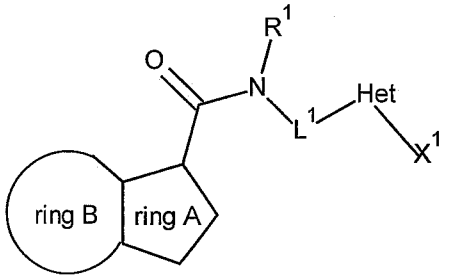
SUMMARY

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



(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);

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);

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:

(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:

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

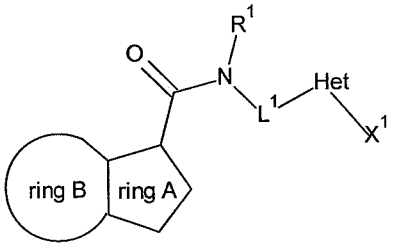
ring B is a 5- or 6-membered ring, which may be aromatic or non-aromatic, optionally containing one to four heteroatoms (preferably selected from nitrogen, oxygen and sulfur);

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 one aspect, there is provided a compound of formula (I) for use in the treatment of tuberculosis



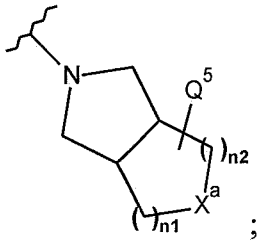
(I)

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);
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);

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

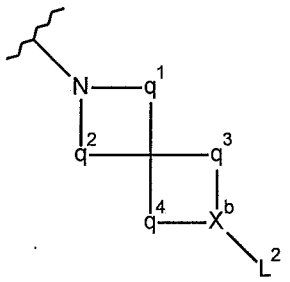
X^1 represents -$N(R^2)(R^3)$;
R^2 and R^3:
(i) independently represent hydrogen or, preferably, C_{1-6} alkyl optionally substituted by one or more substituents selected from Q^1 and =O;

(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:



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 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 $-N(R^{c1})-$;
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;

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);

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

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

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, $-OR^f$, $-C(O)-R^g$, 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 $-SF_5$);

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 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.

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, there is provided a compound as defined herein, for use as a pharmaceutical.

In another aspect, there is provided 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, there is provided a compound as defined herein for use in the treatment of tuberculosis.

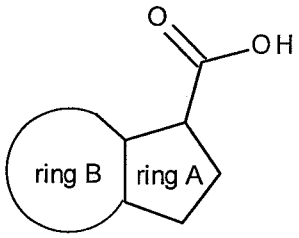
In another aspect, there is provided a use of a compound as defined herein for the manufacture of a medicament for the treatment of tuberculosis.

In another aspect, there is provided a combination of (a) a compound as defined herein, and (b) one or more other anti-tuberculosis agent.

In another aspect, there is provided 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.

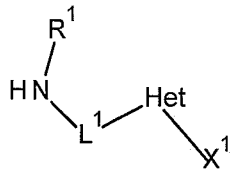
In another aspect, there is provided a process for the preparation of a compound of formula (I) as defined herein, which process comprises:

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



(II)

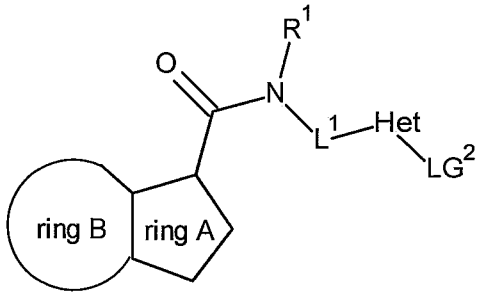
wherein the integers are as defined herein, or a suitable derivative thereof, with a compound of formula (III)



(III)

wherein the integers are as defined herein;

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

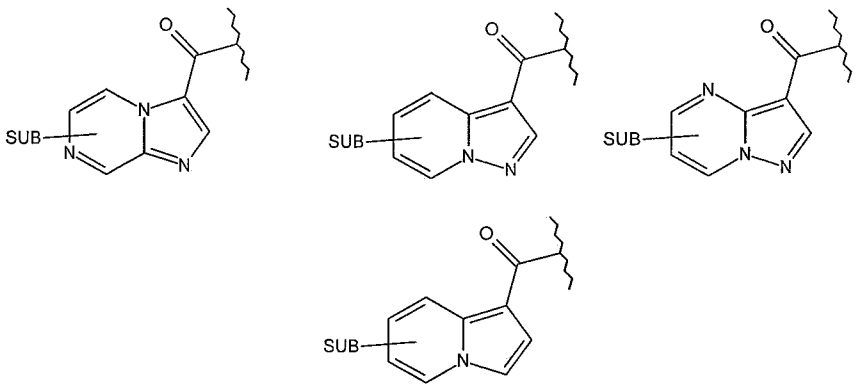


(IV)

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

$$X^1\text{-}H \qquad (V)$$

wherein the integers are as defined herein.



(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.

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.

14. Compound according to any one of claims 9-11 for use in the treatment of tuberculosis.

15. Use of a compound according to any one of claims 1 to 11 for the manufacture of a medicament for the treatment of tuberculosis.

16. A combination of (a) a compound according to any one of claims 1 to 11, and (b) one or more other anti-tuberculosis agent.

17. A product containing (a) a compound according to any one of claims 1 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 claimed in Claim 1, or Claims 9-11, which process comprises: