ANTIMICROBIAL COMPOUNDS BASED UPON 4-AMINOQUINOLINE

There is provided compounds of formula I wherein $R^1$, $R^2$, $R^3$, $R^4$, $X^1$, $X^2$ and A have meanings given in the description. Also provided are medical uses of such compounds, such as the killing clinically latent microorganisms or treating microbial infections.
ANTIMICROBIAL COMPOUNDS BASED UPON 4-AMINOQUINOLINE

This invention relates to certain 4-aminoquinoline-based compounds. As described herein, such compounds may be useful in medicine, such as in the killing of clinically latent microorganisms or the treatment of microbial infections.

The listing or discussion of a prior-published document in this specification should not necessarily be taken as an acknowledgement that the document is part of the state of the art or is common general knowledge.

Before the introduction of antibiotics, patients suffering from acute bacterial infections (e.g. tuberculosis or pneumonia) had a low chance of survival. For example, mortality from tuberculosis was around 50%.

Although the introduction of antibacterial agents in the 1940s and 1950s rapidly changed this picture, bacteria have responded by progressively gaining resistance to commonly used antibiotics. Now, every country in the world has antibiotic-resistant bacteria. Indeed, more than 70% of bacteria that give rise to hospital acquired infections in the USA resist at least one of the main antimicrobial agents that are typically used to fight infection (see Nature Reviews, Drug Discovery 1, 895-910 (2002)).

One way of tackling the growing problem of resistant bacteria is the development of new classes of antimicrobial agents. However, until the introduction of linezolid in 2000, there had been no new class of antibiotic marketed for over 37 years. Moreover, even the development of new classes of antibiotic provides only a temporary solution, and indeed there are already reports of resistance of certain bacteria to linezolid (see Lancet 357, 1179 (2001) and Lancet 358, 207-208 (2001)).

In order to develop more long-term solutions to the problem of bacterial resistance, it is clear that alternative approaches are required. One such alternative approach is to minimise, as much as is possible, the opportunities that bacteria are given for developing resistance to important antibiotics.
Thus, strategies that can be adopted include limiting the use of antibiotics for the treatment of non-acute infections, as well as controlling which antibiotics are fed to animals in order to promote growth.

However, in order to tackle the problem more effectively, it is necessary to gain an understanding of the actual mechanisms by which bacteria generate resistance to antibiotic agents. To do this requires first a consideration of how current antibiotic agents work to kill bacteria.

Antimicrobial agents target essential components of bacterial metabolism. For example, the β-lactams (e.g. penicillins and cephalosporins) inhibit cell wall synthesis, whereas other agents inhibit a diverse range of targets, such as DNA gyrase (quinolones) and protein synthesis (e.g. macrolides, aminoglycosides, tetracyclines and oxazolidinones). The range of organisms against which the antimicrobial agents are effective varies, depending upon which organisms are heavily reliant upon the metabolic step(s) that is/are inhibited. Further, the effect upon bacteria can vary from a mere inhibition of growth (i.e. a bacteriostatic effect, as seen with agents such as the tetracyclines) to full killing (i.e. a bactericidal effect, as seen, for example, with penicillin).

Bacteria have been growing on Earth for more than 3 billion years and, in that time, have needed to respond to vast numbers of environmental stresses. It is therefore perhaps not surprising that bacteria have developed a seemingly inexhaustible variety of mechanisms by which they can respond to the metabolic stresses imposed upon them by antibiotic agents. Indeed, mechanisms by which the bacteria can generate resistance include strategies as diverse as inactivation of the drug, modification of the site of action, modification of the permeability of the cell wall, overproduction of the target enzyme and bypass of the inhibited steps.

Nevertheless, the rate that resistance emerges to a particular agent has been observed to vary widely, depending upon factors such as the agent's mechanism of action, whether the agent’s mode of killing is time- or concentration-dependent, the potency against the population of bacteria and the magnitude and duration of the available serum concentration.
It has been proposed (see *Science* 264, 388-393 (1994)) that agents that target single enzymes (e.g. rifampicin) are the most prone to the development of resistance. Further, the longer that suboptimal levels of antimicrobial agent are in contact with the bacteria, the more likely the emergence of resistance.

Moreover, it is now known that many bacterial infections include sub-populations of bacteria that are *phenotypically* resistant to antimicrobials (see, for example: *J. Antimicrob. Chemother.* 4, 395-404 (1988); *J. Med. Microbiol.* 38, 197-202 (1993); *J. Bacteriol.* 182, 1794-1801 (2000); *ibid.* 182, 6358-6365 (2000); *ibid.* 183, 6746-6751 (2001); *FEMS Microbiol. Lett.* 202, 59-65 (2001); and *Trends in Microbiology* 13, 34-40 (2005)). There appear to be several types of such phenotypically resistant bacteria, including persisters, stationary-phase bacteria, as well as those in the depths of biofilms. However, each of these types is characterised by its low rate of growth (compared to log-phase bacteria under the same conditions). Nutritional starvation and high cell densities are also common characteristics of such bacteria.

Although resistant to antimicrobial agents in their slow-growing state, phenotypically resistant bacteria differ from those that are *genotypically* resistant in that they regain their susceptibility to antimicrobials when they return to a fast-growing state (e.g. when nutrients become more readily available to them).

The presence of phenotypically resistant bacteria in an infection leads to the need for prolonged courses of antimicrobial agents, comprising multiple doses. This is because the resistant, slowly multiplying bacteria provide a pool of "latent" organisms that can convert to a fast-growing state when the conditions allow (thereby effectively re-initiating the infection). Multiple doses over time deal with this issue by gradually killing off the "latent" bacteria that convert to "active" form.

However, dealing with "latent" bacteria by administering prolonged courses of antimicrobials poses its own problems. That is, prolonged exposure of bacteria to suboptimal concentrations of antimicrobial agent can lead to the emergence of genotypically resistant bacteria, which can then multiply rapidly in the presence of even high concentrations of the antimicrobial.
Long courses of antimicrobials are more likely to encourage the emergence of genotypic resistance than shorter courses on the grounds that non-multiplying bacterial will tend to survive and, interestingly, probably have an enhanced ability to mutate to resistance (see, for example: Proc. Natl. Acad. Sci. USA 92, 11736-11740 (1995); J. Bacteriol. 179, 6688-6691 (1997); and Antimicrob. Agents Chemother. 44, 1771-1777 (2000)). For example, non-dividing E. coli continually mutates to ciprofloxacin resistance during a seven-day exposure to the agent. Thus, "latent" bacteria might be one of the sources of genotypically resistant bacteria.

In the light of the above, a new approach to combating the problem of bacterial resistance might be to select and develop antimicrobial agents on the basis of their ability to kill "latent" microorganisms. The production of such agents would allow, amongst other things, for the shortening of chemotherapy regimes in the treatment of microbial infections, thus reducing the frequency with which genotypical resistance arises in microorganisms.

Certain 4-aminoquinoline-based compounds are disclosed in WO 2006/0135782, WO 2006/034235 and CN 1597671. However, these documents do not disclose the use of such compounds to kill clinically latent microorganisms.

We have now found, surprisingly, that 4-aminoquinoline compounds containing an N-substituent that is a bicyclic heterocycle may be used to kill clinically latent microorganisms.

According to a first aspect of the invention, there is provided the use of a compound of formula I, or a pharmaceutically-acceptable derivative thereof, for the preparation of a medicament for killing clinically latent microorganisms, wherein the compound of formula I is represented by the structure
wherein
X$^1$ represents CH or N;
X$^2$ represents N or O;
A represents a fused benzene ring or a fused 5- or 6-membered, aromatic heterocycle containing from one to three heteroatoms selected from N, O and S;

R$^2$ represents
(a) H;
(b) C$_{1-12}$ alkyl, C$_{2-12}$ alkenyl, C$_{2-12}$ alkynyl, C$_{3-12}$ cycloalkyl or C$_{4-12}$ cycloalkenyl, which latter five groups are optionally substituted by one or more substituents selected from halo, nitro, CN, C$_{1-6}$ alkyl, C$_{2-6}$ alkenyl, C$_{2-6}$ alkynyl, C$_{3-8}$ cycloalkyl (which latter three groups are optionally substituted by one or more substituents selected from OH, =O, halo, C$_{1-4}$ alkyl and C$_{1-4}$ alkoxy), 0 R$^{5a}$, S(O)$_n$R$^{5b}$, S(O)$_2$N(R$^{5c}$)(R$^{5d}$), N(R$^{5e}$)S(O)$_2$R$^{5f}$, N(R$^{5g}$)(R$^{5h}$), B$^1$-C(O)-B$^2$.R$^{5i}$, aryl and Het$^1$,
and which C$_{3-12}$ cycloalkyl or C$_{4-12}$ cycloalkenyl groups may additionally be substituted by =O,
(c) aryl or
(d) Het$^2$;

R$^1$ and R$^3$ independently represent H or one or more substituents on the fused benzene or heteroaromatic rings selected from
(a) halo,
(b) CN,
(c) C$_{1-12}$ alkyl, C$_{2-12}$ alkenyl, C$_{2-12}$ alkynyl, C$_{3-12}$ cycloalkyl or C$_{4-12}$ cycloalkenyl, which latter five groups are optionally substituted by one or more substituents selected from halo, nitro, CN, C$_{1-6}$ alkyl, C$_{2-6}$ alkenyl, C$_{2-6}$ alkynyl, C$_{3-8}$ cycloalkyl (which latter three groups are optionally substituted by one or more substituents selected from OH, =O, halo, C$_{1-4}$ alkyl and C$_{1-4}$ alkoxy), 0 R$^{6a}$, S(O)$_p$R$^{6b}$, S(O)$_2$N(R$^{6c}$)(R$^{6d}$), N(R$^{6e}$)S(O)$_2$R$^{6f}$, N(R$^{6g}$)(R$^{6h}$), B$^3$-C(O)-B$^4$.R$^{6i}$, aryl and Het$^3$,
and which C$_{3-12}$ cycloalkyl or C$_{4-12}$ cycloalkenyl groups may additionally be substituted by =O,
(d) 0 R$^{7a}$,
(e) S(O)$_q$R$^{7b}$,
(f) S(O)$_2$N(R$^{7c}$)(R$^{7d}$),
(g) N(R$^{7e}$)S(O)$_2$R$^{7f}$,
N(R^7)(R^7h),

B^5-C(O)-B^5-R^7i,

aryl or

Het^4;

R^4 represents, when X^2 represents N, H or a substituent selected from

(a) C_{1-12} alkyl, C_{2-12} alkenyl, C_{2-12} alkynyl, C_{3-12} cycloalkyl or C_{4-12} cycloalkenyl,

which latter five groups are optionally substituted by one or more substituents selected from halo, nitro, CN, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-8} cycloalkyl (which latter three groups are optionally substituted by one or more substituents selected from OH, =0, halo, C_{1-4} alkyl and C_{1-4} alkoxy), OR^8a, S(O)R^8b, S(O)NR^8c(R^8d), N(R^8e)S(O)R^8f, N(R^8g)(R^8h), B^7-C(O)-B^8-R^8i, aryl and Het^5, and which C_{3-12} cycloalkyl or C_{4-12} cycloalkenyl groups may additionally be substituted by =0,

(b) aryl or

(c) Het^6,

or, when X^2 represents O, R^4 is absent;

R^5a to R^5i, R^6a to R^6i, R^7a to R^7i and R^8a to R^8i independently represent, at each occurrence,

(a) H,

(b) C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl (which latter three groups are optionally substituted by one or more substituents selected from halo, OH, C_{1-6} alkoxy, aryl and Het^7),

(c) C_{3-10} cycloalkyl, C_{4-10} cycloalkenyl (which latter two groups are optionally substituted by one or more substituents selected from halo, OH, =0, C_{1-6} alkyl, C_{1-6} alkoxy, aryl and Het^8),

(d) aryl or

(e) Het^9,

provided that R^5b, R^6b, R^7b or R^8b does not represent H when n, p, q or r, respectively is 1 or 2;

each aryl independently represents a C_{6-10} carbocyclic aromatic group, which group may comprise either one or two rings and may be substituted by one or more substituents selected from
(a) halo,
(b) CN,
(c) C\textsubscript{1-12} alkyl, C\textsubscript{2-12} alkenyl, C\textsubscript{2-12} alkynyl, C\textsubscript{3-12} cycloalkyl or C\textsubscript{4-12} cycloalkenyl, which latter five groups are optionally substituted by one or more substituents selected from halo, nitro, CN, C\textsubscript{1-6} alkyl, C\textsubscript{2-6} alkenyl, C\textsubscript{2-7} alkynyl, C\textsubscript{3-9} cycloalkyl or C\textsubscript{4-12} cycloalkenyl, (which latter three groups are optionally substituted by one or more substituents selected from OH, =0, halo, C\textsubscript{1-4} alkyl and C\textsubscript{1-4} alkoxy), 0 R\textsuperscript{9a}, S(O)\textsubscript{1}R\textsuperscript{9b}, S(O)\textsubscript{2}N(R\textsuperscript{9c})(R\textsuperscript{9d}), N(R\textsuperscript{9e})S(O)\textsubscript{2}R\textsuperscript{9f}, N(R\textsuperscript{9g})(R\textsuperscript{9h}), B\textsuperscript{9a}C(O)-B \textsuperscript{10a}.R\textsuperscript{9i}, phenyl, naphthyl (which latter two groups are optionally substituted by one or more substituents selected from OH, halo, C\textsubscript{1-4} alkyl and C\textsubscript{1-4} alkoxy) and Het \textsuperscript{10}, and which C\textsubscript{3-12} cycloalkyl or C\textsubscript{4-12} cycloalkenyl groups may additionally be substituted by =0,
(d) OR\textsuperscript{10a},
(e) S(O)\textsubscript{1}uR\textsuperscript{10b},
(f) S(O)\textsubscript{2}N(R\textsuperscript{10c})(R\textsuperscript{10d}),
(g) N(R\textsuperscript{10e})S(O)\textsubscript{2}R\textsuperscript{10f},
(h) N(R\textsuperscript{10g})(R\textsuperscript{10h}),
(i) B\textsuperscript{11a}-C(O)-B \textsuperscript{12a}.R\textsuperscript{10i},
(j) phenyl (which latter group is optionally substituted by one or more substituents selected from OH, halo, C\textsubscript{1-4} alkyl and C\textsubscript{1-4} alkoxy) or
(k) Het \textsuperscript{11}.

R\textsuperscript{9a} to R\textsuperscript{9i} and R\textsuperscript{10a} to R\textsuperscript{10i} independently represent, at each occurrence,
(a) H,
(b) C\textsubscript{1-12} alkyl, C\textsubscript{2-12} alkenyl, C\textsubscript{2-12} alkynyl, C\textsubscript{3-12} cycloalkyl, C\textsubscript{4-12} cycloalkenyl (which latter five groups are optionally substituted by one or more substituents selected from halo, OH, C\textsubscript{1-6} alkyl, C\textsubscript{2-6} cycloalkyl, C\textsubscript{4-12} cycloalkenyl (which latter two groups are optionally substituted by one or more substituents selected from OH, =0, halo, C\textsubscript{1-4} alkyl and C\textsubscript{1-4} alkoxy), C\textsubscript{2-6} alkyl, NH\textsubscript{2}, N(H)-C \textsubscript{1-6} alkyl, N(C\textsubscript{1-6} alkyl)\textsubscript{2}, phenyl (which latter group is optionally substituted by one or more substituents selected from OH, halo, C\textsubscript{1-4} alkyl and C\textsubscript{1-4} alkoxy) and Het \textsuperscript{12}, and which C\textsubscript{3-12} cycloalkyl or C\textsubscript{4-12} cycloalkenyl groups may additionally be substituted by =0),
(c) phenyl (which latter group is optionally substituted by one or more substituents selected from OH, CN, halo, C\textsubscript{1-6} alkyl and C\textsubscript{1-6} alkoxy) or
Het\textsuperscript{13},
provided that R\textsuperscript{9b} or R\textsuperscript{10b} does not represent H when t or u, respectively is 1 or 2;

Het\textsuperscript{1} to Het\textsuperscript{13} independently represent 4- to 14-membered heterocyclic groups containing one or more heteroatoms selected from oxygen, nitrogen and/or sulfur, which heterocyclic groups may comprise one, two or three rings and may be substituted by one or more substituents selected from

(a) halo,
(b) CN,
(c) C\textsubscript{1-12} alkyl, C\textsubscript{2-12} alkenyl, C\textsubscript{2-12} alkynyl, C\textsubscript{3-12} cycloalkyl or C\textsubscript{4-12} cycloalkenyl, which latter five groups are optionally substituted by one or more substituents selected from halo, nitro, CN, C\textsubscript{1-4} alkyl, C\textsubscript{2-6} alkenyl, C\textsubscript{2-6} alkynyl, C\textsubscript{3-8} cycloalkyl (which latter three groups are optionally substituted by one or more substituents selected from OH, \(=0\), halo, C\textsubscript{1-4} alkyl and C\textsubscript{1-4} alkoxy), OR\textsuperscript{11a}, S(O)\textsubscript{v}R\textsuperscript{11b}, S(O)\textsubscript{2}N(R\textsuperscript{11c})(R\textsuperscript{11d}), N(R\textsuperscript{11e})S(O)\textsubscript{2}R\textsuperscript{11f}, N(R\textsuperscript{11g})(R\textsuperscript{11h}), B\textsuperscript{13}-C(O)-B\textsuperscript{14}-R\textsuperscript{11i}, phenyl, naphthyl (which latter two groups are optionally substituted by one or more substituents selected from OH, halo, C\textsubscript{1-4} alkyl and C\textsubscript{1-4} alkoxy) and Het\textsuperscript{a}, and which C\textsubscript{3-12} cycloalkyl or C\textsubscript{4-12} cycloalkenyl groups may additionally be substituted by =0,
(d) 0 R\textsuperscript{12a},
(e) =0,
(f) S(O)\textsubscript{w}R\textsuperscript{12b},
(g) S(O)\textsubscript{2}N(R\textsuperscript{12c})(R\textsuperscript{12d}),
(h) N(R\textsuperscript{12e})S(O)\textsubscript{2}R\textsuperscript{12f},
(i) N(R\textsuperscript{12g})(R\textsuperscript{12h}),
(j) B\textsuperscript{15}-C(O)-B\textsuperscript{16}-R\textsuperscript{12i},
(k) phenyl (which latter group is optionally substituted by one or more substituents selected from OH, halo, C\textsubscript{1-4} alkyl and C\textsubscript{1-4} alkoxy) or
(l) Het\textsuperscript{b};

R\textsuperscript{11a} to R\textsuperscript{11i} and R\textsuperscript{12a} to R\textsuperscript{12i} independently represent, at each occurrence,

(a) H,
(b) C\textsubscript{1-12} alkyl, C\textsubscript{2-12} alkenyl, C\textsubscript{2-12} alkynyl, C\textsubscript{3-12} cycloalkyl, C\textsubscript{4-12} cycloalkenyl (which latter five groups are optionally substituted by one or more substituents selected from halo, OH, C\textsubscript{1-6} alkyl, C\textsubscript{3-12} cycloalkyl, C\textsubscript{4-12} cycloalkenyl (which latter two
groups are optionally substituted by one or more substituents selected from OH, =0, halo, C\textsubscript{i}-4 alkyl and C\textsubscript{i}-4 alkoxy), C\textsubscript{i}-6 alkoxy, phenyl (which latter group is optionally substituted by one or more substituents selected from OH, halo, C\textsubscript{i}-4 alkyl and C\textsubscript{i}-4 alkoxy) and Het\textsuperscript{c}, and which C\textsubscript{3-12} cycloalkyl! or C\textsubscript{4-12} cycloalkeny! groups may additionally be substituted by =0),

(c) phenyl (which latter group is optionally substituted by one or more substituents selected from OH, halo, C\textsubscript{i}-4 alkyl and C\textsubscript{n-4} alkoxy) or

(e) Het\textsuperscript{d},

provided that R\textsuperscript{11b} or R\textsuperscript{12b} does not represent H when v or w, respectively is 1 or 2;

B\textsuperscript{1} to B\textsuperscript{16} independently represent a direct bond, O, S, NH or N(R\textsuperscript{13});

n, p, q, r, t, u, v and w independently represent 0, 1 or 2;

R\textsuperscript{13} represents

(a) \textit{C}_{i}\textsubscript{6} alkyl,

(b) phenyl (which latter group is optionally substituted by one or more substituents selected from OH, halo, C\textsubscript{i}-4 alkyl and C\textsubscript{i}-4 alkoxy),

(c) C\textsubscript{3-7} cycloalkyl (which latter group is are optionally substituted by one or more substituents selected from OH, =0, halo, C\textsubscript{i-4} alkyl and C\textsubscript{i-4} alkoxy) or

(e) Het\textsuperscript{d};

Het\textsuperscript{a} to Het\textsuperscript{e} independently represent 5- or 6-membered heterocyclic groups containing one to four heteroatoms selected from oxygen, nitrogen and/or sulfur, which heterocyclic groups may be substituted by one or more substituents selected from halo, =0 and \textit{C}_{i-6} alkyl; and

unless otherwise specified

(i) alkyl, aikenyl, alkynyl, cycloalkyl, and cycloalkeny! groups, as well as the alkyl part of alkoxy groups, may be substituted by one or more halo atoms, and

(ii) cycloalkyl and cycloalkeny! groups may comprise one or two rings and may additionally be ring-fused to one or two benzene rings.

When used herein, the term "pharmaceutically-acceptable derivative" includes references to:
pharmaceutically-acceptable salts with either acids or bases (e.g. acid addition salts); and/or

(b) solvates (e.g. hydrates)

Acid addition salts that may be mentioned include carboxylate salts (e.g. formate, acetate, trifluoroacetate, propionate, isobutyrate, heptanoate, decanoate, caprate, caprylate, stearate, acrylate, caproate, propiolate, ascorbate, citrate, glucuronate, glutamate, glycolate, α-hydroxybutyrate, lactate, tartrate, phenylacetate, mandelate, phenylpropionate, phenylbutyrate, benzoate, chlorobenzoate, methylbenzoate, hydroxybenzoate, methoxybenzoate, dinitrobenzoate, α-acetoxybenzoate, salicylate, nicotinate, isonicotinate, cinnamate, oxalate, malonate, succinate, suberate, sebacate, fumarate, malate, maleate, hydroxymaleate, hippurate, phthalate or terephthalate salts), halide salts (e.g. chloride, bromide or iodide salts), sulfonate salts (e.g. benzenesulfonate, methyl-, bromo- or chloro-benzenesulfonate, xylenesulfonate, methanesulfonate, ethanesulfonate, propanesulfonate, hydroxyethanesulfonate, 1- or 2-naphthalene-sulfonate or 1,5-naphthalenedisulfonate salts) or sulfate, pyrosulfate, bisulfate, sulfate, bisulfite, phosphate, monohydrogenphosphate, dihydrogenphosphate, metaphosphate, pyrophosphate or nitrate salts, and the like.

The term "pharmaceutically-acceptable derivative" also includes references to:
(a) C₁₋₄ alkyl quaternary ammonium salts; or
(b) A/-oxides,

at any tertiary N-atom present in the compound of formula I (e.g. the N-atom of the quinoline ring or a tertiary N-atom in the 8- or 9-membered bicyclic heterocycle (i.e. that containing the ring A)).

For the avoidance of doubt, the definitions of the terms aryl, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl and alkoxy groups provided above apply, unless otherwise stated, at each usage of such terms herein. Further, the one or two benzene rings that may be fused to cycloalkyl groups may bear one or more of the substituents defined in respect of the relevant cycloalkyl group.

The term "halo", when used herein, includes fluoro, chloro, bromo and iodo.
Heterocyclic (Het\textsuperscript{1} to Het\textsuperscript{13} and Hef to Hef) groups may be fully saturated, partly unsaturated, wholly aromatic or partly aromatic in character. Values of heterocyclic (Het\textsuperscript{1} to Het\textsuperscript{13} and Hef to Hef) groups that may be mentioned include 1-azabicyclo[2.2.2]octanyl, benzimidazolyl, benzo[c]isoxazolidinyl, benzisoxazolyl, benzodioxanyl, benzodioxepanyl, benzodioxolyl, benzofuranyl, benzofurazanyl, benzomorpholinyl, 2,1,3-benzoxadiazolyl, benzoxazolidinyl, benzoxazolyl, benzopyrazolyl, benzo[e]pyrimidine, 2,1,3-benzothiaziazolyl, benzothiazolyl, benzothienyl, benzotriazolyl, chromanyl, chromenyl, cinnolinyl, 2,3-dihydrobenzimidazolyl, 2,3-dihydrobenzo[b]furanyl, 1,3-dihydrobenzo[c]furanyl, 1,3-dihydro-2,1-benzisoxazolyl, 2,3-dihydropyrrolo[2,3-b]pyridinyl, dioxanyl, furanyl, hexahydropyrimidinyl, hydantoïnyl, imidazolyl, imidazo[1,2-a]pyridinyl, imidazo[2,3-jb]thiazolyl, indolyl, isoquinolinyl, isoxazolidinyl, isoxazolyl, maleimido, morpholinyl, naphtho[1,2-ib]furanyl, oxadiazolyl, 1,2- or 1,3-oxazinanonyl, oxazolyl, phthalazinyl, piperazinyl, piperidinyl, purinyl, pyranyl, pyrazinyl, pyrazolyl, pyridinyl, pyrimidinyl, pyrroloidinonyl, pyrrolidinyl, pyrrolinyl, pyrrolo[2,3-b]pyridinyl, pyrolo[5,1-b]pyridiniy, pyrrolo[2,3-c]pyridinyl, pyrrolyl, quinazolinyl, quinolinyl, sulfolanyl, 3-sulfolenyl, 4,5,6,7-tetrahydrobenzimidazolyl, 4,5,6,7-tetrahydrobenzopyrazolyl, 5,6,7,8-tetrahydrobenzo[e]-pyrimidine, tetrahydrofuranyl, tetrahydropropargyl, 3,4,5,6-tetrahydropyrimidinyl, 1,2,3,4-tetrahydropyrimidinyl, 3,4,5,6-tetrahydropyrimidinyl, thiadiazolyl, thiazolidinyl, thiazolyl, thienyl, thieno[5,1-c]pyridinyl, thiochromanyl, triazolyl, 1,3,4-triazolo[2,3-b]pyrimidinyl, xanthenyli and the like.

Values of Het\textsuperscript{2} that may be mentioned include morpholinyl (e.g. morpholin-1-yl).

Values of Het\textsuperscript{4} that may be mentioned include piperazinyl (e.g. piperazin-1-yl, such as 4-methylpiperazin-1-yl).

Values of Het\textsuperscript{9} that may be mentioned include pyrimidinyl (e.g. pyrimidin-2-yl).

When used herein, the term "microorganisms" means:

(a) fungi (as defined below); and, particularly

(b) bacteria (as defined below).
References herein to the terms "microbial", "antimicrobial" and "antimicrobially" shall be interpreted in accordance with the definition of "microorganisms". For example, the term "microbial" means fungal or, particularly, bacterial.

When used herein, the term "clinically latent" includes references to microorganisms that are viable but non-culturable (e.g. bacteria that cannot be detected by standard culture techniques but that are detectable and quantifiable by techniques such as broth dilution counting, microscopy, or molecular techniques such as polymerase chain reaction).

The term "clinically latent" also includes references to microorganisms that are phenotypically tolerant, for example microorganisms that:

(a) are sensitive (e.g. in log phase) to the biostatic (e.g. bacteriostatic) effects of conventional antimicrobial agents (i.e. microorganisms for which the minimum inhibitory concentration (MIC) of a conventional antimicrobial is substantially unchanged); but

(b) possess drastically decreased susceptibility to drug-induced killing (e.g. microorganisms for which, with any given conventional antimicrobial agent, the ratio of minimum micbicidal concentration (e.g. minimum bactericidal concentration, MBC) to MIC is 10 or more).

In relation to point (a) above, "substantially unchanged" refers to MIC values that are anywhere from 50 to 200% (e.g. 90 to 110%) of the value determined under standard conditions for the microorganism and conventional antimicrobial agent concerned.

For the avoidance of doubt, the term "clinically latent" excludes references to microorganisms that are genotypically resistant to conventional antimicrobial agents (i.e. microorganisms that differ genetically from antimicrobial-sensitive members of the same genus and that display an increased MIC (e.g. in log phase) for one or more conventional antimicrobial agents compared to said antimicrobial-sensitive microorganisms).

The term "clinically latent" further includes references to microorganisms that:
(i) are metabolically active; but

(ii) have a growth rate that is below the threshold of infectious disease expression.

The term "threshold of infectious disease expression" will be understood by those skilled in the art to include references to the growth rate threshold below which the symptoms of infectious disease (in a patient infected with the relevant microorganism) are absent.

In relation to point (i) above, metabolic activity of latent microorganisms can be determined by several methods known to those skilled in the art, for example by measuring mRNA levels in the microorganisms or by determining their rate of uridine uptake. In this respect, the term "clinically latent further includes references to microorganisms that, compared to the same number of microorganisms under logarithmic growth conditions (in vitro or in vivo), possess reduced but still significant levels of:

(I) mRNA (e.g. from 0.0001 to 50%, such as from 1 to 30, 5 to 25 or 10 to 20%, of the level of mRNA); and/or

(U) uridine (e.g. [3H]uridine) uptake (e.g. from 0.0005 to 50%, such as from 1 to 40, 15 to 35 or 20 to 30% of the level of [3H]uridine uptake).

When used herein, the term "conventional antimicrobial agent(s)" means:

(a) conventional antifungal agents; and, particularly

(b) conventional antibacterial agents,

wherein each of (a) and (b) is as defined below.

When used herein, the term "conventional antibacterial agent(s)" include references to bactericidal and bacteriostatic agents that are known in the prior art (i.e. agents that have been selected and developed on the basis of their MICs - namely their ability to inhibit the growth of bacteria). In this respect, particular conventional antibiotic agents that may be mentioned include any one or more of the following.
(a) **β-Lactams**, including:

(i) **penicillins**, such as

(1) benzylpenicillin, procaine benzylpenicillin, phenoxy-methylpenicillin, methicillin, propicillin, cephamicillin, cyclacillin, hecatillin, 6-aminopenicillanic acid, penicillic acid, penicillanic acid sulphone (subactam), penicillin G, penicillin V, phenethicillin, phenoxyethylpenicillinic acid, azlocillin, carbenicillin, cloxacillin, D-(-)-penicillamine, dicloxacillin, nafcillin and oxacillin,

(K) penicillinase-resistant penicillins (e.g. flucloxacillin),

(11) broad-spectrum penicillins (e.g. ampicillin, amoxicillin, metampicillin and bacampicillin),

(IV) antipseudomonal penicillins (e.g. carboxybenzylpenicillins such as ticarcillin or ureidopenicillins such as piperacillin),

(V) mecillinams (e.g. pivmecillinam), or

(VI) combinations of any two or more of the agents mentioned at (I) to (V) above, or combinations of any of the agents mentioned at (I) to (V) above with a β-lactamase inhibitor such as tazobactam or, particularly, clavulanic acid (which acid is optionally in metal salt form, e.g. in salt form with an alkali metal such as sodium or, particularly, potassium);

(ii) **cephalosporins**, such as ceftarclor, cefadroxil, cefalexin (cephalexin), cefcapene, cefcapene pivoxil, cefdinir, cefditoren, cefditoren pivoxil, cefixime, cefotaxime, cefpirome, cefpodoxime, cefpodoxime proxetil, cefprozil, cefradine, ceftazidime, cefteram, cefteram pivoxil, ceftriaxone, cefuroxime, cefuroxime axetil, cephalaridine, cephalothin, cephacetrile, cephamandole, cephaloglycine, ceftobiprole, PPI-0903 (TAK-599), 7-aminocephalosporanic acid, 7-aminodesacetoxycephalosporanic acid, cefamandole, cefazolin, ceftazidole, cefoperazone, cefsulodin, cephalosporin C zinc salt, cephalothin, cepahipirin; and

(iii) other β-lactams, such as monobactams (e.g. aztreonam), carbapenems (e.g. imipenem (optionally in combination with a renal enzyme inhibitor such as cilastatin), meropenem, ertapenem, doripenem (S-4661) and RO4908463 (CS-023), penems (e.g. faropenem) and 1-oxa-β-lactams (e.g. moxalactam).
(b) Tetracyclines, such as tetracycline, demeclocycline, doxycycline, lymecycline, minocycline, oxytetracycline, chlortetracycline, meclocycline and methacycline, as well as glycyclyclines (e.g. tigecycline).

(c) Aminoglycosides, such as amikacin, gentamicin, netilmicin, neomycin, streptomycin, tobramycin, amastatin, butirosin, butirosin A₁, daunorubicin, dibekacin, dihydrostreptomycin, G 418, hygromycin B, kanamycin B, kanamycin, kirromycin, paromomycin, ribostamycin, sisomicin, spectinomycin, streptozocin and thiostrepton.

(d) (i) Macrolides, such as azithromycin, clarithromycin, erythromycin, roxithromycin, spiramycin, amphotericins B (e.g. amphotericin B), bafilomycins (e.g. bafilomycin A₁), brefeldins (e.g. brefeldin A), concanamycins (e.g. concanamycin A), filipin complex, josamycin, mepartricin, midecamycin, nonactin, nystatin, oleandomycin, oligomycins (e.g. oligomycin A, oligomycin B and oligomycin C), pimaricin, rifampicin, rifamycin, rosamicin, tylosin, virginiamycin and fosfomycin.

(ii) Ketolides such as telithromycin and cethromycin (ABT-773).

(iii) Lincosamines, such as lincomycin.

(e) Clindamycin and clindamycin 2-phosphate.

(f) Phenicois, such as chloramphenicol and thiamphenicol.

(g) Steroids, such as fusidic acid (optionally in metal salt form, e.g. in salt form with an alkali metal such as sodium).

(h) Glycopeptides such as vancomycin, teicoplanin, bleomycin, phleomycin, ristomycin, telavancin, dalbavancin and oritavancin.

(i) Oxazolidinones, such as linezolid and AZD2563.

(j) Streptogramins, such as quinupristin and dalfopristin, or a combination thereof.
(k) (i) Peptides, such as polymyxins (e.g. colistin and polymyxin B),
ysoflaphin, duramycin, actinomycins (e.g. actinomycin C and actinomycin D),
actinonin, 7-aminoactinomycin D, antimycin A, antipain,
bacitracin, cyclosporin A, echinomycin, gramicidins (e.g. gramicidin A and gramicidin C),
myxothiazoli, nisin, paracelsin, valinomycin and viomycin.
(ii) Lipopeptides, such as daptomycin.
(iii) Lipoglycopeptides, such as ramoplanin.

(l) Sulfonamides, such as sulfamethoxazole, sulfadiazine, sulfaquinoxaline,
sulfathiazole (which latter two agents are optionally in metal salt form, e.g. in salt form with an alkali metal such as sodium), succinysulfathiazole,
sulfadimethoxine, sulfaguanidin, sulfamethazine, sulfamonemethoxine,
sulfanilamide and sulfasalazine.

(m) Trimethoprim, optionally in combination with a sulfonamide, such as sulfamethoxazole (e.g. the combination co-trimoxazole).

(n) Antituberculous drugs, such as isoniazid, rifampicin, rifabutin, pyrazinamide,
ethambutol, streptomycin, amikacin, capreomycin, kanamycin, quinolones (e.g. those at (q) below), para-aminosalicylic acid, cycloserine and ethionamide.

(o) Antileprotic drugs, such as dapsone, rifampicin and clofazimine.

(p) (i) Nitroimidazoles, such as metronidazole and tinidazole.
(ii) Nitrofurans, such as nitrofurantoin.

(q) Quinolones, such as nalidixic acid, norfloxacin, ciprofloxacin, ofloxacin,
levofloxacin, moxifloxacin, gatifloxacin, gemifloxacin, garenoxacin, DX-619,
WCK 771 (the arginine salt of S(-)-nadifloxacin), 8-quinolinoi, cinoxacin,
enrofloxacain, flumequine, lomefloxacin, oxolinic acid and pipemidic acid.

(r) Amino acid derivatives, such as azaserine, bestatin, D-cycloserine, 1,10-phenanthroline, 6-diazo-5-oxo-L-norleucine and L-alanyl-L-1-aminoethylphosphonic acid.
Aureolic acids, such as chromomycin A3, mithramycin A and mitomycin C.

Benzochinoides, such as herbimycin A.

Coumarin-glycosides, such as novobiocin.

Diphenyi ether derivatives, such as irgasan.

Epipolythiodixopiperazines, such as gliotoxin from Gliocladium fimbriatum.

Fatty acid derivatives, such as ceruienin.

Glucosamines, such as 1-deoxymannojirimycin, 1-deoxynojirimycin and N-methyl-1-deoxynojirimycin.

Indole derivatives, such as staurosporine.

Diaminopyrimidines, such as iclaprim (AR-100).

Macrolactams, such as ascomycin.

Taxoids, such as paclitaxel.

Statins, such as mevastatin.

Polyphenols acids, such as (+)-usnic acid.

Polyethers, such as lasalocid A, lonomycin A, monensin, nigericin and salinomycin.

Picolinic acid derivatives, such as fusaric acid.

Peptidyl nucleosides, such as blasticidine S, nikkomycin, nourseothricin and puromycin.
(ai) Nucleosides, such as adenine 9-β-D-arabinofuranoside, 5-azacytidine, cordycepin, formycin A, tubercidin and tunicamycin.

(aaj) Pleuromutilins, such as GSK-565154, GSK-275833 and tiamulin.

(ak) Peptide deformylase inhibitors, such as LBM415 (NVP PDF-713) and BB 83698.

(al) Antibacterial agents for the skin, such as fucidin, benzamycin, clindamycin, erythromycin, tetracycline, silver sulfadiazine, chlortetracycline, metronidazole, mupirocin, framycitin, gramicidin, neomycin sulfate, polymyxins (e.g. polymixin B) and gentamycin;

(al) Miscellaneous agents, such as methenamine (hexamine), doxorubicin, piericidin A, stigmatellin, actidione, anisomycin, apramycin, coumermycin A1, L(+)-lactic acid, cytochalasins (e.g. cytochalasin B and cytochalasin D), emetine and ionomycin.

Particular conventional antibiotics that may be mentioned include those listed at (a) to (q) above, such as:

- the β-lactams listed at (a)(i) above (e.g. amoxicillin, ampicillin, phenoxymethylpenicillin or, particularly, co-amoxiclav (co-amoxicillin));
- the cephalosporins listed at (a)(ii) above (e.g. cefuroxime, cefaclor or cefalexin);
- the carbapenems listed at (a)(iii) above (e.g. ertapenem);
- the tetracyclines listed at (b) above (e.g. doxycycline or minocycline);
- the macrolides listed at (d)(i) above (e.g. clarithromycin, erythromycin, roxithromycin or, particularly, azithromycin);
- the ketolides listed at (d) (ii) above (e.g. telithromycin);
- the oxazolidinones listed at (i) above (e.g. linezolid);
- the lipopeptides listed at (k)(ii) above (e.g. daptomycin)
- trimethoprim and the combinations therewith (e.g. co-trimoxazol) listed at (m) above;
- the nitrofurans listed at (p) above (e.g. nitrofurantoin); and
- the quinolones listed at (q) above (e.g. norfloxacin, ciprofloxacin, ofloxacin, or, particularly, levofloxacin or moxifloxacin).
When used herein, the term "conventional antifungal agent(s)" include references to fungicidal and fungistatic agents that are known in the prior art (i.e. agents that have been selected and developed on the basis of their MICs - namely their ability to inhibit the growth of fungi). In this respect, particular conventional antifungal agents that may be mentioned include any one or more of the following.

(a) azole antifungals, such as imidazoles (e.g. clotrimazole, econazole, fenticonazole, ketoconazole, miconazole, suiconazole, and tioconazole) or triazoles (e.g. fluconazole, itraconazole and voriconazole);
(b) polyene antifungals, such as amphotericin and nystatin;
(c) miscellaneous antifungal agents such as griseofulvin, caspofungin or flucytosine, which latter two agents are optionally employed in combination;
(d) allylamine antifungals, such as terbinafine.

Compounds of formula I that may be mentioned include those in which when $X^1$ represents N and $R^2$ represents H and A represents a fused benzene ring, then:

(i) when $R^1$ represents two different OR$^7_a$ substituents at the 6- and 7-positions of the quinazoine ring and $X^2$ represents O then $R^3$ does not represent a single substituent at the 6-position of the benzoxazole ring that is NH$_2$ or, particularly, NHC(O)NHR$^7_b$ (e.g. wherein $R^7_b$ represents phenyl substituted by two substituents selected from methyl, methoxy, trifluoromethyl and chloro); and
(ii) when $R^1$ represents two halo substituents at the 6- and 8-positions of the quinazoine ring, $X^2$ represents N and $R^4$ represents CH$_3$, then $R^3$ does not represent H.

Particular embodiments of the compounds of formula I include those in which:

1. $R^2$ is other than H;
2. $X^1$ represents CH;
3. $X^2$ represents N;
4. $R^3$ represents H.

Other particular embodiments of the compounds of formula I include those in which:

1. A represents a fused benzene ring or a fused 6-membered, aromatic heterocycle containing one or two N-atoms;
2. $R^1$ represents H or, particularly, one to four substituents on the fused benzene ring selected from
halo (e.g. chloro),
CN,
C\textsubscript{1-6} alkyl optionally substituted by one or more substituents selected from halo, CN, and OR\textsubscript{6a},

OR\textsubscript{7a},
S(O)\textsubscript{3}R\textsubscript{7b},
N(H)R\textsubscript{7n},
C(O)R\textsubscript{7},
C(O)OR\textsubscript{7}.

aryl and
Het\textsuperscript{4};

(3) R\textsuperscript{2} represents C\textsubscript{1-6} alkyl optionally substituted by one or more substituents selected from halo, 0 R\textsuperscript{7a}, N(R\textsuperscript{7c})(R\textsuperscript{7h}) and C(O)OR\textsuperscript{5}; or R\textsuperscript{2} represents H or Het\textsuperscript{2};

(4) R\textsuperscript{3} one to four substituents on the fused benzene or heteroaromatic ring selected from
halo (e.g. fluoro or chloro),
CN,
C\textsubscript{1-6} alkyl optionally substituted by one or more substituents selected from halo, CN, and OR\textsubscript{6a},

0 R\textsuperscript{7a},
S(O)\textsubscript{q}R\textsuperscript{7b},
N(H)R\textsubscript{7n},
C(O)R\textsubscript{7},
C(O)OR\textsubscript{7}.

aryl and
Het\textsuperscript{4}

or, particularly, R\textsuperscript{3} represents H;

(5) R\textsuperscript{4}, when X\textsuperscript{2} represents N, represents H or a substituent selected from C\textsubscript{1-6} alkyl and C\textsubscript{3-6} cycloalkyl, which latter two groups are optionally substituted by one or more substituents selected from halo, C\textsubscript{1-2} alkyl, 0-(Ci-2 alkyl), aryl and Het\textsuperscript{5},
or, when X\textsuperscript{2} represents O, R\textsuperscript{4} is absent;

(6) R\textsuperscript{2a} to R\textsuperscript{6}, R\textsuperscript{6a} to R\textsuperscript{8}, R\textsuperscript{7a} to R\textsuperscript{7} and R\textsuperscript{8a} to R\textsuperscript{8b} independently represent, at each occurrence,
H,
21

C_{10} alkyl (optionally substituted by one or more substituents selected from halo and aryl),

C_{3-6} cycloalkyl (optionally substituted by one or more substituents selected from halo, C_{1-4} alkyl and C_{1-4} alkoxy),

aryl or

Het^9,

provided that R^{6b}, R^{7b}, R^{8b} or R^{9b} does not represent H when n, p, q or r, respectively is 1 or 2;

(7) each aryl independently represents a C_{6-10} carbocyclic aromatic group, which group may comprise either one or two rings and may be substituted by one or more substituents selected from halo,

CN, 

C_{1-6} alkyl optionally substituted by one or more substituents selected from halo, C_{3-6} cycloalkyl (which latter groups is optionally substituted by one or more substituents selected from halo, C_{1-4} alkyl and C_{1-4} alkoxy), OR^9a, S(O)_{1-1b},

S(O)_{2}N(H)R^{10c}, N(H)S(O)_{2}R^{10e}, N(R')^{10f}(R^{9b}), B^{9}-C(O)-B^{10}-R^{10f}, phenyl (which latter groups is optionally substituted by one or more substituents selected from OH, halo, methyl and methoxy) and Het^{10},

OR^{10a},

S(O)_{2}R^{10b},

N(R^{10g}XR^{10h}),

B^{11-12}-C(O)-B^{12-13}-R^{10i},

phenyl (which latter group is optionally substituted by one or more substituents selected from OH, halo, C_{1-4} alkyl and C_{1-4} alkoxy) or

Het^{11};

(8) R^{9a} to R^{9b} and R^{10a} to R^{10i} independently represent, at each occurrence,

H,

C_{1-6} alkyl, C_{3-6} cycloalkyl (which latter two groups are optionally substituted by one or more substituents selected from halo, OH, C_{1-4} alkyl, C_{4-6} cycloalkyl (which latter group is optionally substituted by one or more substituents selected from halo, C_{1-4} alkyl and C_{1-4} alkoxy), C_{1-4} alkoxy, NH_{2}, N(H)-C_{1-4} alkyl, N(C_{1-4} alkyl)_{2}, phenyl (which latter group is optionally substituted by one or more substituents selected from OH, halo, methyl and methoxy) and Het^{12},
phenyl (which latter group is optionally substituted by one or more substituents selected from OH, halo, C\textsubscript{1-4} alkyl and C\textsubscript{4-6} alkoxy) or Het\textsuperscript{13},

provided that R\textsuperscript{9b} or R\textsuperscript{10b} does not represent H when t or u, respectively is 1 or 2;

Het\textsuperscript{1} to Het\textsuperscript{13} independently represent 5- to 10-membered heterocyclic groups containing from one to four heteroatoms selected from oxygen, nitrogen and/or sulfur, which heterocyclic groups may comprise one or two rings and may be substituted by one or more substituents selected from halo, C\textsubscript{1-6} alkyl, C\textsubscript{3-6} cycloalkyl, which latter two groups are optionally substituted by one or more substituents selected from halo, OH, C\textsubscript{1-4} alkyl, C\textsubscript{4-6} cycloalkyl (which latter group is optionally substituted by one or more substituents selected from halo, C\textsubscript{1-4} alkyl and C\textsubscript{4-6} alkoxy), C\textsubscript{1-4} alkoxy, phenyl (which latter group is optionally substituted by one or more substituents selected from OH, halo, methyl and methoxy) and Het,

0 R\textsuperscript{12a},
=0,
S(O)\textsubscript{w}R\textsuperscript{12b},
N(R\textsuperscript{12c})(R\textsuperscript{12d}),
B\textsuperscript{15}-C(O)-B\textsuperscript{16}-R\textsuperscript{12i},

phenyl (which latter group is optionally substituted by one or more substituents selected from OH, halo, methyl and methoxy) or Het\textsuperscript{b};

R\textsuperscript{11a} to R\textsuperscript{11i} and R\textsuperscript{12a} to R\textsuperscript{12i} independently represent, at each occurrence, H,

C\textsubscript{1-6} alkyl, C\textsubscript{3-6} cycloalkyl (which latter two groups are optionally substituted by one or more substituents selected from halo, OH, C\textsubscript{1-4} alkyl, C\textsubscript{4-6} cycloalkyl (which latter group is optionally substituted by one or more substituents selected from halo, C\textsubscript{1-4} alkyl and C\textsubscript{4-6} alkoxy), C\textsubscript{1-4} alkoxy, phenyl (which latter group is optionally substituted by one or more substituents selected from OH, halo, methyl and methoxy) and Het,

phenyl (which latter group is optionally substituted by one or more substituents selected from OH, halo, methyl and methoxy) or Het\textsuperscript{d};
provided that R\textsuperscript{11b} or R\textsuperscript{12b} does not represent H when v or w, respectively, is 1 or 2;

(11) B\textsuperscript{1} to B\textsuperscript{16} independently represent a direct bond, O, S or NH;

(12) R\textsuperscript{13} represents Cl\textsubscript{4} alkyl or phenyl (which latter group is optionally substituted by one or more substituents selected from OH, halo, methyl and methoxy);

(13) Het to Het\textsuperscript{e} independently represent 5- or 6-membered heterocyclic groups containing one or heteroatoms selected from oxygen, nitrogen and/or sulfur, which heterocyclic groups may be substituted by one or more substituents selected from halo, =O and methyl;

(14) unless otherwise specified, alkyl, alkenyl, alkynyl, cycloalkyl, and cycloalkenyl groups, as well as the alkyl part of alkoxy groups, are unsubstituted;

(15) unless otherwise specified, cycloalkyl groups comprise one or (if sufficient number of C-atoms is present) two rings and are optionally ring-fused to a benzene ring (so as to form a group such as, for example, 1,2,3,4-tetrahydro-naphthyl or, particularly, indanyl).

In other embodiments of the invention, the compounds of formula I are compounds of formula I\textsubscript{a}

\[
\begin{align*}
&\text{la} \\
&\text{\includegraphics[width=0.5\textwidth]{formula.png}}
\end{align*}
\]

wherein R\textsuperscript{1a} to R\textsuperscript{1d} all independently represents H or a substituent as defined above in respect of R\textsuperscript{1}, and R\textsuperscript{2} to R\textsuperscript{4}, X\textsuperscript{1}, X\textsuperscript{2} and A are as hereinbefore defined.

Particular compounds of formula I\textsubscript{a} that may be mentioned include those in which:

(1) R\textsuperscript{1a} represents H;

(2) R\textsuperscript{1b} and/or R\textsuperscript{1d} represents a substituent as defined above in respect of R\textsuperscript{1}.

(3) R\textsuperscript{1c} represents H.

Other particular embodiments of the compounds of formula I\textsubscript{a} include those in which:

(1) R\textsuperscript{1a} represents halo (e.g. chloro) or, particularly, H;
R\textsuperscript{1b} represents H (e.g. when R\textsuperscript{1c} is other than H) or, particularly, a substituent selected from
halo (e.g. chloro),
CN,
Ci-3 alkyl,
OR\textsuperscript{7a}
N(H)R\textsuperscript{7h} and
Het\textsuperscript{4};
R\textsuperscript{7a} represents H or, particularly,
Ci-3 alkyl (e.g. methyl or ethyl), which latter group is optionally substituted by phenyl,
phenyl, which latter group is optionally substituted as defined above in respect of aryl (e.g. substituted by halo, such as chloro or, particularly, fluoro) or Het\textsuperscript{5};
R\textsuperscript{7h} represents H, Ci-3 alkyl or, particularly, phenyl, which latter group is optionally substituted as defined above in respect of aryl, but is, in a particular embodiment, unsubstituted;
R\textsuperscript{1c} represents halo (e.g. chloro) or, particularly, H;
R\textsuperscript{1d} represents H or (e.g. when R\textsuperscript{1b} is other than H) a substituent selected from OR\textsuperscript{7a} (wherein R\textsuperscript{7a} is as hereinbefore defined) or, particularly, halo (e.g. chloro);
R\textsuperscript{2} represents H, C\textsubscript{1-4} alkyl (e.g. methyl) or Het\textsuperscript{2};
R\textsuperscript{3} one to three substituents on the fused benzene or heteroaromatic ring selected from
halo (e.g. fluoro or chloro),
CN,
Ci-3 alkyl,
0-(C\textsubscript{1-3} alkyl) and
N(H)R\textsuperscript{7h},
or, particularly, R\textsuperscript{3} represents H;
R\textsuperscript{4}, when X\textsuperscript{2} represents N, represents H or Ci-4 alkyl (e.g. methyl),
or, when X\textsuperscript{2} represents O, R\textsuperscript{4} is absent;
Het\textsuperscript{1} to Het\textsuperscript{13} independently represent 5- or 6-membered heterocyclic groups containing from one to three heteroatoms selected from oxygen, nitrogen and/or sulfur, which heterocyclic groups are partially unsaturated or, in particular embodiments, are either fully saturated or aromatic, and which heterocyclic
groups may be substituted by one or more substituents selected from halo, C_{1-3} alkyl and C_{1-3} alkoxy (for example, Het^1 to Het^13 (such as Het^9) may independently represent aromatic 6-membered heterocyclic groups containing one or two nitrogen atoms, e.g. pyrimidinyl, such as pyrimidin-2-yl, or Het^1 to Het^13 (such as Het^2 and Het^4) may independently represent fully saturated 6-membered heterocyclic groups containing one or two heteroatoms selected from oxygen and nitrogen, e.g. piperazinyl or morpholinyi, such as piperazin-1-yl or morpholin-1-yl, which groups are optionally substituted as described hereinbefore).

In still further embodiments of the invention, the compounds of formula I are compounds of formula Ib

![Diagram](image)

wherein R^{1a} to R^{1d}, R^2, X^1, X^2 and R^4 are as hereinbefore defined.

Particular embodiments of the compounds of formula Ib that may be mentioned include those in which:

(1) X^1 represents CH;
(2) X^2 represents N;
(3) R^2 represents H or methyl;
(4) R^{1b} represents H (e.g. when R^{1c} is other than H) or, particularly, a substituent selected from chloro, CN, OR^{7a} and N(H)R^{7h};
(5) R^{7a} represents phenylmethyl (i.e. benzyl) or phenyl, which latter group is optionally substituted by halo (e.g. fluoro, such as a single fluoro substituent in the 4-position);
(6) R^{7h} represents phenyl, which latter group is optionally substituted as defined above in respect of aryl, but is, in a particular embodiment, unsubstituted;
(7) R^{1g} represents halo (e.g. chloro) or, particularly, H;
(8) \( R^1d \) represents H;
(9) \( R^4 \) represents H or, particularly, methyl.

Other particular embodiments of the compounds of formula Ib include those in which \( R^{1a}, R^{1c} \) and \( R^{1d} \) all represent H and \( R^{1b} \) is other than H.

The medicament mentioned in the first aspect of the invention may be utilised in a method of medical treatment. Thus, according to a second aspect of the invention, there is provided a method of killing clinically latent microorganisms in a mammal infected with such latent microorganisms, the method comprising administering to said mammal a microbicidal effective amount of compound of formula I, as hereinbefore defined.

Furthermore, the compound of formula I may be used to kill clinically latent microorganisms. Thus, according to a third aspect of the invention, there is provided the use of a compound of formula I, as hereinbefore defined, to kill clinically latent microorganisms. In one embodiment, the use according to this aspect of the invention is an ex vivo use.

Compounds of formula I might also be employed to kill microorganisms of many different phenotypes, including growing microorganisms.

In this respect, fourth, fifth and sixth aspects of the invention provide, respectively:

(a) the use of a compound of formula I, as hereinbefore defined, for the preparation of a medicament for the treatment of a microbial infection;

(b) a method of treating or preventing a microbial infection in a mammal, the method comprising administering to said mammal an antimicrobially effective amount of a compound of formula I, as hereinbefore defined;

(c) use (e.g. ex vivo use) of a compound of formula I to kill microorganisms.

For the avoidance of doubt, as used herein, the term 'treatment' includes therapeutic and/or prophylactic treatment.
As mentioned above, the uses according to the third and sixth aspects of the invention may be ex wVo uses, such as the use of a compound of formula I, as hereinbefore defined:

(a) as a sterilising agent; or

(b) as a preservative.

Conversely, the compounds of formula I may be employed in methods of sterilisation or preservation, such as:

(i) a method of sterilising an object, the method comprising applying to said object a compound of formula I, as hereinbefore defined; or

(ii) a method of preserving an inorganic or, preferably, an organic material, said method comprising contacting, combining or mixing said material with a compound of formula I, as hereinbefore defined.

In relation to the method described at (i) above, the object is preferably other than a human or animal body. Further, the materials that may be preserved according to the method described at (ii) above include polymers, lubricants, paints, fibres, leather, paper, foodstuffs, water and aqueous mixtures and solutions.

When used to kill clinically latent microorganisms or to treat a microbial infection, the compounds of formula I may be used either alone (i.e. as sole microbicidal or antimicrobial agents) or in combination with any one or more of the conventional antimicrobial agents described above.

Further, when used as a sterilising agent, the compounds of formula I may be used either alone or in combination with a conventional sterilising agent. The term "conventional sterilising agent", when used herein, includes references to alcohols (e.g. industrial methylated spirits or ethanol), sodium chloride, thymol, chlorhexidine, cationic surfactants (e.g. cetrimide), iodine (optionally combined with povidone), phenolics (e.g. triclosan), oxidants (e.g. hydrogen peroxide, potassium permanganate or sodium...
hypochlorite) and any one or more of the conventional antimicrobial agents described above.

Thus, according to seventh and eighth aspects of the invention, there is provided, respectively:

(i) a combination product comprising
   (A) a compound of formula I, as hereinbefore defined, and
   (B) a conventional antibiotic agent, as hereinbefore defined,
   wherein each of components (A) and (B) is formulated in admixture with a pharmaceutically-acceptable adjuvant, diluent or carrier; and

(b) a formulation comprising a compound of formula I, as hereinbefore defined and a conventional sterilising agent, as hereinbefore defined, or a salt and/or solvate thereof.

The combination product according to the seventh aspect of the invention provides for the administration of component (A) in conjunction with component (B), and may thus be presented either as separate formulations, wherein at least one of those formulations comprises component (A) and at least one comprises component (B), or may be presented (i.e. formulated) as a combined preparation (i.e. presented as a single formulation including component (A) and component (B)).

Thus, there is further provided:

(1) a pharmaceutical formulation including a compound of formula I, as hereinbefore defined and a conventional antimicrobial agent, as hereinbefore defined, or a pharmaceutically-acceptable derivative thereof, in admixture with a pharmaceutically-acceptable adjuvant, diluent or carrier (which formulation is hereinafter referred to as a "combined preparation"); and

(2) a kit of parts comprising components:
   (1) a pharmaceutical formulation including a compound of formula I, as hereinbefore defined, in admixture with a pharmaceutically-acceptable adjuvant, diluent or carrier; and
(II) a pharmaceutical formulation including a conventional antimicrobial agent, as hereinbefore defined, or a pharmaceutically-acceptable derivative thereof, in admixture with a pharmaceutically-acceptable adjuvant, diluent or carrier, which components (I) and (II) are each provided in a form that is suitable for administration in conjunction with the other.

Component (I) of the kit of parts is thus component (A) in admixture with a pharmaceutically-acceptable adjuvant, diluent or carrier. Similarly, component (II) is component (B) in admixture with a pharmaceutically-acceptable adjuvant, diluent or carrier.

According to a ninth aspect of the invention, there is provided a method of making a kit of parts as defined above, which method comprises bringing a component (I), as defined above, into association with a component (U), as defined above, thus rendering the two components suitable for administration in conjunction with each other.

By bringing the two components "into association with" each other, we include that components (I) and (II) of the kit of parts may be:

(i) provided as separate formulations (i.e. independently of one another), which are subsequently brought together for use in conjunction with each other in combination therapy; or

(ii) packaged and presented together as separate components of a "combination pack" for use in conjunction with each other in combination therapy.

Thus, there is further provided a kit of parts comprising:

(1) one of components (I) and (II) as defined herein; together with

(2) instructions to use that component in conjunction with the other of the two components.

The kits of parts described herein may comprise more than one formulation including an appropriate quantity/dose of component (A), and/or more than one formulation including an appropriate quantity/dose of component (B), in order to provide for repeat dosing. If more than one formulation (comprising either active compound) is present,
such formulations may be the same, or may be different in terms of the dose of component (A) or component (B), chemical composition and/or physical form.

The combination product according to the seventh aspect of the invention may be used to kill clinically latent microorganisms and/or treat a microbial infection. Thus, further aspects of the invention provide:

(i) the use of a combination product according to the seventh aspect of the invention for the preparation of a medicament for killing clinically latent microorganisms;

(H) a method of killing clinically latent microorganisms in a mammal, the method comprising administering to said mammal a microbicidally effective amount of a combination product according to the seventh aspect of the invention;

(iii) the use of a combination product according to the seventh aspect of the invention for the preparation of a medicament for treating a microbial infection; and

(iv) a method of treating or preventing a microbial infection in a mammal, the method comprising administering to said mammal an antimicrobially effective amount of a combination product according to the seventh aspect of the invention.

The method of (iv) above provides for the advantage that the amount of conventional antimicrobial agent required to treat the microbial infection is reduced compared to that required in the absence of a compound of formula I.

When used herein, the terms "bacteria" (and derivatives thereof, such as "bacterial infection") includes references to organisms (or infections due to organisms) of the following classes and specific types:

Gram-positive cocci, such as Staphylococci (e.g. Staph. aureus, Staph. epidermidis, Staph. saprophyticus, Staph. auricularis, Staph. capitis capitis, Staph. c. urealyticus, Staph. caprae, Staph. cohnii cohnii, Staph. c. urealyticus, Staph. equorum,
Staph. gallinarum, Staph. haemolyticus, Staph. hominis hominis, Staph. h. novobiosepticius, Staph. hyicus, Staph. intermedius, Staph. lundunensis, Staph. pasteuri, Staph. saccharolyticus, Staph. schleiferi schleiferi, Staph. s. coagulans, Staph. sciuri, Staph. simulans, Staph. wameri and Staph. xylosus) and

Streptococci (e.g. beta-haemolytic, pyogenic streptococci (such as Strept. agalactiae, Strept canis, Strept. dysgalactiae dysgalactiae, Strept. dysgalactiae equisimilis, Strept equi equi, Strept. equi zooepidemicus, Strept iniae, Strept. porcinus and Strept. pyogenes), microaerophilic, pyogenic streptococci (Streptococcus "milleri", such as Strept. anginosus, Strept. constellatus constellatus, Strept. constellatus pharyngidis and Strept. intermedius), oral streptococci of the "mitis" (alpha-haemolytic - Streptococcus "viridans", such as Strept. mitis, Strept. oralis, Strept. sanguinis, Strept. cristatus, Strept. gordonii and Strept. parasanguinis), "salivarius" (non-haemofytic, such as Strept salivarius and Strept. vestibularis) and "mutans" (tooth-surface streptococci, such as Strept. criceti, Strept. mutans, Strept. ratti and Strept. sobrinus) groups, Strept. acidominimus, Strept bovis, Strept. faecalis, Strept equinus, Strept. pneumoniae and Strept. suis, or Streptococci alternatively classified as Group A, B, C, D, E, G, L, P, U or V Streptococcus);

Gram-negative cocci, such as Neisseria gonorrhoeae, Neisseria meningitidis, Neisseria cinerea, Neisseria elongata, Neisseria flavescens, Neisseria lactamica, Neisseria mucosa, Neisseria sicca, Neisseria subflava and Neisseria weavers; Bacillaceae, such as Bacillus anthracis, Bacillus subtilis, Bacillus thuringiensis, Bacillus stearothermophilus and Bacillus cereus;

Enterobacteriaceae, such as

Escherichia coli,

Enterobacter (e.g. Enterobacter aerogenes, Enterobacter agglomerans and Enterobacter cloacae)

Citrobacter (such as Citrob. freundii and Citrob. diversis),

Hafnia (e.g. Hafnia alvei),

Erwinia (e.g. Erwinia persicinus),
Morganella morganii,
Salmonella (Salmonella enterica and Salmonella typhi),
Shigella (e.g. Shigella dysenteriae, Shigella flexneri, Shigella boydii and Shigella sonnei),
Klebsiella (e.g. Klebs. pneumoniae, Klebs. oxytoca, Klebs. ornitholytica,
Klebs. pianticola, Klebs. ozaenae, Klebs. terrigena, Klebs. granulomatis
(Calymmatobacterium granulomatis) and Klebs. rhinoscleromatis),
Proteus (e.g. Pr. mirabilis, Pr. rettge and Pr. vulgaris),
Providencia (e.g. Providencia alcalifaciens, Providencia rettgeri and
Providencia stuartii),
Serratia (e.g. Serratia marcescens and Serratia liquefaciens), and
Yersinia (e.g. Yersinia enterocolitica, Yersinia pestis and Yersinia
pseudotuberculosis);
Enterococci (e.g. Enterococcus avium, Enterococcus casseiiflavus,
Enterococcus cecorum, Enterococcus dispar, Enterococcus durans, Enterococcus
faecalis, Enterococcus faecium, Enterococcus flavescens, Enterococcus gallinarum,
Enterococcus hira, Enterococcus ma/odoratus, Enterococcus mundtii, Enterococcus
pseudoavium, Enterococcus raffinosus and Enterococcus solitarius);
Helicobacter (e.g. Helicobacter pylori, Helicobacter cinaedi and Helicobacter
fennelliae);
Acinetobacter (e.g. A. baumanii, A. calcoaceticus, A. haemolyticus, A. johnsonii,
A. junii, A. Iwoffii and A. radioresistens);
Pseudomonas (e.g. Ps. aeruginosa, Ps. maltophilia (Stenotrophomonas
maltophilia), Ps. alcaligenes, Ps. chlororaphis, Ps. fluorescens, Ps. luteola. Ps.
mendocina, Ps. monteillii, Ps. oryzihabitans, Ps. pertocinogena, Ps. pseudalcaligenes,
Ps. putida and Ps. stutzeri);
Bacteriodes fragilis;
Peptococcus (e.g. Peptococcus niger);
Peptostreptococcus;
Clostridium (e.g. C. perfringens, C. difficile, C. botulinum, C. tetani, C.
absonum, C. argentinense, C. baratii, C. bifermentans, C. beijerinckii, C. butyricum, C.
cadaveris, C. carnis, C. celatum, C. clostridioforme, C. cochlea, C. cocieatum, C.
falax, C. ghoni, C. glycolicum, C. haemolyticum, C. hastiforme, C. histolyticum, C.
indois, C. innocuum, C. irregulare, C. leptum, C. limosum, C. malenominatum, C.
noyii, C. oroticum, C. paraputrificum, C. piliforme, C. putrefasciens, C. ramosum, C.
septicum, C. sordellii, C. sphenoides, C. sporogenes, C. subterminale, C. symbiosum and C. tertium);

Mycoplasma (e.g. M. pneumoniae, M. hominis, M. genitalium and M. urealyticum);

Mycobacteria (e.g. Mycobacterium tuberculosis, Mycobacterium avium, Mycobacterium fortuitum, Mycobacterium marinum, Mycobacterium kansasii, Mycobacterium chelonei, Mycobacterium abscessus, Mycobacterium leprae, Mycobacterium smegmatis, Mycobacterium africanum, Mycobacterium alvei, Mycobacterium asiaticum, Mycobacterium aurum, Mycobacterium bohemicum, Mycobacterium bovis, Mycobacterium branderi, Mycobacterium brumae, Mycobacterium celatum, Mycobacterium chubense, Mycobacterium confluentis, Mycobacterium conspicuum, Mycobacterium cookii, Mycobacterium flavescens, Mycobacterium gadium, Mycobacterium gastrin, Mycobacterium genavense, Mycobacterium gordoniae, Mycobacterium goodii, Mycobacterium haemophilum, Mycobacterium hassicum, Mycobacterium intracellulare, Mycobacterium interjectum, Mycobacterium heidelbergense, Mycobacterium lentiflavum, Mycobacterium malmoense, Mycobacterium microgenicum, Mycobacterium microti, Mycobacterium mucogenicum, Mycobacterium neoaurum, Mycobacterium nonchromogenicum, Mycobacterium peregrinum, Mycobacterium phlei, Mycobacterium scrofulaceum, Mycobacterium shimoidei, Mycobacterium simiae, Mycobacterium szulgai, Mycobacterium terrae, Mycobacterium thermoresistibile, Mycobacterium triplex, Mycobacterium trivialis, Mycobacterium tuscae, Mycobacterium ulcerans, Mycobacterium vaccae, Mycobacterium wolinskyi and Mycobacterium xenopi);

Haemophilus (e.g. Haemophilus influenzae, Haemophilus ducreyi, Haemophilus aegyptius, Haemophilus parainfluenzae, Haemophilus haemolyticus and Haemophilus parahaemolyticus);

Actinobacillus (e.g. Actinobacillus actinomycetemcomitans, Actinobacillus equuli, Actinobacillus hominis, Actinobacillus lignieresii, Actinobacillus suis and Actinobacillus ureae);

Actinomyces (e.g. Actinomyces israelii);

Propionibacteria (e.g. Propionibacterium acnes);

Brucella (e.g. Brucella abortus, Brucella canis, Brucella melitensis and Brucella suis);

Campylobacter (e.g. Campylobacter jejuni, Campylobacter coli, Campylobacter /a7 and Campylobacter fetus);
Listeria monocytogenes;
Vibrio (e.g. Vibrio choierae and Vibrio parahaemolyticus, Vibrio alginolyticus, Vibrio carchariae, Vibrio fluvialis, Vibrio furnissii, Vibrio hollisae, Vibrio metschnikovii, Vibrio mimicus and Vibrio vulnificus);
Erysipelothrix rhusopathiae;
Corynebacteriaceae (e.g. Corynebacterium diphthen’a, Corynebacterium jeik’um and Corynebacterium urealyticum);
Spirochaetaceae, such as Borrelia (e.g. Borrelia recurrentis, Borrelia burgdorferi, Borrelia afzelii, Borrelia andersonii, Borrelia bissetii, Borrelia garinii, Borrelia japonica, Borrelia lusitaniae, Borrelia turdi, Borrelia valaisiana, Borrelia caucasica, Borrelia crocidurae, Borrelia duttoni, Borrelia graingeri, Borrelia hermsii, Borrelia hispanica, Borrelia latyschwii, Borrelia mazzottii, Borrelia parkeri, Borrelia persica, Borrelia turicatae and Borrelia venezuelensis) and Treponema (Treponema pallidum ssp. pallidum, Treponema pallidum ssp. endemicum, Treponema pallidum ssp. pertenue and Treponema carateum);
Pasteurella (e.g. Pasteurella aerogenes, Pasteurella bettyae, Pasteurella canis, Pasteurella dagmatis, Pasteurella gallinarum, Pasteurella haemolytica, Pasteurella multocida multocida, Pasteurella multocida gallicida, Pasteurella multocida septica, Pasteurella pneumotropaica and Pasteurella stomatis);
Bordetella (e.g. Bordetella bronchiseptica, Bordetella hin’lli, Bordetella holmsei, Bordetella parapertussis, Bordetella pertussis and Bordetella trematum);
Nocardiaceae, such as Nocardia (e.g. Nocardia asteroides and Nocardia brasiliensis);
Rickettsia (e.g. Ricksettsii or Coxiiella burnetii);
Legionella (e.g. Legionella anisa, Legionella birminghamensis, Legionella bozemanii, Legionella cincinnatiensis, Legionella dumoffii, Legionella feeleii, Legionella gormanii, Legionella hackeliaβ, Legionella israelensis, Legionella jordanis, Legionella lansingensis, Legionella longbeachae, Legionella maceachernii, Legionella micdadei, Legionella oakridgensis, Legionella pneumophila, Legionella sainthelensi, Legionella tucsonensis and Legionella wadsworthii);
Moraxella catarrhalis;
Stenotrophomonas maltophilia;
Burkholderia cepacia;
Francisella tularensis;
Gardnerella (e.g. Gardnerella vaginalis and Gardnerella mobiluncus);
Streptobacillus moniliformis
Fiavobacteriaceae, such as Capnocytophaga (e.g. Capnocytophaga
canimorsus, Capnocytophaga cynodegmi, Capnocytophaga gingivalis,
Capnocytophaga granulosa, Capnocytophaga haemolytica, Capnocytophaga ochracea
and Capnocytophaga sputigena);
Bartonella (Bartonella bacilliformis, Bartonella claridgeiae, Bartonella
elizabethae, Bartonella henselae, Bartonella quintana and Bartonella vinsonii
arupensis);
Leptospira (e.g. Leptospira biflexa, Leptospira borgpetersenii, Leptospira inadai,
Leptospira interrogans, Leptospira kirschneri, Leptospira noguchii, Leptospira
santarosai and Leptospira weilii);
Spirillum (e.g. Spirillum minus);
Bacteroides (e.g. Bacteroides caccae, Bacteroides capillosus, Bacteroides
coagulans, Bacteroides distasonis, Bacteroides eggerthii, Bacteroides
dorsiflexus, Bacteroides fragilis, Bacteroides merdae, Bacteroides ovatus, Bacteroides
putredinis, Bacteroides pyogenes, Bacteroides sphenoides, Bacteroides
tectus, Bacteroides thetaitaomicron, Bacteroides uniformis, Bacteroides
ureolyticus and Bacteroides vulgatus);
Prevotella (e.g. Prevotella bivia, Prevotella buccae, Prevotella
corporis, Prevotella dentalis (Mitsuokella dentalis), Prevotella denticola, Prevotella
diens, Prevotella enjo, Prevotella heparinolytica, Prevotella intermedia, Prevotella
loeschii, Prevotella melaninogenica, Prevotella nigescens, Prevotella oralis, Prevotella
oris, Prevotella oulora, Prevotella tannerae, Prevotella venoralis and Prevotella
zoogloeiformans);
Porphyromonas (e.g. Porphyromonas asaccharolytica, Porphyromonas
canginjralis, Porphyromonas canoris, Porphyromonas cansulci, Porphyromonas
catoniae, Porphyromonas circumdentaria, Porphyromonas crevioricanis,
Porphyromonas endodontalis, Porphyromonas gingivalis, Porphyromonas gingivicanis,
Porphyromonas levi and Porphyromonas macaca);
Chlamydophila (e.g. Chlamydophila abortus (Chlamydia psittaci), Chlamydophiia pneumoniae (Chlamydia pneumoniae) and Chlamydophila psittaci (Chlamydia psittaci));
Leuconostoc (e.g. Leuconostoc citreum, Leuconostoc cremoris, Leuconostoc dextranicum, Leuconostoc lactis, Leuconostoc mesenteroides and Leuconostoc pseudomesenteroides);
Gemella (e.g. Gemella bergeri, Gemella haemolysans, Gemella morbillorum and Gemella sanguinis); and
Ureaplasma (e.g. Ureaplasma parvum and Ureaplasma urealyticum).

In one embodiment of the invention, the term "Jbacferfa" includes references to any of the above classes or specific types of organisms, except for Shigella (e.g. Shigella flexneri) or Salmonella (e.g. Salmonella typhi).

When used herein, the terms "fungf (and derivatives thereof, such as "fungal infection") includes references to organisms (or infections due to organisms) of the following classes and specific types:
Absidia (e.g. Absidia corymbifera);
Ajellomyces (e.g. Ajellomyces capsulatus and Ajellomyces dermatitidis);
Arthroderma (e.g. Arthroderma benhamiae, Arthroderma fulvum, Arthroderma gypseum, Arthroderma incurvatum, Arthroderma otae and Arthroderma vanbreuseghemii);
Aspergillus (e.g. Aspergillus flavus, Aspergillus fumigatus and Aspergillus niger);
Blastomyces (e.g. Blastomyces dermatitidis);
Candida (e.g. Candida albicans, Candida glabrata, Candida guilliermondii, Candida krusei, Candida parapsilosis, Candida tropicalis and Candida pelliculosa);
Cladophialophora (e.g. Cladophialophora carrionii);
Coccidioides (e.g. Coccidioides immitis);
Cryptococcus (e.g. Cryptococcus neoformans);
Cunninghamamella (e.g. Cunninghamamella sp.);
Epidermophyton (e.g. Epidermophyton floccosum);
Exophiala (e.g. Exophiala dermatitidis);
Filobasidiella (e.g. Filobasidiella neoformans);
Fonsecaea (e.g. Fonsecaea pedrosoi);
Fusarium (e.g. *Fusarium solani*);
Geotrichum (e.g. *Geotrichum candidum*);
Histoplasma (e.g. *Histoplasma capsuiatum*);
Hortaea (e.g. *Hortaea werneckii*);
Issatschenkia (e.g. *Issatschenkia orientalis*);
Madurella (e.g. *Madurella grisae*);
Malassezia (e.g. *Malassezia furfur*, *Malassezia globosa*, *Malassezia obtusa*, *Malassezia pachydermatis*, *Malassezia restricta*, *Malassezia slooffiae* and *Malassezia sympodialis*);
Microsporum (e.g. *Microsporum canis*, *Microsporum fulvum* and *Microsporum gypseum*);
Mucor (e.g. *Mucor circinelloides*);
Nectria (e.g. *Nectria haematococca*);
Paecilomyces (e.g. *Paecilomyces variotii*);
Paracoccidioides (e.g. *Paracoccidioides brasiliensis*);
Penicillium (e.g. *Penicillium marneffei*);
Pichia (e.g. *Pichia anomala* and *Pichia guilliermondii*);
Pneumocystis (e.g. *Pneumocystis jiroveci* (*Pneumocystis carinii*));
Pseudallescheria (e.g. *Pseudallescheria boydii*);
Rhizopus (e.g. *Rhizopus oryzae*);
Rhodotorula (e.g. *Rhodotorula rubra*);
Scedosporium (e.g. *Scedosporium apiospermum*);
Schizophyllum (e.g. *Schizophyllum commune*);
Sporothrix (e.g. *Sporothrix schenckii*);
Trichophyton (e.g. *Trichophyton mentagrophytes*, *Trichophyton rubrum*, *Trichophyton verrucosum* and *Trichophyton violaceum*); and
Trichosporon (e.g. *Trichosporon asahii*, *Trichosporon cutaneum*, *Trichosporon inkin* and *Trichosporon mucoides*).

Thus, compounds of formula I, or combination products comprising compounds of formula I, may be used to kill any of the above-mentioned bacterial or fungal organisms (clinically latent or otherwise).

Particular bacteria that may be mentioned in this respect include:
Staphylococci, such as *Staph. aureus* (either Methicillin-sensitive (i.e. MSSA) or Methicillin-resistant (i.e. MRSA)) and *Staph. epidermidis*; Streptococci, such as *Strept. agalactiae* and *Strept. pyogenes*; Bacillaceae, such as *Bacillus anthracis*; Enterobacteriaceae, such as *Escherichia coli*, Klebsiella (e.g. *Klebs. pneumoniae* and *Klebs. oxytoca*) and Proteus (e.g. *Pr. mirabilis*, *Pr. rettgeri* and *Pr. vulgaris*); *Haemophilus influenzae*; Enterococci, such as *Enterococcus faecalis* and *Enterococcus faecium*; Mycobacteria, such as *Mycobacterium tuberculosis*; and Propionibacteria, such as *Propionibacterium acnes*.

Particular fungi that may also be mentioned in this respect include *Aspergillus fumigatus*, *Candida albicans*, *Cryptococcus neoformans*, *Histoplasma capsulatum* and *Pneumocystis jiroveci*.

Particular bacterial or fungal infections that may be mentioned in relation to (i) the use according to the fourth aspect of the invention, (ii) the method according to the sixth aspect of the invention and (iii) the above-described use and method involving the combination product according to the seventh aspect of the invention (i.e. use (iii) above or method (iv) above), include infections with *Staph. aureus* (either Methicillin-sensitive (i.e. MSSA) or Methicillin-resistant (i.e. MRSA)) and *Staph. epidermidis*, Streptococci, such as *Strept. agalactiae* and *Strept. pyogenes*, Bacillaceae, such as *Bacillus anthracis*, Enterobacteriaceae, such as *Escherichia coli*, Klebsiella (e.g. *Klebs. pneumoniae* and *Klebs. oxytoca*) and Proteus (e.g. *Pr. mirabilis*, *Pr. rettgeri* and *Pr. vulgaris*), *Haemophilus influenzae*, Enterococci, such as *Enterococcus faecalis* and *Enterococcus faecium*, Mycobacteria, such as *Mycobacterium tuberculosis* or fungi such as *Aspergillus fumigatus*, *Candida albicans*, *Cryptococcus neoformans*, *Histoplasma capsulatum* and *Pneumocystis jiroveci*. 
in this respect, particular conditions that the compounds of formula I, or combination products comprising compounds of formula I, can be used to treat include tuberculosis (e.g. pulmonary tuberculosis, non-pulmonary tuberculosis (such as tuberculosis lymph glands, genito-urinary tuberculosis, tuberculosis of bone and joints, tuberculosis meningitis) and miliary tuberculosis), anthrax, abscesses, acne vulgaris, actinomycosis, bacillary dysentery, bacterial conjunctivitis, bacterial keratitis, botulism, Buruli ulcer, bone and joint infections, bronchitis (acute or chronic), brucellosis, burn wounds, cat scratch fever, cellulitis, chancroid, cholangitis, cholecystitis, cutaneous diphtheria, cystic fibrosis, cystitis, diffuse panbronchiolitis, diphtheria, dental caries, diseases of the upper respiratory tract, empyema, endocarditis, endometritis, enteric fever, enteritis, epididymitis, epiglottitis, erysipelas, erysipeloid, erythrasma, eye infections, furuncles, Gardnerella vaginitis, gastrointestinal infections (gastroenteritis), genital infections, gingivitis, gonorrhoea, granuloma inguinale, Haverhill fever, infected burns, infections following dental operations, infections in the oral region, infections associated with prostheses, intraabdominal abscesses, Legioneer's disease, leprosy, leptospirosis, listeriosis, liver abscesses, Lyme disease, lymphogranuloma venerium, mastitis, mastoiditis, meningitis and infections of the nervous system, mycetoma, nocardiosis (e.g. Madura foot), non-specific urethritis, ophthaimia (e.g. ophthaimia neonatorum), osteomyelitis, otitis (e.g. otitis externa and otitis media), orchitis, pancreatitis, paronychia, pelveoperitonitis, peritonitis, peritonitis with appendicitis, pharyngitis, phlegmons, pinta, plague, pleural effusion, pneumonia, postoperative wound infections, postoperative gas gangrene, prostatitis, pseudo-membranous colitis, psittacosis, pulmonary emphysema, pyelonephritis, pyoderma (e.g. impetigo), Q fever, rat-bite fever, reticulosis, Ritter's disease, salmonellosis, salpingitis, septic arthritis, septic infections, septicameia, sinusitis, skin infections (e.g. skin granulomas), syphilis, systemic infections, tonsillitis, toxic shock syndrome, trachoma, tularaemia, typhoid, typhus (e.g. epidemic typhus, murine typhus, scrub typhus and spotted fever), urethritis, wound infections, yaws, aspergillosis, candidiasis (e.g. oropharyngeal candidiasis, vaginal candidiasis or balanitis), cryptococcosis, favus, histoplasmosis, intertrigo, mucormycosis, tinea (e.g. tinea corporis, tinea capitis, tinea cruris, tinea pedis and tinea unguium), onychomycosis, pityriasis versicolor, ringworm and sporotrichosis.

Further conditions that may be mentioned in this respect include infections with MSSA, MRSA, Staph. epidermidis, Strept. agalactiae, Strept. pyogenes, Escherichia coli,
Klebs. pneumoniae, Klebs. oxytoca, Pr. mirabilis, Pr. rettgeri, Pr. vulgaris, Haemophilis influenzae, Enterococcus faecalis or Enterococcus faecium.

The use in medicine of certain compounds of formula I, as hereinbefore defined, is, to the knowledge of the inventors, novel.

In this respect, a further aspect of the invention provides a compound of formula Ic for use in medicine, wherein compounds of formula Ic take the same definition as compounds of formula I, as hereinbefore defined, provided that:

(a) when X₁ represents N and R² represents H and A represents a fused benzene ring, then
(i) when R¹ represents two different OR₇ substituents at the 6- and 7-positions of the quinazoline ring and X² represents O then R³ does not represent a single substituent at the 6-position of the benzoxazole ring that is NH₂ or NHC(O)NHR⁷ (e.g. wherein R⁷ represents phenyl substituted by two substituents selected from methyl, methoxy, trifluoromethyl and chloro), and
(ii) when R¹ represents two halo substituents at the 6- and 8-positions of the quinazoline ring, X² represents N and R⁴ represents CH₂, then R³ does not represent H;

(b) when X₁ represents CH, R² represents H and X² represents N, then
(i) when R⁴ represents H and A represents a fused benzene ring (and, for example, R³ represents H), then R¹ does not represent a single halo (e.g. chloro) substituent (e.g. in the 7-position of the quinoline ring), and
(ii) when R⁴ represents H or tetrahydrofuran-2-yl, which latter group is substituted by OH and hydroxymethyl, A represents a fused pyrimidinyl ring and R¹ represents H, then R³ does not represent two substituents that are OH and NH₂.

Particular compounds of formula Ic that may be mentioned include relevant compounds of formula Ia and Ib, as hereinbefore defined. Still further compounds of formula Ic that may be mentioned include those in which:

(1) X₁ represents CH;
(2) X² represents N;
(3) R² is other than H;
(3) R⁴ is other than H.
The use of compounds of formula Ic in medicine includes their use as pharmaceuticals.

The invention therefore further provides for the use of a compound of formula Ic as a pharmaceutical.

Compounds of formula Ic are, to the knowledge of the inventors, novel \emph{per se}. Thus, in a still further aspect of the invention, there is provided a \emph{compound} of formula Ic.

Specific compounds of formula I, Ia, Ib and Ic that may be mentioned include compounds of Examples 1 to 7 below, i.e.:

(i) \((1\text{-methyl-1H-benzimidazol-2-yl})-(6\text{-hydroxy-2-methylquinolin-4-yl})\text{amine;}
(ii) \((1\text{-methyl-1 H-benzimidazol-2-yl})-(2\text{-methyl-6-phenoxyquinolin-4-yl})\text{amine;}
(iii) \((1\text{-methyl-1 H-benzimidazol-2-yl})-(6\text{-chloro-2-methylquinolin-4-yl})\text{amine;}
(iv) \((1\text{-methyl-1 H-benzimidazol-2-yl})-(6\text{-cyano-2-methylquinolin-4-yl})\text{amine;}
(v) \((1\text{-methyl-1 H-benzimidazol-2-yl})-(6\text{-phenoxyquinolin-4-yl})\text{amine;}
(vi) \((1\text{-methyl-1 H-benzimidazol-2-yl})-(6\text{-benzyloxy-2-methylquinolin-4-yl})\text{amine;}
(vii) \((1\text{-methyl-1 H-benzimidazol-2-yl})-(5,6\text{-dichloro-2-methylquinolin-4-yl})\text{amine;}
(viii) \((1\text{-methyl-1 H-benzimidazol-2-yl})-(7\text{-chloro--2-methylquinolin-4-yl})\text{amine hydrochloride;}
(ix) \((1\text{-methyl-1 H-benzimidazol-2-yl})-(6,8\text{-dichloro-2-methylquinolin-4-yl})\text{amine;}
(x) \([6-(4\text{-fluorophenoxy})-2\text{-methylquinolin-4-yl}]-(1\text{-methyl-1 H-benzimidazol-2-yl})\text{amine;}
(xi) \((2\text{-methyl-6-phenyaminoquinolin-4-yl})-(1\text{-methyl-1 H-benzimidazol-2-yl})\text{amine;}
(xii) \((1\text{-H-benzimidazol-2-yl})-(2\text{-methyl-6-phenoxyquinolin-4-yl})\text{amine;}
(xiii) \((benzoxazol-2-yl)-(2\text{-methyl-6-phenoxyquinolin-4-yl})\text{amine;}
(xiv) \((1\text{-H-benzimidazol-2-yl})-(6\text{-chloro-2-methylquinazolin-4-yl})\text{amine;}
(xv) \([2\text{-methyl-6-(pyrimidin-2-yloxy)quinolin-4-yl}]-(1\text{-methyl-1 H-benzimidazol-2-yl})\text{amine;}
(xvi) \((1\text{-methyl-1 H-benzimidazol-2-yl})-(2\text{-methyl-6-(4-methylpiperazin-1-yl)quinolin-4-yl})\text{amine;}
(xvii) \((1\text{-methyl-1 H-benzimidazol-2-yl})-(2\text{-morpholin-4-yl-6-phenoxyquinolin-4-yl})\text{amine and pharmaceutically-acceptable salts and/or solvates thereof.}

In particular, specific compounds of formula I, Ia, Ib and Ic that may be mentioned include compounds (ii) to (xv) above.
As well as having activity against fungi and bacteria, compounds of formulae I (including compounds of formula Ia, Ib or Ic) may also have activity against other organisms, such as protozoa. Therefore, according to further aspects of the invention, there is provided:

(i) the use of a compound of formula I, Ia, Ib or Ic, as hereinbefore defined, for the preparation of a medicament for the treatment of a protozoal disease;

(ii) a method of treating a protozoal disease in a mammal, the method comprising administering to said mammal an effective amount of a compound of formula I, (a, Ib or (c, as hereinbefore defined;

(iii) use (e.g. ex vivo use) of a compound of formula I, Ia, Ib or Ic for killing protozoa.

When used herein, the terms "protozoa" (and derivatives thereof, such as "protozoal disease") includes references to organisms (or infections due to organisms) of the following classes and specific types:

- Leishmania (e.g. Leishmania donovani);
- Plasmodium spp.;
- Trypanosoma spp.;
- Giardia lamblia;
- coccidia (e.g. Cryptosporidium parvum, Isospora belli);
- Toxoplasma (e.g. Toxoplasma gondii);
- Balantidium coli;
- amoeba (e.g. Entamoeba, such as Entamoeba histolytica, Entamoeba coli, Entamoeba hartmanni and Entamoeba polecki); and
- Microsporidia (e.g. Enterocytozoon bieneusi, Encephalitozoon hel/em, Encephalitozoon cuniculi and Septata intestinalis).

Particular conditions that the compounds of formula I, Ia, Ib or Ic can be used to treat include Leishmaniasis, malaria, trypanosomiasis, toxoplasmosis, giardiasis, balantidiasis, amoebiasis (amoebic dysentery), cryptosporidiosis, isosporiasis and microsporidiosis.

Compounds of formula I (including compounds of formula Ia, Ib and Ic) may be prepared in accordance with techniques known to those skilled in the art, for example as described hereinafter.
Thus, according to a further aspect of the invention there is provided a process for the preparation of a compound of formula I (e.g. a compound of formula Ia, Ib or Ic), which comprises:

(a) for compounds of formula I in which $X^2$ represents N, reaction of a compound of formula II,

wherein $L^1$ represents a suitable leaving group (e.g. halo, such as chloro) and $R^1$, $R^2$ and $X^1$ are as hereinbefore defined, with a compound of formula III,

(b) for compounds of formula I in which $X^2$ represents O, reaction of a compound of formula IV,

wherein $R^1$, $R^2$ and $X^1$ are as hereinbefore defined, with a compound of formula V
wherein R\textsuperscript{3}, A and L\textsuperscript{1} are as hereinbefore defined, for example under coupling conditions known to those skilled in the art (e.g. at room temperature or above in the presence of a suitable solvent (e.g. an organic solvent such as N,N-dimethylformamide) and a base (for example, an alkali metal hydride, such as sodium hydride)).

Compounds of formula II may be prepared according to, or by analogy with, methods known to those skilled in the art. For example, for compounds of formula II in which L\textsuperscript{1} represents halo may be prepared by halogenation of a corresponding compound of formula VI,

wherein R\textsuperscript{1}, R\textsuperscript{2} and X\textsuperscript{1} are as hereinbefore defined, using a suitable halogenating agent (for example, a thionyl halide, a phosphorous trihalide (e.g. PCl\textsubscript{3}), a phosphorous pentahalide (e.g. PCl\textsubscript{5}) or, particularly, a phosphorous oxyhalide (e.g. P(O)Cl\textsubscript{3})), for example at elevated temperature (such as from 70 to 120°C).

Compounds of formula IV may be prepared according to, or by analogy with, methods known to those skilled in the art. For example, for compounds of formula IV may be prepared by reaction of a corresponding compound of formula II with ammonia, or a protected derivative thereof (e.g. benzylamine, optionally bearing one or more substituents (e.g. substituents selected from the group comprising methyl, metnoxy, halo and nitro) on the phenyl ring, thus forming compounds such as 2,4-dimethoxybenzylamine). If a protected derivative of ammonia is employed, the protecting group is removed from the resulting protected intermediate (e.g. under standard conditions, such as acid-catalysed cleavage or catalytic hydrogenation) in order to form the compound of formula IV.

Compounds of formula VI\textsuperscript{'} may be prepared according to, or by analogy with, methods known to those skilled in the art.
For example, compounds of formula VI in which $X^1$ represents CH can be prepared by cyclisation of a corresponding compound of formula VH,

![Chemical Structure](image)

or a tautomer thereof, wherein $L^1$ represents a suitable leaving group (e.g. O-C$_{1-4}$ alkyl), and $R^1$ and $R^2$ are as hereinbefore defined, for example at elevated temperature (e.g. at reflux temperature) in the presence of a suitable solvent (such as dioxane) and optionally in the presence of an acid, such as polyphosphoric acid.

Compounds of formula VI in which $X^1$ represents CH can also be prepared by cyclisation of a corresponding compound of formula VIII,

![Chemical Structure](image)

wherein $R^1$ and $R^2$ are as hereinbefore defined, for example at elevated temperature (such as reflux temperature) in the presence of a suitable solvent (e.g. an alcohol such as ethanol, water, or mixtures thereof) and optionally in the presence of a base such as sodium carbonate.

Alternatively, compounds of formula VI in which $X^1$ represents CH can be prepared by decarboxylation of a corresponding compound of formula IX,

![Chemical Structure](image)

wherein $R^1$ and $R^2$ are as hereinbefore defined, for example at elevated temperature (such as from 180 to 220°C) in the presence of a suitable solvent (e.g. 1,2-dichlorobenzene).

Compounds of formula VI in which $X^1$ represents N may be prepared by cyclisation of a corresponding compound of formula X.
wherein $R^1$ and $R^2$ are as hereinbefore defined, for example at elevated temperature in the presence of a base (e.g. an alkali metal hydroxide, such as sodium hydroxide) and an appropriate solvent (e.g. water).

Compounds of formula VI! may be prepared according to, or by analogy with, methods known to those skilled in the art, such as by reaction of a corresponding compound of formula XI,

wherein $R^1$ is as hereinbefore defined, with a compound of formula XII,

wherein $R^2$ and $L^2$ are as hereinbefore defined, for example under conditions known to those skilled in the art (e.g. under conditions described hereinbefore in respect of the preparation of compounds of formula VI).

As will be appreciated by those skilled in the art, it may be possible to effect a "one-pot" conversion of a compound of formula XI to a compound of formula VI in which $X^1$ represents $\text{CH}$ by:

- reacting the compound of formula XI with a compound of formula $XK$ under the conditions described above; and
- continuing the reaction until the intermediate of formula VII has been converted to the corresponding compound of formula VI.

Compounds of formula VIII may be prepared according to, or by analogy with, methods known to those skilled in the art, such as by reduction of a corresponding compound of formula XIII.
wherein $R^1$ and $R^2$ are as hereinbefore defined, in the presence of a reducing agent (such as tin(II) chloride), for example under conditions known to those skilled in the art (such as, when the reducing agent is tin(II) chloride, by reaction at elevated temperature (e.g. reflux temperature) in the presence of an acid (such as concentrated hydrochloric acid) and a suitable solvent (e.g. an alcohol such as ethanol, water, or mixtures thereof).

As will be appreciated by those skilled in the art, it may be possible to effect a "one-pot" conversion of a compound of formula XIII to a compound of formula VI in which $X^1$ represents CH, by:

- reducing the compound of formula XIII under the conditions described above;

and

- continuing heating the reaction mixture, or adding a suitable base (e.g. a carbonate such as sodium carbonate), until the intermediate of formula VIII has been converted to the corresponding compound of formula VI.

Compounds of formula $\omega$ may be prepared according to, or by analogy with, methods known to those skilled in the art, such as by cydisation of a corresponding compound of formula XIV,

or a tautomer thereof, wherein $L^3$ represents $O-C_M$ alkyl, $L^2$ is as hereinbefore defined (and may or may not take the same definition as $L^3$), and $R^1$ and $R^2$ are as hereinbefore defined, for example under conditions known to those skilled in the art (e.g. at elevated temperature (such as from 180 to 220°C) in the presence of a suitable solvent (e.g. 1,2-dichlorobenzene)), followed by hydrolysis of the resulting ester of formula XIVA,
wherein $R^1$, $R^2$ and $L^3$ are as hereinbefore defined, for example under conditions known to those skilled in the art (e.g. at elevated temperature (such as reflux temperature) in the presence of a suitable alkali (such as sodium hydroxide) and an appropriate solvent (such as water)).

Compounds of formula $X(V$ may be prepared according to, or by analogy with, methods known to those skilled in the art, such as by reaction of a compound of formula $X_l$, as hereinbefore defined, with a compound of formula $X_{1V}$,

$$\text{XIVA}$$

wherein $L^2$ and $L^3$ are as hereinbefore defined, and wherein the two $L^3$ groups may be the same as or different from each other, for example under conditions known to those skilled in the art (e.g. at elevated temperature, such as from 80 to 100 °C).

Compounds of formulae $111$, $V$, $X$, $X_l$, $X_{1I}$, $X_{1II}$ and $X_{1V}$ are either commercially available, are known in the literature, or may be obtained by analogy with the processes described herein, or by conventional synthetic procedures, in accordance with standard techniques, from readily available starting materials using appropriate reagents and reaction conditions.

Substituents on alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, aryl and heterocyclic groups in compounds of formulae $I$, $H$, $111$, $IV$, $V$, $VI$, $VII$, $VIII$, $IX$, $X$, $XI$, $X_{1I}$, $X_{1II}$, $X_{1III}$, $X_{1IV}$ and $X_{1IVA}$ may be introduced and/or interconverted using techniques well known to those skilled in the art by way of standard functional groups interconversion, in accordance with standard techniques, from readily available starting materials using appropriate reagents and reaction conditions. For example, benzyloxy may be converted to hydroxy, hydroxy may be converted to alkoxy, phenyl may be halogenated to give halophenyl, halo may be displaced by cyano, etc.
Compounds of formula I may be isolated from their reaction mixtures using conventional techniques. For example, compounds of formula I may be isolated by conversion to an acid (e.g. hydrochloric acid) salt (e.g. by way of addition of acid to the crude product) and then recrystallisation of the salt from a suitable solvent (e.g. methanol or, particularly, ethanol). Alternatively, the salt can simply be washed with or slurried in the presence such a suitable solvent in order to isolate the pure acid salt of the compound of formula I.

In accordance with the present invention, pharmaceutically acceptable derivatives of compounds of formula I also include "protected" derivatives, and/or compounds that act as prodrugs, of compounds of formula I.

Compounds of formula I may exhibit tautomerism. All tautomeric forms and mixtures thereof are included within the scope of the invention.

Compounds of formula I 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. The various stereoisomers may be isolated by separation of a racemic or other mixture of the compounds using conventional, e.g. 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, or by derivatisation, for example with a homochiral acid followed by separation of the diastereomeric derivatives by conventional means (e.g. HPLC, chromatography over silica). All stereoisomers are included within the scope of the invention.

It will be appreciated by those skilled in the art that in the processes described above and hereinafter the functional groups of intermediate compounds may need to be protected by protecting groups.

Functional groups that it is desirable to protect include hydroxy, amino and carboxylic acid. Suitable protecting groups for hydroxy include optionally substituted and/or unsaturated alkyl groups (e.g. methyl, allyl, benzyl or ferf-butyl), trialkylsilyl or diarylalkylsilyl groups (e.g. f-butyldimethylsilyl, f-butyldiphenylsilyl or trimethylsilyl) and
tetrahydropyranyl. Suitable protecting groups for carboxylic acid include C_i-6 alkyl or benzyl esters.

The protection and deprotection of functional groups may take place before or after coupling, or before or after any other reaction in the above-mentioned schemes.

Protecting groups may be removed in accordance with techniques that are well known to those skilled in the art and as described hereinafter.

Persons skilled in the art will appreciate that, in order to obtain compounds of formula I in an alternative, and, on some occasions, more convenient, manner, the individual process steps mentioned hereinbefore may be performed in a different order, and/or the individual reactions may be performed at a different stage in the overall route (i.e. substituents may be added to and/or chemical transformations performed upon, different intermediates to those mentioned hereinbefore in conjunction with a particular reaction). This may negate, or render necessary, the need for protecting groups.

The type of chemistry involved will dictate the need, and type, of protecting groups as we\(\text{al}\) as the sequence for accomplishing the synthesis.


Protected derivatives of compounds of formula I may be converted chemically to compounds of the invention using standard deprotection techniques (e.g. hydrogenation). The skilled person will also appreciate that certain compounds of formula I may also be referred to as being "protected derivatives" of other compounds of formula I.

Those skilled in the art will also appreciate that certain compounds of formula I will be useful as intermediates in the synthesis of certain other compounds of formula I.

When used in the above-described method of treatment, the compounds of formula I may be formulated for administration to a patient. In this respect, according to a still
further aspect of the invention there is provided a pharmaceutical formulation including a compound of formula I (e.g. a compound of formula Ia, lb or lc), in admixture with a pharmaceutically acceptable adjuvant, diluent or carrier.

The above-mentioned medicaments, (components of) combination products and pharmaceutical formulations may be prepared according to methods known to those skilled in the art, for example by mixing a compounds of formula I (e.g. a compound of formula Ia, lb or lc) with excipient or excipients.

When formulated with excipients, the compound of formula I may be present in the above-mentioned medicaments, (components of) combination products and pharmaceutical formulations in a concentration from 0.1 to 99.5% (such as from 0.5 to 95%) by weight of the total mixture.

When administered to patients by way of any of the above-mentioned medicaments, (components of) combination products and pharmaceutical formulations, the compound of formula will normally be administered orally, by any parenteral route or via inhalation.

In the case of animals, compounds of formula I (e.g. compounds of formula Ia, lb or lc) can also be administered by incorporation of the compound of formulae I into feed or drinking water.

Preferred route of administration of compounds of the invention are oral.

Suitable daily doses of the compounds of the invention in prophylactic and/or therapeutic treatment of mammals (e.g. humans) include, for example, 0.001-100 mg/kg body weight at peroral administration and 0.001-50 mg/kg body weight at parenteral administration.

In a particular embodiment of the invention, compounds of formulae I are administered topically. Thus, according to the invention there is provided:

(I) a topical pharmaceutical composition comprising a compound of formula I (e.g. a compound of formula Ia, lb or lc) in admixture with a pharmaceutically acceptable adjuvant, diluent or carrier;
(II) a combination product for topical administration comprising
(A) a compound of formula I (e.g. a compound of formula Ia, Ib or Ic), as hereinbefore defined, and
(B) a conventional antibiotic agent, as hereinbefore defined,

wherein each of components (A) and (B) is formulated in admixture with a pharmaceutically-acceptable adjuvant, diluent or carrier.

In relation to (II) above, the combination product provides for the administration of component (A) in conjunction with component (B), and may thus be presented either as separate topical formulations, wherein at least one of those formulations comprises component (A) and at least one comprises component (B), or may be presented (i.e. formulated) as a combined topical preparation (i.e. presented as a single topical formulation including component (A) and component (B)).

Topical compositions, which are useful for treating disorders of the skin or of membranes accessible by digitation (such as membrane of the mouth, vagina, cervix, anus and rectum), include creams, ointments, lotions, sprays, gels and sterile aqueous solutions or suspensions. As such, topical compositions include those in which the active ingredient(s) is (are) dissolved or dispersed in a dermatological vehicle known in the art (e.g. aqueous or non-aqueous gels, ointments, water-in-oil or oil-in-water emulsions). Constituents of such vehicles may comprise water, aqueous buffer solutions, non-aqueous solvents (such as ethanol, isopropanol, benzyl alcohol, 2-(2-ethoxyethoxy)ethanol, propylene glycol, propylene glycol monolaurate, glycofurol or glycerol), oils (e.g. a mineral oil such as a liquid paraffin, natural or synthetic triglycerides such as Miglyol™, or silicone oils such as dimethicone). Depending, inter alia, upon the nature of the formulation as well as its intended use and site of application, the dermatological vehicle employed may contain one or more components selected from the following list:

- a solubilising agent or solvent (e.g. a β-cyclodextrin, such as hydroxypropyi β-cyclodextrin, or an alcohol or polyl such as ethanol, propylene glycol or glycerol);
- a thickening agent (e.g. hydroxyethylcellulose, hydroxypropylcellulose, carboxymethylcellulose or carbomer);
- a gelling agent (e.g. a polyoxyethylene-polyoxypropylene copolymer);
- a preservative (e.g. benzyl alcohol, benzalkonium chloride, chlorhexidine, chlorbutol, a benzoate, potassium sorbate or EDTA or salt thereof); and
pH buffering agent(s) (such as a mixture of dihydrogen phosphate and hydrogen phosphate salts, or a mixture of citric acid and a hydrogen phosphate salt).

The amount of compound of formula I used in topical compositions or combination products will depend, *inter alia*, upon the particular nature of the composition or combination product, as well as its intended use. In any event, those skilled in the art will be able to determine, by routine and non-inventive methods, amounts of compound of formula I that can be employed. Typically, however, the compound of formula I will be present in the topical composition or combination product at from 0.01 to 25% by weight (e.g. from 0.1 to 10% by weight, such as from 0.1 to 5% by weight or, particularly, from 0.5 to 3% (e.g. 2%) by weight) of the composition or product.

Methods of producing topical pharmaceutical compositions such as creams, ointments, lotions, sprays and sterile aqueous solutions or suspensions are well known in the art.

Suitable methods of preparing topical pharmaceutical compositions are described, for example in WO 95/10999, US 6,974,585, WO 2006/048747, as well as in documents cited in any of these references.

Topical pharmaceutical compositions and combination products according to the present invention may be used to treat a variety of skin or membrane disorders, such as infections of the skin or membranes (e.g. e.g. infections of nasal membranes, axilla, groin, perineum, rectum, dermatitic skin, skin ulcers, and sites of insertion of medical equipment such as i.v. needles, catheters and tracheostomy or feeding tubes) with any of the bacteria, fungi described hereinbefore, (e.g. any of the *Staphylococci, Streptococci, Mycobacteria or Pseudomonas* organisms mentioned hereinbefore, such as *S. aureus* (e.g. Methicillin resistant *S. aureus* (MRSA))).

Particular bacterial conditions that may be treated by topical pharmaceutical compositions and combination products according to the present invention also include the skin- and membrane-related conditions disclosed hereinbefore, as well as: acne vulgaris; rosacea (including eiythematotelangiectatic rosacea, papulopustular rosacea, phymatous rosacea and ocular rosacea); erysipelas; erythrasma; ecdyema; ecdyema gangrenosum; impetigo; paronychia; cellulitis; folliculitis (including hoi tub folliculitis); furunculosis; carbunculosis; staphylococcal scalded skin syndrome; surgical scarlet fever; streptococcal peri-anal disease; streptococcal toxic shock syndrome; pitted
keratolysis; trichomycosis axillaris; pyoderma; external canal ear infections; green nail syndrome; spirochetes; necrotizing fasciitis; Mycobacterial skin infections (such as lupus vulgaris, scrofuloderma, warty tuberculosis, tuberculides, erythema nodosum, erythema induratum, cutaneous manifestations of tuberculoid leprosy or lepromatous leprosy, erythema nodosum leprosum, cutaneous M. kansasii, M. malmoense, M. szulgai, M. simiae, M. gordonae, M. haemophilum, M. avium, M. intracellulare, M. chelonae (including M. abscessus) or M. fortuitum infections, swimming pool (or fish tank) granuloma, lymphadenitis and Buruli ulcer (Baimsdale ulcer, Searles' ulcer, Kakerifu ulcer or Toro ulcer)); intertrigo; as well as infected eczema, bums, abrasions and skin wounds.

Particular fungal conditions that may be treated by topical pharmaceutical compositions and combination products according to the present invention also include include the skin- and membrane-related conditions disclosed hereinbefore, as well as: candidiasis (e.g. oropharyngeal candidiasis, vaginal candidiasis or balanitis); sporotrichosis; ringworm (e.g. tinea pedis, tinea cruris, tinea capitis, tinea unguium or tinea corporis); tinea versicolor; and infections with Trichophyton, Microsporum, Epidermophyton or Pityrosporum ovale fungi.

When employed to treat a microbial infection, the compound of formula 1, whether administered on its own or in combination with a conventional antimicrobial agent, is preferably administered in a smaller number of doses than is necessary for the treatment of the same microbial infection utilising conventional antimicrobial agents only (e.g. in less than 7, 6, 5, 4, or 3 doses, such as in 2 doses or, particularly, 1 dose).

in this respect, a still further aspect of the invention provides a method of reducing the dose of conventional antimicrobial agent required to treat a microbial infection, the method comprising co-administering a compound of formula 1.

Compounds of formulae 1 have the advantage that they may be used to kill clinically latent microorganisms. Further, in treating microbial infections, compounds of formulae I may possess the further advantage that they allow for a shorter period of therapy (either alone or in combination with a conventional antimicrobial agent), thus increasing patient compliance (through, for example, the need to take fewer or smaller closes of
antimicrobial agents) and/or minimising the risk of generating sub-populations of microorganisms that are (genetically) resistant to conventional antimicrobial agents.

Additionally, compounds according to the invention may have the advantage that they may be more efficacious than, be less toxic than, have a broader range of activity than, be more potent than, produce fewer side effects than, or have other useful pharmacological properties over compounds known in the prior art.

**Biological Tests**

Test procedures that may be employed to determine the biological (e.g. bactericidal or antibacterial) activity of the compounds of formula I include those known to persons skilled in the art for determining:

(a) bactericidal activity against stationary-phase or "persistor" bacteria (i.e. "clinically latent" bacteria); and

(b) antibacterial activity against log phase bacteria.

In relation to (b) above, methods for determining activity against log phase bacteria include a determination, under standard conditions (i.e. conditions known to those skilled in the art, such as those described in WO 2005/014585, the disclosures of which document are hereby incorporated by reference), of Minimum Inhibitory Concentration ("MIC") or Minimum Bactericidal Concentration ("MBC") for a test compound.

In relation to (a) above, methods for determining activity against clinically latent bacteria include a determination, under conditions known to those skilled in the art (such as those described in *Nature Reviews, Drug Discovery* 1, 895-910 (2002), the disclosures of which are hereby incorporated by reference), of Minimum Stationary-cidal Concentration ("MSC") or Minimum Dormicidal Concentration ("MDC") for a test compound. Specific examples of such methods are described below.
Protocol for Pyogenic Bacteria

Bacterial strains

The strains used for screening are shown in the following table.

<table>
<thead>
<tr>
<th>Strain</th>
<th>Gram Status</th>
<th>Classification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Staphylococcus aureus (Oxford)</td>
<td>Gram positive</td>
<td>Reference strain</td>
</tr>
<tr>
<td>Escherichia coli K12</td>
<td>Gram negative</td>
<td>Reference strain</td>
</tr>
<tr>
<td>Enterococcus</td>
<td>Gram positive</td>
<td>Clinical isolate</td>
</tr>
<tr>
<td>Pseudomonas</td>
<td>Gram negative</td>
<td>Clinical isolate</td>
</tr>
<tr>
<td>Methicillin resistant S. aureus (MRSA)</td>
<td>Gram positive</td>
<td>Clinical isolate</td>
</tr>
<tr>
<td>Klebsiella aerogrenes</td>
<td>Gram negative</td>
<td>Clinical isolate</td>
</tr>
<tr>
<td>E. coli</td>
<td>Gram negative</td>
<td>Clinical isolate</td>
</tr>
<tr>
<td>Streptococcus pneumoniae</td>
<td>Gram positive</td>
<td>Reference strain</td>
</tr>
<tr>
<td>Streptococcus pyogenes Group A</td>
<td>Gram positive</td>
<td>Reference strain</td>
</tr>
<tr>
<td>Streptococci</td>
<td>Gram positive</td>
<td>Reference strain</td>
</tr>
<tr>
<td>Group B streptococci (Streptococcus agalactiae)</td>
<td>Gram positive</td>
<td>Reference strain</td>
</tr>
<tr>
<td>Streptococcus viridans</td>
<td>Gram positive</td>
<td>Reference strain</td>
</tr>
<tr>
<td>Haemophilus influenzae</td>
<td>Gram negative</td>
<td>Reference strain</td>
</tr>
</tbody>
</table>

Growth of bacteria

The bacteria (except for streptococci and H. influenzae) were grown in 10 mL of nutrient broth (No. 2 (Oxoid)) overnight at 37°C, with continuous shaking at 120 rpm. Streptococci and H. influenzae were grown overnight in Todd-Hewitt broth (Sigma) without shaking. The overnight cultures were diluted (1000 X) in 100 mL of growth medium and then incubated with or without shaking for 10 days. Viability of the bacteria was estimated by colony forming unit (CFU) counts at 2 hours intervals at the first 24 hours and at 12-24 hours afterwards. From serial 10-fold dilutions of the experimental cultures, 100 µl samples were added to triplicate plates of nutrient agar plates (Oxoid) and blood agar plates (Oxoid). Colony forming units (CFU) were counted after incubation of the plates at 37°C for 24 hours.

Log-phase cultures: The above-described overnight cultures were diluted (1000 X) with iso-sensitest broth. The cultures were then incubated at 37°C with shaking for 1-2 hours to reach log CFU 6, which served as log-phase cultures.
Stationary phase cultures: Cultures incubated for more than 24 hours are in stationary phase. For drug screening, 5-6 day old stationary phase cultures are used as shown in Rg. 1 (the periods between two arrows).

Measurements of bactericidal activity against log-phase cultures
Different concentrations of each test compound were incubated with the log-phase cultures in 96 well plates for various periods of time (2, 4, 6, 12, 24 hours). Bactericidal activity was then examined by taking a spectrophotometer reading (using a plate reader) of the resulting cultures, as well as by CFU counts as described above.

Measurements of bactericidal activity against stationary-phase cultures
Different concentrations of each test compound were incubated with stationary phase cultures (5-6 day cultures) in 96 well plates for 24 or 48 hours. Bactericidal activity was then determined by taking CFU counts of the resulting cultures, as described above.

Measurements of bactericidal activity against persistent bacteria
An antibiotic (e.g. gentamicin) was added to 5-6 day stationary-phase cultures to the final concentration of 50 to 100 µg/mL for 24 hours. After 24 hours of antibiotic treatment, the cells are washed 3 times with phosphate buffered saline (PBS), and then resuspended in PBS. The surviving bacterial cells are used as persisters. Viability is estimated by CFU counts. The persisters were then used in measurements of bactericidal activity for test compounds.

Protocol for M. tuberculosis

Growth of M. tuberculosis
M. tuberculosis H37Rv was grown in 10 mL of Middlebrook 7H9 broth containing 0.05% Tween 80 supplemented with 10% ADC without disturbing for up to 100 days. In order to obtain evenly dispersed cultures prior to experimental treatment, clumps in the cultures were broken up by vortexing the cultures in the presence of 2 mm glass
beads (Philip Harris Scientific, Staffordshire, UK) for 2 minutes, followed by sonication in a water bath sonicator (Branson Ultrasonic B. V.) for 5 minutes. The numbers of viable *M. tuberculosis* in the cultures were determined by colony forming unit (CFU) counts on Middlebrook 7H11 agar. Serials of 10-fold dilutions of the cultures are made in Middlebrook 7H9 broth with 0.05% (v/v) Tween 80 but without ADC. Then, 100 µL of samples was added to one-third segments of the agar plates in duplicate. The plates were incubated in polythene bags for 3 weeks at 37°C.

*Measurements of bactericidal activity against log-phase cultures*

Different concentrations of each test compound were incubated with log-phase cultures (4 day cultures) for various time periods (4, 8, 16, 24 days). Bactericidal activity was then determined by taking CFU counts of the resulting cultures, as described above.

*Measurements of bactericidal activity against stationary-phase cultures and persistent bacteria*

**Model 1 - Stationary-phase cultures.** Different concentrations of each test compound were incubated with the sonicated 100-day cultures, each concentration to a separate 10 mL culture. After incubation for 5 days, counts of viable CFU were determined by inoculating a pair of 7H11 plates with 100 µL of 10-fold serial dilutions of the resulting cultures.

**Model 2 - Persistent** bacteria selected by rifampicin. Rifampicin (100 mg/L) was added to each of a set of sonicated 100-day cultures, which cultures were then incubated for 5 days. After the first day of incubation, no colonies could be obtained on plates inoculated from the culture. After washing twice with PBS by centrifugation, fresh (and rifampicin-free) 7H9 medium was added to make up the volume to 10 mL and the test compound was added in the same concentrations as in model 1. After further incubation for 7 days, CFU counts were determined by inoculating 1 mL from each container onto a 7H11 plate. These plates were then incubated for 2 weeks and the very small colonies were counted and marked. After a further 2 weeks of incubation, any additional unmarked colonies (i.e. those that grew slowly) were added to the counts. Control studies have shown that plate counts begin to yield colonies on subculture after about 4 days of incubation of the rifampicin-free cultures.
Model 3. The procedure is similar to model 2, but only different concentrations of the test compound was added to the 100-day culture at three days after the rifampicin treatment. At the end of the 7-day incubation period (4 days with candidate drugs plus rifampicin), all cultures were washed, replacing with medium free of test compound, and then were incubated for a further 7 days before CFU counts were determined.

Skin (topical) models

In addition to in vitro testing against stationary- and log-phase bacteria, compounds of formulae Ia, Ib and Ic may also be tested in various in vivo models, including those known to those skilled in the art. For example, for determination of compound activity against bacteria in or on the skin, protocols that may be followed include those described in Antimicrobial Agents and Chemotherapy 49(8), 3435-41 (2005), as well as the following.

Mouse superficial skin bacterial model (intact skin)

ICR or BALB/c mice aged 6-8 weeks are obtained from Harlan UK. The mice are anesthetized by intraperitoneal injection of 200 µl of Ketamine hydrochloride/Xylazine solution. Fur on the back of the mouse is removed using an electrical clipper. A 2 cm² (2 cm × 1 cm) area of skin is marked with a marker pen. The marked skin area is swabbed using a disposable swab for 3 times in order to examine the bacterial numbers on the skin. The bacteria on the swab will spread on blood agar plates (Oxoid™).

Log-phase or stationary phase bacterial cultures will be used. The cultures will be concentrated by centrifugation to obtain 10⁹ to 10¹⁰ CFU/mL. The cell pellet will be resuspended with nutrient broth or PBS and glycerol (50%). 15-20 µl of the cell suspension is added to the skin area (2 cm²) which gives 10⁶-⁷ CFU on the skin. The skin is allowed to dry for about 15 min. Solutions of test compound at different concentrations will be applied on the skin area for different periods of time.

Bacterial numbers on the skin will be estimated as follows: After the mouse has been euthanised, the skin at the marked area will be cut and added into a 2 mL tube containing 1 mL water and glass beads (1 mm). The skin will be homogenised using a reciprocal shaker (Hybaid Ltd, UK) for 45 seconds (speed setting 6.5) or votexing for
1 tin. Residual test compound will be removed by washing 3 times with water or PBS (if the test compound precipitates in the buffer system, water alone is used for washing). CFU counts will be performed after a serial of 10 fold dilution of the homogenates. 100 µL samples will be added to one third of blood agar plates (Oxoid™) in duplicate. Colony forming units (CFU) will then be counted using aCoLye (a colony counter) after incubation of the plates at 37°C for 24 hours.

Mouse Superficial Skin Infection Model (Tape-stripping infection model)
ICR or BALB/c mice aged 6-8 weeks are obtained from Harlan UK. The mice are anesthetized by intraperitoneal injection of 200 µL of Ketamine hydrochloride/Xylazine solution. The fur of the mice on the back will be removed by electric clipper. An area of 2 cm² skin is tape-stripped using autoclave tape. The skin will be striped 10 times in succession. After this procedure, the skin become visibly damaged and is characterized by reddening and glistening but no regular bleeding. Buprenorphine will be given during the anaesthetic period and every 12 hours for up to 3 days to reduce prolonged pain. After stripping of the skin, a bacterial infection is initiated by placing a 10 µL of bacterial cell suspension containing 10⁷ cells from overnight or stationary phase cultures on the damaged skin area. At 0 and 4 hours after infection, 3 mice will be killed to estimate the CFU counts on the skin. After 24 hours, solutions of test compound at different concentrations will be applied on the skin area for different periods of time. The experiments will be terminated 18 h after the last topical treatment.

Bacterial numbers of the wounds will be estimated as follow: After the mouse has been euthanised, the wounds, approximately 2 cm² will be cut and added to a 2 ml tube containing 1 mL water and glass beads (1 mm). The skin will be homogenised using a reciprocal shaker (Hybaid Ltd, UK) for 45 seconds (speed setting 6.5). Residual test compound will be removed by washing 3 times with water. CFU counts will be performed after a serial of 10 fold dilution of the homogenises. 100 µL samples are added to one third of blood agar plates (Oxoid™) in duplicate. Colony forming units (CFU) are counted using aCoLye (a colony counter) after incubation of the plates at 37°C for 24 hours.
Examples

The invention will now be described in detail with reference to the following examples. It will be appreciated that the invention is described by way of example only and modification of detail may be made without departing from the scope of the invention.

\(^{1}\)H NMR spectra were recorded at ambient temperature using either a Varian Unity Inova (400 MHz) spectrometer or a Bruker Advance DRX (400 MHz) spectrometer, both with a triple resonance 5 mm probe. Chemical shifts are expressed in ppm relative to tetramethyisilane. The following abbreviations have been used: br = broad signal, s = singlet, d = doublet, dd = double doublet, t = triplet, q = quartet, m = multiplet.

High Pressure Liquid Chromatography - Mass Spectrometry (LCMS) experiments to determine retention times and associated mass ions were performed using the following methods:

Method A: Experiments performed on a Micromass Platform LCT spectrometer with positive ion electrospray and single wavelength UV 254 nm detection using a Higgins Clipeus C18 5 μm 100 x 3.0 mm column and a 1 mL / minute flow rate. The initial solvent system was 95% water containing 0.1% formic acid (solvent A) and 5% acetonitrile containing 0.1% formic acid (solvent B) for the first minute followed by a gradient up to 5% solvent A and 95% solvent B over the next 14 minutes. The final solvent system was held constant for a further 5 minutes.

Method B: Experiments performed on a Micromass Platform ZQ Quadrupole spectrometer with positive ion electrospray and single wavelength UV 254 nm detection using a Higgins Clipeus C18 5 μm 100 x 3.0 mm column and a 1 mL / minute flow rate. The initial solvent system was 95% solvent A and 5% solvent B for the first minute followed by a gradient up to 5% solvent A and 95% solvent B over the next 14 minutes. The final solvent system was held constant for a further 5 minutes.

Method C: Experiments performed on a Micromass Platform LC spectrometer with positive and negative ion electrospray and ELS/Diode array detection using a Phenomenex Luna C18(2) 30 x 4.6 mm column and a 2 mL / minute flow rate. The solvent system was 95% solvent A and 5% solvent B for the first 0.50 minutes followed...
by a gradient up to 5% solvent A and 95% solvent B over the next 4 minutes. The final solvent system was held constant for a further 1 minute.

Microwave experiments were carried out using either a Personal Chemistry Smith Synthesizer™ or Emrys Optimizer™ which use a single-mode resonator and dynamic field tuning, both of which give reproducibility and control. Temperatures from 40-250 °C can be achieved, and pressures of up to 20 bar can be reached.

Preparative HPLC was carried out using a 150x20.6 mm 7 micron Genesis C$_8$ column eluting at 10 mL/min with a gradient of water/MeCN (+0.1% formic acid or 0.1% trifluoroacetic acid). The fractions containing the desired product were concentrated. In some cases the compound was then converted to the hydrochloride salt by treatment with 1 M hydrochloric acid, followed by evaporation.

Preparations

Preparation 1

4-Hydroxy-2-methyl-6-phenoxyquinoline

A mixture of 4-phenoxyaniline (1.85 g), ethyl acetoacetate (1.27 mL), polyphosphoric acid (-10 g) in dioxane (40 mL) was heated at reflux overnight. The mixture was diluted with water and basified to pH 13 with sodium hydroxide. After sonication to break up the precipitate that formed, the mixture was acidified with hydrochloric acid (5 M) to pH 5 and extracted with ethyl acetate. The organic layer was washed with brine solution, dried (MgSO$_4$) and filtered. The filtrate was evaporated to dryness and the residue was triturated with diethyl ether. The solid was collected by filtration to give the title compound (0.8 g) as a white solid.

LCMS (method C) retention time 2.48 minutes (M+H$^+$) 252.

Preparation 2

The following compounds were prepared by a procedure analogous to that described in Preparation 1 above, utilising appropriate substituted anilines in place of 4-phenoxy-aniline.
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(i) 6-Cyano-4-hydroxy-2-methylquinoline.
A crude yellow solid, prepared from 4-cyanoaniline. The crude product was used without purification.

(ii) 7-Chloro-4-hydroxy-2-methylquinoline.
A crude cream-coloured solid, prepared from 3-chloroaniline as a mixture with 5-chloro-4-hydroxy-2-methylquinoline. The crude product was used without further purification.

(iii) 6,8-Dichloro-4-hydroxy-2-methylquinoline.
A cream-coloured solid, prepared from 2,4-dichloroaniline. The crude product was used without further purification.

Preparation 3

Diethyl 2-[1-(4-phenoxyphenylamino)ethylidene]malonate
A stream of nitrogen was passed through a mixture of diethyl ethoxymethylene malonate (4.04 mL) and 4-phenoxyaniline (3.7 g), whilst the mixture was heated at 100°C for 2 hours. The resultant mixture was cooled to give the title compound (6.0 g) as a dark brown solid.

LCMS (method C) retention time 4.25 minutes (M+H+) 356.

Preparation 4

The following compounds were prepared by a procedure analogous to that described in Preparation 3 above, utilising appropriate substituted anilines in place of 4-phenoxyaniline, and ethyl acetoacetate in place of diethyl ethoxymethylene malonate.

(i) Ethyl 3-(4-benzyloxyphenylamino)but-2-enoate.
Prepared from 4-benzyloxyaniline and ethyl acetoacetate.

\[ ^1H \text{NMR (CDCl}_3\text{)} δ 10.15 (br s, 1H), 7.4 (m, 5H), 7.0 (d, 2H), 6.9 (d, 2H), 5.05 (s, 2H), 4.65 (s, 1H), 4.15 (q, 2H), 1.9 (s, 3H), 1.25 (t, 3H). \]

(ii) Ethyl 3-[4-(4-fluorophenoxy)phenylamino]but-2-enoate.
A brown solid prepared from 4-(4-fluorophenoxy)aniline and ethyl acetoacetate.

LCMS (method C) retention time 4.6 minutes (M+H+) 316.
(iii) Ethyl 3-[4-(phenylamino)phenylamino]but-2-enoate.
A brown solid prepared from 4-phenylaminoaniline and ethyl acetoacetate.
$^1$H NMR (DMSO$_d_6$) δ 10.15 (s, 1H), 8.2 (s, 1H), 7.2 (t, 2H), 7.05 (m, 6H), 6.8 (t, 1H),
4.6 (s, 1H), 4.05 (q, 2H), 1.9 (s, 3H), 1.2 (t, 3H).

Preparation 5

Ethyl 4-hydroxy-6-phenoxyquinoline-3-carboxylate
A mixture of diethyl 2-[1-(4-phenoxyphenylamino)ethylidene]malonate (6.0 g; see Preparation 3 above) and 1,2-dichlorobenzene (15 ml) was stirred and heated in a microwave oven at 220°C for a total of 5 hours. The resultant solid was collected by filtration and washed with pentane to give the title compound (0.8 g) as an off-white solid.
$^1$H NMR (DMSO$_d_6$) δ 12.4 (br s, 1H), 8.55 (s, 1H), 7.7 (d, 1H), 7.55 (d, 1H), 7.5 (m, 3H), 7.25 (t, 1H), 7.1 (dd, 2H), 4.2 (q, 2H), 1.3 (t, 3H).

Preparation 6
The following compounds were prepared by a procedure analogous to that described in Preparation 5 above, utilising appropriate compounds of Preparation 4 in place of diethyl 2-[1-(4-phenoxyphenylamino)ethylidene]malonate.

(i) 6-Benzylxy-4-hydroxy-2-methylquinoline.
An off-white solid prepared from ethyl 3-[4-benzylxyphenylamino]but-2-enoate (see Preparation 4(i) above), with heating in a microwave oven at 220°C for 45 minutes.
$^1$H NMR (DMSO$_d_6$) δ 11.5 (br s, 1H), 7.55 (d, 1H), 7.45 (m, 3H), 7.4 (m, 2H), 7.35 (m, 2H), 5.9 (s, 1H), 5.15 (s, 2H), 2.35 (s, 3H).

(ii) 6-(4-Fluorophenoxy)-4-hydroxy-2-methylquinoline.
An off-white solid prepared from ethyl 3-[4-(4-fluorophenoxy)phenylamino]but-2-enoate (see Preparation 4(ii) above), with heating in a microwave oven at 220°C for 2 hours 50 minutes.
$^1$H NMR (DMSO$_d_6$) 11.65 (br s, 1H), 7.55 (d, 1H), 7.4 (m, 2H), 7.25 (t, 2H), 7.15 (m, 2H), 5.9 (s, 1H), 2.35 (s, 3H).
(iii) 4-Hydroxy-2-methyl-6-phenylaminoquinoline.

An off-white solid prepared from ethyl 3-[4-(phenylamino)phenylamino]but-2-enoate (see Preparation 4(iii) above), with heating in a microwave oven at 220°C for 1 hour 30 minutes.

1H NMR (DMSO-d6) δ 11.45 (br s, 1H), 8.3 (s, 1H), 7.7 (d, 1H), 7.45 (d, 1H), 7.35 (dd, 1H), 7.25 (t, 2H), 7.1 (d, 2H), 6.85 (t, 1H), 5.8 (s, 1H), 2.3 (s, 3H).

Preparation 7

4-Hydroxy-6-phenoxyquinoline

(i) 4-Hydroxy-6-phenoxyquinoline-3-carboxylic acid

A mixture of ethyl 4-hydroxy-6-phenoxyquinoline-3-carboxylate (0.65 g; see Preparation 5 above) and aqueous sodium hydroxide solution (10%, 6 ml) was stirred and heated at reflux for 90 minutes to give a clear solution. The mixture was acidified with concentrated hydrochloric acid and the resultant solid was collected by filtration to give the sub-title compound (0.51 g) as a white solid.

LCMS (method C) retention time 3.24 minutes (M+H+) 282.

(ii) 4-Hydroxy-6-phenoxyquinoline

A mixture of 4-hydroxy-6-phenoxyquinoline-3-carboxylic acid (0.5 g; see step (i) above) and 1,2-dichlorobenzene (10 mL) was heated in a microwave oven at 220°C for a total of 2 hours. The mixture was cooled, diluted with pentane and the resulting solid was collected by filtration to give the title compound (0.397 g) as a white solid.

1H NMR (DMSO-d6) δ 11.9 (br s, 1H), 7.9 (t, 1H), 7.6 (d, 1H), 7.45 (m, 4H), 7.2 (t, 1H), 7.05 (d, 2H), 6.0 (d, 1H).

Preparation 8

5,6-Dichloro-4-hydroxy-2-methylquinoline

(i) 2,3-Dichloro-6-nitrobenzoic acid

2,3-Dichlorobenzaldehyde (10.5 g) was added to a cooled mixture of concentrated sulphuric acid (20 mL) and concentrated nitric acid (20 mL). The resultant mixture was stirred and heated at 90°C overnight. The mixture was poured carefully into a mixture of ice and water and the resultant white solid was collected by filtration. The solid was dissolved in diethyl ether, dried (MgSO4) and filtered. The filtrate was evaporated to
dryness and the residue was purified by chromatography on silica, eluting with a mixture of methanol, dichloromethane and acetic acid (2:97:1 increasing to 3:96:1), collecting the main component as the sub-title compound (1.57 g, an off-white solid).

$^1$H NMR (DMSO-d$_6$) $\delta$ 8.24 (d, 1H), 8.05 (d, 1H), 7.75 (d, 0.2H), 7.7 (d, 0.8H), 5.65 (s, 0.8H), 4.05 (s, 0.4H), 2.45 (s, 0.6H), 2.15 (s, 2.4H).

(ii) 2,3-Dichloro-6-nitrobenzoyl chloride

Oxaly chloride (11.0 mL) was added dropwise to a solution of 2,3-dichloro-6-nitrobenzoic acid (1.5 g; see step (i) above) in dichloromethane (50 mL) containing a few drops of $\Lambda$, $\Lambda$-dimethylformamide. The resultant mixture was stirred at room temperature for 2 hours then evaporated to dryness. The residue was purified by chromatography on silica, eluting with a mixture of ethyl acetate and cyclohexane (1:4) to give the sub-title compound (1.3 g) as a pale yellow oil.

$^1$H NMR (CDCl$_3$) $\delta$ 8.2 (d, 1H), 7.8 (d, 1H).

(iii) 1-(2,3-Dichloro-6-nitrophenyl)butan-1,3-dione

tert-Butyl acetoacetate (1.12 mL) was added to a suspension of magnesium (0.165 g) in methanol (5 mL). A few drops of carbon tetrachloride were added and the mixture was stirred at room temperature overnight. The resultant suspension was evaporated to dryness and the residue was suspended in dry acetonitrile (10 mL). 2,3-Dichloro-6-nitrobenzoyl chloride (1.3 g; see step (ii) above) was added to the suspension and the mixture was stirred at room temperature overnight then at 60°C for 2 hours. The mixture was evaporated to dryness and the residue was dissolved in ethyl acetate and washed with saturated brine solution, dried (MgSO$_4$) and then filtered. The filtrate was evaporated to dryness and the residue was dissolved in toluene (20 mL) and 4-toluene-sulphonic acid (0.43 g) was added. The resulting solution was heated at reflux for 3 hours. After cooling, the mixture was washed with water, dried (MgSO$_4$) and filtered. The filtrate was evaporated to dryness and the residue was purified by chromatography on silica, eluting with a mixture of ethyl acetate and cyclohexane. The main component was triturated with diethyl ether and the product collected by filtration to give the sub-title compound (0.73 g) as an orange solid.

$^1$H NMR showed a mixture of keto and enol forms in a ratio of ~1:4.

$^1$H NMR (CDCl$_3$) $\delta$ 8.1 (d, 0.2H), 8.05 (d, 0.8H), 7.75 (d, 0.2H), 7.7 (d, 0.8H), 5.65 (s, 0.8H), 4.05 (s, 0.4H), 2.45 (s, 0.6H), 2.15 (s, 2.4H).
(iv) **5,6-Dichloro-4-hydroxy-2-methylquinoline**

A solution of stannous chloride dihydrate (1.83 g) in concentrated hydrochloric acid (5 mL) was added to a solution of 1-(2,3-dichloro-6-nitrophenyl)butan-1,3-dione (0.56 g; see step (iii) above) in ethanol (50 mL) and the mixture was heated at reflux for 1 hour. The mixture was basified to pH 9 by addition of an aqueous solution of sodium carbonate and the product was extracted into ethyl acetate, dried (MgSO₄) and filtered. The filtrate was evaporated to dryness, the residue was triturated with diethyl ether and the product collected by filtration to give the title compound (0.19 g) as a crude yellow solid, which was used without further purification.

**Preparation 9**

**6-Chloro-4-hydroxy-2-methylquinazoline**

A solution of 2-amino-5-chlorobenzoic acid (9.74 g) in acetic anhydride (30 mL) was heated at reflux for 1 hour. The mixture was cooled to 0°C and the resultant solid was collected by filtration. This solid was added to aqueous ammonia solution (33%, 50 mL) and the mixture was stirred at room temperature for 2 hours. A solution of sodium hydroxide (10%) was added and the mixture was heated until the solid dissolved. The mixture was then treated with activated charcoal and filtered through Celite™. The filtrate was acidified to pH 8 by addition of concentrated hydrochloric acid and the product was collected by filtration. This was recrystallised from ethanol to give the title compound (5.31 g) as a fluffy, white solid.

LCMS (method C) retention time 2.26 minutes (M+H⁺) 195.

**Preparation 10**

**4-Chloro-2-methyl-6-phenoxyquinoline**

A solution of 4-hydroxy-2-methyl-6-phenoxyquinoline (0.8 g; see Preparation 1 above) in phosphorus oxychloride was stirred and heated at 80°C for 1 hour. After cooling to room temperature, the solution was added carefully to water (with cooling, as required). The mixture was basified by addition of solid sodium carbonate and then extracted with ethyl acetate, washed with saturated brine solution, dried (MgSO₄) and filtered. The filtrate was evaporated to dryness to give the title compound (0.8 g) as a brown oil.

¹H NMR (CDCl₃) 8.0 (d, 1H), 7.65 (d, 1H), 7.5 (dd, 1H), 7.4 (m, 3H), 7.2 (t, 1H), 7.1 (m, 2H), 2.7 (s, 3H).
The following compounds were prepared by a procedure analogous to that described in Preparation 10 above, utilising appropriate compounds of Preparations 2 or 6 to 9 above in place of 4-hydroxy-2-methyl-6-phenoxyquinoline.

(i) 4,6-Dichloro-2-methylquinoline.
An off-white solid, prepared from 6-chloro-4-hydroxy-2-methylquinoline.
$\text{H NMR (CDCl}_3 \delta 8.15 \text{ (d, 1H), 7.95 \text{ (d, 1H), 7.65 \text{ (dd, 1H), 7.4 \text{ (s, 1H), 2.75 \text{ (s, 3H).)}}}$

(ii) 4-Chloro-6-cyano-2-methylquinoline.
A yellow oil, prepared from 6-cyano-4-hydroxy-2-methylquinoline (see Preparation 2(ii) above).
$\text{H NMR (CDCl}_3 \delta 9.6 \text{ (d, 1H), 8.1 \text{ (d, 1H), 7.95 \text{ (dd, 1H), 7.55 \text{ (s, 1H), 2.75 \text{ (s, 3H).)}}}$

(iii) 4-Chloro-6-phenoxyquinoline.
A brown oil, prepared from 4-hydroxy-6-phenoxyquinoline (see Preparation 7 above).
LCMS (method C) retention time 4.05 minutes (M+H$^+$) 256.

(iv) 6-Benzylx0-4-chloro-2-methylquinoline.
An off-white solid, prepared from 6-benzylx0-4-hydroxy-2-methylquinoline (see Preparation 6(i) above).
$\text{H NMR (CDCl}_3 \delta 7.95 \text{ (d, 1H), 7.5 \text{ (m, 3H), 7.4 \text{ (m, 3H), 7.35 \text{ (m, 2H), 5.2 \text{ (s, 2H), 2.7 \text{ (s, 3H).)}}}$

(v) 2-Methyl-4,5,6-trichloroquinoline.
An off-white solid, prepared from 5,6-dichloro-4-hydroxy-2-methylquinoline (see Preparation 8 above).
$\text{H NMR (CDCl}_3 \delta 7.9 \text{ (d, 1H), 7.75 \text{ (d, 1H), 7.45 \text{ (s, 1H), 2.7 \text{ (s, 3H).)}}$

(vi) 4,7-Dichloro-2-methylquinoline.
Isolated (by column chromatography on silica gel, eluting with a mixture of ethyl acetate and cyclohexane) from a mixture with 4,5-dichloro-2-methylquinoline, which mixture was prepared from a mixture of 7-chloro-4-hydroxy-2-methylquinoline and 5-chloro-4-hydroxy-2-methylquinoline (see Preparation 2(ii) above).
$\text{H NMR (CDCl}_3 \delta 8.1 \text{ (d, 1H), 8.05 \text{ (d, 1H), 7.55 \text{ (dd, 1H), 7.4 \text{ (s, 1H), 2.7 \text{ (s, 3H).)}}}$
(vii) 2-Methyl-4,6,8-trichloroquinoline.  
A pink solid, prepared from 6,8-dichloro-4-hydroxy-2-methylquinoline (see Preparation 2(iii) above). 
$^1$H NMR (CDCl$_3$) $\delta$ 8.1 (d, 1H), 7.85 (d, 1H), 7.5 (s, 1H), 2.8 (s, 3H).

(viii) 4,6-Dichloro-2-methylquinazoline.  
An off-white solid, prepared from 6-chloro-4-hydroxy-2-methylquinazoline (see Preparation 9 above). 
$^1$H NMR (DMSO-d$_6$) $\delta$ 8.05 (d, 1H), 7.95 (dd, 1H), 7.80 (d, 1H), 2.55 (s, 3H).

(ix) 4-Chloro-6-(4-fluorophenoxy)-2-methylquinoline.  
A brown oil, prepared from 6-(4-fluorophenoxy)-4-hydroxy-2-methylquinoline (see Preparation 6(ii) above). 
$^1$H NMR (DMSO-d$_6$) $\delta$ 8.6 (d, 1H), 8.3 (s, 1H), 7.95 (dd, 1H), 7.55 (d, 1H), 7.35 (m, 4H), 2.0 (s, 3H).

(x) 4-Chloro-2-methyl-6-phenylaminoquinoline.  
A brown oil, prepared from 4-hydroxy-2-methyl-6-phenylaminoquinoline (see Preparation 6(iii) above).  
LCMS (method C) retention time 2.69 minutes (M+H$^+$) 269.

Preparation 12  
4-Amino-2-methyl-6-phenoxyquinoline

(i) 4-(2,4-Dimethoxybenzylamino)-2-methyl-6-phenoxyquinoline  
A mixture of 4-chloro-2-methyl-6-phenoxyquinoline (10.0 g; see Preparation 10 above), 2,4-dimethoxybenzylamine (11.1 mL), and 1,8-diazabicyclo[5.4.0]undec-7-ene (16.6 mL) in dimethylsulphoxide (100 mL) was stirred and heated at 150°C for 2 hours. After stirring at room temperature overnight, heating was continued at 160°C for 4 hours before the mixture was cooled, diluted with water and extracted with ethyl acetate. The organic layer was dried (MgSO$_4$) and filtered. The filtrate was evaporated to dryness and the residue was purified by chromatography on silica, eluting with a mixture of methanol and dichloromethane (1:100, gradually increasing to 1:10) to give the sub-title compound (5.89 g) as an orange solid.
1H NMR (CDCl₃) δ 7.9 (d, 1H), 7.35 (m, 3H), 7.25 (m, 1H), 7.2 (d, 1H), 7.1 (t, 1H), 7.0 (dd, 2H), 6.5 (d, 1H), 6.45 (dd, 1H), 6.4 (s, 1H), 5.05 (br s, 1H), 4.4 (d, 2H), 3.85 (s, 3H), 3.8 (s, 3H), 2.6 (s, 3H).

(ii) 4-Amino-2-methyl-6-phenoxyquinoline
A solution of 4-(2,4-dimethoxybenzylamino)-2-methyl-6-phenoxyquinoline (6.37 g see step (i) above) in dichloromethane (20 mL) and trifluoroacetic acid (20 mL) was stirred at room temperature for 100 minutes. The mixture was added carefully to potassium carbonate (10% aqueous solution), with stirring, and the resultant solid was collected by filtration. The solid was suspended in a mixture of dichloromethane and methanol (1:1, 500 mL) and the insoluble material was removed by filtration. The filtrate was evaporated to dryness and the residue was triturated with diethyl ether to give the title compound (4.45 g) as a yellow solid.

1H NMR (DMSO-de) δ 8.6 (br s, 2H), 8.05 (d, 1H), 7.85 (d, 1H), 7.65 (dd, 1H), 7.45 (t, 2H), 7.2 (t, 1H), 7.05 (d, 2H), 6.6 (s, 1H), 2.6 (s, 3H).

Preparation 13
6-(4-Methylpiperazin-1-yl)-4-chloro-2-methylquinoline

(i) 3-[4-(4-Methylpiperazin-1-yl)phenylamino]but-2-enoic acid ethyl ester
The sub-title compound was prepared by a procedure analogous to that described in Preparation 3 above, utilising 4-(4-methylpiperazin-1-yl)phenylamine in place of 4-phenoxyaniline, and ethyl acetoacetate in place of diethyl ethoxymethylene malonate.

(ii) 6-(4-Methyl-piperazin-1-yl)-4-hydroxy-2-methylquinoline
3-[4-(4-Methylpiperazin-1-yl)phenylamino]but-2-enoic acid ethyl ester (180 mg; see step (i) above) was heated in the microwave at 220°C for 45 minutes. The reaction mixture was diluted with pentane and the resulting precipitate filtered and washed with more pentane to give the sub-title compound as an off-white solid (105 mg).

(iii) 6-(4-Methylpiperazin-1-yl)-H-chloro-2-methylquinoline
A mixture of 6-(4-methylpiperazin-1-yl)-4-hydroxy-2-methylquinoline (680 mg; see step (ii) above) and phosphorus oxychloride (15 mL) was heated at 110°C for 2 hours. The mixture was poured carefully onto ice/water and the resulting solution neutralised with solid sodium carbonate. The product was extracted with ethyl acetate, dried (MgSO₄).
and filtered. The filtrate was evaporated to dryness to give the title compound (150 mg).

\[ ^1H \text{NMR (CDCl}_3\text{)} \delta 8.0 \text{ (d, 1H), 7.4 (d, 1H), 7.4 (s, 1H), 7.3 (s, 1H), 3.5 (m, 4H), 2.8 (m, 4H), 2.6 (s, 3H), 2.5 (s, 3H)} \]

Preparation 14

4-Chloro-2-morpholin-4-yl-6-phenoxyquinoline

\( \alpha \)-6-Phenoxyquinoline-2,4-diol

A mixture of \( \delta \)-phenoxyquinoline-2,4-diol (1.7 g; commercially available) was added to polyphosphoric acid (18 g), with stirring, and heated to 120°C for 15 minutes. Water (20 mL) was added and the liquid decanted. The residue was partitioned between 1 M NaOH and ethyl acetate. The aqueous layer was acidified to pH 1 with 1 N HCl and the resulting white precipitate isolated by filtration. The filtrate was evaporated to dryness to give the sub-title compound (95 mg).

(ii) 2,4-Dichloro-6-phenoxyquinoline

A mixture of 2,4-dichloro-6-phenoxyquinoline (145 mg; see step (i) above) and phosphorus oxychloride (3 mL) was heated at 110°C for 2 hours. The mixture was poured carefully onto ice/water and the resulting solution neutralised with solid sodium carbonate. The product was extracted with ethyl acetate, dried (MgSO\(_4\)) and filtered. The filtrate was evaporated to dryness to give the sub-title compound (125 mg).

\[ ^1H \text{NMR (CDCl}_3\text{)} \delta 8.0 \text{ (d, 1H), 7.6 (s, 1H), 7.5 (d, 1H), 7.4 (s, 1H), 7.3 (m, 2H), 7.2-7.1 (m, 1H), 7.0 (d, 2H)} \]

(iii) 4-Chloro-2-morpholin-4-yl-6-phenoxyquinoline

A mixture of 2,4-dichloro-6-phenoxyquinoline (0.05 g; see step (ii) above), morpholine (0.01 g) and diisopropylethylamine (0.03 g) in dioxane (1 mL) was heated at 140°C for 24 hours. The mixture was diluted with water and extracted with ethyl acetate, washed with water, dried (MgSO\(_4\)), filtered and evaporated to dryness. The residue was purified by chromatography on silica, eluting with a mixture of ethyl acetate and pentane (5:95, gradually increasing to 10:90). Evaporation of the minor product gave the title compound (0.002 g).

\[ ^1H \text{NMR (CDCl}_3\text{)} \delta 7.7 \text{ (d, 1H), 7.6 (s, 1H), 7.4-7.0 (m, 7H), 3.8 (m, 4H), 3.7 (m, 4H)} \]
Synthesis of Compounds of Formula I

Example 1
(1-Methyl-1H-benzimidazol-2-yl)-(6-hydroxy-2-methylquinolin-4-yl)amine
A suspension of (1-methyl-1H-benzimidazol-2-y1)-(6-benzyloxy-2-methyl-quinolin-4-y1)amine (0.05 g; see Example 3(iv) below) in ethanol (20 mL) was treated with palladium on carbon (10%, 0.005 g) and hydrogenated under a balloon of hydrogen for 4 hours. The resultant mixture was filtered through Celite™ and the filtrate was evaporated to dryness to give the title compound (0.36 g) as an orange gum.

LCMS (method C) retention time 2.14 minutes (M+H+) 305.

Example 2
(1-Methyl-1H-benzimidazol-2-ylH2-methyl-6-phenoxyquinolin-4-vnamine hydrochloride
A mixture of 4-chloro-2-methyl-6-phenoxyquinoline (0.081 g; see Preparation 10 above), 2-amino-1-methyl-1H-benzimidazole (0.088 g), 2-dicyclohexylphosphino-2'-dimethylaminobiphenyl (0.014 g), fr/s-(dibenzylideneacetone)dipalladium (0.014 g), sodium fe/f-butoxide (0.035 g) and toluene (1.5 mL) was stirred and heated in a microwave oven at 140°C for 20 minutes. The mixture was partitioned between water and dichloromethane and the organic layer was washed with saturated brine solution, dried (MgSO₄) and filtered. The filtrate was evaporated to dryness and the residue was purified by chromatography on silica, eluting with a mixture of methanol and dichloromethane (0:100 gradually increasing to 1:9) and collecting the major, yellow product. The product was further purified by preparative HPLC and the major component was converted to the hydrochloride salt to give the title compound (0.07 g) as a bright yellow solid.

1H NMR (DMSO-d₆) δ 14.0 (br s, 1H), 13.2 (br, 1H), 8.0 (m, 2H), 7.65 (dd, 1H), 7.55 (dd, 1H), 7.5 (m, 3H), 7.35 (m, 2H), 7.25 (t, 1H), 7.1 (m, 3H), 3.65 (s, 3H), 2.7 (s, 3H).

LCMS (method B) retention time 7.62 minutes (M+H⁺) 381

Example 3
The following compounds were prepared by a procedure analogous to that described in Example 2 above, utilising appropriate compounds of Preparation 11 above in place of 4-chloro-2-methyl-6-phenoxyquinoline.
(i) (1-Methyl-1H-benzimidazol-2-yl)-(6-chloro-2-methylquinolin-4-yl)amine hydrochloride.
A bright yellow solid, prepared from 4,6-dichloro-2-methylquinoline (see Preparation 11(i) above).

$^1$H NMR (DMSO-d$_6$) $\delta$ 14.05 (br s, 1H), 13.3 (br, 1H), 8.55 (dd, 1H), 7.95 (d, 1H), 7.9 (dd, 1H), 7.65 (dd, 1H), 7.5 (dd, 1H), 7.35 (m, 2H), 7.15 (s, 1H), 3.75 (s, 3H), 2.65 (s, 3H).

LCMS (method A) retention time 7.79 minutes (M+H$^+$) 323.

(ii) (1-Methyl-1H-benzimidazol-2-yl)-(6-cyano-2-methylquinolin-4-yl)amine hydrochloride.
A bright yellow solid, prepared from 4-chloro-6-cyano-2-methylquinoline (see Preparation 11(ii) above).

$^1$H NMR (DMSO-d$_6$) $\delta$ 13.95 (br s, 1H), 13.4 (br, 1H), 9.0 (d, 1H), 8.2 (dd, 1H), 8.0 (d, 1H), 7.7 (dd, 1H), 7.55 (dd, 1H), 7.4 (m, 2H), 7.15 (s, 1H), 3.8 (s, 3H), 2.65 (s, 3H).

LCMS (method A) retention time 6.81 minutes (M+H$^+$) 314.

(iii) (1-Methyl-1H-benzimidazol-2-yl)-(6-phenoxyquinolin-4-yl)amine hydrochloride.
A bright yellow solid, prepared from 4-chloro-6-phenoxyquinoline (see Preparation 11(iii) above).

$^1$H NMR (DMSO-d$_6$) $\delta$ 14.4 (br s, 1H), 8.5 (d, 1H), 8.1 (d, 1H), 8.05 (d, 1H), 7.7 (dd, 1H), 7.55 (dd, 1H), 7.5 (m, 3H), 7.3 (m, 2H), 7.25 (t, 1H), 7.15 (m, 3H), 3.65 (s, 3H).

LCMS (method B) retention time 7.56 minutes (M+H$^+$) 367.

(iv) (1-Methyl-1H-benzimidazol-2-yl)-(6-benzyloxy-2-methylquinolin-4-yl)amine.
A bright yellow solid (isolated as the free base), prepared from 4-chloro-6-benzyloxy-2-methylquinoline (see Preparation 11(iv) above).

$^1$H NMR (CDCl$_3$) $\delta$ 7.6 (d, 1H), 7.5 (s, 1H), 7.45 (dd, 2H), 7.4 (d, 1H), 7.3 (m, 2H), 7.25 (m, 2H), 7.15 (m, 4H), 6.9 (s, 1H), 5.15 (s, 2H), 3.65 (s, 3H), 2.15 (s, 3H).

LCMS (method B) retention time 7.98 minutes (M+H$^+$) 395.

(v) (1-Methyl-1H-benzimidazol-2-yl)-(5,6-dichloro-2-methylquinolin-4-yl)amine hydrochloride.
A bright yellow solid, prepared from 4,5,6-trichloro-2-methylquinoline (see Preparation 11(v) above).
H NMR (DMSO-de) δ 13.7 (br s, 1H), 13.15 (br S, 1H), 8.05 (d, 1H), 7.85 (d, 1H), 7.65 (dd, 1H), 7.5 (dd, 1H), 7.35 (m, 2H), 7.00 (ε, 1H), 3.7 (s, 3H), 2.55 (s, 3H).

LCMS (method B) retention time 7.72 mins (M+H+)<sup>+</sup> 357/359.

(vi) (1-Methyl-1H-benzimidazol-2-yl)-(7-chloro-2-methylquinolin-4-yl)amine hydrochloride.

A bright yellow solid, prepared from 4,7-dichloro-2-methylquinoline (see Preparation 11(vi) above).

H NMR (DMSO-d<sub>6</sub>) δ 14.05 (br s, 1H), 13.3 (br, 1H), 8.6 (d, 1H), 8.0 (d, 1H), 7.6 (m, 2H), 7.5 (dd, 1H), 7.35 (m, 2H), 7.1 (s, 1H), 3.75 (s, 3H), 2.65 (s, 3H).

LCMS (method B) retention time 6.88 minutes (M+H+)<sup>+</sup> 323.

(vii) (1-Methyl-1H-benzimidazol-2-yl)(6,8-dichloro-2-methylquinolin-4-yl)amine hydrochloride.

A bright yellow solid, prepared from 4,6,8-trichloro-2-methylquinoline (see Preparation 11(vii) above).

H NMR (DMSO-d<sub>6</sub>) δ 13.2-12.9 (br, 2H), 8.5 (s, 0.5H), 8.2 (d, 1H), 7.65 (dd, 1H), 7.55 (dd, 1H), 7.35 (m, 2H), 7.15 (br s, 1H), 3.75 (s, 3H), 2.7 (s, 3H).

LCMS (method B) retention time 7.56 minutes (M+H+)<sup>+</sup> 357/359.

(viii) [6-(4-Fluorophenoxy)-2-methylquinolin-4-yl]-(1-methyl-1H-benzimidazol-2-yl)amine formate.

A bright yellow solid (isolated by preparative HPLC, without conversion to the hydrochloride salt), prepared from 4-chloro-6-(4-fluorophenoxy)-2-methylquinoline (see Preparation 11(ix) above).

H NMR (DMSO-d<sub>6</sub>) δ 13.5-11.0 (br, 1H), 8.2 (s, 0.5H), 8.0 (d, 1H), 7.8 (dd, 1H), 7.5 (m, 2H), 7.4 (m, 2H), 7.3 (m, 2H), 7.15 (m, 4H), 3.65 (s, 3H), 2.55 (s, 3H).

LCMS (method A) retention time 8.52 minutes (M+H+)<sup>+</sup> 399.

(ix) (2-Methyl-6-phenylaminoquinolin-4-yl)-(1-methyl-1H-benzimidazol-2-yl)amine formate.

A bright yellow solid (isolated by preparative HPLC, without conversion to the hydrochloride salt), prepared from 4-chloro-2-methyl-6-phenylaminoquinoline (see Preparation 11(ix) above).
\[1^H\text{NMR (DMSO-d}_6\]\( \delta \) 8.55 (s, 1 H), 8.25 (br s, 1 H), 8.2 (s, 0.5H), 7.65 (s, 1 H), 7.6 (d, 1H), 7.5 (dd, 1H), 7.4 (m, 1H), 7.35 (m, 1H), 7.25 (m, 2H), 7.2 (m, 2H), 7.1 (m, 2H), 6.85 (t, 1H), 3.7 (s, 3H), 2.5 (s, 3H).

LCMS (method A) retention time 8.10 minutes (M+H\(^+\)) 380.

Example 4

(1H-Benzimidazol-2-yl)-(2-methyl-6-phenoxyquinolin-4-yl)amine

A mixture of 4-chloro-2-methy!-6-phenoxyquinoline (0.2 g; see Preparation 10 above), 2-amino-1H-benzimidazole (0.1 g), 1,1'-/b/s-(diphenylphosphino)ferrocine palladium(II) chloride dichloromethane adduct (0.072 g), sodium t\(/f\)-butoxide (0.078 g) in tetrahydrofuran (2.5 mL) and toluene (2.5 mL) was heated in a microwave oven at 140\(^\circ\)C for 30 minutes. The mixture was partitioned between water and dichloromethane and the organic layer was dried (MgSO\(_4\)) and filtered. The filtrate was evaporated to dryness and the residue was purified by chromatography on silica, eluting with a mixture of methanol and dichloromethane (1:30 gradually increasing to 1:9) and collecting the major, yellow component. The product was triturated with a mixture of dichloromethane and diethyl ether, followed by methanol to give the title compound (0.08 g) as a yellow solid.

\[1^H\text{NMR (CD}_3\text{OD)} \delta \) 7.9 (d, 2H), 7.8 (d, 1H), 7.4 (m, 3H), 7.35 (t, 2H), 7.15 (m, 3H), 7.05 (d, 2H), 2.7 (s, 3H).

LCMS (method B) retention time 7.01 minutes (M+H\(^+\)) 367.

Example 5

(Benzoxazol-2-yl)-(2-methyl-6-phenoxyquinolin-4-yl)amine hydrochloride

A mixture of 2-chlorobenzoxazole (0.046 g) and 4-amino-2-methy!-6-phenoxyquinoini \(\beta\) (0.05 g; see Preparation 12 above) was added to a suspension of sodium hydride (60% oil dispersion, 0.016 g) in \(\Lambda,\Lambda\)-dimethylformamide (2 mL). The mixture was stirred at room temperature for 4 hours then it was diluted with water and extracted with ethyl acetate. The organic layer was dried (MgSO\(_4\)) and filtered. The filtrate was evaporated to dryness and the residue was purified by chromatography on silica, eluting with a mixture of ethyl acetate and cyclohexane (1:2), collecting the major component, which was converted to the hydrochloride salt to give the title compound (0.025 g) as a white solid.

\[1^H\text{NMR (DMSO-d}_6\]\( \delta \) 8.5 (br s, 1H), 8.35 (br s, 1H), 8.2 (d, 1H), 7.8 (dd, 1H), 7.65 (d, 1H), 7.6 (d, 1H), 7.5 (t, 2H), 7.3 (m, 3H), 7.15 (dd, 2H), 2.85 (s, 3H).
LCMS (method B) retention time 7.62 minutes (M+H⁺) 368.

Example 6

(1H-Benzimidazol-2-vn-(6-chloro-2-methylquinazolin-4-vnamine hydrochloride)

A mixture of 4,6-dichloro-2-methylquinazoline (0.25 g; see Preparation 11(viii) above), 2-amino-1H-benzimidazoie (0.194 g) and N,N-di-isopropyl-N'-ethylamine (0.408 mL) in 1,2-dimethoxyethane (5 mL) was heated in a microwave oven at 170°C for 30 minutes. The resultant mixture was diluted with ethyl acetate and washed with water and saturated brine solution then dried (Na₂SO₄) and filtered. The filtrate was evaporated to dryness and the residue was purified by chromatography on silica, eluting with a mixture of dichloromethane, methanol, acetic acid and water (600:20:3:2 gradually increasing to 120:20:3:2) to give a major, yellow component, which was converted to the hydrochloride salt. The resulting yellow solid was recrystallised from ethanol and then triturated with diethyl ether to give the title compound (0.054 g) as a yellow solid.

¹H NMR (DMSO-d₆) δ 14.75 (br s, 1H), 13.3 (br s, 2H), 8.35 (d, 1H), 7.95 (dd, 1H), 7.85 (d, 1H), 7.65 (m, 2H), 7.4 (m, 2H), 2.85 (s, 3H).

Example 7

(1-methyl-1H-benzimidazol-2-yl)(1-amino-2-Bromo-pyrimidin-2-yl)amine hydrochloride

A solution of (1-methyl-1H-benzimidazol-2-yl)-(6-hydroxy-2-methylquinolin-4-yl)amine (0.108 g; see Example 1 above) in N,N-dimethylformamide (6 mL) was added to a suspension of sodium hydride (60% oil dispersion, 0.018 g) in N,N-dimethylformamide (3 mL) and the resultant mixture was stirred at room temperature for 1 hour. 2-Bromo-pyrimidine (0.067 g) was added and the mixture was stirred at 100°C overnight. The mixture was partitioned between water and ethyl acetate and the organic layer was washed with water, dried (MgSO₄) and filtered. The filtrate was evaporated to dryness and the residue was purified by chromatography on silica, eluting with a mixture of methanol and dichloromethane (1:20) and collecting the major, yellow component. This was further purified by chromatography on silica, eluting with a mixture of methanol and ethyl acetate (1:20 increasing to 1:10), collecting the major component, which was converted to the hydrochloride salt to give the title compound (0.025 g) as a yellow solid.
Example 8
(1-Methyl-1H-benzimidazol-2-yl)-2-methyl-6-(4--methylpiperazin-1-yl)--quinolin-4-yi
amine hydrochloride
A mixture of 6-(4-methylpipera2in-1-yl)-4-chloro-2-methylquinoline (see Preparation 1
above; 0.1 g), 2-arnino-1-methyl-1/-/-benzimidazole (0.046 g), 2-dicyclohexylphospnino-
2'-dimethylaminobiphenyl (0.012 g), fr7S-(dibenzylidene-acetone)dipalladium (0.016 g),
sodium ferf-butoxide (0.052 g) and toluene (4 mL) was stirred and heated in a
microwave at 140°C for 30 minutes. The mixture was partitioned between water and ethyl acetate and the organic layer was washed with saturated brine solution, dried
(MgSO₄) and filtered. The filtrate was evaporated to dryness and the residue was
purified by chromatography on silica eluting with a mixture of methanol and dichloromethane (5:95, gradually increasing to 20:80), coiiecting the major product. The filtrate was evaporated to dryness and the residue was purified by chromatography on silica eluting with a mixture of 2 M ammonia in methanol and ethyl acetate (5:95, gradually increasing to 20:80). The desired fractions were concentrated, hydrochloric acid was added, and the solvent evaporated to give the title compound (0.009 g) as a
bright yellow solid.

1H NMR (D₆-DMSO) δ 7.9 (s, 1H), 7.8 (s, 2H), 7.6 (d, 1H), 7.5 (d, 1H), 7.3 (m, 2H), 7.1
(s, 1H), 4.1 (m, 2H), 3.8 (s, 3H), 3.6 (m, 2H), 3.3 (t, 2H), 3.1 (t, 2H), 2.8 (s, 3H), 2.6 (s,
3H)

LCMS (Method C) retention time 4.91 minutes (M+H⁺) 387

Example 9
(1-Methyl-1H-benzimidazol-2-yl)-(2-morpholin-4-yl-6-phenoxyquinolin-4-yl)amine
hydrochloride
A mixture of 4-chloro-2-morpholin-4-yl-6-phenoxyquinoline (see Preparation 14 above;
0.1 g), 2-amino-1-methyl-1/-/-benzimidazole (0.044 g), 2-dicyclohexy)-phosphino-2'-
dimethylaminobiphenyl (0.012 g), fr/s-(dibenzylideneacetone)-dipalladium (0.015 g),
sodium ferf-butoxide (0.048 g) and toluene (4 mL) was stirred and heated in a
microwave at 140°C for 1 hour. The mixture was partitioned between water and ethyl
acetate and the organic layer was washed with saturated brine solution, dried (MgSO₄) and filtered. The filtrate was evaporated to dryness and the residue was purified by chromatography on silica, eluting with a mixture of methanol and dichloromethane, collecting the major product. The filtrate was evaporated to dryness and the residue was purified again by chromatography on silica, eluting with a mixture of ethyl acetate and pentane. Evaporation of the desired fractions gave a yellow oil. This oil was dissolved in methanol, and hydrochloric acid was added to the resulting solution. Evaporation of the methanolic mixture then gave the title compound.

LCMS (Method C) retention time 8.63 minutes (M+H⁺) 452

Example 10
Compounds of Examples 1 to 9 above were found to possess activity in biological tests described above. Biological activity that was determined included a log kill, at 20 µg/mL of test compound, of above 0.5 (e.g. from 0.5 to 7) against stationary phase and/or persister bacteria of the types Enterococcus, Staphylococcus aureus, Streptococcus pyogenes and Mycobacterium tuberculosis.

Indeed, the following compounds had the activity indicated.

(a) The compound of Example 2 demonstrated a log kill, at 20 µg/mL of test compound, from 5.87 to 7.05 for stationary phase bacteria of the types Enterococcus, Staphylococcus aureus (including MRSA), Streptococcus pyogenes, Streptococcus agalactiae and Mycobacterium tuberculosis.

(b) The compound of Example 3(iv) demonstrated a log kill, at 20 µg/mL of test compound, from 5.90 to 6.51 for stationary phase bacteria of the types Enterococcus, Staphylococcus aureus (including MRSA), Streptococcus pyogenes, Streptococcus agalactiae and Mycobacterium tuberculosis.

(c) The compound of Example 3(ix), when tested against Mycobacterium tuberculosis persister bacteria at 20 µg/mL of test compound, displayed a log kill of 4.67.
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
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<tr>
<td>br</td>
<td>broad (in relation to NMR)</td>
</tr>
<tr>
<td>d</td>
<td>doublet (in relation to NMR)</td>
</tr>
<tr>
<td>DMSO</td>
<td>dimethylsulfoxide</td>
</tr>
<tr>
<td>EDTA</td>
<td>ethylenediaminetetraacetic acid</td>
</tr>
<tr>
<td>HPLC</td>
<td>high performance liquid chromatography</td>
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<tr>
<td>LC</td>
<td>liquid chromatography</td>
</tr>
<tr>
<td>m</td>
<td>multiplet (in relation to NMR)</td>
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<tr>
<td>MBC</td>
<td>minimum bactericidal concentration</td>
</tr>
<tr>
<td>min.</td>
<td>minute(s)</td>
</tr>
<tr>
<td>MIC</td>
<td>minimum inhibitory concentration</td>
</tr>
<tr>
<td>MRSA</td>
<td>methiciulin-resistant <em>Staphylococcus aureus</em></td>
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<tr>
<td>t</td>
<td>triplet (in relation to NMR)</td>
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</tbody>
</table>

Prefixes n-, s-, /-, t- and tert- have their usual meanings: normal, secondary, *iso*, and tertiary.
Claims

1. A compound of formula I,

\[ \text{wherein} \]

- \( X^1 \) represents CH or N;
- \( X^2 \) represents N or O;
- \( A \) represents a fused benzene ring or a fused 5- or 6-membered, aromatic heterocycle containing from one to three heteroatoms selected from N, O and S;
- \( R^2 \) represents
  - (a) \( C_{1-12} \) alkyl, \( C_{2-12} \) alkenyl, \( C_{2-12} \) alkynyl, \( C_{3-12} \) cycloalkyl or \( C_{4-12} \) cycloalkenyl, which latter five groups are optionally substituted by one or more substituents selected from halo, nitro, CN, \( C_{1-6} \) alkyl, \( C_{2-8} \) alkenyl, \( C_{2-6} \) alkynyl, \( C_{3-8} \) cycloalkyl (which latter three groups are optionally substituted by one or more substituents selected from OH, =0, halo, \( C_{1-14} \) alkyl and \( C_{1-14} \) alkoxy), \( 0 R^{ca} \), \( S(O)_n R^{se} \), \( S(O)_2 N(R^{sc})(R^{sd}) \), \( N(R^{se})S(O)_2 R^{sf} \), \( N(R^{se})R^{sh} \), \( B_1-C(O)-B_2-R^{si} \), aryl and Het\(^1\), and which \( C_{3-12} \) cycloalkyl or \( C_{4-12} \) cycloalkenyl groups may additionally be substituted by =0,
  - (b) aryl or
  - (C) Het\(^2\);

- \( R^1 \) and \( R^3 \) independently represent H or one or more substituents on the fused benzene or heteroaromatic rings selected from
  - (a) halo,
  - (b) CN,
  - (c) \( C_{1-2} \) alkyl, \( C_{2-12} \) alkenyl, \( C_{2-12} \) alkynyl, \( C_{3-12} \) cycloalkyl or \( C_{4-12} \) cycloalkenyl, which latter five groups are optionally substituted by one or more substituents selected from halo, nitro, CN, \( C_{1-6} \) alkyl, \( C_{2-6} \) alkenyl, \( C_{2-6} \) alkynyl, \( C_{3-8} \) cycloalkyl
(which latter three groups are optionally substituted by one or more substituents selected from OH, =0, halo, C_{1-4} alkyl and C_{1-4} alkoxy), OR^{a}, S(O)_{2}R^{b}, S(O)_{2}N(R^{c})(R^{d}), N(R^{e})S(O)_{2}R^{f}, N(R^{g})(R^{h}), B^{3}-C(O)-B^{4}-R^{i}, aryl and Het^{3}, and which C_{3-12} cycloalkyl or C_{4-12} cycloalkenyl groups may additionally be substituted by =0,

(d) 0 R^{a},

(e) S(O)_{q}R^{b},

(f) S(O)_{q}N(R^{c})(R^{d}),

(g) N(R^{e})S(O)_{q}R^{f},

(h) N(R^{f})(R^{g}),

(i) B^{5}-C(O)-B^{6}-R^{i},

aryl or

(k) Het^{4};

R^{4} represents, when X^{2} represents N, H or a substituent selected from

(a) C_{1-12} alkyl, C_{2-12} alkenyl, C_{2-12} alkynyl, C_{3-12} cycloalkyl or C_{4-12} cycloalkenyl, which latter five groups are optionally substituted by one or more substituents selected from halo, nitro, CN, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-8} cycloalkyl (which latter three groups are optionally substituted by one or more substituents selected from OH, =0, halo, C_{1-4} alkyl and C_{1-4} alkoxy), 0 R^{a}, S(O)_{2}R^{b}, S(O)_{2}N(R^{c})(R^{d}), N(R^{e})S(O)_{2}R^{f}, N(R^{g})(R^{h}), B^{7}-C(O)-B^{8}-R^{i}, aryl and Het^{5}, and which C_{3-12} cycloalkyl or C_{4-12} cycloalkenyl groups may additionally be substituted by =0,

(b) aryl or

(C) Het^{6},

or, when X^{2} represents O, R^{4} is absent;

R^{a} to R^{5}, R^{6} to R^{i}, R^{7} to R^{i} and R^{8} to R^{8} independently represent, at each occurrence,

(a) H,

(b) C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl (which latter three groups are optionally substituted by one or more substituents selected from halo, OH, C_{1-8} alkoxy, aryl and Het^{7}),
(c) C₃₋₁₀ cycloalkyl, C₄₋₁₀ cycloalkenyl (which latter two groups are optionally substituted by one or more substituents selected from halo, OH, =0, C₁₋₆ alkyl, C₁₋₆ alkoxy, aryl and Het⁹),
(d) aryl or
(e) Het⁹,
provided that R₄ᵇ, R₅ᵇ, R₇ᵇ or R₈ᵇ does not represent H when n, p, q or r, respectively, is 1 or 2;

each aryl independently represents a C₆₋₁₀ carbocyclic aromatic group, which group may comprise either one or two rings and may be substituted by one or more substituents selected from
(a) halo,
(b) CN,
(c) C₁₋₁₂ alkyl, C₂₋₁₂ alkenyl, C₃₋₁₂ cycloalkyl or C₄₋₁₂ cycloalkenyl, which latter five groups are optionally substituted by one or more substituents selected from halo, nitro, CN, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₈ cycloalkyl (which latter three groups are optionally substituted by one or more substituents selected from OH, =0, halo, C₁₋₄ alkyl and Cl₋₄ alkoxy), 0 R₉ᵃ, S(O)ᵢ'R₉ᵇ, S(O)ᵢ'N(R₉ᶜ)(R₉ᵈ), N(R₉ʰ)S(O)ᵢ'R₉ʰ, N(Rᵢ゛)R₉ᵢ゛, Bᵢ゛-C(O)-Bᵢ゛-Rᵢ゛, phenyl, naphthyl (which latter two groups are optionally substituted by one or more substituents selected from OH, halo, C₁₋₄ alkyl and Cl₋₄ alkoxy) and Het¹₀, and which C₃₋₁₂ cycloalkyl or C₄₋₁₂ cycloalkenyl groups may additionally be substituted by =0,
(d) OR¹₀ᵃ,
(e) S(O)ᵢ'R₁₀ᵇ,
(f) S(O)ᵢ²N(R¹₀ᶜ)(R¹₀ᵈ),
(g) N(R¹₀ᵉ)S(O)₂R¹₀ᶠ,
(h) N(R¹₀ᵍ)(R¹₀ʰ),
(i) B¹゛-C(O)-B₁゛⁻R¹₀ⁱ, phenyl (which latter group is optionally substituted by one or more substituents selected from OH, halo, C₁₋₄ alkyl and C₁₋₄ alkoxy) or
(k) Het¹″;

R₉ᵃ to R₉ᵇ and R¹₀ᵃ to R¹₀ⁱ independently represent, at each occurrence,
(a) H,
(b) C_{1-12} alkyl, C_{2-12} alkenyl, C_{2-12} alkynyl, C_{3-12} cycloalkyl, C_{4-12} cycloalkenyl (which latter five groups are optionally substituted by one or more substituents selected from halo, OH, C_{1-6} alkyl, C_{3-12} cycloalkyl, C_{4-12} cycloalkenyl (which latter two groups are optionally substituted by one or more substituents selected from OH, =0, halo, C_{1-4} alkyl and C_{1-4} alkoxy), C_{1-6} alkoxy, NH_{2}, N(H)-Ci_{-6} alkyl. N(C_{1-6} alkyl)_{2}, phenyl (which latter group is optionally substituted by one or more substituents selected from OH, halo, C_{1-4} alkyl and C_{1-4} alkoxy) and Het^{12}, and which C_{3-12} cycloalkyl or C_{4-12} cycloalkenyl groups may additionally be substituted by =0),

c) phenyl (which latter group is optionally substituted by one or more substituents selected from OH, CN, halo, C_{1-6} alkyl and C_{1-6} alkoxy) or Het^{"}, provided that R^{1b} or R^{10b} does not represent H when t or u, respectively, is 1 or 2;

Het^{1} to Het^{13} independently represent 4- to 14-membered heterocyclic groups containing one or more heteroatoms selected from oxygen, nitrogen and/or sulfur, which heterocyclic groups may comprise one, two or three rings and may be substituted by one or more substituents selected from

(a) halo,

(b) CN,

c) C_{1-12} alkyl, C_{2-12} alkenyl, C_{2-12} alkynyl, C_{3-12} cycloalkyl or C_{4-12} cycloalkenyl, which latter five groups are optionally substituted by one or more substituents selected from halo, nitro, CN, C_{1-6} alkyl, C_{2-6} akenyl, C_{2-6} alkynyl, C_{3-8} cycloalkyl (which latter three groups are optionally substituted by one or more substituents selected from OH, =0, halo, C_{1-4} alkyl and C_{1-4} alkoxy), 0 R^{11a}, S(O)_{v}R^{11b}, S(O)_{2}N(R^{11c})(R^{11d}), N(R^{11e})S(O)_{2}R^{11f}, N(R^{11g})(R^{11h}), B^{13}-C(O)-B^{u} -R^{11i}, phenyl, naphthyl (which latter two groups are optionally substituted by one or more substituents selected from OH, halo, C_{1-4} alkyl and C_{1-4} alkoxy) and Het^{8}, and which C_{3-12} cycloalkyl or C_{4-12} cycloalkenyl groups may additionally be substituted by =0,

(d) 0 R^{12a},

(e) =0,

(f) S(O)_{w}R^{12b},

g) S(O)_{2}N(R^{12c})(R^{12d}),

(h) N(R^{12e})S(O)_{2}R^{12f},
N(R\textsuperscript{129})(R\textsuperscript{12h}),

B\textsuperscript{15}-C(O)-B\textsuperscript{16}-R\textsuperscript{121},

phenyl (which latter group is optionally substituted by one or more substituents selected from OH, halo, C\textsubscript{i-4} alkyl and C\textsubscript{i-4} alkoxy) or

(l) Het\textsuperscript{b};

R\textsuperscript{11a} to R\textsuperscript{11n} and R\textsuperscript{12a} to R\textsuperscript{12n} independently represent, at each occurrence,

(a) H,

(b) C\textsubscript{1-12} alkyl, C\textsubscript{2-12} alkenyl, C\textsubscript{2-12} alkynyl, C\textsubscript{3-12} cycloalkyl, C\textsubscript{4-12} cycloalkenyl (which latter five groups are optionally substituted by one or more substituents selected from halo, OH, C\textsubscript{i-4} alkyl, C\textsubscript{3-12} cycloalkyl, C\textsubscript{4-12} cycloalkenyl (which latter two groups are optionally substituted by one or more substituents selected from OH, =0, halo, C\textsubscript{i-4} alkyl and C\textsubscript{1-4} alkoxy), C\textsubscript{1-6} alkoxy, phenyl (which latter group is optionally substituted by one or more substituents selected from OH, halo, C\textsubscript{1-4} alkyl and C\textsubscript{1-4} alkoxy) and Het\textsuperscript{c}, and which C\textsubscript{3-12} cycloalkyl or C\textsubscript{4-12} cycloalkenyl groups may additionally be substituted by =0),

(c) phenyl (which latter group is optionally substituted by one or more substituents selected from OH, halo, C\textsubscript{1-4} alkyl and C\textsubscript{1-4} alkoxy) or

(e) Het\textsuperscript{d},

provided that R\textsuperscript{11b} or R\textsuperscript{12b} does not represent H when v or w, respectively is 1 or 2;

B\textsuperscript{1} to B\textsuperscript{16} independently represent a direct bond, O, S, NH or N(R\textsuperscript{13});

n, p, q, r, s, t, u, v and w independently represent o, 1 or 2;

R\textsuperscript{13} represents

(a) C\textsubscript{1-6} alkyl,

(b) phenyl (which latter group is optionally substituted by one or more substituents selected from OH, halo, C\textsubscript{i-4} alkyl and C\textsubscript{i-4} alkoxy),

(c) C\textsubscript{3-7} cycloalkyl (which latter group is optionally substituted by one or more substituents selected from OH, =0, halo, C\textsubscript{i-4} alkyl and C\textsubscript{i-4} alkoxy) or

(e) HeF;

Het\textsuperscript{a} to HeF independently represent 5- or 6-membered heterocyclic groups containing one to four heteroatoms selected from oxygen, nitrogen and/or sulfur, which
heterocyclic groups may be substituted by one or more substituents selected from halo, =0 and C_{1-5} alkyl; and

unless otherwise specified

(i) alkyl, alkenyl, alkynyl, cycloalkyl, and cycloalkenyl groups, as well as the alkyl part of alkoxy groups, may be substituted by one or more halo atoms, and

(ii) cycloalkyl and cycloalkenyl groups may comprise one or two rings and may additionally be ring-fused to one or two benzene rings,

or a pharmaceutically-acceptable derivative thereof.

2. A compound as claimed in Claim 1, wherein the compound is of formula Ib

\[
\begin{array}{c}
\text{ Ib} \\
R^1 \quad R^4 \\
R^1a \quad R^1d \\
R^1b \quad R^1c \\
\end{array}
\]

wherein

R^{1a} to R^{1d} all independently represents H or a substituent as defined in Claim 1 in respect of R^1; and

R^2, X^1, X^2 and R^4 are as defined in Claim 1, or a pharmaceutically-acceptable derivative thereof.

3. A compound as claimed in Claim 2, wherein

X^1 represents CH;
X^2 represents N;
R^2 represents methyl;
R^{1b} represents halo or H;
R^{1b} represents H or a substituent selected from chloro, CN, OR^{7a} and N(H)R^{7h};
R^{7a} represents phenylmethyl or phenyl, which latter group is optionally substituted by halo;
R⁷th represents phenyl, which latter group is optionally substituted as defined in Claim 1 in respect of aryl;
R¹c represents halo or H;
R¹d represents H; and
R⁴ represents H or methyl,
or a pharmaceutically-acceptable derivative thereof.

4. A compound as claimed in Claim 1, wherein the compound is:
   (i) (1-methyl-1 H-benzimidazol-2-yl)-(6-hydroxy-2-methylquinolin-4-yl)amine;
   (ii) (1-methyl-1 H-benzimidazol-2-yl)-(2-methyl-6-phenoxyquinolin-4-yl)amine;
   (iii) (1-methyl-1 H-benzimidazol-2-yl)-(6-chloro-2-methylquinolin-4-yl)amine;
   (iv) (1-methyl-1 H-benzimidazol-2-yl)-(6-cyano-2-methylquinolin-4-yl)amine;
   (v) (1-methyl-1 H-benzimidazol-2-yl)-(6-benzyloxy-2-methylquinolin-4-yl)amine;
   (vi) (1-methyl-1 H-benzimidazol-2-yl)-(5,6-dichloro-2-methylquinolin-4-yl)amine;
   (vii) (1-methyl-1 H-benzimidazol-2-yl)(7-chloro-2-methylquinolin-4-yl)amine hydrochloride;
   (viii) (1-methyl-1 H-benzimidazol-2-yl)-(6,8-dichloro-2-methylquinolin-4-yl)amine;
   (ix) [6-(4-fluorophenoxy)-2-methylquinolin-4-yl]-(1-methyl-1 H-benzimidazol-2-yl)amine;
   (x) (2-methyl-6-phenylaminoquinolin-4-yl)-(1-methyl-1 H-benzimidazol-2-yl)amine;
   (xi) (1 H-benzimidazol-2-yl)-(2-methyl-6-phenoxyquinolin-4-yl)amine;
   (xii) (benzoxazol-2-yl)-(2-methyl-6-phenoxyquinolin-4-yl)amine;
   (xiii) (1 H-benzimidazol-2-yl)-(6-chloro-2-methylquinazolin-4-yl)amine;
   (xiv) [2-methyl-6-(pyrimidin-2-yl)oxyquinolin-4-yl]-(1-methyl-1 H-benzimidazol-2-yl)amine;
   (xv) (1-methyl-1 H-benzimidazol-2-yl)-(2-methyl-6-((4-methylpiperazin-1-yl)quinolin-4-yl)amine;
   (xvi) (1-methyl-1 H-benzimidazol-2-yl)-(2-morpholin-4-yl-6-phenoxyquinolin-4-yl)amine
or a pharmaceutically-acceptable salt and/or solvate thereof.

5. A compound of formula I or Ib, as defined in any one of Claims 1 to 4, or a pharmaceutically-acceptable derivative thereof, for use in medicine.

6. A compound of formula I or Ib, as defined in any one of Claims 1 to 4, or a pharmaceutically-acceptable derivative thereof, for use in the killing of microorganisms.
7. A compound of formula I or Ib, as defined in any one of Claims 1 to 4, or a pharmaceutically-acceptable derivative thereof, for use in the killing of clinically latent microorganisms.

8. A compound for use as defined in Claim 6 or Claim 7 wherein the use is ex vivo.

9. A compound of formula I or Ib, as defined in any one of Claims 1 to 4, or a pharmaceutically-acceptable derivative thereof, for use as a sterilising agent or as a preservative.

10. A compound of formula I or Ib, as defined in any one of Claims 1 to 4, or a pharmaceutically-acceptable derivative thereof, for use in the treatment of a microbial infection.

11. Use of a compound of formula I or Ib, as defined in any one of Claims 1 to 4, or a pharmaceutically-acceptable derivative thereof, to kill microorganisms.

12. Use of a compound of formula I or Ib, as defined in any one of Claims 1 to 4, or a pharmaceutically-acceptable derivative thereof, to kill clinically latent microorganisms.

13. Use according to Claim 11 or Claim 12, which use is ex vivo.

14. Use of a compound of formula I or Ib, as defined in any one of Claims 1 to 4, or a pharmaceutically-acceptable derivative thereof, as a sterilising agent or as a preservative.

15. Use of a compound of formula I or Ib, as defined in any one of Claims 1 to 4, or a pharmaceutically-acceptable derivative thereof, for the preparation of a medicament for killing microorganisms.

16. Use of a compound of formula I or Ib, as defined in any one of Claims 1 to 4, or a pharmaceutically-acceptable derivative thereof, for the preparation of a medicament for killing clinically latent microorganisms.
17. Use of a compound of formula I or Ib, as defined in any one of Claims 1 to 4, or a pharmaceutically-acceptable derivative thereof, for the preparation of a medicament for the treatment of a microbial infection.

18. Use according to any one of Claims 15 to 17 wherein the compound of formula I or Ib, or pharmaceutically-acceptable derivative thereof, is the sole microbicidal or antimicrobial agent in the medicament.

19. A method of killing microorganisms in a mammal infected with such microorganisms, the method comprising administering to said mammal a compound of formula I or Ib, as defined in any one of Claims 1 to 4, or a pharmaceutically-acceptable derivative thereof.

20. A method of killing clinically latent microorganisms in a mammal infected with such latent microorganisms, the method comprising administering to said mammal a compound of formula I or Ib, as defined in any one of Claims 1 to 4, or a pharmaceutically-acceptable derivative thereof.

21. A method of treating or preventing a microbial infection in a mammal, the method comprising administering to said mammal a compound of formula I or Ib, as defined in any one of Claims 1 to 4, or a pharmaceutically-acceptable derivative thereof.

22. A method of sterilising an object, the method comprising applying to said object a compound of formula I or Ib, as defined in any one of Claims 1 to 4, or a pharmaceutically-acceptable derivative thereof.

23. A method of preserving an inorganic or organic material, said method comprising contacting, combining or mixing said material with a compound of formula I or Ib, as defined in any one of Claims 1 to 4, or a pharmaceutically-acceptable derivative thereof.

24. A pharmaceutical formulation including a compound of formula I or Ib, as defined in any one of Claims 1 to 4, or a pharmaceutically-acceptable derivative
thereof, in admixture with a pharmaceutically acceptable adjuvant, diluent or carrier

A combination product comprising

(A) a compound of formula I or Ib, as defined in any one of Claims 1 to 4, or a pharmaceutically-acceptable derivative thereof, and

(B) a conventional antimicrobial agent,

wherein each of components (A) and (B) is formulated in admixture with a pharmaceutically-acceptable adjuvant, diluent or carrier

A combination product according to Claim 25, wherein the conventional antimicrobial agent is a penicillin (optionally combined with a β-lactamase inhibitor), a cephalosporin, a monobactam, a carbapenem (optionally combined with a renal enzyme inhibitor), a 1-oxa-β-lactam, a tetracycline, an aminoglycoside, a macrolide, a ketolide, a lincosamine, clindamycin, clindamycin 2-phosphate, a phenicol, a steroid, a glycopeptide, an oxazolidinone, a streptogramin (or a combination of streptogramms), a polymyxin, a iysostaphin, an actinomycin, actinonin, 7-aminoact unomycin D, antimycin A, antipain, bacitracin, cyclosporin A, echinomycin, a gramicidin, myxothiazol, nisin, paracelsin, valinomycin, viomycin, a hpoptide, a sulfonamide (optionally in combination with trimethoprim), trimethoprim, isoniazid, rifampicin, rifabutin, pyrazinamide, ethambutol, streptomycin, dapsone, clofazimine, a nitroimidazole, a nitrofuran, a quinolone, azaseπne, bestatin, D-cycloserine, 1,10-phenanthrone, 6-diazo-5-oxo-L-norleucine, L-alanyl-L-1-aminoethy-phosphonic acid, an aureolic acid, a benzochinoide a coumarazine-glycoside, irgasan, an epipolythiodioxopiperazine, cerulenin a glucosamine, staurospoπne, a macro lactam, a taxoid, a statin, a polyphenols acid, lasalocid A, lonomycin A, monensin, nigericin, salinomycin, fusaric acid, blasticidine S, nikkomycin, nourseothricin, puromycin, adenine 9-β-D-arabinofuranoside, 5-azacytidine, cordycepin, formycin A, tubercidin, tunicamycin, methenamine (hexamine), pieπcidin A, stigmatellin, actidione, anisomycin, apramycin, coumermycin A1, L(+)lactic acid, a cytochaisasin, emetine, lonomycin, anazole antifungal, a polyene antifungal, gorsefulvin, caspofungin or flucytosine (which latter two agents are optionally employed in combination) or an allylamine antifungal
27. A compound of formula I or Ib, as defined in any one of Claims 1 to 4, or a pharmaceutically-acceptable derivative thereof, or a combination product according to Claim 25 or Claim 26, for use in the treatment of tuberculosis, anthrax, abscesses, acne vulgaris, actinomycosis, bacillary dysentery, bacterial conjunctivitis, bacterial keratitis, botulism, Buruli ulcer, bone and joint infections, bronchitis (acute or chronic), brucellosis, bum wounds, cat scratch fever, cellulitis, chancroid, cholangitis, cholecystitis, cutaneous diphtheria, cystic fibrosis, cystitis, diffuse panbronchiolitis, diphtheria, dental caries, diseases of the upper respiratory tract, empyema, endocarditis, endometritis, enteric fever, enteritis, epididymitis, epiglottitis, erysipelas, erysipeloïd, erythrasma, eye infections, furuncles, Gardnerella vaginitis, gastrointestinal infections, genital infections, gingivitis, gonorrhea, granuloma inguinale, Haverhill fever, infected burns, infections following dental operations, infections in the oral region, infections associated with prostheses, intraabdominal abscesses, Legionnaire's disease, leprosy, leptospirosis, listeriosis, liver abscesses, Lyme disease, lymphogranuloma venerium, mastitis, mastoiditis, meningitis and infections of the nervous system, mycetoma, nocardiosis, non-specific urethritis, ophthalmia, osteomyelitis, otitis, orchitis, pancreatitis, paronychia, pelveoperitonitis, peritonitis, peritonitis with appendicitis, pharyngitis, phlegmons, pinta, plague, pleural effusion, pneumonia, postoperative wound infections, postoperative gas gangrene, prostatitis, pseudo-membranous colitis, psittacosis, pulmonary emphysema, pyelonephritis, pyoderma, Q fever, rat-bite fever, reticulosis, Ritter's disease, salmonellosis, salpingitis, septic arthritis, septic infections, septicameia, sinusitis, skin infections, syphilis, systemic infections, tonsillitis, toxic shock syndrome, trachoma, tularaemia, typhoid, typhus, urethritis, wound infections, yaws, aspergillosis, candidiasis, cryptococcosis, favus, histoplasmosis, intertrigo, mucormycosis, tinea, onychomycosis, pityriasis versicolor, ringworm, sporotrichosis, or infections with MSSA, MRSA, Staph, *epidermidis*, *Strept. agalactiae*, *Strept. pyogenes*, *Escherichia coli*, *Klebs. pneumoniae*, *Klebs. oxytoca*, *Pr. mirabilis*, *Pr. rettgeri*, *Pr. vulgaris*, *Haemophilis influenzae*, *Enterococcus faecalis* or *Enterococcus faecium*.

28. The use of a compound of formula I or Ib, as defined in any one of Claims 1 to 4, or a pharmaceutically-acceptable derivative thereof, or a combination product according to Claim 25 or Claim 26, for the preparation of a medicament for the

29. A method of treating tuberculosis, anthrax, abscesses, acne vulgaris, actinomycosis, bacillary dysentry, bacterial conjunctivitis, *bacterial* keratitis, botulism, Buruli ulcer, bone and joint infections, bronchitis (acute or chronic), brucellosis, burn wounds, cat scratch fever, cellulitis, chancroid, cholangitis, cholecystitis, cutaneous diphtheria, cystic fibrosis, cystitis, diffuse
peribronchiolitis, diphtheria, dental caries, diseases of the upper respiratory tract, empyema, endocarditis, endometritis, enteric fever, enteritis, epididymitis, epiglottitis, erysipelas, erysipeloid, erythrasma, eye infections, furuncles, Gardnerella vaginitis, gastrointestinal infections, genital infections, gingivitis, gonorrhoea, granuloma inguinale, Haverhill fever, infected burns, infections following dental operations, infections in the oral region, infections associated with prostheses, intraabdominal abscesses, Legionnaire's disease, leprosy, leptospirosis, listeriosis, liver abscesses, Lyme disease, lymphogranuloma venerium, mastitis, mastoiditis, meningitis and infections of the nervous system, mycetoma, nocardiosis, non-specific urethritis, ophthalmia, osteomyelitis, otitis, orchitis, pancreatitis, paronychia, pelveoperitonitis, peritonitis, peritonitis with appendicitis, pharyngitis, phlegmons, pinta, plague, pleural effusion, pneumonia, postoperative wound infections, postoperative gas gangrene, prostatitis, pseudo-membranous colitis, psittacosis, pulmonary emphysema, pyelonephritis, pyoderma, Q fever, rat-bite fever, reticulosis, Ritter's disease, salmonellosis, salpingitis, septic arthritis, septic infections, septicamβia, sinusitis, skin infections, syphilis, systemic infections, tonsillitis, toxic shock syndrome, trachoma, tularaemia, typhoid; typhus, urethritis, wound infections, yaws, aspergillosis, candidiasis, cryptococcosis, favus, histoplasmosis, intertrigo, mucormycosis, tinea, onychomycosis, pityriasis versicolor, ringworm, sporotrichosis, or infections with MSSA, MRSA, Staph. epidermidis, Strept. agalactiae, Strept pyogenes, Escherichia coli, Klebs. pneumoniae, Klebs. oxytoca, Pr. mirabilis, Pr. rettgeri, Pr. vulgaris, Haemophilis influenzae, Enterococcus faecalis or Enterococcus faecium in a mammal, the method comprising administering to said mammal a compound of formula I or lb, as defined in any one of Claims 1 to 4 , or a pharmaceutically-acceptable derivative thereof, or a combination product according to Claim 25 or Claim 26.

30. A method of reducing the dose of conventional antimicrobial agent required to treat a microbial infection, the method comprising co-administering a compound of formula I or lb, as defined in any one of Claims 1 to 4 , or a pharmaceutically-acceptable derivative thereof.

31. Use of a compound of formula I or lb, as defined in any one of Claims 1 to 4 , for the preparation of a medicament for the treatment of a protozoal disease.
32. A method of treating a protozoal disease in a mammal, the method comprising
administering to said mammal a compound of formula I or Ib, as defined in any
one of Claims 1 to 4.

33. A process for the preparation of a compound of formula I, as defined in Claim 1,
which process comprises

(a) for compounds of formula I in which $X^2$ represents N, reaction of a compound of
formula II,

$$\text{II}$$

wherein $L^1$ represents a leaving group and $R^1$, $R^2$ and $X^1$ are as defined in
Claim 1, with a compound of formula III,

$$\text{III}$$

wherein $R^3$, $R^4$ and A are as defined in Claim 1;

(b) for compounds of formula I in which $X^2$ represents O, reaction of a compound of
formula IV,

$$\text{IV}$$

wherein $R^1$, $R^2$ and $X^1$ are as defined in Claim 1, with a compound of formula V

$$\text{V}$$

wherein $R^3$ and A are as defined in Claim 1 and $L^1$ is as defined above; or

(c) deprotection of a protected derivative of a compound of formula I as defined in
Claim 1.
INTERNATIONAL SEARCH REPORT

A. CLASSIFICATION OF SUBJECT MATTER

Inv. C07D401/12 C07D403/12 C07D413/12 A61P31/00 A61K31/4184
A61K31/423 A61K31/4709

According to International Patent Classification (IPC) or to both national classification and IPC.

B. DOCUMENTS CONSIDERED TO BE RELEVANT

Page 261, left-hand column, paragraph 1, compound 20

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<table>
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<tr>
<th>Category</th>
<th>Citation of document with indication where appropriate, of the relevant passages</th>
<th>Relevant to claim No</th>
</tr>
</thead>
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<td>X</td>
<td>US 2 623 878 A (HANS ISLER ET AL) 30 December 1952 (1952-12-30) column 1, line 38; example 22 column 1, line 20 - line 25</td>
<td>1-33</td>
</tr>
</tbody>
</table>
INTERNATIONAL SEARCH REPORT

Box No II Observations where certain claims were found unsearchable (Continuation of Item 2 of first sheet)

This international search report has not been established in respect of certain claims under Art IC 17(2)(a); for the following reasons:

1. Claims Nos. 11-13, 19-23, 29-30 and 32 are directed to a method of treatment of the human/animal body, and the search has been carried out and based on the alleged effects of the compound/composition.

2. Claims Nos. because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. Claims Nos. because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 64(a);

Box No III Observations where unity of invention is lacking (Continuation of Item 3 of first sheet)

This international Searching Authority found multiple inventions in this international application, as follows:

1. As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fees.

3. As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid specifically claims Nos.

4. No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims, it is covered by claims Nos.

Remark on Protest:

- The additional search fees were accompanied by the applicant’s protest and, where applicable, the payment of a protest fee.
- The additional search fees were accompanied by the applicant’s protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- No protest accompanied the payment of additional search fees.
<table>
<thead>
<tr>
<th>Patent document cited in search report</th>
<th>Publication date</th>
<th>Patent family member(s)</th>
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<tr>
<td>US 2623878 A</td>
<td>30-12-1952</td>
<td>NONE</td>
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