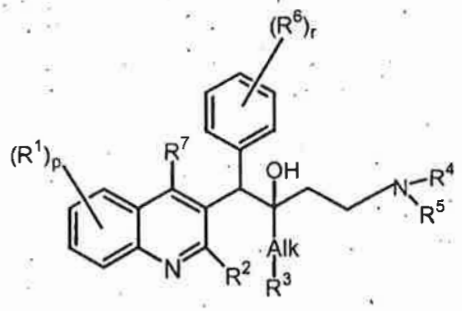
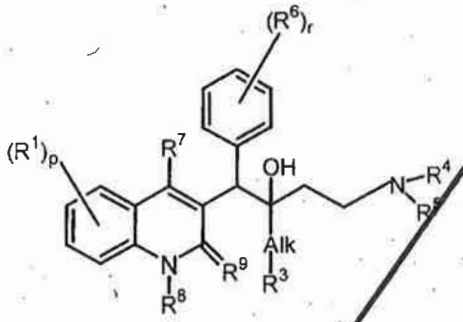
Claims

1. Use of a compound for the manufacture of a medicament for the treatment of a bacterial infection, said compound being a compound of formula (Ia) or (Ib)



(Ia)

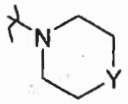


(Ib)

a pharmaceutically acceptable acid or base addition salt thereof, a stereochemically isomeric form thereof, a tautomeric form thereof or a *N*-oxide form thereof, wherein

R^1 is hydrogen, halo, haloalkyl, cyano, hydroxy, Ar, Het, alkyl, alkyloxy, alkylthio, alkyloxyalkyl, alkylthioalkyl, Ar-alkyl or di(Ar)alkyl ;

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

R^2 is hydrogen, hydroxy, mercapto, alkyloxy, alkyloxyalkyloxy, alkylthio, mono or di(alkyl)amino or a radical of formula  wherein Y is CH_2, O, S, NH or *N*-alkyl ;

R^3 is Ar or Het;

R^4 and R^5 each independently are hydrogen, alkyl or benzyl; or

R^4 and R^5 together and including the N to which they are attached may form a radical selected from the group of pyrrolidinyl, 2-pyrrolinyl, 3-pyrrolinyl, pyrrolyl, imidazolidinyl, pyrazolidinyl, 2-imidazolinyl, 2-pyrazolinyl, imidazolyl, pyrazolyl, triazolyl, piperidinyl, pyridinyl, piperazinyl, pyridazinyl, pyrimidinyl, pyrazinyl, triazinyl, morpholinyl and thiomorpholinyl, optionally substituted with alkyl, halo, haloalkyl, hydroxy, alkyloxy, amino, mono- or dialkylamino, alkylthio, alkyloxyalkyl, alkylthioalkyl or pyrimidinyl ;

R^6 is hydrogen, halo, haloalkyl, hydroxy, Ar, alkyl, alkyloxy, alkylthio, alkyloxyalkyl, alkylthioalkyl, Ar-alkyl or di(Ar)alkyl ; or

two vicinal R^6 radicals may be taken together to form a bivalent radical of formula -CH=CH-CH=CH- ;

r is an integer equal to 1, 2, 3, 4 or 5 ;

R^7 is hydrogen, alkyl, Ar or Het ;

R^8 is hydrogen or alkyl ;

R^9 is oxo ; or

R^8 and R^9 together form the radical –CH=CH-N=;

alkyl is a straight or branched saturated hydrocarbon radical having from 1 to 6 carbon atoms ; or is a cyclic saturated hydrocarbon radical having from 3 to 6 carbon atoms ; or is a cyclic saturated hydrocarbon radical having from 3 to 6 carbon atoms attached to a straight or branched saturated hydrocarbon radical having from 1 to 6 carbon atoms; wherein each carbon atom can be optionally substituted with hydroxy, alkyloxy or oxo;

Alk is a straight or branched saturated hydrocarbon radical having from 1 to 6 carbon atoms ;

Ar is a homocycle selected from the group of phenyl, naphthyl, acenaphthyl and tetrahydronaphthyl, each homocycle optionally substituted with 1, 2 or 3 substituents, each substituent independently selected from the group of hydroxy, halo, cyano, nitro, amino, mono- or dialkylamino, alkyl, haloalkyl, alkyloxy, haloalkyloxy, carboxyl, alkyloxycarbonyl, aminocarbonyl, morpholinyl and mono- or dialkylaminocarbonyl ;

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

halo is a substituent selected from the group of fluoro, chloro, bromo and iodo; and

haloalkyl is a straight or branched saturated hydrocarbon radical having from 1 to 6 carbon atoms or a cyclic saturated hydrocarbon radical having from 3 to 6 carbon atoms or a cyclic saturated hydrocarbon radical having from 3 to 6 carbon atoms attached to a straight or branched saturated hydrocarbon radical

having from 1 to 6 carbon atoms; wherein one or more carbon atoms are substituted with one or more halo atoms;

provided that the bacterial infection is other than a Mycobacterial infection.

2. Use according to claim 1 wherein R^1 is hydrogen, halo, alkyl, alkyloxy, Ar or Het.

3. Use according to claim 2 wherein R^1 is hydrogen, halo, alkyl or alkyloxy.

4. Use according to claim 3 wherein R^1 is hydrogen or halo.

5. Use according to claim 4 wherein R^1 is halo.

6. Use according to any one of the preceding claims wherein p is equal to 1.

7. Use according to claim 6 wherein the R^1 substituent is placed in position 6 of the quinoline ring.

8. Use according to any one of the preceding claims wherein R^2 is alkyloxy, alkylthio, mono-or di(alkyl)amino or alkyloxyalkyloxy.

9. Use according to any one of claims 1 to 7 wherein R^2 is hydrogen, alkyloxy or alkylthio.

10. Use according to claim 8 or 9 wherein R^2 is C_{1-4}alkyloxy.

11. Use according to any one of the preceding claims wherein R^3 is Ar.

12. Use according to claim 11 wherein R^3 is naphthyl or phenyl, optionally substituted with 1 or 2 halo.

13. Use according to any one of the preceding claims wherein R^4 and R^5 each independently are hydrogen or C_{1-4}alkyl.

14. Use according to any one of the preceding claims wherein R^6 is hydrogen.

15. Use according to any one of the preceding claims wherein R^7 is hydrogen.

16. Use according to any one of the preceding claims wherein Alk is methylene or ethylene.

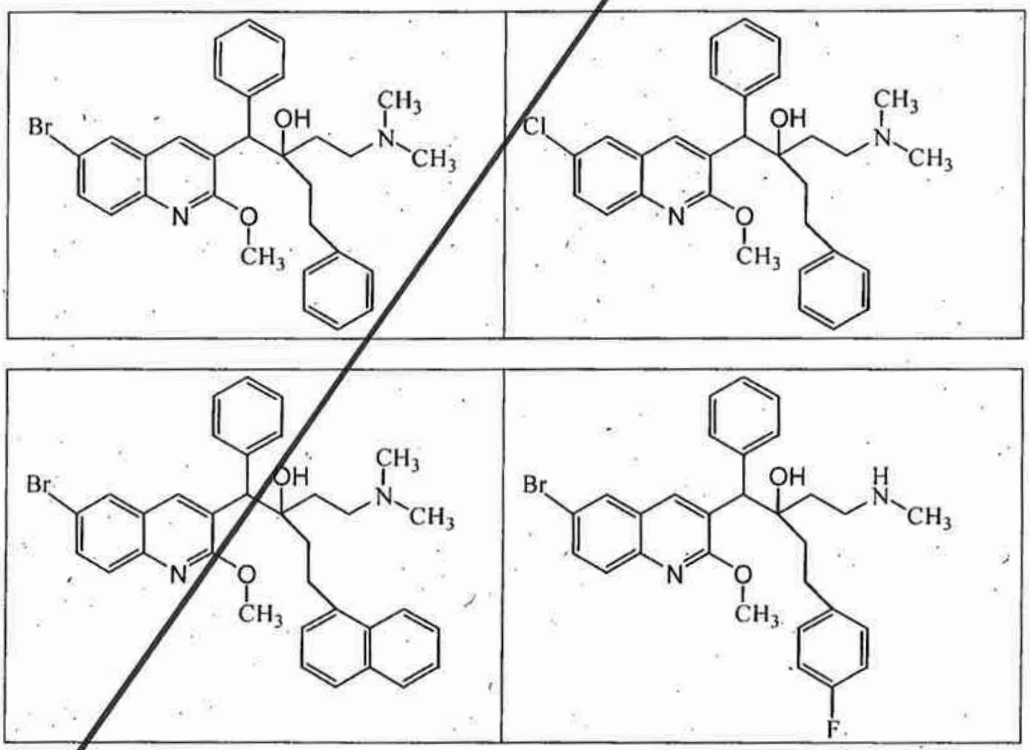
17. Use according to claim 16 wherein Alk is ethylene.

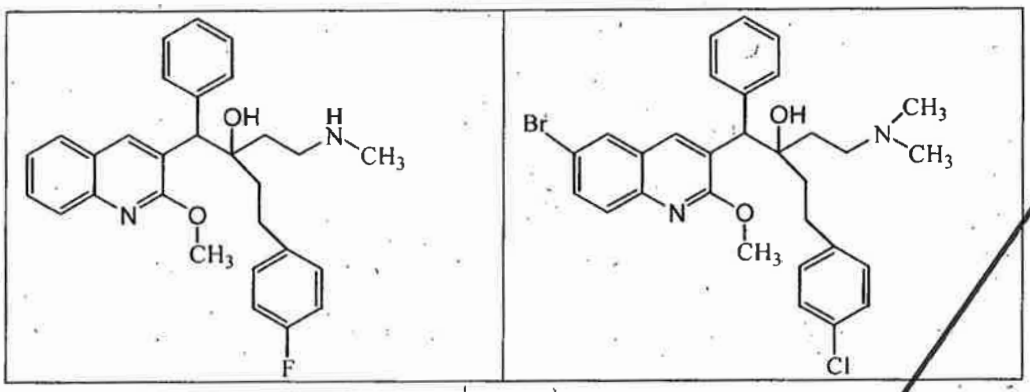
18. Use according to any one of the preceding claims wherein the compound is a compound according to formula (Ia).

19. Use according to claim 1 wherein the compound is a compound of formula (Ia) wherein R^1 is hydrogen, halo, C_{1-4}alkyl, C_{1-4}alkyloxy, Ar or Het; p = 1 or 2; R^2 is C_{1-4}alkyloxy, C_{1-4}alkylthio, mono-or di(C_{1-4}alkyl)amino, C_{1-4}alkyloxyC_{1-4}alkyloxyC_{1-4}alkyloxy; R^3 is optionally substituted naphthyl or phenyl; R^4 and R^5 each independently are hydrogen or C_{1-4}alkyl; or R^4 and R^5 together and including the N to which they are attached form a piperidinyl; R^6 is hydrogen, halo, C_{1-4}alkyl or C_{1-4}alkyloxy; r is equal to 1; R^7 is hydrogen; Alk is methylene or ethylene.

20. Use according to any one of the preceding claims wherein the bacterial infection is an infection with a gram-positive bacterium.

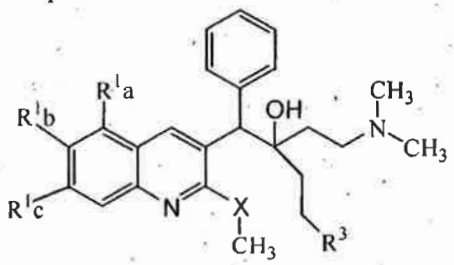
21. Use according to any one of the preceding claims wherein the compound is selected from





a pharmaceutically acceptable acid or base addition salt thereof, a stereochemically isomeric form thereof, a tautomeric form thereof or a *N*-oxide form thereof.

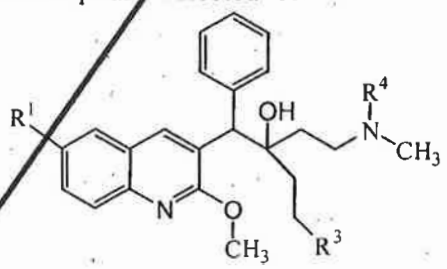
22. A compound selected from



R^1_a	R^1_b	R^1_c	R^3	X
H	H	H	phenyl	O
H	CH_3	H	phenyl	O
H	OCH_3	H	phenyl	O
H	Br	H	phenyl	S
H	Br	H	1-naphthyl	O
H	Br	CH_3	phenyl	O
H	Cl	H	phenyl	O
Br	H	H	phenyl	O

a pharmaceutically acceptable acid or base addition salt thereof, a stereochemically isomeric form thereof, a tautomeric form thereof or a *N*-oxide form thereof.

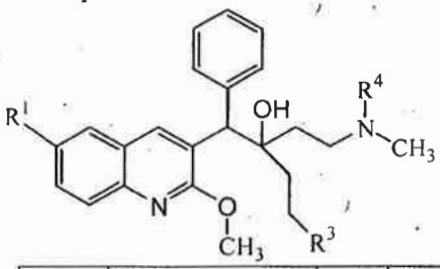
23. A compound selected from



R^1	R^3	R^4
Br	4-fluorophenyl	H
H	4-fluorophenyl	H
Br	4-chlorophenyl	CH_3

a pharmaceutically acceptable acid or base addition salt thereof, a stereochemically isomeric form thereof, a tautomeric form thereof or a *N*-oxide form thereof.

24. A compound selected from



R^1	R^3	R^4	stereochemistry
Br	4-fluorophenyl	H	(A)
Br	4-fluorophenyl	H	(B)
H	4-fluorophenyl	H	(A)
H	4-fluorophenyl	H	(B)
Br	4-chlorophenyl	CH_3	(B)

a pharmaceutically acceptable acid or base addition salt thereof, a stereochemically isomeric form thereof, a tautomeric form thereof or a *N*-oxide form thereof.

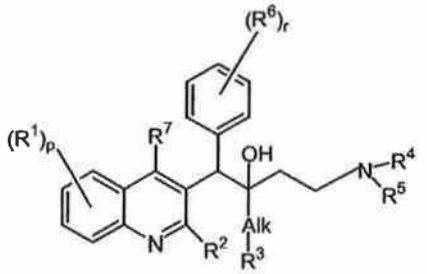
25. A combination of (a) a compound of formula (Ia) or (Ib) as defined in any one of the preceding claims, and (b) one or more other antibacterial agents provided that the one or more other antibacterial agents are other than antimycobacterial agents.

26. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and, as active ingredient, a therapeutically effective amount of (a) a compound of formula (Ia) or (Ib) as defined in any one of claims 1 to 24, and (b) one or more other antibacterial agents provided that the one or more other antibacterial agents are other than antimycobacterial agents.

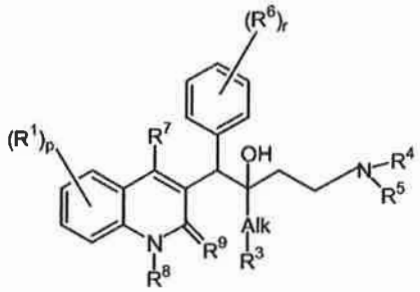
27. The use of a combination as claimed in claim 25 or a pharmaceutical composition as claimed in claim 26 for the manufacture of a medicament for the treatment of a bacterial infection.

Claims

1. Use of a compound for the manufacture of a medicament for the treatment of a bacterial infection, said compound being a compound of formula (Ia) or (Ib)



(Ia)

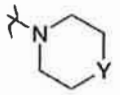


(Ib)

a pharmaceutically acceptable acid or base addition salt thereof, a stereochemically isomeric form thereof, a tautomeric form thereof or a *N*-oxide form thereof, wherein

R^1 is hydrogen, halo, haloalkyl, cyano, hydroxy, Ar, Het, alkyl, alkyloxy, alkylthio, alkyloxyalkyl, alkylthioalkyl, Ar-alkyl or di(Ar)alkyl ;

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

R^2 is hydrogen, hydroxy, mercapto, alkyloxy, alkyloxyalkyloxy, alkylthio, mono or di(alkyl)amino or a radical of formula  wherein Y is CH_2, O, S, NH or *N*-alkyl ;

R^3 is Ar or Het;

R^4 and R^5 each independently are hydrogen, alkyl or benzyl; or

R^4 and R^5 together and including the N to which they are attached may form a radical selected from the group of pyrrolidinyl, 2-pyrrolinyl, 3-pyrrolinyl, pyrrolyl, imidazolidinyl, pyrazolidinyl, 2-imidazolinyl, 2-pyrazolinyl, imidazolyl, pyrazolyl, triazolyl, piperidinyl, pyridinyl, piperazinyl, pyridazinyl, pyrimidinyl, pyrazinyl, triazinyl, morpholinyl and thiomorpholinyl, optionally substituted with alkyl, halo, haloalkyl,

hydroxy, alkyloxy, amino, mono- or dialkylamino, alkylthio, alkyloxyalkyl, alkylthioalkyl or pyrimidinyl ;

R^6 is hydrogen, halo, haloalkyl, hydroxy, Ar, alkyl, alkyloxy, alkylthio, alkyloxyalkyl, alkylthioalkyl, Ar-alkyl or di(Ar)alkyl ; or

two vicinal R^6 radicals may be taken together to form a bivalent radical of formula -CH=CH-CH=CH- ;

r is an integer equal to 1, 2, 3, 4 or 5 ;

R^7 is hydrogen, alkyl, Ar or Het ;

R^8 is hydrogen or alkyl ;

R^9 is oxo ; or

R^8 and R^9 together form the radical -CH=CH-N=;

alkyl is a straight or branched saturated hydrocarbon radical having from 1 to 6 carbon atoms ; or is a cyclic saturated hydrocarbon radical having from 3 to 6 carbon atoms ; or is a cyclic saturated hydrocarbon radical having from 3 to 6 carbon atoms attached to a straight or branched saturated hydrocarbon radical having from 1 to 6 carbon atoms; wherein each carbon atom can be optionally substituted with hydroxy, alkyloxy or oxo;

Alk is a straight or branched saturated hydrocarbon radical having from 1 to 6 carbon atoms ;

Ar is a homocycle selected from the group of phenyl, naphthyl, acenaphthyl and tetrahydronaphthyl, each homocycle optionally substituted with 1, 2 or 3 substituents, each substituent independently selected from the group of hydroxy, halo, cyano, nitro, amino, mono- or dialkylamino, alkyl, haloalkyl, alkyloxy, haloalkyloxy, carboxyl, alkyloxycarbonyl, aminocarbonyl, morpholinyl and mono- or dialkylaminocarbonyl ;

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

halo is a substituent selected from the group of fluoro, chloro, bromo and iodo; and

haloalkyl is a straight or branched saturated hydrocarbon radical having from 1 to 6 carbon atoms or a cyclic saturated hydrocarbon radical having from 3 to 6 carbon atoms or a cyclic saturated hydrocarbon radical having from 3 to 6 carbon atoms attached to a straight or branched saturated hydrocarbon radical having from 1 to 6 carbon atoms; wherein one or more carbon atoms are substituted with one or more halo atoms;

provided that the bacterial infection is other than a Mycobacterial infection.

2. Use according to claim 1 wherein R^1 is hydrogen, halo, alkyl, alkyloxy, Ar or Het.

3. Use according to claim 2 wherein R^1 is hydrogen, halo, alkyl or alkyloxy.

4. Use according to claim 3 wherein R^1 is hydrogen or halo.

5. Use according to claim 4 wherein R^1 is halo.

6. Use according to any one of the preceding claims wherein p is equal to 1.

7. Use according to claim 6 wherein the R^1 substituent is placed in position 6 of the quinoline ring.

8. Use according to any one of the preceding claims wherein R^2 is alkyloxy, alkylthio, mono-or di(alkyl)amino or alkyloxyalkyloxy.

9. Use according to any one of claims 1 to 7 wherein R^2 is hydrogen, alkyloxy or alkylthio.

10. Use according to claim 8 or 9 wherein R^2 is C_{1-4}alkyloxy.

11. Use according to any one of the preceding claims wherein R^3 is Ar.

12. Use according to claim 11 wherein R^3 is naphthyl or phenyl, optionally substituted with 1 or 2 halo.

13. Use according to any one of the preceding claims wherein R^4 and R^5 each independently are hydrogen or C_{1-4}alkyl.

14. Use according to any one of the preceding claims wherein R^6 is hydrogen.

15. Use according to any one of the preceding claims wherein R^7 is hydrogen.

16. Use according to any one of the preceding claims wherein Alk is methylene or ethylene.

17. Use according to claim 16 wherein Alk is ethylene.

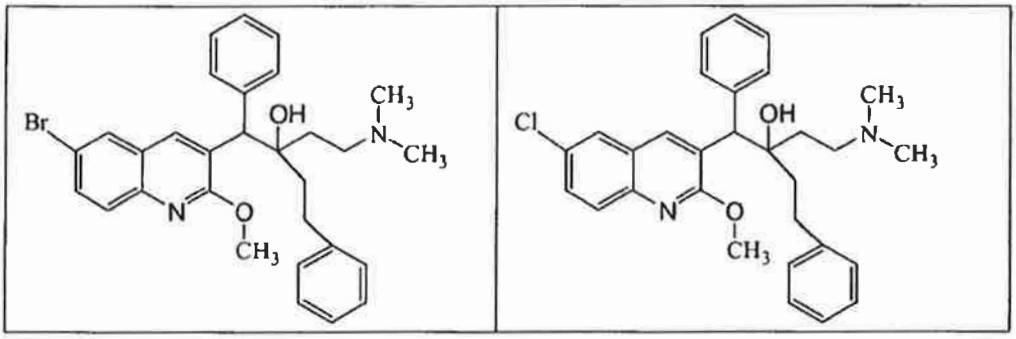
18. Use according to any one of the preceding claims wherein the compound is a compound according to formula (Ia).

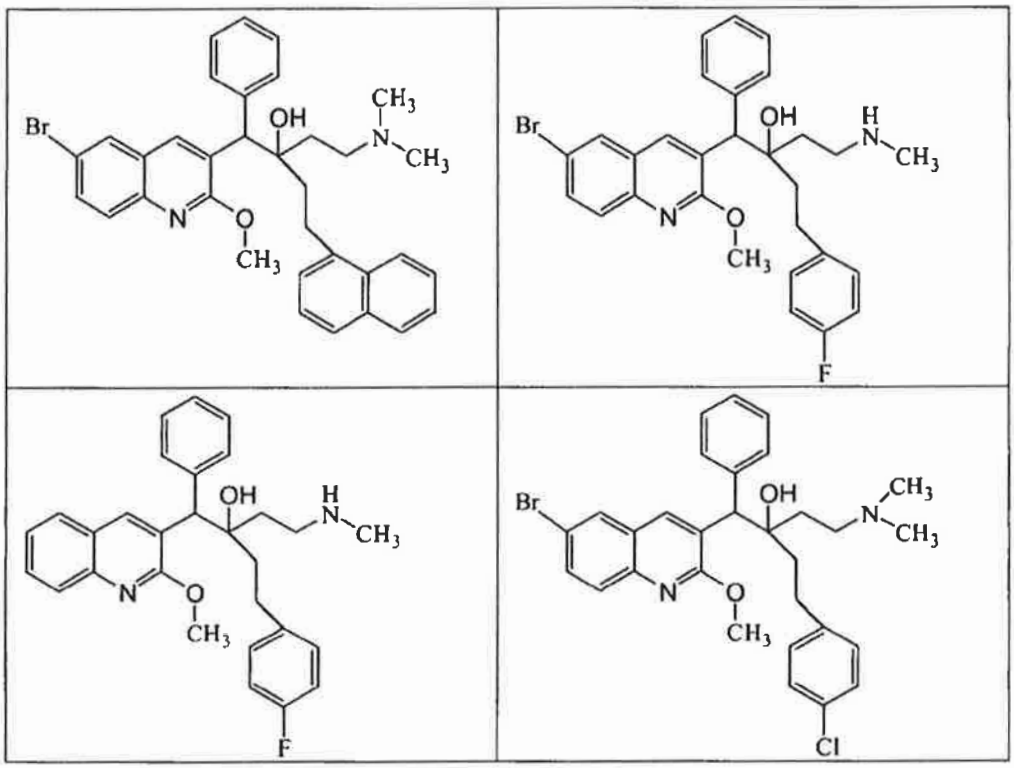
19. Use according to any one of the preceding claims wherein alkyl represents C_{1-6} alkyl.

20. Use according to claim 1 wherein the compound is a compound of formula (Ia) wherein R^1 is hydrogen, halo, C_{1-4}alkyl, C_{1-4}alkyloxy, Ar or Het; p = 1 or 2; R^2 is C_{1-4}alkyloxy, C_{1-4}alkylthio, mono-or di(C_{1-4}alkyl)amino, C_{1-4}alkyloxyC_{1-4}alkyloxyC_{1-4}alkyloxy; R^3 is optionally substituted naphthyl or phenyl; R^4 and R^5 each independently are hydrogen or C_{1-4}alkyl; or R^4 and R^5 together and including the N to which they are attached form a piperidinyl; R^6 is hydrogen, halo, C_{1-4}alkyl or C_{1-4}alkyloxy; r is equal to 1; R^7 is hydrogen; Alk is methylene or ethylene.

21. Use according to any one of the preceding claims wherein the bacterial infection is an infection with a gram-positive bacterium.

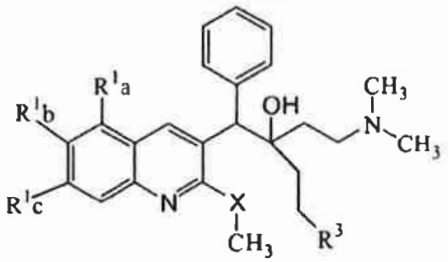
22. Use according to any one of the preceding claims wherein the compound is selected from





a pharmaceutically acceptable acid or base addition salt thereof, a stereochemically isomeric form thereof or a *N*-oxide form thereof.

23. A compound selected from



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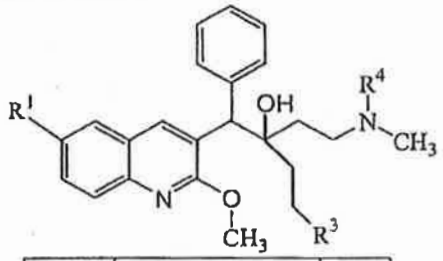
R^1_a	R^1_b	R^1_c	R^3	X
H	H	H	phenyl	O
H	CH_3	H	phenyl	O
H	OCH_3	H	phenyl	O
H	Br	H	phenyl	S
H	Br	H	1-naphthyl	O
H	Br	CH_3	phenyl	O
H	Cl	H	phenyl	O
Br	H	H	phenyl	O

a pharmaceutically acceptable acid or base addition salt thereof, a stereochemically isomeric form thereof or a *N*-oxide form thereof.

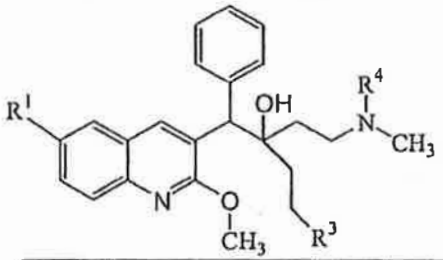
24. A compound selected from



R^1	R^3	R^4
Br	4-fluorophenyl	H
H	4-fluorophenyl	H
Br	4-chlorophenyl	CH_3

a pharmaceutically acceptable acid or base addition salt thereof, a stereochemically isomeric form thereof or a *N*-oxide form thereof.

25. A compound selected from



R^1	R^3	R^4	stereochemistry
Br	4-fluorophenyl	H	(A)
Br	4-fluorophenyl	H	(B)
H	4-fluorophenyl	H	(A)
H	4-fluorophenyl	H	(B)
Br	4-chlorophenyl	CH_3	(B)

a pharmaceutically acceptable acid or base addition salt thereof, a stereochemically isomeric form thereof or a *N*-oxide form thereof.

26. Use of a combination in the treatment of a bacterial infection other than a mycobacterial infection, wherein the combination comprises (a) a compound of formula (Ia) or (Ib) as defined in any one of claims 1 to 20 or a compound as defined in any one of claims 22 to 25, and (b) one or more other antibacterial agents provided that the one or more other antibacterial agents are other than antimycobacterial agents.

27. Use of a pharmaceutical composition in the treatment of a bacterial infection other than a mycobacterial infection, wherein the composition comprises a pharmaceutically acceptable carrier and, as active ingredient, a therapeutically effective amount of (a) a compound of formula (Ia) or (Ib) as defined in any one of claims 1 to 20 or a compound as defined in any one of claims 22 to 25, and (b) one or more other antibacterial agents provided that the one or more other antibacterial agents are other than antimycobacterial agents.

28. The use of the combination as defined in claim 26 or the use of the pharmaceutical composition as defined in claim 27 for the manufacture of a medicament for the treatment of a bacterial infection other than a mycobacterial infection.

29. Use of a product in the treatment of a bacterial infection other than a mycobacterial infection, wherein the product comprises (a) a compound of formula (Ia) or (Ib) as defined in any one of claims 1 to 20 or a compound as defined in any one of claims 22 to 25, and (b) one or more other antibacterial agents provided that the one or more other antibacterial agents are other than antimycobacterial agents, as a combined preparation for simultaneous, separate or sequential use in the treatment of a bacterial infection other than a mycobacterial infection.

30. Use according to any one of claims 1 to 22 and 28 wherein the bacterial infection is an infection with a gram-positive bacterium.

31. Use according to any one of claims 1 to 22, 28 and 30 wherein the bacterial infection is an infection with Staphylococci, Enterococci or Streptococci.

32. Use according to any one of claims 1 to 22, 28 and 30 wherein the bacterial infection is an infection with methicillin resistant *Staphylococcus aureus* (MRSA), methicillin resistant coagulase negative staphylococci (MRCNS), penicillin resistant *Streptococcus pneumoniae* or multiple resistant *Enterococcus faecium*.

33. Use according to any one of claims 1 to 22, 28 and 30 wherein the bacterial infection is an infection with *Staphylococcus aureus* or *Streptococcus pneumoniae*.

34. Use according to any one of claims 1 to 22, 28 and 30 wherein the bacterial infection is an infection with methicillin resistant *Staphylococcus aureus (MRSA)*.