

ANTIBACTERIAL QUINOLINE DERIVATIVES

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

BACKGROUND OF THE INVENTION

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

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

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

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

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

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

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

- Another factor in the control of the TB epidemic is the problem of latent TB. In spite of decades of tuberculosis (TB) control programs, about 2 billion people are infected by
35 M. tuberculosis, though asymptotically. About 10% of these individuals are at risk of developing active TB during their lifespan. The global epidemic of TB is fuelled by infection of HIV patients with TB and rise of multi-drug resistant TB strains

- (MDR-TB). The reactivation of latent TB is a high risk factor for disease development and accounts for 32% deaths in HIV infected individuals. To control TB epidemic, the need is to discover new drugs that can kill dormant or latent bacilli. The dormant TB can get reactivated to cause disease by several factors like suppression of host
- 5 immunity by use of immunosuppressive agents like antibodies against tumor necrosis factor α or interferon- γ . In case of HIV positive patients the only prophylactic treatment available for latent TB is two- three months regimens of rifampicin, pyrazinamide. The efficacy of the treatment regime is still not clear and furthermore the length of the treatments is an important constrain in resource-limited environments.
- 10 Hence there is a drastic need to identify new drugs, which can act as chemoprophylatic agents for individuals harboring latent TB bacilli.
- The tubercle bacilli enter healthy individuals by inhalation; they are phagocytosed by the alveolar macrophages of the lungs. This leads to potent immune response and formation of granulomas, which consist of macrophages infected with *M. tuberculosis*
- 15 surrounded by T cells. After a period of 6-8 weeks the host immune response cause death of infected cells by necrosis and accumulation of caseous material with certain extracellular bacilli, surrounded by macrophages, epitheloid cells and layers of lymphoid tissue at the periphery. In case of healthy individuals, most of the mycobacteria are killed in these environments but a small proportion of bacilli still
- 20 survive and are thought to exist in a non-replicating, hypometabolic state and are tolerant to killing by anti-TB drugs like isoniazid. These bacilli can remain in the altered physiological environments even for individual's lifetime without showing any clinical symptoms of disease. However, in 10% of the cases these latent bacilli may reactivate to cause disease. One of the hypothesis about development of these
- 25 persistent bacteria is patho-physiological environment in human lesions namely, reduced oxygen tension, nutrient limitation, and acidic pH. These factors have been postulated to render these bacteria phenotypically tolerant to major anti-mycobacterial drugs.
- 30 In addition to the management of the TB epidemic, there is the emerging problem of resistance to first-line antibiotic agents. Some important examples include penicillin-resistant *Streptococcus pneumoniae*, vancomycin-resistant enterococci, methicillin-resistant *Staphylococcus aureus*, multi-resistant salmonellae.
- 35 The consequences of resistance to antibiotic agents are severe. Infections caused by resistant microbes fail to respond to treatment, resulting in prolonged illness and greater risk of death. Treatment failures also lead to longer periods of infectivity, which

increase the numbers of infected people moving in the community and thus exposing the general population to the risk of contracting a resistant strain infection.

Hospitals are a critical component of the antimicrobial resistance problem worldwide. The combination of highly susceptible patients, intensive and prolonged antimicrobial use, and cross-infection has resulted in infections with highly resistant bacterial pathogens.

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

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

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

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

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

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

growth of bacterial microorganisms.

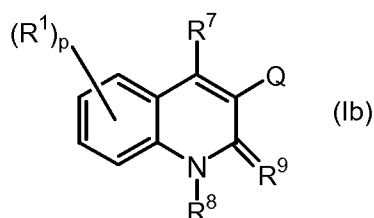
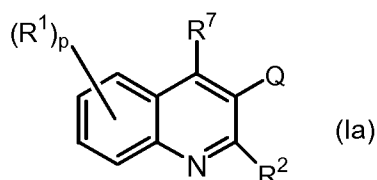
The purpose of the present invention is to provide novel compounds, in particular substituted quinoline derivatives, having the property of inhibiting bacterial growth especially of Streptococci, Staphylococci or mycobacteria and therefore useful for the treatment of bacterial diseases, particularly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

- 10 The compounds according to the present invention are characterized by the presence of a unsaturated carbon chain attached to the 3-position of the quinoline nucleus and thus have a different basic structure to the quinoline derivatives described in the above-mentioned prior art documents. The compounds according to the present invention therefore have the advantage that they are able to form fewer enantiomers. The compounds of the present invention show not only activity against mycobacterial strains, but they also have improved activity against other bacterial strains, especially against Streptococci and/or Staphylococci.

SUMMARY OF THE INVENTION

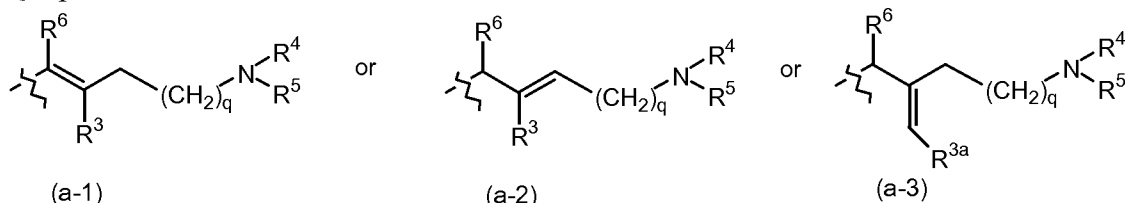
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The present invention relates to novel substituted quinoline derivatives according to formula (Ia) or (Ib):



including any stereochemically isomeric form thereof, wherein

Q represents a radical of formula

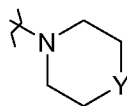


p is an integer equal to 1, 2, 3 or 4;

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

5 R^1 is hydrogen, cyano, formyl, carboxyl, halo, alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, haloalkyl, hydroxy, alkyloxy, alkylthio, alkylthioalkyl, $-C=N-OR^{11}$, amino, mono or di(alkyl)amino, aminoalkyl, mono or di(alkyl)aminoalkyl, alkylcarbonylaminoalkyl, aminocarbonyl, mono or di(alkyl)aminocarbonyl, arylalkyl, arylcarbonyl, $R^{5a}R^{4a}$ Nalkyl, di(aryl)alkyl, aryl, $R^{5a}R^{4a}N-$, $R^{5a}R^{4a}N-C(=O)-$, or Het;

10 R^2 is hydrogen, alkyloxy, aryl, aryloxy, hydroxy, mercapto, alkyloxyalkyloxy, alkylthio, mono or di(alkyl)amino, pyrrolidino or a



radical of formula wherein Y is CH_2 , O, S, NH or N-alkyl ;

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

15 Het-alkyl, Het-O-alkyl, Het-alkyl-O-alkyl or phenyl;

R^{3a} is hydrogen, cyano, alkyl, arylalkyl, aryl-O-alkyl, aryl-alkyl-O-alkyl, aryl, aryl-aryl, Het, Het-alkyl, Het-O-alkyl, or Het-alkyl-O-alkyl;

R^4 and R^5 each independently is hydrogen; alkyl; alkyloxyalkyl; arylalkyl; Het-alkyl; mono- or dialkylaminoalkyl; bicyclo[2.2.1]heptyl; Het; aryl; or $-C(=NH)-NH_2$; or

20 R^4 and R^5 together with the nitrogen atom to which they are attached form a radical selected from the group consisting of pyrrolidino, piperidino, piperazino, morpholino, 4-thiomorpholino, 1,1-dioxide-thiomorpholinyl, azetidiny, 2,3-dihydroisoindol-1-yl, thiazolidin-3-yl, 1,2,3,6-tetrahydropyridyl, hexahydro-1H-azepinyl, hexahydro-1H-1,4-diazepinyl, hexahydro-1,4-oxazepinyl, 1,2,3,4-tetrahydroisoquinolin-2-yl, 2,5-diazabicyclo[2.2.1]heptyl, pyrrolinyl, pyrrolyl, imidazolidinyl, pyrazolidinyl, 2-imidazolinyl, 2-pyrazolinyl, imidazolyl, pyrazolyl, triazolyl, pyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl and triazinyl, each radical optionally substituted with 1, 2, 3 or 4 substituents, each substituent independently selected from alkyl, haloalkyl, alkylcarbonyl,

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- halo, arylalkyl, hydroxy, alkyloxy, amino, mono- or dialkylamino, aminoalkyl, mono- or dialkylaminoalkyl, alkylthio, alkylthioalkyl, aryl, pyridyl, pyrimidinyl, piperidinyl optionally substituted with alkyl or pyrrolidinyl optionally substituted with arylalkyl;
- 5 R^{4a} and R^{5a} together with the nitrogen atom to which they are attached form a radical selected from the group consisting of pyrrolidino, piperidino, piperazino, morpholino, 4-thiomorpholino, 2,3-dihydroisoindol-1-yl, thiazolidin-3-yl, 1,2,3,6-tetrahydropyridyl, hexahydro-1*H*-azepinyl, hexahydro-1*H*-1,4-diazepinyl, hexahydro-1,4-oxazepinyl, 1,2,3,4-
- 10 tetrahydroisoquinolin-2-yl, pyrrolinyl, pyrrolyl, imidazolidinyl, pyrazolidinyl, 2-imidazolinyl, 2-pyrazolinyl, imidazolyl, pyrazolyl, triazolyl, pyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl and triazinyl, each radical optionally substituted with 1, 2, 3 or 4 substituents, each substituent independently selected from alkyl, haloalkyl, halo, arylalkyl,
- 15 hydroxy, alkyloxy, amino, mono- or dialkylamino, alkylthio, alkylthioalkyl, aryl, pyridyl or pyrimidinyl;
- R^6 is aryl¹ or Het;
- R^7 is hydrogen, halo, alkyl, aryl or Het;
- R^8 is hydrogen or alkyl;
- 20 R^9 is oxo; or
- R^8 and R^9 together form the radical $-\text{CH}=\text{CH}-\text{N}=\text{}$;
- R^{11} is hydrogen or alkyl;
- aryl¹ is a homocycle selected from phenyl, naphthyl, acenaphthyl or tetrahydronaphthyl, each being optionally substituted with 1, 2 or 3
- 25 substituents, each substituent being independently selected from hydroxy, halo, cyano, nitro, amino, mono- or dialkylamino, alkyl, C₂₋₆alkenyl optionally substituted with phenyl, haloalkyl, alkyloxy, haloalkyloxy, carboxyl, alkyloxycarbonyl, aminocarbonyl, morpholinyl or mono- or dialkylaminocarbonyl;
- 30 aryl¹ is a homocycle selected from phenyl, naphthyl, acenaphthyl or tetrahydronaphthyl, each being optionally substituted with 1, 2 or 3 substituents, each substituent being independently selected from hydroxy, halo, cyano, nitro, amino, mono- or dialkylamino, alkyl, haloalkyl, alkyloxy, alkylthio, haloalkyloxy, carboxyl,
- 35 alkyloxycarbonyl, aminocarbonyl, morpholinyl, Het or mono- or dialkylaminocarbonyl;

Het is a monocyclic heterocycle selected from *N*-phenoxypiperidinyl, piperidinyl, pyrrolyl, pyrazolyl, imidazolyl, furanyl, thienyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, pyridinyl, pyrimidinyl, pyrazinyl or pyridazinyl; or a bicyclic heterocycle selected from quinolinyl, quinoxalinyl, indolyl, benzimidazolyl, benzoxazolyl, benzisoxazolyl, benzothiazolyl, benzisothiazolyl, benzofuranyl, benzothienyl, 2,3-dihydrobenzo[1,4]dioxinyl or benzo[1,3]dioxolyl; each monocyclic and bicyclic heterocycle being optionally substituted with 1, 2 or 3 substituents, each substituent independently selected from halo, hydroxy, alkyl or alkyloxy; the *N*-oxides thereof, the pharmaceutically acceptable salts thereof or the solvates thereof.

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

The compounds of formula (Ia) and (Ib) are interrelated in that e.g. a compound according to formula (Ib), with R⁹ equal to oxo and R⁸ equal to hydrogen, is the tautomeric equivalent of a compound according to formula (Ia) with R² equal to hydroxy (keto-enol tautomerism).

In the definition of Het, it is meant to include all the possible isomeric forms of the heterocycles, for instance, pyrrolyl comprises 1*H*-pyrrolyl and 2*H*-pyrrolyl.

The aryl, aryl¹ or Het listed in the definitions of the substituents of the compounds of formula (Ia) or (Ib) (see for instance R³) as mentioned hereinbefore or hereinafter may be attached to the remainder of the molecule of formula (Ia) or (Ib) through any ring carbon or heteroatom as appropriate, if not otherwise specified. Thus, for example, when Het is imidazolyl, it may be 1-imidazolyl, 2-imidazolyl, 4-imidazolyl and the like.

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

The pharmaceutically acceptable salts as mentioned hereinbefore or hereinafter are meant to comprise the therapeutically active non-toxic acid addition salt forms which

the compounds according to formula (Ia) or formula (Ib) are able to form. Said acid addition salts can be obtained by treating the base form of the compounds according to formula (Ia) or formula (Ib) with appropriate acids, for example inorganic acids, for example hydrohalic acid, in particular hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid and phosphoric acid; organic acids, for example acetic acid, hydroxyacetic acid, propanoic acid, lactic acid, pyruvic acid, oxalic acid, malonic acid, succinic acid, maleic acid, fumaric acid, malic acid, tartaric acid, citric acid, methanesulfonic acid, ethanesulfonic acid, benzenesulfonic acid, p-toluenesulfonic acid, cyclamic acid, salicylic acid, p-aminosalicylic acid and pamoic acid.

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

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

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The term pharmaceutically acceptable salt also comprises the quaternary ammonium salts (quaternary amines) which the compounds of formula (Ia) or (Ib) are able to form by reaction between a basic nitrogen of a compound of formula (Ia) or (Ib) and an appropriate quaternizing agent, such as, for example, an optionally substituted C₁₋₆alkylhalide, arylC₁₋₆alkylhalide, C₁₋₆alkylcarbonylhalide, arylcarbonylhalide, HetC₁₋₆alkylhalide or Hetcarbonylhalide, e.g. methyl iodide or benzyl iodide.

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Preferably, Het represents a monocyclic heterocycle selected from furanyl or thienyl; or

a bicyclic heterocycle selected from benzofuranyl or benzothienyl; each monocyclic and bicyclic heterocycle may optionally be substituted with 1, 2 or 3 substituents, each substituent independently selected from the group of halo, alkyl and aryl. Preferably, the quaternizing agent is C₁₋₆alkylhalide. Other reactants with good leaving groups may also be used, such as C₁₋₆alkyl trifluoromethanesulfonates, C₁₋₆alkyl methanesulfonates, and C₁₋₆alkyl *p*-toluenesulfonates. A quaternary amine has a positively charged nitrogen. Pharmaceutically acceptable counterions include chloro, bromo, iodo, trifluoroacetate, acetate, triflate, sulfate, sulfonate. Preferably, the counterion is iodo. The counterion of choice can be introduced using ion exchange resins.

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

In the framework of this application, a compound according to the invention is inherently intended to comprise all stereochemically isomeric forms thereof. The term "stereochemically isomeric forms" as used hereinbefore or hereinafter defines all the possible stereoisomeric forms which the compounds of formula (Ia) and (Ib), and their *N*-oxides, pharmaceutically acceptable salts, solvates or physiologically functional derivatives may possess. Unless otherwise mentioned or indicated, the chemical designation of compounds denotes the mixture of all possible stereochemically isomeric forms.

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

Stereochemically isomeric forms of the compounds of formula (Ia) and (Ib) are obviously intended to be embraced within the scope of this invention. Of special interest are those compounds of formula (Ia) or (Ib) which are stereochemically pure.

Following CAS-nomenclature conventions, when two stereogenic centers of known absolute configuration are present in a molecule, an *R* or *S* descriptor is assigned (based on Cahn-Ingold-Prelog sequence rule) to the lowest-numbered chiral center, the reference center. The configuration of the second stereogenic center is indicated using

relative descriptors $[R^*, R^*]$ or $[R^*, S^*]$, where R^* is always specified as the reference center and $[R^*, R^*]$ indicates centers with the same chirality and $[R^*, S^*]$ indicates centers of unlike chirality. For example, if the lowest-numbered chiral center in the molecule has an *S* configuration and the second center is *R*, the stereo descriptor would be specified as *S*- $[R^*, S^*]$. If “ α ” and “ β ” are used : the position of the highest priority substituent on the asymmetric carbon atom in the ring system having the lowest ring number, is arbitrarily always in the “ α ” position of the mean plane determined by the ring system. The position of the highest priority substituent on the other asymmetric carbon atom in the ring system relative to the position of the highest priority substituent on the reference atom is denominated “ α ”, if it is on the same side of the mean plane determined by the ring system, or “ β ”, if it is on the other side of the mean plane determined by the ring system.

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

In particular, in view of the fact that the compounds of formula (Ia) or (Ib) contain in substituent Q at least 1 double bond, the compounds can have an E configuration at that double bond, they can have a Z configuration at that double bond or they can be a mixture of E and Z configuration at that double bond. Preferably, the compound of formula (Ia) or (Ib) as defined hereinbefore or hereinafter has a particular configuration at that double bond (substantially free of the other configuration).

Compounds of formula (Ia) or (Ib) wherein Q is a radical of formula (a-2) or (a-3) also contain at least one chiral center, *i.e.* the carbon atom attaching substituent Q to the quinoline moiety. These compounds can have R configuration at that carbon atom, S configuration at that carbon atom or they can be a mixture of R and S at that carbon atom. Preferably, the compound of formula (Ia) or (Ib) as defined hereinbefore or hereinafter has a particular configuration at that carbon atom (substantially free of the other configuration).

The compounds of either formula (Ia) and (Ib) may be synthesized in the form of mixtures, in particular racemic mixtures, of enantiomers which can be separated from one another following art-known resolution procedures. The racemic compounds of

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

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

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

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

In the framework of this application, a compound according to the invention is

inherently intended to comprise all isotopic combinations of its chemical elements. In the framework of this application, a chemical element, in particular when mentioned in relation to a compound according to formula (Ia) or (Ib), comprises all isotopes and isotopic mixtures of this element, either naturally occurring or synthetically produced, either with natural abundance or in an isotopically enriched form. In particular, when hydrogen is mentioned, it is understood to refer to ^1H , ^2H , ^3H and mixtures thereof; when carbon is mentioned, it is understood to refer to ^{11}C , ^{12}C , ^{13}C , ^{14}C and mixtures thereof; when nitrogen is mentioned, it is understood to refer to ^{13}N , ^{14}N , ^{15}N and mixtures thereof; when oxygen is mentioned, it is understood to refer to ^{14}O , ^{15}O , ^{16}O , ^{17}O , ^{18}O and mixtures thereof; and when fluorine is mentioned, it is understood to refer to ^{18}F , ^{19}F and mixtures thereof.

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

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

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

In the framework of this application, alkyl is a straight or branched saturated hydrocarbon radical having from 1 to 6 carbon atoms ; or is a cyclic saturated hydrocarbon radical having from 3 to 6 carbon atoms ; or is a cyclic saturated hydrocarbon radical having from 3 to 6 carbon atoms attached to a straight or branched saturated hydrocarbon radical having from 1 to 6 carbon atoms ; wherein each carbon atom can be optionally substituted with cyano, hydroxy, C₁₋₆alkyloxy or oxo.

Preferably alkyl is a straight or branched saturated hydrocarbon radical having from 1 to 6 carbon atoms ; or is a cyclic saturated hydrocarbon radical having from 3 to 6 carbon atoms ; wherein each carbon atom can be optionally substituted with hydroxyl or C₁₋₆alkyloxy.

Preferably, alkyl is methyl, ethyl or cyclohexylmethyl, more preferably methyl or ethyl. An interesting embodiment of alkyl in all definitions used hereinbefore or hereinafter is C₁₋₆alkyl 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 C₁₋₆alkyl is C₁₋₄alkyl 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.

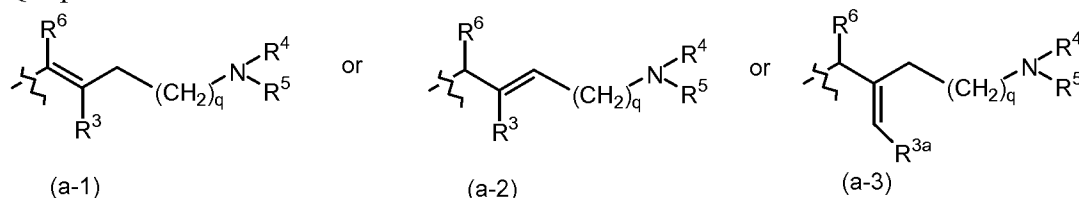
In the framework of this application C₂₋₆alkenyl is a straight or branched hydrocarbon radical having from 2 to 6 carbon atoms containing a double bond such as ethenyl, propenyl, butenyl, pentenyl, hexenyl and the like; C₂₋₆alkynyl is a straight or branched hydrocarbon radical having from 2 to 6 carbon atoms containing a triple bond such as ethynyl, propynyl, butynyl, pentynyl, hexynyl and the like; C₃₋₆cycloalkyl is a cyclic saturated hydrocarbon radical having from 3 to 6 carbon atoms and is generic to cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl

In the framework of this application, halo is a substituent selected from the group of fluoro, chloro, bromo and iodo and haloalkyl is a straight or branched saturated hydrocarbon radical having from 1 to 6 carbon atoms or a cyclic saturated hydrocarbon radical having from 3 to 6 carbon atoms or a cyclic saturated hydrocarbon radical having from 3 to 6 carbon atoms attached to a straight or branched saturated hydrocarbon radical having from 1 to 6 carbon atoms; wherein one or more carbon atoms are substituted with one or more halo atoms. Preferably, halo is bromo, fluoro or chloro; in particular chloro or bromo. Preferably, haloalkyl is polyhaloC₁₋₆alkyl which is defined as mono- or polyhalosubstituted C₁₋₆alkyl, for example, methyl with one or more fluoro atoms, for example, difluoromethyl or trifluoromethyl, 1,1-difluoro-ethyl and the like. In case more than one halo atom is attached to an alkyl or C₁₋₆alkyl group

within the definition of haloalkyl or polyhaloC₁₋₆alkyl, they may be the same or different.

A first interesting embodiment relates to a compound of formula (Ia) or (Ib) wherein

5 Q represents a radical of formula

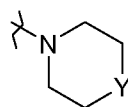


p is an integer equal to 1, 2, 3 or 4;

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

10 R¹ is hydrogen, cyano, formyl, carboxyl, halo, alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, haloalkyl, hydroxy, alkyloxy, alkylthio, alkylthioalkyl, -C=N-OR¹¹, amino, mono or di(alkyl)amino, aminoalkyl, mono or di(alkyl)aminoalkyl, alkylcarbonylaminoalkyl, aminocarbonyl, mono or di(alkyl)aminocarbonyl, arylalkyl, arylcarbonyl, R^{5a}R^{4a}Nalkyl, di(aryl)alkyl, aryl, R^{5a}R^{4a}N-, R^{5a}R^{4a}N-C(=O)-, or Het;

15 R² is hydrogen, alkyloxy, aryl, aryloxy, hydroxy, mercapto, alkyloxyalkyloxy, alkylthio, mono or di(alkyl)amino, pyrrolidino or a



radical of formula wherein Y is CH₂, O, S, NH or N-alkyl ;

R³ is alkyl, arylalkyl, aryl-O-alkyl, aryl-alkyl-O-alkyl, aryl, Het, Het-alkyl, Het-O-alkyl, Het-alkyl-O-alkyl or phenyl;

20 R^{3a} is hydrogen, cyano, alkyl, arylalkyl, aryl-O-alkyl, aryl-alkyl-O-alkyl, aryl, Het, Het-alkyl, Het-O-alkyl, or Het-alkyl-O-alkyl;

R⁴ and R⁵ each independently is hydrogen; alkyl; alkyloxyalkyl; arylalkyl; Het-alkyl; mono- or dialkylaminoalkyl; Het; aryl; or -C(=NH)-NH₂; or

25 R⁴ and R⁵ together with the nitrogen atom to which they are attached form a radical selected from the group consisting of pyrrolidino, piperidino, piperazino, morpholino, 4-thiomorpholino, 2,3-dihydroisoindol-1-yl, thiazolidin-3-yl, 1,2,3,6-tetrahydropyridyl, hexahydro-1H-azepinyl, hexahydro-1H-1,4-diazepinyl, hexahydro-1,4-oxazepinyl, 1,2,3,4-tetrahydroisoquinolin-2-yl, 2,5-diazabicyclo[2.2.1]heptyl, pyrrolinyl, pyrrolyl, imidazolidinyl, pyrazolidinyl, 2-imidazolynyl, 2-pyrazolinyl,

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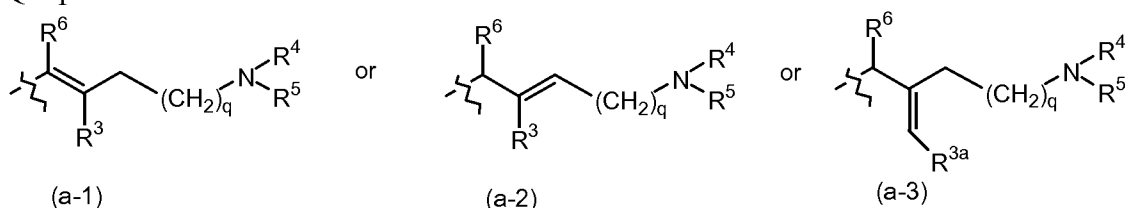
- imidazolyl, pyrazolyl, triazolyl, pyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl and triazinyl, each radical optionally substituted with 1, 2, 3 or 4 substituents, each substituent independently selected from alkyl, haloalkyl, alkylcarbonyl, halo, arylalkyl, hydroxy, alkyloxy, amino, mono- or dialkylamino, alkylthio, alkylthioalkyl, aryl, pyridyl, pyrimidinyl, piperidinyl or pyrrolidinyl optionally substituted with arylalkyl;
- R^{4a} and R^{5a} together with the nitrogen atom to which they are attached form a radical selected from the group consisting of pyrrolidino, piperidino, piperazino, morpholino, 4-thiomorpholino, 2,3-dihydroisoindol-1-yl, thiazolidin-3-yl, 1,2,3,6-tetrahydropyridyl, hexahydro-1*H*-azepinyl, hexahydro-1*H*-1,4-diazepinyl, hexahydro-1,4-oxazepinyl, 1,2,3,4-tetrahydroisoquinolin-2-yl, pyrrolinyl, pyrrolyl, imidazolidinyl, pyrazolidinyl, 2-imidazoliny, 2-pyrazolinyl, imidazolyl, pyrazolyl, triazolyl, pyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl and triazinyl, each radical optionally substituted with 1, 2, 3 or 4 substituents, each substituent independently selected from alkyl, haloalkyl, halo, arylalkyl, hydroxy, alkyloxy, amino, mono- or dialkylamino, alkylthio, alkylthioalkyl, aryl, pyridyl or pyrimidinyl;
- R^6 is aryl¹ or Het;
- R^7 is hydrogen, halo, alkyl, aryl or Het;
- R^8 is hydrogen or alkyl;
- R^9 is oxo; or
- R^8 and R^9 together form the radical $-\text{CH}=\text{CH}-\text{N}=\text{}$;
- R^{11} is hydrogen or alkyl;
- aryl is a homocycle selected from phenyl, naphthyl, acenaphthyl or tetrahydronaphthyl, each being optionally substituted with 1, 2 or 3 substituents, each substituent being independently selected from hydroxy, halo, cyano, nitro, amino, mono- or dialkylamino, alkyl, haloalkyl, alkyloxy, haloalkyloxy, carboxyl, alkyloxycarbonyl, aminocarbonyl, morpholinyl or mono- or dialkylaminocarbonyl;
- aryl¹ is a homocycle selected from phenyl, naphthyl, acenaphthyl or tetrahydronaphthyl, each being optionally substituted with 1, 2 or 3 substituents, each substituent being independently selected from hydroxy, halo, cyano, nitro, amino, mono- or dialkylamino, alkyl, haloalkyl, alkyloxy, alkylthio, haloalkyloxy, carboxyl,

alkyloxycarbonyl, aminocarbonyl, morpholinyl, Het or mono- or dialkylaminocarbonyl;

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

A second interesting embodiment relates to a compound of formula (Ia) or (Ib) wherein

Q represents a radical of formula



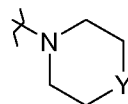
p is an integer equal to 1, 2, 3 or 4;

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

R¹ is hydrogen, cyano, formyl, carboxyl, halo, C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, haloC₁₋₆alkyl, hydroxy, C₁₋₆alkyloxy, C₁₋₆alkylthio, C₁₋₆alkylthioC₁₋₆alkyl, -C=N-OR¹¹, amino, mono or di(C₁₋₆alkyl)amino, aminoC₁₋₆alkyl, mono or di(C₁₋₆alkyl)aminoC₁₋₆alkyl, C₁₋₆alkylcarbonylaminoC₁₋₆alkyl, aminocarbonyl, mono or di(C₁₋₆alkyl)aminocarbonyl, arylC₁₋₆alkyl, arylcarbonyl, R^{5a}R^{4a}NC₁₋₆alkyl, di(aryl)C₁₋₆alkyl, aryl, R^{5a}R^{4a}N-, R^{5a}R^{4a}N-C(=O)-, or Het;

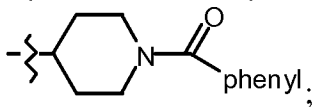
R² is hydrogen, C₁₋₆alkyloxy, aryl, aryloxy, hydroxy, mercapto, C₁₋₆alkyloxyC₁₋₆alkyloxy, C₁₋₆alkylthio, mono or di(C₁₋₆alkyl)amino,

pyrrolidino or a radical of formula



wherein Y is CH₂, O, S,

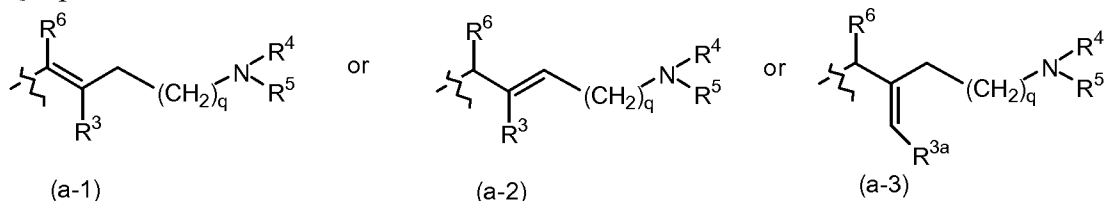
NH or *N*-C₁₋₆alkyl ;

- R^3 is C_{1-6} alkyl, aryl C_{1-6} alkyl, aryl-O- C_{1-6} alkyl, aryl- C_{1-6} alkyl-O- C_{1-6} alkyl, aryl, aryl-aryl, Het, Het- C_{1-6} alkyl, Het-O- C_{1-6} alkyl, Het- C_{1-6} alkyl-O- C_{1-6} alkyl or ; R^{3a} is hydrogen, cyano, C_{1-6} alkyl, aryl C_{1-6} alkyl, aryl-O- C_{1-6} alkyl, aryl- C_{1-6} alkyl-O- C_{1-6} alkyl, aryl, aryl-aryl, Het, Het- C_{1-6} alkyl, Het-O- C_{1-6} alkyl, or Het- C_{1-6} alkyl-O- C_{1-6} alkyl; R^4 and R^5 each independently is hydrogen; C_{1-6} alkyl; C_{1-6} alkyloxy C_{1-6} alkyl; aryl C_{1-6} alkyl; Het- C_{1-6} alkyl; mono- or di C_{1-6} alkylamino C_{1-6} alkyl; bicyclo[2.2.1]heptyl; Het; aryl; or $-C(=NH)-NH_2$; or together with the nitrogen atom to which they are attached form a radical selected from the group consisting of pyrrolidino, piperidino, piperazino, morpholino, 4-thiomorpholino, 1,1-dioxide-thiomorpholinyl, azetidiny, 2,3-dihydroisoindol-1-yl, thiazolidin-3-yl, 1,2,3,6-tetrahydropyridyl, hexahydro-1*H*-azepinyl, hexahydro-1*H*-1,4-diazepinyl, hexahydro-1,4-oxazepinyl, 1,2,3,4-tetrahydroisoquinolin-2-yl, 2,5-diazabicyclo[2.2.1]heptyl, pyrrolinyl, pyrrolyl, imidazolidinyl, pyrazolidinyl, 2-imidazolinyl, 2-pyrazolinyl, imidazolyl, pyrazolyl, triazolyl, pyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl and triazinyl, each radical optionally substituted with 1, 2, 3 or 4 substituents, each substituent independently selected from alkyl, halo C_{1-6} alkyl, C_{1-6} alkylcarbonyl, halo, aryl C_{1-6} alkyl, hydroxy, C_{1-6} alkyloxy, amino, mono- or di C_{1-6} alkylamino, amino C_{1-6} alkyl, mono- or di C_{1-6} alkylamino C_{1-6} alkyl, C_{1-6} alkylthio, C_{1-6} alkylthio C_{1-6} alkyl, aryl, pyridyl, pyrimidinyl, piperidinyl optionally substituted with C_{1-6} alkyl or pyrrolidinyl optionally substituted with aryl C_{1-6} alkyl; R^{4a} and R^{5a} together with the nitrogen atom to which they are attached form a radical selected from the group consisting of pyrrolidino, piperidino, piperazino, morpholino, 4-thiomorpholino, 2,3-dihydroisoindol-1-yl, thiazolidin-3-yl, 1,2,3,6-tetrahydropyridyl, hexahydro-1*H*-azepinyl, hexahydro-1*H*-1,4-diazepinyl, hexahydro-1,4-oxazepinyl, 1,2,3,4-tetrahydroisoquinolin-2-yl, pyrrolinyl, pyrrolyl, imidazolidinyl, pyrazolidinyl, 2-imidazolinyl, 2-pyrazolinyl, imidazolyl, pyrazolyl, triazolyl, pyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl and triazinyl, each radical optionally substituted with 1, 2, 3 or 4 substituents, each substituent independently selected from C_{1-6} alkyl, halo C_{1-6} alkyl, halo,

		arylC ₁₋₆ alkyl, hydroxy, C ₁₋₆ alkyloxy, amino, mono- or diC ₁₋₆ alkylamino, C ₁₋₆ alkylthio, C ₁₋₆ alkylthioC ₁₋₆ alkyl, aryl, pyridyl or pyrimidinyl;
	R ⁶	is aryl ¹ or Het;
	R ⁷	is hydrogen, halo, C ₁₋₆ alkyl, aryl or Het;
5	R ⁸	is hydrogen or C ₁₋₆ alkyl;
	R ⁹	is oxo; or
	R ⁸ and R ⁹	together form the radical –CH=CH–N=;
	R ¹¹	is hydrogen or C ₁₋₆ alkyl;
10	aryl	is a homocycle selected from phenyl, naphthyl, acenaphthyl or tetrahydronaphthyl, each being optionally substituted with 1, 2 or 3 substituents, each substituent being independently selected from hydroxy, halo, cyano, nitro, amino, mono- or diC ₁₋₆ alkylamino, C ₁₋₆ alkyl, C ₂₋₆ alkenyl optionally substituted with phenyl, haloC ₁₋₆ alkyl, C ₁₋₆ alkyloxy, haloC ₁₋₆ alkyloxy, carboxyl, C ₁₋₆ alkyloxycarbonyl, aminocarbonyl, morpholinyl or mono- or diC ₁₋₆ alkylaminocarbonyl;
15	aryl ¹	is a homocycle selected from phenyl, naphthyl, acenaphthyl or tetrahydronaphthyl, each being optionally substituted with 1, 2 or 3 substituents, each substituent being independently selected from hydroxy, halo, cyano, nitro, amino, mono- or diC ₁₋₆ alkylamino, C ₁₋₆ alkyl, haloC ₁₋₆ alkyl, C ₁₋₆ alkyloxy, C ₁₋₆ alkylthio, haloC ₁₋₆ alkyloxy, carboxyl, C ₁₋₆ alkyloxycarbonyl, aminocarbonyl, morpholinyl, Het or mono- or diC ₁₋₆ alkylaminocarbonyl;
20		
	Het	is a monocyclic heterocycle selected from <i>N</i> -phenoxypiperidinyl, piperidinyl, pyrrolyl, pyrazolyl, imidazolyl, furanyl, thienyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, pyridinyl, pyrimidinyl, pyrazinyl or pyridazinyl; or a bicyclic heterocycle selected from quinolinyl, quinoxalinyl, indolyl, benzimidazolyl, benzoxazolyl, benzisoxazolyl, benzothiazolyl, benzisothiazolyl, benzofuranyl, benzothienyl, 2,3-dihydrobenzo[1,4]dioxinyl or benzo[1,3]dioxolyl; each monocyclic and bicyclic heterocycle being optionally substituted with 1, 2 or 3 substituents, each substituent independently selected from halo, hydroxy, C ₁₋₆ alkyl or C ₁₋₆ alkyloxy.
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A third interesting embodiment relates to a compound of formula (Ia) or (Ib) wherein

Q represents a radical of formula



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

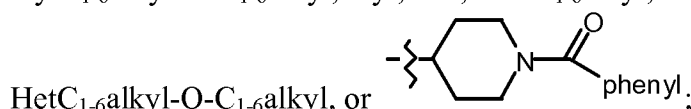
q is an integer equal to zero, 1, 2, 3 or 4 ;

5 R^1 is hydrogen, cyano, formyl, carboxyl, halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, polyhalo C_{1-6} alkyl, hydroxy, C_{1-6} alkyloxy, C_{1-6} alkylthio, C_{1-6} alkyloxy C_{1-6} alkyl, C_{1-6} alkylthio C_{1-6} alkyl, hydroxy C_{1-6} alkyl, $-C=N-OR^{11}$, amino, mono or di(C_{1-6} alkyl)amino, amino C_{1-6} alkyl, mono or di(C_{1-6} alkyl)amino C_{1-6} alkyl, C_{1-6} alkylcarbonylamino C_{1-6} alkyl, aminocarbonyl, mono or di(C_{1-6} alkyl)aminocarbonyl, aryl C_{1-6} alkyl, arylcarbonyl, $R^{5a}R^{4a}NC_{1-6}$ alkyl, di(aryl) C_{1-6} alkyl, aryl, $R^{5a}R^{4a}N-$, $R^{5a}R^{4a}N-C(=O)-$, or Het;

R^2 is hydrogen, C_{1-6} alkyloxy, aryl, aryloxy, hydroxy, mercapto, C_{1-6} alkyloxy C_{1-6} alkyloxy, C_{1-6} alkylthio, mono or di(C_{1-6} alkyl)amino,

15 pyrrolidino or a radical of formula wherein Y is CH_2 , O, S, NH or $N-C_{1-6}$ alkyl ;

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



20 R^{3a} is hydrogen, cyano, C_{1-6} alkyl, C_{3-6} cycloalkyl, aryl C_{1-6} alkyl, aryl-O- C_{1-6} alkyl, aryl C_{1-6} alkyl-O- C_{1-6} alkyl, aryl, Het, Het- C_{1-6} alkyl, Het-O- C_{1-6} alkyl or Het C_{1-6} alkyl-O- C_{1-6} alkyl;

R^4 and R^5 each independently is hydrogen, C_{1-6} alkyl, C_{1-6} alkyloxy C_{1-6} alkyl, aryl C_{1-6} alkyl, Het C_{1-6} alkyl, mono- or di(C_{1-6} alkyl)amino C_{1-6} alkyl, Het, aryl, or $-C(=NH)-NH_2$, or

25 R^4 and R^5 together with the nitrogen atom to which they are attached form a radical selected from the group consisting of pyrrolidino, piperidino, piperazino, morpholino, 4-thiomorpholino, 2,3-dihydroisoindol-1-yl, thiazolidin-3-yl, 1,2,3,6-tetrahydropyridyl, hexahydro-1H-azepinyl, hexahydro-1H-1,4-diazepinyl, hexahydro-1,4-oxazepinyl, 1,2,3,4-tetrahydroisoquinolin-2-yl, 2,5-diazabicyclo[2.2.1]heptyl, pyrrolinyl,

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- pyrrolyl, imidazolidinyl, pyrazolidinyl, 2-imidazolinyl, 2-pyrazolinyl, imidazolyl, pyrazolyl, triazolyl, pyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl and triazinyl, each radical optionally substituted with 1, 2, 3 or 4 substituents, each substituent independently selected from C₁₋₆alkyl, polyhaloC₁₋₆alkyl, C₁₋₆alkylcarbonyl, halo, arylC₁₋₆alkyl, hydroxy, C₁₋₆alkyloxy, C₁₋₆alkyloxyC₁₋₆alkyl, amino, mono- or di(C₁₋₆alkyl)amino, C₁₋₆alkylthio, C₁₋₆alkyloxyC₁₋₆alkyl, C₁₋₆alkylthioC₁₋₆alkyl, aryl, pyridyl, pyrimidinyl, piperidinyl or pyrrolidinyl optionally substituted with arylC₁₋₆alkyl;
- 5 together with the nitrogen atom to which they are attached form a radical selected from the group consisting of pyrrolidino, piperidino, piperazino, morpholino, 4-thiomorpholino, 2,3-dihydroisoindol-1-yl, thiazolidin-3-yl, 1,2,3,6-tetrahydropyridyl, hexahydro-1*H*-azepinyl, hexahydro-1*H*-1,4-diazepinyl, hexahydro-1,4-oxazepinyl, 1,2,3,4-tetrahydroisoquinolin-2-yl, pyrrolinyl, pyrrolyl, imidazolidinyl, pyrazolidinyl, 2-imidazolinyl, 2-pyrazolinyl, imidazolyl, pyrazolyl, triazolyl, pyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl and triazinyl, each radical optionally substituted with 1, 2, 3 or 4 substituents, each substituent independently selected from C₁₋₆alkyl, polyhaloC₁₋₆alkyl, halo, arylC₁₋₆alkyl, hydroxy, C₁₋₆alkyloxy, C₁₋₆alkyloxyC₁₋₆alkyl, amino, mono- or di(C₁₋₆alkyl)amino, C₁₋₆alkylthio, C₁₋₆alkyloxyC₁₋₆alkyl, C₁₋₆alkylthioC₁₋₆alkyl, aryl, pyridyl or pyrimidinyl;
- 10 R^{4a} and R^{5a} is aryl¹ or Het;
- R⁶ is hydrogen, halo, C₁₋₆alkyl, aryl or Het;
- 15 R⁷ is hydrogen or C₁₋₆alkyl;
- R⁸ is oxo; or
- R⁹ together form the radical -CH=CH-N=;
- 20 R⁸ and R⁹ is hydrogen or C₁₋₆alkyl;
- R¹¹ is a homocycle selected from phenyl, naphthyl, acenaphthyl or tetrahydronaphthyl, each being optionally substituted with 1, 2 or 3 substituents, each substituent being independently selected from hydroxy, halo, cyano, nitro, amino, mono- or di(C₁₋₆alkyl)amino, C₁₋₆alkyl, polyhaloC₁₋₆alkyl, C₁₋₆alkyloxy, haloC₁₋₆alkyloxy, carboxyl, C₁₋₆alkyloxycarbonyl, aminocarbonyl, morpholinyl or mono- or di(C₁₋₆alkyl)aminocarbonyl;
- 25 aryl¹ is a homocycle selected from phenyl, naphthyl, acenaphthyl or tetrahydronaphthyl, each being optionally substituted with 1, 2 or 3
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substituents, each substituent being independently selected from hydroxy, halo, cyano, nitro, amino, mono- or di(C₁₋₆alkyl)amino, C₁₋₆alkyl, polyhaloC₁₋₆alkyl, C₁₋₆alkyloxy, C₁₋₆alkylthio, haloC₁₋₆alkyloxy, carboxyl, C₁₋₆alkyloxycarbonyl, aminocarbonyl, morpholinyl, Het or mono- or di(C₁₋₆alkyl)aminocarbonyl;

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

10 hydroxy, C₁₋₆alkyl or C₁₋₆alkyloxy.

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A fourth interesting embodiment relates to a compound of formula (Ia) or (Ib) or any subgroup thereof as mentioned hereinbefore as interesting embodiment wherein R¹ is hydrogen, cyano, halo, alkyl, haloalkyl, hydroxy, alkyloxy, alkylthio, alkyloxyalkyl, alkylthioalkyl, arylalkyl, di(aryl)alkyl, aryl, or Het; in particular R¹ is hydrogen, halo, aryl, Het, alkyl or alkyloxy; more in particular R¹ is halo. Most preferably, R¹ is bromo. Or R¹ represents formyl, carboxyl, C₂₋₆alkenyl, C₂₋₆alkynyl, -C=N-OR¹¹, amino, mono or di(alkyl)amino, aminoalkyl, mono or di(alkyl)aminoalkyl, alkylcarbonylaminoalkyl, aminocarbonyl, mono or di(alkyl)aminocarbonyl, arylcarbonyl, R^{5a}R^{4a}Nalkyl, R^{5a}R^{4a}N-, R^{5a}R^{4a}N-C(=O)-; more in particular C₂₋₆alkenyl, C₂₋₆alkynyl, -C=N-OR¹¹, amino, mono or di(alkyl)amino, aminoalkyl, mono or di(alkyl)aminoalkyl, alkylcarbonylaminoalkyl, aminocarbonyl, mono or di(alkyl)aminocarbonyl, R^{5a}R^{4a}Nalkyl, R^{5a}R^{4a}N-, R^{5a}R^{4a}N-C(=O)-; even more in particular C₂₋₆alkenyl, C₂₋₆alkynyl, -C=N-OR¹¹, R^{5a}R^{4a}Nalkyl, R^{5a}R^{4a}N-, R^{5a}R^{4a}N-C(=O)-; even further in particular C₂₋₆alkenyl or -C=N-OR¹¹.

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

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A sixth interesting embodiment relates to a compound of formula (Ia) or (Ib) or any subgroup thereof as mentioned hereinbefore as interesting embodiment wherein R² is

hydrogen, alkyloxy or alkylthio, in particular hydrogen, C₁₋₆alkyloxy or C₁₋₆alkylthio. More in particular, R² is C₁₋₆alkyloxy, preferably methyloxy.

5 A seventh interesting embodiment relates to a compound of formula (Ia) or (Ib) or any subgroup thereof as mentioned hereinbefore as interesting embodiment wherein R³ is alkyl, arylalkyl, aryl, or Het; in particular C₁₋₆alkyl, arylC₁₋₆alkyl, aryl, or Het; more in particular C₁₋₆alkyl, optionally substituted phenyl, optionally substituted naphthyl, arylC₁₋₆alkyl wherein aryl represents optionally substituted phenyl or optionally substituted naphthyl, or Het; even more in particular C₁₋₆alkyl, phenyl, naphthyl, 10 arylC₁₋₆alkyl wherein aryl represents phenyl or naphthyl, or thienyl. Preferably R³ is C₁₋₆alkyl, in particular methyl; phenyl; naphthyl; phenylC₁₋₆alkyl or naphthylC₁₋₆alkyl; more preferably, R³ is C₁₋₆alkyl, in particular methyl, phenyl, naphthyl or phenylC₁₋₆alkyl.

15 An eighth interesting embodiment relates to a compound of formula (Ia) or (Ib) or any subgroup thereof as mentioned hereinbefore as interesting embodiment wherein R^{3a} is hydrogen, cyano, C₁₋₆alkyl, arylC₁₋₆alkyl, aryl, Het or Het-C₁₋₆alkyl; in particular cyano, C₁₋₆alkyl or arylC₁₋₆alkyl; more in particular phenylC₁₋₆alkyl.

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

A tenth interesting embodiment relates to a compound of formula (Ia) or (Ib) or any 25 subgroup thereof as mentioned hereinbefore as interesting embodiment wherein R⁴ and R⁵ each independently represent hydrogen or C₁₋₆alkyl, in particular C₁₋₆alkyl, more in particular methyl or ethyl. Preferably R⁴ and R⁵ are methyl.

An eleventh interesting embodiment relates to a compound of formula (Ia) or (Ib) or 30 any subgroup thereof as mentioned hereinbefore as interesting embodiment wherein R⁴ and R⁵ together with the nitrogen atom to which they are attached form a radical selected from the group consisting of piperidino, piperazino, morpholino, imidazolyl, triazolyl, each of said rings optionally substituted with C₁₋₆alkyl; more in particular piperidino, piperazino or morpholino, each of said rings optionally substituted with 35 C₁₋₄alkyl; even more in particular piperidino, piperazino optionally substituted with C₁₋₄alkyl, or morpholino; or R⁴ and R⁵ together with the nitrogen atom to which they are attached form a radical selected from the group consisting of 1,1-dioxide-

thiomorpholinyl, azetidiny, 2,3-dihydroisoindol-1-yl, thiazolidin-3-yl, 1,2,3,6-tetrahydropyridyl, hexahydro-1*H*-azepinyl, hexahydro-1*H*-1,4-diazepinyl, hexahydro-1,4-oxazepinyl, 1,2,3,4-tetrahydroisoquinolin-2-yl, 2,5-diazabicyclo[2.2.1]heptyl, each of said rings optionally substituted with C₁₋₆alkyl or arylC₁₋₆alkyl; more in particular
5 hexahydro-1*H*-1,4-diazepinyl or 2,5-diazabicyclo[2.2.1]heptyl, each of said rings optionally substituted with C₁₋₆alkyl or arylC₁₋₆alkyl.

A twelfth interesting embodiment relates to a compound of formula (Ia) or (Ib) or any subgroup thereof as mentioned hereinbefore as interesting embodiment wherein R⁶ is
10 phenyl optionally substituted with halo, cyano or C₁₋₆alkyloxy; in particular phenyl optionally substituted with halo.

A thirteenth interesting embodiment relates to a compound of formula (Ia) or (Ib) or any subgroup thereof as mentioned hereinbefore as interesting embodiment wherein R⁷
15 is hydrogen.

A fourteenth interesting embodiment relates to a compound of formula (Ia) or (Ib) or any subgroup thereof as mentioned hereinbefore as interesting embodiment wherein the compound is a compound of formula (Ia).
20

A fifteenth interesting embodiment relates to a compound of formula (Ia) or (Ib) or any subgroup thereof as mentioned hereinbefore as interesting embodiment wherein the compound is a compound of formula (Ib) and wherein R⁸ is hydrogen and R⁹ is oxo.

25 A sixteenth interesting embodiment relates to a compound of formula (Ia) or (Ib) or any subgroup thereof as mentioned hereinbefore as interesting embodiment wherein the compound is a compound of formula (Ib), in particular wherein R⁸ is alkyl, more preferable C₁₋₆alkyl, e.g. methyl.

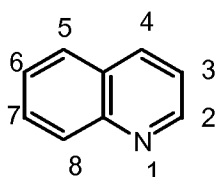
30 A seventeenth interesting embodiment relates to a compound of formula (Ia) or (Ib) or any subgroup thereof as mentioned hereinbefore as interesting embodiment wherein Q is a radical of formula (a-1) or (a-2).

An eighteenth interesting embodiment is a compound of formula (Ia) or (Ib) or any
35 subgroup thereof as mentioned hereinbefore as interesting embodiment wherein aryl is naphthyl or phenyl, more preferably phenyl, each optionally substituted with one or

two substituents selected from halo, for example chloro; cyano; alkyl for example methyl; or alkyloxy, for example methyloxy.

A nineteenth interesting embodiment relates to a compound of formula (Ia) or (Ib) or any subgroup thereof as mentioned hereinbefore as interesting embodiment wherein R¹ is placed in position 6 of the quinoline ring.

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



10

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

A twenty first 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 IC₉₀ < 15 µl/ml against at least one bacterium, in particular a gram-positive bacterium; preferably a IC₉₀ < 10 µl/ml; more preferably a IC₉₀ < 5 µl/ml; the IC₉₀ value being determined as described hereinafter.

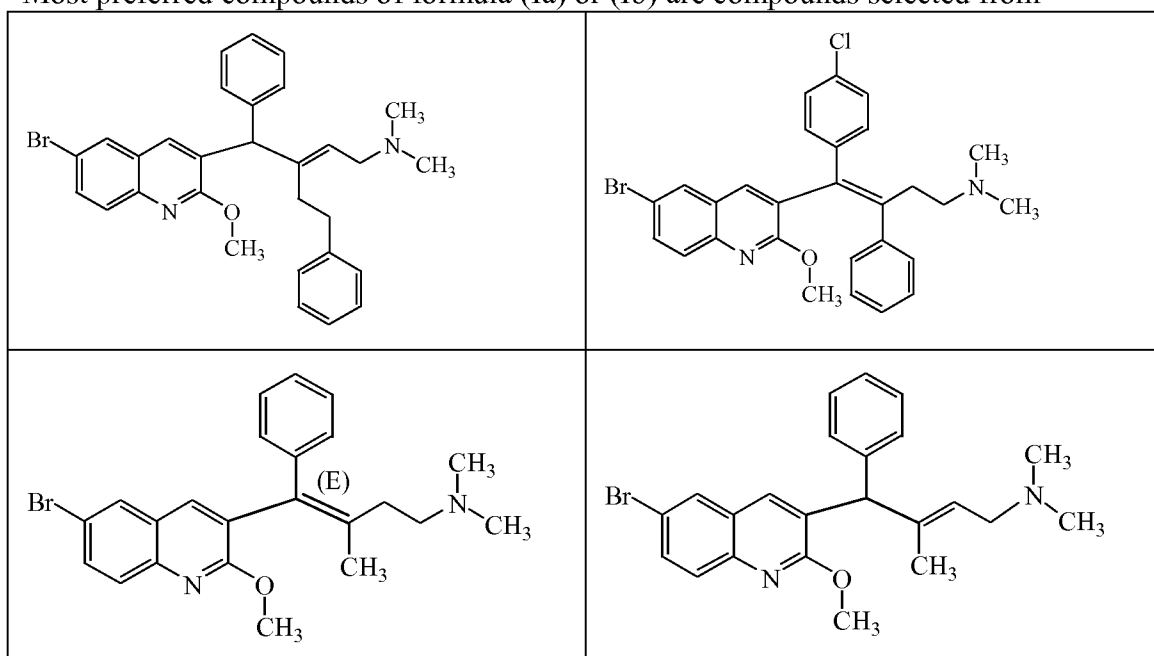
A twenty second interesting embodiment relates to a compound of formula (Ia) or any subgroup thereof as mentioned hereinbefore as interesting embodiment wherein one or more, preferably all, of the following definitions apply :

R¹ is hydrogen, halo, aryl, Het, alkyl or alkyloxy; in particular hydrogen, halo, aryl, Het, C₁₋₆alkyl or C₁₋₆alkyloxy; more in particular halo, preferably bromo;
 R² is hydrogen, alkyloxy or alkylthio, in particular hydrogen, C₁₋₆alkyloxy or C₁₋₆alkylthio; more in particular C₁₋₆alkyloxy, preferably methyloxy;
 R³ is alkyl, arylalkyl, aryl, or Het; in particular C₁₋₆alkyl, arylC₁₋₆alkyl, aryl, or Het; more in particular C₁₋₆alkyl, in particular methyl, phenyl, naphthyl or phenylC₁₋₆alkyl;
 R⁴ and R⁵ are C₁₋₆alkyl; in particular methyl; or R⁴ and R⁵ together with the nitrogen atom to which they are attached form a radical selected from the group consisting of

- piperidino, piperazino, morpholino, imidazolyl, triazolyl, hexahydro-1*H*-1,4-diazepinyl or 2,5-diazabicyclo[2.2.1]heptyl, each of said rings optionally substituted with C₁₋₆alkyl or arylC₁₋₆alkyl; more in particular piperidino, piperazino optionally substituted with C₁₋₄alkyl, morpholino, hexahydro-1*H*-1,4-diazepinyl optionally substituted with C₁₋₆alkyl, or 2,5-diazabicyclo[2.2.1]heptyl, optionally substituted with arylC₁₋₆alkyl; in particular R⁴ and R⁵ are C₁₋₆alkyl, preferably methyl;
- R⁶ is phenyl optionally substituted with halo, cyano or C₁₋₆alkyloxy; in particular phenyl optionally substituted with halo;
- R⁷ is hydrogen;
- q is 1, 2 or 3;
- p is 1;
- Q is a radical of formula (a-1), (a-2) or (a-3); in particular (a-1) or (a-2).

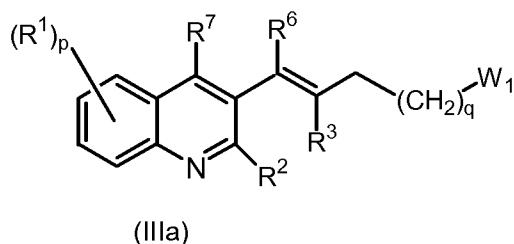
- Preferably, in the compounds of formula (Ia) and (Ib) or any subgroup thereof as mentioned hereinbefore as interesting embodiment, the term “alkyl” represents C₁₋₆alkyl, more preferably C₁₋₄alkyl, and the term haloalkyl represents polyhaloC₁₋₆alkyl.

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



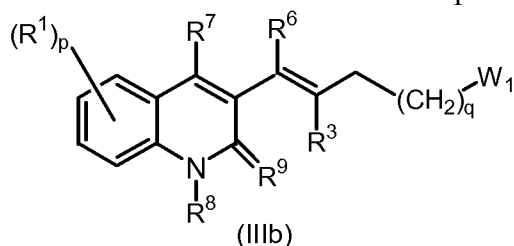
- a pharmaceutically acceptable salt thereof or a *N*-oxide form thereof or a solvate thereof.

The invention also further relates to a compound of formula



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

5 The invention also relates to a compound of formula



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

10

PHARMACOLOGY

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

20

Further, the present invention also relates to the use of a compound of formula (Ia) or (Ib), the pharmaceutically acceptable salts thereof or the *N*-oxide forms thereof or the solvates thereof, as well as any of the pharmaceutical compositions thereof as described hereinafter for the manufacture of a medicament for the treatment of a bacterial
 25 infection including a mycobacterial infection.

Accordingly, in another aspect, the invention provides a method of treating a patient suffering from, or at risk of, a bacterial infection, including a mycobacterial infection,

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

- In addition to their activity against mycobacteria, the compounds according to the invention are also active against other bacteria. In general, bacterial pathogens may be classified as either gram-positive or gram-negative pathogens. Antibiotic compounds with activity against both gram-positive and gram-negative pathogens are generally regarded as having a broad spectrum of activity. The compounds of the present invention are regarded as active against gram-positive and/or gram-negative bacterial pathogens, in particular against gram-positive bacterial pathogens. In particular, the present compounds are active against at least one gram-positive bacterium, preferably against several gram-positive bacteria, more preferably against one or more gram-positive bacteria and/or one or more gram-negative bacteria.
- 15 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. pyogenes*; 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*.
- 20 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*.
- 25 The compounds of the present invention also show activity against resistant bacterial strains.

- The compounds of the present invention are especially active against *Streptococcus pneumoniae* and *Staphylococcus aureus*, including resistant *Staphylococcus aureus* such as for example methicillin resistant *Staphylococcus aureus* (MRSA).
- 35

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

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

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

20 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
25 respiratory tract infections, lower respiratory tract infections, genitourinary infections, gastrointestinal infections, gynaecological infections, septicemia, bone and joint infections, skin and skin structure infections, bacterial endocarditis, burns, antibacterial prophylaxis of surgery, and antibacterial prophylaxis in immunosuppressed patients, such as patients receiving cancer chemotherapy, or organ transplant patients.

30 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.

35 The invention also relates to a composition comprising a pharmaceutically acceptable carrier and, as active ingredient, a therapeutically effective amount of a compound according to the invention. The compounds according to the invention may be

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

Depending on the mode of administration, the pharmaceutical composition will preferably comprise from 0.05 to 99 % by weight, more preferably from 0.1 to 70 % by weight, even more preferably from 0.1 to 50 % by weight of the active ingredient(s), and, from 1 to 99.95 % by weight, more preferably from 30 to 99.9 % by weight, even more preferably from 50 to 99.9 % by weight of a pharmaceutically acceptable carrier, all percentages being based on the total weight of the composition.

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

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

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

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

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

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

A pharmaceutical composition comprising a pharmaceutically acceptable carrier and, as active ingredient, a therapeutically effective amount of (a) a compound according to the invention, and (b) one or more other antibacterial agents, is also comprised by the present invention.

The weight ratio of (a) the compound according to the invention and (b) the other antibacterial agent(s) when given as a combination may be determined by the person skilled in the art. Said ratio and the exact dosage and frequency of administration depends on the particular compound according to the invention and the other antibacterial agent(s) used, the particular condition being treated, the severity of the

condition being treated, the age, weight, gender, diet, time of administration and general physical condition of the particular patient, the mode of administration as well as other medication the individual may be taking, as is well known to those skilled in the art. Furthermore, it is evident that the effective daily amount may be lowered or
5 increased depending on the response of the treated subject and/or depending on the evaluation of the physician prescribing the compounds of the instant invention. A particular weight ratio for the present compound of formula (Ia) or (Ib) and another antibacterial agent may range from 1/10 to 10/1, more in particular from 1/5 to 5/1, even more in particular from 1/3 to 3/1.

10

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

The other antibacterial agents which may be combined with the compounds of formula
20 (Ia) or (Ib) are for example antibacterial agents known in the art. The other antibacterial agents comprise antibiotics of the β -lactam group such as natural penicillins, semisynthetic penicillins, natural cephalosporins, semisynthetic cephalosporins, cephamycins, 1-oxacephems, clavulanic acids, penems, carbapenems, nocardicins, monobactams; tetracyclines, anhydrotetracyclines, anthracyclines;
25 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,
30 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.

35 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
- 5 hydrochloride, pivmecillinam, cephalixin, 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,
- 10 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,
- 15 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,
- 20 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
- 25 hydrochloride, flavophospholipol, cycloserine, pecilocin, griseofulvin, chloramphenicol, chloramphenicol palmitate, mitomycin C, pyrrolnitrin, fosfomycin, fusidic acid, bicozamycin, tiamulin, siccanin.

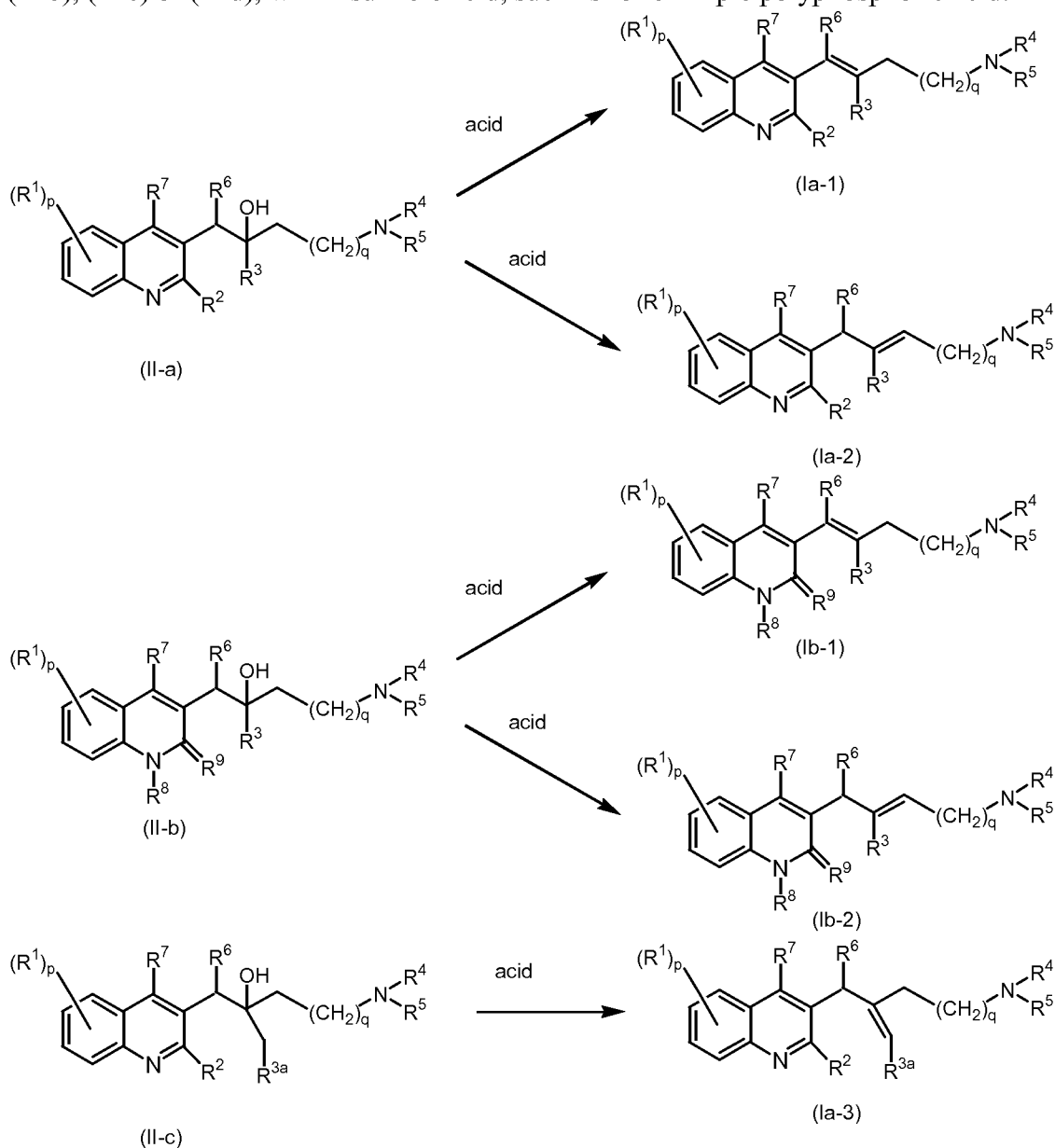
- Other Mycobacterial agents which may be combined with the compounds of formula
- 30 (Ia) or (Ib) are for example rifampicin (=rifampin); isoniazid; pyrazinamide; amikacin; ethionamide; ethambutol; streptomycin; para-aminosalicylic acid; cycloserine; capreomycin; kanamycin; thioacetazone; PA-824; quinolones/fluoroquinolones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

GENERAL PREPARATION

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

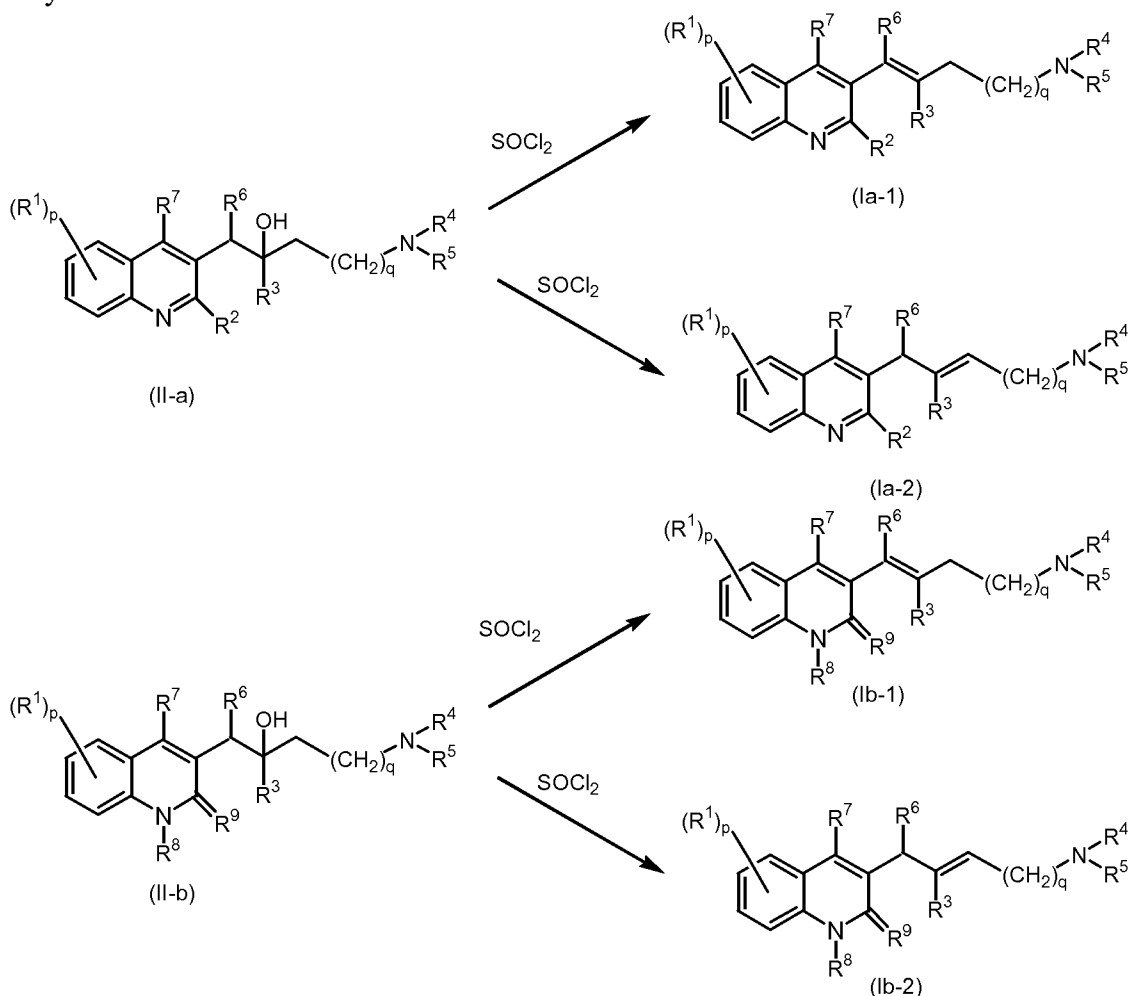
5

Compounds of formula (Ia) or (Ib), wherein Q represents a radical of formula (a-1), (a-2) or (a-3), these compounds being represented by formula (Ia-1), (Ia-2), (Ib-1), (Ib-2), (Ia-3) or (Ib-3), can be prepared by reacting an intermediate of formula (II-a), (II-b), (II-c) or (II-d), with a suitable acid, such as for example polyphosphoric acid.





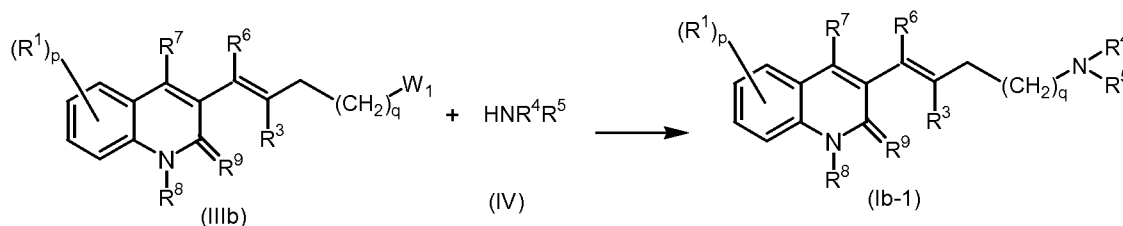
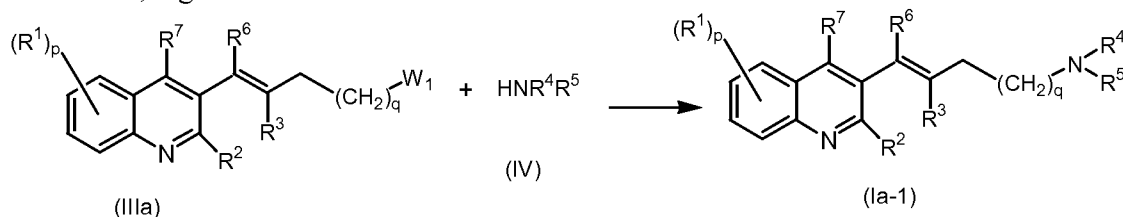
Compounds of formula (Ia-1), (Ia-2), (Ib-1) or (Ib-2) can also be prepared by reacting an intermediate of formula (II-a), (II-b) with SOCl_2 in the presence of a suitable solvent, such as for example pyridine, triethyl amine, diisopropyl amine, diisopropyl ethyl amine.



The reaction in the presence of a suitable acid such as for example polyphosphoric acid, is preferred for the preparation of compounds of formula (Ia-1) and (Ib-1), especially (Ia-1). The reaction in the presence of SOCl_2 is preferred for the preparation of compounds of formula (Ia-2) and (Ib-2), especially (Ia-2). Instead of SOCl_2 , also diethylamino sulfurtrifluoride can be used or other reagents which are well-known to the skilled person.

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

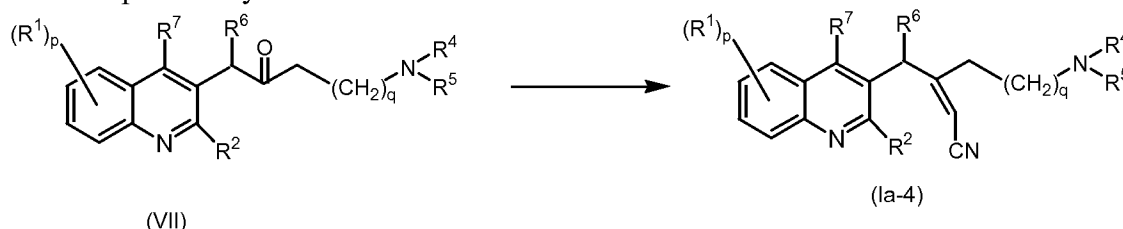
- 5 Compounds of formula (Ia-1) or (Ib-1) can also be prepared by reacting an intermediate of formula (IIIa) or (IIIb) wherein W_1 represents a suitable leaving group, such as for example halo, e.g. chloro, with an intermediate of formula (IV) in the presence of a suitable base, such as for example Na_2CO_3 , and a suitable solvent, such as for example an alcohol, e.g. methanol.



10

Compounds of formula (Ia) wherein Q represents a radical of formula (a-3) and wherein R^{3a} represents cyano, said compounds being represented by formula (Ia-4), can be prepared by reacting an intermediate of formula (VII) with diethyl cyanomethylacetate in the presence of sodium hydride and a suitable solvent, such as for example tetrahydrofuran.

15



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.

20

- 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, peroalkanoic acids, e.g. peroacetic acid, alkylhydroperoxides, e.g. tert.butyl hydro-peroxide. Suitable solvents are, for example, water, lower alcohols, e.g. ethanol and the like, hydrocarbons, e.g. toluene, ketones, e.g. 2-butanone, halogenated hydrocarbons, e.g. dichloromethane, and mixtures of such solvents.
- 15 Compounds of formula (Ia) or (Ib) wherein R^1 represents halo, e.g. bromo, can be converted into a compound of formula (Ia) or (Ib) wherein R^1 represents Het, by reaction with Het-B(OH)₂ in the presence of a suitable catalyst, such as for example Pd(OAc)₂ or Pd(PPh₃)₄, in the presence of a suitable base, such as for example K₃PO₄ or Na₂CO₃, and a suitable solvent, such as for example toluene or 1,2-dimethoxyethane (DME).
- 20 Similarly, compounds of formula (Ia) or (Ib) in which R^1 is halo, for example bromo, may be converted into compounds of formula (Ia) or (Ib) in which R^1 is alkyl, for example methyl, by treatment with an appropriate alkylating agent such as CH₃B(OH)₂ or (CH₃)₄Sn in the presence of a suitable catalyst, such as for example Pd(PPh₃)₄, in a suitable solvent such as for example toluene or 1,2-dimethoxyethane (DME).
- 25 Compounds of formula (Ia) or (Ib) wherein R^1 is halo, in particular bromo, can be converted into a compound of formula (Ia) or (Ib) wherein R^1 is hydrogen, by reaction with HCOONH₄ in the presence of a suitable catalyst such as for example palladium on charcoal, and in the presence of a suitable solvent, such as for example an alcohol, e.g. methanol. The same reaction conditions can be used to convert a compound of formula (Ia) or (Ib) wherein R^4 or R^5 is benzyl into a compound of formula (Ia) or (Ib) wherein R^4 or R^5 is hydrogen.
- 30 Compounds of formula (Ia) or (Ib) wherein R^1 is halo, in particular bromo, can also be converted into a compound wherein R^1 is formyl by reaction with *N,N*-dimethylformamide in the presence of *n*BuLi and a suitable solvent, such as for
- 35

example tetrahydrofuran. These compounds can then further be converted into a compound of formula (Ia) or (Ib) wherein R^1 is $-\text{CH}_2\text{-OH}$ by reaction with a suitable reducing agent, such as for example NaBH_4 and in the presence of a suitable solvent, such as for example an alcohol, e.g. methanol, and tetrahydrofuran.

5

Compounds of formula (Ia) or (Ib) wherein R^1 represents C_{2-6} alkenyl, can be prepared by reacting a compound of formula (Ia) or (Ib) wherein R^1 is halo, e.g. bromo and the like, with tributyl(C_{2-6} alkenyl)tin, such as for example tributyl(vinyl)tin, in the presence of a suitable catalyst, such as for example $\text{Pd}(\text{PPh}_3)_4$, in the presence of a suitable solvent, such as for example *N,N*-dimethylformamide. This reaction is preferably performed at elevated temperature.

10

Compounds of formula (Ia) or (Ib) wherein R^1 represents $\text{R}^{5a}\text{R}^{4a}\text{N-}$, can be prepared from a compound of formula (Ia) or (Ib) wherein R^1 is halo, e.g. bromo and the like, by reaction with $\text{R}^{5a}\text{R}^{4a}\text{NH}$ in the presence of a suitable catalyst, such as for example tris(dibenzylideneacetone)palladium, a suitable ligand, such as for example 2-(di-*t*-butylphosphino)biphenyl, a suitable base, such as for example sodium *t*-butoxide, and a suitable solvent, such as for example toluene.

15

Compounds of formula (Ia) or (Ib) wherein R^1 represents $-\text{C}=\text{N-OR}^{11}$, can be prepared from a compound of formula (Ia) or (Ib) wherein R^1 is formyl, by reaction with hydroxylamine hydrochloride or C_{1-6} alkoxyamine hydrochloride in the presence of a suitable solvent, such as for example pyridine.

20

Compounds of formula (Ia) or (Ib) wherein R^1 represents $-\text{CH}_2\text{-NH}_2$, can be prepared from a compound of formula (Ia) or (Ib) wherein R^1 is formyl, by reduction in the presence of H_2 , a suitable catalyst, such as for example palladium on charcoal, and a suitable solvent, such as for example NH_3 /alcohol, e.g. NH_3 /methanol. Compounds of formula (Ia) or (Ib) wherein R^1 represents $-\text{CH}_2\text{-NH}_2$ can be converted into a compound of formula (Ia) or (Ib) wherein R^1 represents $-\text{CH}_2\text{-N}(\text{C}_{1-6}\text{alkyl})_2$ by reaction with a suitable aldehyde or ketone reagent, such as for example paraformaldehyde or formaldehyde, in the presence of sodium cyanoborohydride, acetic acid and a suitable solvent, such as for example acetonitrile.

30

Compounds of formula (Ia) or (Ib) wherein R^1 represents $\text{R}^{5a}\text{R}^{4a}\text{N-CH}_2\text{-}$, can be prepared by reacting a compound of formula (Ia) or (Ib) wherein R^1 is formyl, with a suitable reagent of formula $\text{R}^{5a}\text{R}^{4a}\text{N-H}$ in the presence of a suitable reducing agent,

35

such as for example BH_3CN , a suitable solvent, such as for example acetonitrile and tetrahydrofuran, and a suitable acid, such as for example acetic acid.

Compounds of formula (Ia) or (Ib) wherein R^1 represents amino, can be prepared by reacting a compound of formula (Ia) or (Ib) wherein R^1 is carboxyl, with a suitable azide, such as for example diphenylphosphorylazide (DPPA), and a suitable base, such as for example triethylamine, in a suitable solvent, such as for example toluene. The obtained product undergoes a Curtius reaction, and by adding trimethylsilylethanol a carbamate intermediate is formed. In a next step, this intermediate is reacted with tetrabutylammonium bromide (TBAB) in a suitable solvent, such as for example tetrahydrofuran to obtain the amino derivative.

Compounds of formula (Ia) or (Ib) wherein R^1 represents aminocarbonyl, mono or di(alkyl)aminocarbonyl or $\text{R}^{5a}\text{R}^{4a}\text{N}-\text{C}(=\text{O})-$, can be prepared by reacting a compound of formula (Ia) or (Ib) wherein R^1 is carboxyl, with a suitable amine, a suitable coupling reagent such as for example hydroxybenzotriazole, a suitable activating reagent such as for example 1,1'-carbonyldiimidazole or *N,N'*-dicyclohexylcarbodiimide or 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide, a suitable base, such as for example triethylamine, and a suitable solvent, such as for example tetrahydrofuran and methylenechloride.

Compounds of formula (Ia) or (Ib) wherein R^1 represents arylcarbonyl, can be prepared by reacting in a first step (a) a compound of formula (Ia) or (Ib) wherein R^1 is halo, e.g. bromo and the like, with a suitable arylaldehyde in the presence of nBuLi and a suitable solvent, such as for example tetrahydrofuran. This reaction is preferably performed at low temperature such as for example -70°C . In a next step (b), the product obtained in step (a) is oxidized with a suitable oxidans, such as for example manganese oxide, in the presence of a suitable solvent, such as for example methylene chloride.

Compounds of formula (Ia) or (Ib) wherein R^4 and R^5 represent a ring moiety substituted with alkylcarbonyl, can be prepared from the corresponding compound wherein the ring moiety is unsubstituted by reaction with an appropriate acyl chloride, e.g. acetyl chloride, in the presence of a suitable base, such as for example triethylamine, and a suitable solvent, such as for example methylene chloride.

Compounds of formula (Ia) or (Ib) wherein R^4 and R^5 represent an unsubstituted ring moiety, can be prepared from the corresponding compound wherein the ring moiety is

substituted with arylalkyl, by reaction with ammonium formate in the presence of a suitable catalyst, such as for example palladium on charcoal, and a suitable solvent, such as for example an alcohol, e.g. methanol.

- 5 Compounds of formula (Ia) or (Ib) wherein R^6 represents phenyl substituted with halo, can be converted into a compound of formula (Ia) or (Ib) wherein R^6 represents phenyl substituted with Het, by reaction with Het-B(OH)_2 in the presence of a suitable catalyst, such as for example $\text{Pd(PPh}_3)_4$, in the presence of a suitable base, such as for example Na_2CO_3 , and a suitable solvent, such as for example toluene or 1,2-dimethoxyethane
10 (DME) and an alcohol, for example methanol.

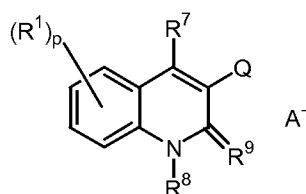
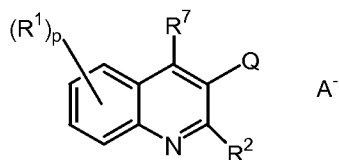
- A compound of formula (Ia) wherein R^2 represents methoxy, can be converted into the corresponding compound of formula (Ib) wherein R^8 is hydrogen and R^9 is oxo, by hydrolysis in the presence of a suitable acid, such as for example hydrochloric acid, and
15 a suitable solvent, such as for example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

- Compounds of formula (Ia) or (Ib) wherein R^4 and R^5 are taken together with the nitrogen to which they are attached to form 1,1-dioxide-thiomorpholinyl, can be prepared from the corresponding thiomorpholine derivative by reaction with an
20 appropriate organic or inorganic peroxide. Appropriate inorganic peroxides comprise, for example, hydrogen peroxide, alkali metal or earth alkaline metal peroxides, e.g. sodium peroxide, potassium peroxide; appropriate organic peroxides may comprise peroxy acids such as, for example, benzenecarboperoxoic acid or halo substituted benzenecarboperoxoic acid, e.g. 3-chlorobenzenecarboperoxoic acid, peroxyalkanoic
25 acids, e.g. peroxyacetic acid, alkylhydroperoxides, e.g. tert.butyl hydro-peroxide. Suitable solvents are, for example, water, lower alcohols, e.g. ethanol and the like, hydrocarbons, e.g. toluene, ketones, e.g. 2-butanone, halogenated hydrocarbons, e.g. dichloromethane, and mixtures of such solvents.

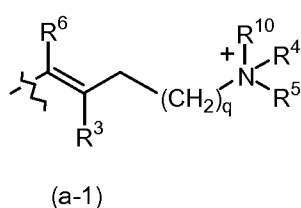
- 30 Compounds of formula (Ia) or (Ib) can also be converted into a quaternary amine by reaction with a suitable quaternizing agent, such as, for example, an optionally substituted C_{1-6} alkylhalide, aryl C_{1-6} alkylhalide, C_{1-6} alkylcarbonylhalide, arylcarbonylhalide, $\text{Het}^1\text{C}_{1-6}$ alkylhalide or Het^1 carbonylhalide, e.g. methyl iodide or benzyl iodide, in the presence of a suitable solvent, such as for example acetone wherein
35 Het^1 represents furanyl or thienyl; or a bicyclic heterocycle selected from benzofuranyl or benzothienyl; each monocyclic and bicyclic heterocycle may optionally be substituted with 1, 2 or 3 substituents, each substituent independently selected from the

group of halo, C₁₋₆alkyl and aryl. Said quaternary amines are represented by the below formula wherein R¹⁰ represents C₁₋₆alkyl, C₁₋₆alkylcarbonyl, arylC₁₋₆alkyl, arylcarbonyl, Het¹C₁₋₆alkyl or Het¹carbonyl and wherein A⁻ represents a pharmaceutically acceptable counter ion, such as for example iodide.

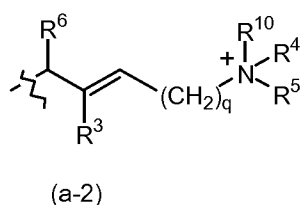
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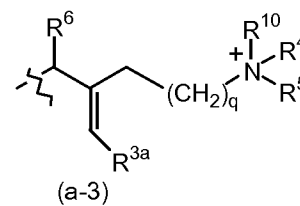
wherein Q represents a radical of formula



or



or



10

It is evident that in the foregoing and in the following reactions, the reaction products may be isolated from the reaction medium and, if necessary, further purified according to methodologies generally known in the art, such as extraction, crystallization and chromatography. It is further evident that reaction products that exist in more than one enantiomeric form, may be isolated from their mixture by known techniques, in particular preparative chromatography, such as preparative HPLC, chiral chromatography. Individual diastereoisomers or individual enantiomers can also be obtained by Supercritical Fluid Chromatography (SCF).

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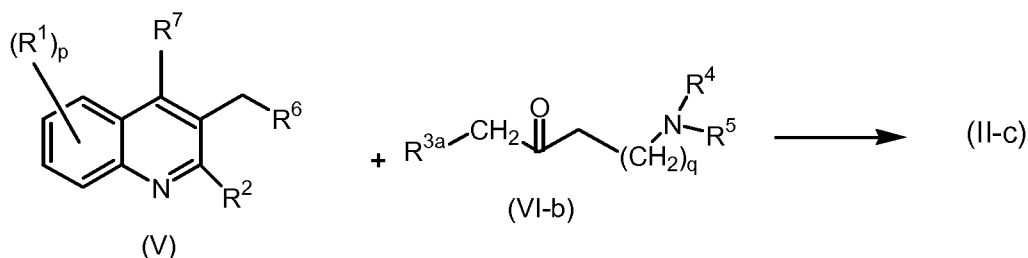
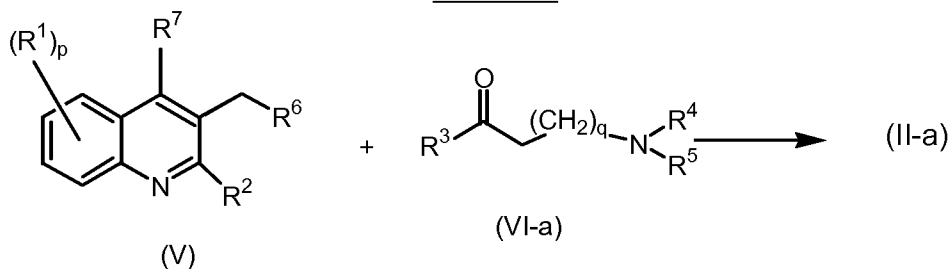
The starting materials and the intermediates are compounds that are either commercially available or may be prepared according to conventional reaction procedures generally known in the art. For example, the intermediates of formula (IIa) to (IId) can be prepared according to the methods described in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

25

In particular, the intermediates of formula (IIa) and (IIc) can be prepared by reacting an intermediate of formula (V) with an intermediate of formula (VI-a) or (VI-b) according to the following reaction scheme (1) :

5

Scheme 1

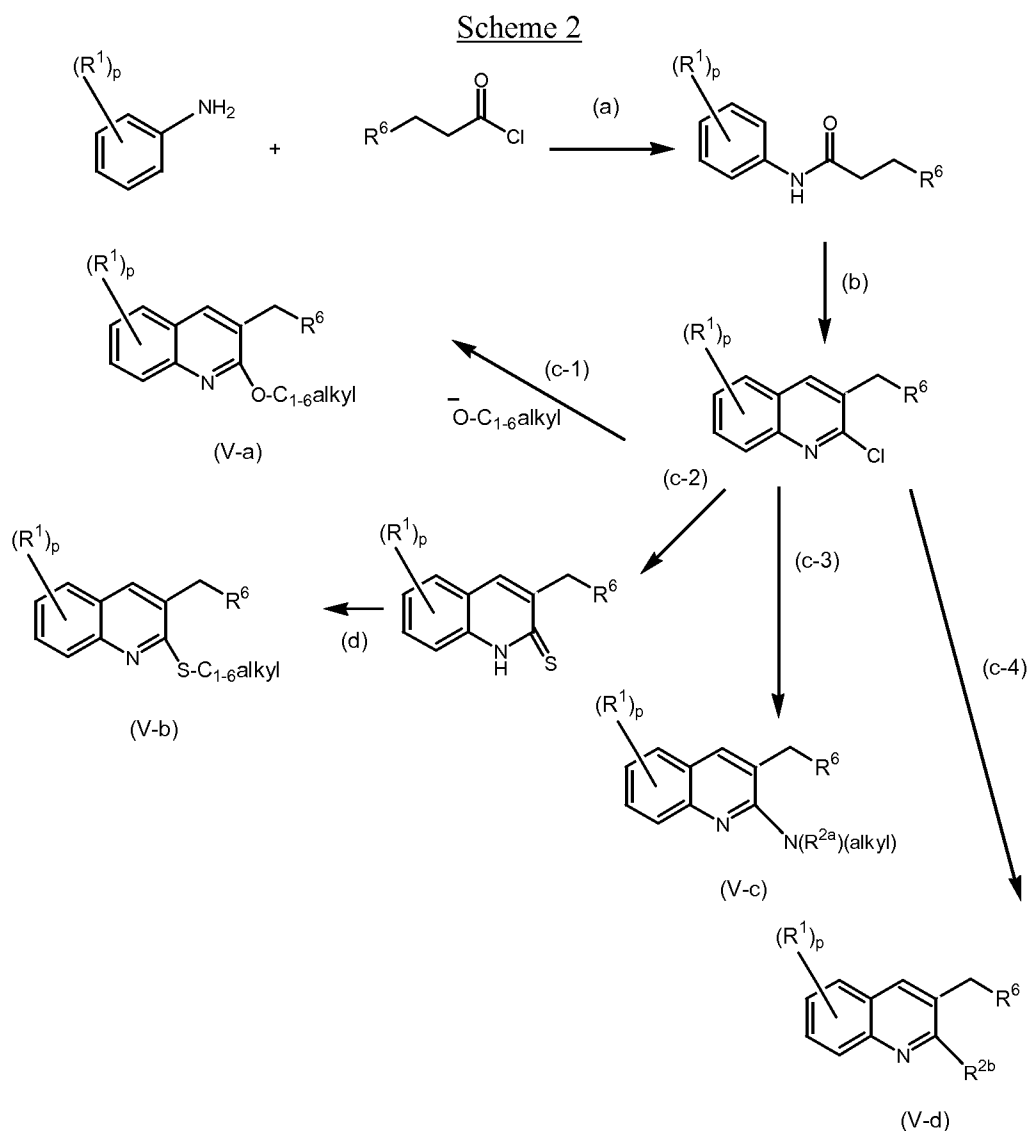


using nBuLi in a mixture of diisopropyl amine and tetrahydrofuran, wherein all variables are defined as in formula (Ia). Stirring may enhance the rate of the reaction.

10 The reaction may conveniently be carried out at a temperature ranging between -20 and -70 °C.

The same reaction procedure can be used to synthesize compounds of formula (IIb) or (II d) starting from intermediates of formula (V').

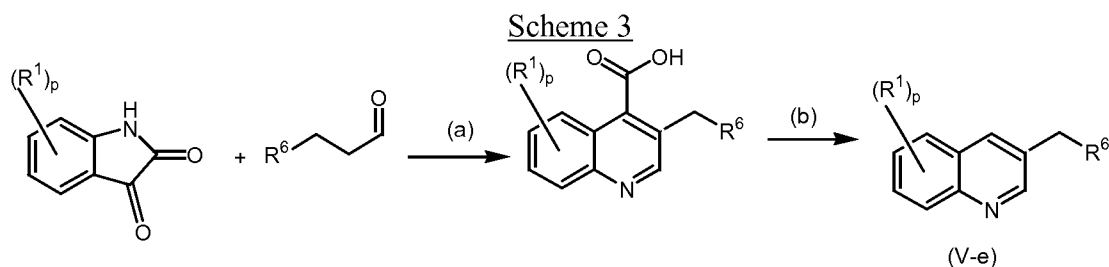
15 The intermediates of formula (V) may be prepared according to the following reaction scheme (2):



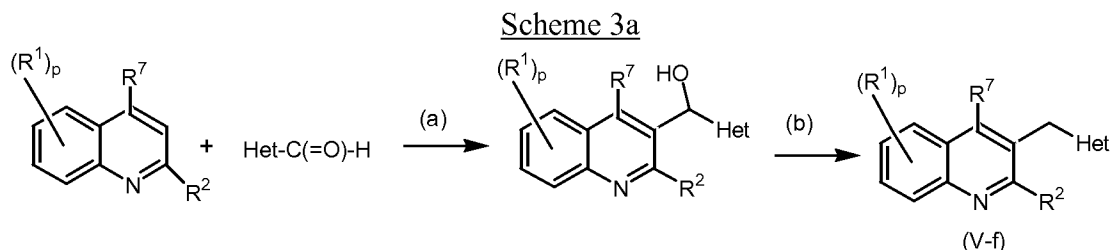
- wherein all variables are defined as in formula (Ia). Reaction scheme (2) comprises step (a) in which an appropriately substituted aniline is reacted with an appropriate acylchloride such as for example 3-phenylpropionyl chloride,
- 5 3-fluorobenzenepropionyl chloride or *p*-chlorobenzenepropionyl 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.
- 10 In a next step (b) the adduct obtained in step (a) is reacted with phosphoryl chloride (POCl_3) in the presence of *N,N*-dimethylformamide (Vilsmeier-Haack formylation followed by cyclization). The reaction may conveniently be carried out at a temperature ranging between room temperature and reflux temperature. In a next step (c-1), a specific R^2 -group, wherein R^2 is for example a C_{1-6} alkyloxy radical is

introduced by reacting the intermediate compound obtained in step (b) with $\text{HO-C}_{1-6}\text{alkyl}$ in the presence of a suitable solvent, such as for example $\text{HO-C}_{1-6}\text{alkyl}$. The intermediate obtained in step (b) can also be converted into an intermediate wherein R^2 is for example a $\text{C}_{1-6}\text{alkylthio}$ radical by reaction with $\text{S=C(NH}_2)_2$ in the presence of a suitable solvent, such as for example an alcohol, e.g. ethanol, or an alcohol/water mixture, optionally in the presence of a suitable base, such as for example KOH, (see step (c-2)) followed by reaction with $\text{C}_{1-6}\text{alkyl-I}$ in the presence of a suitable base, such as for example K_2CO_3 and a suitable solvent, such as for example 2-propanone (see step (d)). The intermediate obtained in step (b) can also be converted into an intermediate wherein R^2 is $-\text{N(R}^{2a})\text{(alkyl)}$ wherein R^{2a} is hydrogen or alkyl, by reaction with a suitable salt of $\text{NH(R}^{2a})\text{(alkyl)}$ in the presence of a suitable base, such as for example potassium carbonate, and a suitable solvent, such as for example acetonitrile (step (c-3)). The intermediate obtained in step (b) can also be converted into an intermediate wherein R^2 is $\text{C}_{1-6}\text{alkyloxyC}_{1-6}\text{alkyloxy}$ optionally substituted with $\text{C}_{1-6}\text{alkyloxy}$, said R^2 being represented by R^{2b} , by reaction with $\text{C}_{1-6}\text{alkyloxyC}_{1-6}\text{alkylOH}$ optionally substituted with $\text{C}_{1-6}\text{alkyloxy}$, in the presence of NaH and a suitable solvent, such as for example tetrahydrofuran (step (c-4)).

Intermediates of formula (V) wherein R^2 and R^7 represent hydrogen, said intermediates being represented by formula (V-e), may be prepared according to the following reaction scheme (3), wherein in a first step (a) a substituted indole-2,3-dione is reacted with an optionally substituted 3-phenylpropionaldehyde in the presence of a suitable base such as sodium hydroxide (Pfitzinger reaction), after which the carboxylic acid compound is decarboxylated in a next step (b) at high temperature in the presence of a suitable reaction-inert solvent such as diphenylether.

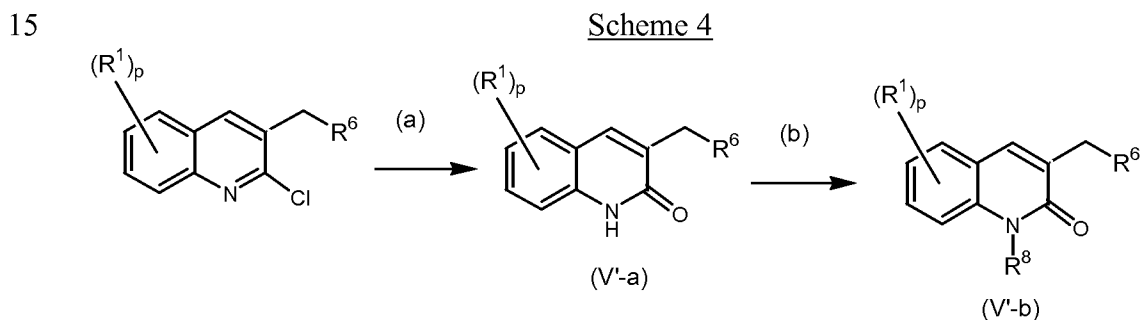


Intermediates of formula (V) wherein R^6 represents Het, said intermediates being represented by formula (V-f), can be prepared according to the following reaction scheme 3a.



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

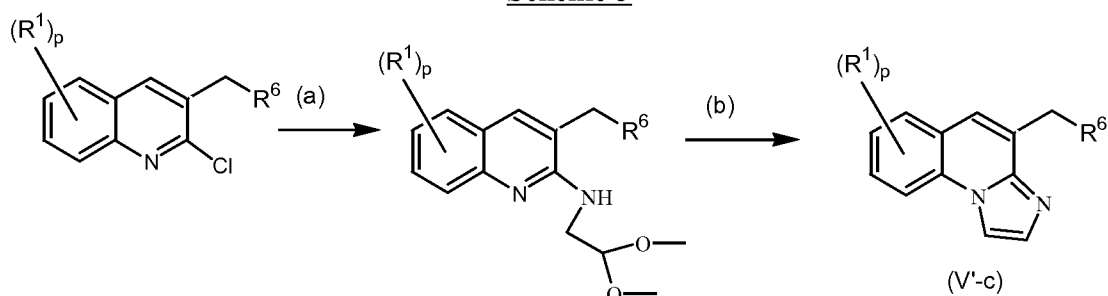
Intermediates of formula (V'), in particular (V'-a) or (V'-b), can be prepared according to the following reaction scheme (4).



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

Intermediates of formula (V') wherein the R^8 and R^9 are taken together to form the radical $-\text{CH}=\text{CH}-\text{N}=\text{}$, said intermediates being represented by formula (V'-c), can be prepared according to the following reaction scheme (5).

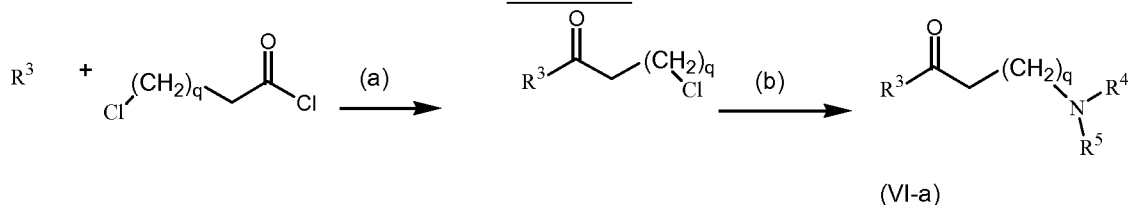
Scheme 5



Reaction scheme (5) comprises step (a) in which the intermediate is reacted with
 5 $\text{NH}_2\text{-CH}_2\text{-CH(OCH}_3\text{)}_2$. In a next step (b), the fused imidazolyl moiety is formed by
 reaction with acetic acid in the presence of a suitable solvent, such as for example
 xylene.

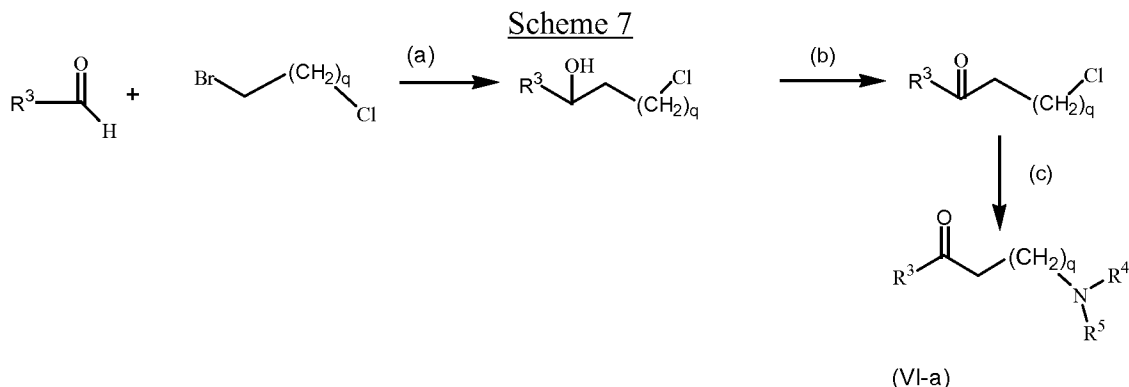
The intermediates of formula (VI-a) are compounds that are either commercially
 10 available or may be prepared according to conventional reaction procedures generally
 known in the art. For example, intermediates of formula (VI-a) may be prepared
 according to the following reaction scheme (6):

Scheme 6



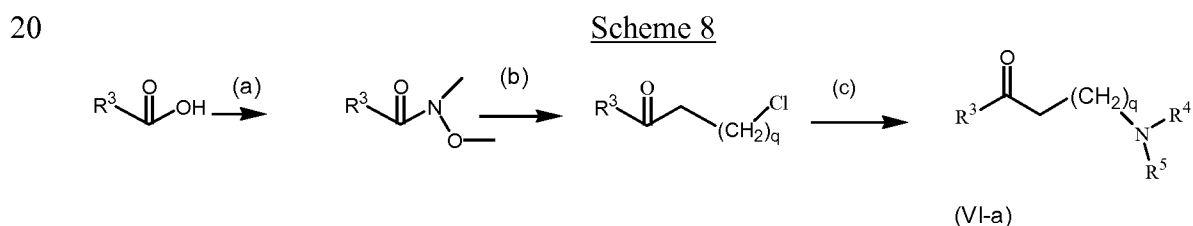
Reaction scheme (6) comprises step (a) in which R^3 , in particular an appropriately
 15 substituted aryl, more in particular an appropriately substituted phenyl, is reacted by
 Friedel-Craft reaction with an appropriate acylchloride such as 3-chloropropionyl
 chloride or 4-chlorobutyryl chloride, in the presence of a suitable Lewis acid, such as
 20 for example AlCl_3 , FeCl_3 , SnCl_4 , TiCl_4 or ZnCl_2 and a suitable reaction-inert solvent,
 such as methylene chloride or ethylene dichloride. The reaction may conveniently be
 carried out at a temperature ranging between room temperature and reflux temperature.
 In a next step (b), an amino group ($-\text{NR}^4\text{R}^5$) is introduced by reacting the intermediate
 obtained in step (a) with a primary or secondary amine (HNR^4R^5).

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



- Reaction scheme (7) comprises step (a) in which $R^3-C(=O)-H$, for instance an appropriately substituted arylcarboxaldehyde, more in particular an appropriately substituted phenyl or naphthylcarboxaldehyde, is reacted with an appropriate intermediate compound such as for example 1-bromo-4-chlorobutane, in the presence of Grignard reagent and a suitable solvent, such as for example diethyl ether, tetrahydrofuran. The reaction may conveniently be carried out at a low temperature for instance $5^\circ C$. In a next step (b), an oxidation is performed in the presence of Jones' reagent in a suitable solvent, such as for example acetone. In a next step (c), an amino group ($-NR^4R^5$) is introduced by reacting the intermediate compound obtained in step (b) with a primary or secondary amine HNR^4R^5 in the presence of a suitable solvent, such as for example acetonitrile, and a suitable base, such as for example K_2CO_3 .

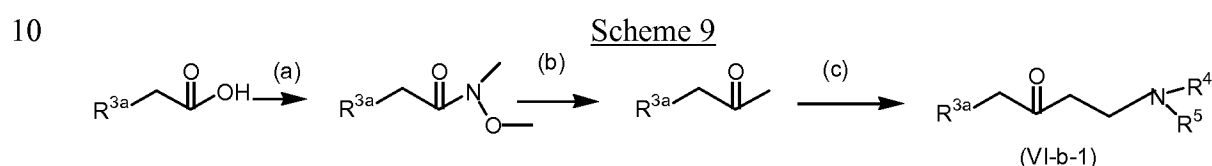
Alternatively, intermediates of formula (VI-a) may be prepared according to the following reaction scheme (8):



- Reaction scheme (8) comprises step (a) in which for instance a suitable acid is reacted with $NH(CH_3)(OCH_3)$ in the presence of 1,1'-carbonyldiimidazole and a suitable solvent, such as for example CH_2Cl_2 . In a next step (b), the product obtained in step (a) is reacted with a suitable Grignard reagents, e.g. 4-chlorobutyl magnesium bromide, in the presence of a suitable solvent, such as for example tetrahydrofuran. In a next step (c), an amino group ($-NR^4R^5$) is introduced by reacting the intermediate obtained in step (b) with a primary or secondary amine HNR^4R^5 in the presence of a suitable

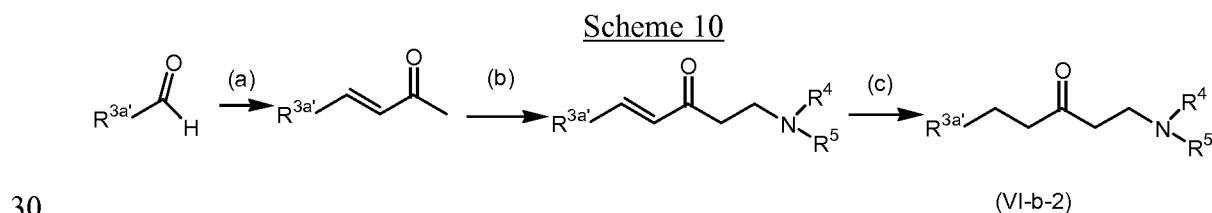
solvent, such as for example acetonitrile, and a suitable base, such as for example K_2CO_3 .

The intermediates of formula (VI-b) are compounds that are either commercially available or may be prepared according to conventional reaction procedures generally known in the art. For example, intermediates of formula (VI-b) wherein q represents 1, said intermediates being represented by formula (VI-b-1), may be prepared according to the following reaction scheme (9):



Reaction scheme (9) comprises step (a) in which for instance a suitable acid is reacted with $NH(CH_3)(OCH_3)$ in the presence of 1,1'-carbonyldiimidazole and a suitable solvent, such as for example CH_2Cl_2 . In a next step (b), the product obtained in step (a) is reacted with Grignard reagents CH_3MgCl in the presence of a suitable solvent, such as for example tetrahydrofuran. In a next step (c), an amino group ($-NR^4R^5$) is introduced by reacting the intermediate obtained in step (b) with a primary or secondary amine HNR^4R^5 in the presence of $CH_2(=O)$, a suitable acid, such as for example hydrochloric acid and the like, and a suitable solvent, such as for example an alcohol, e.g. ethanol.

Intermediates of formula (VI-b) wherein $R^{3a}-CH_2-$, represents $R^{3a'}-CH_2-CH_2-$ (which is possible for those intermediates of formula (VI-b) wherein R^{3a} represents alkyl, arylalkyl, aryl-O-alkyl or aryl-alkyl-O-alkyl and $R^{3a'}$ is the same as R^{3a} but with 1 carbon atom less in the alkyl chain attached to CH_2) and wherein q represents 1, said intermediates being represented by formula (VI-b-2), can be prepared according to the following reaction scheme (10):



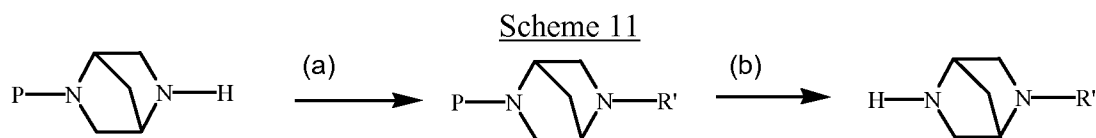
Reaction scheme 10 comprises step (a) wherein a suitable aldehyde is reacted with acetone in the presence of a suitable base, such as for example sodium hydroxide. In a next step (b), the product obtained in step (a) is reacted with a primary or secondary

amine HNR^4R^5 in the presence of $\text{CH}_2(=\text{O})$, a suitable acid, such as for example hydrochloric acid and the like, and a suitable solvent, such as for example an alcohol, e.g. ethanol. In a next step (c), the product obtained in step (b) is hydrogenated (H_2) in the presence of a suitable catalyst, such as for example palladium on charcoal, and a
 5 suitable solvent, such as for example water and an alcohol, e.g. ethanol.

Intermediates of formula (IV) wherein R^3 represents a halo substituted phenyl, may be converted into an intermediate of formula (IV) wherein R^3 represents phenyl substituted with aryl, by reaction with arylboronic acid in the presence of a suitable
 10 base, such as for example potassium phosphate, a suitable catalyst, such as for example palladium acetate, and a suitable ligand, such as for example 2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl, in an appropriate solvent, such as for example toluene.

Intermediates of formula (IV) wherein R^3 represents a halo substituted phenyl, may also be converted into an intermediate of formula (IV) wherein R^3 represents phenyl substituted with C_{2-6} alkenyl optionally substituted with phenyl, by reaction with an appropriate C_{2-6} alkene, such as for example styrene, in the presence of a suitable base, such as for example triethylamine, a suitable catalyst, such as for example palladium acetate, and a suitable ligand, such as for example tri-*o*-tolylphosphine, in an
 15 appropriate solvent, such as for example DMF.

In case in the above reaction schemes, the suitable amine HNR^4R^5 represents substituted 2,5-diazabicyclo[2.2.1]heptyl, said amine can be prepared according to the following reaction scheme (11):
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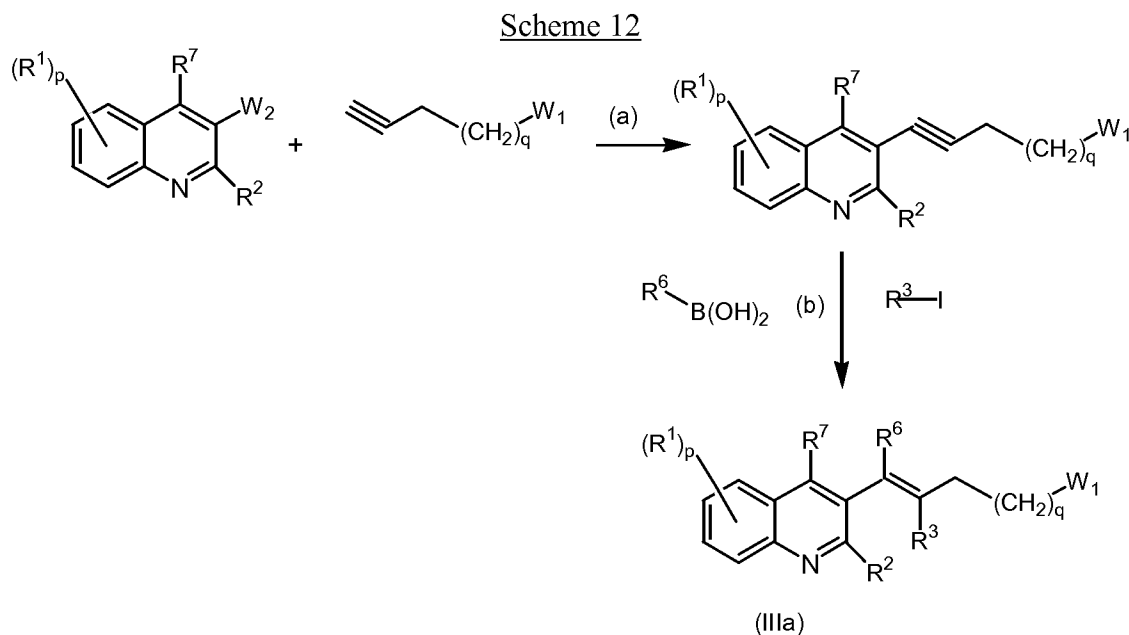


Reaction scheme (11) comprises the step of reacting an appropriately protected 2,5-diazabicyclo[2.2.1]heptyl wherein P represents for instance *tert*-butoxycarbonyl, with an appropriate reagents of formula $\text{W-R}'$ wherein W represents a suitable leaving group, such as for example halo, e.g. bromo and the like, and wherein R' represents the
 30 substituent to be introduced, in the presence of a suitable base, such as for example K_2CO_3 , NaHCO_3 or triethylamine, a suitable phase transfer reagent, such as for example tetra-*n*-butylammonium chloride, a suitable solvent, such as for example acetonitrile, and optionally KI to increase the speed of the reaction. In a next step (b), the protective group is removed by reaction with a suitable acid, such as for example
 35

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

Intermediates of formula (III-a) may be prepared according to the following reaction

5 Scheme (12):

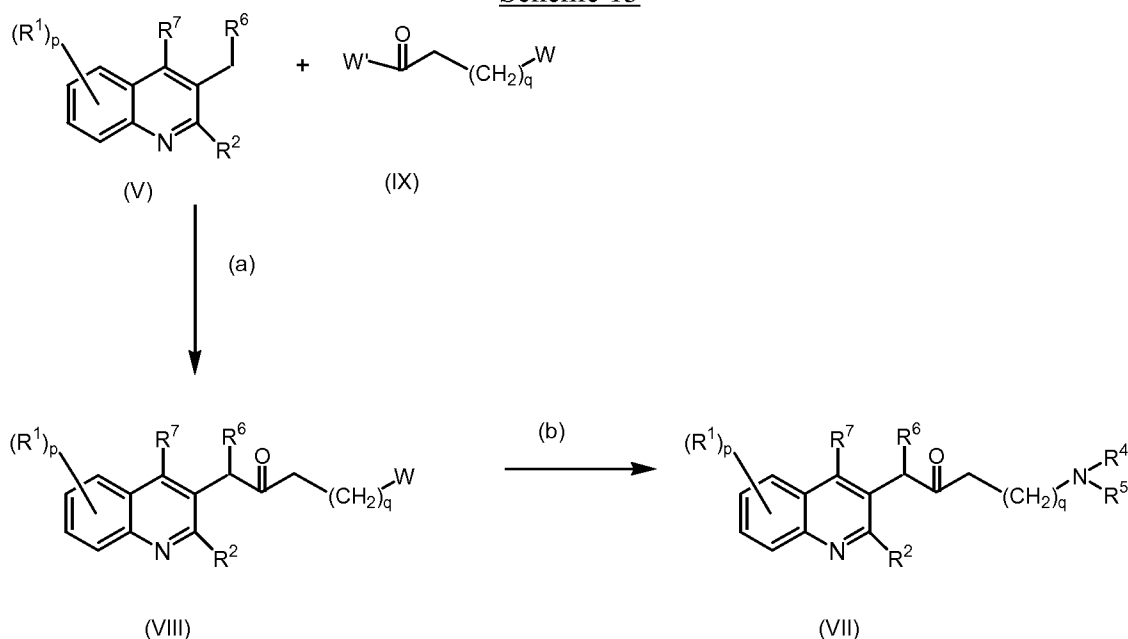


Reaction scheme (12) comprises step (a) wherein a suitable quinoline derivative, wherein W_2 represents a suitable leaving group, such as for example halo, e.g. bromo, is reacted with a suitable alkyne derivative wherein W_1 represents a suitable leaving group, such as for example halo, e.g. chloro, in the presence of a suitable catalyst, such as for example $\text{PdCl}_2(\text{PhCN})_2$, a suitable ligand, such as for example X-PHOS, a suitable base, such as for example Cs_2CO_3 , and a suitable solvent, such as for example *N,N*-dimethylformamide. In a next step (b), the product obtained in step (a) is reacted with $\text{R}^6\text{-B(OH)}_2$ and $\text{R}^3\text{-I}$ in the presence of a suitable catalyst, such as for example $\text{PdCl}_2(\text{PhCN})_2$, a suitable base, such as for example KHCO_3 , and a suitable solvent, such as for example 1-methyl-2-pyrrolidinone and water.

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

Intermediates of formula (VII) can be prepared according to reaction scheme 13.

Scheme 13



- In reaction scheme 13, in step (a) an intermediate of formula (V) is reacted with an intermediate of formula (IX) wherein W' represents a suitable leaving group, such as for example *1H*-benzotriazole, and W represents a suitable leaving group, such as for example halo, e.g. chloro, in the presence of *n*BuLi, a suitable base, such as for example *N*-(1-methylethyl)-2-propanamine, and a suitable solvent, such as for example tetrahydrofuran. The reaction may conveniently be carried out at a temperature ranging between -20 and -70 °C. In a next step (b), the resulting intermediate of formula (VIII) is reacted with a primary or secondary amine HNR^4R^5 in the presence of a suitable base, such as for example potassium carbonate, and a suitable solvent, such as for example acetonitrile.

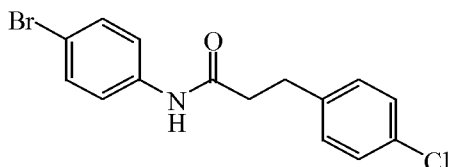
- The following examples illustrate the present invention without being limited thereto.

EXPERIMENTAL PART

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

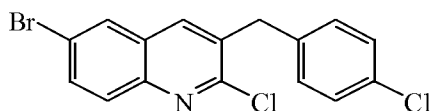
methods such as, for example, X-ray diffraction or NMR. It is considered to be within the knowledge of the skilled person to recognize the most appropriate method to determine the actual stereochemical configuration.

- In case "A" and "B" are stereoisomeric mixtures, in particular mixtures of enantiomers, they can be further separated whereby the respective first fractions isolated are designated "A1" respectively "B1" and the second as "A2" respectively "B2", without further reference to the actual stereochemical configuration. However, said "A1", "A2" and "B1", "B2" isomeric forms, in particular said "A1", "A2" and "B1", "B2" enantiomeric forms, can be unambiguously characterized by a person skilled in the art, using art-known methods such as, for example, X-ray diffraction.
- For example, an intermediate of formula (II-a), (II-b), (II-c) or (II-d) is indicated as a particular diastereoisomer (substantially free of the other diastereoisomer(s)). In case said intermediate of formula (II-a), (II-b), (II-c) or (II-d) has two chiral centers this means that the intermediate is a mixture, in particular a racemic mixture of the (R,S) and (S,R) enantiomers or a racemic mixture of the (R,R) and (S,S) enantiomer.
- Hereinafter, the mixtures of 2 enantiomers are indicated as diastereoisomer A or B. Whether the mixture is indicated as A or B depends on whether it is first isolated in the synthesis protocol (i.e. A) or second (i.e. B). When said intermediate is indicated as a particular enantiomer (substantially free of the other enantiomers), this means that the intermediate is the (R,S), (S,R), (R,R) or (S,S) enantiomer. Hereinafter, said particular enantiomers are indicated as A1, A2, B1 or B2. Whether the enantiomer is indicated as A1, A2, B1 or B2 depends on whether it is isolated first or second (1 or 2) in the synthesis protocol and whether it is separated from the A (A1, A2) or B (B1, B2) diastereoisomer.
- In some cases, when an intermediate, indicated as a particular diastereoisomer or enantiomer, is converted into another intermediate, the latter may inherit the indication for diastereoisomer (A or B) or enantiomer (A1, A2, B1, B2) from the former. Whenever this applies, this also counts for the final compound.
- Hereinafter, "DMF" is defined as *N,N*-dimethylformamide, "THF" is defined as tetrahydrofuran, "DIPE" is defined as diisopropylether, "DCM" is defined as dichloromethane, "PPA" is defined as polyphosphoric acid.

Experimental partA. Preparation of the intermediate compoundsExample A1a. Preparation of intermediate 1

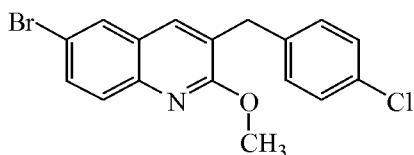
- 5 4-chlorobenzenepropanoyl chloride (0.466 mol) was added slowly at 5°C to a solution of 4-bromobenzenamine (0.388 mol) in Et₃N (70 ml) and CH₂Cl₂ (700 ml). The mixture was stirred at room temperature for 1 hour. H₂O was added. The precipitate was filtered off, washed with H₂O and dried. The residue was recrystallized from diethyl ether. The precipitate was filtered off and dried. Yield: 110 g of **intermediate 1** (83 %) (m.p. 194°C).

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b. Preparation of intermediate 2

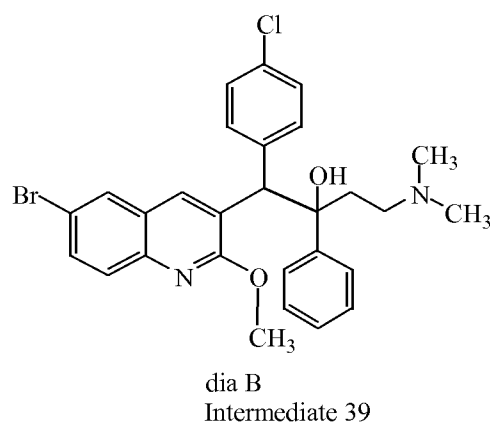
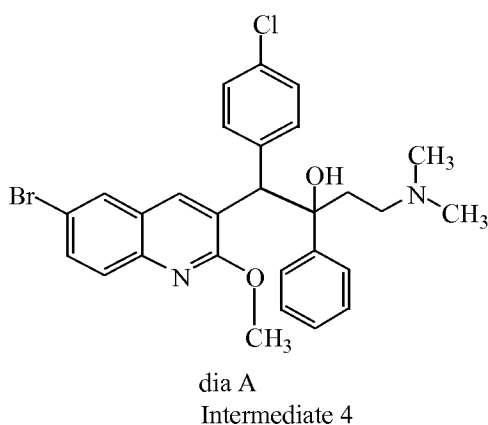
- 15 POCl₃ (192.6 ml) was added slowly at 5°C to DMF (35.4 ml). **Intermediate 1** (prepared according to A1.a) (0.296 mol) was added. The mixture was stirred at 80°C for 12 hours, poured out slowly on ice and extracted with CH₂Cl₂. The organic layer was separated, dried (MgSO₄), filtered and the solvent was evaporated. The product was used without further purification. Yield: 150 g of **intermediate 2**.

c. Preparation of intermediate 3



A mixture of **intermediate 2** (prepared according to A1.b) (0.409 mol) in CH₃ONa (300 ml) and CH₃OH (300 ml) was stirred and refluxed for 15 hours. The mixture was poured out on ice and extracted with CH₂Cl₂. The organic layer was separated, dried (MgSO₄), filtered and the solvent was evaporated. The residue (150 g) was purified by column chromatography over silica gel (eluent: cyclohexane/CH₂Cl₂ 90/10; 35-70 μm). The pure fractions were collected and the solvent was evaporated. The residue was crystallized from diethyl ether. The precipitate was filtered off and dried. Yield: 27 g of **intermediate 3** (18 %) (m.p. 100°C).

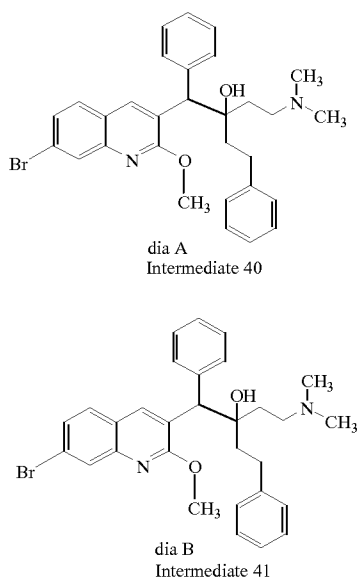
d. Preparation of intermediate 4 and 39



10 *n*BuLi 1.6M (0.061 mol) was added slowly at -20°C to a solution of *N*-(1-methylethyl)-2-propanamine (0.061 mol) in THF (85 ml). The mixture was stirred at -20°C for 30 minutes and then cooled to -70°C. A solution of **intermediate 3** (prepared according to A1.c) (0.055 mol) in THF (200 ml) was added slowly. The mixture was stirred at -70°C for 30 minutes. A solution of 3-(dimethylamino)-1-phenyl-1-propanone (0.066 mol) in THF (120 ml) was added. The mixture was stirred at -70°C for 1 hour, then hydrolyzed at -30°C with ice water and extracted with EtOAc. The organic layer was separated, dried (MgSO₄), filtered and the solvent was evaporated.

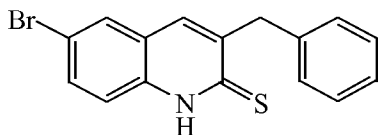
The residue (31 g) was purified by column chromatography over silica gel (eluent: $\text{CH}_2\text{Cl}_2/\text{CH}_3\text{OH}/\text{NH}_4\text{OH}$ 99.5/0.5/0.05; 20-40 μm). Three pure fractions were collected and their solvents were evaporated. Yield: 6.5 g of fraction 1, 2.4 g of fraction 2 and 2.4 g of fraction 3. Fraction 1 and fraction 2 (fraction 3 is mixture) were crystallized from diethyl ether. The precipitate was filtered off and dried. Yield: 5.19 g of **intermediate 4** (diastereoisomer A) (17 %) and 1.8 g **intermediate 39** (diastereoisomer B) (6 %).

Following intermediates were prepared according to the previous procedure and were purified as indicated.

Intermediate 40 and 41	The residue (4.7 g) was purified by column chromatography over silica gel (eluent: $\text{CH}_2\text{Cl}_2/\text{CH}_3\text{OH}/\text{NH}_4\text{OH}$ 92/8/0.2; 15-40μm). Two fractions were collected and the solvent was evaporated. Yield: 0.45 g of fraction 1 and 0.4 g of fraction 2. Fraction 1 and fraction 2 were crystallized from DIPE. The precipitate was filtered off and dried. Yield: 0.367 g of intermediate 40 (diastereoisomer A) (m.p. 160°C) and 0.298 g of intermediate 41 (diastereoisomer B) (m.p. 194°C).	
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Example A2

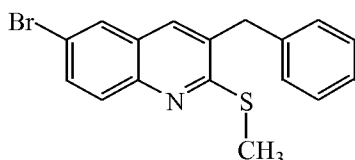
a. Preparation of intermediate 5



A mixture of 6-bromo-2-chloro-3-(phenylmethyl)-quinoline (prepared according to the teachings in WO2005/070924 of which the content is incorporated herein by reference) (0.045 mol) and thiourea (0.05 mol) in ethanol (150 ml) was stirred and refluxed for 8 hours and then brought to room temperature. A solution of KOH (0.068 mol) in H_2O

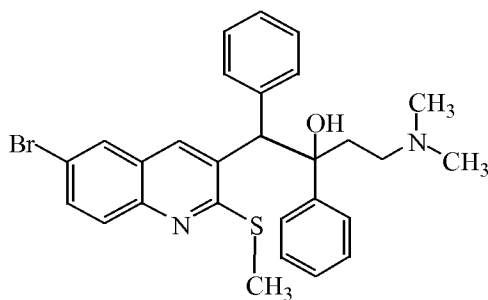
(15 ml) was added. The mixture was stirred and refluxed for 1 hour and poured out on ice. The precipitate was filtered off, washed with H₂O and dried. Yield: 11 g of **intermediate 5** (74 %).

b. Preparation of intermediate 6

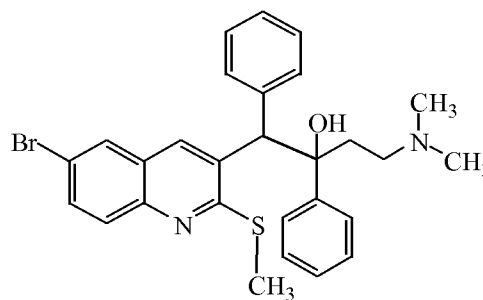


- 5 CH₃I (0.037 mol) was added slowly at room temperature to a mixture of **intermediate 5** (prepared according to A2.a) (0.033 mol) and K₂CO₃ (0.037 mol) in 2-propanone (150 ml). The mixture was stirred at room temperature for 8 hours, poured out into H₂O and extracted with CH₂Cl₂. The organic layer was separated, dried (MgSO₄), filtered and the solvent was evaporated. Yield: 11.2 g of a first fraction (97 %). Part of
10 this fraction (2 g) was crystallized from diethyl ether. The precipitate was filtered off and dried. Yield: 1.45 g of **intermediate 6** (70 %) (m.p. 88°C).

c. Preparation of intermediate 7 and 8



A
Intermediate 7



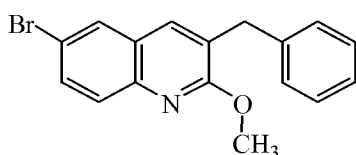
B
Intermediate 8

- n*BuLi 1.6M in hexane (0.027 mol) was added slowly at -20°C to a solution of *N*-(1-methylethyl)-2-propanamine (0.027 mol) in THF (40 ml). The mixture was
15 cooled again to -70°C. A solution of intermediate 6 (0.024 mol) in THF (100 ml) was added slowly. The mixture was stirred at -70°C for 30 minutes. A solution of 3-(dimethylamino)-1-phenyl-1-propanone (0.029 mol) in THF (60 ml) was added slowly. The mixture was stirred at -70°C for 2 hours, hydrolyzed at -20°C with ice water and extracted with EtOAc. The organic layer was separated, dried (MgSO₄),
20 filtered and the solvent was evaporated. The residue (13.2 g) was purified by column chromatography over silica gel (eluent: CH₂Cl₂/CH₃OH/NH₄OH 99.25/0.75/0.1; 20-45

5 μm). Two pure fractions were collected and their solvents were evaporated. Fraction 1 was crystallized from diethyl ether. The precipitate was filtered off and dried. Yield: 1 g of **intermediate 7** (8 %) (m.p. 208°C). Fraction 2 was crystallized from diethyl ether and DIPE. The precipitate was filtered off and dried. Yield: 1.75 g of **intermediate 8** (13 %) (m.p. 196°C).

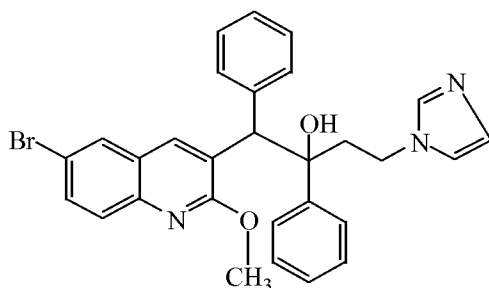
Example A3

a. Preparation of intermediate 9

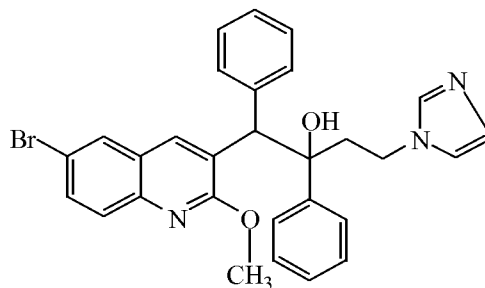


10 A mixture of 6-bromo-2-chloro-3-(phenylmethyl)-quinoline (prepared according to the teachings in WO2005/070924 of which the content is incorporated herein by reference) (0.233 mol) in CH_3ONa 30% in CH_3OH (222.32 ml) and CH_3OH (776 ml) was stirred and refluxed overnight, then poured out on ice and extracted with CH_2Cl_2 . The organic layer was separated, dried (MgSO_4), filtered and the solvent was evaporated. The residue was purified by column chromatography over silica gel (eluent: $\text{CH}_2\text{Cl}_2/\text{cyclohexane}$ 20/80 and then 100/0; 20-45 μm). The pure fractions were
 15 collected and the solvent was evaporated. Yield: 25 g of **intermediate 9** (33 %).

b1. Preparation of intermediate 10 and 11



dia A
Intermediate 10



dia B
Intermediate 11

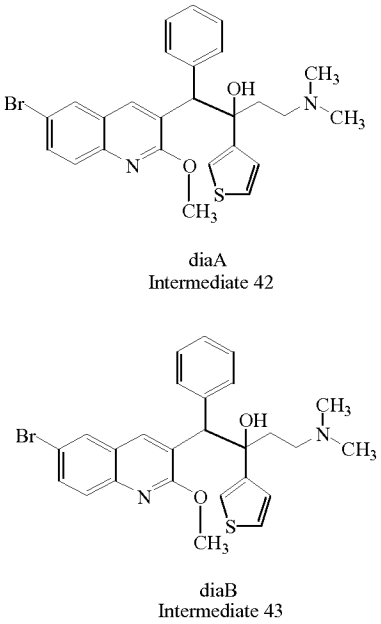
$n\text{BuLi}$ 1.6 M in hexane (0.04 mol) was added slowly at -20°C to a solution of *N*-(1-methylethyl)-2-propanamine (0.04 mol) in THF (60 ml). The mixture was stirred at -20°C for 15 minutes and then cooled to -60°C . A solution of **intermediate 9** (prepared

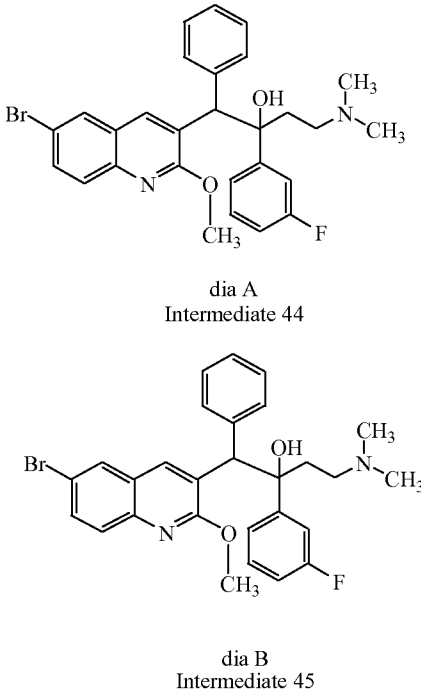
according to A3.a) (0.037 mol) in THF (120 ml) was added slowly. The mixture was stirred at -60°C for 30 minutes. A solution of 3-(1*H*-imidazol-1-yl)-1-phenyl-1-propanone (0.044 mol) in THF (90 ml) was added. The mixture was stirred at -60°C for 1 hour, then hydrolyzed at -30°C with ice water and extracted with EtOAc. The organic layer was separated, dried (MgSO_4), filtered and the solvent was evaporated.

The residue (31 g) was purified by column chromatography over silica gel (eluent: $\text{CH}_2\text{Cl}_2/\text{CH}_3\text{OH}/\text{NH}_4\text{OH}$ 98/2/0.1; 20-45 μm). Two pure fractions were collected and their solvents were evaporated. Yield: 1.2 g of fraction 1 and 1.9 g of fraction 2.

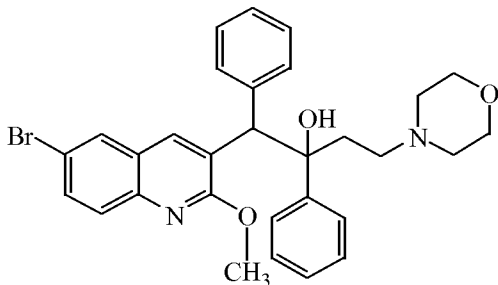
Fraction 1 was crystallized from diethyl ether. The precipitate was filtered off and dried. Yield: 1.05 g of **intermediate 10** (6 %) (m.p. 216°C). Fraction 2 was crystallized from 2-propanone and diethyl ether. The precipitate was filtered off and dried. Yield: 1.64 g of **intermediate 11** (8.5 %) (m.p. 230°C).

Following intermediates were prepared according to the previous procedure and were purified as indicated.

Intermediate 42 and 43	The residue (20 g) was purified by column chromatography over silica gel (eluent: $\text{CH}_2\text{Cl}_2/\text{CH}_3\text{OH}/\text{NH}_4\text{OH}$ 99/1/0.1; 15-40 μm). Two pure fractions were collected and the solvent was evaporated. Yield: 1.7 g of fraction 1 and 3.8 g of fraction 2. Fraction 1 was crystallized from DIPE. The precipitate was filtered off and dried. Yield: 1.1 g of intermediate 42 (6 %). Fraction 2 was crystallized from diethyl ether. The precipitate was filtered off and dried. Yield: 2.2 g of intermediate 43 (12 %).	 Chemical structures of Intermediate 42 (diaA) and Intermediate 43 (diaB) are shown. Both structures are 4-bromo-2-(4-(dimethylamino)-4-phenyl-2-methyl-1,3-dithienyl)-5-nitrophenol.
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Intermediate 44 and 45	The residue (20 g) was purified by column chromatography over silica gel (eluent: CH₂Cl₂/CH₃OH/NH₄OH 99.5/0.5/0.1; 15-40 μm). Three pure fractions were collected and their solvent were evaporated. Yield: 2.8 g of fraction 1, 3.4 g of fraction 2 and 2.7 g of fraction 3. Fraction 1 and fraction 2 were crystallized from DIPE. The precipitate was filtered off and dried. Yield: 1.45 g of intermediate 44 (7 %) and 1.55 g of intermediate 45 (8 %).	 dia A Intermediate 44 dia B Intermediate 45
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b2. Preparation of intermediate 12

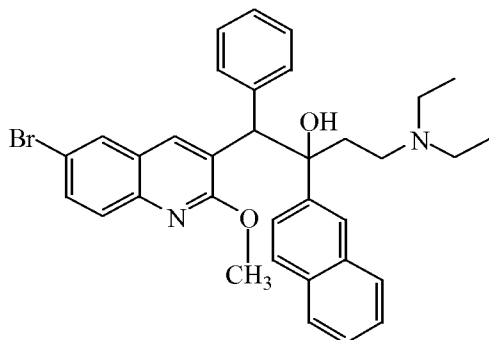


dia A + dia B: 60/40

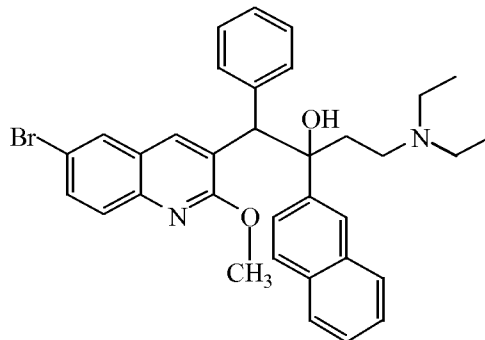
- n*BuLi 1.6 M (0.007 mol) in hexane was added dropwise at –20°C to a solution of *N*-(1-methylethyl)-2-propanamine (0.0069 mol) in THF (10 ml) under N₂ flow. The mixture was stirred at 80°C for 20 minutes, then cooled to –70°C. A solution of **intermediate 9** (prepared according to A3.a) (0.006 mol) in THF (10 ml) was added. The mixture was stirred at –70°C for 2 hours. A solution of 3-(4-morpholinyl)-1-phenyl-1-propanone (0.0091 mol) in THF (10 ml) was added. The mixture was stirred at –70°C for 2 hours, then brought to –30°C, poured out into H₂O at 0°C and extracted with CH₂Cl₂. The organic layer was separated, dried (MgSO₄), filtered and the solvent was evaporated.
- The residue (4.1 g) was purified by column chromatography over silica gel (eluent:

CH₂Cl₂ 100; 15-40 μm). The pure fractions were collected and the solvent was evaporated. Yield: 0.9 g of **intermediate 12** (27 %).

b3. Preparation of intermediate 17 and 18



dia A
Intermediate 17

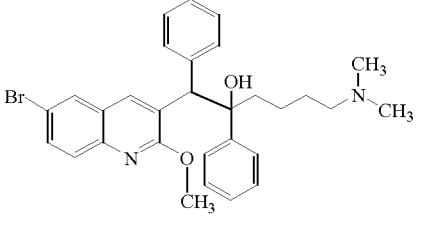
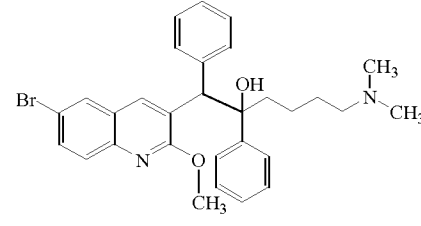


dia B
Intermediate 18

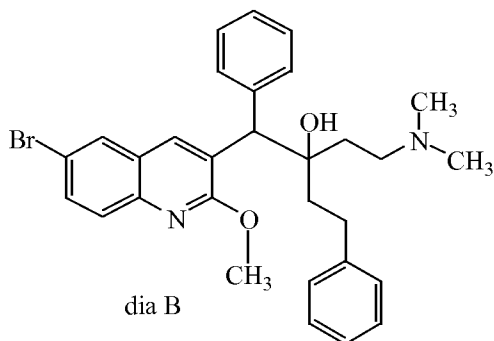
5 *n*BuLi 1.6 M (0.008 mol) in hexane was added dropwise at –20°C to a solution of *N*-(1-methylethyl)-2-propanamine (0.008 mol) in THF (16 ml) under N₂ flow. The mixture was stirred at –20°C for 20 minutes, then cooled to –70°C. A solution of **intermediate 9** (prepared according to A3.a) (0.0067 mol) in THF (25 ml) was added. The mixture was stirred for 1 hour and 30 minutes. A solution of 3-(diethylamino)-1-(2-naphthalenyl)-1-propanone (0.008 mol) in THF (25 ml) was added. The mixture was
10 stirred at –70°C for 3 hours, then poured out on ice at –30°C and extracted with EtOAc. The organic layer was separated, dried (MgSO₄), filtered and the solvent was evaporated.

The residue was purified by column chromatography over silica gel (eluent: CH₂Cl₂/CH₃OH/NH₄OH 98/2/0.1; 15-40 μm). Two fractions were collected and the
15 solvent was evaporated. Yield: 1.8 g of fraction 1 and 0.5 g of fraction 2. Both fractions were purified by column chromatography over silica gel (eluent: cyclohexane/EtOAc 70/30; 15-40 μm). Two fractions were collected and the solvent was evaporated. Yield: 0.47 g of fraction A and 0.43 g of fraction B. Both fractions were crystallized from DIPE/diethyl ether. The precipitate was filtered off and dried.
20 Yield: 0.32 g **intermediate 17** (8.2 %) (m.p.: 134°C) and 0.23 g of **intermediate 18** (5 %) (m.p.: 184°C).

Following intermediates were prepared according to the previous procedure and were purified as indicated.

Intermediate 46 and 47	The residue (6 g) was purified by column chromatography over silica gel (eluent: CH ₂ Cl ₂ /CH ₃ OH/NH ₄ OH 94/6/0.2; 15-40 μm). Two fractions were collected and the solvent was evaporated. Yield: 1.25 g of intermediate 46 (26 %) and 0.9 g of intermediate 47 (19 %).	 dia A Intermediate 46  dia B Intermediate 47
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b4. Preparation of intermediate 19

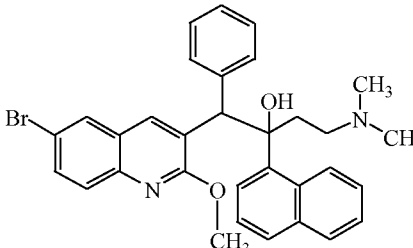


- 5 *n*BuLi 1.6 M (0.01 mol) in hexane was added dropwise at −20°C to a solution of *N*-(1-methylethyl)-2-propanamine (0.01 mol) in THF (15 ml) under N₂ flow. The mixture was stirred at −20°C for 15 minutes, then cooled to −70°C. A solution of **intermediate 9** (prepared according to A3.a) (0.0009 mol) in THF (30 ml) was added dropwise. The mixture was stirred at −70°C for 30 minutes. A solution of 1-(dimethylamino)-5-phenyl-3-pentanone (0.0128 mol) in THF (15 ml) was added. The mixture was stirred at −70°C for 2 hours, poured out at −30°C on ice and extracted with CH₂Cl₂. The organic layer was separated, dried (MgSO₄), filtered, and the solvent was evaporated.
- 10

The residue (5.5 g) was purified by column chromatography over silica gel (eluent: CH₂Cl₂/CH₃OH 98/2; 15-40 μm). Three fractions were collected and the solvent was evaporated. Yield: 0.8 g of fraction 1, 0.65 g of fraction 2 and 0.216 g of fraction 3.

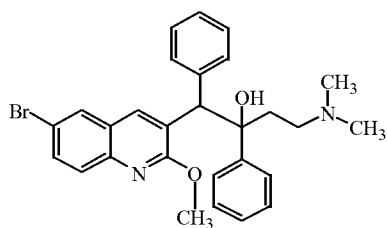
Fraction 3 was crystallized from petroleum ether. The precipitate was filtered off and dried. Yield: 0.136 g of **intermediate 19** (5 %).

Following intermediates were prepared according to the previous procedure:

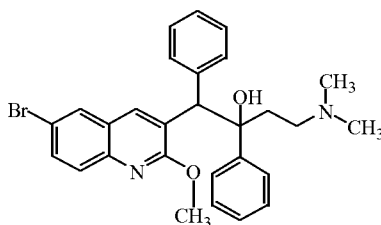
Intermediate 48	The residue (350 g) was purified by column chromatography over silica gel (eluent: CH ₂ Cl ₂ / <i>i</i> PrOH/NH ₄ OH 99.5/0.5/0.2; 20-45 μm). Three fractions were collected and the solvent was evaporated. Yield: 133 g of starting material A, 20.1 g of fraction B (dia B) and 33 g of fraction C (dia B). Fraction C was crystallized from DIPE. The precipitate was filtered off and dried. Yield: 25 g of intermediate 48 (B1).	 (R*,R*) Intermediate 48 (B1)
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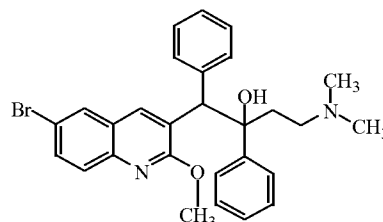
b5. Preparation of intermediate 25, 26 and 27



dia A
Intermediate 25



dia B
Intermediate 26

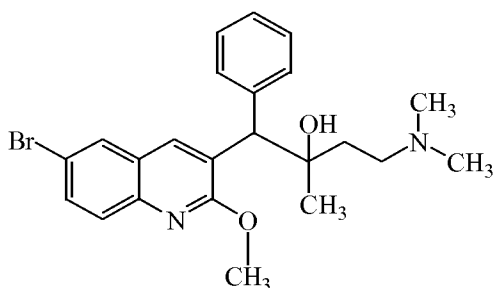


dia A + dia B
Intermediate 27

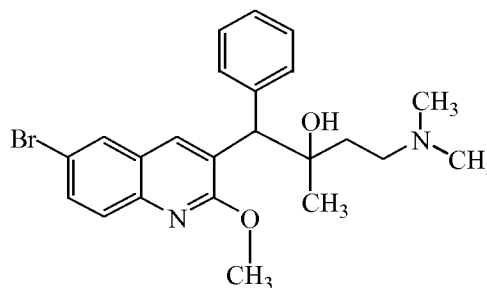
*n*BuLi 1.6 M (0.0686 mol) in hexane was added dropwise at -78°C under N₂ flow to a solution of *N*-(1-methylethyl)-2-propanamine (0.0686 mol) in THF (70 ml), and the mixture was allowed to warm to 0°C. **Intermediate 9** (prepared according to A3.a) (0.624 mol) in THF (205 ml) was added dropwise at -78°C and the mixture was stirred at -78°C for 1 hour. 3-(Dimethylamino)-1-phenyl-1-propanone (0.0748 mol) in THF (133 ml) was added, the mixture was stirred at -78°C for one hour and then allowed to warm to 0°C. The mixture was poured out in a saturated NH₄Cl solution, and extracted with EtOAc. The organic layer was separated, dried (MgSO₄), filtered, and the solvent was evaporated. The residue was purified by column chromatography over silica gel (eluent: CH₂Cl₂/CH₃OH/NH₄OH 99/1/0.1; 15-40 μm). Two pure fractions were collected and their solvents were evaporated. Fraction 1 (3.56 g) was crystallized from

2-propanone and diethyl ether. The precipitate was filtered off and dried. Yield: 1.14 g of **intermediate 25** (4 %). Fraction 2 (7.67 g) was crystallized from 2-propanone and diethyl ether. The precipitate was filtered off and dried. Yield: 2.65 g of **intermediate 26** (8 %). The mother layers of fraction 1 and 2 were combined and the solvent was
 5 evaporated. Yield: 4.53 g of **intermediate 27**.

b6. Preparation of intermediate 28 and 29



dia A
Intermediate 28

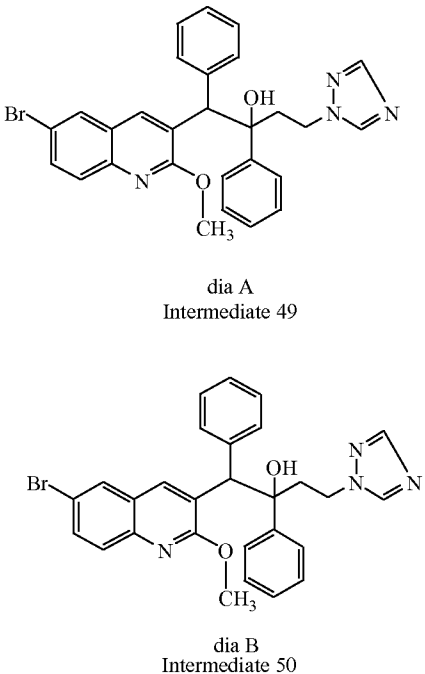
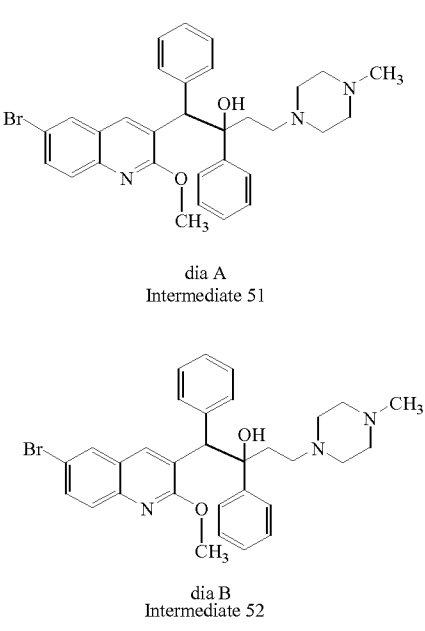


dia B
Intermediate 29

*n*BuLi 1.6 M (0.04 mol) in hexane was added dropwise at -78°C under N_2 flow to a solution of *N*-(1-methylethyl)-2-propanamine (0.04 mol) in THF (70 ml). The mixture was brought to 0°C and then cooled again to -78°C . A solution of **intermediate 9**
 10 (prepared according to A3.a) (0.0365 mol) in THF (70 ml) was added dropwise. The mixture was stirred at -78°C for 1 hour. A solution of 4-(dimethylamino)-2-butanone (0.0438 mol) in THF (70 ml) was added. The mixture was stirred at -78°C for 1 hour, brought to -30°C , poured out on ice and extracted with EtOAc. The organic layer was separated, dried (MgSO_4), filtered and the solvent was evaporated.

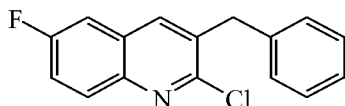
15 The residue (17 g) was purified by column chromatography over silica gel (eluent: $\text{CH}_2\text{Cl}_2/\text{CH}_3\text{OH}/\text{NH}_4\text{OH}$ 97/3/0.2; 15-40 μm). Two pure fractions were collected and their solvents were evaporated. The residue was crystallized from diethyl ether. The precipitate was filtered off and dried. Yield: 1.2 g of **intermediate 28** (9.2 %) and 1 g of **intermediate 29** (7.4 %).

Following intermediates were prepared according to the previous procedure and were purified as indicated.

Intermediate 49 and 50	The residue (23 g) was purified by column chromatography over silica gel (eluent: CH₂Cl₂/CH₃OH/NH₄OH 99/1/0.1). Two pure fractions were collected and the solvent was evaporated. Yield: 2.5 g of fraction 1 and 2 g of fraction 2. Fraction 1 was crystallized from DIPE. The precipitate was filtered off and dried. Yield: 1.93 g of intermediate 49 (13 %) (m.p. 180°C). Fraction 2 was crystallized from EtOAc. The precipitate was filtered off and dried. Yield: 1.23 g of intermediate 50 (10.6 %) (m.p. 142°C).	 dia A Intermediate 49 dia B Intermediate 50
Intermediate 51 and 52	The residue (20.8 g) was purified by column chromatography over silica gel (eluent: CH₂Cl₂/CH₃OH/NH₄OH 99/1/0.1). Two pure fractions were collected and their solvents were evaporated. Fraction 1 was crystallized from DIPE. The precipitate was filtered off and dried. Yield: 1.21 g of intermediate 51 (7.3 %) (m.p. 150°C). Fraction 2 was crystallized from EtOAc. The precipitate was filtered off and dried. Yield: 4.13 g of intermediate 52 (34 %) (m.p. 230°C).	 dia A Intermediate 51 dia B Intermediate 52

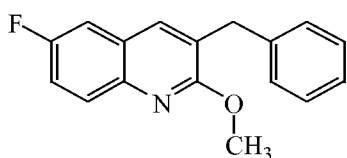
Example A4

a. Preparation of intermediate 13



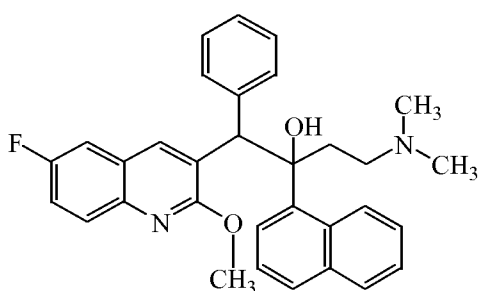
POCl₃ (3.453 mol) was added slowly at 5°C to DMF (120 ml). After complete addition, 4'-fluoro-hydrocinnamanilide (0.492 mol) was added. The mixture was stirred at 80°C overnight, then brought to room temperature and poured out on ice. EtOAc was added. The mixture was stirred for 1 hour while ice was added and then
5 extracted with EtOAc. The organic layer was separated, washed twice with H₂O, dried (MgSO₄), filtered and the solvent was evaporated. Yield: 80.2 g of **intermediate 13** (60 %).

b. Preparation of intermediate 14

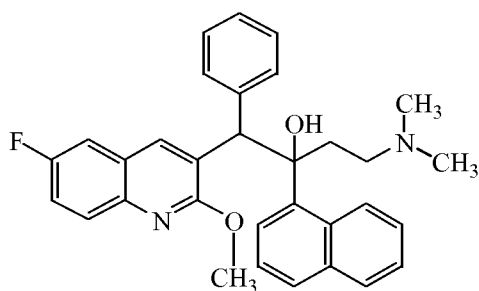


A mixture of **intermediate 13** (prepared according to A4.a) (0.295 mol) in CH₃ONa 30 % in CH₃OH (250 ml) and CH₃OH (250 ml) was stirred at 80°C overnight. The mixture was brought to room temperature, poured out on ice and extracted with EtOAc. The organic layer was separated, washed with H₂O, dried (MgSO₄), filtered and the solvent was evaporated. The residue (57 g) was purified by column chromatography over silica gel (eluent: CH₂Cl₂/cyclohexane 20/80; 20-45 µm). The pure fractions were collected and the solvent was evaporated. Yield: 27 g of **intermediate 14** (34 %).

c. Preparation of intermediate 15 and 16



dia A
Intermediate 15



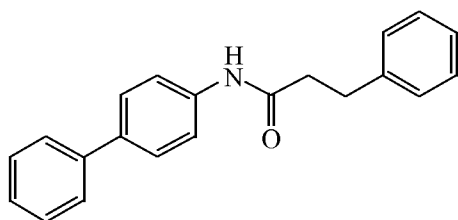
dia B
Intermediate 16

nBuLi 1.6 M (0.067 mol) in hexane was added dropwise at -30°C under N_2 flow to a solution of *N*-(1-methylethyl)-2-propanamine (0.067 mol) in THF (150 ml). The mixture was stirred at -20°C for 30 minutes and then cooled to -70°C . A solution of **intermediate 14** (prepared according to A4.b) (0.044 mol) in THF (50 ml) was added dropwise. The mixture was stirred at -70°C for 45 minutes. A solution of 3-

(dimethylamino)-1-phenyl-1-propanone (0.053 mol) in THF (50 ml) was added dropwise. The mixture was stirred at -60°C for 2 hours, hydrolyzed with ice water and extracted with EtOAc. The organic layer was separated, dried (MgSO_4), filtered and the solvent was evaporated. The residue (22 g) was purified by column chromatography over silica gel (eluent: $\text{CH}_2\text{Cl}_2/\text{CH}_3\text{OH}/\text{NH}_4\text{OH}$ 99.25/0.75/0.1; 15-40 μm). Three pure fractions were collected and their solvents were evaporated. Yield: 4 g of fraction 1, 3 g of fraction 2 and 1.3 g of fraction 3. Fraction 1 was crystallized from EtOAc and diethyl ether. The precipitate was filtered off and dried. Yield: 2.9 g of **intermediate 15** (14.8 %). Fraction 2 was crystallized from EtOAc and diethyl ether. The precipitate was filtered off and dried. Yield: 1.5 g of **intermediate 16** (7.7 %).

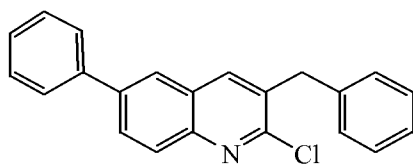
Example A5

a. Preparation of intermediate 20



Benzenepropanoyl chloride (0.53 mol) was added slowly at 5°C under N_2 flow to a solution of [1,1'-biphenyl]-4-amine (0.443 mol) and Et_3N (0.719 mol) in CH_2Cl_2 (750 ml). After complete addition, the mixture was stirred at 5°C for 1 hour, at room temperature for 2 hours and poured out into HCl 3N and ice. CH_2Cl_2 was added. The mixture was stirred at room temperature for 30 minutes and extracted with CH_2Cl_2 . The organic layer was separated, washed with H_2O , dried (MgSO_4), filtered and the solvent was evaporated. The residue was taken up in diethyl ether, filtered off and dried. Yield: 112 g of **intermediate 20** (84 %).

b. Preparation of intermediate 21

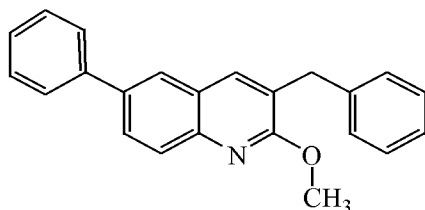


POCl_3 (2.24 mol) was added dropwise at 5°C to DMF (76.8 ml). **Intermediate 20** (prepared according to A5.a) (0.32 mol) was added. The mixture was stirred at 80°C overnight, then poured out on ice, stirred for 30 minutes and extracted with EtOAc.

The organic layer was separated, dried (MgSO₄), filtered and the solvent was evaporated. The residue (136 g) was purified by column chromatography over silica gel (eluent: CH₂Cl₂/cyclohexane 70/30; 20-45 μm). The desired fractions were collected and the solvent was evaporated. Yield: 26 g of **intermediate 21** (84 %).

5

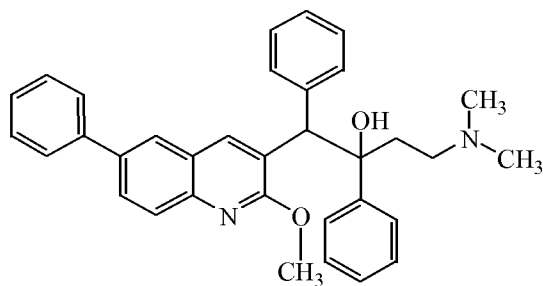
c. Preparation of intermediate 22



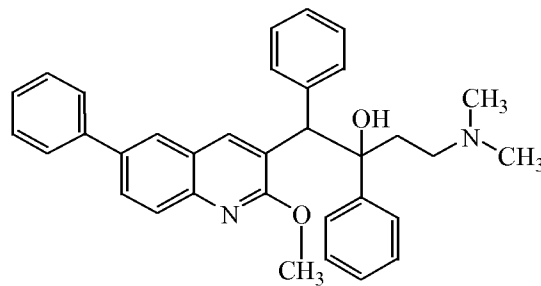
A mixture of **intermediate 21** (prepared according to A5.b) (0.0788 mol) in CH₃ONa 30% in CH₃OH (50 ml) and CH₃OH (200 ml) was stirred at 80°C overnight. The mixture was brought to room temperature, poured out into ice water and extracted with EtOAc. The organic layer was separated, washed with H₂O, dried (MgSO₄), filtered and the solvent was evaporated. The residue (30 g) was purified by column chromatography over silica gel (eluent: CH₂Cl₂/cyclohexane 70/30; 20-45 μm). The pure fractions were collected and the solvent was evaporated. Yield: 17 g of **intermediate 22** (66 %).

10

d1. Preparation of intermediate 23 and 24



dia A
Intermediate 23



dia B
Intermediate 24

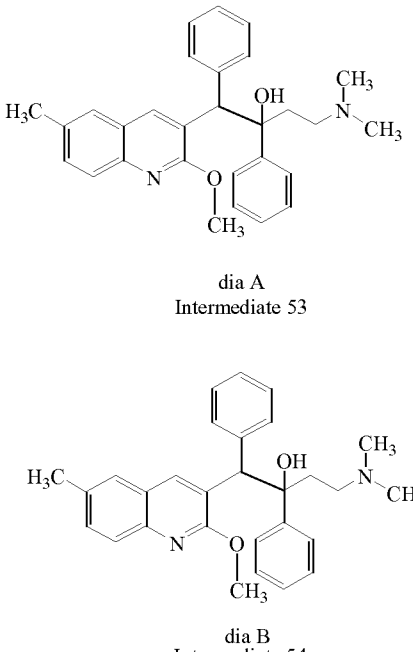
*n*BuLi 1.6 M (0.055 mol) in hexane was added dropwise at -30°C under N₂ flow to a solution of *N*-(1-methylethyl)-2-propanamine (0.055 mol) in THF (150 ml). The mixture was stirred at -20°C for 30 minutes and then cooled to -70°C. A solution of intermediate 22 (prepared according to A5.c) (0.036 mol) in THF (50 ml) was added dropwise. The mixture was stirred at -70°C for 45 minutes. A solution of 3-(dimethylamino)-1-phenyl-1-propanone (0.044 mol) in THF (50 ml) was added

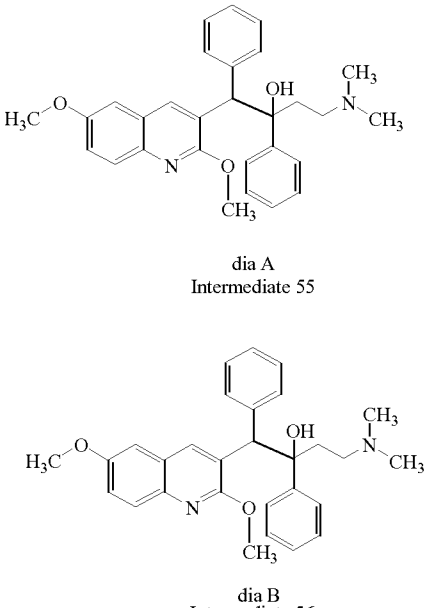
20

dropwise. The mixture was stirred at -70°C for 2 hours, hydrolyzed with ice water and extracted with EtOAc. The organic layer was separated, dried (MgSO_4), filtered and the solvent was evaporated.

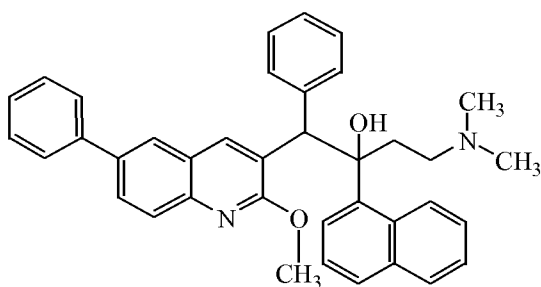
- The residue (19 g) was purified by column chromatography over silica gel (eluent: $\text{CH}_2\text{Cl}_2/\text{CH}_3\text{OH}/\text{NH}_4\text{OH}$ 99.5/0.5/0.1; 15-40 μm). Two pure fractions were collected and their solvents were evaporated. Yield: 1.3 g of Fraction 1 and 1.5 g of Fraction 2. Fraction 1 was crystallized from EtOAc and diethyl ether. The precipitate was filtered off and dried. Yield: 0.85 g of **intermediate 23** (4.7 %) (m.p. 174°C). Fraction 2 was crystallized from diethyl ether and DIPE. The precipitate was filtered off and dried.
- Yield: 1 g of **intermediate 24** (5.5 %) (m.p. 192°C).

Following intermediates were prepared according to the previous procedure and were purified as indicated.

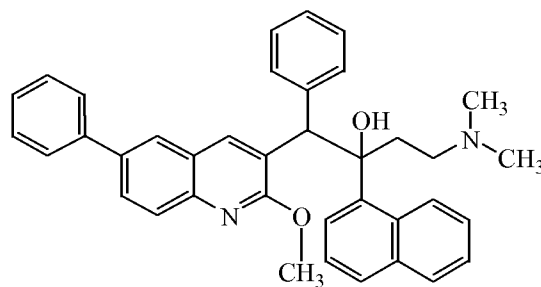
Intermediate 53 and 54	The residue (21 g) was purified by column chromatography over silica gel (eluent: $\text{CH}_2\text{Cl}_2/\text{CH}_3\text{OH}/\text{NH}_4\text{OH}$ 99.5/0.5/0.1; 20-45 μm). Two pure fractions were collected and the solvent was evaporated. Yield: 1.8 g of fraction 1 and 1.5 g of fraction 2. Fraction 1 was crystallized from DIPE. The precipitate was filtered off and dried. Yield: 1.7 g of intermediate 55 (8 %) (m.p. 148°C). Fraction 2 was crystallized from diethyl ether. The precipitate was filtered off and dried. Yield: 1.1 g of intermediate 54 (7 %) (m.p. 165°C).	 dia A Intermediate 53 dia B Intermediate 54
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Intermediate 55 and 56	The residue (23 g) was purified by column chromatography over silica gel (eluent: CH₂Cl₂/CH₃OH/NH₄OH 9.5/0.5/0.1; 20-45 μm). Two pure fractions were collected and their solvents were evaporated. Fraction 1 was crystallized from diethyl ether. The precipitate was filtered off and dried. Yield: 1.8 g of intermediate 55 (8 %) (m.p. 165°C). Fraction 2 was crystallized from diethyl ether and DIPE. The precipitate was filtered off and dried. Yield: 1.6 g of intermediate 56 (7 %) (m.p. 165°C).	 dia A Intermediate 55 dia B Intermediate 56
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d2. Preparation of intermediate 36 and 37



dia A
Intermediate 36



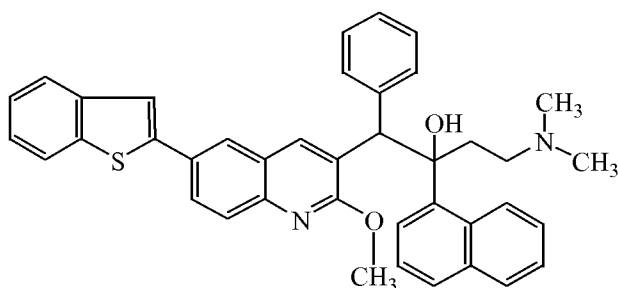
dia B
Intermediate 37

- A mixture of *N*-(1-methylethyl)-2-propanamine hydrochloride (1:1) (0.0102 mol) in THF (10 ml) was stirred at −20°C. *n*BuLi 1.6 M in hexane (0.0102 mol) was added dropwise. The mixture was kept at this temperature for 15 minutes, then cooled to −70°C. A solution of intermediate 22 (prepared according to A5.c) (0.0092 mol) in THF (10 ml) was added dropwise at −70°C. The mixture was stirred at this temperature for 30 minutes. A solution of 3-(dimethylamino)-1-(1-naphthalenyl)-1-propanone (0.0111 mol) in THF (10 ml) was added dropwise. The mixture was stirred at −70°C for 3 hours, then poured out into ice water, NaCl and extracted with EtOAc. The organic layer was separated, dried (MgSO₄), filtered, and the solvent was evaporated. Yield: 6 g. This fraction was purified by column chromatography over silica gel (eluent: CH₂Cl₂/CH₃OH/NH₄OH 99/1/0.1; 15-40 μm). Two fractions were collected and the

solvent was evaporated. Yield: 0.3g of fraction 1 and 0.4 g of fraction 2. Fraction 1 was crystallized from diethyl ether. The precipitate was filtered off and dried. Yield: 0.1 g of **intermediate 36** (2 %) (m.p. 248°C) (dia A). Fraction 2 was crystallized from diethyl ether. The precipitate was filtered off and dried. Yield: 0.28 g of **intermediate**
 5 **37** (6 %) (m.p. 214°C) (dia B).

Example A6

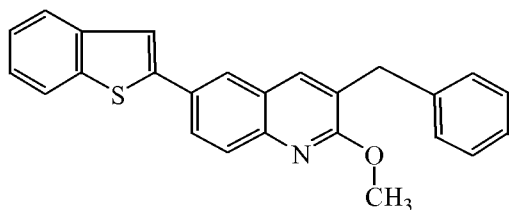
Preparation of intermediate 32



Methylbenzene (2 ml) was added to a mixture of benzo[b]thien-2-ylboronic acid (0.0016 mol), Pd(OAc)₂ (0.002 g), K₃PO₄ (0.0021 mol) and dicyclohexyl(2',6'-
 10 dimethoxy[1,1'-biphenyl]-2-yl)phosphine (0.008 g) under N₂ flow. The mixture was stirred for 5 minutes. A solution of compound 15 of WO2004/011436 (dia B) (0.00108 mol) in methylbenzene (1 ml) was added. The mixture was stirred at 100°C for 4 hours. The residue was purified by column chromatography over kromasil (eluent: CH₂Cl₂/CH₃OH 99/1 then CH₂Cl₂/EtOAc/NH₄OH 95/5/0.5; 10µm). The pure fractions
 15 were collected and the solvent was evaporated. Yield: 0.125 g of **intermediate 32** (dia B) (19 %).

Example A7

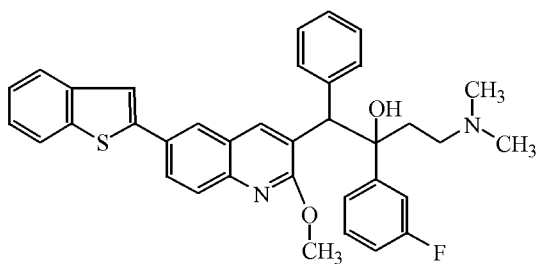
a. Preparation of intermediate 33



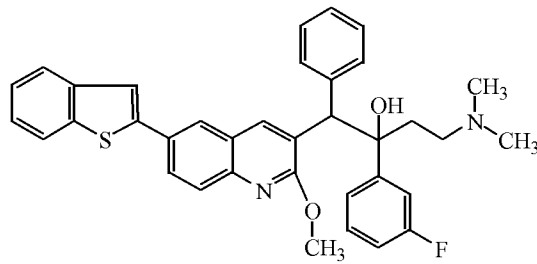
A mixture of **intermediate 9** (prepared according to A3.a) (0.0076 mol),
 20 benzo[b]thien-2-ylboronic acid (0.009 mol), K₂CO₃ (0.02 mol) and Pd(PPh₃)₄ (0.0003

mol) in CH₃CH₂OH (2 ml) and toluene (25 ml) was stirred and refluxed for 16 hours, then cooled to room temperature and extracted with EtOAc. The organic layer was washed with saturated aqueous NaCl, dried (MgSO₄), filtered, and the solvent was evaporated. The residue (4 g) was purified by column chromatography over silica gel (eluent: CH₂Cl₂/cyclohexane 30/70; 15-40μm). The pure fractions were collected and the solvent was evaporated. Yield: 1.45 g of **intermediate 33**.

b. Preparation of intermediate 34 and 35

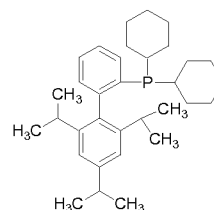
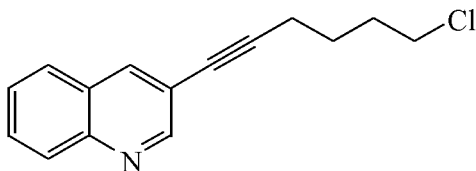


dia A
Intermediate 34

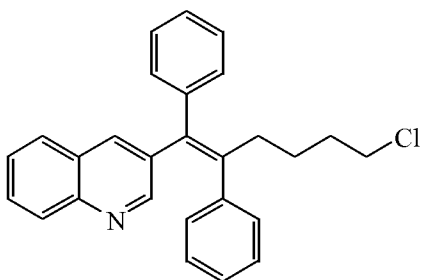


dia B
Intermediate 35

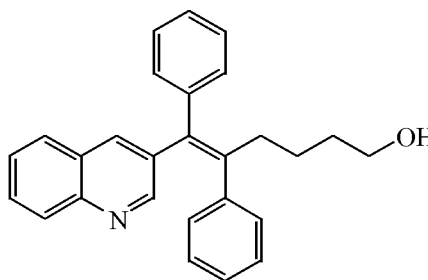
*n*BuLi 1.6 M in hexane (0.0045 mol) was added at -70°C to a mixture of *N*-(1-methylethyl)-2-propanamine hydrochloride (1:1) (0.0044 mol) in THF (10 ml). The mixture was stirred at -20°C for 20 minutes. A solution of **intermediate 33** (prepared according to A7.a) (0.0037 mol) in THF (10 ml) was added at -70°C. The mixture was stirred at -70°C for 2 hours. A solution of 3-(dimethylamino)-1-(3-fluorophenyl)-1-propanone (0.0037 mol) in THF (5 ml) was added at -70°C. The mixture was stirred at -70°C for 3 hours. NH₄Cl 10 % was added. The mixture was extracted with EtOAc. The organic layer was separated, dried (MgSO₄), filtered, and the solvent was evaporated. Yield: 3 g. This fraction was purified by column chromatography over silica gel (eluent: CH₂Cl₂/CH₃OH/NH₄OH 99/1/0.1; 15-40μm). Two fractions were collected and the solvent was evaporated. Yield: 0.35 g of fraction 1 and 0.38 g of fraction 2. Fraction 1 was crystallized from DIPE. The precipitate was filtered off and dried. Yield: 0.249 g of **intermediate 34** (melting point: 225°C). Fraction 2 was crystallized from DIPE. The precipitate was filtered off and dried. Yield: 0.303 g of **intermediate 35** (melting point: 216°C).

Example A8a. Preparation of intermediate 68

A suspension of $\text{PdCl}_2(\text{PhCN})_2$ (0.25 g, 0.00065 mol), Cs_2CO_3 (0.13 mol) in DMF (65 ml) was flushed with N_2 . 3-Bromoquinoline (13.5 g, 0.065 mol) was added and the mixture was stirred for 10 minutes at room temperature. 6-chloro-1-hexyne (9.1 g, 0.078 mol) was then added dropwise and the mixture was stirred for 6 hours at 80 °C. More 6-chloro-1-hexyne (0.039 mol) was added and the reaction mixture was stirred for one more hour at 80 °C, then for 18 hours at room temperature. The mixture was cooled down to room temperature and diluted with water (100 ml), then extracted with CH_2Cl_2 (3 x 200 ml). The organic layer was separated, washed with brine, then separated again. The combined organic layers were dried (MgSO_4), filtered and the solvent was evaporated. The residue was purified by reversed-phase high-performance liquid chromatography (Column: Xterra Prep MS C18, Length: 10 cm, I.D.: 19 mm, particle size: 5 μm ; eluent: (0.2 % NH_4HCO_3 in H_2O)/ CH_3OH (optional)/ CH_3CN gradient). The product fractions were combined and the solvent was evaporated to afford **intermediate 68** (9 g, 57 %).

b. Preparation of intermediate 69 and 70

Intermediate 69

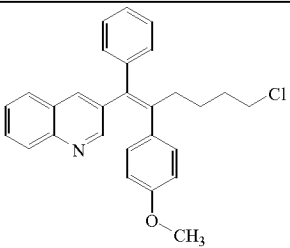
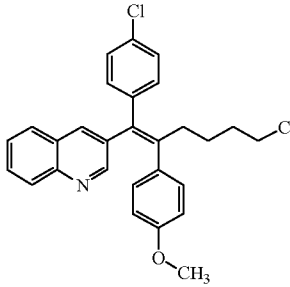
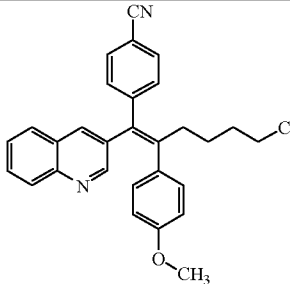


Intermediate 70

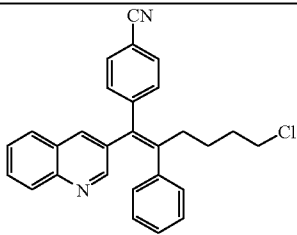
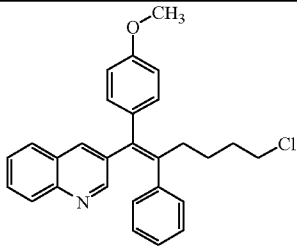
A mixture of **intermediate 68** (prepared according to A8.a) (0.00205 mol), (4-chlorophenyl)-boronic acid (0.0062 mol, 3 equiv), jodiumbenzene (0.0041 mol, 2

- equiv), KHCO_3 (0.0041 mol) in 1-methyl-2- pyrrolidinone (16 ml) and water (4 ml) was stirred for 10 minutes at 100 °C. A suspension of $\text{PdCl}_2(\text{PhCN})_2$ (0.000021 mol) in 1-methyl-2- pyrrolidinone (0.16 ml) was added, and the mixture was stirred 18 hours at 100 °C. The solvent was then evaporated. The residue was partitioned between
- 5 water (1.5 ml) and CH_2Cl_2 (9 ml). This mixture was stirred vigorously, and then filtered through an Isolute HM-N filter. The filter residue was washed twice with CH_2Cl_2 (4.5 ml) and once with CH_2Cl_2 (3 ml). The solvent was evaporated and the residue was purified by reversed-phase HPLC. Yield : **Intermediate 69** (53 mg) and **intermediate 70** (106 mg). Following intermediates summoned in Table 1 (E/Z
- 10 configuration not determined) were prepared according to the previous procedure:

Table 1

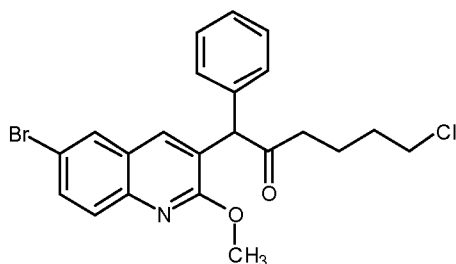
Intermediate No.	Structure
57	
58	
59	

Intermediate No.	Structure
60	 <chem>COc1ccc(cc1)C(=C2C=CC=CC=C2N3C=CC=CC=C3)C(=C4C=CC(=CC=C4)Cl)C(=C5C=CC(=CC=C5)Cl)OCC</chem>
61	 <chem>N#Cc1ccc(cc1)C(=C2C=CC=CC=C2N3C=CC=CC=C3)C(=C4C=CC(=CC=C4)Cl)C(=C5C=CC(=CC=C5)Cl)OCC</chem>
62	 <chem>COc1ccc(cc1)C(=C2C=CC=CC=C2N3C=CC=CC=C3)C(=C4C=CC(=CC=C4)Cl)C(=C5C=CC(=CC=C5)Cl)OCC</chem>
63	 <chem>Clc1ccc(cc1)C(=C2C=CC=CC=C2N3C=CC=CC=C3)C(=C4C=CC(=CC=C4)Cl)C(=C5C=CC(=CC=C5)Cl)OCC</chem>
64	 <chem>c1ccccc1C(=C2C=CC=CC=C2N3C=CC=CC=C3)C(=C4C=CC(=CC=C4)Cl)C(=C5C=CC(=CC=C5)Cl)OCC</chem>
65	 <chem>c1ccccc1C(=C2C=CC=CC=C2N3C=CC=CC=C3)C(=C4C=CC(=CC=C4)Cl)C(=C5C=CC(=CC=C5)Cl)OCC</chem>

Intermediate No.	Structure
66	
67	

Example A9

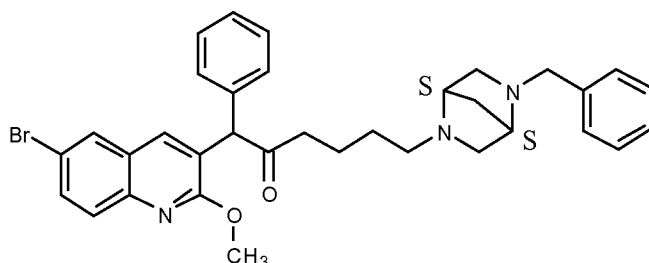
a. Preparation of intermediate 71



- $n\text{BuLi}$ 1.6M in hexane (0.0346 mol) was added dropwise at -20°C to a solution of N -(1-methylethyl)-2-propanamine (0.0346 mol) in THF (70 ml) under N_2 flow. The mixture was stirred at -20°C for 20 minutes, then cooled to -70°C . A solution of 6-bromo-2-methoxy-3-(phenylmethyl)-quinoline (intermediate compound 3 (Ex. A3) of WO2004/011436) (0.029 mol) in THF (90 ml) was added. The mixture was stirred at -70°C for 1 hour. A solution of 1-(5-chloro-1-oxopentyl)-1H-benzotriazole (0.0576 mol) in THF (100 ml) was added. The mixture was stirred at -70°C for 3 hours. H_2O was added. The mixture was extracted with EtOAc. The organic layer was washed with H_2O , then with saturated aqueous NaCl solution, dried (MgSO_4), filtered and the solvent was evaporated. The residue (19 g) was purified by column chromatography over silica gel (eluent: Cyclohexane/AcOEt 93/7; 20-45 μm). The fraction was collected and the solvent was evaporated. Yield: 3.85 g of crude residue (30%). After

crystallization from DIPE, the precipitate was filtered off and dried. Yield: 2.65 g of **intermediate 71** (21%).

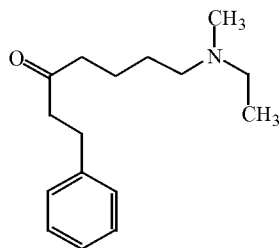
b. Preparation of intermediate 72



A mixture of **intermediate 71** (0.00224 mol), (1S,4S)-2-benzyl-2,5-diazabicyclo[2.2.1]heptane dihydrobromide (0.0045 mol) and potassium carbonate (0.009 mol) in acetonitrile (20 ml) was stirred under reflux for 24 hours and was then cooled to room temperature. H₂O was added. The mixture was extracted with EtOAc. The organic layer was washed with H₂O, then with saturated aqueous NaCl solution, dried (MgSO₄), filtered and the solvent was evaporated. The residue (1.55 g) was purified by column chromatography over silica gel (eluent: CH₂Cl₂/CH₃OH/NH₄OH 95/5/0.1; 15-40 μm). The fraction was collected and the solvent was evaporated. Yield: 1.1 g of **intermediate 72** (82%).

Example A10

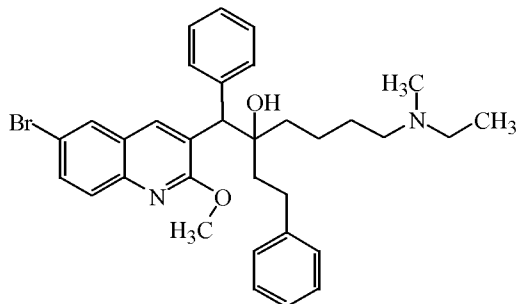
a. Preparation of intermediate 74



A mixture of 7-chloro-1-phenyl-3-heptanone (prepared according to the procedures of WO2007/000435) (3 g, 13.3 mmol), *N*-ethylmethylamine (2.8 ml, 26.6 mmol) and K₂CO₃ (4.1 g, 29.3 mmol) in acetonitrile (30 ml) was stirred and refluxed overnight. The reaction mixture was cooled down to room temperature, poured out into water and extracted with EtOAc. The organic layer was separated, washed with water and brine, dried over MgSO₄ and evaporated till dryness. The residue was purified by column

chromatography (SiO₂ 15-40µm, eluent : DCM/MeOH/NH₄OH.aqueous : 97/3/0.1 to 95/5/0.5). The pure fractions were collected and the solvent was evaporated till dryness. Yield : 1.7 g of **intermediate 74**, 60%.

b. Preparation of intermediate 73

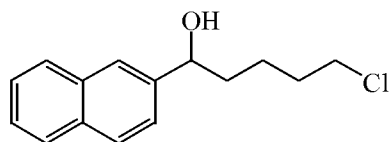


Intermediate 73 (mixture of diastereoisomers)

- 5 *n*-BuLi (1.6 M in hexanes, 7.4 ml, 11.8 mmol) was added drop wise to a solution of diisopropylamine (1.6 ml, 11.8 mmol) in THF (8 ml) at -20°C under nitrogen. The reaction mixture was stirred for 30 minutes and was then cooled down to -78 °C. A solution of 6-bromo-2-methoxy-3-(phenylmethyl)-quinoline (intermediate compound 3 (Ex. A3) of WO2004/011436) (1.9 g, 5.9 mmol) in THF (10 ml) was added dropwise and was then stirred for 1 hour at -78 °C. A solution of **intermediate 74** (1.9 g, 7.68
- 10 mmol) in THF (10 ml) was added dropwise then stirred for 1 hour at -78 °C. Water and EtOAc were added, the organic layer was separated, washed with water and brine, dried over MgSO₄ and evaporated till dryness. The residue was purified by column chromatography (SiO₂ 15-40 µm, eluent: DCM/MeOH/NH₄OH aq: 97/3/0.5). The pure fractions were collected and the solvent was evaporated till dryness. The second
- 15 fraction from the column yielded **intermediate 73** (0.22 g, 7 %) as a mixture of diastereoisomers.

Example A11

a. Preparation of intermediate 75

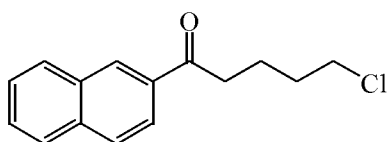


20

A solution of 1-bromo-4-chlorobutane (22.25 ml, 0.19 mol) in diethyl ether (100 ml) was added dropwise (under N₂ atmosphere) to a suspension of activated Mg turnings (4.67 g, 0.19 mol) in diethyl ether (100 ml). Some crystals of iodine were also added.

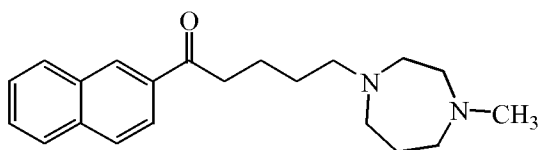
The temperature in the flask increased, and the orange colour turned to white. Once the addition of 1-bromo-4-chlorobutane was completed, the reaction was cooled in an ice-bath and 2-naphthalenecarboxaldehyde (20.00 g, 0.13 mol) was added dropwise as a solution in THF (200 ml, dry). The reaction mixture was stirred in the ice-bath for 4 hours. Then the mixture was quenched with NH_4Cl 1 N. Both phases were separated. The organic layer was washed with brine, dried (MgSO_4), filtered and the solvent was evaporated. The residue was purified by flash chromatography (eluent: *n*-hexane/EtOAc 20:1). The desired fractions were collected and the solvent was evaporated, yielding **intermediate 75**.

b. Preparation of intermediate 76

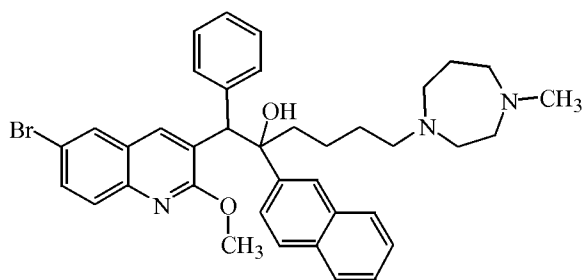


Intermediate 75 (9.97 g, 0.04 mol) was dissolved in CH_2Cl_2 (120 ml) and the flask was cooled in an ice-bath. MnO_2 (34.85 g, 0.40 mol) was added and the reaction mixture was stirred in the ice-bath for 1 hour and then overnight at room temperature. The next morning, an additional amount of MnO_2 (10 equivalent) was added, and in the afternoon again an additional amount of MnO_2 (10 equivalent) was added. The mixture was stirred overnight at room temperature. Then MnO_2 was removed by filtration over Celite. The product was purified by flash chromatography (eluent: *n*-hexane/EtOAc 40:1). Yield: 6.91 g of **intermediate 76** (70 %).

c. Preparation of intermediate 77

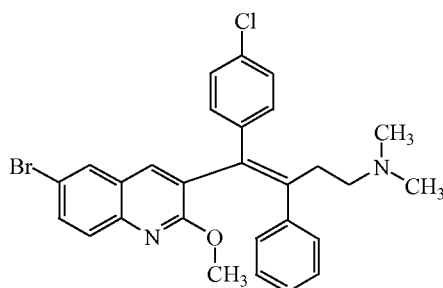


A mixture of **intermediate 76** (1.00 g, 0.00405 mol), 1-methylhomopiperazine (1.01 ml, 0.0081 mol) and K_2CO_3 (1.68 g, 0.0081 mol) in CH_3CN (12.16 ml) was refluxed at 80 °C over the weekend. Inorganic salts were removed by filtration and the crudes were purified by flash chromatography (eluent: *n*-hexane/EtOAc). The desired fractions were collected and the solvent was evaporated. Yield: 0.26 g of **intermediate 77** (20 %).

d. Preparation of intermediate 78

Intermediate 78 (mixture of diastereoisomers)

- Lithium diisopropylamine (1.44 ml of a 2 M solution in THF/heptanes; 0.00288 mol) was dissolved in THF (9.61 ml; dry) and this solution was cooled to -70 °C. 6-bromo-2-methoxy-3-(phenylmethyl)-quinoline (intermediate compound 3 (Ex. A3) of WO2004/011436) (0.79 g, 0.0024 mol) was added dropwise as a solution in THF (7.21 ml; dry) and the mixture was stirred for 2 hours at -70 °C. Then **intermediate 77** (0.78 g, 0.0024 mol) was added dropwise as a solution in THF (7.21 ml; dry) and the reaction mixture was stirred for 3 hours at -70 °C. Then H₂O (q.s.) was added (quenching at -70 °C), followed by EtOAc. The layers were separated and the organic layer was washed with brine, dried (MgSO₄), filtered and the solvent was evaporated. The residue was purified by flash chromatography. The desired fractions were collected and the solvent was evaporated. Yield: 0.429 g of **intermediate 78** as a mixture of diastereoisomers.

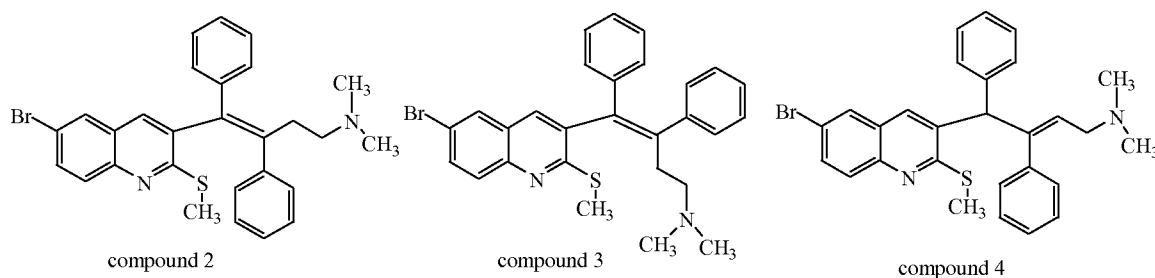
B. Preparation of the final compoundsExample B1Preparation of compound 1

A mixture of **intermediate 4 (prepared according to A1.d)** (0.0003 mol) and PPA (1.6 g) was stirred at 100°C overnight. H₂O and K₂CO₃ were added. The mixture was extracted with CH₂Cl₂. The organic layer was separated, dried (MgSO₄), filtered, and the solvent was evaporated. The residue was purified by column chromatography over kromasil (eluent: CH₂Cl₂/CH₃OH/NH₄OH 99/1/0.1 to 94/6/0.6; 3.5µm). The pure fractions were collected and the solvent was evaporated. Yield: 0.13 g (84 %). This fraction was purified by column chromatography over C18 (eluent: CH₃OH/NH₄HCO₃ 0.5 % 85/15; 5 µm). The pure fractions were collected and the solvent was evaporated. Yield: 0.13 g of **compound 1**.

10

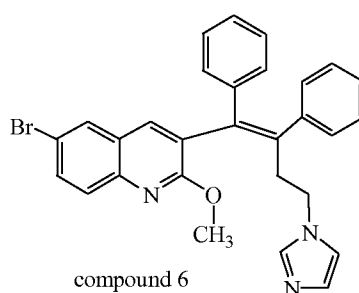
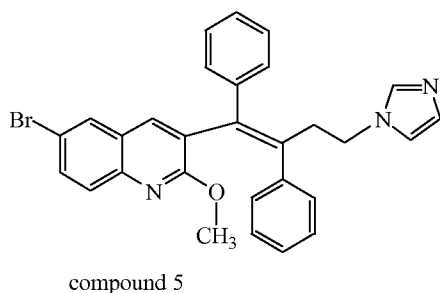
Example B2

Preparation of compound 2, 3 and 4



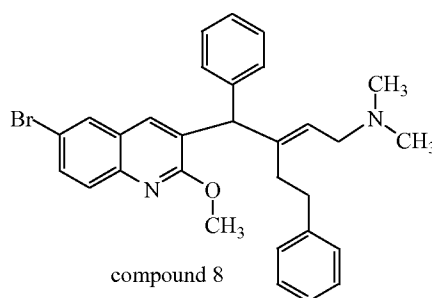
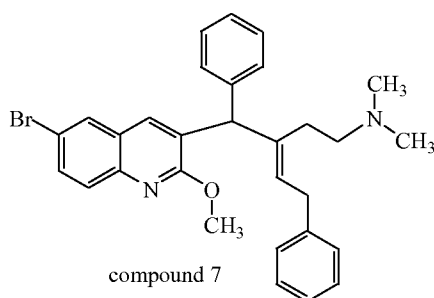
A mixture of **intermediate 7 (prepared according to A2.c)** (0.0002 mol) and PPA (1.3 g) was stirred at 100°C for 18 hours, then cooled down to room temperature, poured out into H₂O, basified with K₂CO₃ and extracted with EtOAc. The organic layer was washed with saturated aqueous NaCl, dried (MgSO₄), filtered, and the solvent was evaporated. The residue was purified by column chromatography over kromasil (eluent: CH₂Cl₂/CH₃OH/NH₄OH 99/1/0.1 to 94/6/0.6; 5µm). Two fractions were collected and the solvent was evaporated. Yield: 0.021 g of fraction 1 and 0.046 g of fraction 2. Each fraction was purified by column chromatography over C18 (eluent: CH₃OH/NH₄HCO₃ 0.5% 85/15 to 80/20; 5µm). Fraction 1 gave rise to 0.003 g of **compound 3** and 0.008 g of **compound 4**, and fraction 2 yielded 0.027 g of **compound 2**.

20

Example B3Preparation of compound 5 and 6

- A mixture of **intermediate 11** (prepared according to A3.b1) (0.0002 mol) and PPA (1.5 g) was stirred at 100°C overnight, then cooled down to room temperature, poured out into H₂O, basified with K₂CO₃ and extracted with EtOAc. The organic layer was washed with H₂O and saturated aqueous NaCl, dried (MgSO₄), filtered, and the solvent was evaporated. The residue (0.17 g) was purified by column chromatography over kromasil (eluent: CH₂Cl₂/CH₃OH/NH₄OH 99/1/0.1 to 94/6/0.6; 5µm). Two fractions were collected and the solvent was evaporated. Yield: 0.011 g of **compound 5** (8 %) and 0.075 g of **compound 6** (52 %).

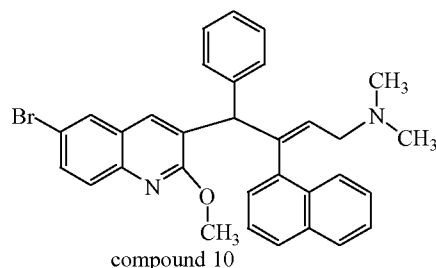
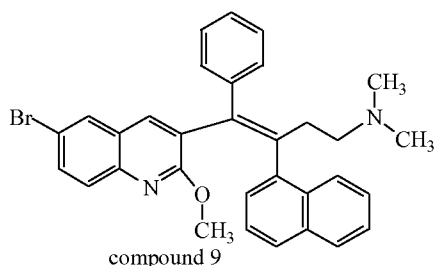
10

Example B4a. Preparation of compound 7 and 8

- A mixture of intermediate 19 (0.00037 mol) and PPA (2 g) was stirred at 100°C overnight, then brought to room temperature, poured out into H₂O, basified with K₂CO₃ 10% and extracted with EtOAc. The organic layer was separated, dried (MgSO₄), filtered and the solvent was evaporated. The residue (0.397 g) was purified by column chromatography over kromasil (eluent: CH₂Cl₂/CH₃OH/NH₄OH 97/3/0.1; 10µm). Two fractions were collected and the solvent was evaporated. Yield: 0.1 g of compound 7 and 0.006 g of compound 8.

15

b. Preparation of compound 9 and 10

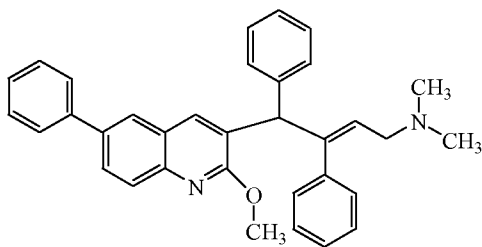


A mixture of intermediate 48 (prepared according to A3.b4) (0.009 mol) and PPA (50 g) was stirred at 100°C for 2 hours, poured out on ice, alkalinized with K_2CO_3 and extracted with CH_2Cl_2 . The organic layer was separated, dried ($MgSO_4$), filtered, and the solvent was evaporated. The residue (5 g) was purified by column chromatography over silica gel (eluent: $CH_2Cl_2/CH_3OH/NH_4OH$ 97/3/0.1; 15-40 μm). Two fractions were collected and the solvent was evaporated. Yield: 2 g of fraction A and 0.9 g of fraction B. Fraction B was taken up in DIPE. The precipitate was filtered off, washed with activated carbon in 2-propanone and dried. Yield: 0.27 g of **compound 9**.

Fraction A was purified by column chromatography over silica gel (eluent: $CH_2Cl_2/iPrOH/NH_4OH$ 97/3/0.2; 15-35 μm). The desired fractions were collected, the solvent was evaporated and the residue was dried. Yield: 0.3 g of **compound 10**.

Example B5

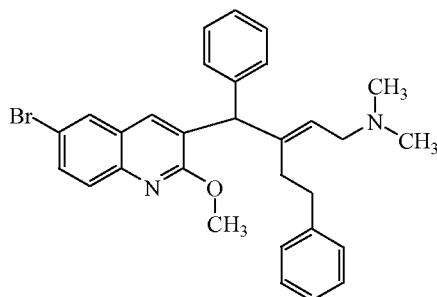
a. Preparation of compound 11



$SOCl_2$ (0.0002 mol) was added dropwise at 5°C to a solution of intermediate 24 (prepared according to A5.d1) (0.0002 mol) in pyridine (1 ml). The mixture was stirred at 5°C for 2 hours, then stirred at room temperature overnight, diluted in H_2O and extracted with EtOAc. The organic layer was washed with saturated aqueous NaCl, dried ($MgSO_4$), filtered and the solvent was evaporated. The residue was purified by column chromatography over kromasil (eluent: $CH_2Cl_2/CH_3OH/NH_4OH$ 99/1/0.1 to

94/6/0.6; 5 μ m). The pure fractions were collected and the solvent was evaporated. Yield: 0.086 g of **compound 11** (68 %).

b. Preparation of compound 8

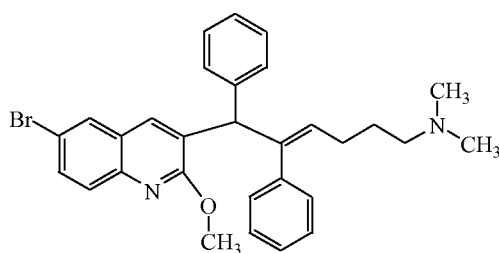


SOCl₂ (0.0064 mol) was added at 0°C to a solution of intermediate 19 (prepared according to A3.b4) (0.0058 mol) in pyridine (4.4 ml). The mixture was stirred at 0°C for 1 hour, poured out into H₂O and extracted with EtOAc. The organic layer was washed with saturated NaCl, dried (MgSO₄), filtered and the solvent was evaporated. The residue (2 g) was purified by column chromatography over silica gel (eluent: CH₂Cl₂/CH₃OH/NH₄OH 97/3/0.1; 15-40 μ m). Yield: 1.7g (57 %). Crystallization from CH₃CN gave rise to 1.2 g of **compound 8** (40 %) (melting point: 128°C).

10

Example B6

Preparation of compound 12

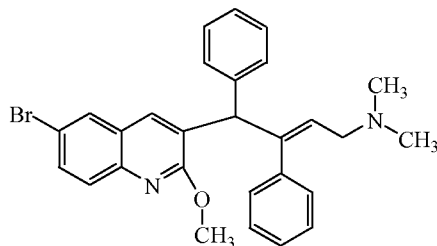


SOCl₂ (0.0011 mol) was added dropwise at 0°C to a solution of **intermediate 46** (prepared according to A3.b3) (0.001 mol) in pyridine (6 ml). The mixture was stirred at 0°C for 2 hours, then stirred at room temperature for 24 hours, poured out into K₂CO₃ 10 % (aqueous) and extracted with EtOAc. The organic layer was washed with H₂O, then with saturated aqueous NaCl, dried (MgSO₄), filtered and the solvent was evaporated. The residue (1g) was purified by column chromatography over silica gel (eluent: CH₂Cl₂/CH₃OH/NH₄OH 95/5/0.5; 15-40 μ m). The pure fractions were collected and the solvent was evaporated. The residue (0.15 g) was crystallized from

diethyl ether. The precipitate was filtered off and dried. Yield: 0.052 g of **compound 12** (10 %) (melting point: 145°C).

Example B7

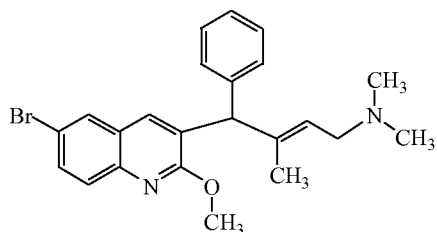
Preparation of compound 13



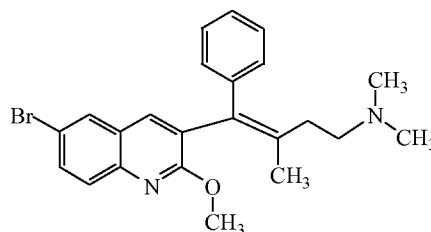
- 5 SOCl_2 (0.0108 mol) was added dropwise to a solution of **intermediate 27** (prepared according to A3.b5) (0.0098 mol) in pyridine (50 ml). The mixture was poured out on ice and extracted with EtOAc. The organic layer was separated, washed with a solution of K_2CO_3 10 %, dried over MgSO_4 , filtered and the solvent was evaporated. The residue (4.5 g) was purified by column chromatography over silica gel (eluent:
- 10 $\text{CH}_2\text{Cl}_2/\text{CH}_3\text{OH}/\text{NH}_4\text{OH}$ 99/1/0.1). The pure fractions were collected and the solvent was evaporated. Yield: 3.6 g (73.4 %). Part of this fraction (2 g) was crystallized from DIPE. The precipitate was filtered off and dried. Yield: 1.6 g of **compound 13**.

Example B8

Preparation of compound 14 and 15



compound 14



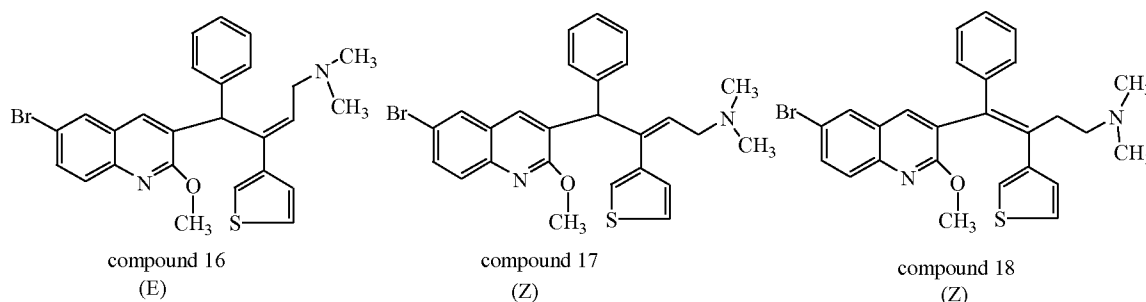
compound 15

- 15 SOCl_2 (0.0004 mol) was added dropwise at 5°C to a solution of **intermediate 28** (prepared according to A3.b6) (0.0003 mol) in pyridine (1.8 ml). The mixture was stirred at 5°C for 2 hours, then stirred at room temperature overnight, diluted in H_2O and extracted with EtOAc. The organic layer was washed with saturated aqueous

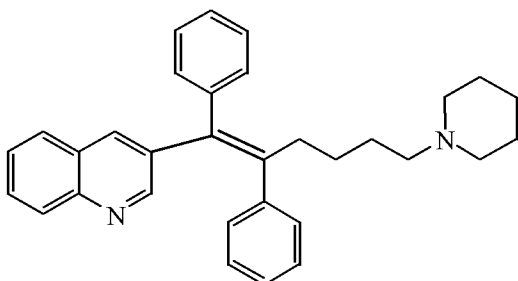
- NaCl, dried (MgSO_4), filtered and the solvent was evaporated. The residue was purified by column chromatography over kromasil (eluent: $\text{CH}_2\text{Cl}_2/\text{CH}_3\text{OH}/\text{NH}_4\text{OH}$ 99/1/0.1 to 94/6/0.6; $5\mu\text{m}$). The pure fractions were collected and the solvent was evaporated. The residue was purified by column chromatography over C18 (eluent: $\text{CH}_3\text{OH}/\text{NH}_4\text{HCO}_3$ 0.5 % 85/15; $5\mu\text{m}$). The pure fractions were collected and the solvent was evaporated. Yield: 0.021 g of **compound 15** (11 %) and 0.036 g of **compound 14** (19 %).

Example B9

Preparation of compound 16, 17 and 18



- 10 SOCl_2 (0.0003 mol) was added slowly at 5°C to a solution of **intermediate 43** (prepared according to A3.b1) (0.0002 mol) in pyridine (1.3 ml). The mixture was stirred at 5°C for 2 hours, then stirred at room temperature overnight. The residue was purified by column chromatography over kromasil (eluent: $\text{CH}_2\text{Cl}_2/\text{CH}_3\text{OH}/\text{NH}_4\text{OH}$ 97/3/0.1; $10\mu\text{m}$). Three fractions were collected and the solvent was evaporated.
- 15 Yield: 0.073 g of fraction A, 0.012 g of fraction B and 0.012 g of **compound 16** (8 %). Fraction A and fraction B were purified by column chromatography over C18 (eluent: $\text{CH}_3\text{OH}/\text{NH}_4\text{HCO}_3$ 0.5% 85/15; $5\mu\text{m}$). Two fractions were collected and the solvent was evaporated. Yield: 0.048 g of **compound 17** (33 %) and 0.01 g of **compound 18** (7 %).

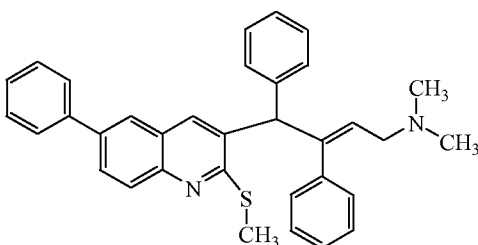
Example B10Preparation of compound 49

- Piperidine (3 equiv) was added to a suspension of **intermediate 69** (prepared according to A8.b) (0.0001 mol) and Na_2CO_3 (2 equiv) in CH_3OH (3 ml). The reaction mixture was refluxed for 18 hours. The mixture was then cooled down. The solvent was
- 5 evaporated. CH_2Cl_2 (9 ml) and H_2O (1 ml) were added. The biphasic mixture was stirred vigorously for 10 minutes, then filtered through an Isolute HM-N filter. The filter residue was washed with CH_2Cl_2 (3 x 3ml) and the filtrate was evaporated. The residue was dissolved in CH_2Cl_2 (2 ml), then purified using a Sep-Pak Vac 6cc Silica Cartridge (1 g; Waters catalog # WAT036910; the column was pre-wetted with CH_2Cl_2
- 10 (5 ml); a solution of the sample in 2 ml of CH_2Cl_2 was loaded; eluent: $\text{CH}_2\text{Cl}_2/\text{CH}_3\text{OH}$ 100/0 (7.5 ml), 99/1 (15 ml), 95/5 (10 ml); 0/100 (10 ml)). The product fractions were collected and the solvent was evaporated. Yield: 0.033 g of **compound 49**.

Compound 19 was prepared according to an analogous procedure.

15 Example B11

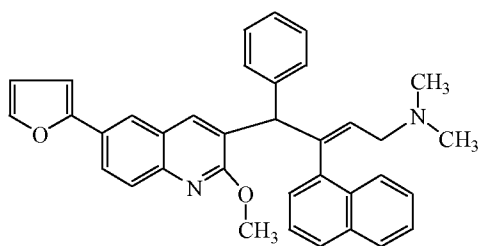
a. Preparation of compound 20



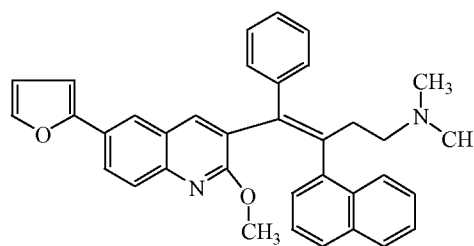
A mixture of **compound 4** (prepared according to B2) (0.154 mol), phenylboronic acid (0.232 mol), $\text{Pd}(\text{OAc})_2$ (0.0003 g), K_3PO_4 (0.308 mol) and 2-dicyclohexylphosphino-2',6'-dimethoxy-1,1'-biphenyl (0.0013 g) in methylbenzene (1 ml) was stirred at 100°C for 4 hours under N_2 flow, then diluted in H_2O and extracted with CH_2Cl_2 . The organic

- layer was separated, dried (MgSO_4), filtered and the solvent was evaporated. The residue was purified by column chromatography over silica gel (eluent: $\text{CH}_2\text{Cl}_2/\text{CH}_3\text{OH}/\text{NH}_4\text{OH}$ 94/6/0.6; $5\mu\text{m}$). The pure fractions were collected and the solvent was evaporated. Yield: 0.019 g (24 %). This fraction was purified by column chromatography over C18 (eluent: $\text{CH}_3\text{OH}/\text{NH}_4\text{HCO}_3$ 90/10; $5\mu\text{m}$). The pure fractions were collected and the solvent was evaporated. Yield: 0.009 g of **compound 20**.

b. Preparation of compound 21 and 22

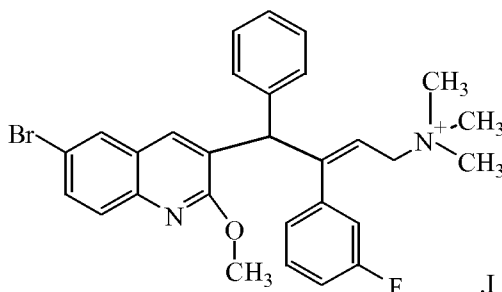


compound 21



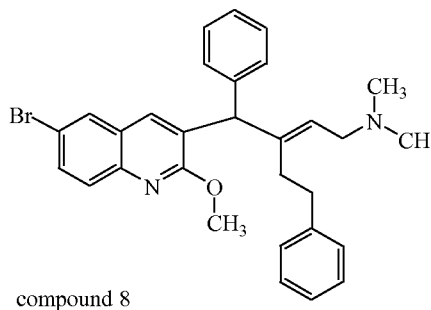
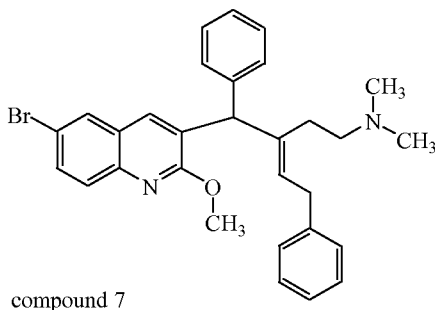
compound 22

- A mixture of **compound 10** (prepared according to B4.b) (0.0005 mol), 2-furanylboronic acid (0.0011 mol) and $\text{Pd}(\text{PPh}_3)_4$ (0.0022 mol) in Na_2CO_3 2M (16 ml) was stirred at 80°C overnight, then diluted in H_2O and extracted with EtOAc. The organic layer was washed with H_2O , dried (MgSO_4), filtered and the solvent was evaporated. The residue (0.38 g) was purified twice by column chromatography over kromasil (eluent: $\text{CH}_2\text{Cl}_2/\text{CH}_3\text{OH}/\text{NH}_4\text{OH}$ 97/3/0.1; $10\mu\text{m}$ then $\text{CH}_3\text{CN}/\text{NH}_4\text{HCO}_3$ 0.5% 93/7; $5\mu\text{m}$). Two fractions were collected and the solvent was evaporated. Yield: 0.013 g of **compound 22** (4 %) and 0.109 g of fraction 1. Fraction 1 was purified by column chromatography over silica gel (eluent: $\text{CH}_3\text{OH}/\text{NH}_4\text{HCO}_3$ 80/20; $5\mu\text{m}$). Three fractions were collected and the solvent was evaporated. Yield: 0.041 g of **compound 21** (first fraction) (the two other fractions were mixtures of compound 21 and 22).

Example B12Preparation of compound 23

A mixture of **compound 25** (prepared according to B5) (0.0002 mol) and CH_3I (0.0003 mol) in $\text{CH}_3\text{-C(=O)-CH}_3$ (3 ml) was stirred at room temperature for 14 hours, then evaporated. Yield: 0.107 g of **compound 23** (83 %).

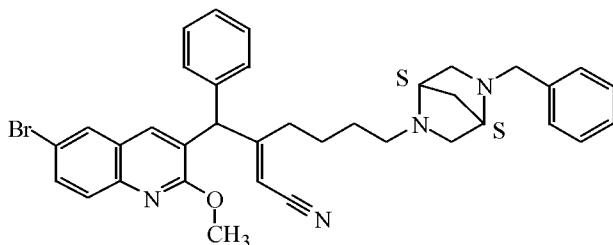
5

Example B13Preparation of compound 7 and 8

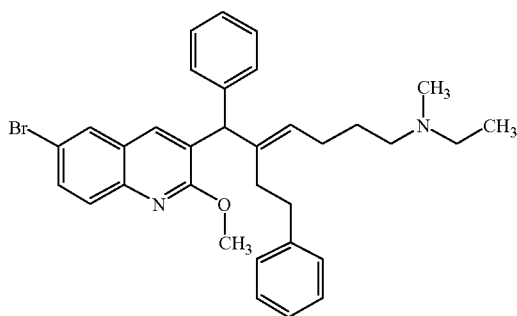
SOCl_2 (0.14 ml) was added at 0°C to a solution of **intermediate 19** (prepared according to A3.b4) (0.0016 mol) in pyridine (1.33 ml). The mixture was stirred at 0°C for 1 hour, then stirred at room temperature for 30 minutes, poured out into H_2O and extracted with EtOAc. The organic layer was washed with saturated NaCl, dried (MgSO_4), filtered and the solvent was evaporated. The residue was purified by column chromatography over kromasil (eluent: $\text{CH}_2\text{Cl}_2/\text{CH}_3\text{OH}/\text{NH}_4\text{OH}$ 97/3/0.1; $10\mu\text{m}$). Three fractions were collected and the solvent was evaporated. Yield: 0.6 g of fraction A (69 %), 0.015 g of fraction B and 0.12 g of **compound 7** (14 %). Fraction A was crystallized from DIPE/ CH_3CN . The precipitate was filtered off and dried. Yield: 0.31 g of **compound 8** (36 %) (melting point: 128°C).

15

See also B4a and B5.b

Example B14Preparation of compound 60

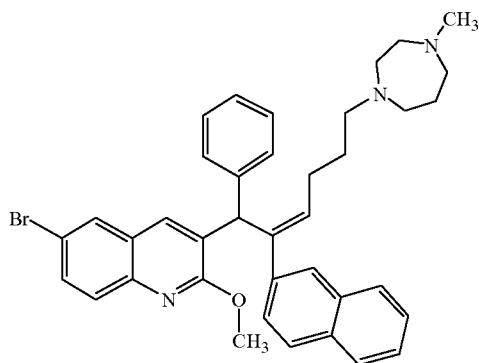
- A solution of diethyl cyanomethylacetate (0.0005mol) in THF (4ml) was stirred and cooled at 0°C. Sodium hydride (60% in mineral oil) (0.0005mol) was added
- 5 portionwise then stirred 30 minutes at 0°C. **Intermediate 72** (prepared according to A9.b) in THF (2ml) was added at 0°C then the mixture was stirred for 18 hours at room temperature. H₂O was added. The mixture was extracted with EtOAc. The organic layer was washed with H₂O, then with saturated aqueous NaCl solution, dried (MgSO₄), filtered and the solvent was evaporated. The residue (0.22g) was purified by
- 10 column chromatography over kromasil (eluent: CH₂Cl₂/CH₃OH/NH₄OH 98/2/0.2 then CH₂Cl₂/CH₃OH/NH₄OH 90/10/1; 3-5 μm). The fraction was collected and the solvent was evaporated. Yield: 0.06 g of **compound 60** (30%).

Example B15a. Preparation of compound 61

- 15 Thionylchloride (0.0004 mol) was added dropwise at 0°C to a solution of **intermediate 73** (0.0003 mol) in pyridine (0.4ml). The mixture was stirred at 0°C for 1 hour. H₂O was added. The mixture was extracted with EtOAc. The organic layer was washed with H₂O, then with saturated aqueous NaCl solution, dried (MgSO₄), filtered and the solvent was evaporated. The residue was purified by column chromatography over

kromasil (eluent: CH₂Cl₂ then CH₂Cl₂/CH₃OH/NH₄OH 92 /8/0.8; 3-5 μm). The fraction was collected and the solvent was evaporated. Yield: 0.02 g of **compound 61** (E-isomer) (13%).

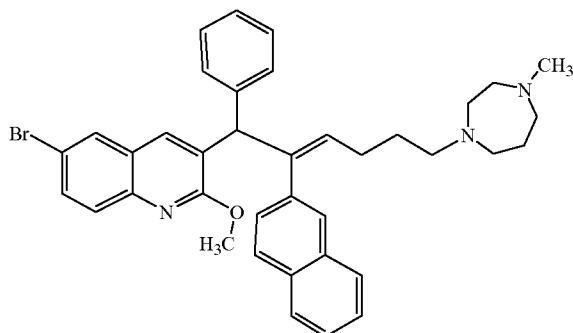
b. Preparation of compound 62



Compound 62 (fumarate salt)

- 5 **Compound 62** was prepared according to Example B15.a, but starting from **intermediate 78**. The residue was purified by column chromatography over kromasil (eluent: CH₂Cl₂ then CH₂Cl₂/CH₃OH/NH₄OH 94 /6/0.5; 10 μm). Two fractions were collected and the solvent was evaporated F1 (0.07 g) and F2 (0.084 g). F1 was purified again by column chromatography over kromasil (eluent: CH₂Cl₂ then
- 10 CH₂Cl₂/CH₃OH/NH₄OH 94 /6/0.6; 250x30mm). F1.1 (0.037g) was taken up with ethanol/acetone (5/95) and 1eq. of fumaric acid in acetone was added at room temperature. The precipitate was filtered off and dried. Yield: 0.019 g of **compound 62** (3%; E-isomer; fumaric acid salt), mp°C: 204.

c. Preparation of compound 63



Compound 63 (fumarate salt)

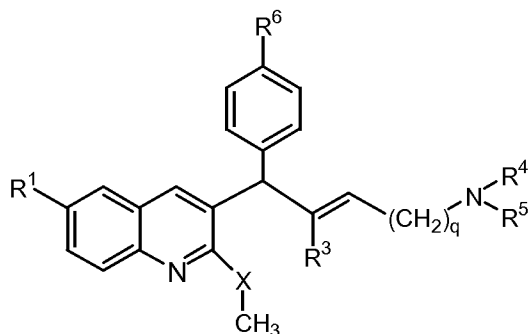
Diethylaminosulfur trifluoride (0.0015 mol) was added dropwise at 0°C to a solution of **intermediate 78** (0.0015 mol) in THF (90ml). The mixture was stirred at room temperature for 2 days. The mixture was quenched with Na₂CO₃ then extracted with EtOAc. The organic layer was dried (MgSO₄), filtered and the solvent was evaporated.

- 5 The residue (0.96g) was pre-purified by column chromatography over Kromasil (eluent: CH₂Cl₂ then CH₂Cl₂/CH₃OH/NH₄OH 95 /5/0.5; 15-40 μm). The new fraction (0.63g) was purified by column chromatography over Xbridge (eluent: gradient of CH₃OH/NH₄HCO₃, 5%: 18-5 μm). Fraction 1 (0.08g) was taken up with ethanol/acetone (5/95) and 1 equivalent of fumaric acid in acetone was added at room
- 10 temperature. The precipitate was filtered off and dried. Yield: 0.07 g of **compound 63** (Z-isomer; fumaric acid salt) (6 %), mp°C: 179.

Tables 2 to 9 list the compounds of formula (Ia) which were prepared according to one of the above samples (Ex. No.)

15

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

Table 2

Comp. No.	Exp. No.	R ¹	X	R ⁶	R ³	q	R ⁴	R ⁵	Properties
14	B8	-Br	O	-H	-CH ₃	1	-CH ₃	-CH ₃	E or Z
16	B9	-Br	O	-H		1	-CH ₃	-CH ₃	E
17	B9	-Br	O	-H		1	-CH ₃	-CH ₃	Z
24	B5	-F	O	-H		1	-CH ₃	-CH ₃	Z
13	B7	-Br	O	-H		1	-CH ₃	-CH ₃	Z m.p. 150 °C
12	B6	-Br	O	-H		3	-CH ₃	-CH ₃	E or Z m.p. 145°C
25	B5	-Br	O	-H		1	-CH ₃	-CH ₃	Z
8	B5.a	-Br	O	-H		1	-CH ₃	-CH ₃	E m.p. 128 °C
61	B15.a	-Br	O	-H		3	-CH ₂ CH ₃	-CH ₃	E
10	B5.b	-Br	O	-H		1	-CH ₃	-CH ₃	75/25 ratio of isomers
28	B8	-Br	O	-H		1	-CH ₂ CH ₃	-CH ₂ CH ₃	Z
29	B5	-Br	O	-F		1	-CH ₃	-CH ₃	Z
4	B1	-Br	S	-H		1	-CH ₃	-CH ₃	Z

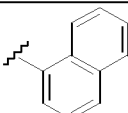
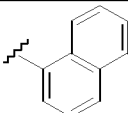
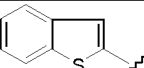
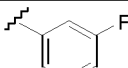
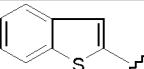
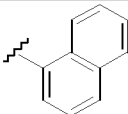
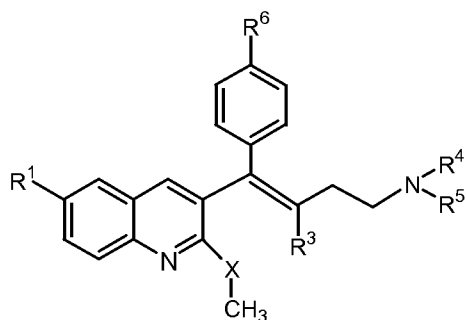
Comp. No.	Exp. No.	R ¹	X	R ⁶	R ³	q	R ⁴	R ⁵	Properties
30	B5	-CH ₃	O	-H		1	-CH ₃	-CH ₃	Z
31	B5	-OCH ₃	O	-H		1	-CH ₃	-CH ₃	Z
21	B11.b		O	-H		1	-CH ₃	-CH ₃	E/Z 60/40
11	B5		O	-H		1	-CH ₃	-CH ₃	Z
32	B5		O	-H		1	-CH ₃	-CH ₃	60/40 ratio of isomers
20	B11.a		S	-H		1	-CH ₃	-CH ₃	Z
33	B5		O	-H		1	-CH ₃	-CH ₃	Z
34	B5		O	-H		1	-CH ₃	-CH ₃	60/40 ratio of isomers m.p. 122°C

Table 3

Comp. No.	Exp. No.	R ¹	X	R ⁶	R ³	R ⁴	R ⁵	Properties
15	B8	-Br	O	-H	-CH ₃	-CH ₃	-CH ₃	E or Z
35	B1	-Br	O	-H	-CH ₃	-CH ₃	-CH ₃	75/25 ratio of isomers
18	B9	-Br	O	-H		-CH ₃	-CH ₃	Z

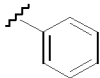
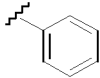
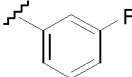
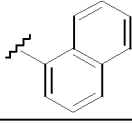
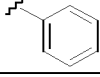
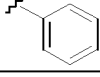
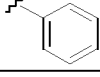
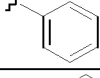
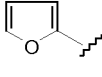
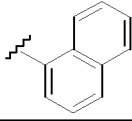
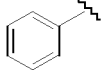
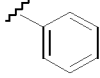
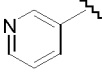
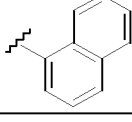
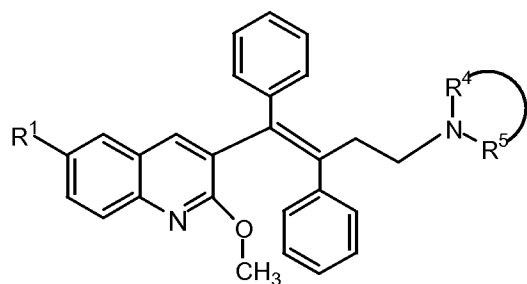
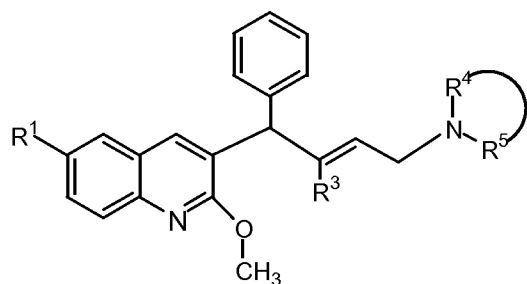
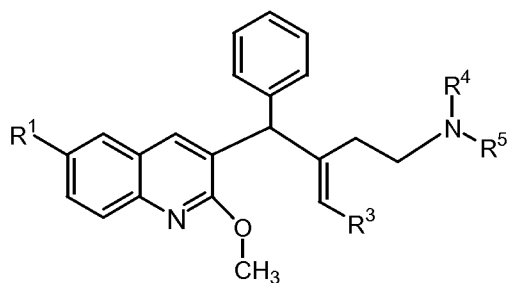
Comp. No.	Exp. No.	R ¹	X	R ⁶	R ³	R ⁴	R ⁵	Properties
36	B1	-Br	O	-H		-CH ₃	-CH ₃	E/Z n.d. m.p. 135°C
37	B1	-Br	O	-H		-CH ₂ CH ₃	-CH ₂ CH ₃	Z
38	B1	-Br	O	-H		-CH ₃	-CH ₃	Z
9	B5.b	-Br	O	-H		-CH ₃	-CH ₃	Z
1	B1	-Br	O	-Cl		-CH ₃	-CH ₃	Z
3	B1	-Br	S	-H		-CH ₃	-CH ₃	E or Z
2	B1	-Br	S	-H		-CH ₃	-CH ₃	E or Z
39	B1	-F	O	-H		-CH ₃	-CH ₃	E or Z
22	B11.b		O	-H		-CH ₃	-CH ₃	mixture of isomers
40	B11.a		S	-H		-CH ₃	-CH ₃	E or Z
41	B11.b		O	-H		-CH ₃	-CH ₃	Z m.p. 176°C

Table 4

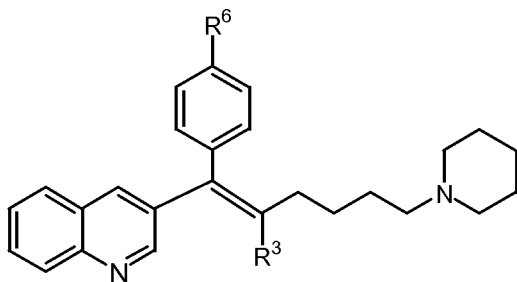
Comp. No.	Exp. No	R¹		Properties
6	B3	-Br		E or Z
5	B3	-Br		E or Z
42	B8	-Br		E or Z
43	B1	-Br		Z/E 90/10
44	B8	-Br		Z/E 60/40
45	B1	-Br		Z/E 90/10
46	B11.a			Z

Table 5

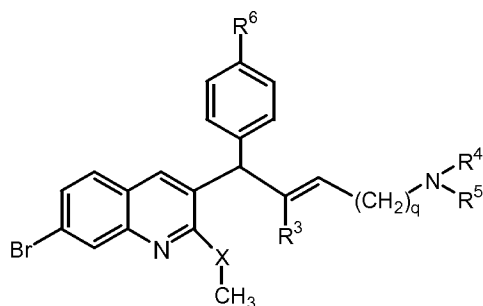
Comp. No.	Exp. No.	R ¹	R ³		Properties
47	B8	-Br			E
48	B8	-Br			Z
23	B12	-Br			Z iodide salt
62	B15.b	-Br			E .fumarate m.p. 204°C
63	B15.c	-Br			Z .fumarate m.p. 179°C

5 **Table 6**

Comp. No.	Exp. No.	R ¹	R ³	R ⁴	R ⁵	Properties
7	B5.a	-Br		-CH ₃	-CH ₃	E/Z 75/25

Table 7

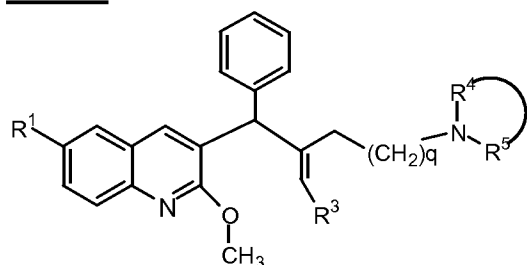
Comp. No.	Exp. No.	R^6	R^3	Properties
49	B10	-H		E/Z n.d.
50	B10	-H		E/Z n.d.
51	B10	-H		E/Z n.d.
19	B10	-Cl		E/Z n.d.
52	B10	-Cl		E/Z n.d.
53	B10	-Cl		E/Z n.d.
54	B10	-CN		E/Z n.d.
55	B10	-CN		E/Z n.d.
56	B10	-CN		E/Z n.d.
57	B10	-OCH ₃		E/Z n.d.
58	B10	-OCH ₃		E/Z n.d.
59	B10	-OCH ₃		E/Z n.d.

Table 8

Comp. No.	Exp. No.	R ¹	X	R ⁶	R ³	q	R ⁴	R ⁵	Properties
26	B8	-Br	O	-H		2	-CH ₃	-CH ₃	E
27	B8	-Br	O	-H		2	-CH ₃	-CH ₃	Z

- 5 when “E” or “Z” is indicated in the above Tables this means that the compound is a pure isomer, but the absolute configuration is not determined.

when “E/Z n.d.” is indicated in the above Tables this means that the configuration has not been determined.

10 **Table 9**

Comp. No.	Exp. No.	R ¹	R ³	q		Properties
60	B14	-Br	-CN	3		E

C. Analytical Part

LCMS conditions

5 General procedure A

The LC measurement was performed using an Acquity UPLC (Waters) system comprising a binary pump, a sample organizer, a column heater (set at 55 °C), a diode-array detector (DAD) and a column as specified in the respective methods below. Flow from the column was split to a MS spectrometer. The MS detector was configured with an electrospray ionization source. Mass spectra were acquired by scanning from 100 to 1000 in 0.18 seconds using a dwell time of 0.02 seconds. The capillary needle voltage was 3.5 kV and the source temperature was maintained at 140 °C. Nitrogen was used as the nebulizer gas. Data acquisition was performed with a Waters-Micromass MassLynx-Openlynx data system.

15

General procedure B

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

20
25

General procedure C

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

Method 1

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

Method 2

In addition to general procedure A: Reversed phase UPLC (Ultra Performance Liquid
25 Chromatography) was carried out on a bridged ethylsiloxane/silica hybrid (BEH) C18 column (1.7 µm, 2.1 x 50 mm; Waters Acquity) with a flow rate of 0.8 ml/min. Two mobile phases (mobile phase A: 0.1 % formic acid in H₂O/methanol 95/5; mobile phase B: methanol) were used to run a gradient condition from 95 % A and 5 % B to 5 % A and 95 % B in 1.3 minutes and hold for 0.2 minutes. An injection volume of 0.5 µl was
30 used. Cone voltage was 10 V for positive ionization mode and 20 V for negative ionization mode.

Method 3

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

Method 4

In addition to the general procedure B: Reversed phase HPLC was carried out on a Xterra-MS C18 column (3.5 μ m, 4.6 x 100 mm) with a flow rate of 0.8 ml/min. Two mobile phases (mobile phase A: 100 % 7 mM ammonium acetate; mobile phase B: 100 % acetonitrile; were employed to run a gradient condition from 80 % A , 20 % B (hold for 0.5 minute) to 10 % A, 90 % B in 4.5 minutes, hold at 10 % A and 90 % B for 4 minutes and reequilibrated with initial conditions for 3 minutes. An injection volume of 10 μ l was used. Cone voltage was 20 V for positive and negative ionization mode. Mass spectra were acquired by scanning from 100 to 1000 in 0.4 seconds using an interscan delay of 0.3 seconds.

Method 5

For compound (51) only the mass spectrum was recorded (no R(t)). The MS detector was configured with an electrospray ionization source. Mass spectra were acquired by scanning from 100 to 1000 in 1 second using a dwell time of 0.1 second. The capillary needle voltage was 3 kV and the source temperature was maintained at 140 °C. Nitrogen was used as the nebulizer gas. Data acquisition was performed with a Waters-Micromass MassLynx-Openlynx data system. Cone voltage was 10 V for positive ionization mode.

Method 6

In addition to general procedure C: Reversed phase UPLC was carried out on a Waters Acquity BEH (bridged ethylsiloxane/silica hybrid) C18 column (1.7 μ m, 2.1 x 100 mm) with a flow rate of 0.35 ml/min. Two mobile phases (mobile phase A: 95 % 7 mM ammonium acetate / 5 % acetonitrile; mobile phase B: 100 % acetonitrile) were employed to run a gradient condition from 90 % A and 10 % B (hold for 0.5 minutes) to 8 % A and 92 % B in 3.5 minutes, hold for 2 min and back to the initial conditions in 0.5 min, hold for 1.5 minutes. An injection volume of 2 μ l was used. Cone voltage was 20 V for positive and negative ionization mode. Mass spectra were acquired by scanning from 100 to 1000 in 0.2 seconds using an interscan delay of 0.1 seconds.

Method 7

In addition to general procedure C: Reversed phase UPLC was carried out on a Waters Acquity BEH (bridged ethylsiloxane/silica hybrid) C18 column (1.7 μ m, 2.1 x 100 mm) with a flow rate of 0.35 ml/min. Two mobile phases (mobile phase A: 95 % 7 mM ammonium acetate / 5 % acetonitrile; mobile phase B: 100 % acetonitrile) were employed to run a gradient condition from 90 % A and 10 % B (hold for 0.5 minutes) to 8 % A and 92 % B in 3.5 minutes, hold for 2 min and back to the initial conditions in 0.5 min, hold for 1.5 minutes. An injection volume of 2 μ l was used. Cone voltages were 20, 30, 45, 60 V for positive ionization mode. Mass spectra were acquired by scanning from 100 to 1000 in 0.2 seconds using an interscan delay of 0.1 seconds.

Method 8

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

Method 9

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

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

Table 10 : Analytical data (R(t) means retention time in minutes; MH(+) means protonated molecular ion (of the free base); procedure refers to the method used for LCMS).

LCMS Comp. Nr.	R(t)	MH(+)	Procedure
36	1.21	487	2
10	1.30	537	2
9	1.26	537	2
6	6.17	510	1
1	6.44	521	1
29	6.50	521	1
2	6.23	503	1
4	6.50	503	1
24	5.34	427	1
5	6.17	510	1
3	6.28	503	1
47	7.76	511	1
25	6.20	505	1
42	7.67	511	1
38	5.98	505	1
8	6.79	515	1
7	6.57	515	1
12	6.53	515	1
17	5.97	493	1
16	6.04	493	1
18	5.96	493	1

LCMS			
Comp. Nr.	R(t)	MH(+)	Procedure
44	6.17	542	1
48	6.19	542	1
45	6.14	542	1
43	6.63	529	1
39	5.13	427	1
35	5.41	425	1
15	5.57	425	1
14	5.47	425	1
11	6.49	485	1
33	5.04	559	3
31	7.52	439	4
30	5.77	423	1
32	4.49	535	3
20	4.19	501	3
46	7.00	508	1
40	4.18	501	3
34	5.12	591	3
22	3.65	525	3
21	4.30	525	3
41	4.84	536	1
28	4.60	565	3
37	4.25	565	3
23	6.37	520	1
26	4.12	515	3
27	4.12	515	3
49	1.13	447	2
19	1.20	481	2
54	1.06	472	2
57	1.13	477	2
50	1.18	481	2
52	1.24	515	2
55	1.09	506	2
58	1.17	511	2
51	n.d.	477	5
53	1.20	511	2
56	1.06	502	2
59	1.08	507	2
62	6.26	634	6
63	5.68	634	7
61	5.67	557	8
60	5.18	621	9

D. Pharmacological examples

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

Flat-bottom, sterile 96-well plastic microtiter plates were filled with 100 µl of Middlebrook (1x) broth medium. Subsequently, stock solutions (10 x final test concentration) of compounds were added in 25 µl volumes to a series of duplicate wells in column 2 so as to allow evaluation of their effects on bacterial growth. Serial five-fold dilutions were made directly in the microtiter plates from column 2 to 11 using a customised robot system (Zymark Corp., Hopkinton, MA). Pipette tips were changed after every 3 dilutions to minimize pipetting errors with high hydrophobic compounds.

Untreated control samples with (column 1) and without (column 12) inoculum were included in each microtiter plate. Approximately 5000 CFU per well of *Mycobacterium tuberculosis* (strain H37RV), in a volume of 100 µl in Middlebrook (1x) broth medium, was added to the rows A to H, except column 12. The same volume of broth medium without inoculum was added to column 12 in row A to H. The cultures were incubated at 37°C for 7 days in a humidified atmosphere (incubator with open air valve and continuous ventilation). One day before the end of incubation, 6 days after inoculation, Resazurin (1:5) was added to all wells in a volume of 20 µl and plates were incubated for another 24 hours at 37°C. On day 7 the bacterial growth was quantitated fluorometrically.

The fluorescence was read in a computer-controlled fluorometer (Spectramax Gemini EM, Molecular Devices) at an excitation wavelength of 530 nm and an emission wavelength of 590 nm. The percentage growth inhibition achieved by the compounds was calculated according to standard methods and expressed as IC₉₀ (µg/ml) (90 % inhibitory concentration for bacterial growth) values.

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

Flat-bottom, sterile 96-well plastic microtiter plates were filled with 180 µl of sterile deionized water, supplemented with 0.25 % BSA. Subsequently, stock solutions (7.8 x final test concentration) of compounds were added in 45 µl volumes to a series of duplicate wells in column 2 so as to allow evaluation of their effects on bacterial growth. Serial five-fold dilutions (45 µl in 180 µl) were made directly in the microtiter plates from column 2 to 11 using a customised robot system (Zymark Corp., Hopkinton, MA). Pipette tips were changed after every 3 dilutions to minimize pipetting errors with high hydrophobic compounds. Untreated control samples with

(column 1) and without (column 12) inoculum were included in each microtiter plate. Approximately 250 CFU per well of bacteria inoculum, in a volume of 100 μ l in 2.8x Mueller-Hinton broth medium, was added to the rows A to H, except column 12. The same volume of broth medium without inoculum was added to column 12 in row A to H. The cultures were incubated at 37°C for 48 hours in a humidified 5% CO₂ atmosphere (incubator with open air valve and continuous ventilation). At the end of incubation, two days after inoculation, the bacterial growth was quantitated fluorometrically. Therefore Alamar Blue (10x) was added to all wells in a volume of 20 μ l and plates were incubated for another 2 hours at 50°C.

10

The fluorescence was read in a computer-controlled fluorometer (Cytofluor, Biosearch) at an excitation wavelength of 530 nm and an emission wavelength of 590 nm (gain 30). The percentage growth inhibition achieved by the compounds was calculated according to standard methods and expressed as IC₉₀ (μ g/ml) which defines the 90 % inhibitory concentration for bacterial growth. The results are shown in Table 11.

15

Table 11: Results of an in vitro-screening of the compounds according to the invention for *M. smegmatis* (IC₉₀ (μ g/ml)).

Co.No.	<i>M. smegmatis</i> IC ₉₀ (μ g/ml)
13	1.73
10	0.43
9	1.7
6	10.18
1	1.65
29	1.65
2	1.59
4	7.98
24	5.37
5	5.1
3	2.0
47	20.36
25	40.15
42	22.84
38	8.01

Co.No.	<i>M. smegmatis</i> IC ₉₀ (µg/ml)
8	1.63
7	1.63
12	40.95
17	39.2
16	1.75
18	9.85
44	4.31
48	1.72
45	9.65
43	4.21
39	16.98
35	3.79
15	1.35
14	1.35
11	1.53
33	7.03
31	6.95
30	2.67
32	1.69
20	1.41
46	1.61
40	1.58
34	2.35
22	1.66
21	14.79
41	3.79
28	1.79
37	2.01
23	1.85
26	4.09
27	5.78
49	7.08
19	1.52
54	11.85

Co.No.	<i>M. smegmatis</i> IC ₉₀ (µg/ml)
57	7.55
50	1.92
52	1.63
55	8.02
58	8.10
51	7.55
53	2.03
59	8.03
56	7.95
36	1.94
60	1.97
61	1.76
62	8.97
63	3.57

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

Preparation of bacterial suspensions for susceptibility testing:

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

Anti bacterial Susceptibility testing: IC₉₀ determination

- 15 *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
- 20 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
5 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
10 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 IC₉₀ (expressed in µg/ml) was defined as the 90 % inhibitory
15 concentration for bacterial growth. The results are shown in Table 12.

Agar dilution method.

MIC₉₉ values (the minimal concentration for obtaining 99 % inhibition of bacterial growth) can be determined by performing the standard Agar dilution method according
20 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

25 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. aureus* and MRSA is 10⁶ CFU / ml in Muller Hinton broth. The antibacterial compounds are used at the concentration of 0.1 to 10 times the MIC (i.e.
30 IC₉₀ 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
35 24 hrs and the number of colonies are determined. Killing curves can be constructed by plotting the log₁₀CFU per ml versus time. A bactericidal effect is commonly defined as 3-log₁₀ decrease in number of CFU per ml as compared to untreated inoculum. The

potential carryover effect of the drugs is removed by serial dilutions and counting the colonies at highest dilution used for plating.

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

5

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 OD₄₀₅ nm and calculate the CFU/ml. Dilute the cultures to 1 x 10⁶ CFU/ml (final concentration for ATP measurement: 1 x 10⁵ CFU/100 µl per well) and add test compound at 0.1 to 10 times the MIC (i.e. IC₉₀ 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.

20

Table 12 : IC₉₀ values (µg/ml) determined according to the Microtitre plate assay.

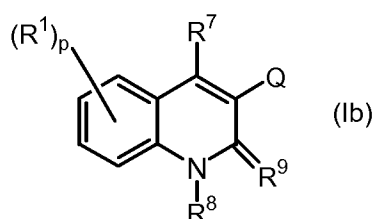
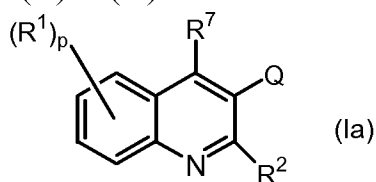
Comp.No.	IC90 (µg/ml)						
	STA 29213	SPN 6305	EFA 29212	SPY 8668	PAE 27853	STA RMETH	STA 25923
1	8.27	1.65					
2	7.98	1.59					
3	7.98	1.59					
4	40	17.87					
5	36.14	36.14					
6	10.18	10.18					
7	1.63	2.05					
8	8.17	2.05					
9	2.69	9.56	10.72	10.72	9.56	3.81	5.38
10	4.79	12.03	5.38	9.56	21.4	12.03	4.27
11	1.53	1.22	15.33	7.68	7.68		
12	8.17	10.29					
13		8.67	12.24	9.73	12.24		10.91
14	33.79	1.35	37.91	26.84	37.91		
15	33.79	6.74					
16	7.82	1.56					
17	15.6	7.82	39.2	19.65	43.98		

Comp.No.	IC90 (µg/ml)						
	STA 29213	SPN 6305	EFA 29212	SPY 8668	PAE 27853	STA RMETH	STA 25923
18	17.51	8.78					
20	1.58	1.41					
21	41.68	23.44					
22	20.89	20.89					
23	1.65	1.85		1.65	6.55		
24	33.88	1.51					
25	22.58	8.01	40.15	17.93	40.15		
26	3.65	2.05					
27	8.17	4.59					
28	8.96	2.01					
29	8.27	1.85					
30	6.7	1.34	11.91	6.7	13.36		
31	39.09	7.8					
32	1.69	1.9	9.51	3.79	3.79		
33	8.86	7.89					
34		10.51					
35	33.79	1.35	15.09	1.35	15.09		
36	9.73	5.47	12.24	9.73	12.24	12.24	10.91
37	8.96	2.01					
38	10.08	8.01	8.01	3.58	8.99		
39	33.88	8.51					
40	19.93	3.98	15.83	7.94			
41	8.49	9.53					
42							
43	52.95	8.39					
44	10.82	10.82					
45	43.09	10.82					
46	9.03	8.05					
47							
48	10.82	2.72					
49	44.66	8.91					
50		9.6					
51	47.67	21.29					
52	10.29	10.29					
53	9.09	10.2					
54	42.04	47.17					
55	8.02	10.1					
56		12.6					
57		9.51					
58	10.2	12.84					
59		11.34					
60	1.97	2.48					
61	1.76	1.76					
62	22.52						
63	2.25						

- STA 29213 means *Staphylococcus aureus* (ATCC29213); SPN 6305 means *Streptococcus pneumoniae* (ATCC6305); EFA 29212 means *Enterococcus faecalis* (ATCC29212); SPY 8668 means *Streptococcus pyogenes* (ATCC8668); PAE 27853 means *Pseudomonas aeruginosa* (ATCC27853); STA RMETH means methicilline resistant *Staphylococcus aureus* (MRSA) (a clinical isolate from the University of Antwerp); STA 25923 means *Staphylococcus aureus* (ATCC25923).
ATCC means American type tissue culture.
- 5

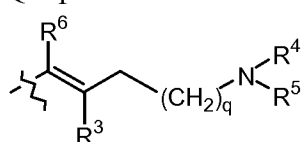
CLAIMS

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

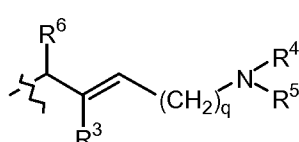


including any stereochemically isomeric form thereof, wherein

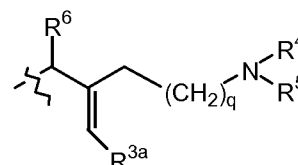
- 5 Q represents a radical of formula



or



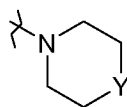
or



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

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

- 10 R¹ is hydrogen, cyano, formyl, carboxyl, halo, alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, haloalkyl, hydroxy, alkyloxy, alkylthio, alkylthioalkyl, -C=N-OR¹¹, amino, mono or di(alkyl)amino, aminoalkyl, mono or di(alkyl)aminoalkyl, alkylcarbonylaminoalkyl, aminocarbonyl, mono or di(alkyl)aminocarbonyl, arylalkyl, arylcarbonyl, R^{5a}R^{4a}Nalkyl, di(aryl)alkyl, aryl, R^{5a}R^{4a}N-, R^{5a}R^{4a}N-C(=O)-, or Het;
- 15 R² is hydrogen, alkyloxy, aryl, aryloxy, hydroxy, mercapto, alkyloxyalkyloxy, alkylthio, mono or di(alkyl)amino, pyrrolidino or a



radical of formula wherein Y is CH₂, O, S, NH or N-alkyl ;

R³ is alkyl, arylalkyl, aryl-O-alkyl, aryl-alkyl-O-alkyl, aryl, aryl-aryl, Het,

Het-alkyl, Het-O-alkyl, Het-alkyl-O-alkyl or phenyl;

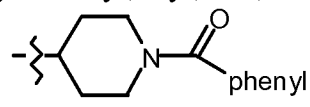
- 20 R³ᵃ is hydrogen, cyano, alkyl, arylalkyl, aryl-O-alkyl, aryl-alkyl-O-alkyl, aryl, aryl-aryl, Het, Het-alkyl, Het-O-alkyl, or Het-alkyl-O-alkyl;

- R⁴ and R⁵ each independently is hydrogen; alkyl; alkyloxyalkyl; arylalkyl; Het-alkyl; mono- or dialkylaminoalkyl; bicyclo[2.2.1]heptyl; Het; aryl; or -C(=NH)-NH₂; or
- 5 R⁴ and R⁵ together with the nitrogen atom to which they are attached form a radical selected from the group consisting of pyrrolidino, piperidino, piperazino, morpholino, 4-thiomorpholino, 1,1-dioxide-thiomorpholinyl, azetidiny, 2,3-dihydroisoindol-1-yl, thiazolidin-3-yl, 1,2,3,6-tetrahydropyridyl, hexahydro-1*H*-azepinyl, hexahydro-1*H*-1,4-diazepinyl, hexahydro-1,4-oxazepinyl, 1,2,3,4-tetrahydroisoquinolin-2-yl, 2,5-diazabicyclo[2.2.1]heptyl, pyrrolinyl, pyrrolyl, imidazolidinyl, 10 pyrazolidinyl, 2-imidazoliny, 2-pyrazolinyl, imidazolyl, pyrazolyl, triazolyl, pyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl and triazinyl, each radical optionally substituted with 1, 2, 3 or 4 substituents, each substituent independently selected from alkyl, haloalkyl, alkylcarbonyl, halo, arylalkyl, hydroxy, alkyloxy, amino, mono- or dialkylamino, 15 aminoalkyl, mono- or dialkylaminoalkyl, alkylthio, alkylthioalkyl, aryl, pyridyl, pyrimidinyl, piperidinyl optionally substituted with alkyl or pyrrolidinyl optionally substituted with arylalkyl;
- R^{4a} and R^{5a} together with the nitrogen atom to which they are attached form a radical selected from the group consisting of pyrrolidino, piperidino, piperazino, morpholino, 4-thiomorpholino, 2,3-dihydroisoindol-1-yl, thiazolidin-3-yl, 1,2,3,6-tetrahydropyridyl, hexahydro-1*H*-azepinyl, hexahydro-1*H*-1,4-diazepinyl, hexahydro-1,4-oxazepinyl, 1,2,3,4-tetrahydroisoquinolin-2-yl, pyrrolinyl, pyrrolyl, imidazolidinyl, 25 pyrazolidinyl, 2-imidazoliny, 2-pyrazolinyl, imidazolyl, pyrazolyl, triazolyl, pyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl and triazinyl, each radical optionally substituted with 1, 2, 3 or 4 substituents, each substituent independently selected from alkyl, haloalkyl, halo, arylalkyl, hydroxy, alkyloxy, amino, mono- or dialkylamino, alkylthio, 30 alkylthioalkyl, aryl, pyridyl or pyrimidinyl;
- R⁶ is aryl¹ or Het;
- R⁷ is hydrogen, halo, alkyl, aryl or Het;
- R⁸ is hydrogen or alkyl;
- R⁹ is oxo; or
- 35 R⁸ and R⁹ together form the radical -CH=CH-N=;
- R¹¹ is hydrogen or alkyl;

- aryl is a homocycle selected from phenyl, naphthyl, acenaphthyl or tetrahydronaphthyl, each being optionally substituted with 1, 2 or 3 substituents, each substituent being independently selected from hydroxy, halo, cyano, nitro, amino, mono- or dialkylamino, alkyl, C₂₋₆alkenyl optionally substituted with phenyl, haloalkyl, alkyloxy, haloalkyloxy, carboxyl, alkyloxycarbonyl, aminocarbonyl, morpholinyl or mono- or dialkylaminocarbonyl;
- aryl¹ is a homocycle selected from phenyl, naphthyl, acenaphthyl or tetrahydronaphthyl, each being optionally substituted with 1, 2 or 3 substituents, each substituent being independently selected from hydroxy, halo, cyano, nitro, amino, mono- or dialkylamino, alkyl, haloalkyl, alkyloxy, alkylthio, haloalkyloxy, carboxyl, alkyloxycarbonyl, aminocarbonyl, morpholinyl, Het or mono- or dialkylaminocarbonyl;
- Het is a monocyclic heterocycle selected from *N*-phenoxypiperidinyl, piperidinyl, pyrrolyl, pyrazolyl, imidazolyl, furanyl, thienyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, pyridinyl, pyrimidinyl, pyrazinyl or pyridazinyl; or a bicyclic heterocycle selected from quinolinyl, quinoxalinyl, indolyl, benzimidazolyl, benzoxazolyl, benzisoxazolyl, benzothiazolyl, benzisothiazolyl, benzofuranyl, benzothienyl, 2,3-dihydrobenzo[1,4]dioxinyl or benzo[1,3]dioxolyl; each monocyclic and bicyclic heterocycle being optionally substituted with 1, 2 or 3 substituents, each substituent independently selected from halo, hydroxy, alkyl or alkyloxy;
- a *N*-oxide thereof, a pharmaceutically acceptable salt thereof or a solvate thereof.

2. A compound according to claim 1 wherein

- R³ is alkyl, arylalkyl, aryl-O-alkyl, aryl-alkyl-O-alkyl, aryl, Het, Het-alkyl, Het-O-alkyl, Het-alkyl-O-alkyl or
- R^{3a} is hydrogen, cyano, alkyl, arylalkyl, aryl-O-alkyl, aryl-alkyl-O-alkyl, aryl, Het, Het-alkyl, Het-O-alkyl, or Het-alkyl-O-alkyl;
- R⁴ and R⁵ each independently is hydrogen; alkyl; alkyloxyalkyl; arylalkyl; Het-alkyl; mono- or dialkylaminoalkyl; Het; aryl; or -C(=NH)-NH₂;
- or
- R⁴ and R⁵ together with the nitrogen atom to which they are attached form a radical selected from the group consisting of pyrrolidino, piperidino,

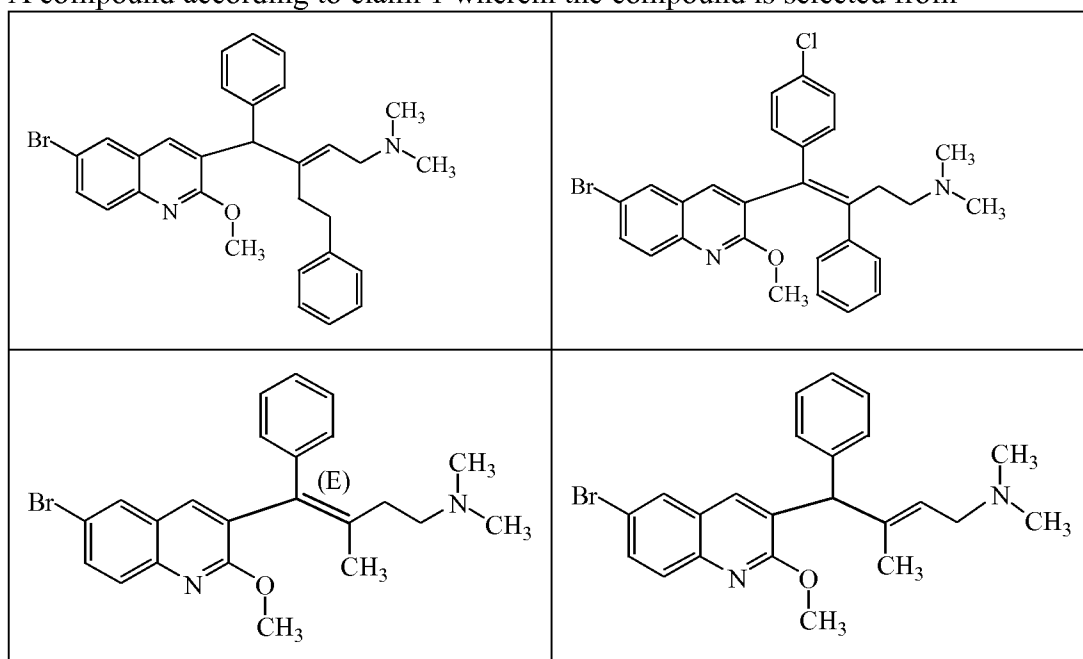


- piperazino, morpholino, 4-thiomorpholino, 2,3-dihydroisoindol-1-yl,
 thiazolidin-3-yl, 1,2,3,6-tetrahydropyridyl, hexahydro-1*H*-azepinyl,
 hexahydro-1*H*-1,4-diazepinyl, hexahydro-1,4-oxazepinyl, 1,2,3,4-
 tetrahydroisoquinolin-2-yl, 2,5-diazabicyclo[2.2.1]heptyl, pyrrolinyl,
 5 pyrrolyl, imidazolidinyl, pyrazolidinyl, 2-imidazolinyl, 2-pyrazolinyl,
 imidazolyl, pyrazolyl, triazolyl, pyridinyl, pyridazinyl, pyrimidinyl,
 pyrazinyl and triazinyl, each radical optionally substituted with 1, 2, 3
 or 4 substituents, each substituent independently selected from alkyl,
 haloalkyl, alkylcarbonyl, halo, arylalkyl, hydroxy, alkyloxy, amino,
 10 mono- or dialkylamino, alkylthio, alkylthioalkyl, aryl, pyridyl,
 pyrimidinyl, piperidinyl or pyrrolidinyl optionally substituted with
 arylalkyl;
 aryl is a homocycle selected from phenyl, naphthyl, acenaphthyl or
 tetrahydronaphthyl, each being optionally substituted with 1, 2 or 3
 15 substituents, each substituent being independently selected from
 hydroxy, halo, cyano, nitro, amino, mono- or dialkylamino, alkyl,
 haloalkyl, alkyloxy, haloalkyloxy, carboxyl, alkyloxycarbonyl,
 aminocarbonyl, morpholinyl or mono- or dialkylaminocarbonyl.
- 20 3. A compound according to claim 1 or 2 wherein alkyl represents C₁₋₆alkyl.
4. A compound according to any one of the preceding claims wherein R¹ is
 hydrogen, halo, aryl, Het, C₁₋₆alkyl or C₁₋₆alkyloxy.
- 25 5. A compound according to any one of the preceding claims wherein p is equal
 to 1.
6. A compound according to any one of the preceding claims wherein R² is
 hydrogen, C₁₋₆alkyloxy or C₁₋₆alkylthio.
- 30 7. A compound according to claim 6 wherein R² is methyloxy.
8. A compound according to any one of the preceding claims wherein R³ is
 C₁₋₆alkyl, arylC₁₋₆alkyl, aryl, or Het.
- 35 9. A compound according to any one of claims 1 to 7 wherein R^{3a} is cyano, C₁₋₆alkyl
 or arylC₁₋₆alkyl.

10. A compound according to any one of the preceding claims wherein q is equal to 1, 2 or 3.
- 5 11. A compound according to any one of the preceding claims wherein R⁴ and R⁵ represent C₁₋₆alkyl.
- 10 12. A compound according to any one of claims 1 to 10 wherein R⁴ and R⁵ are taken together with the nitrogen atom to which they are attached and form a radical selected from the group consisting of piperidino, piperazino, morpholino, imidazolyl, triazolyl, each of said rings optionally substituted with C₁₋₆alkyl.
- 15 13. A compound according to any one of claims 1 to 10 wherein R⁴ and R⁵ together with the nitrogen atom to which they are attached form a radical selected from the group consisting of 1,1-dioxide-thiomorpholinyl, azetidiny, 2,3-dihydroisoindol-1-yl, thiazolidin-3-yl, 1,2,3,6-tetrahydropyridyl, hexahydro-1*H*-azepinyl, hexahydro-1*H*-1,4-diazepinyl, hexahydro-1,4-oxazepinyl, 1,2,3,4-tetrahydroisoquinolin-2-yl, 2,5-diazabicyclo[2.2.1]heptyl, each of said rings optionally substituted with C₁₋₆alkyl or arylC₁₋₆alkyl.
- 20 14. A compound according to claim 13 wherein R⁴ and R⁵ together with the nitrogen atom to which they are attached form a radical selected from the group consisting of hexahydro-1*H*-1,4-diazepinyl or 2,5-diazabicyclo[2.2.1]heptyl, each of said rings optionally substituted with C₁₋₆alkyl or arylC₁₋₆alkyl.
- 25 15. A compound according to any one of the preceding claims wherein R⁶ is phenyl optionally substituted with halo, cyano or C₁₋₆alkyloxy.
- 30 16. A compound according to any one of the preceding claims wherein R⁷ is hydrogen.
17. A compound according to any one of the preceding claims wherein the compound is a compound of formula (Ia).
- 35 18. A compound according to any one of the preceding claims wherein Q is a radical of formula (a-1).

19. A compound according to any one of claims 1 to 17 wherein Q is a radical of formula (a-2).
20. A compound according to claim 1 wherein R¹ is hydrogen, halo, aryl, Het, C₁₋₆alkyl or C₁₋₆alkyloxy; R² is hydrogen, C₁₋₆alkyloxy or C₁₋₆alkylthio; R³ is C₁₋₆alkyl, arylC₁₋₆alkyl, aryl, or Het; R⁴ and R⁵ are C₁₋₆alkyl; or R⁴ and R⁵ together with the nitrogen atom to which they are attached form a radical selected from the group consisting of piperidino, piperazino, morpholino, imidazolyl, triazolyl, hexahydro-1*H*-1,4-diazepinyl or 2,5-diazabicyclo[2.2.1]heptyl, each of said rings optionally substituted with C₁₋₆alkyl or arylC₁₋₆alkyl; R⁶ is phenyl optionally substituted with halo, cyano or C₁₋₆alkyloxy; R⁷ is hydrogen; q is 1, 2 or 3; p is 1; Q is a radical of formula (a-1), (a-2) or (a-3).

21. A compound according to claim 1 wherein the compound is selected from



- 15 a pharmaceutically acceptable salt thereof, a *N*-oxide form thereof or a solvate thereof.
22. A compound according to any one of the preceding claims for use as a medicine.
- 20 23. A compound according to any one of claims 1 to 21 for use as a medicine for the treatment of a bacterial infection.

24. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and, as active ingredient, a therapeutically effective amount of a compound as defined in any one of claims 1 to 21.

5 25. Use of a compound according to any one of claims 1 to 21 for the manufacture of a medicament for the treatment of a bacterial infection.

26. Use according to claim 25 wherein the bacterial infection is an infection with a gram-positive bacterium.

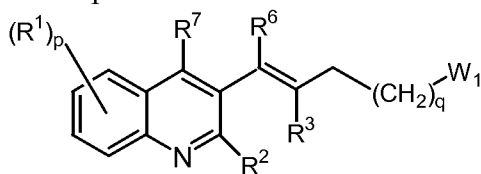
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27. Use according to claim 26 wherein the gram-positive bacterium is *Streptococcus pneumoniae*.

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28. Use according to claim 26 wherein the gram-positive bacterium is *Staphylococcus aureus*.

29. A compound of formula

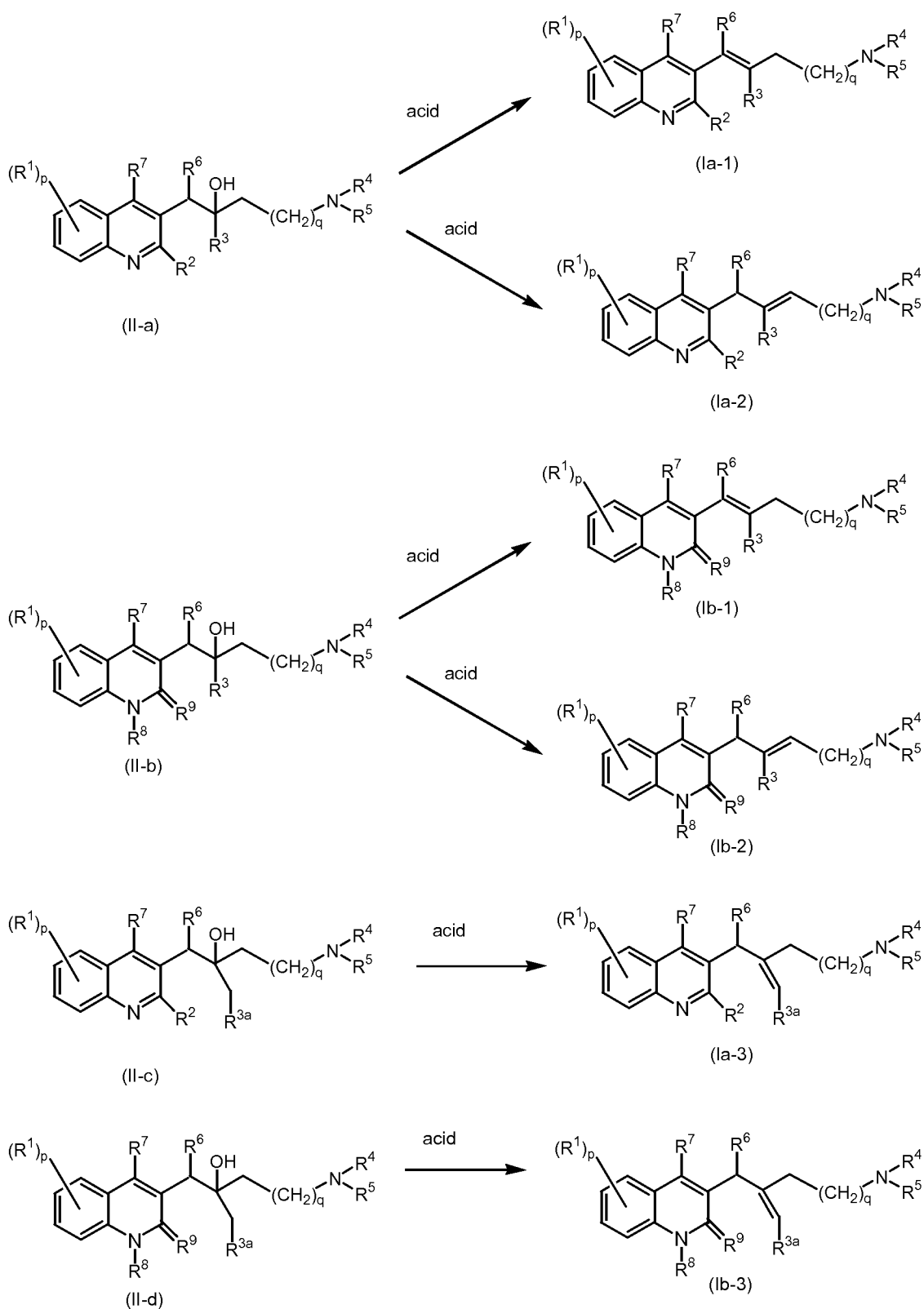


(IIIa)

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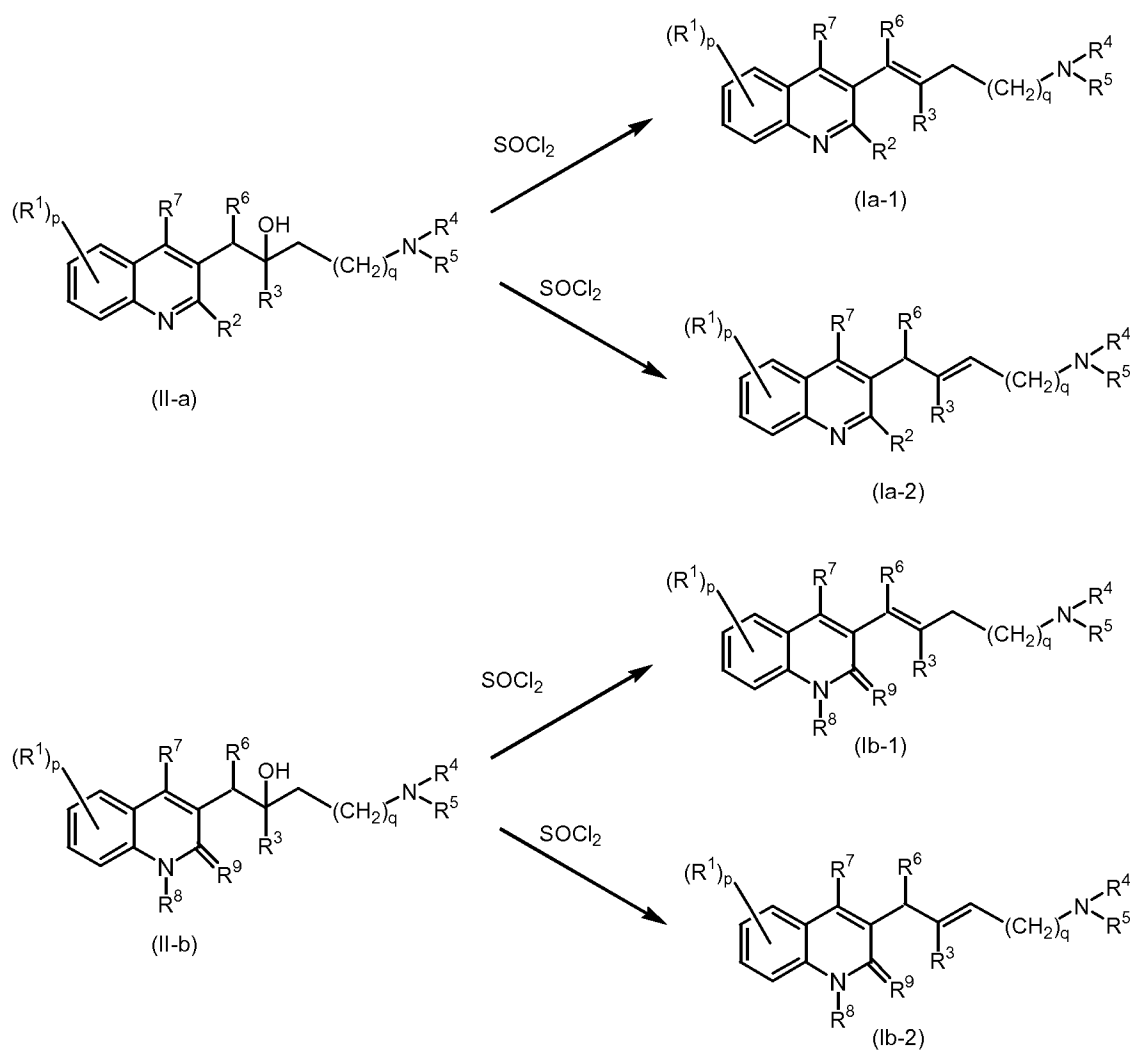
a pharmaceutically acceptable salt thereof, a *N*-oxide form thereof or a solvate thereof.

30. A process to prepare a compound according to claim 1 characterized by
a) reacting an intermediate of formula (II-a), (II-b), (II-c) or (II-d) with a suitable acid,

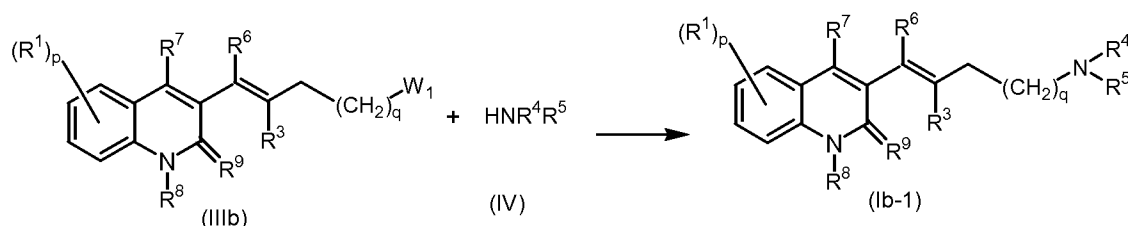
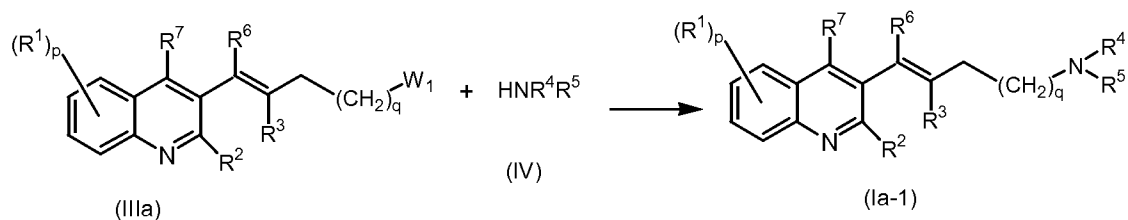


wherein R^1 , R^2 , R^3 , R^{3a} , R^4 , R^5 , R^6 , R^7 , R^8 , R^9 , p and q are as defined in claim 1;

- 10 b) reacting an intermediate of formula (II-a), (II-b) with SOCl_2 in the presence of a suitable solvent

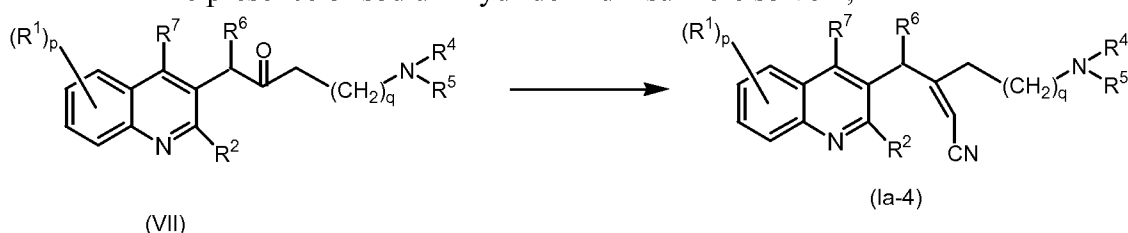


- 5 wherein R¹, R², R³, R⁴, R⁵, R⁶, R⁷, R⁸, R⁹, p and q are as defined in claim 1;
- c) reacting an intermediate of formula (IIIa) or (IIIb) with an intermediate of formula (IV) in the presence of a suitable base and a suitable solvent.



wherein R¹, R², R³, R⁴, R⁵, R⁶, R⁷, R⁸, R⁹, p and q are as defined in claim 1
and wherein W₁ represents a suitable leaving group;

- 5 d) reacting an intermediate of formula (VII) with diethyl cyanomethylacetate in the presence of sodium hydride and a suitable solvent,



wherein R¹, R², R⁴, R⁵, R⁶, R⁷, p and q are as defined in claim 1;

- 10 or, if desired, converting compounds of formula (Ia) or (Ib) into each other following art-known transformations, and further, if desired, converting the compounds of formula (Ia) or (Ib), into a therapeutically active non-toxic acid addition salt by treatment with an acid, or into a therapeutically active non-toxic base addition salt by treatment with a base, or conversely, converting the acid addition salt form into the free base by treatment with alkali, or
- 15 converting the base addition salt into the free acid by treatment with acid; and, if desired, preparing stereochemically isomeric forms, quaternary amines or N-oxide forms thereof.
- 20 31. A combination of (a) a compound according to any one of claims 1 to 21, and (b) one or more other antibacterial agents.

32. A product containing (a) a compound according to any one of claims 1 to 21, and (b) one or more other antibacterial agents, as a combined preparation for simultaneous, separate or sequential use in the treatment of a bacterial infection.