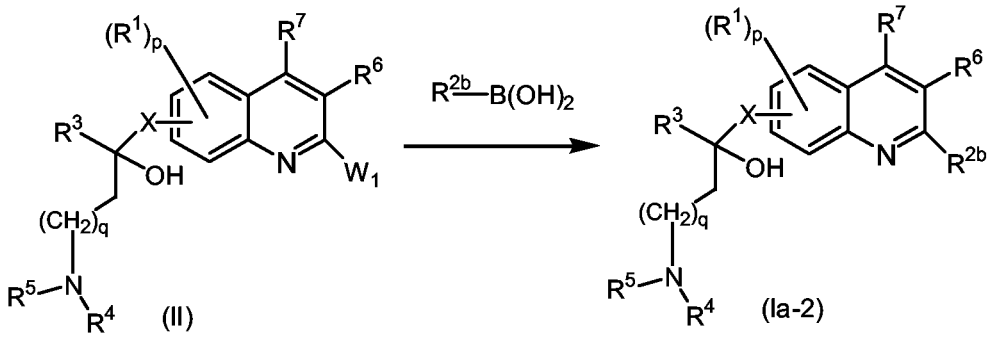
The compounds according to the invention can generally be prepared by a succession of steps, each of which is known to the skilled person.

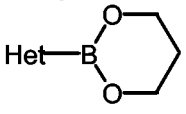
Compounds of Formula (Ia) wherein R^2 represents alkoxy; a radical of formula  wherein t and Z are defined as hereinabove; alkyloxy substituted with a radical of formula  wherein t and Z are defined as hereinabove; mono or di(alkyl)amino wherein alkyl may optionally be substituted with one or two substituents each independently be selected from alkyloxy or Ar or Het or morpholinyl or 2-oxopyrrolidinyl, said R^2 being represented by R^{2a}, and said compounds being represented by Formula (Ia-1), can be prepared by reacting an intermediate of formula (II), wherein W_1 represents a suitable leaving group, such as for example halo, e.g. chloro and the like, with H-R^{2a} or with a suitable salt form of R^{2a}-H optionally in the presence of a suitable solvent, such as for example an alcohol, e.g. methanol and the

like, acetonitrile, and optionally in the presence of a suitable base, such as for example KOH, dipotassium carbonate.

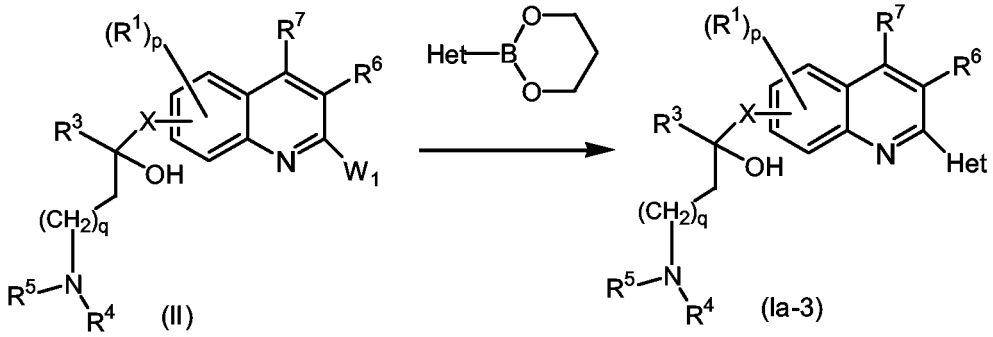


Compounds of Formula (Ia) wherein R^2 represents Het or alkyl, said R^2 being represented by formula R^{2b} and said compounds being represented by Formula (Ia-2), can be prepared by reacting an intermediate of formula (II) with R^{2b}-$B(OH)_2$, in the presence of a suitable catalyst, such as for example $Pd(PPh_3)_4$, a suitable solvent, such as for example dimethylether or an alcohol, e.g. methanol and the like, and a suitable base, such as for example disodium carbonate or dipotassium carbonate.

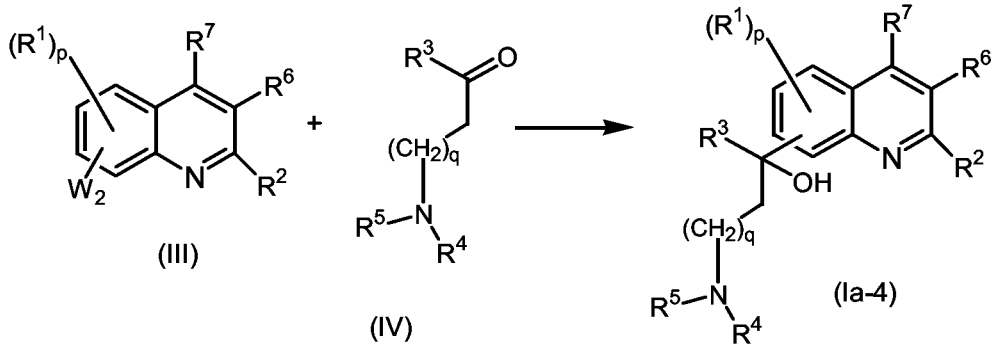


Compounds of Formula (Ia) wherein R^2 represents Het, e.g. pyridyl, said R^2 being represented by Het and said intermediates being represented by Formula (Ia-3), can be prepared by reacting an intermediate of formula (II) with 

, in the presence of a suitable catalyst, such as for example $Pd(PPh_3)_4$, a suitable solvent, such as for example dimethylether or an alcohol, e.g. methanol and the like, and a suitable base, such as for example disodium carbonate or dipotassium carbonate.

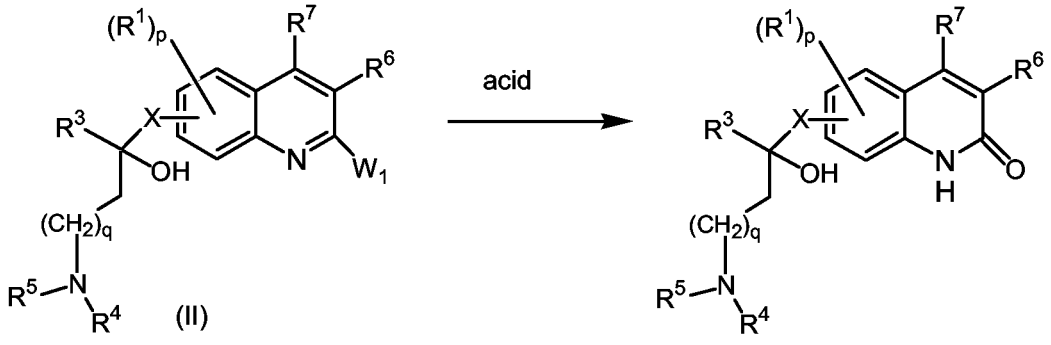


Compounds of Formula (Ia) wherein X is a direct bond, said intermediates being represented by Formula (Ia-4), can be prepared by reacting an intermediate of formula (III) wherein W_2 represents a suitable leaving group, such as for example halo, e.g. bromo, chloro and the like, with an intermediate of formula (IV) in the presence of a suitable coupling agent, such as for example n-butyl lithium, secBuLi, and in the presence of a suitable solvent, such as for example tetrahydrofuran, and optionally in the presence of a suitable base, such as for example 2,2,6,6-tetramethylpiperidine, $NH(CH_2CH_2CH_3)_2$, *N,N*-diisopropylamine or trimethylethylenediamine.



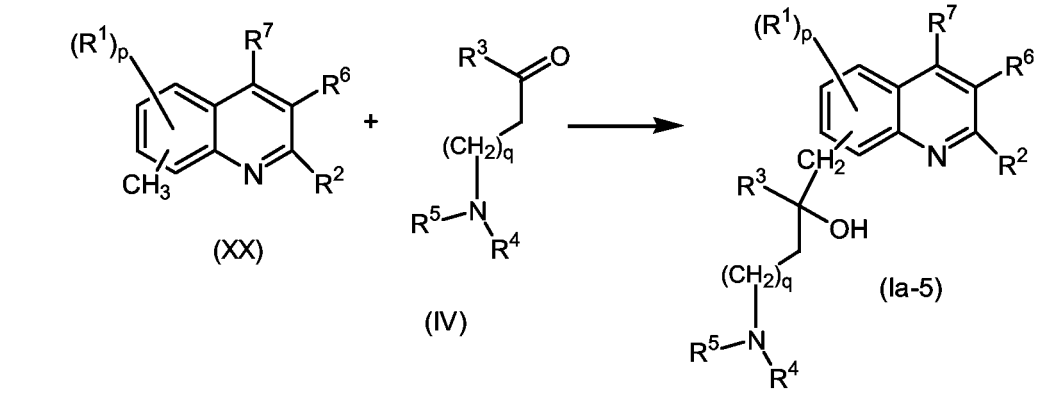
(III) (IV) (Ia-4)

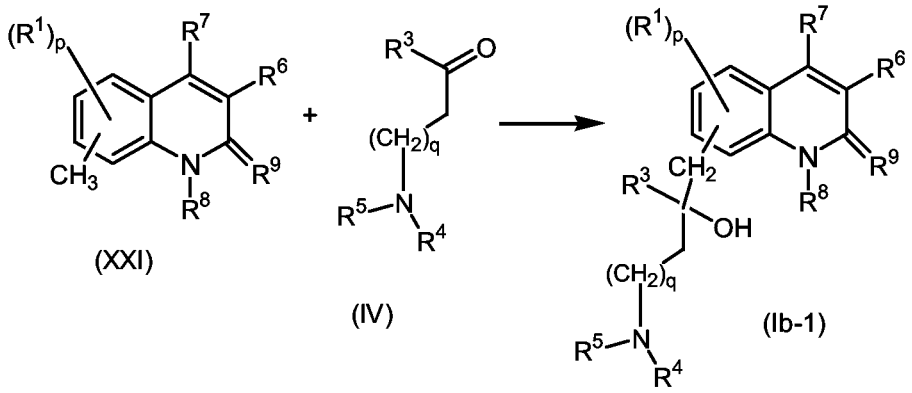
Compounds of Formula (Ib) wherein R^9 represents oxo, can be prepared by reacting an intermediate of formula (II) with a suitable acid, such as for example HCl, in the presence of a suitable solvent, such as for example tetrahydrofuran.



(II) (Ib)

Compounds of Formula (Ia) or (Ib) wherein X represents CH_2, said compounds being represented by Formula (Ia-5) or (Ib-1), can be prepared by reacting an intermediate of formula (XX) or (XXI) with an intermediate of formula (IV) in the presence of a suitable coupling agent, such as nBuLi, secBuLi, and in the presence of a suitable solvent, such as for example tetrahydrofuran, and optionally a suitable base, such as for example 2,2,6,6-tetramethylpiperidine, $NH(CH_2CH_2CH_3)_2$, *N,N*-diisopropylamine or trimethylethylenediamine.





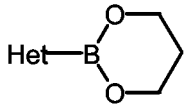
In the above reactions, the obtained compound of Formula (Ia) or (Ib) can be isolated, and, if necessary, purified according to methodologies generally known in the art such as, for example, extraction, crystallization, distillation, trituration and chromatography.

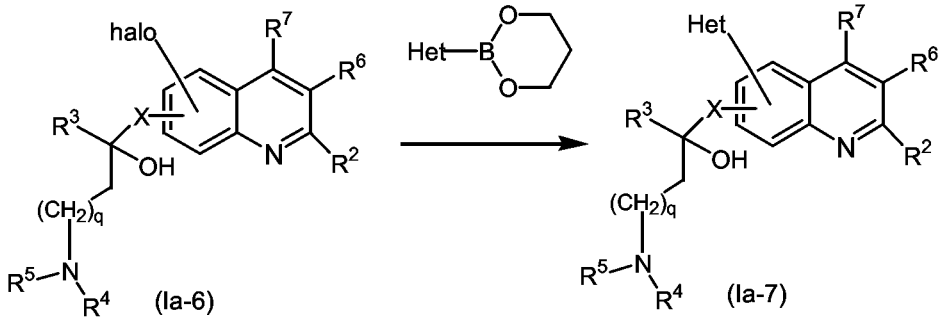
In case the compound of Formula (Ia) or (Ib) crystallizes out, it can be isolated by filtration. Otherwise, crystallization can be caused by the addition of an appropriate solvent, such as for example water; acetonitrile; an alcohol, such as for example methanol, ethanol; and combinations of said solvents. Alternatively, the reaction mixture can also be evaporated to dryness, followed by purification of the residue by chromatography (e.g. reverse phase HPLC, flash chromatography and the like). The reaction mixture can also be purified by chromatography without previously evaporating the solvent. The compound of Formula (Ia) or (Ib) can also be isolated by evaporation of the solvent followed by recrystallisation in an appropriate solvent, such as for example water; acetonitrile; an alcohol, such as for example methanol; and combinations of said solvents.

The person skilled in the art will recognise which method should be used, which solvent is the most appropriate to use or it belongs to routine experimentation to find the most suitable isolation method.

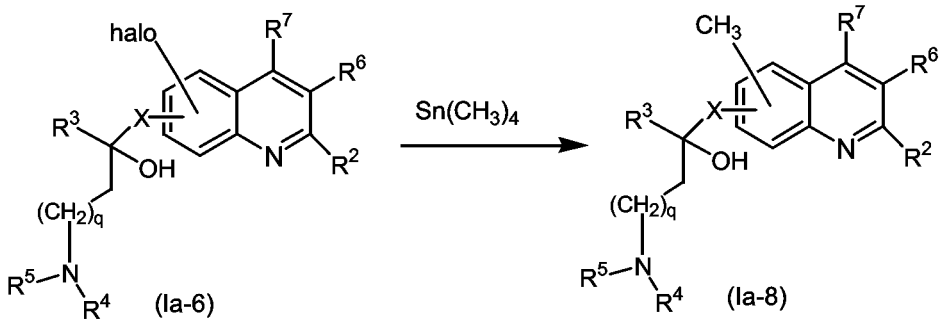
The compounds of Formula (Ia) or (Ib) may further be prepared by converting compounds of Formula (Ia) or (Ib) into each other according to art-known group transformation reactions.

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. 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.

Compounds of Formula (Ia) wherein R^1 represents halo, said compounds being represented by Formula (Ia-6), can be converted into a compound of Formula (Ia) wherein R^1 represents Het, e.g. pyridyl, said compounds being represented by Formula (Ia-7), by reaction with , in the presence of a suitable catalyst, such as for example $Pd(PPh_3)_4$, a suitable solvent, such as for example dimethylether or an alcohol, e.g. methanol and the like, and a suitable base, such as for example disodium carbonate or dipotassium carbonate.



Compounds of Formula (Ia-6) can also be converted into a compound of Formula (Ia) wherein R^1 represents methyl, said compound being represented by Formula (Ia-8), by reaction with $Sn(CH_3)_4$ in the presence of a suitable catalyst, such as for example $Pd(PPh_3)_4$, a suitable solvent, such as for example toluene.



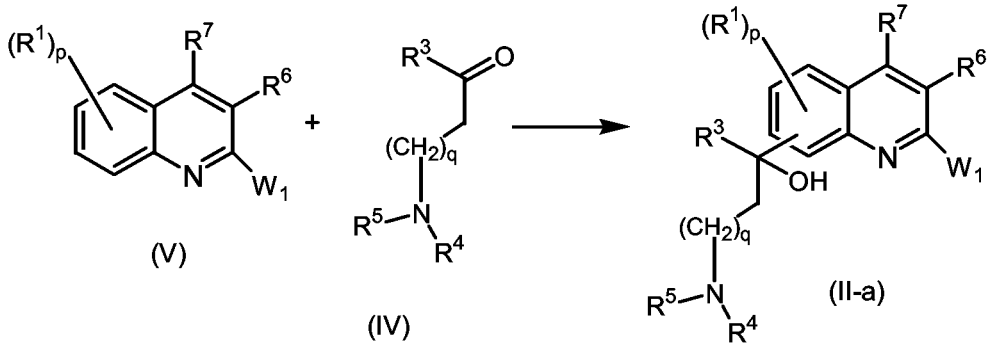
Some of the compounds of Formula (Ia) or (Ib) and some of the intermediates in the present invention may consist of a mixture of stereochemically isomeric forms. Pure stereochemically isomeric forms of said compounds and said intermediates can be obtained by the application of art-known procedures. For example, diastereoisomers can be separated by physical methods such as selective crystallization or chromatographic techniques, e.g. counter current distribution, liquid chromatography and the like methods. Enantiomers can be obtained from racemic mixtures by first converting said racemic mixtures with suitable resolving agents such as, for example, chiral acids, to mixtures of diastereomeric salts or compounds; then physically separating said mixtures of diastereomeric salts or compounds by, for example, selective crystallization or chromatographic techniques, e.g. liquid chromatography and the like methods; and finally converting said separated diastereomeric salts or compounds into the corresponding enantiomers. Pure stereochemically isomeric forms may also be obtained from the pure stereochemically isomeric forms of the appropriate intermediates and starting materials, provided that the intervening reactions occur stereospecifically.

An alternative manner of separating the enantiomeric forms of the compounds of Formula (Ia) or (Ib) and intermediates involves liquid chromatography, in particular liquid chromatography using a chiral stationary phase.

It is to be understood that in the above or the following preparations, 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, for example, extraction, crystallization, distillation, trituration and chromatography.

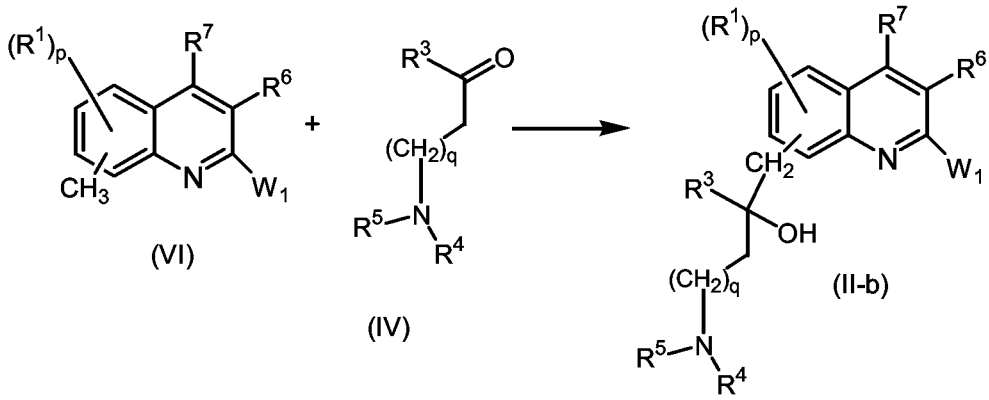
Some of the intermediates and starting materials are known compounds and may be commercially available or may be prepared according to art-known procedures or procedures described in WO2004/011436 or WO2005/070430, which is incorporated herein by reference.

Intermediates of formula (II) wherein X is a direct bond, such intermediates being represented by formula (II-a), can be prepared by reacting an intermediate of formula (V) wherein W_1 is as defined hereinabove, with an intermediate of formula (IV) in the presence of a suitable coupling agent, such as nBuLi, secBuLi, and in the presence of a suitable solvent, such as for example tetrahydrofuran, and a suitable base, such as for example 2,2,6,6-tetramethylpiperidine, $NH(CH_2CH_2CH_3)_2$, *N,N*-diisopropylamine or trimethylethylenediamine.



(V) (IV) (II-a)

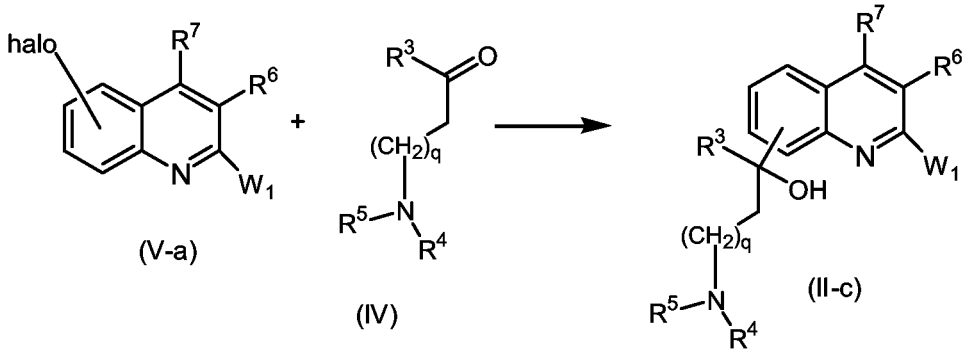
Intermediates of formula (II) wherein X represents CH_2, said intermediates being represented by formula (II-b), can be prepared by reacting an intermediate of formula (VI) with an intermediate of formula (IV) in the presence of a suitable coupling agent, such as nBuLi, secBuLi, and in the presence of a suitable solvent, such as for example tetrahydrofuran, and a suitable base, such as for example 2,2,6,6-tetramethylpiperidine, $NH(CH_2CH_2CH_3)_2$, *N,N*-diisopropylamine or trimethylethylenediamine.



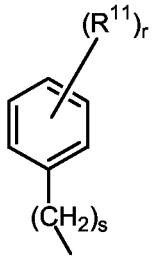
(VI) (IV) (II-b)

Intermediates of formula (II) wherein R^1 is hydrogen, said intermediates being represented by formula (II-c), can be prepared by reacting an intermediate of formula (V) wherein R^1 is halo, said intermediates being represented by formula (V-a), with an intermediate of formula (IV), in the presence of a suitable strong base, such as for example nBuLi, secBuLi, and in the presence of a suitable solvent, such as for example

tetrahydrofuran.

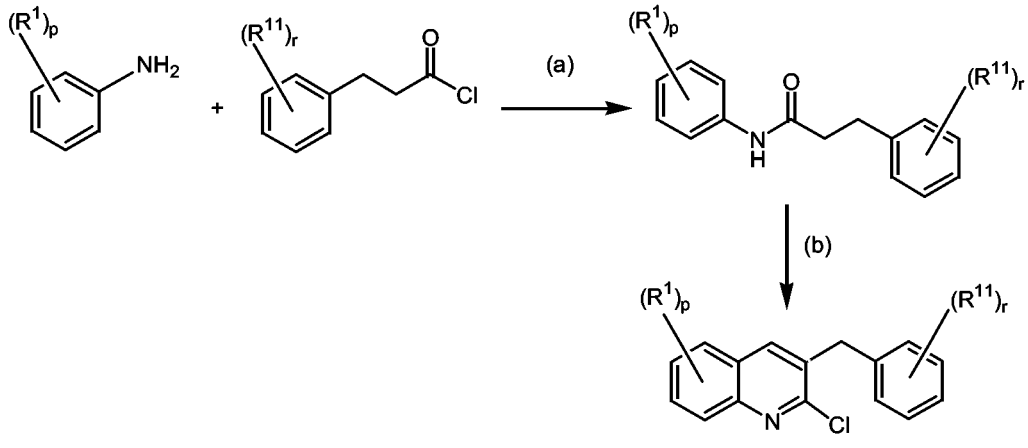


The intermediates of formula (V) are compounds that are either commercially available or may be prepared according to conventional reaction procedures generally known in the art. For example, intermediates of formula (V) wherein R^7 is hydrogen, R^6 is a



radical of formula wherein s is an integer equal to 1 and W_1 is chloro, said intermediates being represented by formula (V-b) may be prepared according to the following reaction scheme (1):

Scheme 1



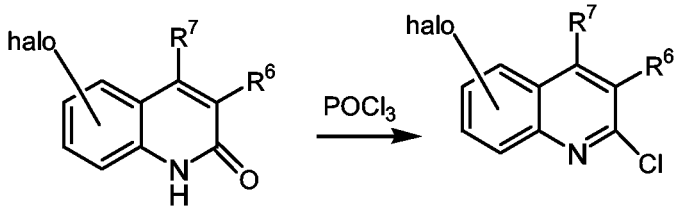
(V-b)

wherein all variables are defined as in Formula (Ia). Reaction scheme (1) comprises step (a) in which an appropriately substituted aniline is reacted with an appropriate acylchloride such as 3-phenylpropionyl chloride, 3-fluorobenzenepropionyl chloride or

p-chlorobenzenepropionyl chloride, in the presence of a suitable base, such as triethylamine and a suitable reaction-inert solvent, such as methylene chloride or ethylene dichloride. The reaction may conveniently be carried out at a temperature ranging between room temperature and reflux temperature. In a next step (b) the adduct obtained in step (a) is reacted with phosphoryl chloride ($POCl_3$) in the presence of a suitable solvent, such as for example *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.

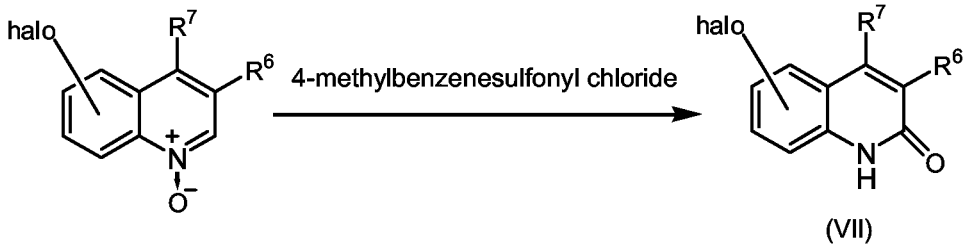
It is evident that in the foregoing and in the following reactions, the reaction products may be isolated from the reaction medium and, if necessary, further purified according to methodologies generally known in the art, such as extraction, crystallization and chromatography. It is further evident that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

Intermediates of formula (V-a) wherein W_1 represents chloro, said intermediates being represented by formula (V-a-1), can be prepared by reacting an intermediate of formula (VII) with $POCl_3$.



(VII) (V-a-1)

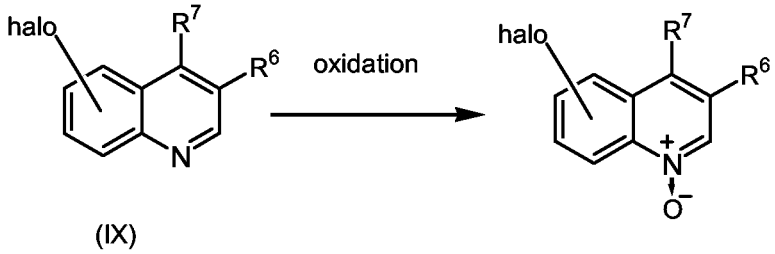
Intermediates of formula (VII) can be prepared by reacting an intermediate of formula (VIII) with 4-methylbenzenesulfonyl chloride in the presence of a suitable solvent, such as for example methylene chloride, and a suitable base, such as for example dipotassium carbonate.



(VIII) (VII)

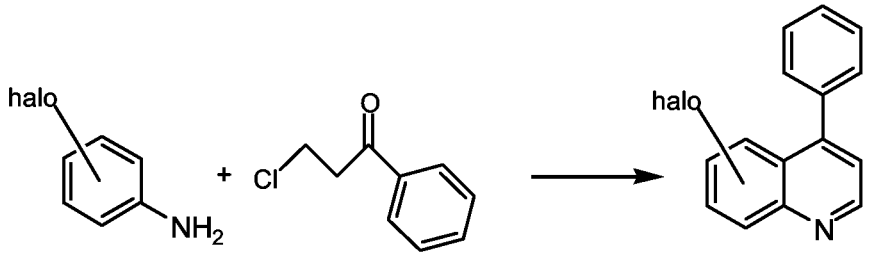
Intermediates of formula (VIII) can be prepared by reacting an intermediate of formula (IX) with a suitable oxidizing agent, such as for example 3-

chlorobenzenecarboperoxoic acid, in the presence of a suitable solvent, such as for example methylene chloride.



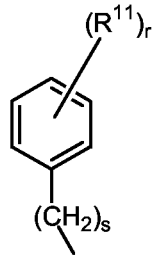
(IX) (VIII)

Intermediates of formula (IX) wherein R^6 is hydrogen and R^7 is phenyl, said intermediates being represented by formula (IX-a), can be prepared by reacting an intermediate of formula (X) with 3-chloro-1-phenyl-1-propanone in the presence of a suitable acid, such as for example hydrochloric acid, iron chloride hexahydrate, zinc chloride and a suitable solvent, such as for example diethyl ether and a suitable alcohol, e.g. ethanol.

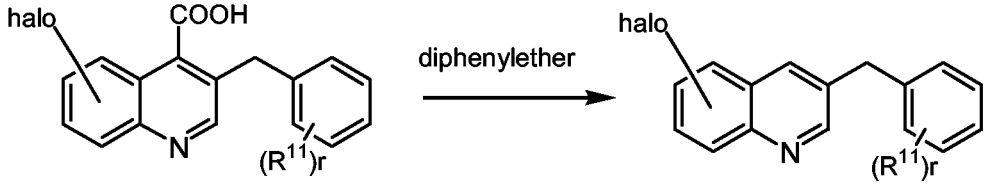


(X) (IX-a)

Intermediates of formula (IX) wherein R^7 is hydrogen and R^6 is a radical of formula



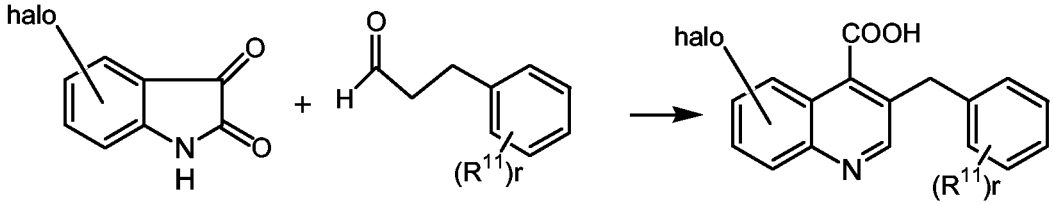
wherein s is an integer equal to 1, said intermediates being represented by formula (IX-b), can be prepared by reacting an intermediate of formula (XI) in the presence of diphenyl ether.



(XI) (IX-b)

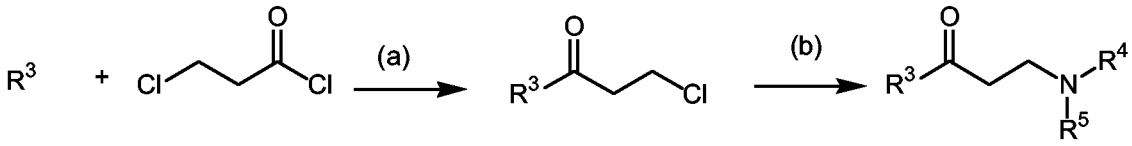
Intermediates of formula (XI) can be prepared by reacting an intermediate of formula (XII) with an intermediate of formula (XIII) in the presence of a suitable base, such as

for example sodium hydroxide.



Intermediates of formula (IV) are compounds that are either commercially available or may be prepared according to conventional reaction procedures generally known in the art. For example, intermediate compounds of formula (IV) wherein q is equal to 1, said intermediates being represented by formula (IV-a), can be prepared according to the following reaction scheme (2):

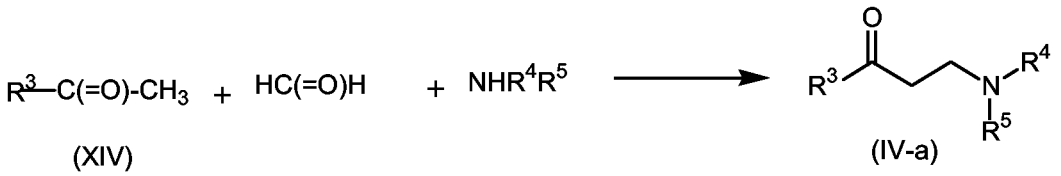
Scheme 2



(IV-a)

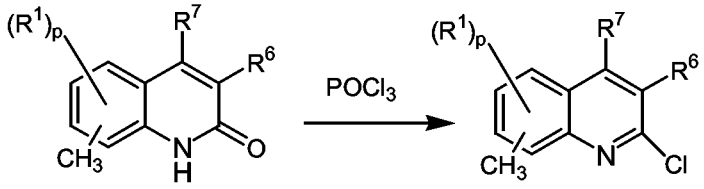
Reaction scheme (2) comprises step (a) in which an appropriate R^3 is reacted by Friedel-Craft reaction with an appropriate acylchloride such as 3-chloropropionyl chloride or 4-chlorobutyryl chloride, in the presence of a suitable Lewis acid, such as $AlCl_3$, $FeCl_3$, $SnCl_4$, $TiCl_4$ or $ZnCl_2$ and a suitable reaction-inert solvent, such as methylene chloride or ethylene dichloride. The reaction may conveniently be carried out at a temperature ranging between room temperature and reflux temperature. In a next step (b) an amino group (e.g. $-NR^4R^5$) is introduced by reacting the intermediate compound obtained in step (a) with an appropriate amine HNR^4R^5.

Intermediates of formula (IV-a) can also be prepared by reacting an intermediate of formula (XIV) with HC(=O)H and a suitable aminogroup HNR^4R^5, such as for example $NH(CH_3)_2.HCl$ in the presence of a suitable solvent, such as for example an alcohol, e.g. methanol, ethanol and the like, and a suitable acid, such as for example hydrochloric acid.

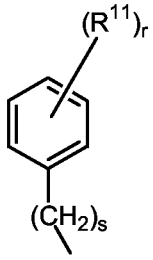


(XIV) (IV-a)

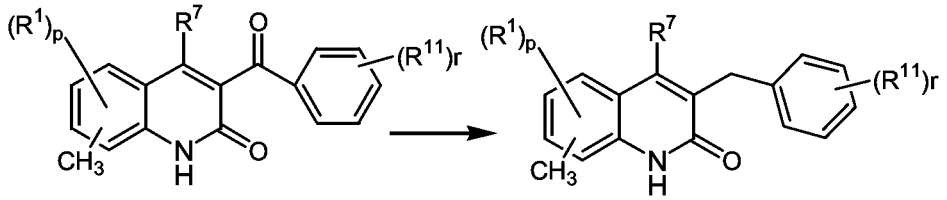
Intermediates of formula (VI) wherein W_1 represents chloro, said intermediates being represented by formula (VI-a) can be prepared by reacting an intermediate of formula (XV) with $POCl_3$ in the presence of benzyltriethylammonium chloride (Phase transfert agent) and a suitable solvent, such as for example acetonitrile.



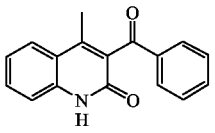
(XV) (VI-a)



Intermediates of formula (XV) wherein R^6 represents a radical of formula wherein s is an integer equal to 1, said intermediates being represented by formula (XV-a), can be prepared by reacting an intermediate of formula (XVI) with NH_2-NH_2 in the presence of a suitable base, such as for example potassium hydroxide and a suitable solvent, such as for example 1,2-ethanediol.

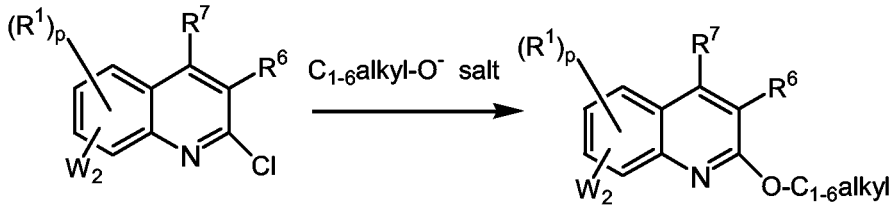


(XVI) (XV-a)



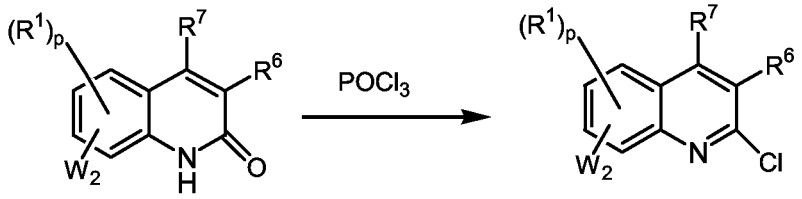
which is an intermediate of formula (XVI) can be prepared by reacting 1-(2-aminophenyl)ethanone and β-oxobenzenepropanoic acid ethyl ester.

Intermediates of formula (III) wherein R^2 represents C_{1-6}alkyloxy, said intermediates being represented by formula (III-a), can be prepared by reacting an intermediate of formula (XVII) with the appropriate C_{1-6}alkylO- salt in the presence of a suitable solvent, such as for example the corresponding C_{1-6}alkylOH.

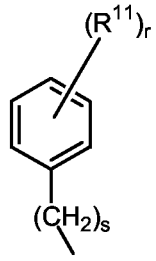


(XVII) (III-a)

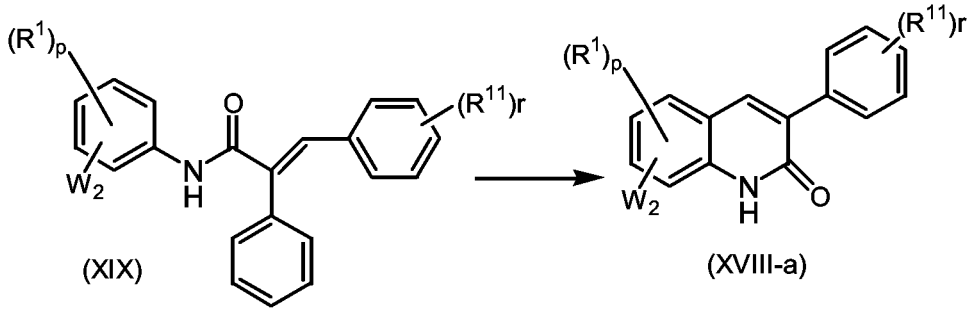
Intermediates of formula (XVII) can be prepared by reacting an intermediate of formula (XVIII) with $POCl_3$.



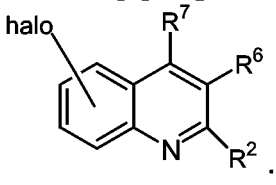
(XVIII) (XVII)

Intermediates of formula (XVIII) wherein R^7 is hydrogen and R^6 represents a radical of formula 

wherein s is an integer equal to 0, said intermediates being represented by formula (XVIII-a), can be prepared by cyclization of an intermediate of formula (XIX) in the presence of $AlCl_3$ and a suitable solvent, such as for example chlorobenzene.



(XIX) (XVIII-a)

In the intermediates of formula (III) the R^1 substituent may represent halo and then this halo substituent may take the place of the W_2 leaving group. Said intermediates of formula (III) being represented by formula 

.

Intermediates of formula (XX) wherein R_2 represents C_{1-6}alkyloxy, said intermediates being represented by formula (XX-a), can be prepared by reacting an intermediate of formula (VI-a) with C_{1-6}alkyloxy Na, in a suitable alcohol, such as C_{1-6}alkylOH.

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

EXPERIMENTAL PART

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

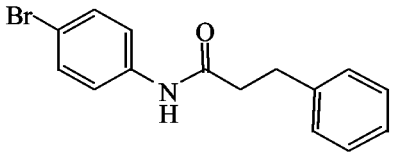
For the synthesis of the present compounds, reference is made to WO2005/070430, which is incorporated herein by reference.

Hereinafter, the term 'M.P.' means melting point, 'DIPE' means diisopropyl ether, 'DMF' means *N,N*-dimethylformamide, 'THF' means tetrahydrofuran, 'EtOAc' means ethyl acetate, 'DCM' means dichloromethane.

A. Preparation of the intermediates

Example A1

Preparation of intermediate 1

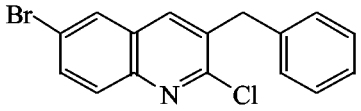


Benzenepropanoyl chloride (0.488 mol) was added dropwise at room temperature to a solution of 4-bromo benzenamine (0.407 mol) in Et_3N (70ml) and DCM (700ml) and the mixture was stirred at room temperature overnight. The mixture was poured out into water and concentrated NH_4OH, and extracted with DCM. The organic layer was dried ($MgSO_4$), filtered, and the solvent was evaporated. The residue was crystallized from diethyl ether. The residue (119.67g) was taken up in DCM and washed with HCl

1N. The organic layer was dried ($MgSO_4$), filtered, and the solvent was evaporated, yielding 107.67g of intermediate 1 (87%).

Example A2

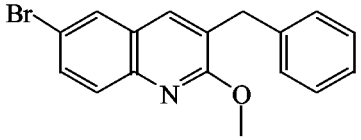
Preparation of intermediate 2



Phosphoric trichloride (1.225 mol) was added dropwise at 10°C to DMF (0.525 mol). Then intermediate 1 (0.175 mol) was added at room temperature. The mixture was stirred overnight at 80°C, poured out on ice and extracted with DCM. The organic layer was dried ($MgSO_4$), filtered, and the solvent was evaporated. The product was used without further purification, yielding 77.62 g of intermediate 2 (67%).

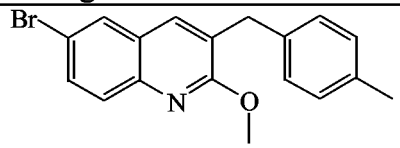
Example A3

a) Preparation of intermediate 3

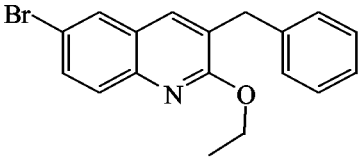


A mixture of intermediate 2 (0.233 mol) in a 30% MeONa in MeOH solution (222.32 ml) and MeOH (776 ml) was stirred and refluxed overnight, then poured out on ice and extracted with DCM. The organic layer was separated, dried ($MgSO_4$), filtered and the solvent was evaporated. The residue was purified by column chromatography over silica gel (eluent: DCM/cyclohexane 20/80 and then 100/0; 20-45µm). The pure fractions were collected and the solvent was evaporated, yielding 25g of intermediate 3 (33%).

The following intermediate was prepared according to the method described above.

intermediate 29	

b) Preparation of intermediate 4

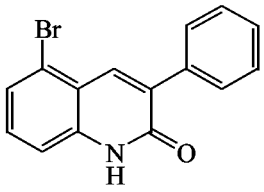


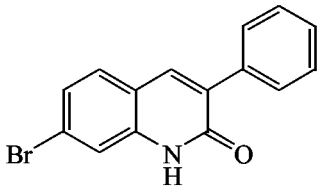
A mixture of intermediate 2 (0.045 mol) in a 21% EtONa in EtOH solution (50 ml) and EtOH (150 ml) was stirred and refluxed for 12 hours. The mixture was poured out on

ice and extracted with DCM. The organic layer was separated, dried ($MgSO_4$), filtered and the solvent was evaporated, yielding 15.2 g of intermediate 4 (98%).

Example A4

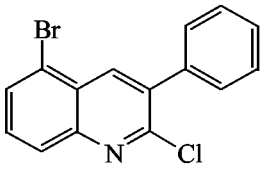
a) Preparation of intermediate 5



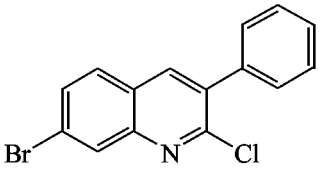


Aluminum chloride (1.31 mol) was added at room temperature to a mixture of *N*-(3-bromophenyl)-α-(phenylmethylene)benzeneacetamide (0.1311 mol) in chlorobenzene (500 ml). The mixture was stirred and refluxed for 3 hours, then cooled to room temperature, poured out into ice water and filtered. The filtrate was washed with H_2O, then with cyclohexane and dried, yielding 35.5 g of intermediate 5 (95%).

b) Preparation of intermediate 6 and intermediate 7



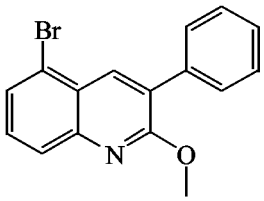
intermediate 6



intermediate 7

A mixture of intermediate 5 (0.2815 mol) in phosphoric trichloride (320 ml) was stirred and refluxed for 1 hour, then cooled to room temperature and the solvent was evaporated till dryness. The residue was taken up in H_2O. The mixture was extracted with DCM. The organic layer was separated, dried ($MgSO_4$), filtered, and the solvent was evaporated till dryness. The residue (58.2 g) was purified by column chromatography over silica gel (eluent: toluene/cyclohexane 80/20; 15-35µm). Two fractions were collected and the solvent was evaporated, yielding 21 g of intermediate 6 and 34.5 g of intermediate 7.

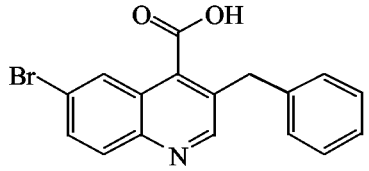
c) Preparation of intermediate 8



A mixture of intermediate 6 (0.0659 mol) and a 30 % MeONa in MeOH solution (0.329 mol) in MeOH (300 ml) was stirred and refluxed for 2 days, then cooled to room temperature, poured out into ice water and filtered. The filtrate was washed with H_2O and dried, yielding 19 g of intermediate 8 (92%).

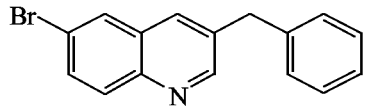
Example A5

a) Preparation of intermediate 9



A mixture of 5-bromo-1H-indole-2,3-dione (0.28 mol) in 3N NaOH (650 ml) was stirred and heated at 80°C for 30 minutes, then cooled to room temperature. Benzenepropanal (0.28 mol) was added and the mixture was stirred and refluxed overnight. The mixture was allowed to cool to room temperature and acidified till pH 5 with HOAc. The precipitate was filtered off, washed with H_2O and dried (vacuum), yielding 50 g of intermediate 9 (52%).

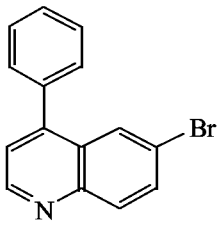
b) Preparation of intermediate 10



A mixture of intermediate 9 (0.035 mol) in 1,1'-oxybisbenzene (100 ml) was stirred and heated at 300°C for 8 hours, then allowed to cool to room temperature. This procedure was carried out four times. The four mixtures were combined and then purified by column chromatography over silica gel (eluent: DCM/MeOH 100/0, then 99/1). The pure fractions were collected and the solvent was evaporated, yielding 25.6 g of intermediate 10 (61%).

Example A6

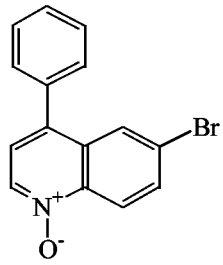
a) Preparation of intermediate 11



HCl/diethyl ether (30 ml) was added to a solution of 4-bromobenzenamine (0.139 mol) in EtOH (250 ml) and the mixture was stirred for 30 minutes. Iron chloride hexahydrate (0.237 mol) and then zinc chloride (0.014 mol) were added and the mixture was stirred at 80°C for 30 minutes. 3-Chloro-1-phenyl-1-propanone (0.146 mol) was added and the mixture was stirred at 80°C for one night. The mixture was poured into water and extracted with EtOAc. The organic layer was washed with water, then with K_2CO_3 10%, dried ($MgSO_4$), filtered off and evaporated. The residue (25 g) was purified by column chromatography over silica gel (eluent : DCM/MeOH 100/0 and then 97/3)

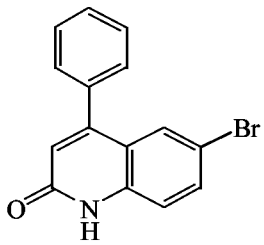
(35-70µm). The pure fractions were collected and evaporated, yielding 17.5g of intermediate 11 (44%).

b) Preparation of intermediate 12



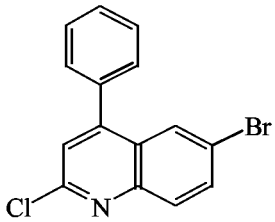
3-Chlorobenzenecarboperoxoic acid (0.12 mol) was added portionwise at room temperature to a solution of intermediate 11 (0.0598 mol) in DCM (200 ml) and the mixture was stirred at room temperature for one night. K_2CO_3 10% was added, the organic layer was decanted, dried ($MgSO_4$), filtered off and evaporated till a volume of 150 ml of intermediate 12 was left.

c) Preparation of intermediate 13



4-Methylbenzenesulfonyl chloride (0.075 mol) was added portionwise at room temperature to a solution of intermediate 12 (0.0598 mol) in a 10 % K_2CO_3 solution (150 ml) and DCM (150ml) and the mixture was stirred at room temperature for one night. Diethyl ether was added and filtered off. The precipitate was washed with diethyl ether and evaporated till dryness, yielding 14 g of intermediate 13 (78%).

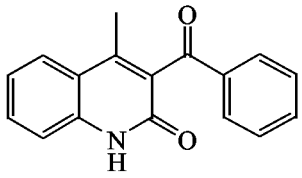
d) Preparation of intermediate 14



A mixture of intermediate 13 (0.047 mol) in phosphoric trichloride (150 ml) was stirred and refluxed for 48 hours. The mixture was evaporated, the residue was taken up in NH_4OH and extracted with DCM. The organic layer was dried ($MgSO_4$), filtered off and evaporated, yielding 13 g of intermediate 14 (87%).

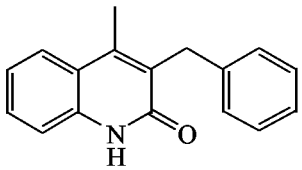
Example A7

a) Preparation of intermediate 15



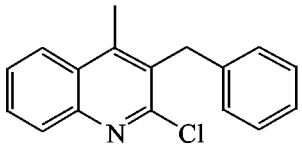
A mixture of 1-(2-aminophenyl)ethanone (0.37 mol) and β-oxobenzenepropanoic acid ethyl ester (1.48 mol) was stirred at 180°C overnight. The mixture was brought to room temperature. The precipitate was filtered, washed with diethyl ether and dried. The residue was crystallized from DIPE. The precipitate was filtered off and dried, yielding 56.6 g of intermediate 15 (58%).

b) Preparation of intermediate 16



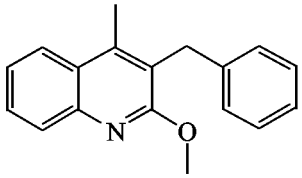
A mixture of intermediate 15 (0.076 mol) and hydrazine (0.76 mol) in 1,2-ethanediol (240 ml) was stirred at 100°C for 1 hour. KOH (0.266 mol) was added. The mixture was stirred at 180°C overnight. H_2O was added. The mixture was acidified and extracted with DCM. The organic layer was separated, dried ($MgSO_4$), filtered, and the solvent was evaporated. The residue (12.05 g) was crystallized from DIPE. The precipitate was filtered off and dried, yielding 4.74 g of intermediate 16.

c) Preparation of intermediate 17



Phosphoric trichloride (0.057 mol) was added slowly at 80°C to a mixture of intermediate 16 (0.019 mol) and benzyltriethylammonium chloride (0.0532 mol) in acetonitrile (50 ml). The mixture was stirred overnight. The solvent was evaporated. The mixture was poured out into ice and Na_2CO_3 10% and extracted with DCM. The organic layer was separated, dried ($MgSO_4$), filtered, and the solvent was evaporated, yielding 4.08 g of intermediate 17.

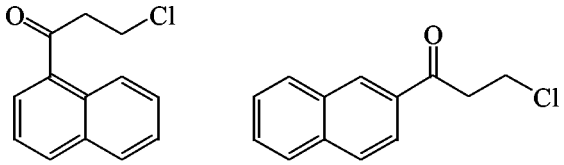
d) Preparation of intermediate 17a



A mixture of intermediate 17 (0.0153 mol) and sodium methoxide (30wt% solution in MeOH, 7 ml) in MeOH (35 ml) was stirred at 80°C for 24 hours. Water was added. The mixture was extracted with EtOAc. The organic layer was separated, dried over magnesium sulfate, filtered and the solvent was evaporated till dryness. The residue was crystallized from diisopropylether. The precipitate was filtered off and dried. Yield : 2.77g of intermediate 17a (69%).

Example A8

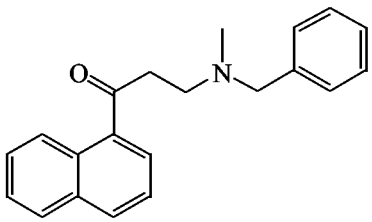
a) Preparation of intermediate 18 and intermediate 19



intermediate 18 intermediate 19

A mixture of aluminium chloride (0.257 mol) and 3-chloropropanoyl chloride (0.234 mol) in 1,2-dichloroethane (100 ml) was stirred at 0°C. A solution of naphthalene (0.234 mol) in 1,2-dichloroethane (100 ml) was added. The mixture was stirred at 0°C for 1 hour and poured out into ice water. The organic layer was separated, dried ($MgSO_4$), filtered, and the solvent was evaporated. The residue (56 g) was purified by column chromatography over silica gel (eluent: cyclohexane/DCM 60/40; 20-45µm). Two fractions were collected and the solvent was evaporated, yielding 2 fractions, 31 g of fraction 1 as intermediate 18 (61%) and 14 g of fraction 2. Fraction 2 was taken up in DIPE, then the resulting precipitate was filtered off and dried, yielding 8.2 g of intermediate 19.

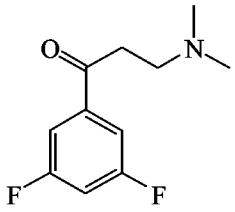
b) Preparation of intermediate 20



A mixture of intermediate 18 (0.0137 mol), *N*-methylbenzenemethanamine (0.015 mol) and K_2CO_3 (2 g) in acetonitrile (100 ml) was stirred at 80°C for 2 hours. H_2O was added. The mixture was extracted with DCM. The organic layer was separated, dried ($MgSO_4$), filtered, and the solvent was evaporated, yielding 4.2 g of intermediate 20 (100%).

Example A9

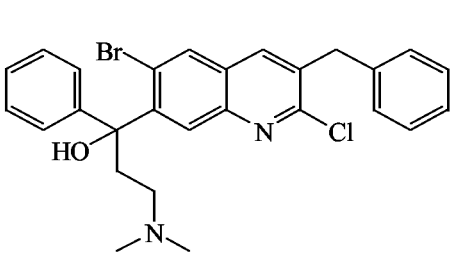
Preparation of intermediate 21



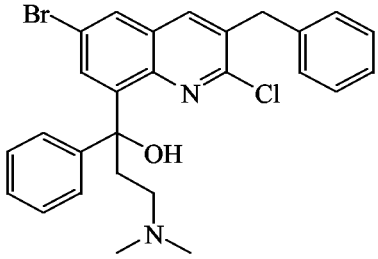
A mixture of 1-(3,5-difluorophenyl)ethanone (0.013 mol), formaldehyde (0.05 mol) and *N*-methylmethanamine hydrochloride (0.052 mol) in concentrated HCl (0.1ml) in EtOH (20 ml) was stirred at 80°C for 20 hours, then cooled to room temperature. The solvent was evaporated till dryness. The residue was taken up in HCl 3N. The mixture was washed with diethyl ether, basified with K_2CO_3 and extracted with diethyl ether. The organic layer was separated, dried ($MgSO_4$), filtered, and the solvent was evaporated, yielding 2 g of intermediate 21.

Example A10

a) Preparation of intermediate 22 and intermediate 23



intermediate 22

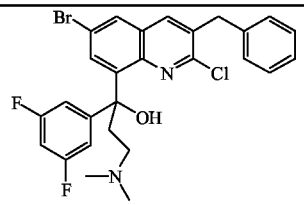
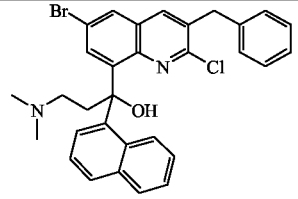


intermediate 23

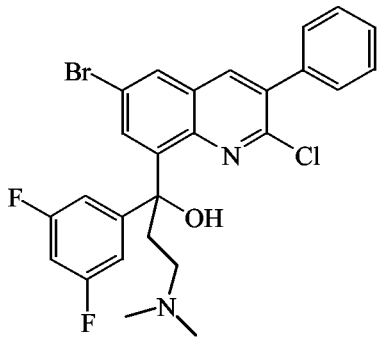
1.6M Butyllithium (0.12 mol) was added dropwise at –10°C under N_2 flow to a solution of 2,2,6,6-tetramethylpiperidine (0.12 mol) in THF (200 ml). The mixture was stirred at –10°C for 20 minutes and then cooled to –70°C. A mixture of intermediate 2 (0.1 mol) in THF (100 ml) was added. The mixture was stirred at –70°C for 45 minutes. A solution of 3-(dimethylamino)-1-phenyl-1-propanone (0.1 mol) in THF (100 ml) was added. The mixture was stirred at –70°C for 1 hour, brought to –50°C and hydrolysed. H_2O (100 ml) was added at –50°C. The mixture was stirred at room temperature for 30 minutes and extracted with EtOAc. The organic layer was separated, dried ($MgSO_4$), filtered and the solvent was evaporated. The residue was taken up in EtOAc. The precipitate was filtered off, washed with EtOAc and diethyl ether and dried in vacuo, yielding 4 g of intermediate 23 (8%). The mother layer was evaporated. The residue (26g) was purified by column chromatography over silica gel (eluent: DCM/MeOH/NH_4OH 97/3/0.1; 15-40µm). The desired fractions were collected and the

solvent was evaporated. The residue was crystallized from diethyl ether. The precipitate was filtered off and dried, yielding 1g of intermediate 22.

The following intermediates were prepared according to the method described above.

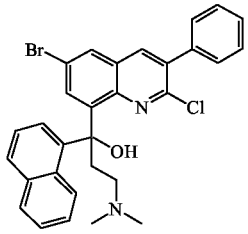
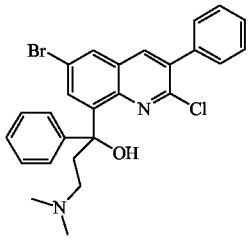
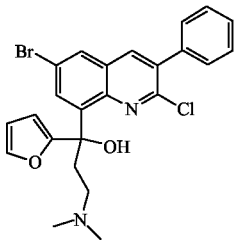
intermediate 30	
intermediate 31	

b) Preparation of intermediate 24

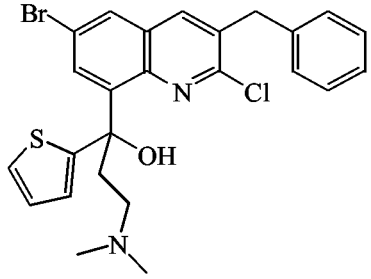


1.6M Butyllithium (0.0094 mol) was added dropwise at –20°C to a mixture of 2,2,6,6-tetramethylpiperidine (0.0094 mol) in THF (20 ml) under N_2 flow. The mixture was stirred at –20°C for 20 minutes, then cooled to –70°C. A solution of 6-bromo-2-chloro-3-phenylquinoline (0.0062 mol) in THF (40 ml) was added. The mixture was stirred at –70°C for 1 hour. A solution of intermediate 21 (0.0094 mol) in THF (25 ml) was added. The mixture was stirred from –70°C to room temperature for 18 hours. H_2O and EtOAc were added. The organic layer was washed with saturated NaCl, dried ($MgSO_4$), filtered, and the solvent was evaporated. The residue (4.3 g) was purified by column chromatography over silica gel (eluent: DCM/MeOH/NH_4OH 97/3/0.1; 10µm). The pure fractions were collected and the solvent was evaporated, yielding 0.77 g of intermediate 24 (23%).

The following intermediates were prepared according to the method described above.

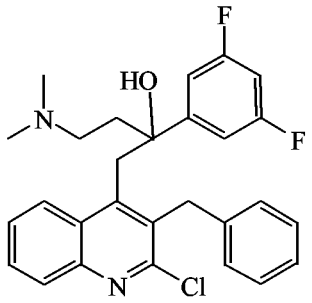
intermediate 32	
intermediate 33	
intermediate 34	

c) Preparation of intermediate 28



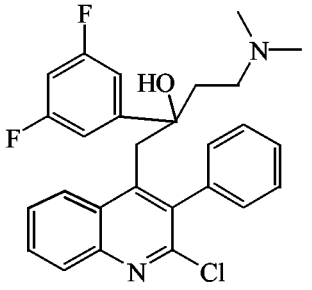
1.6M Butyllithium (0.029 mol) was added at –10°C to a solution of *N*-propyl-1-propanamine (0.029 mol) in THF (50 ml) under N_2 flow. The mixture was stirred for 20 minutes, then cooled to –70°C. A solution of intermediate 2 (0.024 mol) in THF (30 ml) was added. The mixture was stirred at –70°C for 1 hour. A solution of 3-(dimethylamino)-1-(2-thienyl)-1-propanone (0.029 mol) in THF (20 ml) was added. The mixture was stirred at –70°C for 1 hour, then brought to –20°C and 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: DCM/MeOH/NH_4OH 96/4/0.1; 20-45µm). The pure fractions were collected and the solvent was evaporated. The residue (4.65 g) was crystallized from DIPE. The precipitate was filtered off and dried, yielding 2.7 g of intermediate 28 (M.P.: 168°C). The mother layer was evaporated, yielding another 1.7g of intermediate 28.

d) Preparation of intermediate 25



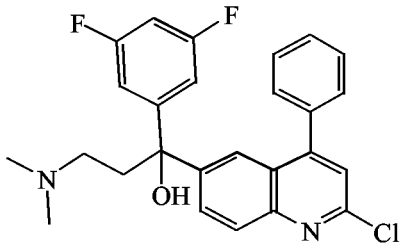
1.6M Butyllithium (0.0112 mol) was added dropwise at –20°C to a solution of *N*-(1-methylethyl)-2-propanamine (0.0112 mol) in THF (20 ml) under N_2 flow. The mixture was stirred at –20°C for 30 minutes, then cooled to –70°C. A solution of intermediate 17 (0.0094 mol) in THF (20 ml) was added. The mixture was stirred for 45 minutes. A solution of intermediate 21 (0.0112 mol) in THF (10 ml) was added. The mixture was stirred at –70°C for 2 hours, poured out into H_2O at –30°C and extracted with EtOAc. The organic layer was separated, dried ($MgSO_4$), filtered, and the solvent was evaporated. The residue (4 g) was purified by column chromatography over silica gel (eluent: DCM/MeOH 98/2; 15-40µm). The pure fractions were collected and the solvent was evaporated. The residue (3 g) was crystallized from DIPE. The precipitate was filtered off and dried, yielding 1.94 g of intermediate 25 (43%) (M.P.: 140°C).

e) Preparation of intermediate 26



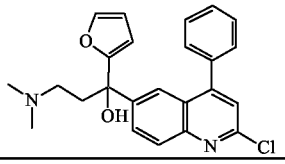
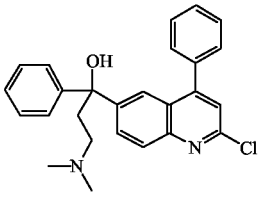
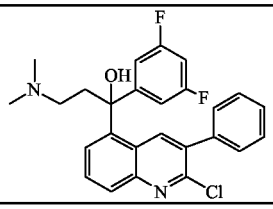
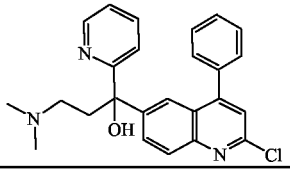
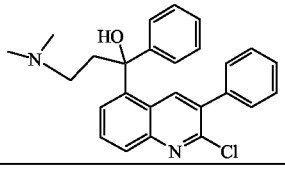
1.6M Butyllithium (0.013 mol) was added dropwise at –30°C to a mixture of *N*-(1-methylethyl)-2-propanamine (0.013 mol) in THF (20 ml) under N_2 flow. The mixture stirred at –20°C for 30 minutes, then cooled to –70°C. A solution of 2-chloro-4-methyl-3-phenylquinoline (0.011 mol) in THF (20 ml) was added. The mixture was stirred for 45 minutes. A solution of intermediate 21 (0.013 mol) in THF (10 ml) was added. The mixture was stirred at –70°C for 2 hours, poured out into H_2O and extracted with EtOAc. The organic layer was separated, dried ($MgSO_4$), filtered, and the solvent was evaporated. The residue (5 g) was purified by column chromatography over silica gel (eluent: DCM/MeOH 98/2; 15-40µm). The pure fractions were collected and the solvent was evaporated, yielding 4 g of intermediate 26 (78%).

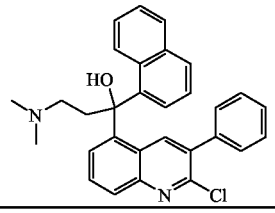
f) Preparation of intermediate 27



1.6M Butyllithium in hexane (0.0075 mol) was added dropwise at –70°C to a mixture of intermediate 14 (0.0062 mol) in THF (20 ml) under N_2 flow. The mixture was stirred at –70°C for 1 hour. A solution of intermediate 21 (0.0075 mol) in THF (10 ml) was added at –70°C. The mixture was stirred from –70°C to room temperature then stirred for 18 hours. H_2O was added. The mixture was extracted with EtOAc. The organic layer was washed with saturated NaCl, dried ($MgSO_4$), filtered and the solvent was evaporated. The residue (3 g) was purified by column chromatography over silica gel (eluent: DCM/MeOH/NH_4OH 97/3/0.1; 15-40µm). The pure fractions were collected and the solvent was evaporated, yielding 1.1 g of intermediate 27 (39%).

The following intermediates were prepared according to the method described above.

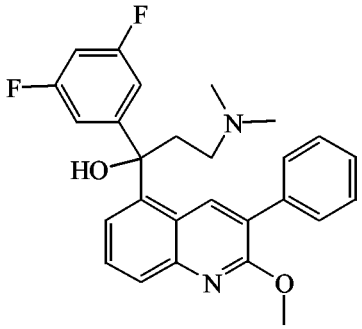
intermediate 35	
intermediate 36	
intermediate 37	
intermediate 38	
intermediate 39	

intermediate 40	

B. Preparation of the final compounds

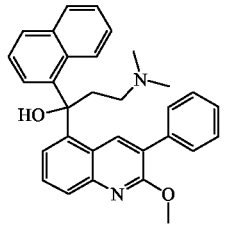
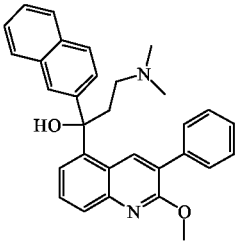
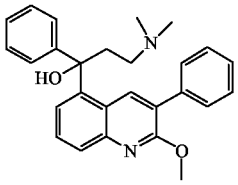
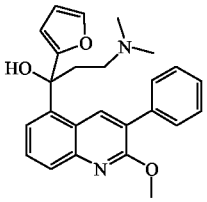
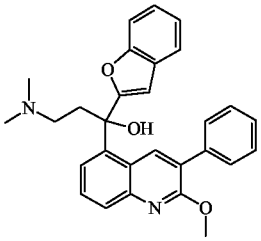
Example B1

a) Preparation of compound 1

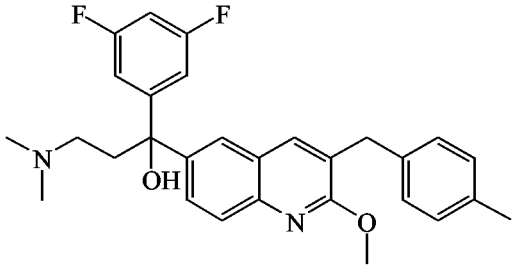


1.6M Butyllithium (0.0019 mol) was added dropwise at –70°C to a mixture of intermediate 8 (0.0016 mol) in THF (5 ml) under N_2 flow. The mixture was stirred at –70°C for 1 hour. A solution of intermediate 21 (0.0019 mol) in THF (2 ml) was added. H_2O was added. The mixture was extracted with DCM. The organic layer was separated, dried ($MgSO_4$), filtered, and the solvent was evaporated The residue was purified by column chromatography over silica gel (eluent: DCM/MeOH/NH_4OH 98/2/0.1; 10µm). The pure fractions were collected and the solvent was evaporated, yielding 0.2 g of compound 1 (28%, MH+: 449).

The following final compounds were prepared according to the method described above.

compound 2 (MH+: 463)	
compound 3 (MH+: 463)	
compound 4 (M.P.: 173°C)	
compound 5 (MH+: 403)	
compound 6 (MH+: 453)	

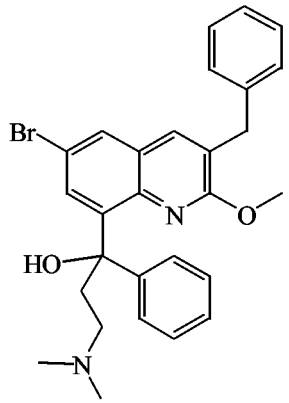
b) Preparation of compound 7



Butyllithium (0.0035 mol) was added dropwise at –20°C to a solution of *N*-(1-methylethyl)-2-propanamine (0.0034 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 intermediate (0.0029 mol) in THF (10 ml) was added. The mixture was stirred at –70°C for 2 hours. A solution of intermediate 21 (0.0032 mol) in THF (10 ml) was added at –70°C. The mixture was stirred at –70°C for 3 hours, poured out into ice water and extracted with DCM. The organic layer was separated, dried ($MgSO_4$), filtered, and the solvent was evaporated. The residue (1.4 g) was purified by column chromatography over silica gel (eluent: DCM/MeOH/NH_4OH 99/1/0.1; 15-40µm). The desired fraction was collected and the solvent was evaporated. The residue (0.968 g) was purified by column chromatography over silica gel (eluent: DCM/MeOH/NH_4OH 98/2/0.2; 15-40µm). The pure fractions were collected and the solvent was evaporated. The residue was dried, yielding 0.151g of compound 7 (11%, oil, NMR confirms structure).

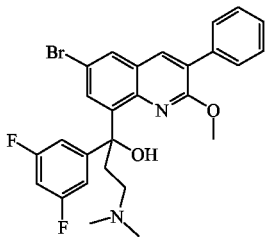
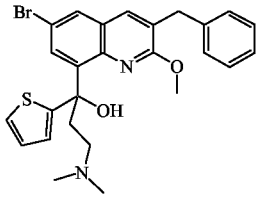
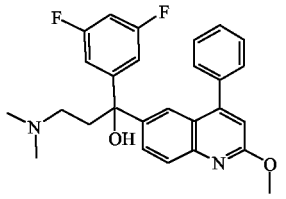
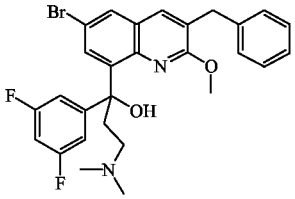
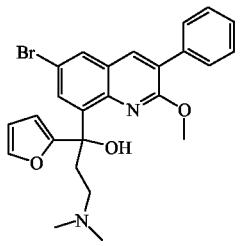
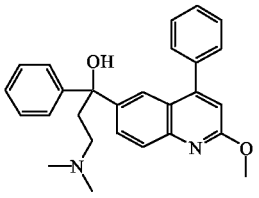
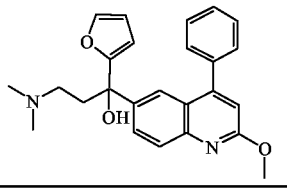
Example B2

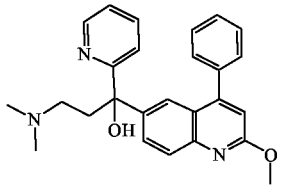
a) Preparation of compound 8



A 30% MeONa solution (2 ml) was added at room temperature to a mixture of intermediate 23 (0.002 mol) in MeOH (2ml). The mixture was stirred and refluxed overnight, poured out on ice and extracted with DCM. The organic layer was separated, dried ($MgSO_4$), filtered, and the solvent was evaporated. The residue (0.62 g) was purified by column chromatography over silica gel (eluent: DCM/MeOH/NH_4OH 95/5/0.5; 15-40µm). The pure fractions were collected and the solvent was evaporated. The obtained residue (0.39 g) was crystallized from DIPE. The precipitate was filtered off and dried, yielding 0.15 g of compound 8 (M.P.: 66°C).

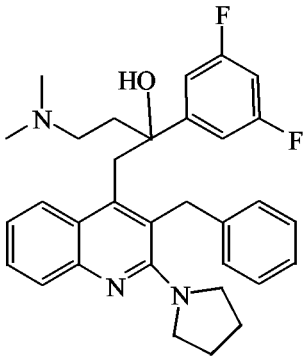
The following final compounds were prepared according to the method described above.

compound 9 (M.P.: 170°C)	
compound 10 (M.P.: 138°C)	
compound 11 (M.P.: 215°C) as an ethanedioic acid salt (1:1)	
compound 12 (M.P.: 160°C) (was prepared as ethane dioic acid)	
compound 13 (M.P.: 60°C)	
compound 14 (M.P.: 144°C)	
compound 15 (MH+: 403)	

compound 16 (M.P.: 132°C) as an ethanedioic acid salt (1:1)	

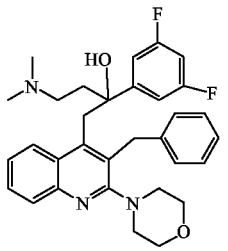
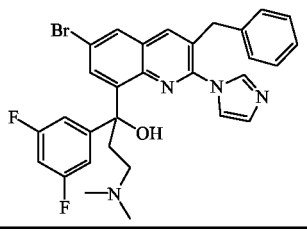
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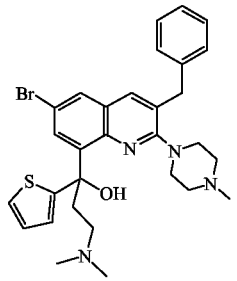
b) Preparation of compound 17



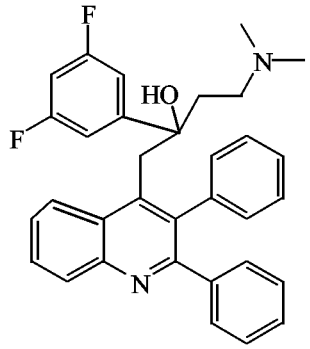
A mixture of intermediate 25 (0.0004 mol) and pyrrolidine (0.0021 mol) was stirred at 90°C overnight, then poured out into H_2O and extracted with DCM. The organic layer was separated, dried ($MgSO_4$), filtered, and the solvent was evaporated. The residue (0.18 g) was purified by column chromatography over silica gel (eluent: DCM/MeOH/NH_4OH 98/2/0.1; 10µm). The desired fraction was collected and the solvent was evaporated, yielding 0.043g of compound 17 (20%, MH+: 516).

The following final compounds were prepared according to the method described above.

compound 18 (MH+: 532)	
compound 19 (M.P.: 195°C)	

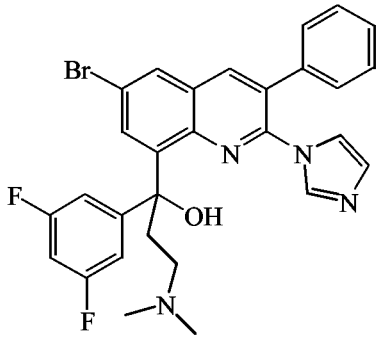
compound 20 (MH+: 579)	

c) Preparation of compound 21



A mixture of intermediate 26 (0.0006 mol), phenyl boronic acid (0.0019 mol), $Pd(PPh_3)_4$ (0.00006 mol) and Na_2CO_3 (0.0032 mol) in dimethyl ether (10ml) was stirred at 90°C overnight, poured out into H_2O and extracted with CH_2Cl_2. The organic layer was separated, dried ($MgSO_4$), filtered, and the solvent was evaporated. The residue (0.48g) was purified by column chromatography over silica gel (eluent: CH_2Cl_2/CH_3OH 99/1; 10µm). The pure fractions were collected and the solvent was evaporated. Yield: 0.054g of compound 21 (16%, M.P.: 173°C).

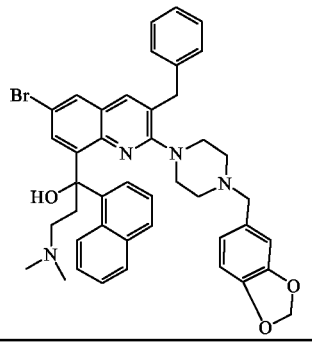
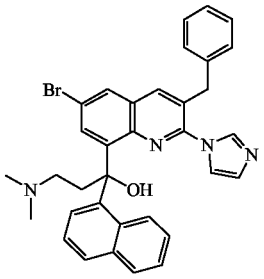
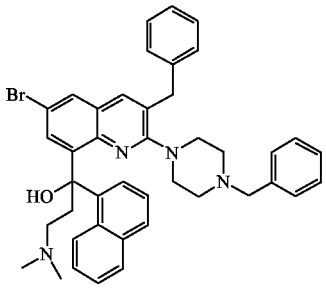
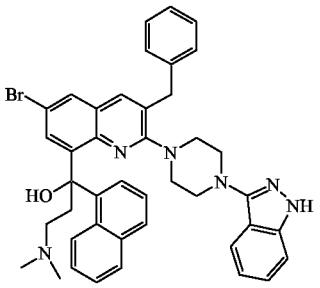
d) Preparation of compound 22

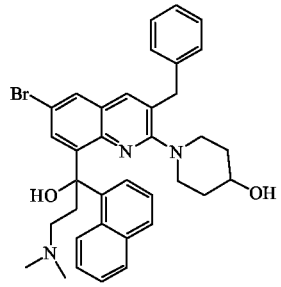
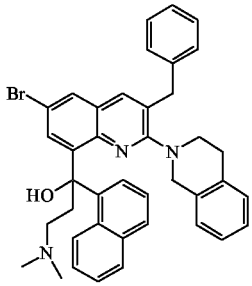
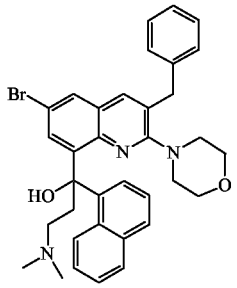
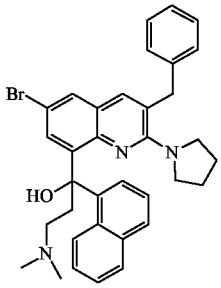
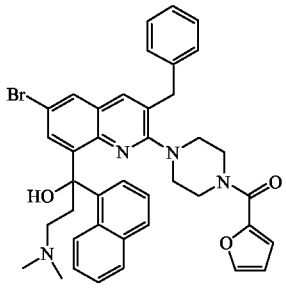


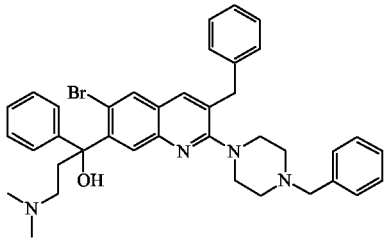
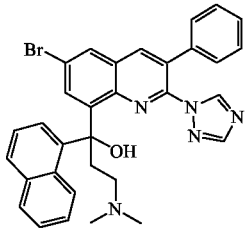
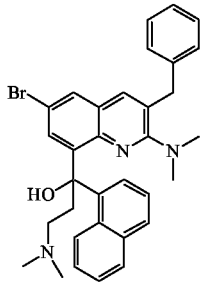
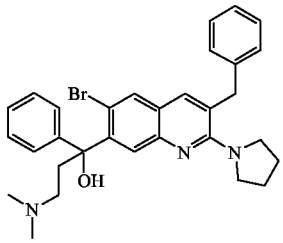
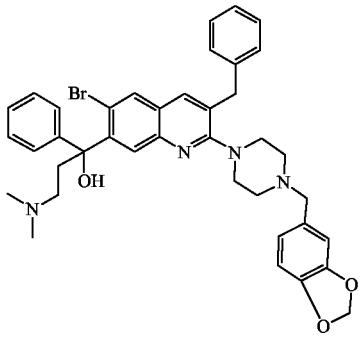
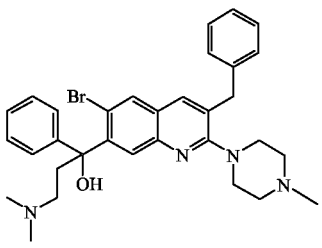
A mixture of intermediate 24 (0.0003 mol), imidazole (0.0018 mol) and K_2CO_3 (0.0011 mol) in acetonitrile (10ml) was stirred and refluxed for 48 hours, then cooled to room temperature. H_2O was added. The mixture was extracted with EtOAc. The organic layer was washed with saturated aqueous NaCl solution, dried ($MgSO_4$), filtered, and

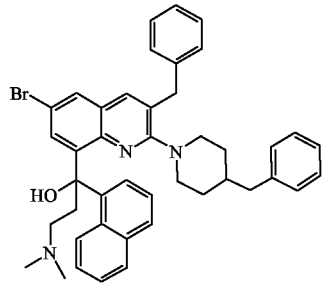
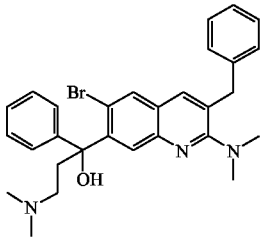
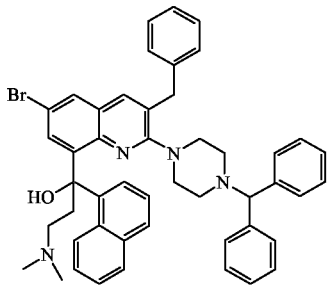
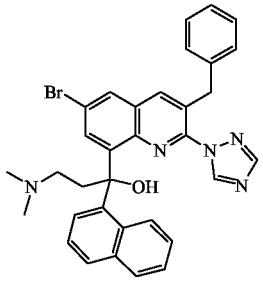
the solvent was evaporated. The residue (0.23g) was purified by column chromatography over silica gel (eluent: $CH_2Cl_2/CH_3OH/NH_4OH$ 97/3/0.1). The pure fractions were collected and the solvent was evaporated. Yield : 0.09g of compound 22 (42%) (melting point: 136°C).

The following final compounds were prepared according to the method described above.

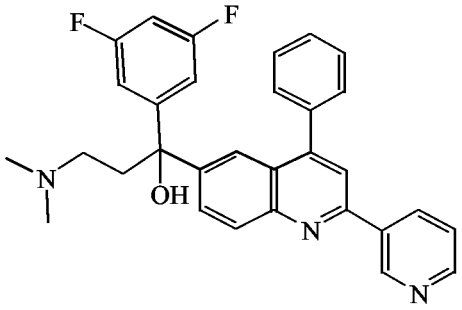
compound 23 (MH+: 743)	
compound 24 (M.P.: 200°C)	
compound 25 (MH+: 699)	
compound 26 (MH+: 725)	

compound 27 (MH+: 624)	
compound 28 (MH+: 656)	
compound 29 (MH+: 610)	
compound 30 (MH+: 594)	
compound 31 (MH+: 703)	

compound 32 (MH+: 649)	
compound 33 (M.P.: 167°C)	
compound 34 (MH+: 568)	
compound 35 (MH+: 544)	
compound 36 (MH+: 693)	
compound 37 (MH+: 573)	

compound 38 (MH+: 698)	
compound 39 (MH+: 518)	
compound 40 (MH+: 775)	
compound 41 (M.P.: 217°C)	

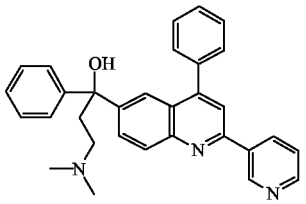
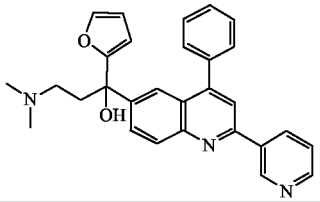
e) Preparation of compound 42



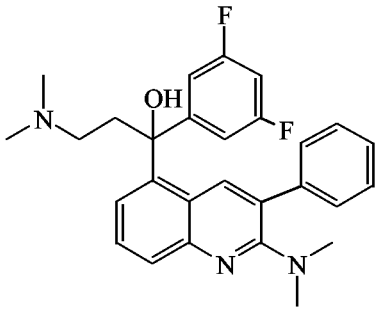
A mixture of intermediate 27 (0.0005 mol), 3-(1,3,2-dioxaborinan-2-yl)pyridine (0.0008 mol), tetrakis(triphenylphosphine)palladium (0.0005 mol) and a 2M K_2CO_3 solution (0.0027 mol) in dimethyl ether (7ml) and MeOH (3ml) was stirred at 100°C

for 18 hours under N_2 flow, then cooled to room temperature. H_2O was added. The mixture was extracted with EtOAc. The organic layer was washed with saturated aqueous NaCl solution, dried ($MgSO_4$), filtered, and the solvent was evaporated. The residue (0.34 g) was taken up in 2-propanone (6 ml). Oxalic acid was added. The mixture was stirred. The precipitate was filtered off and dried at 60°C under a vacuo, yielding 0.29 g of compound 42 as an ethanedioic acid salt (1:2) (80%, M.P.: 151°C).

The following final compounds were prepared according to the method described above.

compound 43 (MH+: 460)	
compound 44 (MH+: 450)	

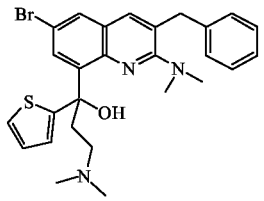
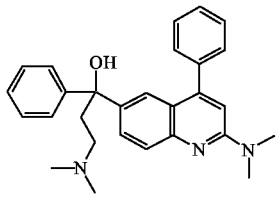
f) Preparation of compound 45



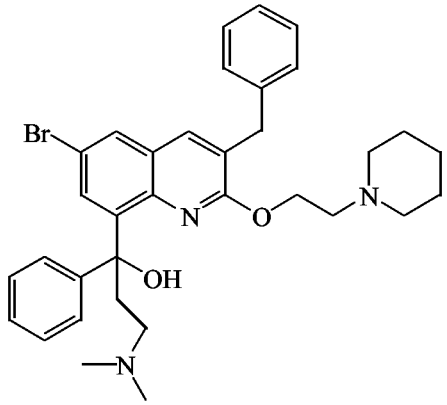
. ethanedioic acid (1:2.5)

A mixture of intermediate 37 (0.0007 mol) in *N*-methylmethanamine (10 ml) and acetonitrile (10 ml) was stirred at 90°C for 12 hours, poured out into H_2O/K_2CO_3 and extracted with DCM. The organic layer was separated, dried ($MgSO_4$), filtered, and the solvent was evaporated. The obtained fraction (0.25 g) was stirred at 90°C for 72 hours and purified by column chromatography over kromasil (eluent: DCM/MeOH 99/1; 10µm). The desired product fraction was collected and the solvent was evaporated. The residue (0.08 g) was dissolved in oxalic acid/2-propanol and converted into the ethanedioic acid salt (1:2.5). The precipitate was filtered off and dried, yielding 0.07 g of compound 45 (14%, M.P.: 136°C).

The following final compounds were prepared according to the method described above.

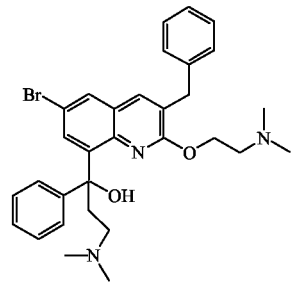
compound 46 (MH+: 524)	
compound 47 (MH+: 426)	

g) Preparation of compound 48

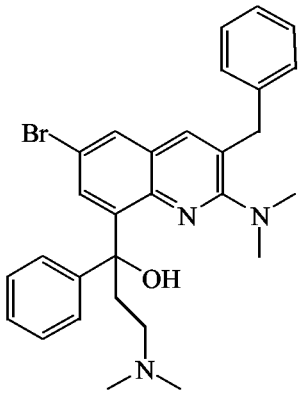


A mixture of KOH (0.0011 mol) in 1-piperidineethanol (2 ml) was stirred at 80°C till KOH disappeared. Intermediate 23 (0.0009 mol) was added. The mixture was stirred at 80°C overnight, poured out on ice and extracted with DCM. The organic layer was separated, dried ($MgSO_4$), filtered, and the solvent was evaporated. The residue (2.49 g) was crystallized from DIPE. The precipitate was filtered off and dried, yielding 0.308 g of compound 48 (M.P.: 131°C).

The following final compound was prepared according to the method described above.

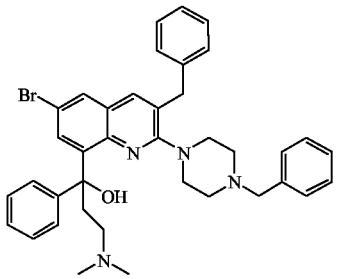
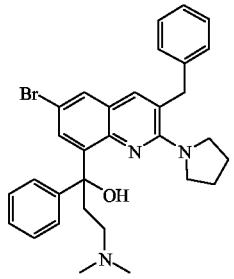
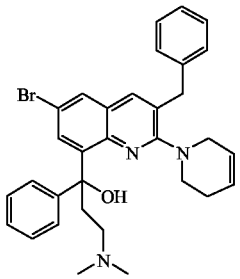
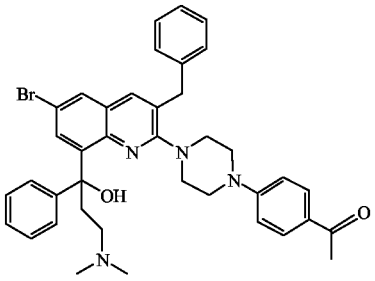
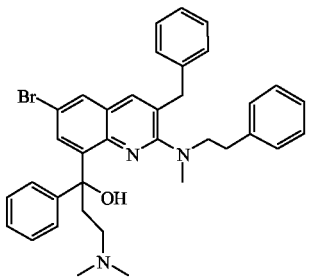
compound 49 (M.P.: 141°C)	

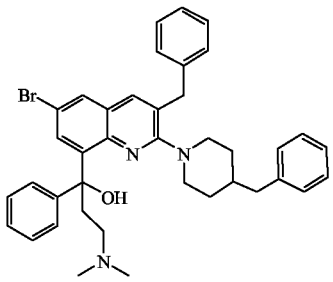
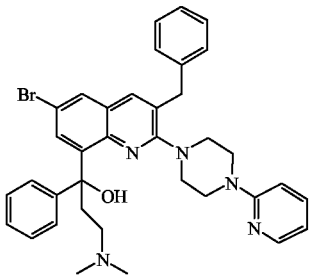
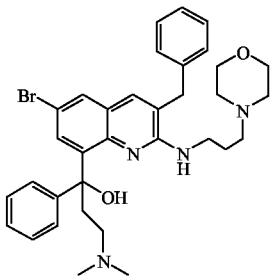
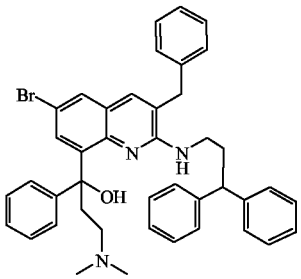
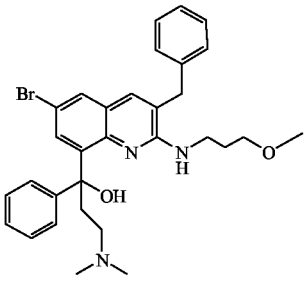
h) Preparation of compound 50

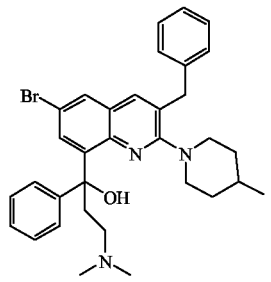
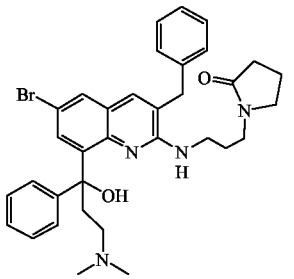
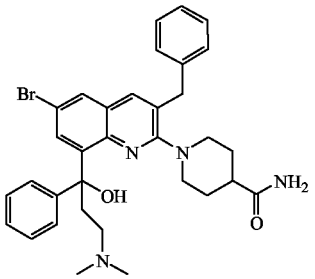


A mixture of intermediate 23 (0.000137 mol), *N*-methylmethanamine (0.000412 mol, 3 equiv.) and K_2CO_3 (3 equiv.) in acetonitrile (2 ml) was stirred at 80°C for 12 hours, poured out into H_2O and extracted with DCM. The organic layer was separated, dried ($MgSO_4$), filtered, and the solvent was evaporated. The obtained fraction was purified by column chromatography over silica gel, then the desired product fraction was collected and the solvent was evaporated, yielding 0.07 g of compound 50 (54.79%, MH+: 518).

The following final compounds were prepared according to the method described above.

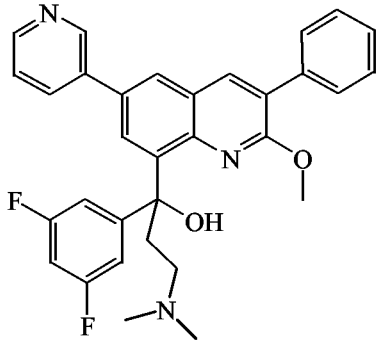
compound 51 (MH+: 649)	
compound 52 (MH+: 544)	
compound 53 (MH+: 556)	
compound 54 (MH+: 677)	
compound 55 (MH+: 608)	

compound 56 (MH+ 648)	
compound 57 (MH+: 636)	
compound 58 (MH+: 617)	
compound 59 (MH+: 684)	
compound 60 (MH+: 562)	

compound 61 (MH+: 572)	
compound 62 (MH+: 615)	
compound 63 (MH+: 601)	

Example B3

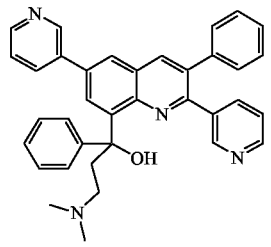
a) Preparation of compound 64



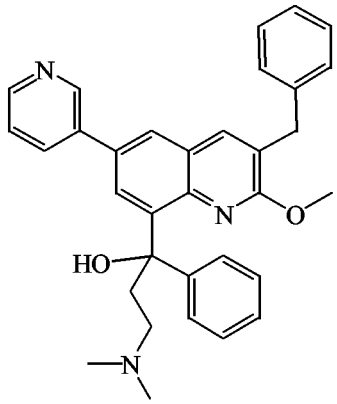
A mixture of compound 9 (0.0003 mol), 3-(1,3,2-dioxaborinan-2-yl)pyridine (0.0006 mol), tetrakis(triphenylphosphine)palladium (0.00003 mol) and a 2M K_2CO_3 solution (0.0015 mol) in dimethyl ether (6 ml) and MeOH (2 ml) was stirred at 100°C for 18 hours under N_2 flow, then cooled to room temperature. H_2O was added. The mixture was extracted with EtOAc. The organic layer was washed with saturated NaCl, dried ($MgSO_4$), filtered, and the solvent was evaporated. The residue (0.14 g) was taken up in

2-propanone (2 ml). Oxalic acid (2 equivalents) was added. The mixture was stirred for 10 minutes. The precipitate was filtered, washed with 2-propanone and dried at 70°C under a vacuo, yielding 0.077 g of compound 64 as ethanedioic acid salt (1:1.5) (38%, M.P.: 156°C).

The following final compound was prepared according to the method described above.

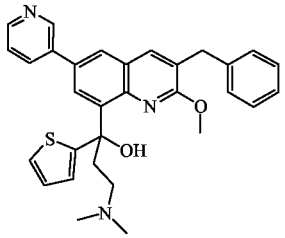
compound 65 (M.P.: 177°C)	

b) Preparation of compound 66

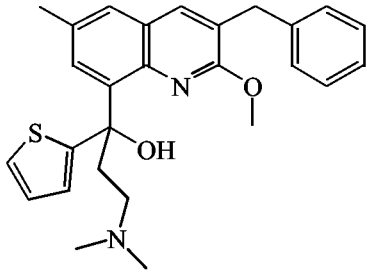


A mixture of compound 8 (0.0003 mol), tetrakis(triphenylphosphine)-palladium (0.00003 mol), a 2M Na_2CO_3 solution (0.0019 mol) and 3-(1,3,2-dioxaborinan-2-yl)pyridine (0.0011 mol) in dimethyl ether (6 ml) was stirred at 100°C overnight, then poured out into H_2O and extracted with DCM. The organic layer was separated, dried ($MgSO_4$), filtered, and the solvent was evaporated. The residue was purified by column chromatography over kromasil (eluent: toluene/2-propanol/NH_4OH 80/20/1; 10µm). The pure fractions were collected and the solvent was evaporated. The residue (0.1 g, 51%) was crystallized from DIPE/acetonitrile. The precipitate was filtered off and dried, yielding 0.057 g of compound 66 (M.P.: 180°C).

The following final compound was prepared according to the method described above.

compound 67 (M.P.: 199°C)	

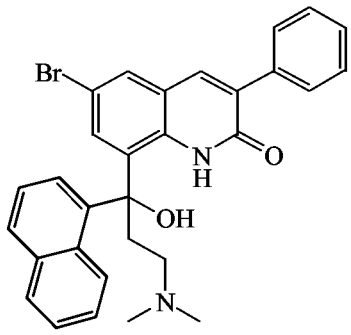
c) Preparation of compound 68



A mixture of compound 10 (0.0007 mol), tetrakis(triphenylphosphine)-palladium (0.00007 mol) and tetramethylstannane (0.0016 mol) in toluene (6 ml) was stirred and refluxed overnight. H_2O was added. The mixture was extracted with DCM. 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: DCM/MeOH/NH_4OH 95/5/0.3; 20µm). The pure fractions were collected and the solvent was evaporated, yielding 0.038 g of compound 68 (11%, MH+: 447).

Example B4

Preparation of compound 69

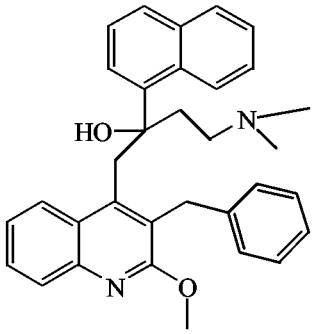


A mixture of intermediate 32 (0.0016 mol) in 6N HCl (5 ml) and THF (10 ml) was stirred at 80°C for 48 hours, then cooled to room temperature, poured out into a 10 % K_2CO_3 solution and extracted with EtOAc. The organic layer was washed with saturated NaCl, dried ($MgSO_4$), filtered and the solvent was evaporated. The residue was crystallized from diethyl ether/2-propanone. The precipitate was filtered off and

dried. Part of this fraction (0.3 g of 0.6 g (44%)) was taken up in hot 2-propanone. The precipitate was filtered off and dried, yielding 0.2 g of compound 69 (15%, M.P.: 190°C).

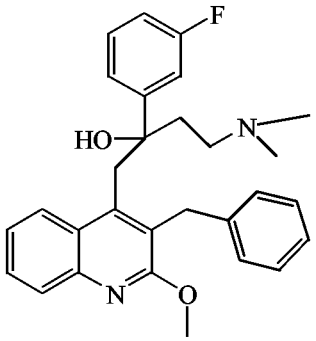
Example B5

a) Preparation of compound 70



n-Butyl lithium (0.0022 mol) was added slowly at –20°C to a mixture of diisopropyl amine (0.0022 mol) in THF (10 ml) under N_2. The mixture was stirred for 20 minutes and then cooled to –70°C. A solution of intermediate 17a (0.0019 mol) in THF (10 ml) was added. The mixture was stirred for 1 hour. A solution of 3-(dimethylamino)-1-(1-naphthalenyl)-1-propanone, (0.0028 mol) in THF (10 ml) was added at –70°C. The mixture was stirred for 1 hour. H_2O was added. The mixture was extracted with EtOAc. The organic layer was separated, dried over magnesium sulfate, filtered and the solvent was evaporated. The residue (1.13 g) was purified by column chromatography over silica gel (eluent: CH_2Cl_2/iPrOH/NH_4OH 96/4/0.2; 15-40μm). The pure fractions were collected and the solvent was evaporated. Yield : 0.04 g of compound 70 (4%; MH+:491).

b) Preparation of compound 71



This compound has been prepared according to B5a).

The residue (1g) was purified by column chromatography over silica gel (eluent: CH_2Cl_2/MeOH/NH_4OH 99/1/0.1; 15-40μm). The pure fractions were collected and the solvent was evaporated. The residue (0.32 g, 37%) was crystallized from diisopropylether. The precipitate was filtered off and dried. Yield : 0.133 g of compound 71 (15%, melting point: 123°C).

C. Analytical methods

The mass of the compounds was recorded with LCMS (liquid chromatography mass spectrometry). Three methods were used which are described below. The data are gathered in Table 1 below.

LCMS-method 1

LCMS analysis was carried out (electrospray ionization in positive mode, scanning mode from 100 to 900 amu) on a Kromasil C18 column (Interchim, Montluçon, FR; 5 μm, 4.6 x 150 mm) with a flow rate of 1 ml/minute. Two mobile phases (mobile phase A: 30% 6.5mM ammonium acetate + 40% acetonitrile + 30% formic acid (2ml/l); mobile phase B: 100% acetonitrile) were employed to run a gradient condition from 100 % A for 1 minute to 100% B in 4 minutes, 100% B for 5 minutes to 100 % A in 3 minutes, and reequilibrate with 100 % A for 2 minutes.

LCMS-method 2

LCMS analysis was carried out (electrospray ionization in both positive and negative (pulsed) mode scanning from 100 to 1000 amu) on a Kromasil C18 column (Interchim, Montluçon, FR; 3.5 μm, 4.6 x 100 mm) with a flow rate of 0.8 ml/minute. Two mobile phases (mobile phase A: 35% 6.5mM ammonium acetate + 30% acetonitrile + 35% formic acid (2ml/l); mobile phase B: 100% acetonitrile) were employed to run a gradient condition from 100 % A for 1 minute to 100% B in 4 minutes, 100% B at a flow rate of 1.2 ml/minute for 4 minutes to 100 % A at 0.8ml/minute in 3 minutes, and reequilibrate with 100 % A for 1.5 minute.

LCMS-method 3

LCMS analysis was carried out (electrospray ionization in positive mode, scanning from 100 to 900 amu) on a Xterra MS C18 column (Waters, Milford, MA; 5 μm, 4.6 x 150 mm) with a flow rate of 1 ml/minute. Two mobile phases (mobile phase A: 85% 6.5mM ammonium acetate + 15% acetonitrile; mobile phase B: 20% 6.5 mM ammonium acetate + 80% acetonitrile) were employed to run a gradient condition from 100 % A for 3 minutes to 100% B in 5 minutes, 100% B at a flow rate of 1.2 ml/minute

for 6 minutes to 100 % A at 0.8ml/minute in 3 minutes, and reequilibrate with 100 % A for 3 minutes.

Table 1 : Analytical method used

Compound No	LC/GC/MS Method
1	1
68	2
2	1
3	1
5	1
6	1
15	1
17	3
18	1
20	1
23	2
25	2
26	2
27	2
28	2
29	2
30	2
31	2
32	1
34	2
35	1
36	1
37	1
38	2
39	1
40	2
43	3
44	3
46	1
47	3
50	1
51	1
52	1
53	1

Compound No	LC/GC/MS Method
54	1
55	1
56	1
57	1
58	1
59	1
60	1
61	1
62	1
63	1
70	1

Pharmacological examples

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 and colony forming units (CFUs) were determined. In general, an inoculum level of approximately 100 CFUs 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 2.

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. No carryover effect is observed at the dilution of 10^{-2} used for plating. This results in limit of detection 5 X 10^2 CFU / ml or <2.7 log CFU/ml.

* 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.

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Table 2 : IC_{90} values (µg/ml) determined according to the Microtitre plate assay.

IC90 (µg/ml)															
Comp No.	**STA 29213**	**SPN 6305**	**SPY 8668**	**SMU 33402**	**EFA 29212**	**LMO 49594**	**BSU 43639**	**ECO 35218**	**PAE 27853**	**STA RMETHIC**	**STA 25923**	**STA 43300**	**EFA 14506**	**ECO 1403**	**ECO 25922**
64	8.3	10.5	2.1	2.1	13.2	13.2	8.3		13.2	11.8	6.6		10.5		
8	10.1	11.3	10.1	10.1		40.2	12.7		12.7	11.3	11.3		11.3		
46	10.5	10.5	10.5	10.5	10.5	10.5	10.5		10.5	9.3	11.7	10.5	10.5		
12	10.8	12.1	10.8	10.8	13.6	13.6	13.6		10.8	12.1	12.1	10.8	10.8		
10	12.9	11.5	10.2	10.2	10.2	10.2			12.9	10.2	11.5	12.9			
24	11.8	14.9	11.8	11.8	14.9	14.9	11.8		14.9	14.9	13.2		11.8		
9	10.5	13.3	10.5	10.5	10.5	10.5			10.5	11.8	11.8	13.3	11.8		
13	12.1	10.8	12.1		12.1	12.1	12.1		12.1	12.1	12.1				
22	14.2	12.6	11.2	11.2	14.2	14.2			14.2	14.2	12.6				
33	14.5	14.5	11.5	11.5	14.5	14.5	11.5		14.5	14.5	14.5		46.0		
20	11.6	14.6	11.6	14.6	14.6	14.6	14.6	11.6	14.6	46.0	13.0			13.0	14.6
65	13.5	13.5	13.5	13.5	13.5	13.5	13.5		13.5	13.5	13.5				
19	14.5	14.5	11.5	11.5	14.5	14.5	14.5		14.5	14.5	12.9	11.5			
59	15.3	17.2	15.3	15.3	17.2	10.9	10.9	15.3	17.2	54.4	54.4	17.2	54.4		
54	17.0	17.0	17.0	17.0	17.0				17.0						
26	16.3	3.6	2.9	2.9	3.6	3.6	14.5		2.9	18.2	7.3		14.5		
66	40.0	50.4	40.0	40.0	50.4	50.4	50.4		40.0	50.4	50.4				

IC90 (µg/ml)															
Comp No.	STA 29213	SPN 6305	SPY 8668	SMU 33402	EFA 29212	LMO 49594	BSU 43639	ECO 35218	PAE 27853	STA RMETHIC	STA 25923	STA 43300	EFA 14506	ECO 1403	ECO 25922
67	51.0	22.8	51.0		51.0	51.0	51.0		51.0	51.0	51.0				
49	44.7	56.3	22.4	44.7	56.3	56.3	56.3		56.3	56.3	56.3				56.3
48	53.7	60.3	47.9	47.9	60.3	60.3	60.3		47.9	60.3	53.7				
70	12.3	12.3	9.8	9.8	49.1	39.0	12.3		9.8	12.3	12.3				
71	11.5	11.5	9.2	9.2	11.5	9.2	11.5		11.5	11.5	11.5				
21	12.8	12.8	12.8		12.8	12.8	12.8		12.8	12.8	12.8				
6	9.0	11.4	9.0	9.0	11.4	11.4	11.4		9.0	10.1	11.4	9.0			
45	9.2	11.6	9.2	9.2	11.6	11.6	9.2		11.6	46.2	10.3		10.3		
2	9.2	11.6	9.2	9.2	11.6	11.6	9.2		9.2	11.6	11.6	9.2	8.2		
5	10.1	10.1	10.1		10.1	10.1	10.1		10.1	9.0	10.1				
4	10.4	10.4	10.4		10.4	10.4	10.4		10.4	10.4	10.4				
1	11.3	11.3	9.0	9.0	11.3	11.3	11.3		11.3	11.3	11.3		11.3		
3	11.6	5.2	9.2	9.2	11.6	11.6	11.6		9.2	11.6	11.6	9.2			
7	9.5	12.0	12.0		10.7	7.6	37.9		10.7	37.9	7.6				
11	11.3	11.3	9.0		11.3	11.3	11.3		11.3	11.3	11.3				
14	10.4	10.4	10.4		10.4	10.4	10.4		10.4	10.4	10.4				
15	10.1	10.1	10.1		10.1	10.1	10.1		10.1	10.1	10.1				
16	10.4	10.4	10.4		10.4	10.4	10.4		10.4	10.4	10.4				
42	39.4	12.5	12.5		12.5	39.4	12.5		12.5	49.6	9.9				

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IC90 (µg/ml)															
Comp No.	**STA 29213**	**SPN 6305**	**SPY 8668**	**SMU 33402**	**EFA 29212**	**LMO 49594**	**BSU 43639**	**ECO 35218**	**PAE 27853**	**STA RMETHIC**	**STA 25923**	**STA 43300**	**EFA 14506**	**ECO 1403**	**ECO 25922**
43	11.5	11.5	11.5		11.5				11.5						
44	11.3	11.3	11.3		11.3	11.3	11.3		11.3	11.3	11.3				
47	10.7	10.7	10.7		10.7	10.7	10.7		10.7	10.7	10.7				
69	13.3	13.3	13.3		13.3	41.9	52.8		13.3	52.8	52.8				

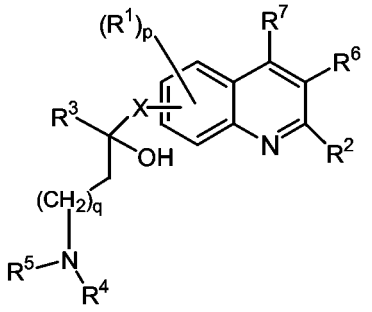
BSU 43639 means *Bacillus subtilis* (ATCC43639); ECO 25922 means *Escherichia coli* (ATCC25922); ECO 35218 means *Escherichia coli* (ATCC35218); ECO 1403 means *Escherichia coli* (ATCC1403);EFA 14506 means *Enterococcus faecalis* (ATCC14506); EFA 29212 means *Enterococcus faecalis* (ATCC29212); LMO 49594 means *Listeria monocytogenes* (ATCC49594); PAE 27853 means *Pseudomonas aeruginosa* (ATCC27853); SMU 33402 means *Streptococcus mutans* (ATCC33402); SPN 6305 means *Streptococcus pneumoniae* (ATCC6305); SPY 8668 means *Streptococcus pyogens* (ATCC8668); STA 43300 means *Staphylococcus aureus* (ATCC43300); STA 25923 means *Staphylococcus aureus* (ATCC25923); STA 29213 means *Staphylococcus aureus* (ATCC29213); STA RMETH means methicilline resistant *Staphylococcus aureus* (MRSA) (a clinical isolate from the University of Antwerp).

ATCC means American type tissue culture.

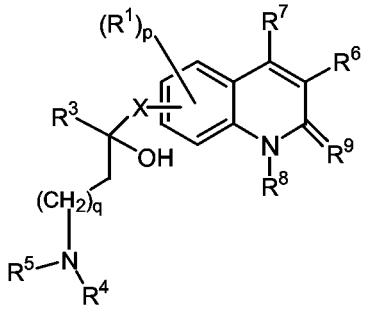
SUBSTITUTE SHEET (RULE 26)

CLAIMS

1. Use of a compound for the manufacture of a medicament for the treatment of a bacterial infection, said compound being a compound of Formula (Ia) and (Ib)



(Ia)



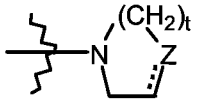
(Ib)

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

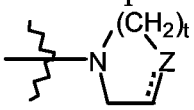
R^1 is hydrogen, halo, haloalkyl, cyano, hydroxy, Ar, Het, alkyl, alkyloxy, alkylthio, alkyloxyalkyl, alkylthioalkyl, Ar-alkyl or di(Ar)alkyl ;

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

R^2 is hydrogen; alkyl; hydroxy; mercapto; alkyloxy optionally substituted with amino or mono or di(alkyl)amino or a radical of formula



wherein Z is CH_2, CH-R^{10}, O, S, N-R^{10} and t is an integer equal to 1 or 2 and the dotted line represents an optional bond; alkyloxyalkyloxy; alkylthio; mono or di(alkyl)amino wherein alkyl may optionally be substituted with one or two substituents each independently be selected from alkyloxy or Ar or Het or morpholinyl or 2-oxopyrrolidinyl; Ar; Het or a radical of formula



wherein Z is CH_2, CH-R^{10}, O, S, N-R^{10} ; t is an integer equal to 1 or 2; and the dotted line represents an optional bond;

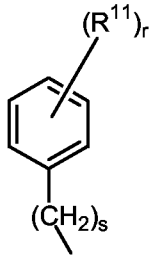
R^3 is alkyl, Ar, Ar-alkyl, Het or Het-alkyl;

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

X is a direct bond or CH_2;

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, pyrazolidinyl, 2-imidazolinyl, 2-pyrazolinyl, imidazolyl, pyrazolyl, triazolyl, piperidinyl, pyridinyl, piperazinyl, imidazolidinyl, pyridazinyl, pyrimidinyl, pyrazinyl, triazinyl, morpholinyl and thiomorpholinyl, each of said rings optionally being substituted with alkyl, halo, haloalkyl, hydroxy, alkyloxy, amino, mono- or dialkylamino, alkylthio, alkyloxyalkyl, alkylthioalkyl or pyrimidinyl;

R^6 is hydrogen or a radical of formula  wherein s is an integer equal to zero, 1, 2, 3 or 4; r is an integer equal to 1, 2, 3, 4 or 5 ; and R^{11} is hydrogen, halo, haloalkyl, hydroxy, Ar, alkyl, alkyloxy, alkylthio, alkyloxyalkyl, alkylthioalkyl, Ar-alkyl or di(Ar)alkyl ; or two vicinal R^{11} radicals may be taken together to form together with the phenyl ring to which they are attached a naphthyl;

R^7 is hydrogen, alkyl, Ar or Het;

R^8 is hydrogen or alkyl ;

R^9 is oxo ; or

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

R^{10} is hydrogen, alkyl, hydroxyl, aminocarbonyl, mono-or di(alkyl)aminocarbonyl, Ar, Het, alkyl substituted with one or two Het, alkyl substituted with one or two Ar, Het-C(=O)-, Ar-C(=O)-;

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

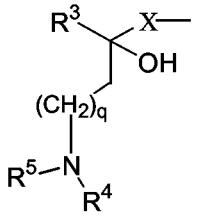
radical having from 1 to 6 carbon atoms ; wherein each carbon atom can be optionally substituted with hydroxy, alkyloxy or oxo;

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

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

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

haloalkyl is a straight or branched saturated hydrocarbon radical having from 1 to 6 carbon atoms or a cyclic saturated hydrocarbon radical having from 3 to 6 carbon atoms 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;



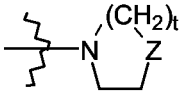
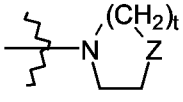
provided that when R^7 is hydrogen then the radical may also be placed in position 4 of the quinoline ring; and

provided that the bacterial infection is other than a Mycobacterial infection.

2. Use according to claim 1 wherein R^1 is hydrogen, halo or Het.

3. Use according to claim 2 wherein R^1 is halo.

4. Use according to any one of the preceding claims wherein p is equal to 1.

5. Use according to any one of the preceding claims wherein R^2 is alkyloxy; Het; Ar; mono or di(alkyl)amino wherein alkyl may optionally be substituted with one or two Ar substituents; a radical of formula  wherein Z is N-R^{10} ; t is an integer equal to 2; alkyloxy substituted with amino or mono or di(alkyl)amino or a radical of formula  wherein Z is CH_2 and t is an integer equal to 2.

6. Use according to claim 5 wherein R^2 is alkyloxy.

7. Use according to any one of the preceding claims wherein R^3 is naphthyl, phenyl or Het, each optionally substituted with 1 or 2 substituents.

8. Use according to claim 7 wherein R^3 is naphthyl, phenyl, 3,5-dihalophenyl, thienyl, furanyl or benzofuranyl.

9. Use according to any one of the preceding claims wherein q is equal to 1.

10. Use according to any one of the preceding claims wherein R^4 and R^5 each independently are alkyl.

11. Use according to any one of the preceding claims wherein R^6 is benzyl or phenyl.

12. Use according to any one of the preceding claims wherein R^7 is hydrogen.

13. Use according to any one of the preceding claims wherein X is a direct bond.

14. Use according to any one of claims 1 to 12 wherein X is CH_2.

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

16. Use according to any one of the preceding claims wherein the bacterial infection is an infection with a gram-positive bacterium.

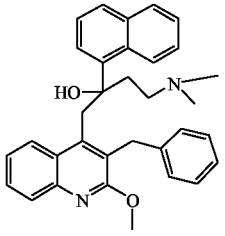
17. A combination of (a) a compound of Formula (Ia) or (Ib) as defined in any one of claims 1 to 15, and (b) one or more other antibacterial agents provided that the one or more other antibacterial agents are other than antimycobacterial agents.

18. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and, as active ingredient, a therapeutically effective amount of (a) a compound of Formula (Ia) or (Ib) as defined in any one of claims 1 to 15, and (b) one or more other antibacterial agents provided that the one or more other antibacterial agents are other than antimycobacterial agents.

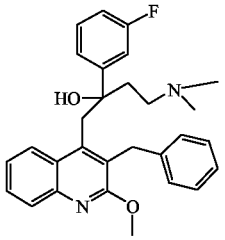
19. The use of a combination as claimed in claim 17 or a pharmaceutical composition as claimed in claim 18 for the treatment of a bacterial infection.

20. A product containing (a) a compound of Formula (Ia) or (Ib) as defined in any one of claims 1 to 15, and (b) one or more other antibacterial agents provided that the one or more other antibacterial agents are other than antimycobacterial agents, as a combined preparation for simultaneous, separate or sequential use in the treatment of a bacterial infection.

21. A compound selected from



or



,

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