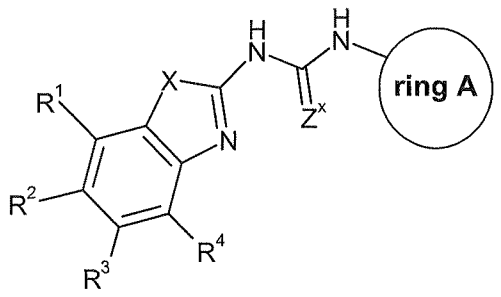
SUMMARY

There is now provided a compound of formula (I) for use in the treatment of a bacterial infection (e.g. a mycobacterial infection), wherein the compound of formula (I) represents:



(I)

wherein

R^1, R^2, R^3 and R^4 each independently represent hydrogen, halo, -CN, R^{t1}, -O-R^{t2}, -C(O)N(R^{t3})(R^{t4}), -SO_2R^{t5}, -N(H)SO_2R^{t6}, -N(R^{t7})(R^{t8}) or an aryl or heterocyclic group (which latter two groups are themselves optionally substituted by one or more substituents selected from halo and C_{1-6} alkyl);

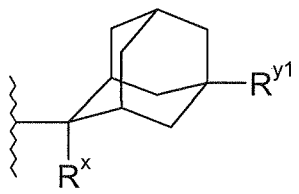
R^{t1}, R^{t2}, R^{t3}, R^{t4}, R^{t5}, R^{t6}, R^{t7} and R^{t8} independently represent hydrogen or C_{1-6} alkyl optionally substituted by one or more halo atoms, or, R^{t3} and R^{t4} and/or R^{t7} and R^{t8} may be linked together with the nitrogen atom to which they are attached to form a 3- to 7-membered ring, optionally containing one to three (e.g. one) further heteroatom(s) and optionally contain one to three double bonds;

Z^x represents O or S;

X represents S or O;

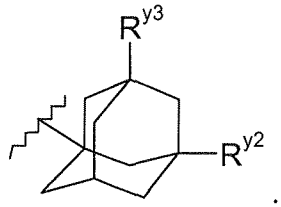
ring A represents either:

(i)



; or

(ii)



;

R^x represents hydrogen or C_{1-6} alkyl optionally substituted by one or more subsitutents selected from fluoro, -CN, $-OR^{x1}$, $-C(O)R^{x2}$ and $-C(O)NR^{x3}$;

R^{x1}, R^{x2} and R^{x3} independently represent hydrogen or C_{1-6} alkyl;

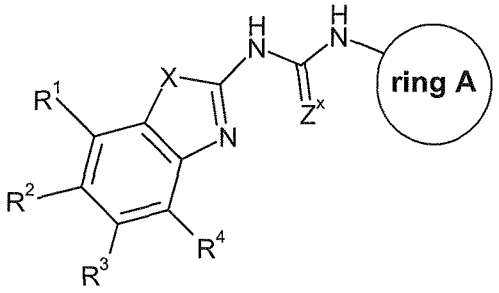
R^{y1}, R^{y2} and R^{y3} independently represent hydrogen, halo (e.g. fluoro), C_{1-6} alkyl, $-OR^{y4}$, $-C(O)-R^{y5}$ or $-CH_2-OR^{y6}$;

R^{y4}, R^{y5} and R^{y6} independently represent hydrogen or C_{1-6} alkyl;

or a pharmaceutically acceptable salt (e.g. acid addition salt) thereof.

The above-mentioned compounds of formula (I) (or salts thereof) may be referred to herein as "compounds of the invention". Such compounds are indicated as being useful in the treatment of a bacterial infection. However, some compounds mentioned above may also be useful as medicaments, and some compounds may be novel.

Hence, there is a compound of formula I, for use as a pharmaceutical, as defined herein, but in which:
R^1, R^2, R^3 and R^4 each independently represent hydrogen, fluoro or C_{1-6} alkyl (optionally substituted by one or more halo subsituents). Such compounds may also be contained/comprised in pharmaceutical formulations/compositons. Thus, in another aspect, there is provided a compound of formula I



(I)

wherein

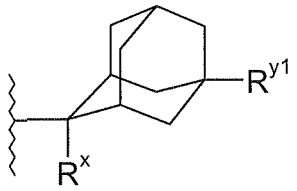
R^1, R^2, R^3 and R^4 each independently represent hydrogen, fluoro or C_{1-6} alkyl substituted by one or more halo subsituents;

Z^x represents O or S;

X represents S or O;

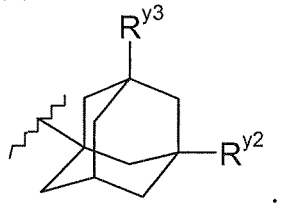
ring A represents either:

(i)



; or

(ii)



;

R^x represents hydrogen or C_{1-6} alkyl optionally substituted by one or more subsitutents selected from fluoro, -CN, $-OR^{x1}$, $-C(O)R^{x2}$ and $-C(O)NR^{x3}$;

R^{x1}, R^{x2} and R^{x3} independently represent hydrogen or C_{1-6} alkyl;

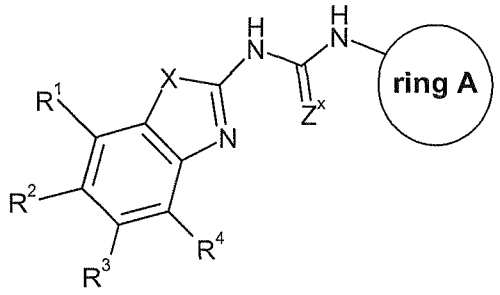
R^{y1}, R^{y2} and R^{y3} independently represent hydrogen, halo (e.g. fluoro), C_{1-6} alkyl, $-OR^{y4}$, $-C(O)-R^{y5}$ or $-CH_2-OR^{y6}$;

R^{y4}, R^{y5} and R^{y6} independently represent hydrogen or C_{1-6} alkyl;
or a pharmaceutically acceptable salt (e.g. acid addition salt) thereof,
for use as a pharmaceutical. In another aspect, there is a pharmaceutical composition comprising a compound as defined herein and a pharmaceutically acceptable carrier.

In a further embodiment of the disclosure, there is provided novel compounds *per se*. In this respect, there is provided a compound of formula I, as defined herein, but in which:

R^1, R^2, R^3 and R^4 each independently represent hydrogen, fluoro or C_{1-6} alkyl optionally substituted by one or more halo subsituents (but which alkyl group is preferably substituted with one or more halo atoms);
for instance, in which:
one or two of R^1 to R^4 represents fluoro, and the remaining represent hydrogen;
one of R^1 to R^4 represents $-CF_3$, and the remaining represent hydrogen.

Thus, in another aspect, there is provided a compound of formula I



(I)

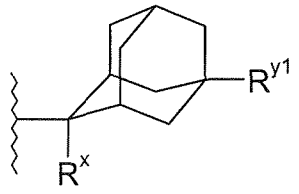
wherein
one or two of R^1, R^2, R^3 or R^4 represents fluoro, and the remaining of R^1, R^2, R^3 or R^4 represent hydrogen, or
one of R^1, R^2, R^3 or R^4 represents $-CF_3$, and the remaining of R^1, R^2, R^3 or R^4 represent hydrogen;

Z^x represents O or S;

X represents S or O;

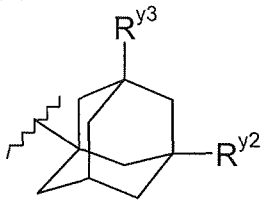
ring A represents either:

(i)



; or

(ii)



;

R^x represents hydrogen or C_{1-6} alkyl optionally substituted by one or more subsitutents selected from fluoro, -CN, $-OR^{x1}$, $-C(O)R^{x2}$ and $-C(O)NR^{x3}$;

R^{x1}, R^{x2} and R^{x3} independently represent hydrogen or C_{1-6} alkyl;

R^{y1}, R^{y2} and R^{y3} independently represent hydrogen, halo (e.g. fluoro), C_{1-6} alkyl, $-OR^{y4}$, $-C(O)-R^{y5}$ or $-CH_2-OR^{y6}$;

R^{y4}, R^{y5} and R^{y6} independently represent hydrogen or C_{1-6} alkyl;

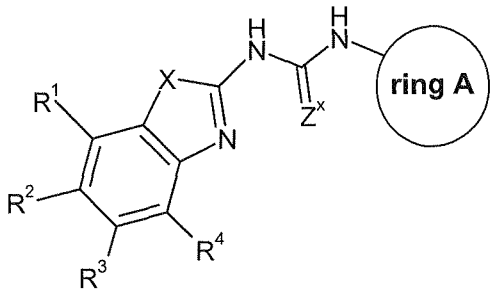
or a pharmaceutically acceptable salt (e.g. acid addition salt) thereof,

provided that the following compounds of formula I are excluded:

those in which X represents S, Z^x represents O, R^1 and R^4 represent H, R^2 represents $-CH_3$, ring A represents ring (ii) in which R^{y2} and R^{y3} both represent hydrogen, and R^3 represents hydrogen or $-CH_3$.

CLAIMS

1. A compound of formula I



(I)

wherein

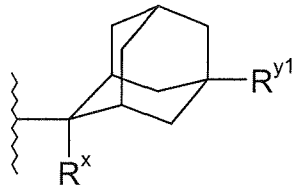
R^1, R^2, R^3 and R^4 each independently represent hydrogen, fluoro or C_{1-6} alkyl substituted by one or more halo subsituents;

Z^x represents O or S;

X represents S or O;

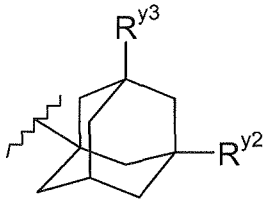
ring A represents either:

(i)



; or

(ii)



;

R^x represents hydrogen or C_{1-6} alkyl optionally substituted by one or more subsitutents selected from fluoro, -CN, $-OR^{x1}$, $-C(O)R^{x2}$ and $-C(O)NR^{x3}$;

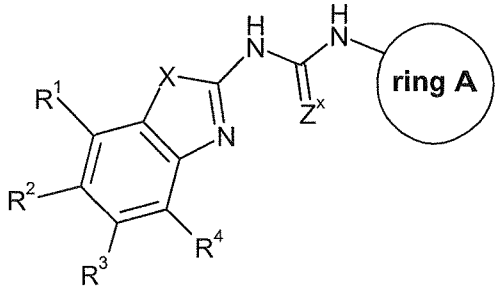
R^{x1}, R^{x2} and R^{x3} independently represent hydrogen or C_{1-6} alkyl;

R^{y1}, R^{y2} and R^{y3} independently represent hydrogen, halo (e.g. fluoro), C_{1-6} alkyl, $-OR^{y4}$, $-C(O)-R^{y5}$ or $-CH_2-OR^{y6}$;

R^{y4}, R^{y5} and R^{y6} independently represent hydrogen or C_{1-6} alkyl;

or a pharmaceutically acceptable salt (e.g. acid addition salt) thereof,
for use as a pharmaceutical.

2. A compound of formula I



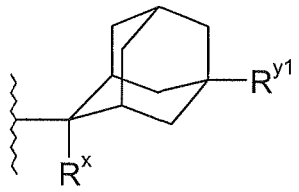
(I)

wherein
one or two of R^1, R^2, R^3 or R^4 represents fluoro, and the remaining of R^1, R^2, R^3 or R^4 represent hydrogen, or
one of R^1, R^2, R^3 or R^4 represents $-CF_3$, and the remaining of R^1, R^2, R^3 or R^4 represent hydrogen;

Z^x represents O or S;

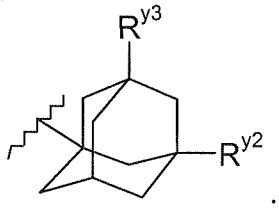
X represents S or O;

ring A represents either:
(i)



; or

(ii)



;

R^x represents hydrogen or C_{1-6} alkyl optionally substituted by one or more subsitutents selected from fluoro, -CN, $-OR^{x1}$, $-C(O)R^{x2}$ and $-C(O)NR^{x3}$;
R^{x1}, R^{x2} and R^{x3} independently represent hydrogen or C_{1-6} alkyl;
R^{y1}, R^{y2} and R^{y3} independently represent hydrogen, halo (e.g. fluoro), C_{1-6} alkyl, $-OR^{y4}$, $-C(O)-R^{y5}$ or $-CH_2-OR^{y6}$;
R^{y4}, R^{y5} and R^{y6} independently represent hydrogen or C_{1-6} alkyl;
or a pharmaceutically acceptable salt (e.g. acid addition salt) thereof,
provided that the following compounds of formula I are excluded:
those in which X represents S, Z^x represents O, R^1 and R^4 represent H, R^2 represents $-CH_3$, ring A represents ring (ii) in which R^{y2} and R^{y3} both represent hydrogen, and R^3 represents hydrogen or $-CH_3$.

3. A pharmaceutical composition comprising a compound as defined in claim 1 or 2 and a pharmaceutically acceptable carrier.

4. A combination for use in the treatment of a bacterial infection, wherein the combination comprises: (i) a compound as defined in claim 1 or 2; and (ii) another therapeutic agent for use in the treatment of a bacterial infection.

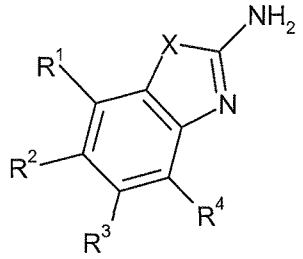
5. A combination for use as claimed in claim 4, wherein the bacterial infection is a mycobacterial infection.

6. A combination for use as claimed in claim 5, wherein the mycobacterial infection is *Mycobacterium tuberculosis*.

7. A process for preparing a composition as claimed in claim 3, wherein a therapeutically active amount of a compound as claimed in claim 1 or 2 is intimately mixed with a pharmaceutically acceptable carrier.

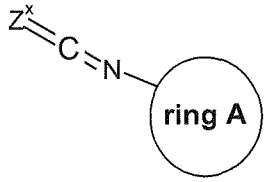
8. A process for the preparation of a compound as defined in claim 2, which process comprises:

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



(II)

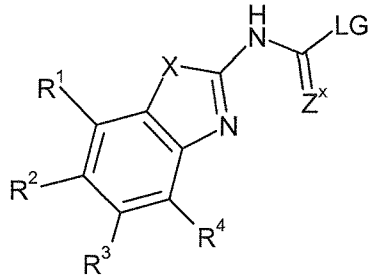
wherein X, R^1, R^2, R^3 and R^4 are as defined in claim 1 or 2, with a compound of formula (III),



(III)

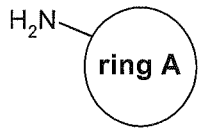
wherein ring A and Z^x are as defined in claim 1 or 2;

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



(IV)

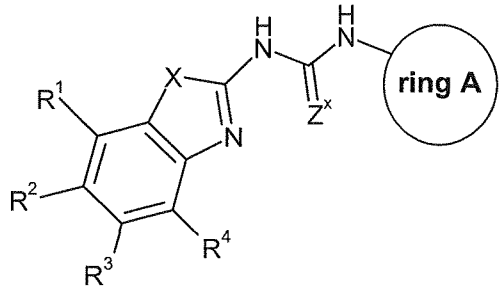
wherein LG represents a suitable leaving group, and R^1, R^2, R^3, R^4, X and Z^x are as defined in claim 1 or 2, with a compound of formula (V),



(V)

wherein ring A is as defined in claim 1 or 2.

9. Use of a compound of formula (I) in the manufacture of a medicament for the treatment of a bacterial infection, wherein the compound of formula (I) represents:



(I)

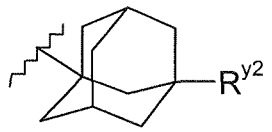
R^{y1}, R^{y2} and R^{y3} independently represent hydrogen, halo (e.g. fluoro), C_{1-6} alkyl, $-OR^{y4}$, $-C(O)-R^{y5}$ or $-CH_2-OR^{y6}$;

R^{y4}, R^{y5} and R^{y6} independently represent hydrogen or C_{1-6} alkyl;

or a pharmaceutically acceptable salt (e.g. acid addition salt) thereof.

10. Use as claimed in claim 9, wherein ring A represents:

(ii)



.

11. Use as claimed in claim 9 or 10, wherein R^{y1} represents fluoro, chloro, C_{1-6} alkyl, -OH, $-C(O)R^{y5}$ or $-CH_2-OR^{y6}$; and R^{y2} represents -OH, C_{1-6} alkyl (e.g. methyl), $-C(O)R^{y5}$ or $-CH_2-OR^{y6}$).

12. Use as claimed in any one of claims 9 to 11, wherein R^1, R^2, R^3 and R^4 each independently represent hydrogen, fluoro or C_{1-6} alkyl substituted by one or more halo subsituents.

13. Use as claimed in any one of claims 9 to 12, wherein
R^1, R^2, R^3 and R^4 each independently represent hydrogen;
Z^x represents O;
X represents O or S; and/or
R^x represents hydrogen.

14. Use as claimed in any one of claims 9 to 12, wherein:
R^1, R^2, R^3 and R^4 each independently represent hydrogen, fluoro or C_{1-6} alkyl optionally substituted by one or more halo subsituents (but preferably unsubstituted); for instance, in which:
one or two of R^1 to R^4 represents fluoro, and the remaining represent hydrogen;
one of R^1 to R^4 represents $-CF_3$, and the remaining represent hydrogen,
provided that the following compounds of formula I are excluded:
those in which X represents S, Z^x represents O, R^1 and R^4 represent H, R^2 represents $-CH_3$, ring A represents ring (ii) in which R^{y2} and R^{y3} both represent hydrogen, and R^3 represents hydrogen or $-CH_3$.

15. Use of a combination in the manufacture of a medicament for the treatment of a bacterial infection, wherein the combination comprises: (i) a compound as defined in any one of claims 9 to 14; and (ii) another therapeutic agent for use in the treatment of a bacterial infection.

16. Use as claimed in any one of claims 9 to 15, wherein the bacterial infection is a mycobacterial infection.

17. Use as claimed in claim 16, wherein the mycobacterial infection is *Mycobacterium tuberculosis*.