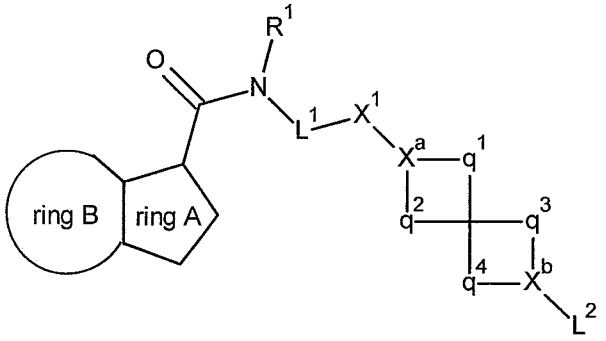
SUMMARY

There is now provided a compound of formula (I)



(I)

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);

X^1 represents an optional aromatic linker group;

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

X^a represents $C(R^c)$ or N;

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

q^1 represents $-X^c-(CH_2)_{n1}-X^d-$;

n1 repesents 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 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 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 repesents 0, 1 or 2;
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;

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_{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 halo, C_{1-6} alkyl (itself optionally substituted by one or more substituents selected from 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 $-SF_5$);

R^f represents hydrogen or C_{1-6} alkyl (optionally substituted by one or more fluoro);

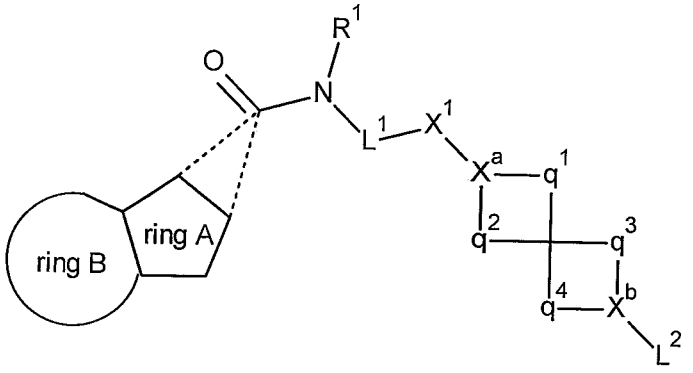
ring A is a 5-membered aromatic ring containing at least one heteroatom (preferably containing at least one nitrogen atom);

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);

either ring A and/or ring B may be optionally substituted by one or more substituents selected from: halo, C_{1-6} alkyl (optionally substituted by one or more halo, e.g. fluoro atoms) and/or $-OC_{1-6}$alkyl (itself optionally substituted by one or more fluoro atoms), or a pharmaceutically-acceptable salt thereof;

which compounds may be referred to herein as "compounds of the invention" or "compounds of the disclosure".

In particular, in a major embodiment of thedisclosure, the following compounds of formula (IA) are provided for use in the treatment of tuberculosis:



(IA)

wherein

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

L^1 represents a linker group $-C(R^a)(R^b)-$;

X^1 represents an optional carbocyclic aromatic linker group (which linker group may itself be optionally substituted by one or more substituents selected from fluoro, -OH, $-OC_{1-6}$ alkyl and C_{1-6} alkyl, wherein the latter two alkyl moieties are themseleves optionally substituted by one or more fluoro atoms);

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

X^a represents $C(R^c)$ or N;

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^c and R^d independently represent H, F or $-OR^e$ (wherein R^e represents H or C_{1-6} alkyl optionally substituted by one or more fluoro atoms), or, R^d and L^2 may be linked together to form a 4- to 6-membered cyclic group (i.e. a spiro-cycle), optionally containing one to three heteroatoms;

q^1 represents $-X^c-(CH_2)_{n1}-X^d-$;

n1 repesents 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;

ring A may be attached to the requisite amide moiety (i.e. the –C(O)-N(R^1)- moiety) *via* either one of two possible bonds represented by the dotted lines, which bonds are linked to ring A at two different atoms (of that ring);

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

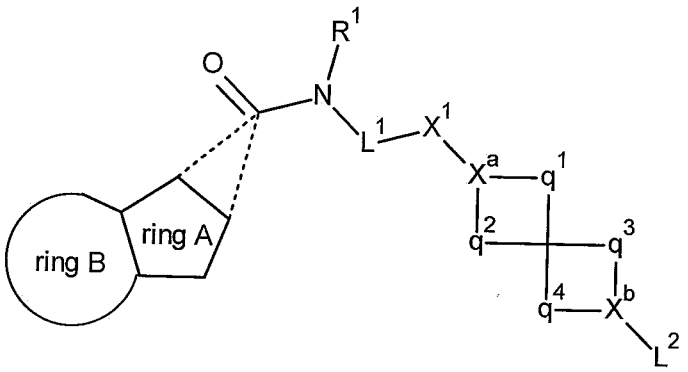
ring B is a 5- or 6-membered ring, which may be aromatic or non-aromatic, optionally containing one to four heteroatoms (preferably selected from nitrogen, oxygen and sulfur);

either ring A and/or ring B may be optionally substituted by one or more substituents selected from: halo, C_{1-6} alkyl (optionally substituted by one or more halo, e.g. fluoro atoms) and/or -OC_{1-6}alkyl (itself optionally substituted by one or more fluoro atoms),

or a pharmaceutically-acceptable salt thereof,

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

In one aspect, the present disclosure relates to a compound of formula (IA) for use in the treatment of tuberculosis



(IA)

wherein

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

L^1 represents a linker group -C(R^a)(R^b)-;

X^1 represents an optional carbocyclic aromatic linker group (which linker group may itself be optionally substituted by one or more substituents selected from fluoro, -OH, -OC_{1-6} alkyl and C_{1-6} alkyl, wherein the latter two alkyl moieties are themseleves optionally substituted by one or more fluoro atoms);

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

X^a represents $C(R^c)$ or N;
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^c and R^d independently represent H, F or $-OR^e$ (wherein R^e represents H or C_{1-6} alkyl optionally substituted by one or more fluoro atoms), or, R^d and L^2 may be linked together to form a 4- to 6-membered cyclic group (i.e. a spiro-cycle), optionally containing one to three heteroatoms;

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

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

when X^b represents $C(R^a)$ 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 halo, C_{1-6} alkyl (itself optionally substituted by one or more substituents selected from 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 $-SF_5$); or, when attached to nitrogen, i.e. when X^b is N, L^2 represents $-S(O)_2-C_{1-6}$alkyl optionally substituted by one or more fluoro atoms (e.g. forming $-S(O)_2CF_3$);

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 themseleves be optionally substituted by one or more fluoro atoms);

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 substuituted 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 may be attached to the requisite amide moiety (i.e. the $-C(O)-N(R^1)-$ moiety) *via* either one of two possible bonds represented by the dotted lines, which bonds are linked to ring A at two different atoms (of that ring);

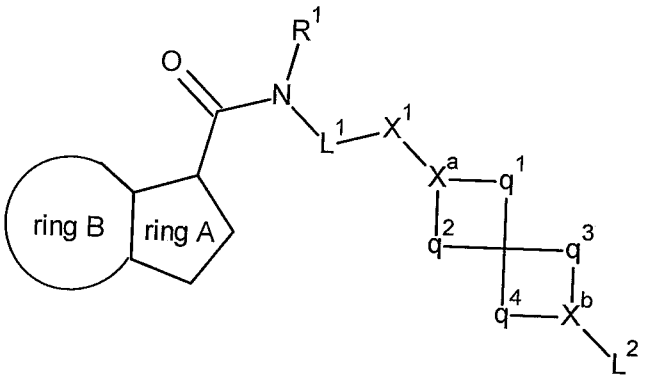
ring A is a 5-membered aromatic ring containing at least one heteroatom (preferably containing at least one nitrogen atom);

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);

either ring A and/or ring B may be optionally substituted by one or more substituents selected from: halo, C_{1-6} alkyl (optionally substituted by one or more halo, e.g. fluoro atoms) and/or $-OC_{1-6}$alkyl (itself optionally substituted by one or more fluoro atoms),

or a pharmaceutically-acceptable salt thereof.

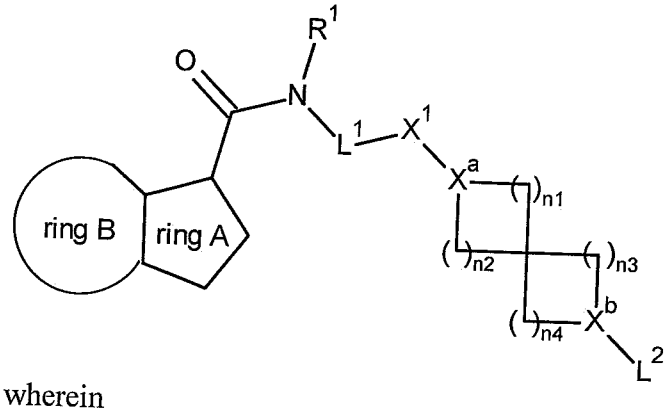
For instance, compounds of formula (IA) may as described above, may be such that the ring A is linked to the amide moiety *via* a specific ring atom, as depicted by compounds of formula (I) below:



(I)

This embodiment is essentially a graphical depiction of ring A being linked to the requisite amido moiety *via* a bond represented by one of the dotted lines in formula (IA).

In another aspect, the present disclosure relates to a compound of formula (IB) as depicted below:



(IB)

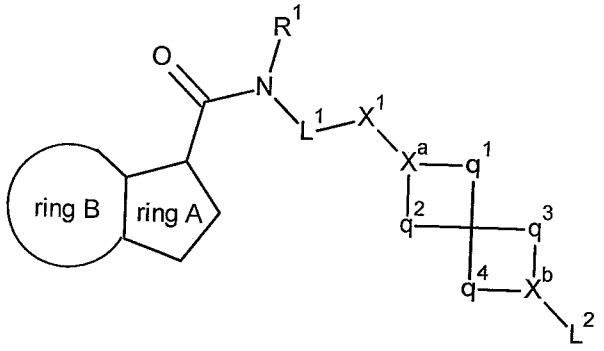
wherein

the integers are as hereinbefore defined, and where, preferably:

n1, n2, n3 and n4 independently represent 1;

at least one of X^a and X^b represents N and the other represents CH or N;

In another aspect, the present disclosure relates to a compound of formula (I)



(I)

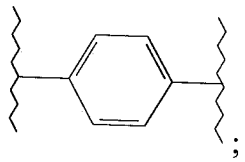
wherein

R^1 represents hydrogen;

L^1 represents $-CH_2-$;

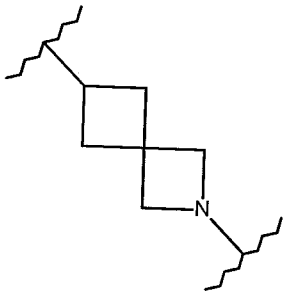
X^1 represents a carbocyclic aromatic linker group that is:

-phenylene- (especially a 1,4-phenylene), e.g.:



;

the spiro-cyclic moiety, i.e. the combined X^a and X^b-containing ring may be represented as follows:



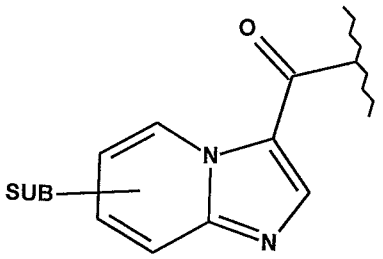
L^2 represents $-S(O)_2$-C_{1-6}alkyl optionally substituted by one or more fluoro atoms (e.g. forming

$-S(O)_2CF_3$);

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

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);

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



optional substituents on ring A and ring B are halo, C_{1-3} alkyl and -OC_{1-3} alkyl,

or a pharmaceutically-acceptable salt thereof.

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

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.

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 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, benzenesulfonic, *p*-toluenesulfonic, cyclamic, salicylic, *p*-aminosalicylic, pamoic and the like acids.

In another aspect, the present disclosure relates to a compound as defined herein, for use as a pharmaceutical.

In another aspect, the present disclosure relates to a pharmaceutical composition comprising a pharmaceutically acceptable carrier and, as active ingredient, a therapeutically effective amount of a compound as defined herein.

In another aspect, the present disclosure relates to a compound as defined herein for use in the treatment of tuberculosis.

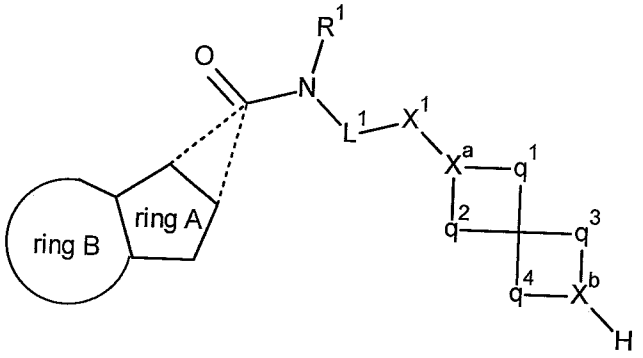
In another aspect, the present disclosure relates to use of a compound as defined herein for the manufacture of a medicament for the treatment of tuberculosis.

In another aspect, the present disclosure relates to a combination of (a) a compound as defined herein, and (b) one or more other anti-tuberculosis agent.

In another aspect, the present disclosure relates to a product containing (a) a compound as defined herein, 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.

In another aspect, the present disclosure relates to a process for the preparation of a compound of formula (IA) as defined herein, which process comprises:

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



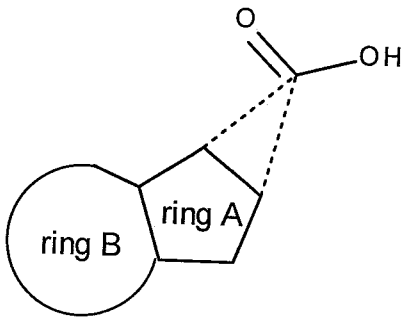
(II)

in which the integers are defined herein, with a compound of formula (III),

$$LG^1\text{-}L^2 \qquad \text{(III)}$$

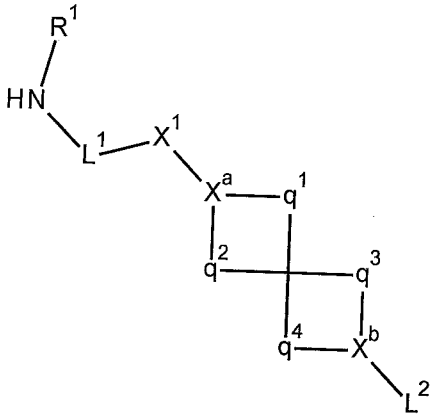
wherein L^2 is as defined herein (but when L^2 is not hydrogen, halo or linked to O or S), and LG^1 is a suitable leaving group;

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



(IV)

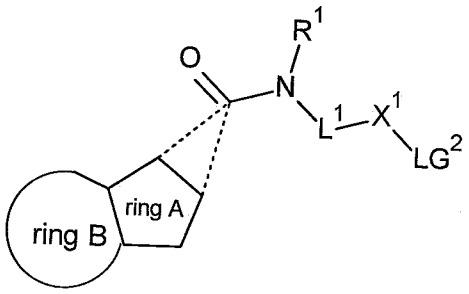
wherein the integers are as defined herein, or a suitable derivative thereof, such as a carboxylic acid ester derivative, with a compound of formula (V)



(V)

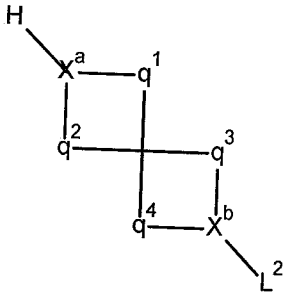
wherein the integers are as hereinbefore defined, under amide coupling reaction conditions;

(iii) coupling of a compound of formula (VI),



(VI)

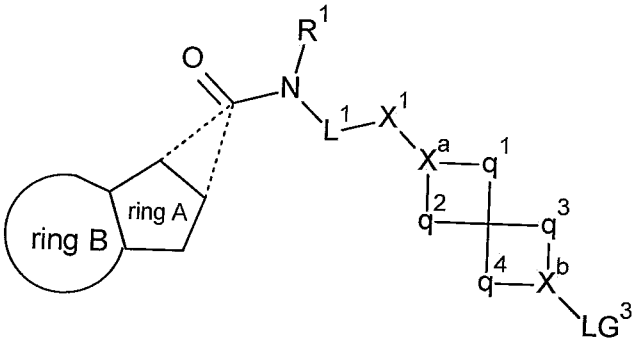
wherein the integers are as defined herein, and LG^2 represents a suitable leaving group, with a compound of formula (VI),



(VII)

wherein the integers are as defined herein;

(iv) coupling of a compound of formula (VIII),



(VIII)

wherein the integers are as defined herein, and LG^3 represents a suitable leaving group as described above with respect to LG^2 (and may particularly represent chloro, bromo or iodo), with a compound of formula (IX),

$$LG^4\text{-}L^2 \qquad \text{(IX)}$$

wherein L^2 is as defined herein (but when L^2 is not hydrogen, halo or linked to O or S), and LG^4 is a suitable group.

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.

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.

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. 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.

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-;
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 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 repesents 0, 1 or 2;
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;

when X^b represents O or C=O, then L^2 is not present;
when X^b represents $C(R^a)$ 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 halo, C_{1-6} alkyl (itself optionally substituted by one or more substituents selected from 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 $-SF_5$); or, when attached to nitrogen, i.e. when X^b is N, L^2 represents $-S(O)_2-C_{1-6}$alkyl optionally substituted by one or more fluoro atoms (e.g. forming $-S(O)_2CF_3$);

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 themseleves be optionally substituted by one or more fluoro atoms);

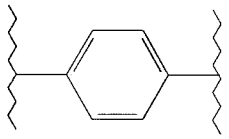
R^g represents hydrogen or C_{1-6}alkyl (optionally substituted by one or more substituents selected from fluoro, or $-OC_{1-3}$ alkyl, which latter moiety is also optionally substuituted by one or more fluoro atoms) or an aromatic group (optionally substituted by one or more substituents selected from halo, C_{1-6} alkyl or $-OC_{1-6}$alkyl);

n4 represents 1 or 2;
q^1 represents $-CH_2-$, $-CH_2-CH_2-$, $-O-CH_2-$ or "-" (i.e. in the latter case, n1 = 0, X^c is not present and X^d is not present);
q^2 represents $-CH_2-$ or $-CH_2-CH_2-$;
q^3 represents $-CH_2-$ or $-CH_2-CH_2-$; and/or
q^4 represents $-CH_2-$ or $-CH_2-CH_2-$.

8. A compound for use as claimed in any one of the preceding claims, wherein L^2 represents hydrogen, halo (e.g. fluoro), $-OR^f$, $-C(O)R^g$, or an aromatic group (optionally substituted by one or two (e.g. one) substituent(s) selected from $-OC_{1-6}$alkyl (itself optionally substituted by one or more fluoro atoms) or $-SF_5$, or, alternatively by halo, e.g. fluoro).

9. A compound for as claimed in Claim 8, wherein R^f represents C_{1-6}alkyl or an aryl group optionally substituted by C_{1-3}alkyl (itself optionally substituted by one or more fluoro atoms, so forming e.g. a $-CF_3$ group) and/or R^g represents C_{1-3}alkyl (optionally substituted by fluoro) or phenyl.

10. A compound of formula (IA) as defined in Claim 1but wherein:
L^1 represents $-CH_2-$;
X^1 is not present or X^1 represents a carbocyclic aromatic linker group;
when X^1 represents a carbocyclic linker group it represents phenylene (e.g. a 1,4-phenylene) for instance:



at least one of X^a and X^b represents N and the other represents $C(R^c)$, N or (in the case of X^b) O;
the X^a and X^b-containing spiro-cycle 3- to 6-membered ring attached to a 4- to 6-membered ring;
in one aspect L^2 represents an aromatic group (as defined herein) optionally substituted as defined herein, and/or, in another aspect L^2 represents $-OR^f$ in which R^f represents an aryl group (as defined herein) optionally substituted as defined herein;
when L^2 represents an (optionally substituted) aromatic group, it may be phenyl or a 5- or 6-membered heterocyclic group (e.g. containing at least one nitrogen atom, so forming a pyridyl, thiazolyl or triazolyl ring; in a major embodiment the heterocyclic group is a pyridyl), where the optional substituents are as defined herein;

optional substituents on aromatic L^2 groups are selected from halo, C_{1-6} alkyl, $-CF_3$, $-OC_{1-6}$ alkyl and $-OCF_3$;

when R^f represents an aryl group, then it is preferably phenyl optionally substituted by C_{1-3} alkyl, itself optionally substituted by fluoro);

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 nitogen 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,

or a pharmaceutically-acceptable salt thereof.

11. A compound as claimed in Claim 10 wherein:

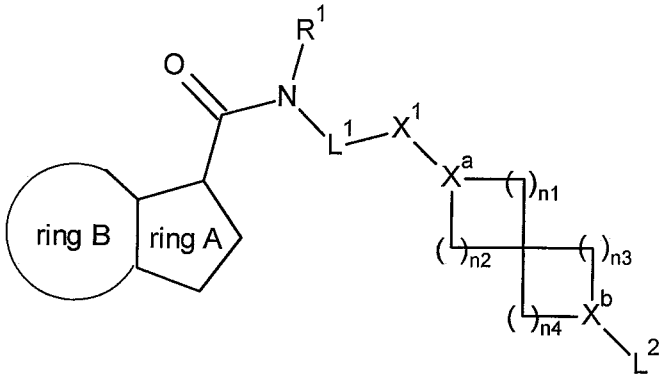
q^1 represents $-CH_2-$, $-CH_2-CH_2-$, $-O-CH_2-$ or "-" (i.e. in the latter case, n1 = 0, X^c is not present and X^d is not present);

q^2 represents $-CH_2-$ or $-CH_2-CH_2-$;

q^3 represents $-CH_2-$ or $-CH_2-CH_2-$;

q^4 represents $-CH_2-$ or $-CH_2-CH_2-$.

12. A compound of formula (IB) as depicted below:



(IB)

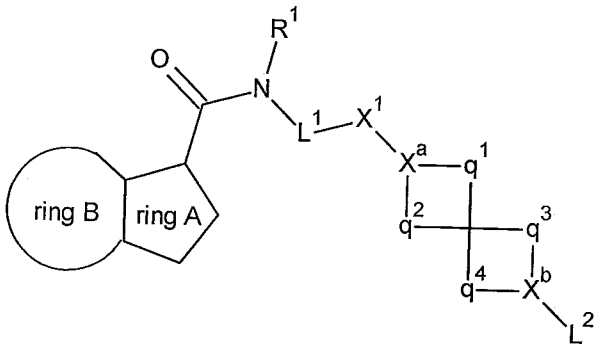
wherein

the integers are as hereinbefore defined, and where, preferably:

n1, n2, n3 and n4 independently represent 1;

at least one of X^a and X^b represents N and the other represents CH or N;

13. A compound of formula (I)



(I)

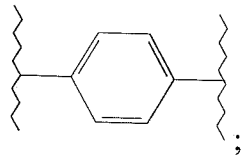
wherein

R^1 represents hydrogen;

L^1 represents $-CH_2-$;

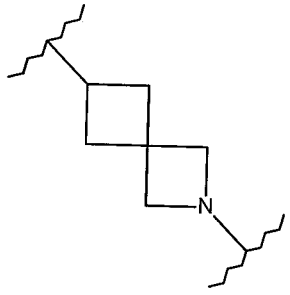
X^1 represents a carbocyclic aromatic linker group that is:

-phenylene- (especially a 1,4-phenylene), e.g.:



;

the spiro-cyclic moiety, i.e. the combined X^a and X^b-containing ring may be represented as follows:



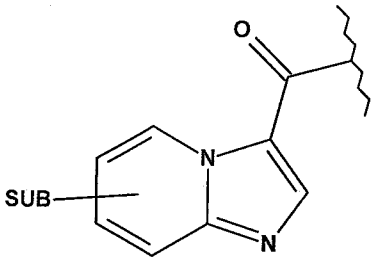
L^2 represents $-S(O)_2$-C_{1-6}alkyl optionally substituted by one or more fluoro atoms (e.g. forming

$-S(O)_2CF_3$);

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

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);

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



optional substituents on ring A and ring B are halo, C_{1-3} alkyl and $-OC_{1-3}$ alkyl,

or a pharmaceutically-acceptable salt thereof.

14. A compound as defined in any one of claims 10 to 13, for use as a pharmaceutical.

15. 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 10-13.

16. Compound according to any one of claims 10-13 for use in the treatment of tuberculosis.

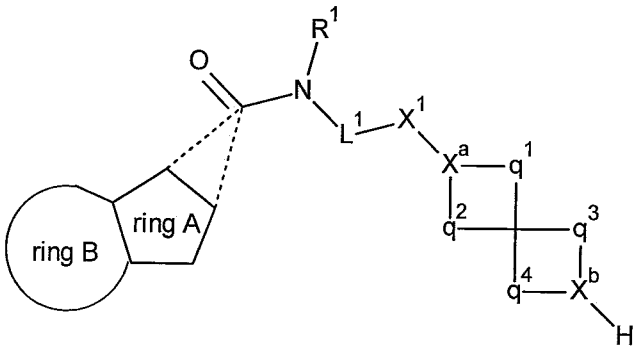
17. Use of a compound according to any one of claims 1 to 13 for the manufacture of a medicament for the treatment of tuberculosis.

18. A combination of (a) a compound according to any one of claims 1 to 13, and (b) one or more other anti-tuberculosis agent.

19. A product containing (a) a compound according to any one of claims 1 to 13, 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.

20. A process for the preparation of a compound of formula (IA) as claimed in Claim 1, or Claims 10-13 , which process comprises:

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



(II)

in which the integers are defined in Claim 1, with a compound of formula (III),

$$LG^1\text{-}L^2 \qquad \text{(III)}$$