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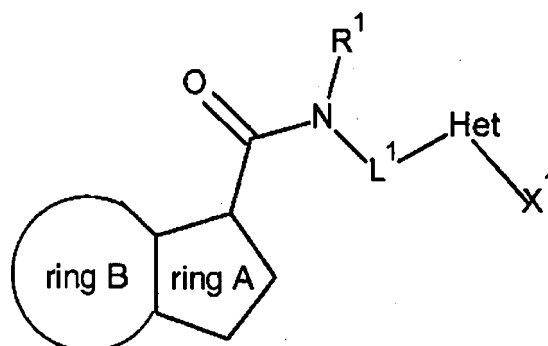
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The present invention relates to the following compounds wherein the integers are as defined in the description, and where the compounds may be useful as medicaments, for instance for use in the treatment of tuberculosis.



ANTIBACTERIAL COMPOUNDS

5 The present invention relates to novel compounds. The invention also relates to such compounds for use as a pharmaceutical and further for the use in the treatment of bacterial diseases, including diseases caused by pathogenic mycobacteria such as *Mycobacterium tuberculosis*. Such compounds may work by interfering with ATP synthase in *M. tuberculosis*, with the inhibition of cytochrome *bc₁* activity as the primary mode of action. Hence, primarily, such compounds are antitubercular agents.

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BACKGROUND OF THE INVENTION

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

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

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

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

(MDR-TB). The reactivation of latent TB is a high risk factor for disease development and accounts for 32% deaths in HIV infected individuals. To control TB epidemic, the need is to discover new drugs that can kill dormant or latent bacilli. The dormant TB can get reactivated to cause disease by several factors like suppression of host immunity by use of immunosuppressive agents like antibodies against tumor necrosis factor α or interferon- γ . In case of HIV positive patients the only prophylactic treatment available for latent TB is two- three months regimens of rifampicin, pyrazinamide. The efficacy of the treatment regime is still not clear and furthermore the length of the treatments is an important constrain in resource-limited environments. Hence there is a drastic need to identify new drugs, which can act as chemoprophylatic agents for individuals harboring latent TB bacilli.

The tubercle bacilli enter healthy individuals by inhalation; they are phagocytosed by the alveolar macrophages of the lungs. This leads to potent immune response and formation of granulomas, which consist of macrophages infected with *M. tuberculosis* surrounded by T cells. After a period of 6-8 weeks the host immune response cause death of infected cells by necrosis and accumulation of caseous material with certain extracellular bacilli, surrounded by macrophages, epitheloid cells and layers of lymphoid tissue at the periphery. In case of healthy individuals, most of the mycobacteria are killed in these environments but a small proportion of bacilli still survive and are thought to exist in a non-replicating, hypometabolic state and are tolerant to killing by anti-TB drugs like isoniazid. These bacilli can remain in the altered physiological environments even for individual's lifetime without showing any clinical symptoms of disease. However, in 10% of the cases these latent bacilli may reactivate to cause disease. One of the hypothesis about development of these persistent bacteria is patho-physiological environment in human lesions namely, reduced oxygen tension, nutrient limitation, and acidic pH. These factors have been postulated to render these bacteria phenotypically tolerant to major anti-mycobacterial drugs.

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

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

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

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

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

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

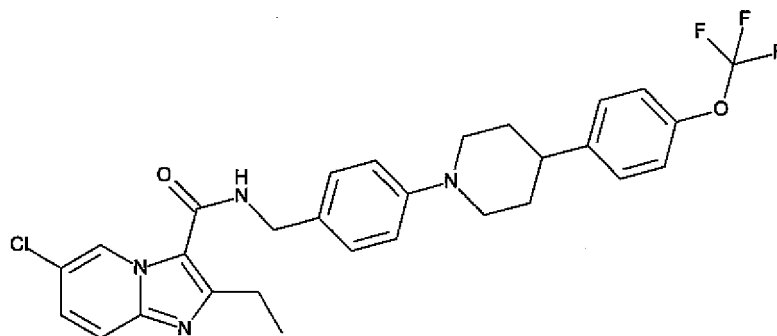
Because of the emerging resistance to multiple antibiotics, physicians are confronted with infections for which there is no effective therapy. The morbidity, mortality, and financial costs of such infections impose an increasing burden for health care systems worldwide.

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

Anti-infective compounds for treating tuberculosis have been disclosed in e.g. international patent application WO 2011/113606. Such a document is concerned with compounds that would prevent *M. tuberculosis* multiplication inside the host macrophage and relates to compounds with a bicyclic core, imidazopyridines, which are linked (e.g. via an amido moiety) to e.g. an optionally substituted benzyl group.

International patent application WO 2014/015167 also discloses compounds that are disclosed as being of potential use in the treatment of tuberculosis. Such compounds disclosed herein have a bicycle (a 5,5-fused bicycle) as an essential element, which is substituted by a linker group (e.g. an amido group), which itself may be attached to another bicycle or aromatic group. Such compounds in this document do not contain a series of more than three rings.

Journal article *Nature Medicine*, **19**, 1157-1160 (2013) by Pethe *et al* "Discovery of Q203, a potent clinical candidate for the treatment of tuberculosis" identifies a specific compound that was tested against *M. tuberculosis*. This compound Q203 is depicted
5 below.



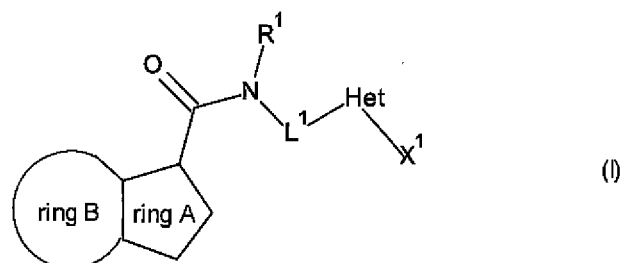
This clinical candidates is also discussed in journal article, *J. Medicinal Chemistry*, 2014, **57** (12), pp5293-5305. It is stated to have activity against MDR tuberculosis, and have activity against the strain *M. tuberculosis* H37Rv at a MIC₅₀ of 0.28 nM inside
10 macrophages. Positive control data (using known anti-TB compounds bedaquiline, isoniazid and moxifloxacin) are also reported. This document also suggests a mode of action, based on studies with mutants. It postulates that it acts by interfering with ATP synthase in *M. tuberculosis*, and that the inhibition of cytochrome *bc*₁ activity is the primary mode of action. Cytochrome *bc*₁ is an essential component of the electron
15 transport chain required for ATP synthesis. It appeared that Q203 was highly active against both replicating and non-replicating bacteria

International patent application WO 2015/014993 also discloses compounds as having activity against *M. tuberculosis*. International patent applications WO 2013/033070
20 and WO 2013/033167 disclose various compounds as kinase modulators.

The purpose of the present invention is to provide compounds for use in the treatment of bacterial diseases, particularly those diseases caused by pathogenic bacteria such as *Mycobacterium tuberculosis* (including the latent disease and including drug resistant
25 *M. tuberculosis* strains). Such compounds may also be novel and may act by interfering with ATP synthase in *M. tuberculosis*, with the inhibition of cytochrome *bc*₁ activity being considered the primary mode of action.

SUMMARY OF THE INVENTION

There is now provided a compound of formula (I) for use in the treatment of tuberculosis



wherein

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

L^1 represents a linker group $-C(R^a)(R^b)-$ (or is not present);

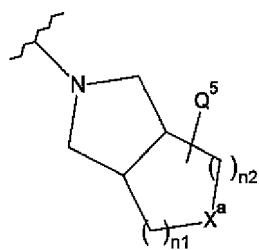
- 10 Het represents a heteroaromatic linker group (which linker group may itself be optionally substituted by one or more substituents selected from fluoro, $-O-R^c$ and C_{1-6} alkyl, wherein the latter alkyl moiety is itself optionally substituted by one or more fluoro atoms);

- 15 R^a , R^b and R^c independently represent hydrogen or C_{1-6} alkyl (optionally substituted by one or more fluoro atoms);

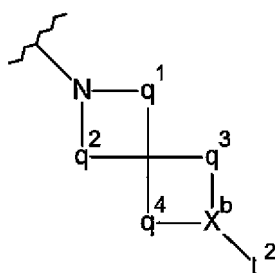
X^1 represents $-N(R^2)(R^3)$;

R^2 and R^3 :

- 20 (i) independently represent hydrogen or, preferably, C_{1-6} alkyl optionally substituted by one or more substituents selected from Q^1 and $=O$;
- (ii) independently represent aryl or heteroaryl, each of which is optionally substituted by one or more substituents selected from Q^2 ;
- (iii) independently represent cycloalkyl or heterocycloalkyl, each of which is
- 25 optionally substituted by one or more substituents selected from Q^3 and $=O$;
- or
- (iv) can be linked together to form:
- a. a 3- to 8-membered ring optionally containing one to three heteroatoms (e.g. nitrogen, oxygen and/or sulfur), and which ring is optionally
- 30 substituted by one or more substituents selected from Q^4 and $=O$;
- b. a "fused" bicyclic ring of the following type:



c. a "spiro" ring of the following type:



- 5 Q¹, Q², Q³, Q⁴ and Q⁵ each independently represent one or more substituents selected from halo, C₁₋₆ alkyl, -OC₁₋₆ alkyl (which latter two alkyl moieties may themselves be optionally substituted by one or more halo, e.g. fluoro, atoms), aryl and heteroaryl (which latter two aromatic groups may themselves be optionally substituted by one or more substituents selected from halo, C₁₋₆ alkyl and -OC₁₋₆ alkyl, which latter two alkyl moieties may themselves be substituted with one or more fluoro atoms);
- 10

n₁ and n₂ independently represent 0 or 1 (hence, the X^a-containing ring may be 3-, 4- or 5-membered, or (when m is 2), 6-membered);

- 15 X^a represents -C(R^{a1})(R^{b1})_m- or -N(R^{c1})-;
m represents 1 or 2;
each R^{a1} and R^{b1} independently represents fluoro, hydrogen or C₁₋₆ alkyl;
R^{c1} represents hydrogen or C₁₋₆ alkyl;
- 20 X^b represents C(R^d), N, O (in which case L² is not present) or C=O (in which case L² is also not present);

R^d represents H, F or -OR^e (wherein R^e represents H or C₁₋₆ alkyl optionally substituted by one or more fluoro atoms);

- 25 q¹ represents -X^e-(CH₂)_{n1}-X^d;
n₁ represents 0, 1 or 2;

q^2 represents $-X^e-(CH_2)_{n2}-X^f$;

$n2$ represents 0, 1 or 2, but wherein $n1$ and $n2$ do not both represent 0;

X^c (which is attached to X^a) is either not present, or, when X^a represents CH, then X^c
5 may represent -O-, -NH- or -S-;

X^d is either not present, or, when $n1$ represents 2 or when X^c is not present, X^a
represents $C(R^c)$ and $n1$ represents 1, then X^d may also represent -O-, -NH- or -S-;
 X^e and X^f independently are either not present, or may independently represent -O-,
-NH- or -S-, provided that the aforementioned heteroatoms are not directly attached to
10 or α to another heteroatom;

q^3 represents $-X^g-(CH_2)_{n3}-X^h$;

q^4 represents $-X^i-(CH_2)_{n4}-X^j$;

$n3$ represents 0, 1 or 2;

15 $n4$ represents 0, 1 or 2, but wherein $n3$ and $n4$ do not both represent 0;

X^g , X^h , X^i and X^j independently are either not present, or may represent -O-, -NH- or
-S-, provided that the aforementioned heteroatoms are not directly attached to or α to
another heteroatom;

20

when X^b represents O or C=O, then L^2 is not present;

when X^b represents $C(R^d)$ (e.g. CH) or N, then L^2 may represent hydrogen, halo, -OR^f,
-C(O)-R^g, C₁₋₆ alkyl (optionally substituted by one or more halo, e.g. fluoro atoms) or
an aromatic group (optionally substituted by one or more substituents selected from
25 halo, C₁₋₆ alkyl (itself optionally substituted by one or more substituents selected from
fluoro, -CF₃ and/or -SF₅), -OC₁₋₆alkyl (itself optionally substituted by one or more
fluoro atoms), -O-phenyl (itself optionally substituted by halo, C₁₋₆alkyl,
C₁₋₆fluoroalkyl and/or -OC₁₋₆alkyl) or -SF₅);

30 R^f represents hydrogen, C₁₋₆ alkyl (optionally substituted by one or more fluoro) or an
aromatic group (itself optionally substituted by one or more substituents selected from
halo, C₁₋₆alkyl and -OC₁₋₆alkyl, where the latter two alkyl moieties may themselves be
optionally substituted by one or more fluoro atoms);

35 R^g represents hydrogen or C₁₋₆alkyl (optionally substituted by one or more substituents
selected from fluoro, or -OC₁₋₃ alkyl, which latter moiety is also optionally substituted
by one or more fluoro atoms) or an aromatic group (optionally substituted by one or
more substituents selected from halo, C₁₋₆ alkyl or -OC₁₋₆alkyl);

ring A is a 5-membered aromatic ring containing at least one heteroatom (preferably containing at least one nitrogen atom);

- 5 ring B is a 5- or 6-membered ring, which may be aromatic or non-aromatic, optionally containing one to four heteroatoms (preferably selected from nitrogen, oxygen and sulfur);

- 10 either ring A and/or ring B may be optionally substituted by one or more substituents selected from: halo, C₁₋₆ alkyl (optionally substituted by one or more halo, e.g. fluoro atoms) and/or -OC₁₋₆alkyl (itself optionally substituted by one or more fluoro atoms),

or a pharmaceutically-acceptable salt thereof,

- 15 which compounds may be referred to herein as "compounds of the invention".

Pharmaceutically-acceptable salts include acid addition salts and base addition salts.

- Such salts may be formed by conventional means, for example by reaction of a free acid or a free base form of a compound of formula I with one or more equivalents of an
20 appropriate acid or base, optionally in a solvent, or in a medium in which the salt is insoluble, followed by removal of said solvent, or said medium, using standard techniques (e.g. *in vacuo*, by freeze-drying or by filtration). Salts may also be prepared by exchanging a counter-ion of a compound of the invention in the form of a salt with another counter-ion, for example using a suitable ion exchange resin.

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The pharmaceutically acceptable acid addition salts as mentioned hereinabove are meant to comprise the therapeutically active non-toxic acid addition salt forms that the compounds of formula (I) are able to form. These pharmaceutically acceptable acid addition salts can conveniently be obtained by treating the base form with such
30 appropriate acid. Appropriate acids comprise, for example, inorganic acids such as hydrohalic acids, e.g. hydrochloric or hydrobromic acid, sulfuric, nitric, phosphoric and the like acids; or organic acids such as, for example, acetic, propanoic, hydroxyacetic, lactic, pyruvic, oxalic (*i.e.* ethanedioic), malonic, succinic (*i.e.* butanedioic acid), maleic, fumaric, malic, tartaric, citric, methanesulfonic, ethanesulfonic,
35 benzenesulfonic, *p*-toluenesulfonic, cyclamic, salicylic, *p*-aminosalicylic, pamoic and the like acids.

For the purposes of this invention solvates, prodrugs, N-oxides and stereoisomers of compounds of the invention are also included within the scope of the invention.

5 The term "prodrug" of a relevant compound of the invention includes any compound that, following oral or parenteral administration, is metabolised *in vivo* to form that compound in an experimentally-detectable amount, and within a predetermined time (e.g. within a dosing interval of between 6 and 24 hours (i.e. once to four times daily)). For the avoidance of doubt, the term "parenteral" administration includes all forms of administration other than oral administration.

10

Prodrugs of compounds of the invention may be prepared by modifying functional groups present on the compound in such a way that the modifications are cleaved, *in vivo* when such prodrug is administered to a mammalian subject. The modifications typically are achieved by synthesising the parent compound with a prodrug substituent.

15

Prodrugs include compounds of the invention wherein a hydroxyl, amino, sulfhydryl, carboxy or carbonyl group in a compound of the invention is bonded to any group that may be cleaved *in vivo* to regenerate the free hydroxyl, amino, sulfhydryl, carboxy or carbonyl group, respectively.

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Examples of prodrugs include, but are not limited to, esters and carbamates of hydroxy functional groups, esters groups of carboxyl functional groups, N-acyl derivatives and N-Mannich bases. General information on prodrugs may be found e.g. in Bundegaard, H. "Design of Prodrugs" p. 1-92, Elsevier, New York-Oxford (1985).

25

Compounds of the invention may contain double bonds and may thus exist as *E* (*entgegen*) and *Z* (*zusammen*) geometric isomers about each individual double bond. Positional isomers may also be embraced by the compounds of the invention. All such isomers (e.g. if a compound of the invention incorporates a double bond or a fused ring, the *cis*- and *trans*- forms, are embraced) and mixtures thereof are included within the scope of the invention (e.g. single positional isomers and mixtures of positional isomers may be included within the scope of the invention).

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Compounds of the invention may also exhibit tautomerism. All tautomeric forms (or tautomers) and mixtures thereof are included within the scope of the invention. The term "tautomer" or "tautomeric form" refers to structural isomers of different energies which are interconvertible *via* a low energy barrier. For example, proton tautomers (also known as prototropic tautomers) include interconversions *via* migration of a

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proton, such as keto-enol and imine-enamine isomerisations. Valence tautomers include interconversions by reorganisation of some of the bonding electrons.

Compounds of the invention may also contain one or more asymmetric carbon atoms and may therefore exhibit optical and/or diastereoisomerism. Diastereoisomers may be separated using conventional techniques, e.g. chromatography or fractional crystallisation. The various stereoisomers may be isolated by separation of a racemic or other mixture of the compounds using conventional, e.g. fractional crystallisation or HPLC, techniques. Alternatively the desired optical isomers may be made by reaction of the appropriate optically active starting materials under conditions which will not cause racemisation or epimerisation (i.e. a 'chiral pool' method), by reaction of the appropriate starting material with a 'chiral auxiliary' which can subsequently be removed at a suitable stage, by derivatisation (i.e. a resolution, including a dynamic resolution), for example with a homochiral acid followed by separation of the diastereomeric derivatives by conventional means such as chromatography, or by reaction with an appropriate chiral reagent or chiral catalyst all under conditions known to the skilled person.

All stereoisomers (including but not limited to diastereoisomers, enantiomers and atropisomers) and mixtures thereof (e.g. racemic mixtures) are included within the scope of the invention.

In the structures shown herein, where the stereochemistry of any particular chiral atom is not specified, then all stereoisomers are contemplated and included as the compounds of the invention. Where stereochemistry is specified by a solid wedge or dashed line representing a particular configuration, then that stereoisomer is so specified and defined.

The compounds of the present invention may exist in unsolvated as well as solvated forms with pharmaceutically acceptable solvents such as water, ethanol, and the like, and it is intended that the invention embrace both solvated and unsolvated forms.

The present invention also embraces isotopically-labeled compounds of the present invention which are identical to those recited herein, but for the fact that one or more atoms are replaced by an atom having an atomic mass or mass number different from the atomic mass or mass number usually found in nature (or the most abundant one found in nature). All isotopes of any particular atom or element as specified herein are contemplated within the scope of the compounds of the invention. Exemplary isotopes

that can be incorporated into compounds of the invention include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorus, sulfur, fluorine, chlorine and iodine, such as ^2H , ^3H , ^{11}C , ^{13}C , ^{14}C , ^{13}N , ^{15}O , ^{17}O , ^{18}O , ^{32}P , ^{33}P , ^{35}S , ^{18}F , ^{36}Cl , ^{123}I , and ^{125}I . Certain isotopically-labeled compounds of the present invention (e.g., those labeled with ^3H and ^{14}C) are useful in compound and for substrate tissue distribution assays. Tritiated (^3H) and carbon-14 (^{14}C) isotopes are useful for their ease of preparation and detectability. Further, substitution with heavier isotopes such as deuterium (i.e., ^2H) may afford certain therapeutic advantages resulting from greater metabolic stability (e.g., increased *in vivo* half-life or reduced dosage requirements) and hence may be preferred in some circumstances. Positron emitting isotopes such as ^{15}O , ^{13}N , ^{11}C and ^{18}F are useful for positron emission tomography (PET) studies to examine substrate receptor occupancy. Isotopically labeled compounds of the present invention can generally be prepared by following procedures analogous to those disclosed in the Scheme 1 and/or in the Examples herein below, by substituting an isotopically labeled reagent for a non-isotopically labeled reagent.

Unless otherwise specified, C_{1-q} alkyl groups (where q is the upper limit of the range) defined herein may be straight-chain or, when there is a sufficient number (i.e. a minimum of two or three, as appropriate) of carbon atoms, be branched-chain, and/or cyclic (so forming a C_{3-q} -cycloalkyl group). Such cycloalkyl groups may be monocyclic or bicyclic and may further be bridged. Further, when there is a sufficient number (i.e. a minimum of four) of carbon atoms, such groups may also be part cyclic. Such alkyl groups may also be saturated or, when there is a sufficient number (i.e. a minimum of two) of carbon atoms, be unsaturated (forming, for example, a C_{2-q} alkenyl or a C_{2-q} alkynyl group).

C_{3-q} cycloalkyl groups (where q is the upper limit of the range) that may be specifically mentioned may be monocyclic or bicyclic alkyl groups, which cycloalkyl groups may further be bridged (so forming, for example, fused ring systems such as three fused cycloalkyl groups). Such cycloalkyl groups may be saturated or unsaturated containing one or more double bonds (forming for example a cycloalkenyl group). Substituents may be attached at any point on the cycloalkyl group. Further, where there is a sufficient number (i.e. a minimum of four) such cycloalkyl groups may also be part cyclic.

The term "halo", when used herein, preferably includes fluoro, chloro, bromo and iodo.

Heterocyclic groups when referred to herein may include aromatic or non-aromatic heterocyclic groups, and hence encompass heterocycloalkyl and heteroaryl. Equally, "aromatic or non-aromatic 5- or 6-membered rings" may be heterocyclic groups (as well as carbocyclic groups) that have 5- or 6-members in the ring.

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- Heterocycloalkyl groups that may be mentioned include non-aromatic monocyclic and bicyclic heterocycloalkyl groups in which at least one (e.g. one to four) of the atoms in the ring system is other than carbon (i.e. a heteroatom), and in which the total number of atoms in the ring system is between 3 and 20 (e.g. between three and ten, e.g. between 3 and 8, such as 5- to 8-). Such heterocycloalkyl groups may also be bridged. Further, such heterocycloalkyl groups may be saturated or unsaturated containing one or more double and/or triple bonds, forming for example a C_{2-q} heterocycloalkenyl (where q is the upper limit of the range) group. C_{2-q} heterocycloalkyl groups that may be mentioned include 7-azabicyclo[2.2.1]heptanyl, 6-azabicyclo[3.1.1]heptanyl, 10 6-azabicyclo[3.2.1]octanyl, 8-azabicyclo-[3.2.1]octanyl, aziridinyl, azetidiny, dihydropyranyl, dihydropyridyl, dihydropyrrolyl (including 2,5-dihydropyrrolyl), dioxolanyl (including 1,3-dioxolanyl), dioxanyl (including 1,3-dioxanyl and 1,4-dioxanyl), dithianyl (including 1,4-dithianyl), dithiolanyl (including 1,3-dithiolanyl), imidazolidinyl, imidazolinyl, morpholinyl, 7-oxabicyclo[2.2.1]- 15 heptanyl, 6-oxabicyclo-[3.2.1]octanyl, oxetanyl, oxiranyl, piperazinyl, piperidinyl, non-aromatic pyranyl, pyrazolidinyl, pyrrolidinonyl, pyrrolidinyl, pyrrolinyl, quinuclidinyl, sulfolanyl, 3-sulfolenyl, tetrahydropyranyl, tetrahydrofuranyl, tetrahydropyridyl (such as 1,2,3,4-tetrahydropyridyl and 1,2,3,6-tetrahydropyridyl), thietanyl, thiiranyl, thiolanyl, thiomorpholinyl, trithianyl (including 1,3,5-trithianyl), tropanyl and the like. 20 Substituents on heterocycloalkyl groups may, where appropriate, be located on any atom in the ring system including a heteroatom. The point of attachment of heterocycloalkyl groups may be *via* any atom in the ring system including (where appropriate) a heteroatom (such as a nitrogen atom), or an atom on any fused carbocyclic ring that may be present as part of the ring system. Heterocycloalkyl 25 groups may also be in the *N*- or *S*- oxidised form. Heterocycloalkyl mentioned herein may be stated to be specifically monocyclic or bicyclic. 30

- Aryl groups that may be mentioned include C_{6-20} , such as C_{6-12} (e.g. C_{6-10}) aryl groups. Such groups may be monocyclic, bicyclic or tricyclic and have between 6 and 12 (e.g. 35 6 and 10) ring carbon atoms, in which at least one ring is aromatic. C_{6-10} aryl groups include phenyl, naphthyl and the like, such as 1,2,3,4-tetrahydronaphthyl. The point of attachment of aryl groups may be *via* any atom of the ring system. For example, when the aryl group is polycyclic the point of attachment may be *via* atom including an atom

of a non-aromatic ring. However, when aryl groups are polycyclic (e.g. bicyclic or tricyclic), they are preferably linked to the rest of the molecule *via* an aromatic ring. Most preferred aryl groups that may be mentioned herein are "phenyl".

- 5 Unless otherwise specified, the term "heteroaryl" when used herein refers to an aromatic group containing one or more heteroatom(s) (e.g. one to four heteroatoms) preferably selected from N, O and S. Heteroaryl groups include those which have between 5 and 20 members (e.g. between 5 and 10) and may be monocyclic, bicyclic or tricyclic, provided that at least one of the rings is aromatic (so forming, for example, a mono-, bi-, or tricyclic heteroaromatic group). When the heteroaryl group is polycyclic the point of attachment may be *via* any atom including an atom of a non-aromatic ring. However, when heteroaryl groups are polycyclic (e.g. bicyclic or tricyclic), they are preferably linked to the rest of the molecule *via* an aromatic ring. Heteroaryl groups that may be mentioned include 3,4-dihydro-1*H*-isoquinolinyl, 1,3-dihydroisoindolyl, 1,3-dihydroisoindolyl (e.g. 3,4-dihydro-1*H*-isoquinolin-2-yl, 1,3-dihydroisoindol-2-yl, 1,3-dihydroisoindol-2-yl; i.e. heteroaryl groups that are linked *via* a non-aromatic ring), or, preferably, acridinyl, benzimidazolyl, benzodioxanyl, benzodioxepinyl, benzodioxolyl (including 1,3-benzodioxolyl), benzofuranyl, benzofurazanyl, benzothiadiazolyl (including 2,1,3-benzothiadiazolyl), benzothiazolyl, benzoxadiazolyl (including 2,1,3-benzoxadiazolyl), benzoxazinyl (including 3,4-dihydro-2*H*-1,4-benzoxazinyl), benzoxazolyl, benzomorpholinyl, benzoselenadiazolyl (including 2,1,3-benzoselenadiazolyl), benzothienyl, carbazolyl, chromanyl, cinnolinyl, furanyl, imidazolyl, imidazo[1,2-*a*]pyridyl, indazolyl, indolinyl, indolyl, isobenzofuranyl, isochromanyl, isoindolinyl, isoindolyl, isoquinolinyl, isothiazolyl, isothiochromanyl, isoxazolyl, naphthyridinyl (including 1,6-naphthyridinyl or, preferably, 1,5-naphthyridinyl and 1,8-naphthyridinyl), oxadiazolyl (including 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl and 1,3,4-oxadiazolyl), oxazolyl, phenazinyl, phenothiazinyl, phthalazinyl, pteridinyl, purinyl, pyranyl, pyrazinyl, pyrazolyl, pyridazinyl, pyridyl, pyrimidinyl, pyrrolyl, quinazolinyl, quinolinyl, quinolizinyl, quinoxalinyl, tetrahydroisoquinolinyl (including 1,2,3,4-tetrahydroisoquinolinyl and 5,6,7,8-tetrahydroisoquinolinyl), tetrahydroquinolinyl (including 1,2,3,4-tetrahydroquinolinyl and 5,6,7,8-tetrahydroquinolinyl), tetrazolyl, thiadiazolyl (including 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl and 1,3,4-thiadiazolyl), thiazolyl, thiochromanyl, thiophenetyl, thienyl, triazolyl (including 1,2,3-triazolyl, 1,2,4-triazolyl and 1,3,4-triazolyl) and the like. Substituents on heteroaryl groups may, where appropriate, be located on any atom in the ring system including a heteroatom. The point of attachment of heteroaryl groups may be *via* any atom in the ring system including (where appropriate) a heteroatom (such as a nitrogen atom), or an atom on

any fused carbocyclic ring that may be present as part of the ring system. Heteroaryl groups may also be in the *N*- or *S*- oxidised form. Heteroaryl groups mentioned herein may be stated to be specifically monocyclic or bicyclic. When heteroaryl groups are polycyclic in which there is a non-aromatic ring present, then that non-aromatic ring may be substituted by one or more =O group. Most preferred heteroaryl groups that may be mentioned herein are 5- or 6-membered aromatic groups containing 1, 2 or 3 heteroatoms (e.g. preferably selected from nitrogen, oxygen and sulfur).

It may be specifically stated that the heteroaryl group is monocyclic or bicyclic. In the case where it is specified that the heteroaryl is bicyclic, then it may consist of a five-, six- or seven-membered monocyclic ring (e.g. a monocyclic heteroaryl ring) fused with another five-, six- or seven-membered ring (e.g. a monocyclic aryl or heteroaryl ring).

Heteroatoms that may be mentioned include phosphorus, silicon, boron and, preferably, oxygen, nitrogen and sulfur.

When "aromatic" groups are referred to herein, they may be aryl or heteroaryl. When "aromatic linker groups" are referred to herein, they may be aryl or heteroaryl, as defined herein, any may be monocyclic or polycyclic (e.g. bicyclic) and attached to the remainder of the molecule *via* any possible atoms of that linker group. However, it may specifically be mentioned that the linker group is a heteroaromatic linker group, in which case such a moiety is aromatic and has to contain at least one heteroatom.

For the avoidance of doubt, where it is stated herein that a group may be substituted by one or more substituents (e.g. selected from C₁₋₆ alkyl), then those substituents (e.g. alkyl groups) are independent of one another. That is, such groups may be substituted with the same substituent (e.g. same alkyl substituent) or different (e.g. alkyl) substituents.

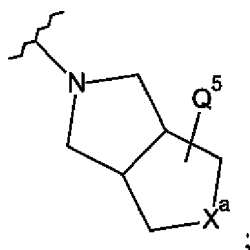
For the avoidance of doubt, where Q⁵ is mentioned herein, this represents one or more optional substituents on the bicycle to which it is attached, and such optional substituents may be situated on either (or both) rings of such bicycle (i.e. the N-containing 5-membered ring and/or the X^a-containing ring).

All individual features (e.g. preferred features) mentioned herein may be taken in isolation or in combination with any other feature (including preferred feature) mentioned herein (hence, preferred features may be taken in conjunction with other preferred features, or independently of them).

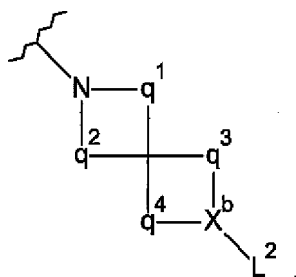
The skilled person will appreciate that compounds of the invention that are the subject of this invention include those that are stable. That is, compounds of the invention include those that are sufficiently robust to survive isolation from e.g. a reaction mixture to a useful degree of purity.

Compounds of the invention that may be mentioned include in which:
 R^2 and R^3 :

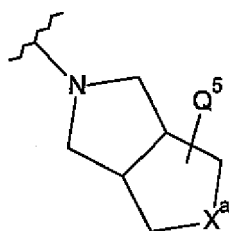
- (i) independently represent hydrogen or, preferably, C_{1-6} alkyl optionally substituted by one or more substituents selected from Q^1 and $=O$;
- (ii) independently represent aryl or heteroaryl, each of which is optionally substituted by one or more substituents selected from Q^2 ;
- (iii) independently represent cycloalkyl or heterocycloalkyl, each of which is optionally substituted by one or more substituents selected from Q^3 and $=O$;
- or
- (iv) can be linked together to form:
 - a. a 3- to 8-membered ring optionally containing one to three heteroatoms (e.g. nitrogen, oxygen and/or sulfur), and which ring is optionally substituted by one or more substituents selected from Q^4 and $=O$;
 - b. a "fused" bicyclic ring of the following type:



- c. a "spiro" ring of the following type:



Hence, in an aspect, when R^2 and R^3 are linked together to form a "fused" bicyclic ring, it is of the following type:



i.e. n1 and n2 independently represent 1.

In two different aspects of the invention:

- 5 - n1 and n2 both represent 1;
 - n1 and n2 both represent 0.

Certain (e.g. preferred) aspects of compounds of the invention include those in which:
 R^e represents hydrogen;

- 10 R^d represents hydrogen;

L¹ preferably represents a linker group as defined by -C(R^a)(R^b)-;

X^c (which is attached to X^a) is either not present, or, when X^a represents CH, then X^c may also represent -O-;

- 15 X^d is either not present, or, when n1 represents 2 or when X^c is not present, X^a represents C(R^e) and n1 represents 1, then X^d may also represent -O-;
 X^e and X^f independently are either not present, or may independently represent -O-, provided that the aforementioned oxygen atom is not directly attached to or α to another heteroatom;

- 20 when X^c and/or X^d represent -O-, -NH- or -S-, it is understood that such heteroatoms may not be attached directly (or α to) to another heteroatom.

More preferred compounds of the invention include those in which:

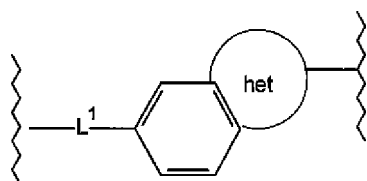
R¹ represents hydrogen;

R^a and R^b independently represent hydrogen;

- 25 L¹ represents -CH₂-;

when X¹ represents a heteroaromatic linker group (where the point of attachment may be *via* any atom of the ring system), then it in a major aspect of the invention:

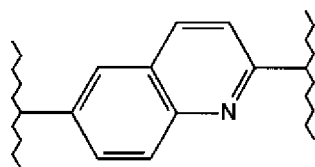
- 30 - it is a bicyclic heteroaromatic linker group;
 - it is a bicyclic heteroaromatic group linked to L¹ (or the amido moiety, when L¹ is not present) via a carbocyclic aromatic moiety, so forming e.g.:



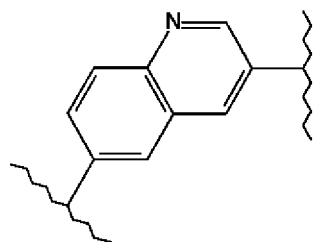
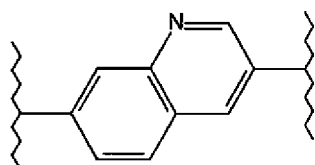
in which "het" (in the above instance) is a heteroaromatic 5- or 6-membered ring;

- 5 - a fused bicyclic ring system comprising a phenyl and/or a 5- or 6-membered monocyclic heteroaryl group (for instance forming a 9- or 10-membered heteroaromatic group, which consists of two separate rings fused with each other, in which each ring is 5- or 6-membered so forming a 6,6- or 6,5- or fused bicyclic ring), hence including groups such as those described below:

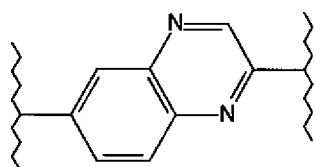
-quinolylene (such as 2-quinolylene or 3-quinolylene), e.g.:



10



-quinoxaliny (such as 2-quinolylene), e.g.:



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- such heteroaromatic linker groups may be optionally substituted by one or more substituents as defined herein. In an aspect, the heteroaromatic linker group is not substituted or is only substituted (where possible) on a heteroatom (e.g. on a

nitrogen heteroatom) – in which case it remains unsubstituted on the carbon atoms. In an aspect, the points of attachment of the linker group are via distal atoms, for instance atoms that as far apart as possible (e.g. in a bicycle of 10 members, those atoms in a 2- and 6- position (or 3- and 7-position) but in another aspect, they are not necessarily the atoms the furthest apart (e.g. in a 10-membered bicycle, the atoms linked to the rest of the molecule has be the 3- and 6-atoms too).

When X^1 represents $-N(R^2)(R^3)$, then:

- 10 (i) R^2 and R^3 independently represent C_{1-3} alkyl (e.g. methyl or ethyl) optionally substituted by one or more (e.g. one) substituent(s) selected from Q^1 ;
- (ii) R^2 and R^3 are linked together to form:
 - 15 a. a 4- to 6-membered ring optionally containing one further heteroatom (e.g. so forming a piperidinyl, piperazinyl or azetidinyl ring), which is optionally (and, in an aspect, preferably) substituted by by one or more (e.g. one or two) substituents selected from Q^4 (in one aspect, e.g. when Q^4 represents an aromatic substituent, then there is only one Q^4 substituent present; in another aspect, e.g. when Q^4 represents a non-aromatic substituent, e.g. fluoro, then one or two Q^4 substituents may be present);
 - 20 b. a fused bicyclic ring in which X^a represents $-CH_2-$ and which is optionally substituted (e.g. at the X^a position) by one or more (e.g. one) Q^5 substituent(s);
 - 25 c. a spiro ring system, in which X^b represents CH and L^2 is present and as defined herein.

Q^1 represents aryl (e.g. phenyl) optionally substituted by e.g. $-OC_{1-3}$ alkyl (itself optionally substituted by one or more fluoro atoms, so forming e.g. a $-OCF_3$ group);

30 Q^4 represents aryl (e.g. phenyl) optionally substituted by e.g. $-OC_{1-3}$ alkyl (itself optionally substituted by one or more fluoro atoms, so forming e.g. a $-OCF_3$ group) or, in another aspect, Q^4 represents fluoro (e.g. two fluoro atoms substituted at the same carbon atom);

Q^5 represents halo (e.g. fluoro);

35 X^c , X^d , X^e and X^f are independently not present;

$n1$ and $n2$ independently represent 1;

X^g , X^h , X^i and X^j are independently not present;

$n3$ and $n4$ independently represent 1;

L^2 represents a fluoro substituent or, in another aspect, an aromatic group (e.g. aryl or phenyl) optionally substituted by one or more (e.g. one) substituent(s) e.g. selected from e.g. $-OC_{1-3}alkyl$ (itself optionally substituted by one or more fluoro atoms, so forming e.g. a $-OCF_3$ group).

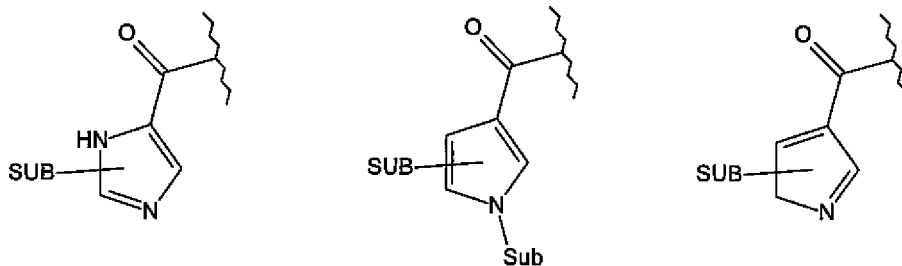
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It is preferred that compounds of the invention comprise:

ring A, which is an aromatic ring containing at least one to three (e.g. one or two) heteroatoms, preferably contains at least one nitrogen atom;

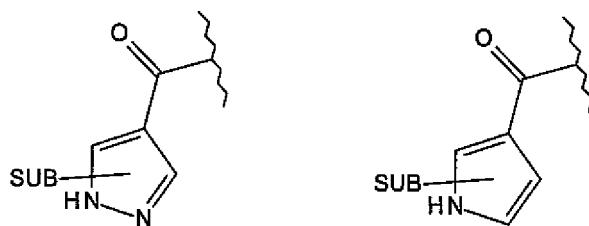
10 ring B is more preferably also an aromatic ring (e.g. a 5- or especially a 6-membered aromatic ring), preferably containing at least one nitrogen atom.

It is preferred that Ring A of the compounds of the invention are represented as follows:



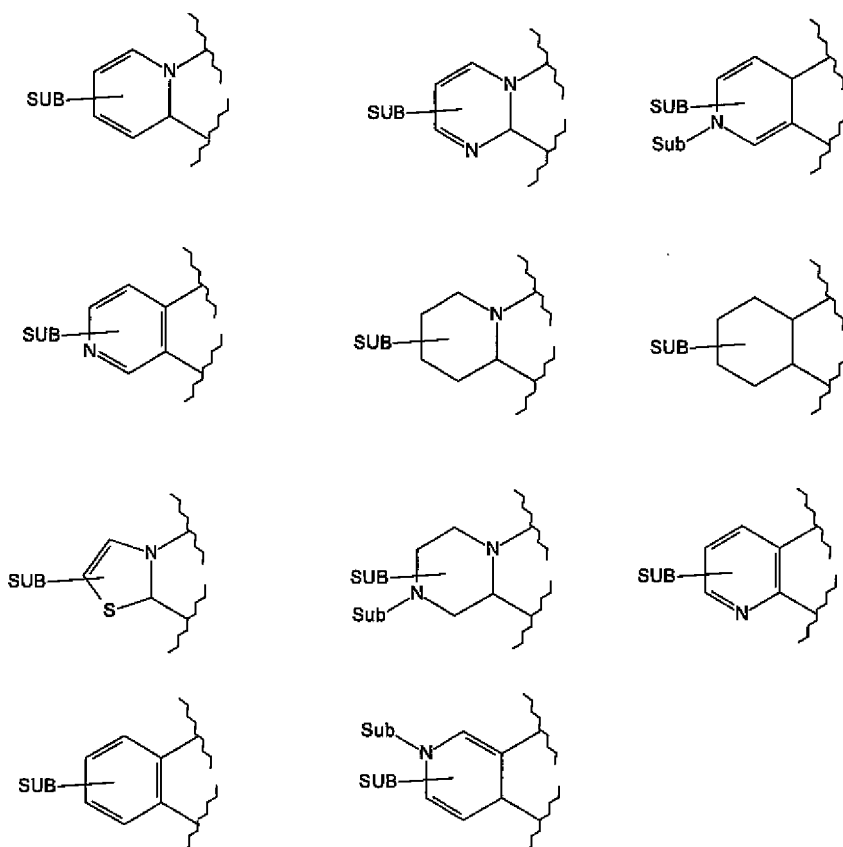
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Other preferred ring A moieties include:



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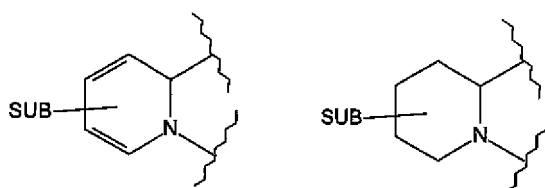
Monocyclic heteroaryl groups that may be mentioned include 5- or 6-membered rings containing one to four heteroatoms (preferably selected from nitrogen, oxygen and sulfur). It is preferred that Ring B of the compounds of the invention are represented as follows:



where "SUB" may be a relevant optional substituent (or more than when relevant substituent, where possible) on a carbon atom or, where possible, on a heteroatom e.g. on a NH, thus replacing the H.

5

Other preferred "Ring B" moieties include:

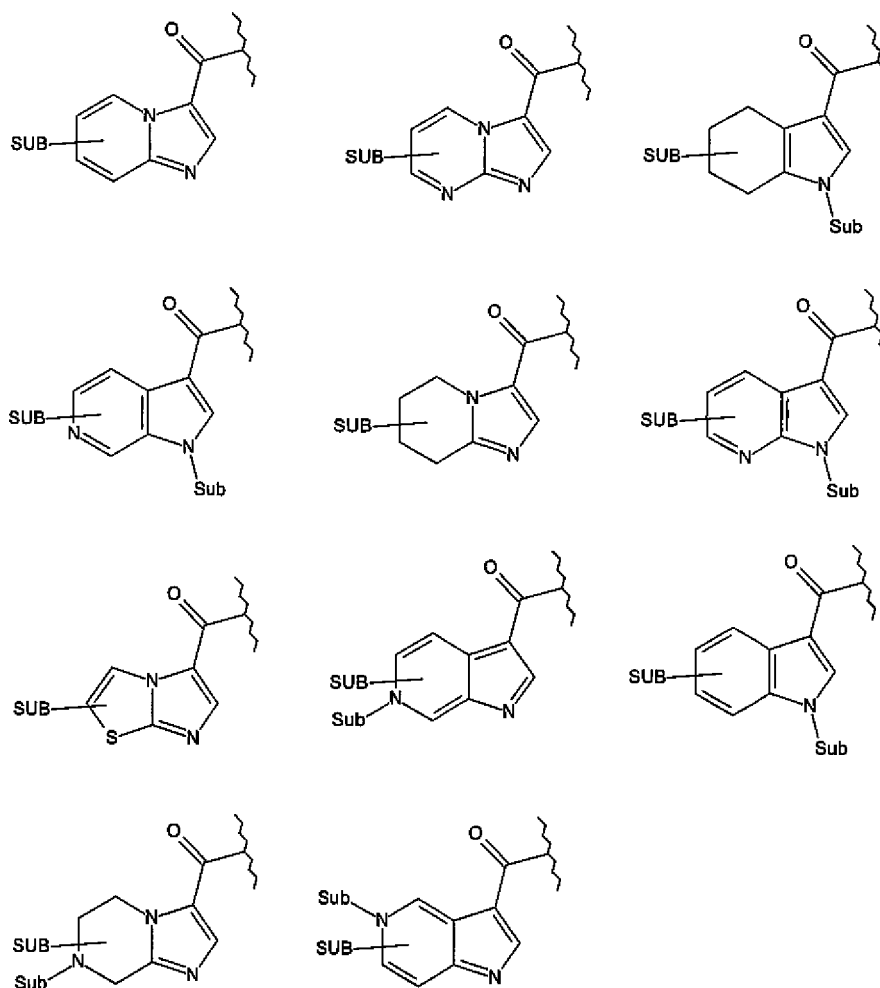


Preferred substituents (when present; e.g such optional substituents may be absent or there may be one) on ring B include C_{1-3} alkyl (e.g. methyl) or halo (e.g. bromo or, more preferably, chloro). Other preferred substituents on ring B include $-OC_{1-6}$ alkyl (e.g. $-OC_{1-3}$ alkyl, such as $-OCH_3$).

Preferred substituents (when present; e.g such optional substituents may be absent or there may be one) on ring B include C_{1-3} alkyl (e.g. methyl) or halo (e.g. bromo or,

more preferably, chloro). Preferred substituents (when present; preferably, there may be one or two substituents) on ring A include C₁₋₃ alkyl (e.g. methyl or ethyl). When L² represents an aromatic group (e.g. phenyl or pyridyl) and such groups are substituted, preferred substituents include halo and especially -OC₁₋₃ alkyl (e.g. -O-methyl), where the latter is substituted by fluoro, so forming for example a -OCF₃ group.

The combined ring systems, i.e. Ring A and Ring B may be represented as follows:

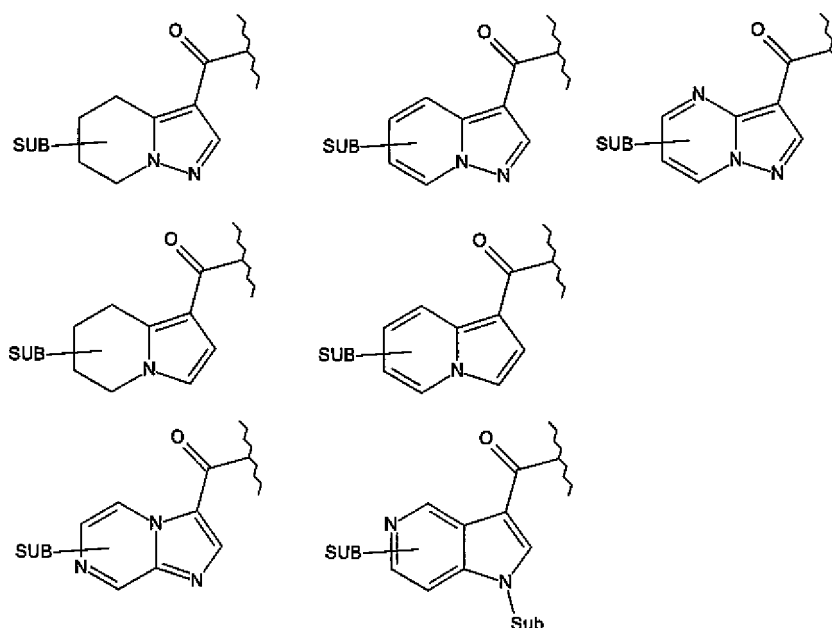


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where "SUB" represents one or more possible substituents on the bicycle (i.e. on ring A and/or on ring B) and "Sub" represents a possible optional substituent on the N atom of the bicycle (unsubstituted in this context would mean "NH").

Other combined ring A and ring B systems that may be mentioned include the following:

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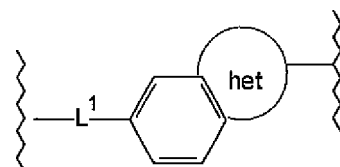


Certain compounds of the invention are mentioned (e.g. hereinbefore) for use in the treatment of tuberculosis. Certain of such compounds mentioned herein may also be novel *per se*. And certain of such compounds mentioned herein may be novel as medicaments/pharmaceuticals (or novel as a component of a pharmaceutical composition/formulation). Hence, in further aspects of the invention, there is provided the following compounds *per se* or following compounds for use as pharmaceuticals/medicaments (in the latter case such compounds may be components of a pharmaceutical composition/formulation):

(I) Compounds of formula (I) as hereinbefore defined and in which:

L^1 represents $-CH_2-$;

Het represents a bicyclic heteroaromatic group linked to L^1 (or the amido moiety, when L^1 is not present) via a carbocyclic aromatic moiety, so forming e.g.:



in which "het" (in the above instance) is a heteroaromatic 5- or 6-membered ring;

when X^1 represents $-N(R^2)(R^3)$, then:

(i) R^2 and R^3 independently represent C_{1-3} alkyl (e.g. methyl or ethyl) optionally substituted by one or more (e.g. one) substituent(s)

selected from Q^1 (but wherein when both R^2 and R^3 represent alkyl, then at least one is substituted by Q^1 in which Q^1 represents an optionally substituted aryl group as defined herein);

(ii) R^2 and R^3 are linked together to form:

- 5 a. a 4- to 6-membered ring optionally containing one further heteroatom (e.g. so forming a piperidinyl, piperazinyl or azetidiny ring), which is substituted by one or two substituents selected from Q^4 (in which at least one Q^4 substituent is present that represents an optionally substituted
- 10 aryl group as defined herein);
- b. a fused bicyclic ring in which X^a represents $-CH_2-$ and which is optionally substituted (e.g. at the X^a position) by one or more (e.g. one) Q^5 substituent(s);
- c. a spiro ring system, in which X^b represents CH and L^2 is present
- 15 and as defined herein;

when Q^1 represents aryl, then it is an optionally substituted as defined herein (e.g. by one or more substituents selected from $-OC_{1-3}alkyl$ (itself optionally substituted by one or more fluoro atoms, so forming e.g. a $-OCF_3$ group));

when Q^4 represents aryl, then it is an optionally substituted phenyl as defined herein (e.g. by one or more substituents selected from $-OC_{1-3}alkyl$ (itself optionally substituted by one or more fluoro atoms, so forming e.g. a $-OCF_3$ group));

when Q^4 represents a non-aromatic substituent, then it may represent e.g. fluoro;

Q^5 represents halo (e.g. fluoro);

X^c , X^d , X^e and X^f are independently not present;

$n1$ and $n2$ independently represent 1;

X^g , X^h , X^i and X^j are independently not present;

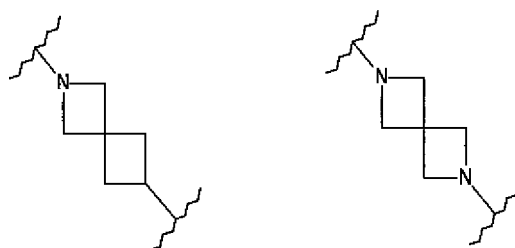
$n3$ and $n4$ independently represent 1;

L^2 represents an aromatic group (e.g. aryl or phenyl) optionally substituted by one or more (e.g. one) substituent(s) e.g. selected from e.g. $-OC_{1-3}alkyl$ (itself optionally substituted by one or more fluoro atoms, so forming e.g. a $-OCF_3$ group);

ring A and ring B together represent a 8 or 9-membered bicyclic ring (ring A is a 5-membered ring and ring B may be a 5 or 6-membered ring, in which both rings are preferably aromatic) containing at least one nitrogen atom (and in a major embodiment, at least one nitrogen atom that is common to both rings);

optional substituents on ring A and ring B are halo, C₁₋₃ alkyl and -OC₁₋₃alkyl; and
other integers are as defined herein;

- 5 (II) Compounds as hereinbefore defined (e.g. at (I) above) and further in which the X^b-containing rings are represented as defined herein or more particularly as follows:

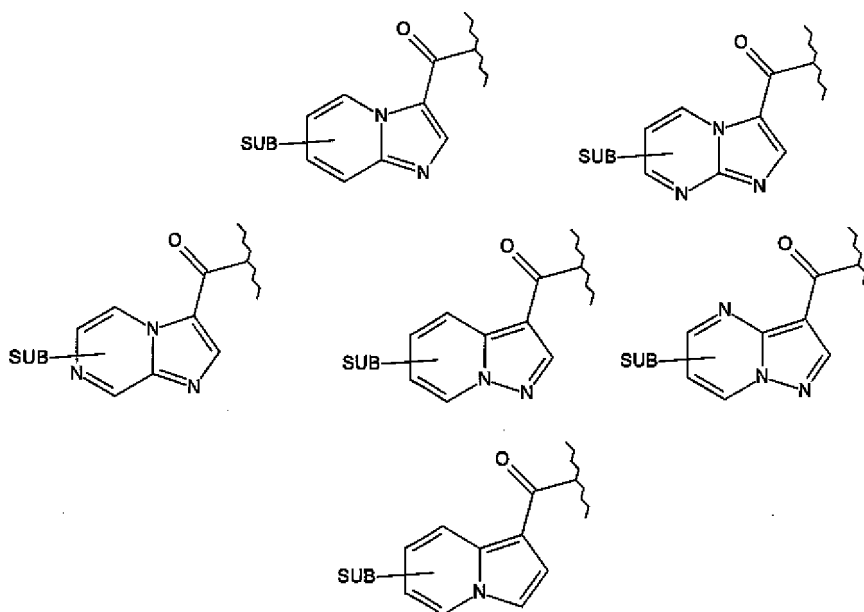


(or any one of the above-mentioned representations); and/or

10

- (III) Compounds as hereinbefore defined (e.g. at (I) and/or (II) above) and further in which the ring A and ring B bicycles are represented as defined herein or more particularly as follows:

15



(or any one of the above-mentioned representations).

In an embodiment (e.g. in aspect (I) mentioned above), R^2 and R^3 may represent either (i) or (ii) mentioned herein. When R^2 and R^3 represent (ii), then they may represent either a, b or c as defined in the sub-definitions (e.g. in aspect (I) above).

5 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). The present
10 invention thus also relates to compounds of the invention as defined hereinabove, for use as a medicine, in particular for use as a medicine for the treatment of a bacterial infection including a mycobacterial infection.

Such compounds of the invention may act by interfering with ATP synthase in *M.*
15 *tuberculosis*, with the inhibition of cytochrome bc_1 activity being the primary mode of action. Cytochrome bc_1 is an essential component of the electron transport chain required for ATP synthesis.

Further, the present invention also relates to the use of a compound of the invention, as
20 well as any of the pharmaceutical compositions thereof as described hereinafter for the manufacture of a medicament for the treatment of a bacterial infection including a mycobacterial infection.

Accordingly, in another aspect, the invention provides a method of treating a patient
25 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.

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

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 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 the invention 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 compound according to the invention, and (b) one or more other antibacterial agents, as
- 15 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 the invention are for example antibacterial agents known in the art. For example, the compounds of the invention may be combined with antibacterial agents known to interfere with the respiratory chain of *Mycobacterium tuberculosis*, including for example direct inhibitors of the ATP synthase (e.g. bedaquiline, bedaquiline fumarate or any other compounds that may have been disclosed in the prior art, e.g. compounds disclosed in WO2004/011436), inhibitors of *ndh2* (e.g. clofazimine) and inhibitors of cytochrome *bd*. Additional mycobacterial agents which may be combined with the compounds of the invention are for example rifampicin (=rifampin); isoniazid; pyrazinamide; amikacin; ethionamide; ethambutol; streptomycin; para-aminosalicylic acid; cycloserine; capreomycin; kanamycin; thioacetazone; PA-824; delamanid; quinolones/fluoroquinolones such as for example moxifloxacin, gatifloxacin, ofloxacin, ciprofloxacin, sparfloxacin; macrolides such as for example clarithromycin, amoxycillin with clavulanic acid; rifamycins; rifabutin; rifapentin; as well as others, which are currently being developed (but may not yet be on the market; see e.g. <http://www.newtbdugs.org/pipeline.php>).

GENERAL PREPARATION

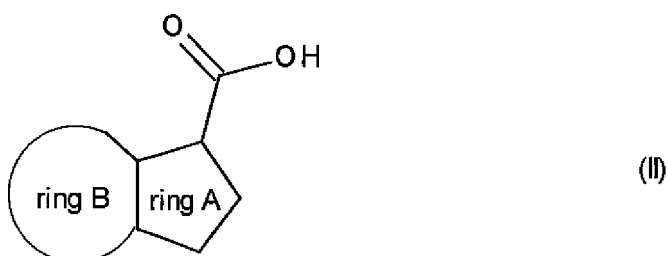
The compounds according to the invention can generally be prepared by a succession of steps, each of which may be known to the skilled person or described herein.

5 EXPERIMENTAL PART

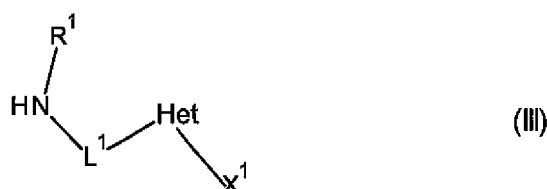
Compounds of formula I may be prepared in accordance with the techniques employed in the examples hereinafter (and those methods known by those skilled in the art), for example by using the following techniques.

Compounds of formula (I) may be prepared by:

- 10 (i) reaction of a compound of formula (II),



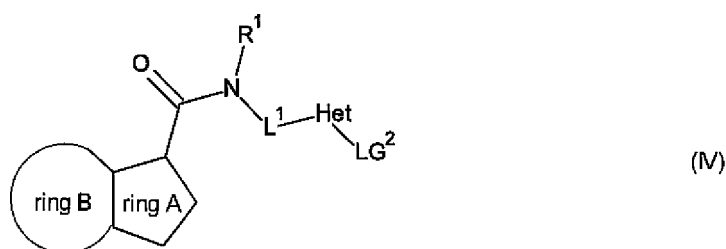
wherein the integers are as hereinbefore defined, or a suitable derivative thereof, such as a carboxylic acid ester derivative, with a compound of formula (III)



- 15 wherein the integers are as hereinbefore defined, under amide coupling reaction conditions, for example in the presence of a suitable coupling reagent (e.g. 1,1'-carbonyldiimidazole, *N,N'*-dicyclohexylcarbodiimide, 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (or hydrochloride thereof) or *N,N'*-disuccinimidyl carbonate), optionally in the presence of a suitable base (e.g. sodium hydride, sodium bicarbonate,
- 20 potassium carbonate, pyridine, triethylamine, dimethylaminopyridine, diisopropylamine, sodium hydroxide, potassium *tert*-butoxide and/or lithium diisopropylamide (or variants thereof) and an appropriate solvent (e.g. tetrahydrofuran, pyridine, toluene, dichloromethane, chloroform, acetonitrile, dimethylformamide, trifluoromethylbenzene, dioxane or triethylamine). Alternatively, the carboxylic acid

group of the compound of formula (IV) may first be converted under standard conditions to the corresponding acyl chloride (e.g. in the presence of POCl_3 , PCl_5 , SOCl_2 or oxalyl chloride), which acyl chloride is then reacted with a compound of formula (V), for example under similar conditions to those mentioned above;

- 5 (ii) coupling of a compound of formula (IV),



wherein the integers are as hereinbefore defined, and LG^2 represents a suitable leaving group, such as iodo, bromo, chloro or a sulfonate group (for example a type of group that may be deployed for a coupling), with a compound of formula (V),

10



wherein the integers are as hereinbefore defined, under standard conditions, for example optionally in the presence of an appropriate metal catalyst (or a salt or complex thereof) such as $\text{Pd}(\text{dba})_2$, $\text{Pd}(\text{OAc})_2$, Cu , $\text{Cu}(\text{OAc})_2$, CuI , NiCl_2 or the like, with an optional additive such as Ph_3P , X-phos or the like, in the presence of an appropriate base (e.g. t-BuONa , or the like) in a suitable solvent (e.g. dioxane or the like) under reaction conditions known to those skilled in the art.

15

Other steps that may be mentioned include:

- nucleophilic aromatic substitution reactions
- 20 - other coupling reactions e.g. in which one compound contains a suitable leaving group such as one described hereinbefore with respect to LG^2 (and may particularly represent chloro, bromo or iodo), with another compound comprising a mutually compatible "leaving group" or another suitable group such as $-\text{B}(\text{OH})_2$, $-\text{B}(\text{OR}^{\text{wx}})_2$ or $-\text{SN}(\text{R}^{\text{wx}})_3$, in which each R^{wx} independently represents a C_{1-6} alkyl group, or, in the case of $-\text{B}(\text{OR}^{\text{wx}})_2$, the respective R^{wx} groups may be linked together to form a 4- to 6-membered cyclic group, thereby forming e.g. a pinacolato boronate ester group (or may represent iodo, bromo or chloro, provided that the "leaving groups" are mutually compatible), and wherein the reaction may be performed in the presence of a suitable catalyst
- 25

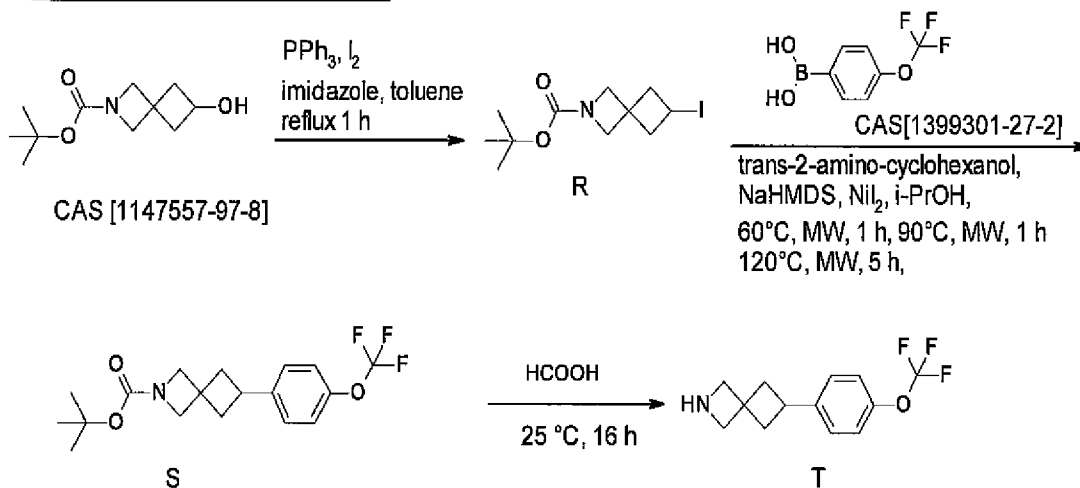
system, e.g. a metal (or a salt or complex thereof) such as Pd, CuI, Pd/C, PdCl₂, Pd(OAc)₂, Pd(Ph₃P)₂Cl₂, Pd(Ph₃P)₄, Pd₂(dba)₃ and/or NiCl₂ (or the like) and a ligand such as PdCl₂(dppf).DCM, t-Bu₃P, (C₆H₁₁)₃P, Ph₃P or the like, in a suitable solvent and under reaction conditions known to those skilled in the art.

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

- The starting materials and the intermediates are compounds that are either commercially available or may be prepared according to conventional reaction procedures generally known in the art.

Synthesis of Compound 1 and Compound 2

Synthesis of Intermediate T



Preparation of intermediate R

Triphenylphosphine (1.89 g, 7.20 mmol), imidazole (735 mg, 10.8 mmol) and iodine (1.37 g, 5.40 mmol) were added to a solution of tert-butyl 6-hydroxy-2-azaspiro[3.3]heptane-2-carboxylate (CAS [1147557-97-8], 768 mg, 3.60 mmol) in toluene (50 mL).

- 25 The resulting mixture was refluxed for 1 hour. The mixture was cooled to 25°C, washed with water (100 mL) and brine (50 mL). The separated organic layer was dried, filtered and the filtrate was concentrated under vacuum. The residue was purified by

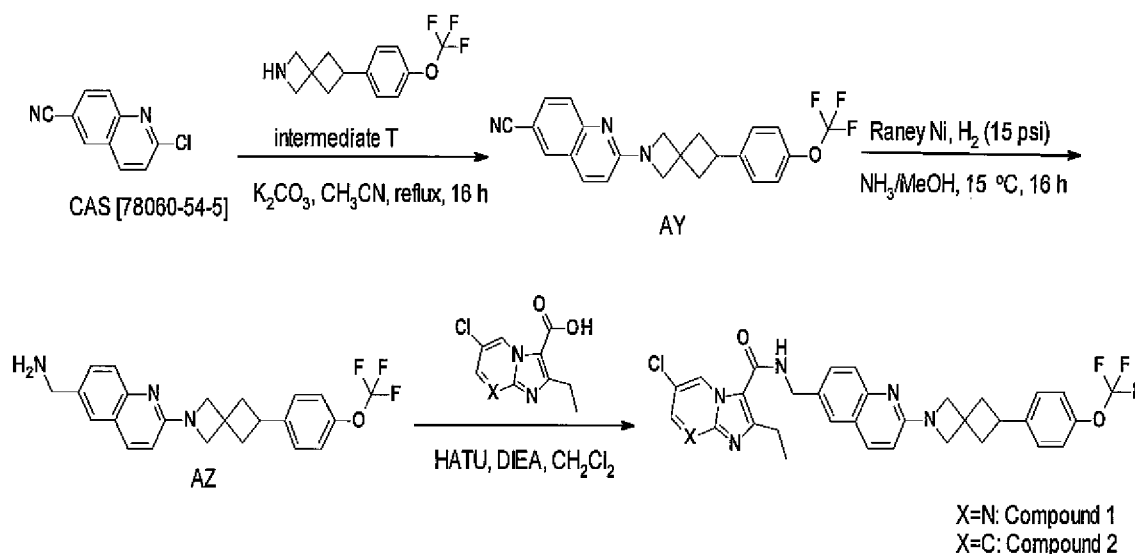
flash column chromatography over silica gel (eluent: petroleum ether/ethyl acetate 1/0 to 1/1) to give intermediate R (1.20 g, yield: 93%).

Preparation of intermediate S

- 5 A mixture of 4-(Trifluoromethoxy)phenylboronic acid (CAS [139301-27-2], 510 mg, 2.48 mmol), trans-2-amino-cyclohexanol (23.0 mg, 0.200 mmol) and nickel iodine (62.5 mg, 0.200 mmol) in isopropanol (4 mL) was stirred at 25 °C for 30 minutes under nitrogen flow. NaHMDS (2.47 mL, 1 M in THF, 2.47 mmol) was added, and the mixture was stirred for 10 minutes under nitrogen flow. Intermediate R (400 mg, 10 1.24 mmol) in isopropanol (1 mL) was added and the mixture was stirred at 60 °C under microwave for 1 hour, at 90 °C for 1 hour and at 120 °C for 5 hours. The mixture was diluted with dichloromethane (50 mL), washed with water (2x50 mL) and brine (20 mL). The organic layer was dried over sodium sulfate, filtered and concentrated under vacuum. The residue was purified by column chromatography over silica gel 15 (eluent: petroleum ether/ethyl acetate 5/1) to give intermediate S (230 mg, yield: 52%).

Preparation of intermediate T

- Intermediate S (220 mg, 0.616 mmol) was added to formic acid (5 mL) at 0 °C under nitrogen atmosphere. The mixture was stirred at 25 °C for 5 hours. The mixture was 20 concentrated under vacuum. The residue was dissolved into dichloromethane (20 mL). The solution was washed with saturated aqueous sodium carbonate solution (20 mL), brine (20 mL), dried over sodium sulfate, filtered and concentrated under vacuum to give Intermediate T (150 mg, yield: 85%).

Synthesis of Compound 1 and Compound 2**Preparation of intermediate AY**

- 5 A mixture of 2-chloro-6-quinolinecarbonitrile (CAS [78060-54-5], 14.7 mg, 0.078 mmol), Intermediate T (20.0 mg, 0.078 mmol) and potassium carbonate (21.6 mg, 0.156 mmol) in acetonitrile (5 mL) was refluxed for 16 hours. The solvent was evaporated under vacuum. The residue was purified by column chromatography over silica gel (eluent: petroleum ether/ethyl acetate 1/1) to give intermediate AY (20.0 mg, 10 yield: 62.8%).

Preparation of intermediate AZ

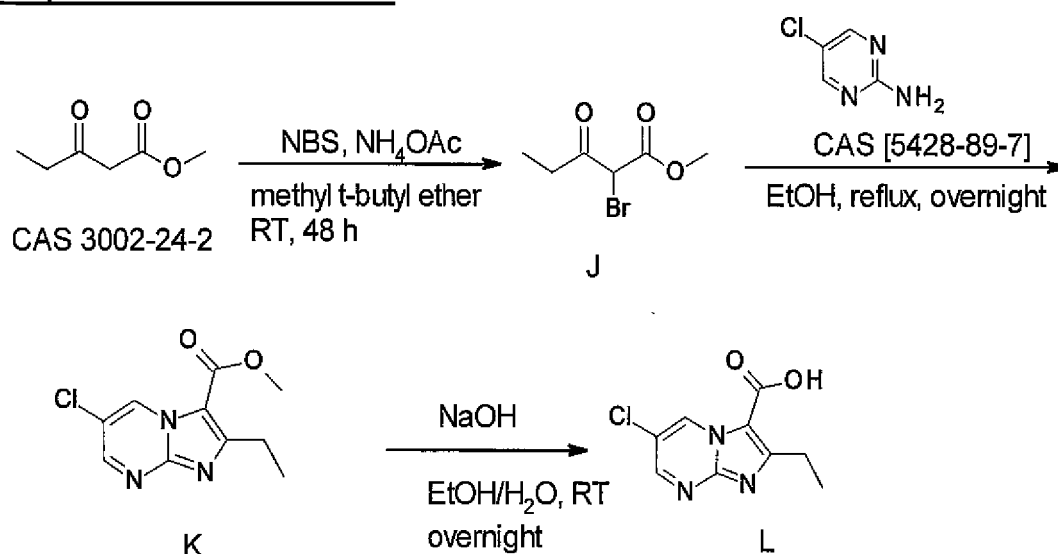
- 15 A solution of intermediate AY (20.0 mg, 0.049 mmol) in $\text{NH}_3 \cdot \text{MeOH}$ (20 mL, 7 M NH_3 in MeOH) was hydrogenated at 15 °C (15 psi) with Raney nickel (3 mg) as a catalyst for 16 hours. The catalyst was filtered off and the filtrate was concentrated under vacuum to give intermediate AZ (20.0 mg, yield: 91.84%).

Preparation of Compound 2

- 20 A solution of 6-chloro-2-ethylimidazo[3,2-a]pyridine-3-carboxylic acid (CAS [1216142-18-5], 9.79 mg, 0.044 mmol), HATU (21.7 mg, 0.057 mmol), DIEA (14.8 mg, 0.114 mmol) in CH_2Cl_2 (10 mL) was stirred for 30 minutes at 25 °C. Intermediate AZ (20 mg, 0.048 mmol) was added to the mixture and the mixture was stirred for 2 hours at 25 °C. The mixture was concentrated under vacuum. The crude product was purified by high performance liquid chromatography over Gemini (eluent: 0.05% ammonia in water/methanol 35/65 to 5/95). The desired fractions were collected and 25 concentrated to give Compound 2 (4.30 mg, 15.91%).

- 1H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 9.56 (s, 1 H) 7.84 (d, $J=8.80$ Hz, 1 H) 7.74 (d, $J=8.56$ Hz, 1 H) 7.59 (s, 1 H) 7.55 (d, $J=9.29$ Hz, 2 H) 7.31 (d, $J=9.78$ Hz, 1 H) 7.22 (d, $J=8.40$ Hz, 2 H) 7.16 (d, $J=8.40$ Hz, 2 H) 6.59 (d, $J=9.05$ Hz, 1 H) 6.13 (br. s., 1 H) 4.79 (d, $J=5.62$ Hz, 2 H) 4.33 (s, 2 H) 4.11 (s, 2 H) 3.50 (t, $J=8.68$ Hz, 1 H) 2.97 (q, $J=7.42$ Hz, 2 H) 2.65 - 2.76 (m, 2 H) 2.33 - 2.44 (m, 2 H) 1.38 (t, $J=7.58$ Hz, 3 H)

Preparation of Intermediate L



10 Preparation of intermediate J

NBS (45.1 g, 254 mmol) and NH_4OAc (5.33 g, 69.2 mmol) were added to a solution of methyl-3-oxovalerate (CAS[30414-53-0], 30 g, 231 mmol) in methyl *t*-butylether (600 mL). The mixture was stirred at room temperature for 48 h. The mixture was filtered and washed with H_2O , dried over Na_2SO_4 and filtered. The filtrate was

- 15 concentrated under vacuum. The residue was purified by column chromatography over silica gel (eluent: petroleum ether/ethyl acetate 20/1) to give intermediate J (20.0 g, yield: 35%).

Preparation of intermediate K

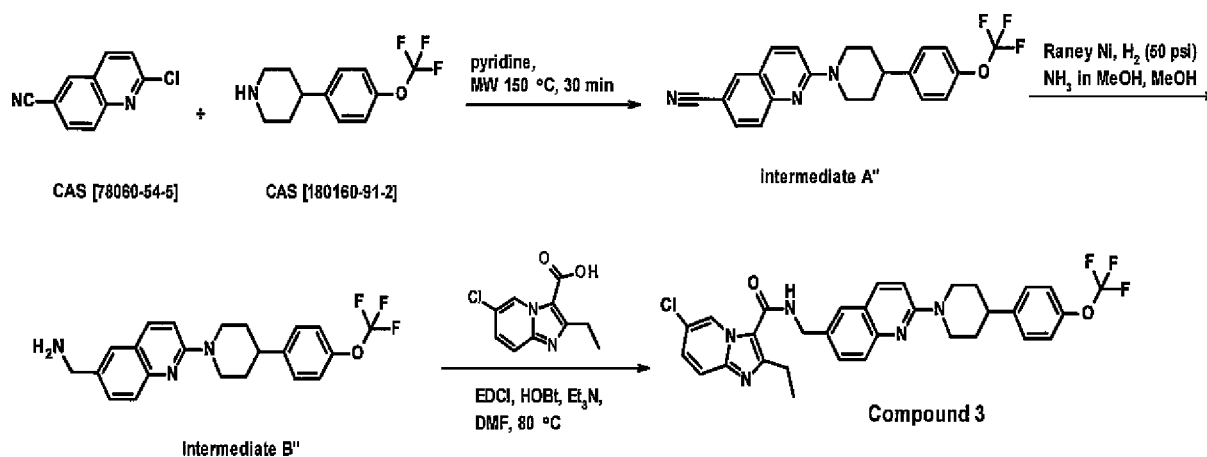
- 20 A solution of 5-Chloro-2-pyridinamine (CAS [5428-89-7], 12.0 g, 93.0 mmol) and intermediate J (25.0 g, 112 mmol) in ethanol (60 mL) was refluxed overnight. The mixture was concentrated under vacuum. The residue was dissolved into ethyl acetate (100 mL). The solution was washed with water (2x100 mL), brine (100 mL), dried over sodium sulfate, filtered and concentrated under vacuum. The residue was purified by
- 25 column chromatography over silica gel (eluent: petroleum ether/ethyl acetate 3/1) to give intermediate K (700 mg, yield: 3%).

Preparation of intermediate L

- A mixture of intermediate K (700 mg, 2.10 mmol) and sodium hydroxide (252 mg, 6.30 mmol) in ethanol (2 ml) and H₂O (2 mL) was stirred overnight at room temperature. Water (20 mL) was added and the solution was acidified with 2 M aqueous hydrochloride to pH ~3. The solution was lyophilized to give crude intermediate L (2 g).

Preparation of Compound 1

- Accordingly, Compound 1 was prepared in the same way as Compound 2 starting from intermediate L and intermediate AZ, yielding 0.037 g, 25%.
- ¹H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 9.83 (d, *J*=2.51 Hz, 1 H) 8.55 (d, *J*=2.51 Hz, 1 H) 7.83 (d, *J*=8.78 Hz, 1 H) 7.75 (d, *J*=8.53 Hz, 1 H) 7.55 (d, *J*=9.20 Hz, 1 H) 7.53 (d, *J*=6.80 Hz, 1 H) 7.22 (d, *J*=8.80 Hz, 2 H) 7.15 (d, *J*=8.40 Hz, 2 H) 6.58 (d, *J*=8.78 Hz, 1 H) 6.26 (t, *J*=5.27 Hz, 1 H) 4.77 (d, *J*=5.60 Hz, 2 H) 4.33 (s, 2 H) 4.11 (s, 2 H) 3.50 (quin, *J*=8.85 Hz, 1 H) 3.01 (q, *J*=7.53 Hz, 2H) 2.65 - 2.74 (m, 2 H) 2.33 - 2.43 (m, 2 H) 1.41 (t, *J*=7.53 Hz, 3 H)

Further Examples20 Synthesis of Compound 3Preparation of intermediate A''

- A mixture of 4-(4-(trifluoromethoxy)phenyl)piperidine (CAS [180160-91-2], 0.2 g, 0.710 mmol) and 2-chloroquinoline-6-carbonitrile (CAS [78060-54-5], 0.161 g, 0.852 mmol) in pyridine (5 mL) was stirred at 150 °C for 30 minutes under microwave. The mixture was evaporated to dryness and diluted with water, extracted with ethyl acetate. The organic layer was dried over sodium sulfate, filtered and concentrated. The

residue was purified by silica gel chromatography eluted with petroleum ether: ethyl acetate= 8:1 to afford intermediate A'', 0.13 g, 46%.

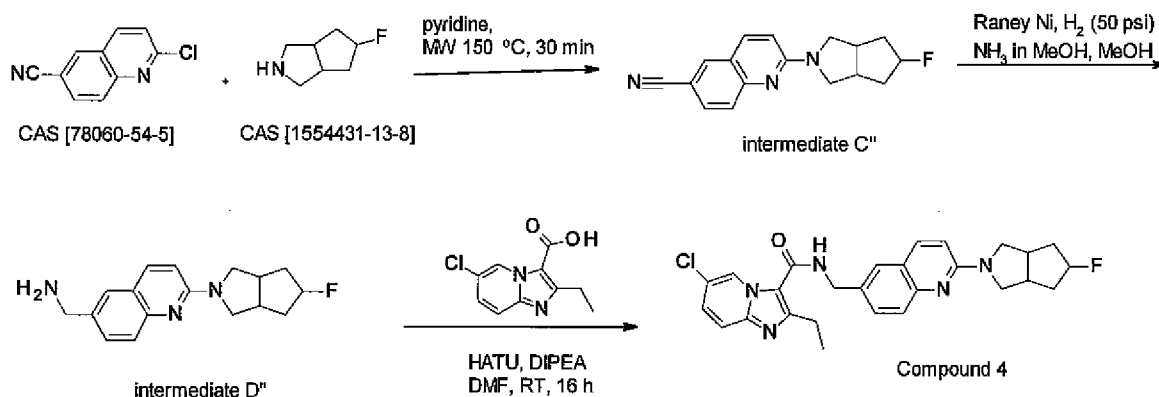
Preparation of intermediate B''

- 5 To a solution of intermediate A'' (0.13 g, 0.327 mmol) in MeOH (20 mL) was added Raney Nickel (65 mg) and ammonia 4M in MeOH (1 mL) under N₂. The suspension was degassed under vacuum and purged with H₂ several times. The mixture was stirred under H₂ (50 psi) at 25 °C for 10 hours. The suspension was filtered through a pad of Celite® was washed with MeOH (20 mL). The combined filtrates were concentrated to dryness to give intermediate B'', 0.12 g, 92%.

Preparation of Compound 3

- To a solution of intermediate B'' (0.1 g, 0.2497 mmol) in DMF (10 mL) were added 6-chloro-2-ethylimidazo[3,2-a]pyridine-3-carboxylic acid (CAS [1216142-18-5], 0.067 g, 0.299 mmol), EDCI (0.072 g, 0.3747 mmol), HOBt (0.04 gg, 0.299 mmol) and triethylamine (0.05 g, 0.498 mmol). The mixture was stirred at 80 °C overnight. The reaction mixture was poured into water and extracted with ethyl acetate. The combined organic layers were dried over sodium sulfate and concentrated to dryness. The residue was purified by silica gel chromatography eluted with dichloromethane: ethyl acetate=10: 1 to give Compound 3, 0.055 g, 36%.
- ¹H NMR (400MHz, CHLOROFORM-d) δ = 9.54 (s, 1H), 7.91 (d, *J*=9.3 Hz, 1H), 7.63 - 7.50 (m, 3H), 7.35 - 7.19 (m, 4H), 7.18 - 7.12 (m, 2H), 7.07 (d, *J*=9.0 Hz, 1H), 6.22 (br.s., 1H), 4.85 - 4.63 (m, 4H), 3.17 - 3.07 (m, 2H), 2.98 (q, *J*=7.4 Hz, 2H), 2.89 - 2.79 (m, 1H), 2.01 (d, *J*=12.5 Hz, 2H), 1.79 (dq, *J*=3.8, 12.6 Hz, 2H), 1.39 (t, *J*=7.5 Hz, 3H).

Synthesis of Compound 4



Preparation of intermediate C''

Accordingly, intermediate C'' was prepared in the same way as intermediate A'' starting from 2-chloroquinoline-6-carbonitrile CAS [78060-54-5] and 5-fluorooctahydro-cyclopenta[c]pyrrole CAS [1554431-13-8] to give 0.15 g, 91%.

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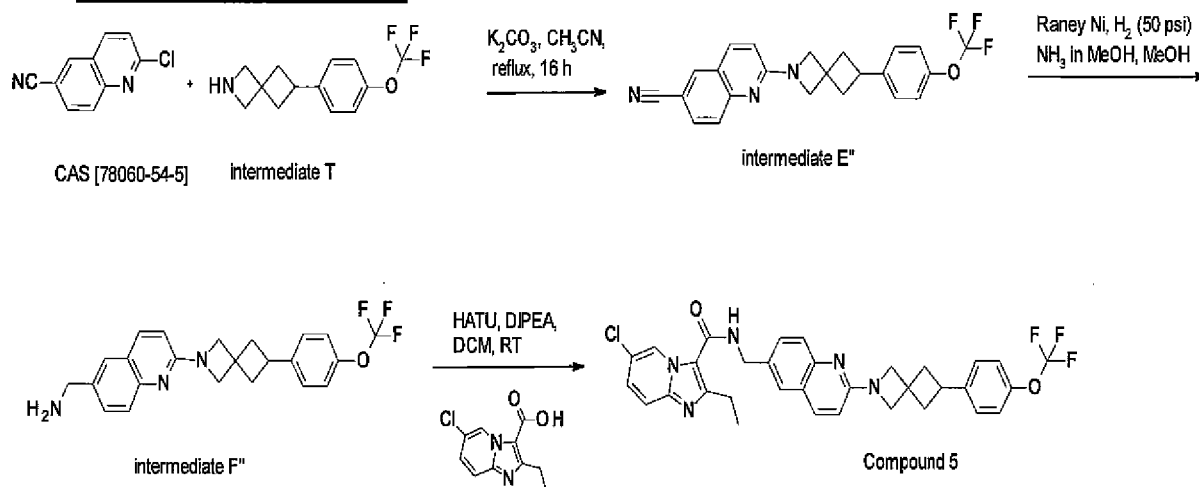
Preparation of intermediate D''

Accordingly, intermediate D'' was prepared in the same way as intermediate B'' starting from intermediate C'' to give 0.15 g, 99%.

10 Preparation of Compound 4

A solution of 6-chloro-2-ethylimidazo[3,2-a]pyridine-3-carboxylic acid (CAS [1216142-18-5], 0.07 g, 0.312 mmol), HATU (0.154 g, 0.405 mmol) and diisopropylethylamine (0.161 g, 1.25 mmol) in DMF (3 mL) was stirred at room temperature for 1 h. Intermediate D'' (0.089 g, 0.312 mmol) was added and the solution was stirred at room temperature overnight. The solvent was evaporated under vacuum. The residue was purified by column chromatography over silica gel (eluent: CH₂Cl₂/methanol 10/1). The desired fractions were concentrated under vacuum to give Compound 4, 0.136 g, 87%.

¹HNMR (400 MHz, CHLOROFORM-d) δ = 9.50 - 9.60 (m, 1 H) 7.80 - 7.87 (m, 1 H) 7.68 - 7.76 (m, 1 H) 7.49 - 7.60 (m, 3 H) 7.27 - 7.33 (m, 1 H) 6.71 - 6.78 (m, 1 H) 6.08 - 6.17 (m, 1 H) 5.18 - 5.35 (m, 1 H) 4.74 - 4.82 (m, 2 H) 3.74 - 3.85 (m, 2 H) 3.48 - 3.57 (m, 2 H) 3.02 - 3.13 (m, 2 H) 2.91 - 3.00 (m, 2 H) 2.25 - 2.40 (m, 2 H) 1.80 - 1.88 (m, 1 H) 1.70 - 1.78 (m, 1 H) 1.33 - 1.43 (m, 3 H)

25 Synthesis of Compound 5

Preparation of intermediate E''

A mixture of 2-chloroquinoline-6-carbonitrile (CAS [78060-54-5], 0.015 g, 0.078 mmol), intermediate T (0.02 g, 0.078 mmol) and potassium carbonate (0.022 g, 0.156 mmol) in acetonitrile (5 mL) was refluxed for 16 hours. The solvent was evaporated under vacuum. The residue was purified by column chromatography over silica gel (eluent: petroleum ether/ethyl acetate 1/1) to give intermediate E'', 0.02 g, 63%.

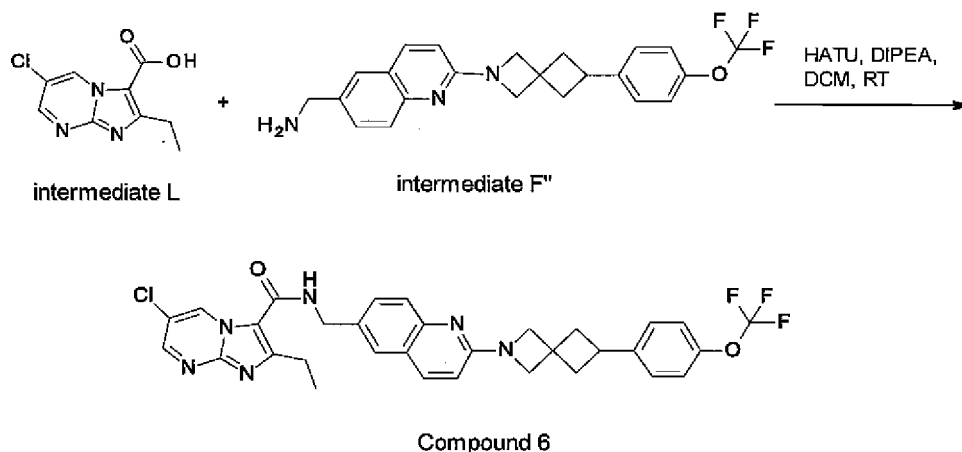
Preparation of intermediate F''

Accordingly, intermediate F'' was prepared in the same way as intermediate B'' starting from intermediate E'' to give 0.02 g, 92%.

Preparation of Compound 5

A solution of 6-chloro-2-ethylimidazo[3,2-a]pyridine-3-carboxylic acid (CAS [1216142-18-5], 0.01 g, 0.044 mmol), HATU (0.022 g, 0.057 mmol), diisopropylethylamine (0.015 g, 0.114 mmol) in CH₂Cl₂ (10 mL) was stirred for 30 minutes at 25 °C. Intermediate F'' (0.02 g, 0.048 mmol) was added to the mixture and the mixture was stirred for 2 hours at 25 °C. The mixture was concentrated under vacuum. The crude product was purified by high performance liquid chromatography over Gemini (eluent: 0.05% ammonia/methanol 35/65 to 5/95). The desired fractions were collected and concentrated to give Compound 5, 0.0043 g, 16%.

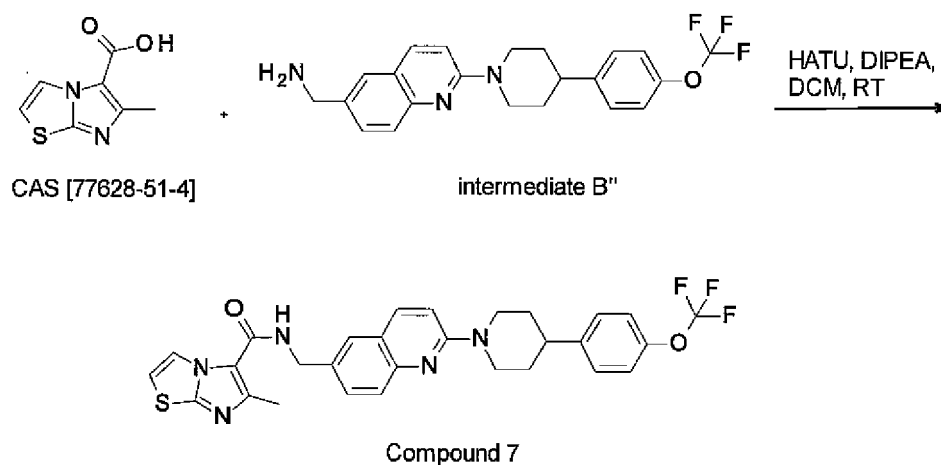
¹H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 9.56 (s, 1 H) 7.84 (d, *J*=8.80 Hz, 1 H) 7.74 (d, *J*=8.56 Hz, 1 H) 7.59 (s, 1 H) 7.55 (d, *J*=9.29 Hz, 2 H) 7.31 (d, *J*=9.78 Hz, 1 H) 7.22 (d, *J*=8.40 Hz, 2 H) 7.16 (d, *J*=8.40 Hz, 2 H) 6.59 (d, *J*=9.05 Hz, 1 H) 6.13 (br. s., 1 H) 4.79 (d, *J*=5.62 Hz, 2 H) 4.33 (s, 2 H) 4.11 (s, 2 H) 3.50 (t, *J*=8.68 Hz, 1 H) 2.97 (q, *J*=7.42 Hz, 2 H) 2.65 - 2.76 (m, 2 H) 2.33 - 2.44 (m, 2 H) 1.38 (t, *J*=7.58 Hz, 3 H)

Synthesis of Compound 6

A solution of intermediate L (0.05 g, 0.222 mmol), HATU (110 mg, 0.289 mmol), diisopropylethylamine (0.075 g, 0.577 mmol) in CH_2Cl_2 (10 mL) was stirred for 30 minutes at 25 °C. Intermediate F'' (101 mg, 0.244 mmol) was added to the mixture and the mixture was stirred for 2 hours at 25 °C. The mixture was concentrated under vacuum. The crude product was purified by high performance liquid chromatography over Gemini (eluent: 0.05% ammonia/methanol 20/80 to 5/95). The desired fractions were collected and concentrated to give Compound 6, 0.037 g, 25%.

^1H NMR (400 MHz, $\text{CHLOROFORM-}d$) δ ppm 9.83 (d, $J=2.51$ Hz, 1 H) 8.55 (d, $J=2.51$ Hz, 1 H) 7.83 (d, $J=8.78$ Hz, 1 H) 7.75 (d, $J=8.53$ Hz, 1 H) 7.55 (d, $J=9.20$ Hz, 1 H) 7.53 (d, $J=6.80$ Hz, 1 H) 7.22 (d, $J=8.80$ Hz, 2 H) 7.15 (d, $J=8.40$ Hz, 2 H) 6.58 (d, $J=8.78$ Hz, 1 H) 6.26 (t, $J=5.27$ Hz, 1 H) 4.77 (d, $J=5.60$ Hz, 2 H) 4.33 (s, 2 H) 4.11 (s, 2 H) 3.50 (quin, $J=8.85$ Hz, 1 H) 3.01 (q, $J=7.53$ Hz, 2 H) 2.65 - 2.74 (m, 2 H) 2.33 - 2.43 (m, 2 H) 1.41 (t, $J=7.53$ Hz, 3 H)

Synthesis of Compound 7

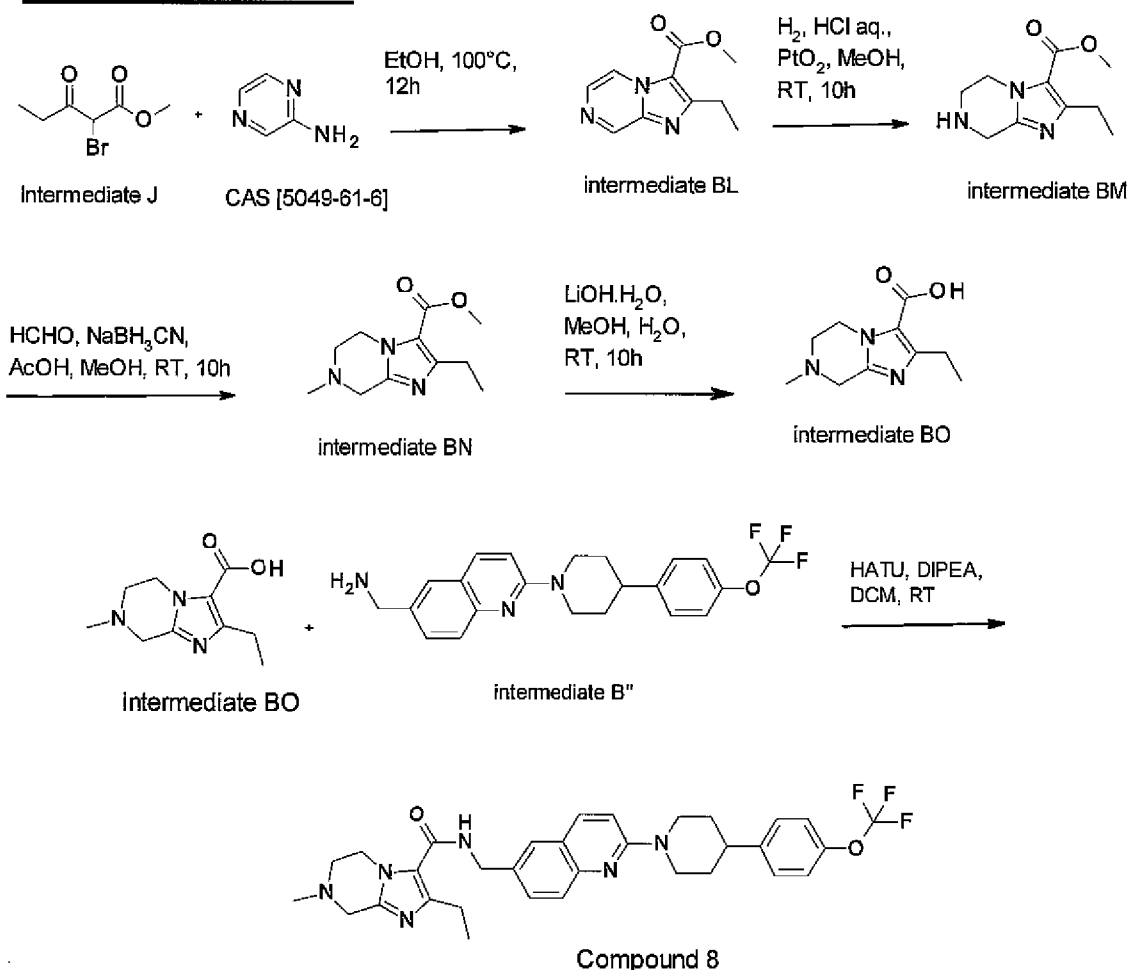


To a solution of intermediate B'' (0.1 g, 0.2497 mmol) in CH_2Cl_2 (15 mL) were added 6-methylimidazo[2,1-b][1,3]thiazole-5-carboxylic acid (CAS [77628-51-4], 0.059 g, 0.324 mmol), HATU (0.142 g, 0.374 mmol) and diisopropylethylamine (0.064 g, 0.498 mmol). The mixture was stirred at room temperature overnight. The reaction mixture was poured into water and extracted with dichloromethane. The combined organic layers were dried over sodium sulfate and concentrated to dryness. The residue was purified by high performance liquid chromatography (Phenomenex Gemini 150x25mmx10um, 25ml/min, mobile phase water (containing 0.1% $\text{NH}_3\cdot\text{H}_2\text{O}$)/Acetonitrile, gradient from 45/55 to 25/85). The desired fraction was

collected and evaporated to remove off CH₃CN in vacuum. The residue was lyophilized to give Compound 7, 0.052 g, 37%.

¹H NMR (400MHz, CHLOROFORM-d) δ = 8.31 (d, J =4.5 Hz, 1H), 7.88 (d, J =9.3 Hz, 1H), 7.72 (d, J =8.8 Hz, 1H), 7.59 - 7.51 (m, 2H), 7.27 - 7.23 (m, 2H), 7.19 - 7.13 (m, 2H), 7.06 (d, J =9.3 Hz, 1H), 6.90 (d, J =4.5 Hz, 1H), 6.03 (br. s., 1H), 4.80 - 4.69 (m, 4H), 3.06 (dt, J =2.3, 12.9 Hz, 2H), 2.84 (tt, J =3.6, 12.2 Hz, 1H), 2.59 (s, 3H), 2.03 - 1.95 (m, 2H), 1.78 (dq, J =4.3, 12.7 Hz, 2H).

Synthesis of Compound 8



Preparation of intermediate BL

15 A mixture of 2-aminopyrazine (CAS [5049-61-6], 12 g, 126.18 mmol) and intermediate J (39.6 g, 189.27 mmol) in EtOH (10 mL) was stirred at 100 °C for 12 h. The solvent was removed in vacuum. The crude product was purified by column chromatography (petroleum ether/ethyl acetate=5/1~1/1). The product fractions were collected and the solvent was evaporated to give intermediate BL, 2 g, 8%.

Preparation of intermediate BM

To a solution of intermediate BL (5 g, 24.36 mmol) in MeOH (20 mL) was added platine dioxide (500 mg) under N₂, followed by addition a drop of con HCl. The suspension was degassed under vacuum and purged with H₂ several times. The mixture was stirred under H₂ (15 psi) at 25 °C for 10 hours. The suspension was filtered through a pad of Celite® and the pad was washed with methanol (50 mL). The combined filtrates were concentrated to dryness to give intermediate BM, 5 g, 98%.

10 Preparation of intermediate BN

To a solution of intermediate BM (5 g, 23.89 mmol) in MeOH (75 mL) was added formaldehyde aqueous solution (9.7 g, 119.47 mmol, 37%) at 0 °C, followed by addition sodium borocyanohydride (7.5 g, 119.47 mmol) and a drop of acetic acid (0.2 mL). Then the mixture was stirred at room temperature for overnight. 10% NH₄Cl solution (25 mL) was added dropwise. The mixture was extracted with ethyl acetate, the combined organic layers were washed with brine, dried over Na₂SO₄, filtered and the solvent was evaporated under vacuum. The residue was purified by column chromatography over silica gel (dichloromethane/methanol=15:1 to 10:1) to give intermediate BN, 1.3 g, 24%.

20 Preparation of intermediate BO

To a solution of intermediate BN (0.55 g, 2.46 mmol) in MeOH (25 mL) and water (5 mL) was added lithium hydroxide monohydrate (0.52 g, 12.32 mmol). The mixture was stirred at room temperature for 10 h. The solvent was removed in vacuum to dryness. The residue was purified by high performance liquid chromatography (DuraShell 150x25mmx5µm, 25ml/min, water (containing 0.05% HCl)/Acetonitrile from 100/0 to 70/30). The desired fraction was collected and evaporated to remove off acetonitrile in vacuum. The residue was lyophilized to give intermediate BO, 0.4 g, 78%.

30 Preparation of Compound 8

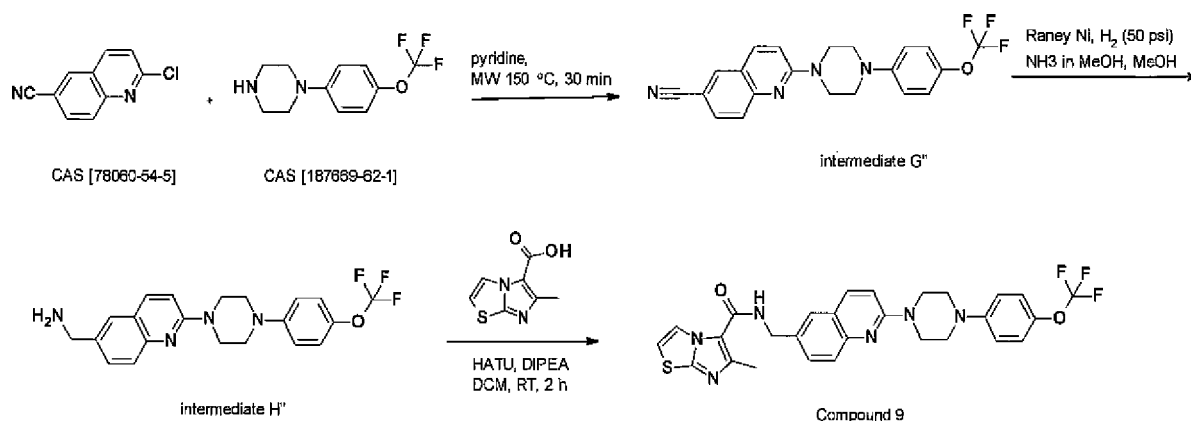
A solution of intermediate BO (0.03 g, 0.143 mmol), HATU (0.071 g, 0.186 mmol) and diisopropylethylamine (0.056 g, 0.430 mmol) in DMF (3 mL) was stirred at room temperature for 1h. Intermediate B'' (0.058 g, 0.143 mmol) was added and the solution was stirred at room temperature overnight. The solvent was evaporated under vacuum. The residue was purified by high performance liquid chromatography over Waters Xbridge Prep OBD C18 100x19mmx5µm (eluent: water (0.05% ammonia hydroxide

v/v)-MeOH 25/75 to 5/95). The desired fractions were lyophilized under vacuum to give Compound 8, 0.045 g, 53%.

¹H NMR (400 MHz, CHLOROFORM-*d*) ppm 7.84 - 7.89 (m, 1 H) 7.68 - 7.73 (m, 1 H) 7.47 - 7.56 (m, 2 H) 7.21 - 7.25 (m, 2 H) 7.12 - 7.18 (m, 2 H) 7.02 - 7.07 (m, 1 H) 5.97 - 6.02 (m, 1 H) 4.69 (m, 4 H) 4.34 (m, 2 H) 3.65 (s, 2 H) 3.00 - 3.09 (m, 2 H) 2.78 - 2.82 (m, 2 H) 2.67 - 2.75 (m, 2 H) 2.45 - 2.50 (s, 3 H) 1.94 - 2.02 (m, 2 H) 1.71 - 1.83 (m, 3 H) 1.23 (m, 3 H)

Synthesis of Compound 9

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Preparation of intermediate G''

Accordingly, intermediate G'' was prepared in the same way as intermediate A'' starting from 2-chloroquinoline-6-carbonitrile (CAS [78060-54-5]) and 1-(4-Trifluoromethoxy-phenyl)-piperazine CAS [187669-62-1] affording 0.15 g, 84%.

Preparation of intermediate H''

Accordingly, intermediate H'' was prepared in the same way as intermediate B'' starting from intermediate G'' affording 0.15 g, 96%.

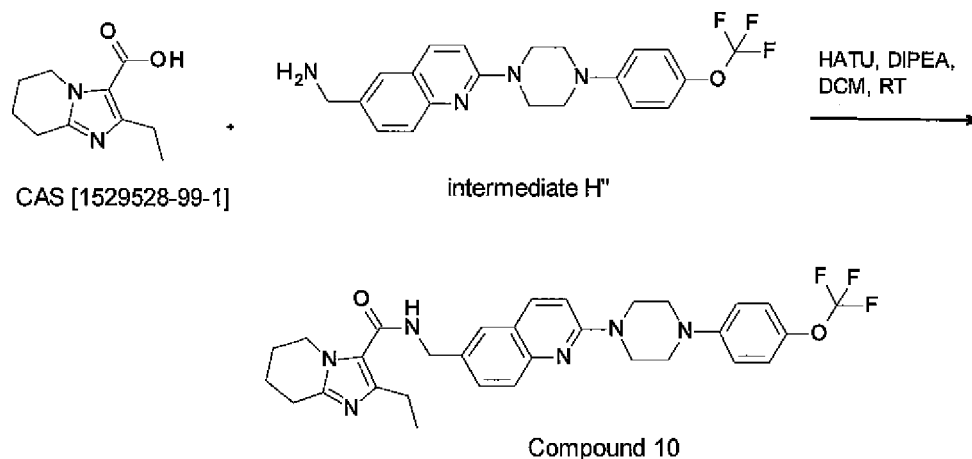
Preparation of Compound 9

A solution of 6-methylimidazo[2,1-B][1,3]thiazole-5-carboxylic acid (CAS [77628-51-4], 0.018 g, 0.1 mmol), HATU (0.049 g, 0.13 mmol) and diisopropylethylamine (0.026 g, 0.20 mmol) in CH₂Cl₂ (5 mL) was stirred at room temperature for 1 h. Intermediate H'' (0.04 g, 0.1 mmol) was added and the solution was stirred at room temperature for 2 hours. The solution was washed with water (10 mL), brine (5 mL), dried over Na₂SO₄, filtered and concentrated under vacuum. The residue was washed with methanol (3 mL). The precipitate was concentrated under vacuum to afford Compound 9, 0.032 g, 57%.

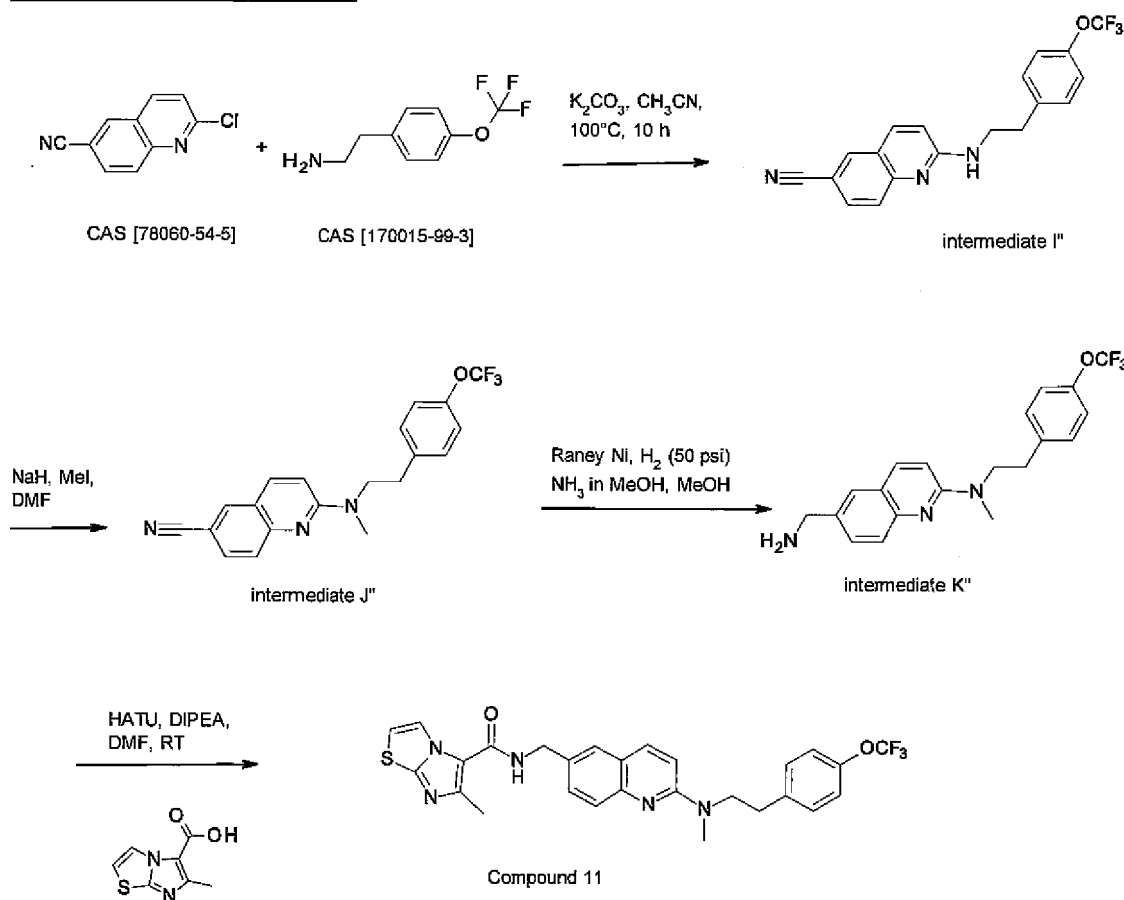
¹H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 8.26 - 8.37 (m, 1 H) 7.86 - 7.96 (m, 1 H) 7.70 - 7.78 (m, 1 H) 7.50 - 7.63 (m, 2 H) 7.11 - 7.20 (m, 2 H) 7.01 - 7.07 (m, 1 H) 6.92 - 7.00 (m, 2 H) 6.85 - 6.91 (m, 1 H) 5.97 - 6.07 (m, 1 H) 4.71 - 4.82 (m, 2 H) 3.83 - 3.99 (m, 4 H) 3.25 - 3.40 (m, 4 H) 2.54 - 2.66 (m, 3 H)

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Synthesis of Compound 10



- 10 A solution of intermediate H' (0.1 g, 0.249 mmol), 2-ethyl-5H,6H,7H,8H-imidazo-[1,2-a]pyridine-3-carboxylic acid CAS [1529528-99-1], 0.107 g, 0.249 mmol), HATU (123 mg, 0.323 mmol) and diisopropylethylamine (96 mg, 0.746 mmol) in CH₂Cl₂ (3 mL) was stirred at room temperature for 1 h. The solvent was evaporated under vacuum. The residue was purified by high performance liquid chromatography over
- 15 Phenomenex Gemini C18 250x21.2mmx5 μ m (eluent: water (0.05% ammonia hydroxide v/v)-MeOH 25/75 to 0/100). The desired fractions were lyophilized under vacuum to give Compound 10, 0.074 g, 52%.
- ¹HNMR (400 MHz, CHLOROFORM-*d*) ppm 7.87 - 7.93 (m, 1 H) 7.69 - 7.75 (m, 1 H) 7.50 - 7.59 (m, 2 H) 7.10 - 7.18 (m, 2 H) 7.01 - 7.07 (m, 1 H) 6.92 - 6.98 (m, 2 H) 5.95 - 6.03 (m, 1 H) 4.66 - 4.74 (m, 2 H) 4.25 (m, 2 H) 3.86 - 3.96 (m, 4 H) 3.28 - 3.37 (m, 4 H) 2.83 - 2.91 (m, 2 H) 2.65 - 2.75 (m, 2 H) 1.85 - 2.00 (m, 4 H) 1.20 - 1.28 (m, 3 H)
- 20

Synthesis of Compound 11**5 Preparation of intermediate I''**

To a solution of 4-(Trifluoromethoxy)phenethylamine (CAS [170015-99-3], 0.5 g, 2.44 mmol) in DMF (30 mL) was added 2-chloroquinoline-6-carbonitrile (CAS [78060-54-5], 0.460 g, 2.44 mmol) and potassium carbonate (0.674 g, 4.87 mmol). The mixture was stirred at 100 °C for 10 h. The mixture was diluted with water (30 mL) and extracted with ethyl acetate (30 mLx3). The organic layers were dried over sodium sulfate and concentrated in vacuum. The crude product was purified by column chromatography (petroleum ether/ethyl acetate=5/1). The product fractions were collected and the solvent was evaporated to give intermediate I'', 0.2 g, 23%.

15 Preparation of intermediate J''

Sodium hydride (0.027 g, 0.67 mmol, 60% in mineral oil) was added to a mixture of intermediate I'' (0.16 g, 0.45 mmol) in DMF (10 mL) at 0 °C under N₂ atmosphere. The mixture was stirred at 0 °C for 30 minutes. Methyl iodide (0.04 mL, 0.537 mmol) was

added to the mixture and stirred at 25 °C for 10 hours. The mixture was quenched with aq. NH₄Cl, diluted with water. The mixture was extracted with ethyl acetate (3x10 mL). The organic layer was washed with brine, dried over sodium sulfate, filtered and concentrated. The residue was purified by column chromatography over silica gel (petroleum ether/ethyl acetate=10/1~4/1). The product fractions were collected and the solvent was evaporated to give intermediate J'', 0.18 g, 84%.

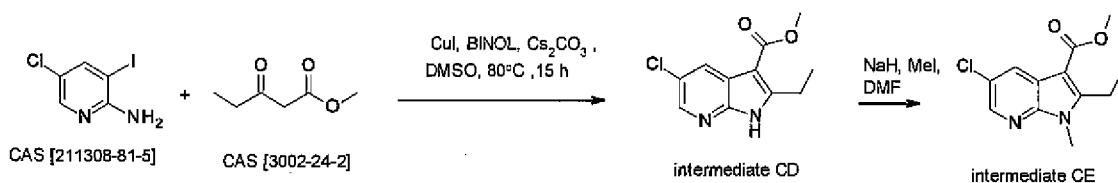
Preparation of intermediate K''

To a solution of intermediate J'' (0.18 g, 0.485 mmol) in ammonia 4M in methanol (10 mL) was added Raney Nickel (50 mg) under N₂. The suspension was degassed under vacuum and purged with H₂ several times. The mixture was stirred under H₂ (15 psi) at 25 °C for 10 hours. The suspension was filtered through a pad of Celite® and the pad was washed with methanol (10 mL). The combined filtrates were concentrated in vacuum to give intermediate K'', 0.18 g, 99%.

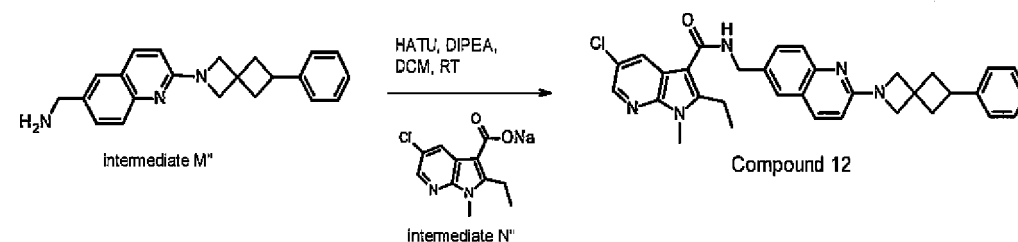
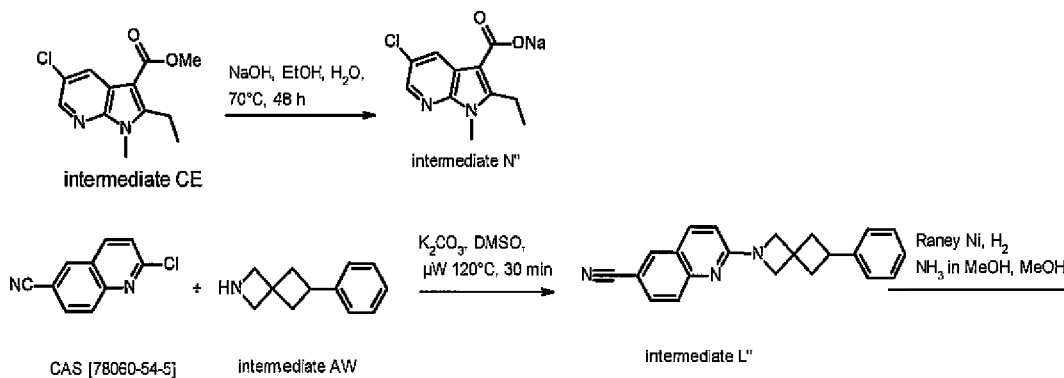
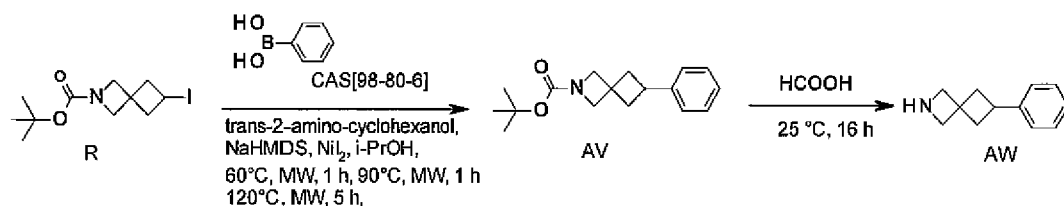
Preparation of Compound 11

To a solution of 6-Methylimidazo[2,1-b][1,3]thiazole-5-carboxylic acid (CAS [77628-51-4], 0.096 g, 0.53 mmol) in DMF (10 mL) was added intermediate K'' (0.18 g, 0.48 mmol), HATU (237.02 mg, 0.62 mmol) and diisopropylethylamine (0.186 g, 1.44 mmol). The mixture was stirred at room temperature overnight. The mixture was diluted with water (20 mL) and extracted with dichloromethane (10 mLx3). The organic layers were dried over sodium sulfate, filtered and concentrated in vacuum. The residue was purified by high performance liquid chromatography (Waters Xbridge Prep OBD C18 150x30x5μ, 25ml/min, mobile phase: water (containing 0.05% NH₃.H₂O)/acetonitrile, gradient from 52/58 to 22/78). The desired fraction was collected and evaporated to remove off acetonitrile in vacuum. The residue was lyophilized to give Compound 11, 0.091 g, 34%.

¹H NMR (400MHz, CHLOROFORM-d) δ = 8.32 (d, *J*=4.4 Hz, 1H), 7.83 (d, *J*=9.3 Hz, 1H), 7.75 - 7.68 (m, 1H), 7.59 - 7.50 (m, 2H), 7.31 - 7.27 (m, 2H), 7.14 (d, *J*=7.9 Hz, 2H), 6.89 (d, *J*=4.4 Hz, 1H), 6.82 (d, *J*=9.3 Hz, 1H), 6.01 (br. s., 1H), 4.77 (d, *J*=5.7 Hz, 2H), 3.90 (t, *J*=7.5 Hz, 2H), 3.13 (s, 3H), 2.98 (t, *J*=7.3 Hz, 2H), 2.59 (s, 3H).

Synthesis of Compound 12

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Preparation of intermediate CD

A mixture of 5-chloro-3-iodopyridin-2-amine (CAS [211308-81-5], 4 g, 15.72 mmol), 2,4-Hexadione (CAS [3002-24-2], 4.50 g, 34.58 mmol), cesium carbonate (5.12 g, 15.71 mmol), BINOL (900.20 mg, 3.14 mmol) and copper iodide (299.39 mg,

- 1.57 mmol) in DMSO (50 mL) was stirred for 15 hours under N₂ flow. Brine and ethyl acetate were added to the mixture. The organic layer was separated, washed with brine, dried over MgSO₄ and filtered. The filtrate was concentrated. The crude product was purified by column chromatography over silica gel (eluent: ethyl acetate/hexane from 0 to 1/1). The desired fractions were collected and concentrated to give intermediate CD, 2.5 g, 67%

Preparation of intermediate CE

Sodium hydride (0.354 g, 8.85 mmol) was added to a solution of intermediate CD (2.2 g, 7.38 mmol) in THF (40 mL) at 0 °C. After stirred for 30 minutes, methyl iodide (1.26 g, 8.85 mmol) was added. The mixture was warmed up to 25 °C and stirred for 3 hours. The mixture was poured into ice water. The mixture was extracted with ethyl acetate (50 mLx2). The organic layers were combined, washed with brine, dried over MgSO₄ and filtered. The filtrate was concentrated. The crude product was purified by column chromatography over silica gel (eluent: ethyl acetate / petroleum ether from 0 to 1/3). The filtrate was concentrated to give intermediate CE, 1.6 g, 86%.

Preparation of intermediate AV

Intermediate AV was prepared in the same way as intermediate S, starting from intermediate R and Phenylboronic acid CAS [98-80-6], yielding 0.3 g, 62%.

Preparation of intermediate AW

Accordingly, intermediate AW was prepared in the same way as intermediate T, starting from intermediate AV, yielding 0.27 g, 99%.

Preparation of intermediate N''

Sodium hydroxide (0.225 g; 5.62 mmol) was added to a solution of intermediate CE (0.5 g; 1.88 mmol) in EtOH (7.5 mL) and H₂O (7.5 mL) and the mixture was stirred at 70 °C for 48 h. The mixture was evaporated in vacuo to give a colorless oil which was azeotroped with toluene (twice) to give 0.777 g of intermediate N'' as white solid (quant).

Preparation of intermediate L''

A suspension of intermediate AW (0.169 g, 806 µmol), 2-chloroquinoline-6-carbonitrile (CAS [78060-54-5], 0.304 g, 1.61 mmol) and potassium carbonate (0.557 g, 4.03 mmol) in DMSO (3 mL) was heated to 120 °C using a single mode microwave (Biotage Initiator60) with a power output ranging from 0 to 400 W for 30 min [fixed hold time on]. The reaction was quenched with water and extracted with EtOAc (3x). The combined organic phases were washed with water (twice) and brine (3x), dried over MgSO₄, filtered and evaporated to dryness. The crude was purified by preparative LC (irregular silica 15-40 µm, 12 g GraceResolv, dry loading (silica), mobile phase: heptane/EtOAc 90/10 to 70/30) to obtain 0.142 g of intermediate L'' (54%).

Preparation of intermediate M''

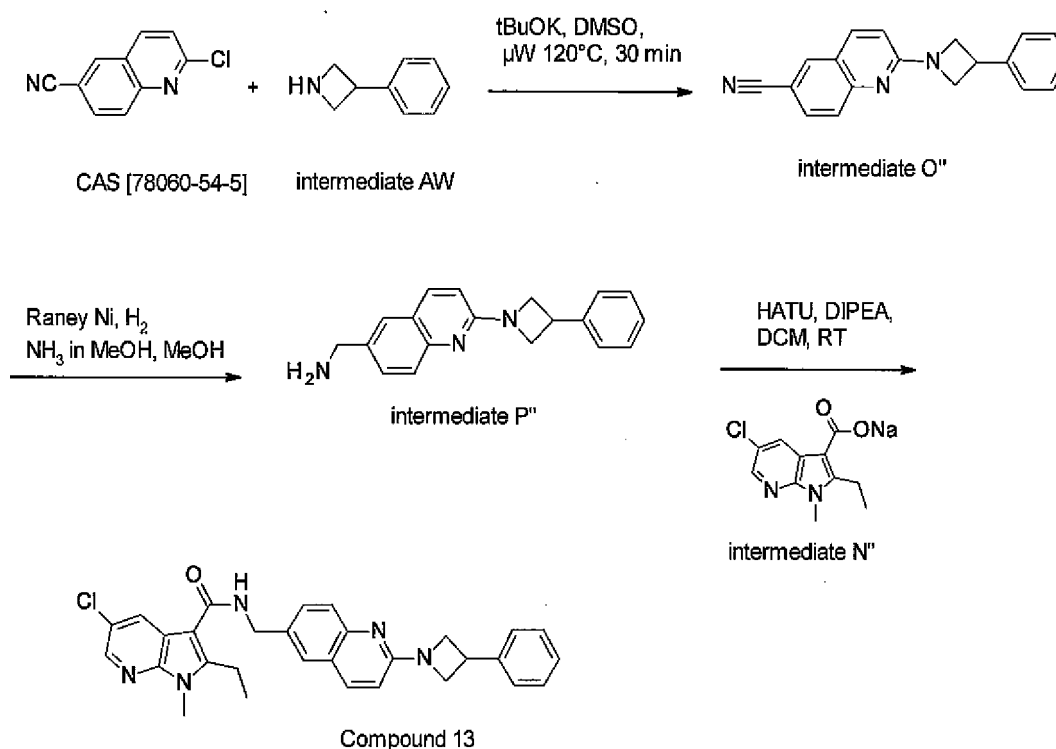
A mixture of intermediate L'' (0.099 g, 0.304 mmol) and Ra-Ni (77.5 mg, 1.32 mmol) in ammonia 7M in MeOH (3.3 mL) was hydrogenated at room temperature under 2 bar overnight. The mixture was filtered through a pad of celite® and rinsed with EtOAc. The filtrate was evaporated until dryness to give 0.098 g of intermediate M'' as a pale grey solid (98%).

Preparation of Compound 12

Diisopropylethylamine (0.12 mL, 0.706 mmol) and HATU (0.14 g, 0.367 mmol) were successively added to a solution of intermediate N'' (0.074 g, 0.282 mmol) in DMF (7.8 mL). The resulting mixture was stirred at room temperature for 30 min, before the addition of intermediate M'' (0.093 g, 0.282 mmol) and the mixture was stirred at room temperature overnight. The reaction mixture was diluted with EtOAc and washed with an aq. sat. NaHCO₃ solution (twice) and brine (twice). The organic phase was dried over MgSO₄, filtered and evaporated to dryness. The crude was purified by preparative LC (Irregular silica 15-40 µm, 14 g Grace Resolv, dry loading (silica), mobile phase gradient: from Heptane/EtOAc 90/10 to 50/50) to obtain a solid which was triturated in Et₂O, filtered and dried under vacuum to obtain 0.079 g of Compound 12 as white solid (51%).

¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 8.34 (t, *J*=5.8 Hz, 1 H) 8.27 (d, *J*=2.0 Hz, 1 H) 8.21 (d, *J*=2.0 Hz, 1 H) 7.99 (d, *J*=9.1 Hz, 1 H) 7.62 (s, 1 H) 7.55 (s, 2 H) 7.17 - 7.34 (m, 5 H) 6.70 (d, *J*=9.1 Hz, 1 H) 4.59 (d, *J*=6.1 Hz, 2 H) 4.23 (s, 2 H) 4.01 (s, 2 H) 3.80 (s, 3 H) 3.34 - 3.50 (m, 1 H) 3.16 (q, *J*=7.6 Hz, 2 H) 2.55 - 2.68 (m, 2 H) 2.27 - 2.44 (m, 2 H) 1.21 (t, *J*=7.6 Hz, 3 H).

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Synthesis of Compound 13**5 Preparation of intermediate O''**

A suspension of intermediate AW (0.127 g, 750 μ mol), 2-chloroquinoline-6-carbonitrile (CAS [78060-54-5], 0.283 g, 1.50 mmol), and Potassium tert-butoxide (0.421 g, 3.75 mmol) in DMSO (2.8 mL) was heated to 120 $^{\circ}C$ using a single mode microwave (Biotage Initiator60) with a power output ranging from 0 to 400 W for 30 min [fixed hold time on]. The reaction was quenched with water and extracted with EtOAc (3x). The combined organic phases were washed with water (2x) and brine (3x), dried over $MgSO_4$, filtered and evaporated to dryness. The crude product was purified by preparative LC (irregular silica 15-40 μ m, 24 g GraceResolv, dry loading (silica), mobile phase: heptane/EtOAc 90/10 to 50/50) to obtain 0.143 g of intermediate O'' as yellow solid (67%).

Preparation of intermediate P''

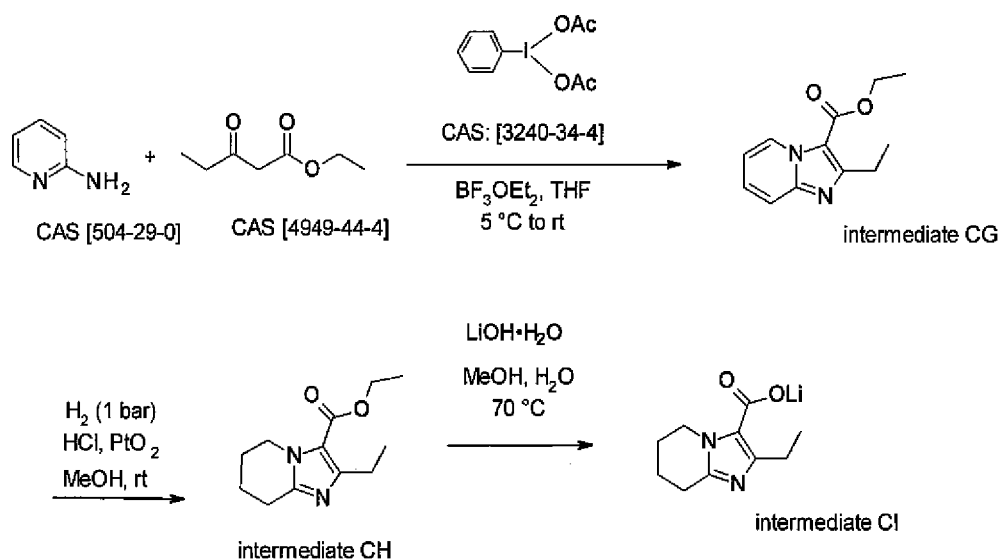
A mixture of intermediate O'' (0.141 g, 0.494 mmol) and Raney Nickel (0.126 g, 2.15 mmol) in ammonia 7M in MeOH (5.4 mL) was hydrogenated at room temperature under 2 bar overnight. The reaction mixture was filtered over Celite®, rinsed with

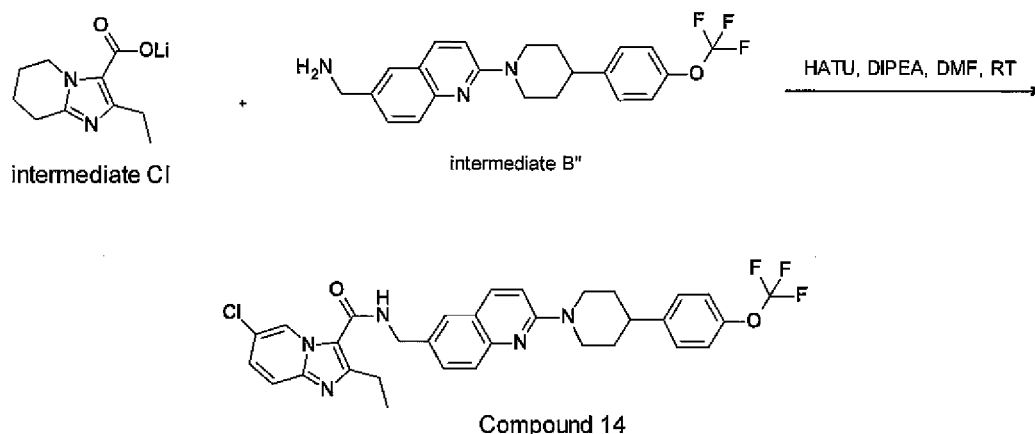
EtOAc and evaporated to dryness to obtain 0.138 g of intermediate P'' as white solid (97%).

Preparation of Compound 13

- 5 To a solution of intermediate N'' (0.17 g, 0.653 mmol) and intermediate P'' (0.156 g, 0.539 mmol) in DMF (18 mL) were added HATU (0.323 g, 0.849 mmol) and diisopropylethylamine (0.28 mL, 1.63 mmol) and the mixture was stirred at room temperature overnight. The reaction mixture was diluted with EtOAc and washed with an aq. sat. NaHCO₃ solution (twice) and brine (twice). The combined organic phases
- 10 were dried over MgSO₄, filtered and evaporated to dryness. The crude was purified by preparative LC (Irregular silica 15-40 μ m, 24 g Grace Resolv, dry loading (silica), mobile phase gradient: from Heptane/EtOAc 90/10 to 10/90) to obtain 0.167 g as a white solid which was triturated in Et₂O and EtOH, filtered and dried under vacuum to obtain 0.116 g of Compound 13 as a white solid (35%).
- 15 ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 8.35 (t, *J*=5.9 Hz, 1 H) 8.27 (s, 1 H) 8.21 (s, 1 H) 8.03 (d, *J*=8.9 Hz, 1 H) 7.65 (s, 1 H) 7.58 (s, 2 H) 7.34 - 7.45 (m, 4 H) 7.24 - 7.29 (m, 1 H) 6.78 (d, *J*=8.6 Hz, 1 H) 4.60 (d, *J*=5.6 Hz, 2 H) 4.51 (t, *J*=8.1 Hz, 2 H) 3.97 - 4.10 (m, 3 H) 3.81 (s, 3 H) 3.13 - 3.19 (m, 2 H) 1.21 (br t, *J*=7.6 Hz, 3 H).

20 Synthesis of Compound 14





Preparation of intermediate CG

A solution of 2-aminopyridine (CAS [504-29-0], 4.0 g; 42.5 mmol) in THF (220 mL) was cooled to 5 °C, before the addition of ethyl propionylacetate (CAS [4949-44-4], 6.1 mL; 42.5 mmol), Iodobenzene Diacetate (CAS [3240-34-4], 13.7 g; 42.5 mmol) and $\text{BF}_3 \cdot \text{OEt}_2$ (556 μL ; 2.13 mmol). The resulting mixture was allowed to warm to rt, then stirred at rt overnight. The mixture was poured into saturated aqueous NaHCO_3 and extracted with EtOAc. The combined organic layers were washed with brine, dried over MgSO_4 , filtered and concentrated to give 18.8 g as an orange solid. The crude was taken-up in Et_2O , leading to precipitation. The precipitate was filtered to give 3.8 g of crude as an off-white solid (41%). The filtrate was purified by preparative LC (Regular silica 30 μm , 25 g, liquid loading (CH_2Cl_2), mobile phase gradient: from Heptane/EtOAc 100/0 to 50/50) to obtain 1.7 g of intermediate 30 as an off-white solid which was taken-up in Et_2O , the solid was filtered and dried under high vacuum to give 1.2 g of intermediate CG as a white solid (13%).

Preparation of intermediate CH

A solution of intermediate CG (1.2 g; 5.50 mmol) in MeOH (27 mL) was degassed by N_2 bubbling for 10 min before the addition of Platinum Oxide (125 mg; 0.55 mmol) and HCl (125 μL ; 1.50 mmol). The resulting mixture was hydrogenated at rt under 1 bar overnight. EtOAc was added and the mixture was filtered through a pad of celite®, the filtrate was concentrated until dryness to give 1.4 g of intermediate CH as colourless oil (quant).

Preparation of intermediate CI

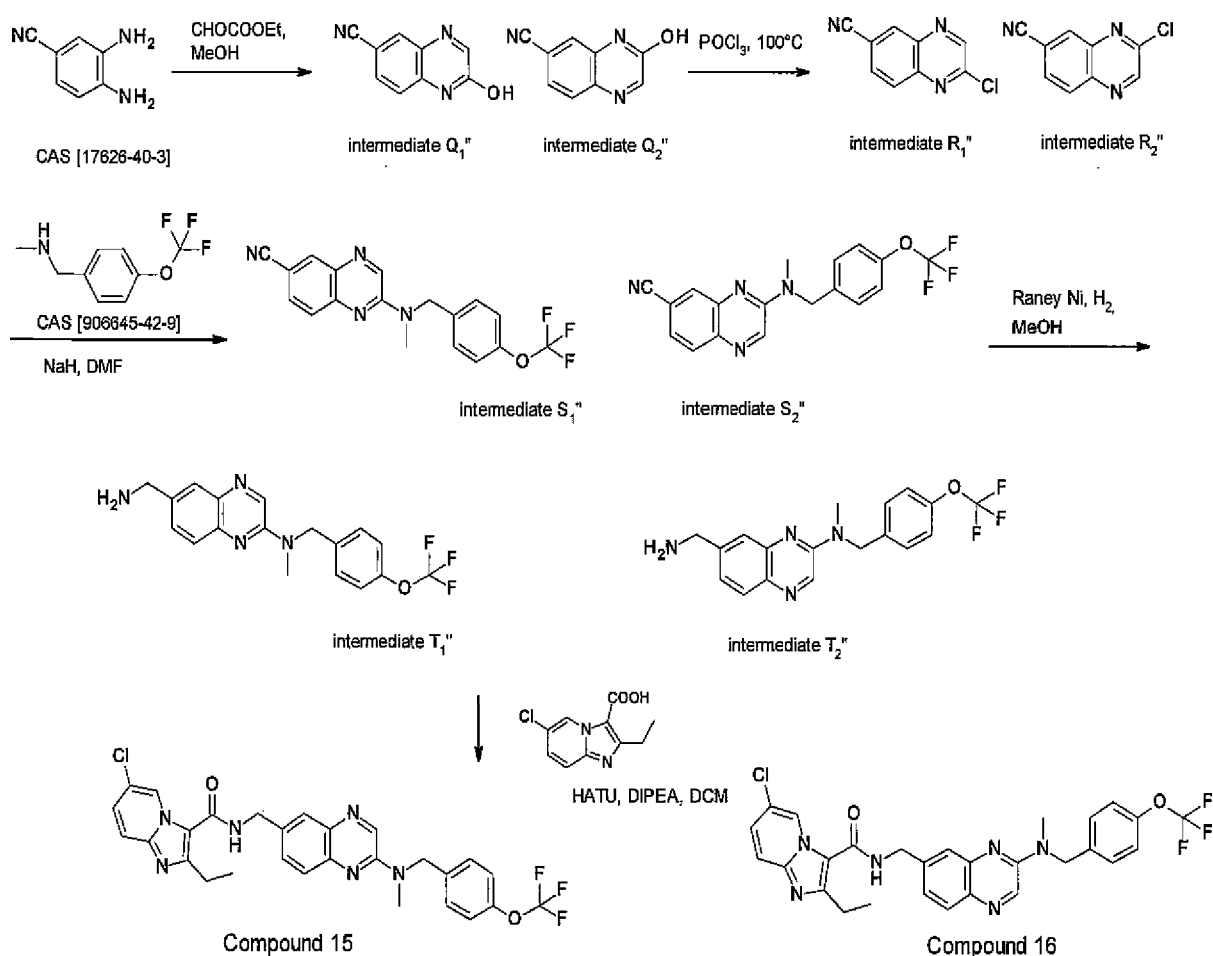
Lithium hydroxide monohydrate (170 mg; 4.05 mmol) was added to a solution of intermediate CH (300 mg; 1.35 mmol) in MeOH (3 mL) and H_2O (158 μL). The resulting mixture was stirred at 50 °C for 48 h. The solvent was evaporated in vacuo

until dryness to give an off-white gum which was azeotroped with toluene (twice), then dried under high vacuum to give 0.353 g of intermediate CI as an off-white solid (used as such in the next step).

5 Preparation of Compound 14

Diisopropylethylamine (0.516 mL; 3.00 mmol) and HATU (0.593 g; 1.56 mmol) were added successively to a solution of intermediate CI (0.24 g; 1.20 mmol) in DMF (36 mL). The resulting mixture was stirred at room temperature for 30 min, before the addition of intermediate B'' (0.481 g; 1.20 mmol) and the mixture was stirred at room temperature for 2 h. The reaction mixture was evaporated in vacuo until dryness then diluted with EtOAc and washed with brine (twice). The organic layer was dried over MgSO₄, filtered and evaporated to dryness. The crude was purified by preparative LC (Regular silica 30 µm, 12 g Interchim, dry loading (Celite®), mobile phase gradient: from Heptane/EtOAc/MeOH 90/8/2 to 50/40/10) to obtain 0.2 g as white solid. The solid was triturated in Et₂O, filtered and dried under high vacuum to give 0.126 g of Compound 14 as white solid (18%).

¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 8.26 (t, *J*=5.8 Hz, 1 H) 7.99 (d, *J*=9.1 Hz, 1 H) 7.47 - 7.58 (m, 3 H) 7.40 (d, *J*=7.8 Hz, 2 H) 7.28 (d, *J*=9.1 Hz, 3 H) 4.70 (br d, *J*=13.6 Hz, 2 H) 4.50 (d, *J*=6.1 Hz, 2 H) 4.00 (t, *J*=5.6 Hz, 2 H) 2.86 - 3.03 (m, 3 H) 2.70 (m, 2 H) 2.63 (m, 2 H) 1.76 - 1.93 (m, 6 H) 1.59 - 1.70 (m, 2 H) 1.10 (t, *J*=7.6 Hz, 3 H).

Synthesis of Compound 15 & Compound 16**5 Preparation of intermediates Q"**

To a solution of 3,4-diaminobenzonitrile (CAS [17626-40-3], 1 g, 7.51 mmol) in MeOH (20 ml) was added ethylglyoxalate (6.81 ml, 34.35 mmol, 35%). After stirring overnight at room temperature, the precipitate was collected and washed with methanol (10 ml) to give a mixture of intermediate Q", 0.6 g, 47%.

10

Preparation of intermediates R"

Intermediate Q" (0.6 g, 3.5 mmol) was dissolved in phosphoryl chloride (20 mL). The mixture was heated to reflux for about 2 h. The mixture was poured into water and basified with aqueous NaHCO_3 till pH = 8 and extracted with dichloromethane (30 mlx3). The organic layer was dried over Na_2SO_4 , filtered and concentrated. The residue was purified by silica gel chromatography eluted with petroleum ether: ethyl acetate= 10:1 to afford product as a mixture of intermediate R", 0.6 g, 90%.

15

Preparation of intermediate S''

A mixture of intermediates R'' (0.5 g, 2.65 mmol), N-Methyl-N-[4-(trifluoromethoxy)benzyl]amine (0.6 g, 2.91 mmol) and potassium carbonate (0.73 g, 5.3 mmol) in acetonitrile (30 mL) was stirred at 100 °C for 10 h. The mixture was evaporated to dryness and diluted with water (30 mL), extracted with ethyl acetate (50 mLx3). The organic layer was dried over Na₂SO₄, filtered and concentrated. The residue was purified by silica gel chromatography eluted with petroleum ether: ethyl acetate= 8:1 to afford product as a mixture of intermediates S'', 0.6 g, 63%.

10 Preparation of intermediates T''

To a solution of intermediates S'' (0.5 g, 1.4 mmol) in MeOH (50 mL) was added Raney Nickel (0.25 g) and ammonia in MeOH (10 mL, 4M) under N₂. The suspension was degassed under vacuum and purged with H₂ several times. The mixture was stirred under H₂ (50 psi) at 25 °C for 10 hours. The suspension was filtered through a pad of Celite® was washed with MeOH (20 mL). The combined filtrates were concentrated to dryness. The residue was purified by high performance liquid chromatography (Phenomenex Synergi C18, 250x21.2mmx4µm, 25ml/min, water (containing 0.05% HCl)/Acetonitrile gradient from 77/23 to 57/43). The desired fraction was collected and evaporated to remove off acetonitrile in vacuum. The residue was adjusted to pH=9 with aqueous NaHCO₃ solution (20 mL) and extracted with dichloromethane (3x50 mL). The combined organic layers were dried over Na₂SO₄ and concentrated in vacuum to give intermediate T₁'', 0.1 g, 20% and T₂'', 0.3 g, 59%.

Preparation of Compound 15

25 To a solution of intermediate T₁'' (0.1 g, 0.276 mmol) in CH₂Cl₂ (25 mL) was added 6 chloro-2-ethylimidazo[3,2-a]pyridine-3-carboxylic acid (CAS [1216142-18-5], 0.056 g, 0.251 mmol), HATU (0.124 g, 0.326 mmol) and diisopropylethylamine (0.084 g, 0.653 mmol). The mixture was stirred at room temperature overnight. The reaction mixture was poured into water and extracted dichloromethane. The combined organic layers were dried over Na₂SO₄ and concentrated to dryness. The residue was purified by high performance liquid chromatography (Waters Xbridge Prep OBD C18 150x30x5µ, 20ml/min, water (containing 0.05% NH₃.H₂O)/Methanol gradient from 25/75 to 0/100). The desired fraction was collected and evaporated to remove off methanol in vacuum. The residue was lyophilized affording Compound 15, 0.054 g, 38%.

35 ¹H NMR (400MHz, CHLOROFORM-d) δ 9.57 (s, 1H), 8.50 (s, 1H), 7.86 (s, 1H), 7.75 - 7.68 (m, 1H), 7.63 (dd, J=1.5, 8.6 Hz, 1H), 7.56 (d, J=9.3 Hz, 1H), 7.36 - 7.29 (m,

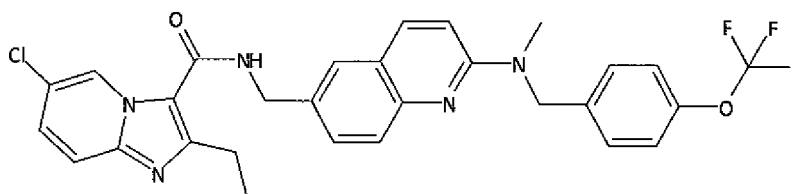
3H), 7.18 (d, $J=7.9$ Hz, 2H), 6.21 (br. s., 1H), 4.97 (s, 2H), 4.86 (d, $J=5.3$ Hz, 2H), 3.28 (s, 3H), 3.01 (q, $J=7.8$ Hz, 2H), 1.42 (t, $J=7.5$ Hz, 3H).

Preparation of Compound 16

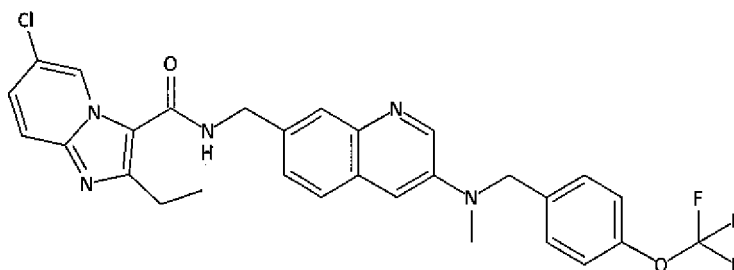
- 5 To a solution of intermediate T₂'' (0.15 g, 0.414 mmol) in CH₂Cl₂ (25 mL) was added 6-chloro-2-ethylimidazo[3,2-a]pyridine-3-carboxylic acid (CAS [1216142-18-5], 0.085 g, 0.376 mmol), HATU (0.186 g, 0.489 mmol) and diisopropylethylamine (0.126 g, 1.11 mmol). The mixture was stirred at room temperature overnight. The reaction mixture was poured into water and extracted dichloromethane. The combined
- 10 organic layers were dried over Na₂SO₄ and concentrated to dryness. The residue was triturated with methanol (20 mL) and filtered to afford Compound 16, 0.121 g, 56%. ¹H NMR (400MHz, CHLOROFORM-d) δ 9.56 (d, $J=1.3$ Hz, 1H), 8.49 (s, 1H), 7.90 (d, $J=8.4$ Hz, 1H), 7.67 (s, 1H), 7.56 (d, $J=9.5$ Hz, 1H), 7.41 (dd, $J=1.7, 8.5$ Hz, 1H), 7.36 - 7.28 (m, 3H), 7.18 (d, $J=8.2$ Hz, 2H), 6.24 (br. s., 1H), 4.96 (s, 2H), 4.86 (d, $J=5.7$ Hz, 2H), 3.27 (s, 3H), 3.02 (q, $J=7.5$ Hz, 2H), 1.43 (t, $J=7.6$ Hz, 3H).
- 15

The following compounds were also prepared in accordance with the procedures described herein:

20 Compound 17



Compound 18



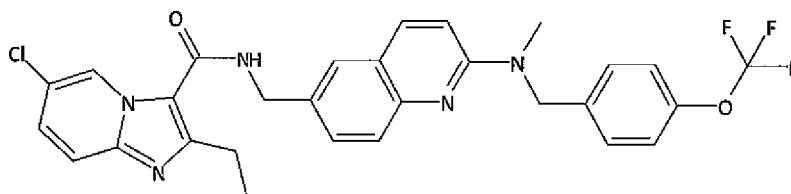
3H), 7.18 (d, $J=7.9$ Hz, 2H), 6.21 (br. s., 1H), 4.97 (s, 2H), 4.86 (d, $J=5.3$ Hz, 2H), 3.28 (s, 3H), 3.01 (q, $J=7.8$ Hz, 2H), 1.42 (t, $J=7.5$ Hz, 3H).

Preparation of Compound 16

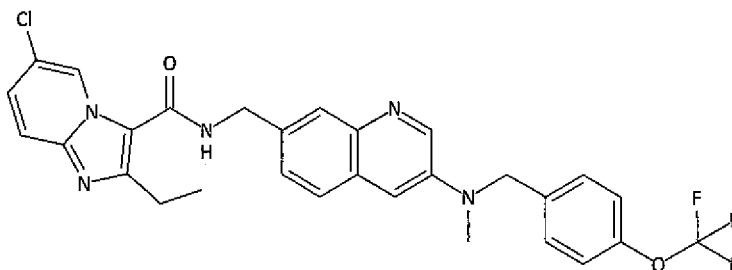
- 5 To a solution of intermediate T₂² (0.15 g, 0.414 mmol) in CH₂Cl₂ (25 mL) was added 6-chloro-2-ethylimidazo[3,2-a]pyridine-3-carboxylic acid (CAS [1216142-18-5], 0.085 g, 0.376 mmol), HATU (0.186 g, 0.489 mmol) and diisopropylethylamine (0.126 g, 1.11 mmol). The mixture was stirred at room temperature overnight. The reaction mixture was poured into water and extracted dichloromethane. The combined
- 10 organic layers were dried over Na₂SO₄ and concentrated to dryness. The residue was triturated with methanol (20 mL) and filtered to afford Compound 16, 0.121 g, 56%. ¹H NMR (400MHz, CHLOROFORM-d) δ 9.56 (d, $J=1.3$ Hz, 1H), 8.49 (s, 1H), 7.90 (d, $J=8.4$ Hz, 1H), 7.67 (s, 1H), 7.56 (d, $J=9.5$ Hz, 1H), 7.41 (dd, $J=1.7, 8.5$ Hz, 1H), 7.36 - 7.28 (m, 3H), 7.18 (d, $J=8.2$ Hz, 2H), 6.24 (br. s., 1H), 4.96 (s, 2H), 4.86 (d, $J=5.7$ Hz, 2H), 3.27 (s, 3H), 3.02 (q, $J=7.5$ Hz, 2H), 1.43 (t, $J=7.6$ Hz, 3H).
- 15

The following compounds were also prepared in accordance with the procedures described herein:

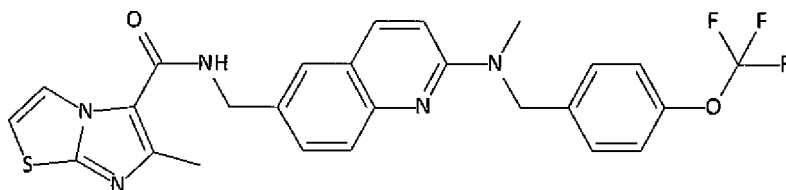
20 Compound 17



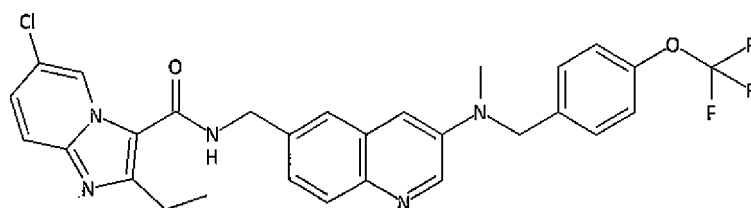
Compound 18



Compound 19

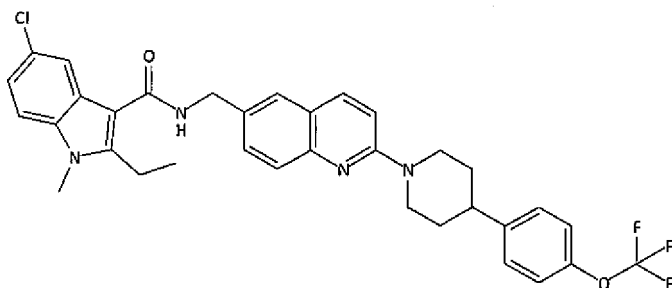


Compound 20

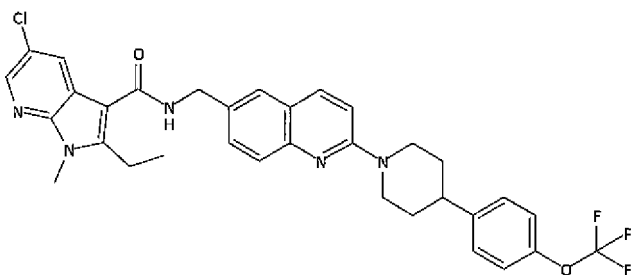


5

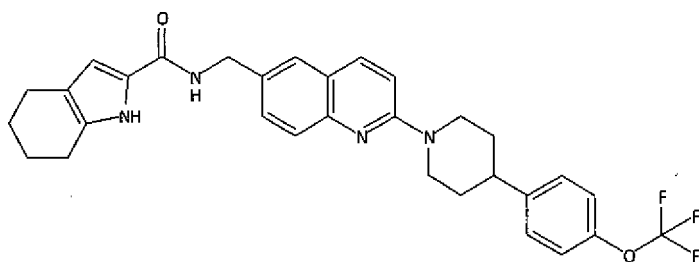
Compound 21



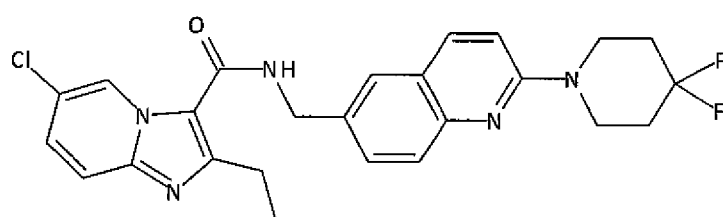
10 Compound 22



Compound 23

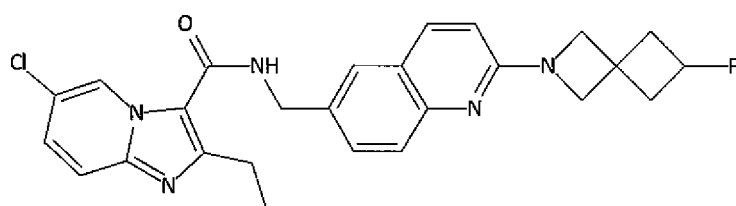


Compound 24

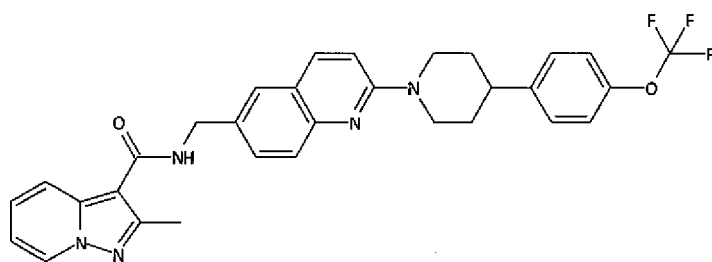


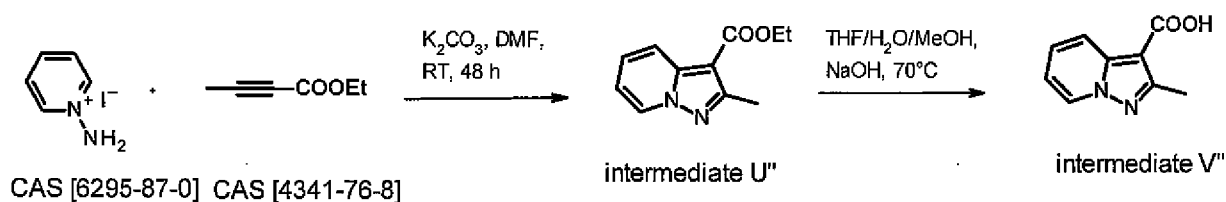
5

Compound 25



10 Compound 26

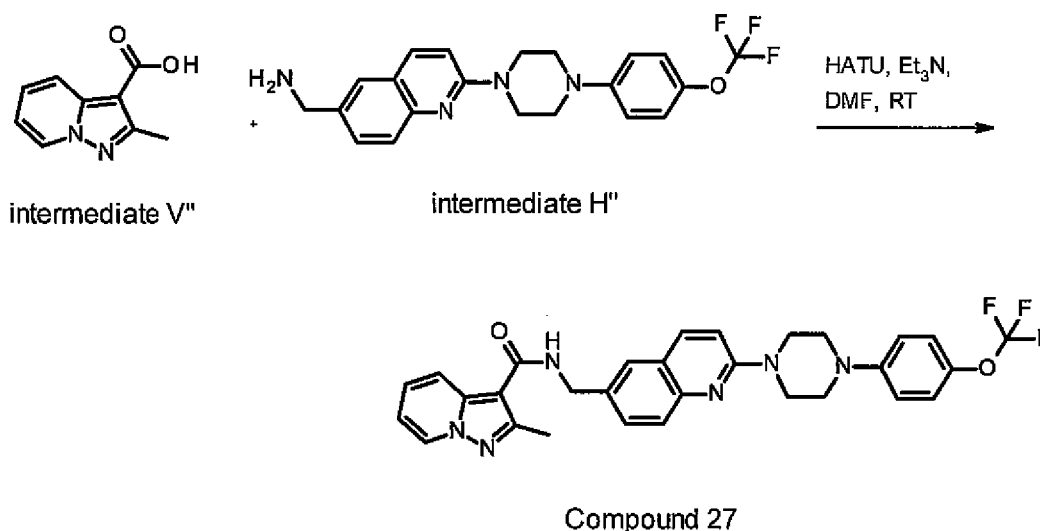


Synthesis of Compound 27**5 Intermediate U''**

Ethyl-2-butynoate (CAS [4341-76-8], 6.2 mL, 54.0 mmol) was added to a solution of 1-aminopyridinium iodide (CAS [6295-37-0], 10 g, 45 mmol) and potassium carbonate (7.5 g, 54 mmol) in DMF (100 mL). The resulting mixture was stirred at room temperature for 72 h. The mixture was evaporated to dryness and the residue was solubilized in EtOAc and washed with brine (3x). The organic layer was dried over MgSO_4 , filtered and evaporated to dryness to give 5.1 g of intermediate U'' as a brown solid (55%).

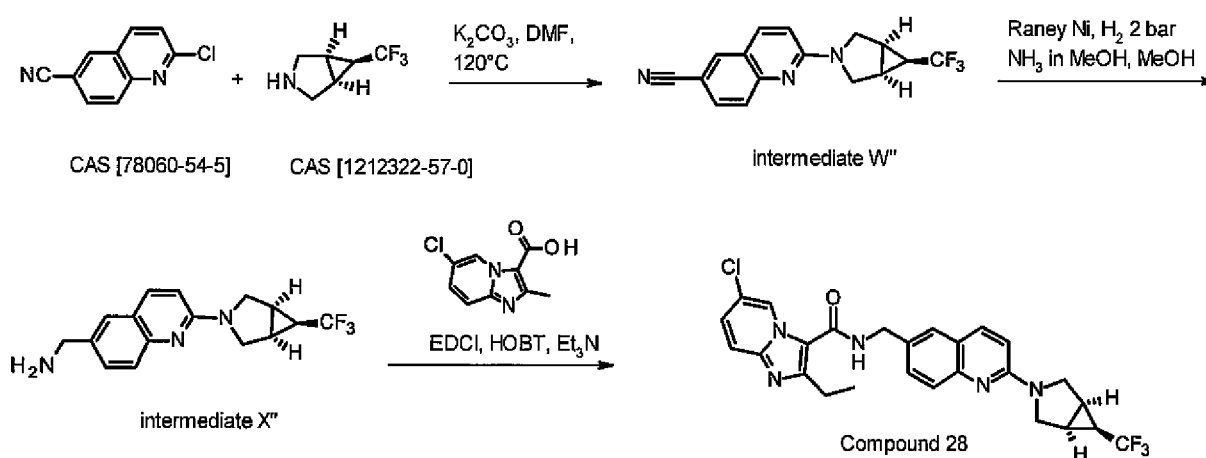
Intermediate V''

Intermediate V'' was prepared in accordance with the following procedure: aqueous sodium hydroxide 8M (e.g. about 164 mmol) is added to a solution of intermediate U'' (e.g. about 32.1 mmol) in THF (e.g. about 39 mL) and methanol (e.g. about 39 mL). The resulting mixture may be stirred at e.g. 70 °C overnight. HCl (1M) may be added to the mixture until pH~7-8. The resulting precipitate may be filtered and dried under high vacuum to give intermediate V'' as an off-white solid.



- A solution of intermediate V'' (0.1 g, 0.57 mmol), HATU (0.237 g, 0.62 mmol) and triethylamine (0.237 mL, 1.70 mmol) in DMF (7 mL) was stirred at room temperature for 30 min before the addition of intermediate H'' (0.24 g, 0.60 mmol) in DMF (5 mL). The resulting mixture was stirred at room temperature for 2 h. The mixture was
- 5 evaporated to dryness. The residue was solubilized in EtOAc and washed with an aq. solution of NaHCO₃ (1%) (2x), water and brine. The organic layer was dried over MgSO₄, filtered and evaporated to dryness. The crude product was purified by preparative LC (Regular SiOH 30 μm, 25 g Interchim, dry loading (Celite®), mobile phase gradient DCM/MeOH from 100/0 to 95/5) to give 0.152 g of Compound 27 as a
- 10 white solid (38%).
- ¹H NMR (500 MHz, DMSO-d₆) δ ppm 8.67 (d, J = 6.9 Hz, 1 H), 8.18 (t, J = 5.8 Hz, 1 H), 8.08 (d, J = 9.1 Hz, 1 H), 7.94 (d, J = 8.8 Hz, 1 H), 7.67 (s, 1 H), 7.59 (s, 2 H), 7.40 (t, J = 7.8 Hz, 1 H), 7.31 (d, J = 9.5 Hz, 1 H), 7.24 (d, J = 8.8 Hz, 2 H), 7.09 (d, J = 9.1 Hz, 2 H), 6.98 (t, J = 6.9 Hz, 1 H), 4.60 (d, J = 6.0 Hz, 2 H), 3.86 – 3.82 (m, 4 H),
- 15 3.33 – 3.30 (m, 4 H), 2.60 (s, 3 H)

Synthesis of Compound 28



20 Preparation of intermediate W''

- A mixture of 2-chloroquinoline-6-carbonitrile ([78060-54-5], 0.464 g, 2.46 mmol), trans-6-(Trifluoromethyl)-3-azabicyclo[3.1.0]-hexane hydrochloride ([1212322-57-0], 0.6 g, 3.20 mmol) and potassium carbonate (1.02 g, 7.38 mmol) in DMF (19 mL) was heated to 120 °C overnight. The mixture was evaporated to dryness. The residue was
- 25 solubilized in EtOAc and washed with brine (2x), dried over MgSO₄, filtered and evaporated to dryness. The crude product was purified by preparative LC (irregular SiOH, 15-40 μm, 80 g, Grace, dry loading (silica), mobile phase gradient

Heptane/EtOAc from 90/10 to 70/30) to give 0.3 g of intermediate W'' as a white solid (40%).

Preparation of intermediate X''

- 5 Accordingly, intermediate X'' was prepared in the same way as intermediate B'', starting from intermediate W'', and yielding 0.291 g, as a white powder, 97%.

Preparation of Compound 28

- 10 To a solution of 6-chloro-2-ethylimidazo[3,2-a]pyridine-3-carboxylic acid ([1216142-18-5], 0.066 g, 0.288 mmol) in DCM (2.9 mL) and triethylamine (0.10 mL) were added EDCI (0.083 g, 0.432 mmol) and HOBt (0.059 g, 0.434 mmol) and the mixture was stirred at room temperature for 30 min. Intermediate X'' (0.094 g, 0.306 mmol) was added and the mixture was stirred at room temperature for 8 h, then heated to 80 °C for 5 h. The mixture was cooled to room temperature and washed with water (2x). The
- 15 organic layer was dried over MgSO₄, filtered and evaporated to dryness. The crude product was purified by preparative LC (irregular SiOH, 15-40 µm, 24 g, Grace, dry loading (silica), mobile phase gradient Heptane/EtOAc from 90/10 to 10/90) to give 0.022 g of Compound 28 as white solid (15%).

- 20 ¹H NMR (500 MHz, DMSO-d₆) δ ppm 9.09 (d, J = 1.6 Hz, 1 H), 8.54 (t, J = 6.0 Hz, 1 H), 8.01 (d, J = 9.1 Hz, 1 H), 7.69 – 7.64 (m, 2 H), 7.55 (s, 2 H), 7.46 (dd, J = 9.6, 2.0 Hz, 1 H), 6.88 (d, J = 9.1 Hz, 1 H), 4.62 (d, J = 5.7 Hz, 2 H), 3.94 (d, J = 10.7 Hz, 2 H), 3.54 (br d, J = 10.1 Hz, 2 H), 3.00 (q, J = 7.6 Hz, 2 H), 2.20 (br s, 2 H), 1.86 - 1.80 (m, 1 H), 1.25 (t, J = 7.6 Hz, 3 H).

25 **Characterising Data Table**

Compound No	Meting Point (Kofler or DSC)	LCMS				
		Rt	UV Area %	MW exact	BPM1/ BPM2	LCMS Method
1		3.69	95.0	620.2	621.2	Method A
2		3.52	100.0	619.2	620.2	Method A

Further Characterising Data

Compound No	Meting Point (Kofler or DSC)	LCMS				
		Rt	UV Area %	MW exact	BPM1/ BPM2	LCMS Method
Cpd 3		3.3	95.0	607.2	608.1	Method D
Cpd 17		4.23	97.4	567.2	568.1	Method C

Compound No	Meting Point (Kofler or DSC)	LCMS				
		Rt	UV Area %	MW exact	BPM1/ BPM2	LCMS Method
Cpd 7		3.19	97.4	565.2	566.1	Method D
Cpd 18		3.29	97.7	567.2	568.1	Method D
Cpd 9		3.19	100.0	566.2	567.1	Method D
Cpd 19		3	99.3	525.1	526.1	Method D
Cpd 5 or Cpd 2		3.52	100.0	619.2	620.2	Method D
Cpd 16		3.8	100.0	568.2	569.1	Method D
Cpd 6 or Cpd 1		3.69	95.0	620.2	621.2	Method D
Cpd 15		3.86	100.0	568.2	569.1	Method D
Cpd 20		3.3	98.2	567.2	568.1	Method D
Cpd 21		3.82	97.1	620.2	621.3	Method D
Cpd 22		3.89	98.9	621.2	622.2	Method D
Cpd 23		3.74	94.4	548.2	549.2	Method D
Cpd 4		2.64	98.3	491.2	492.2	Method D
Cpd 8		3.01	99.8	592.3	593.2	Method D
Cpd 10		2.94	99.7	578.3	579.2	Method D
Cpd 24		2.48	95.1	483.2	484.1	Method D
Cpd 25		2.51	97.5	477.2	478.1	Method D
Cpd 11		5.54	98.4	539.2	540.1	Method E
Cpd 12	171.59°C / -59.2Jg-1, 25°C to 350°C/10°Cmin/40μl Al	3.68	99.4	549.2	550.3/ 608.7 [M+CH ₃ COO] ⁻	Method B
Cpd 14	188.28°C / -72.04Jg-1, 25°C to 350°C/10°Cmin/40μl Al	3.49	97.7	577.3	578.3/ 636.7 [M+CH ₃ COO] ⁻	Method B
Cpd 13	208.76°C / -94.35Jg-1, 25°C to 350°C/10°Cmin/40μl Al	3.42	100.0	509.2	510.2/ 508.3	Method B
Cpd 26	207.61 °C / -95.26 J/g (DSC: 25°C to 350°C/10°Cmin/40 μl Al)	3.55	98.2	559.6	560.2/ 618.5 [M+CH ₃ COO] ⁻	Method B

Compound No	Melting Point (Kofler or DSC)	LCMS				
		Rt	UV Area %	MW exact	BPM1/ BPM2	LCMS Method
Cpd 27	217.14 °C / -83.66 J/g (DSC: 25°C to 350°C/10°Cmin/40 µl Al)	3.4	96	560.2	561.2/ 619.5 [M+CH ₃ COO] ⁻	Method B
Cpd 28	251.69 °C / -79.88 Jg ⁻¹ , 25°C to 350°C/10°Cmin/40 µl Al (DSC: 25°C to 350°C/10°Cmin/40 µl Al)	3.3	98.8	513.2	514.2/ 512.3	Method B

Analytical methods

LCMS

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

General procedure LCMS Methods A

The High Performance Liquid Chromatography (HPLC) measurement was performed using a LC pump, a diode-array (DAD) or a UV detector and a column as specified in the respective methods. If necessary, additional detectors were included (see table of methods below).

Flow from the column was brought to the Mass Spectrometer (MS) which was configured with an atmospheric pressure ion source. It is within the knowledge of the skilled person to set the tune parameters (e.g. scanning range, dwell time, etc) in order to obtain ions allowing the identification of the compound's nominal monoisotopic molecular weight (MW). Data acquisition was performed with appropriate software. Compounds are described by their experimental retention times (*R_t*) and ions. If not specified differently in the table of data, the reported molecular ion corresponds to the [M+H]⁺ (protonated molecule) and/or [M-H]⁻ (deprotonated molecule). In case the compound was not directly ionizable the type of adduct is specified (i.e. [M+NH₄]⁺, [M+HCOO]⁻, etc). For molecules with multiple isotopic patterns (Br, Cl..), the reported value is the one obtained for the lowest isotope mass. All results were obtained with experimental uncertainties that are commonly associated with the method used.

Hereinafter, "MSD" Mass Selective Detector, "DAD" Diode Array Detector.

Table: LCMS Method codes (Flow expressed in mL/min; column temperature (T) in °C; Run time in minutes).

Method code	Instrument	Column	Mobile phase	gradient	Flow	Run time
					50	
<i>Method A</i>	Agilent: 1100/1200 -DAD and MSD	Agilent: TC-C18 (5µm, 2.1x50mm)	A: CF ₃ COOH 0.1% in water; B: CF ₃ COOH 0.05% in CH ₃ CN	90% A for 0.8min, to 20% A in 3.7min, held for 3min, back to 90% A in 2min.	0.8 50	10.5

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.

5

Further Methods

General procedure

The High Performance Liquid Chromatography (HPLC) measurement was performed using a LC pump, a diode-array (DAD) or a UV detector and a column as specified in the respective methods. If necessary, additional detectors were included (see table of methods below).

Flow from the column was brought to the Mass Spectrometer (MS) which was configured with an atmospheric pressure ion source. It is within the knowledge of the skilled person to set the tune parameters (e.g. scanning range, dwell time...) in order to obtain ions allowing the identification of the compound's nominal monoisotopic molecular weight (MW). Data acquisition was performed with appropriate software. Compounds are described by their experimental retention times (R_t) and ions. If not specified differently in the table of data, the reported molecular ion corresponds to the $[M+H]^+$ (protonated molecule) and/or $[M-H]^-$ (deprotonated molecule). In case the compound was not directly ionizable the type of adduct is specified (i.e. $[M+NH_4]^+$, $[M+HCOO]^-$, etc...). For molecules with multiple isotopic patterns (Br, Cl...), the reported value is the one obtained for the lowest isotope mass. All results were obtained with experimental uncertainties that are commonly associated with the method used.

Hereinafter, "SQD" means Single Quadrupole Detector, "RT" room temperature, "BEH" bridged ethylsiloxane/silica hybrid, "HSS" High Strength Silica, "DAD" Diode Array Detector.

Table: LCMS Method codes (Flow expressed in mL/min; column temperature (T) in °C; Run time in minutes).

Method code	Instrument	Column	Mobile phase	gradient	Flow	Run time
					Column T	
Method B	Waters: Acquity UPLC® - DAD and Quattro Micro™	Waters: BEH C18 (1.7µm, 2.1x100 mm)	A: 95% CH ₃ COONH ₄ 7mM / 5% CH ₃ CN, B: CH ₃ CN	84.2% A for 0.49min, to 10.5% A in 2.18min, held for 1.94min, back to 84.2% A in 0.73min, held for 0.73min.	0.343	6.2
					40	
					40	

5 Hereinafter, "MSD" Mass Selective Detector, "DAD" Diode Array Detector.

Table: LCMS Method codes (Flow expressed in mL/min; column temperature (T) in °C; Run time in minutes).

Method Code	Instrument	Column	Mobile phase	gradient	Flow	Run time
					Column T	
Method C	Agilent: 1100/1200 -DAD and MSD	Agilent: TC-C18 (5µm, 2.1x50mm)	A: CF ₃ COOH 0.1% in water, B: CF ₃ COOH 0.05% in CH ₃ CN	100% A for 1min, to 40% A in 4min, to 15% A in 2.5min, back to 100% A in 2min.	0.8	10.5
					50	
Method D	Agilent: 1100/1200 -DAD and MSD	Agilent: TC-C18 (5µm, 2.1x50mm)	A: CF ₃ COOH 0.1% in water, B: CF ₃ COOH 0.05% in CH ₃ CN	90% A for 0.8min, to 20% A in 3.7min, held for 3min, back to 90% A in 2min.	0.8	10.5
					50	
Method E	Agilent: 1100/1200 -DAD and MSD	Waters: XBridge™ Shield RP18 (5µm, 2.1x50mm)	A: NH ₄ OH 0.05% in water, B: CH ₃ CN	100% A for 1min, to 40% A in 4min, held for 2.5min, back to 100% A in 2min.	0.8	10.5
					40	
					50	

Pharmacological examplesMIC determination for testing compounds against *M. tuberculosis*.TEST 1

- Appropriate solutions of experimental and reference compounds were made in 96 well plates with 7H9 medium. Samples of *Mycobacterium tuberculosis* strain H37Rv were taken from cultures in logarithmic growth phase. These were first diluted to obtain an optical density of 0.3 at 600 nm wavelength and then diluted 1/100, resulting in an inoculum of approximately 5×10^5 colony forming units per well. Plates were incubated at 37°C in plastic bags to prevent evaporation. After 7 days, resazurin was added to all wells. Two days later, fluorescence was measured on a Gemini EM Microplate Reader with 543 excitation and 590 nm emission wavelengths and MIC₅₀ and/or pIC₅₀ values (or the like, e.g. IC₅₀, IC₉₀, pIC₉₀, etc) were (or may be) calculated.

TEST 2

- Round-bottom, sterile 96-well plastic microtiter plates are filled with 100 µl of Middlebrook (1x) 7H9 broth medium. Subsequently, an extra 100 µl medium is added to column 2. Stock solutions (200 x final test concentration) of compounds are added in 2 µl volumes to a series of duplicate wells in column 2 so as to allow evaluation of their effects on bacterial growth. Serial 2-fold dilutions are made directly in the microtiter plates from column 2 to 11 using a multipipette. Pipette tips are changed after every 3 dilutions to minimize pipetting errors with high hydrophobic compounds. Untreated control samples with (column 1) and without (column 12) inoculum are included in each microtiter plate. Approximately 10000 CFU per well of *Mycobacterium tuberculosis* (strain H37RV), in a volume of 100 µl in Middlebrook (1x) 7H9 broth medium, is added to the rows A to H, except column 12. The same volume of broth medium without inoculum is added to column 12 in row A to H. The cultures are incubated at 37°C for 7 days in a humidified atmosphere (incubator with open air valve and continuous ventilation). On day 7 the bacterial growth is checked visually. The 90 % minimal inhibitory concentration (MIC₉₀) is determined as the concentration with no visual bacterial growth.

TEST 3: Time kill assays

- Bactericidal or bacteriostatic activity of the compounds can be determined in a time kill assay using the broth dilution method. In a time kill assay on *Mycobacterium tuberculosis* (strain H37RV), the starting inoculum of *M. tuberculosis* is 10^6 CFU / ml in Middlebrook (1x) 7H9 broth. The antibacterial compounds are used at the concentration of 0.1 to 10 times the MIC₉₀. Tubes receiving no antibacterial agent constitute the culture growth control. The tubes containing the microorganism and the

test compounds are incubated at 37 °C. After 0, 1, 4, 7, 14 and 21 days of incubation samples are removed for determination of viable counts by serial dilution (10^{-1} to 10^{-6}) in Middlebrook 7H9 medium and plating (100 μ l) on Middlebrook 7H11 agar. The plates are incubated at 37 °C for 21 days and the number of colonies are determined.

- 5 Killing curves can be constructed by plotting the $\log_{10}$ CFU per ml versus time. A bactericidal effect is commonly defined as 3- $\log_{10}$ decrease in number of CFU per ml as compared to untreated inoculum. The potential carryover effect of the drugs is removed by serial dilutions and counting the colonies at highest dilution used for plating.

10

TEST 4 (see also test 1 above; in this test a different strain of *Mycobacterium tuberculosis* strain is employed)

Appropriate solutions of experimental and reference compounds were made in 96 well plates with 7H9 medium. Samples of *Mycobacterium tuberculosis* strain EH 4.0

- 15 (361.269) were taken from cultures in stationary growth phase. These were first diluted to obtain an optical density of 0.3 at 600 nm wavelength and then diluted 1/100, resulting in an inoculum of approximately 5×10^5 colony forming units per well. Plates were incubated at 37°C in plastic bags to prevent evaporation. After 7 days, resazurin was added to all wells. Two days later, fluorescence was measured on a
- 20 Gemini EM Microplate Reader with 543 nm excitation and 590 nm emission wavelengths and MIC₅₀ and/or pIC₅₀ values (or the like, e.g. IC₅₀, IC₉₀, pIC₉₀, etc) were (or may be) calculated. pIC₅₀ values may be recorded below in μ g/mL.

RESULTS

- 25 Compounds of the invention/examples, for example when tested in Test 1 or Test 2 described above, may typically have an IC₉₀ value from 0.01 to 10 μ g/ml. Compounds of the invention/examples, for example when tested in Test 1 or Test 2 described above, may typically have a pIC₅₀ from 3 to 10 (e.g. from 4.0 to 9.0, such as from 5.0 to 8.0)
- 30 Compounds of the examples were tested in Test 1 described above (in section "Pharmacological Examples") and the following results were obtained:

Biological Data Table

Compound No	pIC ₅₀	pIC ₅₀ *	pIC ₅₀ **
1	6.87	6.88	6.96
2	6.17	6.16	6.23

* and ** denote repeated (2nd and 3rd) tests in the relevant assay; there may be some experimental deviation observed in the results

5

Further Biological Data

Compounds of the examples were tested in Test 4 described above (in section "Pharmacological Examples") and the following results were obtained:

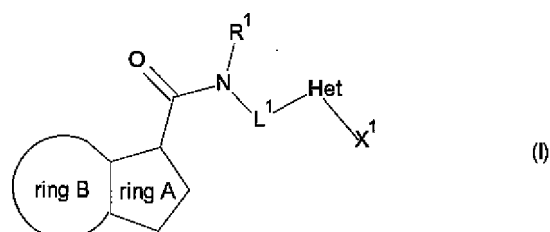
Compound No	pIC ₅₀
Cpd 3	7.3
Cpd 17	7.1
Cpd 7	6.7
Cpd 18	6
Cpd 9	6.85
Cpd 19	6.55
Cpd 5 or Cpd 2	6.7
Cpd 16	6.2
Cpd 6 or Cpd 1	7.4
Cpd 15	6.2
Cpd 20	6.1
Cpd 21	<4.9

Compound No	pIC ₅₀
Cpd 22	<4.9
Cpd 23	<4.9
Cpd 4	7.5
Cpd 8	6.8
Cpd 10	6.9
Cpd 24	8.2
Cpd 25	6.75
Cpd 11	6.45
Cpd 12	<4.9
Cpd 14	6.7
Cpd 13	<4.9
Cpd 26	6.4
Cpd 27	6.1

10

CLAIMS

1. A compound of formula (I) for use in the treatment of tuberculosis



wherein

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

L^1 represents a linker group $-C(R^a)(R^b)-$ (or is not present);

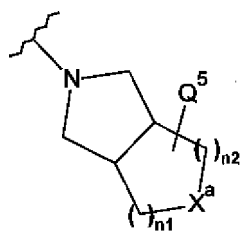
10 Het represents a heteroaromatic linker group (which linker group may itself be optionally substituted by one or more substituents selected from fluoro, $-O-R^c$ and C_{1-6} alkyl, wherein the latter alkyl moiety is itself optionally substituted by one or more fluoro atoms);

15 R^a , R^b and R^c independently represent hydrogen or C_{1-6} alkyl (optionally substituted by one or more fluoro atoms);

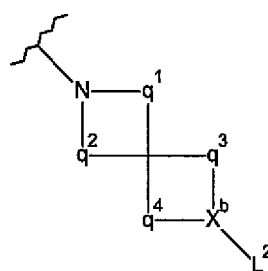
X^1 represents $-N(R^2)(R^3)$;

R^2 and R^3 :

- 20 (i) independently represent hydrogen or, preferably, C_{1-6} alkyl optionally substituted by one or more substituents selected from Q^1 and $=O$;
- (ii) independently represent aryl or heteroaryl, each of which is optionally substituted by one or more substituents selected from Q^2 ;
- (iii) independently represent cycloalkyl or heterocycloalkyl, each of which is
- 25 optionally substituted by one or more substituents selected from Q^3 and $=O$;
- or
- (iv) can be linked together to form:
- a. a 3- to 8-membered ring optionally containing one to three heteroatoms (e.g. nitrogen, oxygen and/or sulfur), and which ring is optionally
- 30 substituted by one or more substituents selected from Q^4 and $=O$;
- b. a "fused" bicyclic ring of the following type:



c. a "spiro" ring of the following type:



- 5 Q^1 , Q^2 , Q^3 , Q^4 and Q^5 each independently represent one or more substituents selected from halo, C_{1-6} alkyl, $-OC_{1-6}$ alkyl (which latter two alkyl moieties may themselves be optionally substituted by one or more halo, e.g. fluoro, atoms), aryl and heteroaryl (which latter two aromatic groups may themselves be optionally substituted by one or more substituents selected from halo, C_{1-6} alkyl and $-OC_{1-6}$ alkyl, which latter two alkyl
- 10 moieties may themselves be substituted with one or more fluoro atoms);

$n1$ and $n2$ independently represent 0 or 1;

X^a represents $-C(R^{a1})(R^{b1})_m-$ or $-N(R^{c1})-$;

- 15 m represents 1 or 2;
each R^{a1} and R^{b1} independently represents fluoro, hydrogen or C_{1-6} alkyl;
 R^{c1} represents hydrogen or C_{1-6} alkyl;

- 20 X^b represents $C(R^d)$, N, O (in which case L^2 is not present) or $C=O$ (in which case L^2 is also not present);

R^d represents H, F or $-OR^e$ (wherein R^e represents H or C_{1-6} alkyl optionally substituted by one or more fluoro atoms);

- 25 q^1 represents $-X^c-(CH_2)_{n1}-X^d$;
 $n1$ represents 0, 1 or 2;
 q^2 represents $-X^e-(CH_2)_{n2}-X^f$;

- n_2 represents 0, 1 or 2, but wherein n_1 and n_2 do not both represent 0;
- X^c (which is attached to X^a) is either not present, or, when X^a represents CH, then X^c may represent -O-, -NH- or -S-;
- 5 X^d is either not present, or, when n_1 represents 2 or when X^c is not present, X^a represents $C(R^c)$ and n_1 represents 1, then X^d may also represent -O-, -NH- or -S-; X^e and X^f independently are either not present, or may independently represent -O-, -NH- or -S-, provided that the aforementioned heteroatoms are not directly attached to or α to another heteroatom;
- 10 q^3 represents $-X^g-(CH_2)_{n_3}-X^h-$;
 q^4 represents $-X^i-(CH_2)_{n_4}-X^j-$;
 n_3 represents 0, 1 or 2;
 n_4 represents 0, 1 or 2, but wherein n_3 and n_4 do not both represent 0;
- 15 X^g , X^h , X^i and X^j independently are either not present, or may represent -O-, -NH- or -S-, provided that the aforementioned heteroatoms are not directly attached to or α to another heteroatom;
- 20 when X^b represents O or C=O, then L^2 is not present;
 when X^b represents $C(R^d)$ (e.g. CH) or N, then L^2 may represent hydrogen, halo, $-OR^f$, $-C(O)-R^g$, C_{1-6} alkyl (optionally substituted by one or more halo, e.g. fluoro atoms) or an aromatic group (optionally substituted by one or more substituents selected from
- 25 fluoro, $-CF_3$ and/or $-SF_5$), $-OC_{1-6}$ alkyl (itself optionally substituted by one or more fluoro atoms), -O-phenyl (itself optionally substituted by halo, C_{1-6} alkyl, C_{1-6} fluoroalkyl and/or $-OC_{1-6}$ alkyl) or $-SF_5$);
- 30 R^f represents hydrogen, C_{1-6} alkyl (optionally substituted by one or more fluoro) or an aromatic group (itself optionally substituted by one or more substituents selected from halo, C_{1-6} alkyl and $-OC_{1-6}$ alkyl, where the latter two alkyl moieties may themselves be optionally substituted by one or more fluoro atoms);
- 35 R^g represents hydrogen or C_{1-6} alkyl (optionally substituted by one or more substituents selected from fluoro, or $-OC_{1-3}$ alkyl, which latter moiety is also optionally substituted by one or more fluoro atoms) or an aromatic group (optionally substituted by one or more substituents selected from halo, C_{1-6} alkyl or $-OC_{1-6}$ alkyl);

ring A is a 5-membered aromatic ring containing at least one heteroatom (preferably containing at least one nitrogen atom);

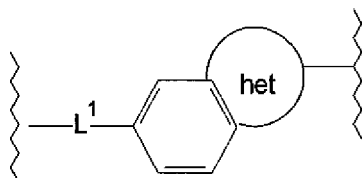
- 5 ring B is a 5- or 6-membered ring, which may be aromatic or non-aromatic, optionally containing one to four heteroatoms (preferably selected from nitrogen, oxygen and sulfur);

10 either ring A and/or ring B may be optionally substituted by one or more substituents selected from: halo, C₁₋₆ alkyl (optionally substituted by one or more halo, e.g. fluoro atoms) and/or -OC₁₋₆alkyl (itself optionally substituted by one or more fluoro atoms), or a pharmaceutically-acceptable salt thereof.

2. A compound for use as claimed in Claim 1, wherein:

- 15 R¹ represents hydrogen;
R^a and R^b independently represent hydrogen; and/or
L¹ represents -CH₂-.

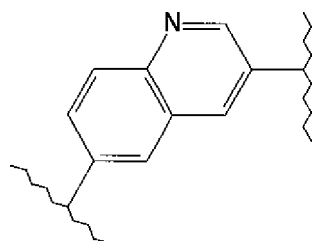
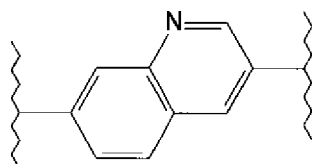
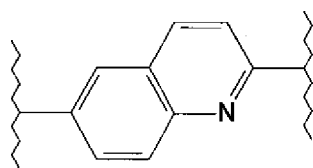
3. A compound for use as claimed in Claim 1 or Claim 2, wherein when X¹ represents a
20 heteroaromatic linker group that is a bicyclic heteroaromatic group linked to L¹ (or the amido moiety, when L¹ is not present) via a carbocyclic aromatic moiety, so forming e.g.:



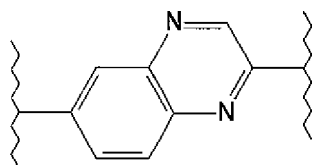
25 in which "het" (in the above instance) is a heteroaromatic 5- or 6-membered ring.

4. A compound for use as claimed in Claim 3, wherein the linker group is a fused bicyclic ring system comprising a phenyl and/or a 5- or 6-membered monocyclic heteroaryl group (for instance forming a 9- or 10-membered heteroaromatic group,
30 which consists of two separate rings fused with each other, in which each ring is 5- or 6-membered so forming a 6,6- or 6,5- or fused bicyclic ring), hence including groups such as those described below:

-quinolylene (such as 2-quinolylene or 3-quinolylene), e.g.:



-quinoxaliny (such as 2-quinoly (ene), e.g.:



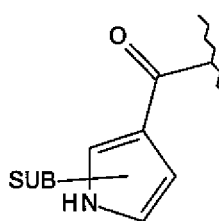
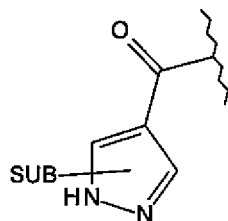
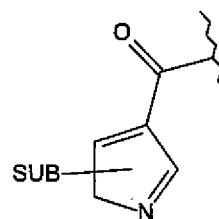
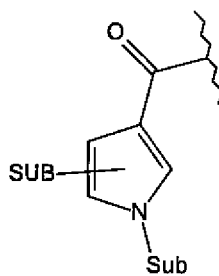
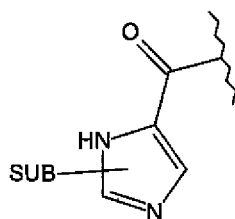
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5. A compound for use as claimed in any of the preceding claims, wherein when X^1 represents $-N(R^2)(R^3)$, then:

- (i) R^2 and R^3 independently represent C_{1-3} alkyl (e.g. methyl or ethyl) optionally substituted by one or more (e.g. one) substituent(s) selected from Q^1 ;
- (ii) R^2 and R^3 are linked together to form:
 - a. a 4- to 6-membered ring optionally containing one further heteroatom (e.g. so forming a piperidinyl, piperazinyl or azetidiny ring), which is optionally (and, in an aspect, preferably) substituted by Q^4 ;
 - b. a fused bicyclic ring in which X^a represents $-CH_2-$ and which is optionally substituted (e.g. at the X^a position) by one or more (e.g. one) Q^5 substituent(s);
 - c. a spiro ring system, in which X^b represents CH and L^2 is present and as defined herein.

20

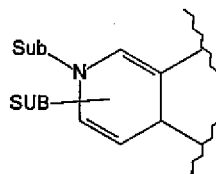
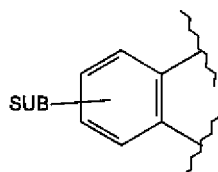
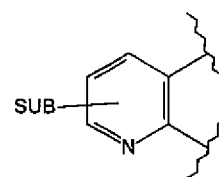
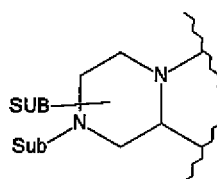
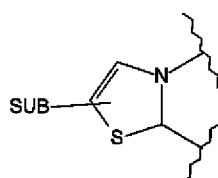
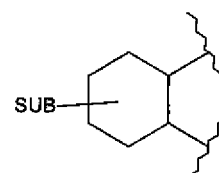
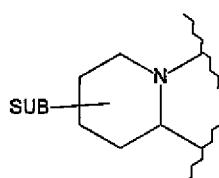
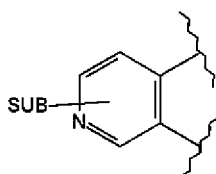
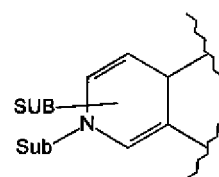
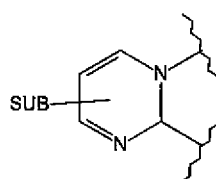
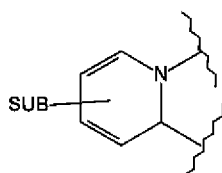
6. A compound for use as claimed in any of the preceding claims wherein: ring A is represented as follows:

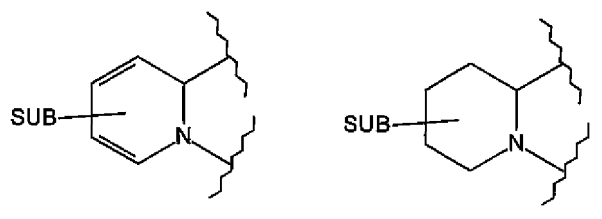


; and/or

ring B is represented as follows:

5

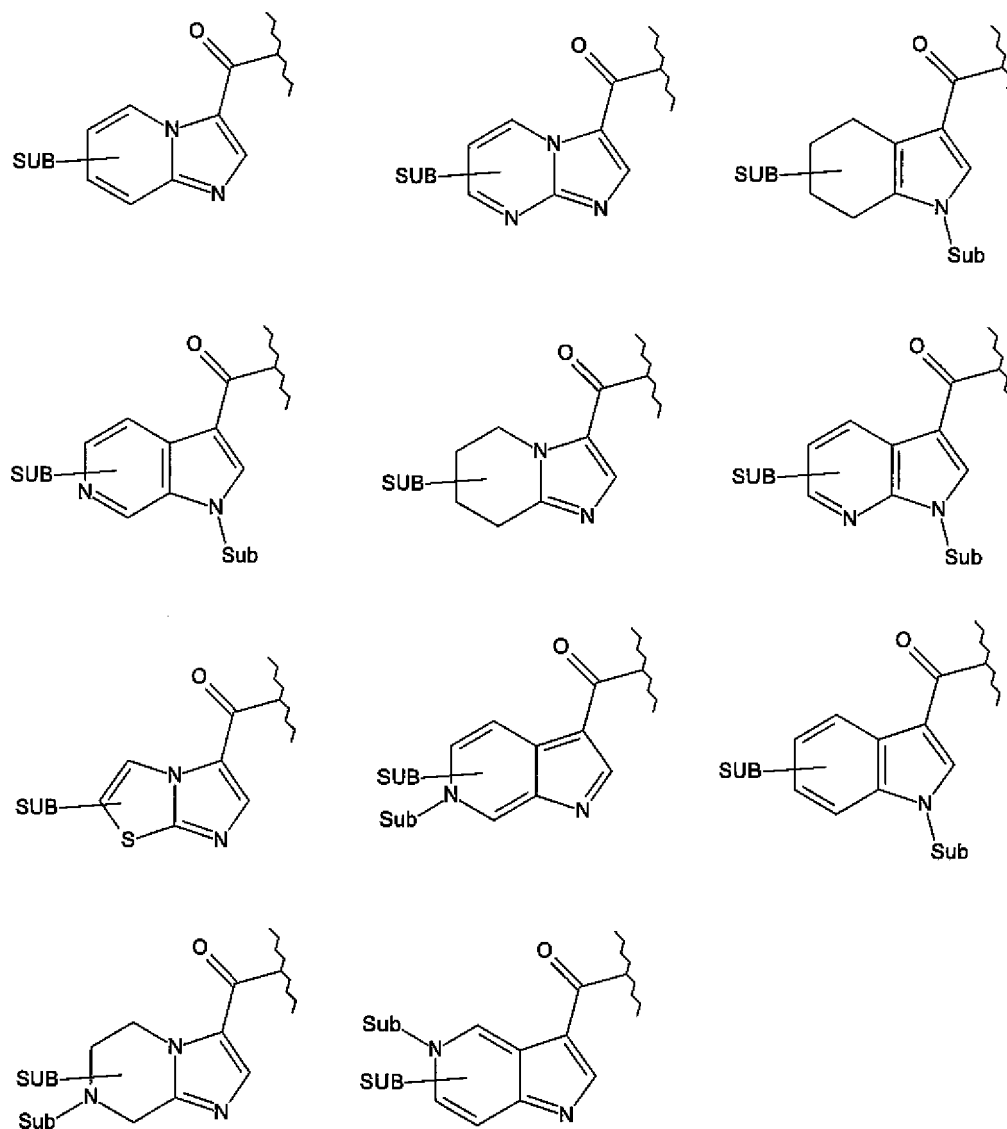


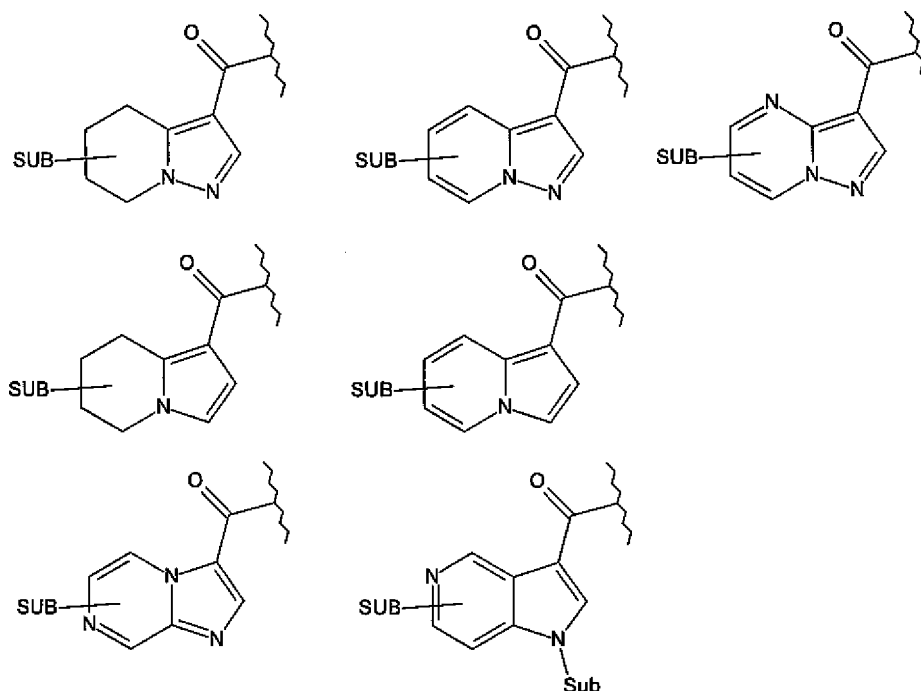


wherein "SUB" and "Sub" represent one or more possible substituents on the relevant atom (e.g. carbon or nitrogen atom).

5

7. A compound for use as claimed in any one of the preceding claims, wherein the combined ring systems, i.e. Ring A and Ring B may be represented as follows:

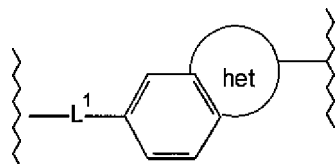




where "SUB" represents one or more possible substituents on the bicycle (i.e. on ring A and/or on ring B) and "Sub" represents a possible optional substituent on the N atom of the bicycle (unsubstituted in this context would mean "NH").

8. A compound for use as claimed in any of the preceding claims, wherein:
 - Q¹ represents aryl (e.g. phenyl) optionally substituted by -OC₁₋₃alkyl (itself optionally substituted by one or more fluoro atoms, so forming e.g. a -OCF₃ group);
 - 10 Q⁴ represents aryl (e.g. phenyl) optionally substituted by -OC₁₋₃alkyl (itself optionally substituted by one or more fluoro atoms, so forming e.g. a -OCF₃ group);
 - Q⁵ represents halo (e.g. fluoro);
 - X^c, X^d, X^e and X^f are independently not present;
 - n1 and n2 independently represent 1;
 - 15 X^g, X^h, Xⁱ and X^j are independently not present;
 - n3 and n4 independently represent 1; and/or
 - L² represents an aromatic group (e.g. aryl or phenyl) optionally substituted by one or more (e.g. one) substituent(s) selected from -OC₁₋₃alkyl (itself optionally substituted by one or more fluoro atoms, so forming e.g. a -OCF₃ group).
 - 20
9. A compound of formula (I) as defined in Claim 1 but wherein:
 - L¹ represents -CH₂-;

Het represents a bicyclic heteroaromatic group linked to L^1 (or the amido moiety, when L^1 is not present) via a carbocyclic aromatic moiety, so forming e.g.:



5 in which "het" (in the above instance) is a heteroaromatic 5- or 6-membered ring; when X^1 represents $-N(R^2)(R^3)$, then:

- (i) R^2 and R^3 independently represent C_{1-3} alkyl (e.g. methyl or ethyl) optionally substituted by one or more (e.g. one) substituent(s) selected from Q^1 (but wherein when both R^2 and R^3 represent alkyl, then at least one is substituted by Q^1 in which Q^1 represents an optionally substituted aryl group as defined herein);
- (ii) R^2 and R^3 are linked together to form:
 - a. a 4- to 6-membered ring optionally containing one further heteroatom (e.g. so forming a piperidinyl, piperazinyl or azetidiny ring), which is substituted by one or two substituents selected from Q^4 (in which at least one Q^4 substituent is present that represents an optionally substituted aryl group as defined herein);
 - b. a fused bicyclic ring in which X^a represents $-CH_2-$ and which is optionally substituted (e.g. at the X^a position) by one or more (e.g. one) Q^5 substituent(s);
 - c. a spiro ring system, in which X^b represents CH and L^2 is present and as defined herein;

L^2 represents an aromatic group (e.g. aryl or phenyl) optionally substituted by one or more (e.g. one) substituent(s) e.g. selected from e.g. $-OC_{1-3}$ alkyl (itself optionally substituted by one or more fluoro atoms, so forming e.g. a $-OCF_3$ group); ring A and ring B together represent a 8 or 9-membered bicyclic ring (ring A is a 5-membered ring and ring B may be a 5 or 6-membered ring, in which both rings are preferably aromatic) containing at least one nitrogen atom (and in a major embodiment, at least one nitrogen atom that is common to both rings); optional substituents on ring A and ring B are halo, C_{1-3} alkyl and $-OC_{1-3}$ alkyl; and other integers are as defined herein.

10. A compound as claimed in claim 9 wherein:

when Q^1 represents aryl, then it is an optionally substituted as defined herein (e.g. by one or more substituents selected from $-OC_{1-3}alkyl$ (itself optionally substituted by one or more fluoro atoms, so forming e.g. a $-OCF_3$ group));

5 when Q^4 represents aryl, then it is an optionally substituted phenyl as defined herein (e.g. by one or more substituents selected from $-OC_{1-3}alkyl$ (itself optionally substituted by one or more fluoro atoms, so forming e.g. a $-OCF_3$ group));

when Q^4 represents a non-aromatic substituent, then it may represent e.g. fluoro;

Q^5 represents halo (e.g. fluoro);

10 X^c , X^d , X^e and X^f are independently not present;

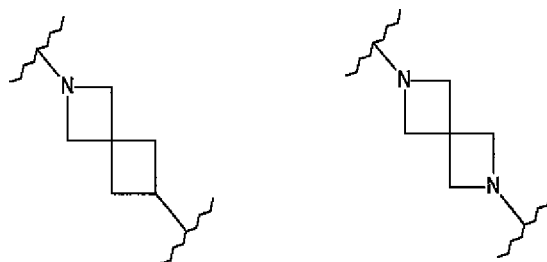
$n1$ and $n2$ independently represent 1;

X^g , X^h , X^i and X^j are independently not present;

$n3$ and $n4$ independently represent 1.

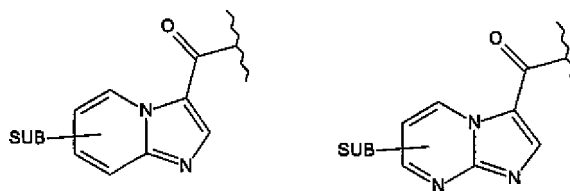
15 11. A compound as claimed in claim 9 or claim 10 wherein:

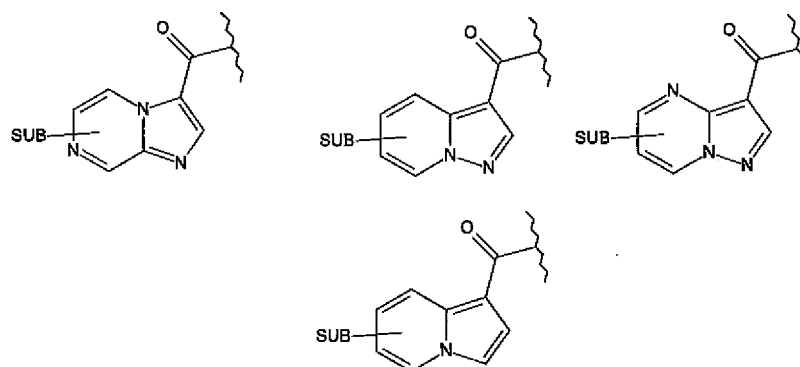
the X^b -containing rings are represented as defined herein or more particularly as follows:



(or any one of the above-mentioned representations); and/or

20 the ring A and ring B bicycles are represented as defined herein or more particularly as follows:

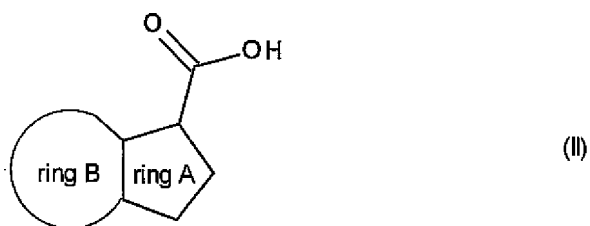




(or any one of the above-mentioned representations).

12. A compound as defined in any of claims 9 to 11, for use as a pharmaceutical.
- 5 13. 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 9-11.
- 10 14. Compound according to any one of claims 9-11 for use in the treatment of tuberculosis.
- 15 15. Use of a compound as defined in any of claims 1 to 8 or use of a compound according to any one of claims 9 to 11 for the manufacture of a medicament for the treatment of tuberculosis.
- 20 16. A combination of (a) a compound as defined in any of claims 1 to 8 or a compound according to any one of claims 9 to 11, and (b) one or more other anti-tuberculosis agent.
- 25 17. A product containing (a) a compound as defined in any of claims 1 to 8 or a compound according to any one of claims 9 to 11, and (b) one or more other anti-tuberculosis agent, as a combined preparation for simultaneous, separate or sequential use in the treatment of a bacterial infection.
18. A process for the preparation of a compound of formula (I) as defined in Claim 1, or according to any one of Claims 9-11, which process comprises:

(i) reaction of a compound of formula (II),



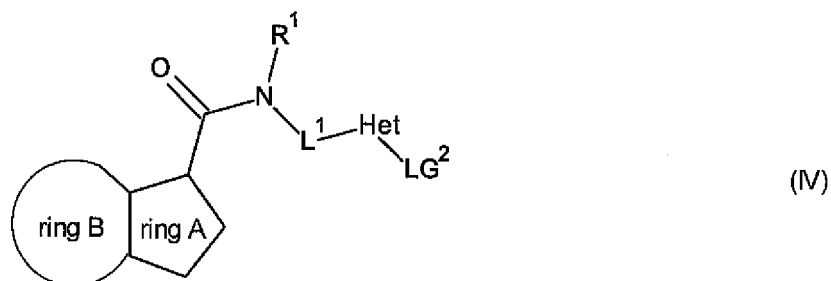
wherein the integers are as defined in Claim 1, or a suitable derivative thereof, with a compound of formula (III)



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wherein the integers are as defined in Claim 1;

(ii) coupling of a compound of formula (IV),



10 wherein the integers are as defined in Claim 1, and LG² represents a suitable leaving group, with a compound of formula (V),



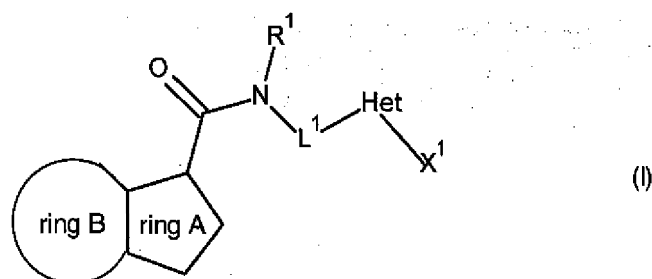
wherein the integers are as defined in Claim 1.

ABSTRACT

ANTIBACTERIAL COMPOUNDS

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The present invention relates to the following compounds



10 wherein the integers are as defined in the description, and where the compounds may be useful as medicaments, for instance for use in the treatment of tuberculosis.