

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
19 June 2008 (19.06.2008)

PCT

(10) International Publication Number
WO 2008/071981 A1

(51) International Patent Classification:
C07D 493/04 (2006.01) *C07D 513/04* (2006.01)
C07D 498/04 (2006.01)

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(21) International Application Number:
PCT/GB2007/004794

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(22) International Filing Date:
13 December 2007 (13.12.2007)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/870,162 15 December 2006 (15.12.2006) US

(81) Designated States (*unless otherwise indicated, for every
kind of national protection available*): AE, AG, AL, AM,
AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH,
CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG,
ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL,
IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK,
LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW,
MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL,
PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SV, SY,
TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA,
ZM, ZW.

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(84) Designated States (*unless otherwise indicated, for every
kind of regional protection available*): ARIPO (BW, GH,
GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM,
ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM),
European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI,
FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, MT, NL, PL,
PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM,
GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

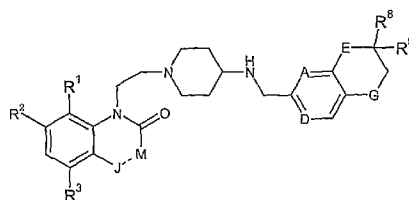
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Published:
— with international search report

(54) Title: PIPERIDINES FOR THE TREATMENT OF BACTERIAL INFECTIONS



(I)

(57) Abstract: The present invention relates to compounds of Formula (I), and pharmaceutically acceptable salts thereof, to their use in the treatment of bacterial infections, and to their methods preparation.

PIPERIDINES FOR THE TREATMENT OF BACTERIAL INFECTIONS

Field of Invention

The present invention relates to novel piperidines, pharmaceutical compositions thereof, and methods of use. In addition, the present invention relates to therapeutic methods for the treatment of bacterial infections.

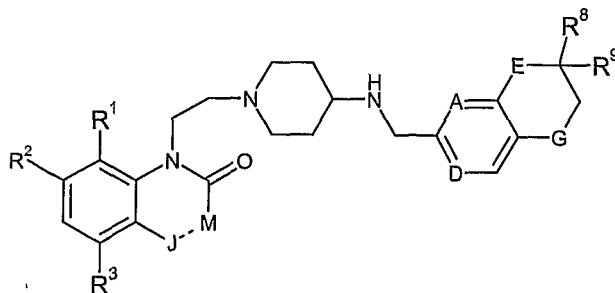
Background

The international health community continues to express serious concern that the evolution of antibacterial resistance will result in strains against which currently available antibacterial agents will be ineffective. For example, resistant strains of Gram-positive pathogens such as methicillin-resistant *Staphylococcus aureus* (MRSA), methicillin-resistant coagulase-negative staphylococci (MRCNS), penicillin-resistant *Streptococcus pneumoniae* and multiple resistant *Enterococcus faecium* are both difficult to treat and difficult to eradicate. Consequently, in order to overcome the threat of widespread multi-drug resistant organisms, there is an on-going need to develop new antibiotics, particularly those with either a novel mechanism of action and/or containing new pharmacophoric groups.

Summary

In accordance with the present invention, the applicants have hereby discovered compounds that possess the ability to act as antimicrobials. Accordingly, the present invention relates to compounds that demonstrate antibacterial activity, processes for their preparation, pharmaceutical compositions containing them as the active ingredient, their use as medicaments, and their use in the manufacture of medicaments for use in the treatment of bacterial infections in warm-blooded animals such as humans.

Accordingly the present invention provides a compound of Formula (I):



Formula (I)

or a pharmaceutically acceptable salt thereof, wherein

A is selected from CH and N;

D is selected from C-R⁷ and N;

wherein at least one of **A** and **D** is carbon;

E is selected from O, NH, and S,

wherein:

- i) **E** is NH if R⁸ and R⁹ together from =O; and
- ii) **E** is O or S if R⁸ and R⁹ are each H;

G is selected from O and S;

J is selected from C-R⁴ and N-R⁵;

M is selected from CH, N, and CH₂;

wherein at least one of **J** and **M** is carbon, and wherein:

- i) if **J** is carbon, the J-M bond is a double bond, and
- ii) if **J** is nitrogen, the J-M bond is a single bond and **M** is CH₂;

R¹ is selected from H, halo, cyano, C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, -OR^{1a}, and -N(R^{1a})₂, wherein said C₁₋₆alkyl, C₂₋₆alkenyl, and C₂₋₆alkynyl are optionally substituted with one or more R¹⁰;

R^{1a} in each occurrence is independently selected from H and C₁₋₆alkyl, wherein said C₁₋₆alkyl is optionally substituted with one or more R¹⁰;

R² is selected from H, halo, cyano, C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, -OR^{2a}, and -N(R^{2a})₂, wherein said C₁₋₆alkyl, C₂₋₆alkenyl, and C₂₋₆alkynyl are optionally substituted with one or more R²⁰;

R^{2a} in each occurrence is independently selected from H and C_{1-6} alkyl, wherein said C_{1-6} alkyl is optionally substituted with one or more R^{20} ;

R^3 is selected from H, halo, cyano, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, $-OR^{3a}$, and $-N(R^{3a})_2$, wherein said C_{1-6} alkyl is optionally substituted with one or more R^{30} ;

R^{3a} is selected from H and C_{1-6} alkyl, wherein said C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl are optionally substituted with one or more R^{30} ;

R^4 is selected from halo, cyano, $-CO_2H$, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, carbocyclyl, heterocyclyl, $-OR^{4a}$, $-N(R^{4a})_2$, and $-S(O)_2R^{4b}$, wherein said C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, carbocyclyl, and heterocyclyl are optionally substituted with one or more R^{40} ;

R^{4a} in each occurrence is independently selected from H and C_{1-6} alkyl, wherein said C_{1-6} alkyl is optionally substituted with one or more R^{40} ;

R^{4b} is C_{1-6} alkyl, wherein said C_{1-6} alkyl may be optionally substituted with one or more R^{40} ;

R^5 is selected from C_{1-6} alkyl, carbocyclyl, heterocyclyl, and $-SO_2R^{5b}$, wherein said C_{1-6} alkyl, carbocyclyl, and heterocyclyl are optionally substituted with one or more R^{50} ;

R^{5b} is C_{1-6} alkyl, wherein said C_{1-6} alkyl is optionally substituted with one or more R^{50} ;

R^7 is selected from H, halo, cyano, C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl, wherein said C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl are optionally substituted with one or more R^{70} ;

R^8 and R^9 are each hydrogen, or R^8 and R^9 together form $=O$; and

R^{10} , R^{20} , R^{30} , R^{40} , R^{50} , and R^{70} in each occurrence are each, independently, selected from halo, hydroxy, cyano, $-CO_2H$, C_{1-6} alkoxy, C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl.

Detailed Description of the Invention

In this specification the prefix C_{x-y} as used in terms such as C_{x-y}alkyl and the like (where x and y are integers) indicates the numerical range of carbon atoms that are present in the group; for example, C₁₋₄alkyl includes C₁alkyl (methyl), C₂alkyl (ethyl), C₃alkyl (propyl and isopropyl) and C₄alkyl (butyl, 1-methylpropyl, 2-methylpropyl, and *t*-butyl).

As used herein the term “alkyl” refers to both straight and branched chain saturated hydrocarbon radicals having the specified number of carbon atoms. References to individual alkyl groups such as “propyl” are specific for the straight chain version only and references to individual branched chain alkyl groups such as ‘isopropyl’ are specific for the branched chain version only.

The term “alkenyl” refers to both straight and branched chain hydrocarbon radicals having the specified number of carbon atoms and containing at least one carbon-carbon double bond. For example, “C₂₋₈alkenyl” includes, but is not limited to, groups such as C₂₋₆alkenyl, C₂₋₄alkenyl, ethenyl, 2-propenyl, 2-methyl-2-propenyl, 3-butenyl, 4-pentenyl, 5-hexenyl, 2-heptenyl, and 2-methyl-1-heptenyl.

The term “alkynyl” refers to both straight and branched chain hydrocarbon radicals having the specified number of carbon atoms and containing at least one carbon-carbon triple bond. For example, “C₂₋₈alkynyl” includes, but is not limited to, groups such as C₂₋₆alkynyl, C₂₋₄alkynyl, ethynyl, 2-propynyl, 2-methyl-2-propynyl, 3-butylnyl, 4-pentylnyl, 5-hexynyl, 2-heptynyl, and 4-methyl-5-heptynyl.

The term “halo” refers to fluoro, chloro, and bromo.

Where optional substituents are chosen from “one or more” groups it is to be understood that this definition includes all substituents being chosen from one of the specified groups or the substituents being chosen from two or more of the specified groups.

The term “carbocyclyl” refers to a saturated, partially saturated, or unsaturated, mono or bicyclic carbon ring that contains 3-12 ring atoms, wherein one or more -CH₂- groups can optionally be replaced by a corresponding number of -C(O)- groups. In one aspect, the term

“carbocyclyl” may refer to a monocyclic ring containing 3 to 6 ring atoms or a bicyclic ring containing 9 or 10 atoms. In another aspect, the term “carbocyclyl” may refer to a monocyclic ring containing 5 or 6 atoms. Illustrative examples of “carbocyclyl” include, but are not limited to, adamantyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclopentenyl, cyclohexyl, cyclohexenyl, 1-oxocyclopentyl, phenyl, naphthyl, tetralinyl, indanyl or 1-oxoindanyl. A particular example of a “carbocyclyl” group is phenyl.

The term “heterocyclyl” refers to a saturated, partially saturated or unsaturated, mono or bicyclic ring containing 4-12 ring atoms of which at least one ring atom is selected from nitrogen, sulfur, and oxygen, and which may, unless otherwise specified, be carbon or nitrogen linked, wherein a -CH₂- group can optionally be replaced by a -C(O)-. Ring sulfur atoms may be optionally oxidized to form S-oxides. Ring nitrogen atoms may be optionally oxidized to form N-oxides. Illustrative examples of the term “heterocyclyl” include, but are not limited to, 1,3-benzodioxolyl, 3,5-dioxopiperidinyl, imidazolyl, indolyl, isoquinolone, isothiazolyl, isoxazolyl, morpholino, 2-oxopyrrolidinyl, 2-oxo-1,3-thiazolidinyl, piperazinyl, piperidyl, pyranyl, pyrazolyl, pyridinyl, pyrrolyl, pyrrolidinyl, pyrrolinyl, pyrimidyl, pyrazinyl, pyrazolyl, pyridazinyl, 4-pyridone, quinolyl, tetrahydropyranyl, thiazolyl, thiadiazolyl, thiazolidinyl, thienyl, thiomorpholino, thiophenyl, pyridine-*N*-oxide and quinoline-*N*-oxide. In one aspect of the invention the term “heterocyclyl” may refer to a saturated, partially saturated or unsaturated, monocyclic ring containing 5 or 6 atoms of which at least one atom is selected from nitrogen, sulfur, and oxygen, and may, unless otherwise specified, be carbon or nitrogen linked, and a ring nitrogen atom may be optionally oxidized to form an N-oxide.

Where a particular R group is present in a compound of Formula (I) more than once, it is intended that each selection for that R group is independent at each occurrence.

Unless specifically stated, the bonding atom of a group may be any suitable atom of that group; for example, propyl includes prop-1-yl and prop-2-yl.

As used herein, the term "optionally substituted," indicates that substitution is optional and therefore it is possible for the designated group to be either substituted or unsubstituted. In the event a substitution is desired, any number of hydrogens on the designated group may be

replaced with a selection from the indicated substituents, provided that the normal valency of the atoms on a particular substituent is not exceeded, and that the substitution results in a stable compound which exhibits an antibacterial effect.

As used herein, the term "pharmaceutically acceptable" refers to those compounds, materials, compositions, and/or dosage forms which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of human beings and animals without excessive toxicity, irritation, allergic response, or other problem or complication, commensurate with a reasonable benefit/risk ratio.

As used herein, the phrase "effective amount" means an amount of a compound or composition which is sufficient enough to significantly and positively modify the symptoms and/or conditions to be treated (e.g., provide a positive clinical response). The effective amount of an active ingredient for use in a pharmaceutical composition will vary with the particular condition being treated, the severity of the condition, the duration of the treatment, the nature of concurrent therapy, the particular active ingredient(s) being employed, the particular pharmaceutically-acceptable excipient(s)/carrier(s) utilized, and like factors within the knowledge and expertise of the attending physician.

Compounds and substituent definitions of the present invention have been named with the aid of ACD/Name by ACD/Labs®.

Compounds of Formula (I) may form stable pharmaceutically acceptable acid or base salts, and in such cases administration of a compound as a salt may be appropriate, and pharmaceutically acceptable salts may be made by conventional methods well-known in the art.

A suitable pharmaceutically acceptable salt of a compound of the invention is, for example, an acid-addition salt of a compound of the invention which is sufficiently basic, for example, an acid-addition salt with, for example, an inorganic or organic acid, for example hydrochloric, hydrobromic, sulfuric, phosphoric, trifluoroacetic, citric or maleic acid. In addition a suitable pharmaceutically acceptable salt of a compound of the invention which is sufficiently acidic is an alkali metal salt, for example a sodium or potassium salt, an alkaline

earth metal salt, for example a calcium or magnesium salt, an ammonium salt or a salt with an organic base which affords a physiologically-acceptable cation, for example a salt with methylamine, dimethylamine, trimethylamine, piperidine, morpholine or tris-(2-hydroxyethyl)amine.

Some compounds of Formula (I) may have chiral centres and/or geometric isomeric centres (E- and Z- isomers), and it is to be understood that the invention encompasses all such optical, diastereoisomers and geometric isomers that possess antibacterial activity. The invention further relates to any and all tautomeric forms of the compounds of Formula (I) that possess antibacterial activity.

It is also to be understood that certain compounds of Formula (I) can exist in solvated as well as unsolvated forms such as, for example, hydrated forms. It is to be understood that the invention encompasses all such solvated forms which possess antibacterial activity.

Additional embodiments of the invention are as follows. These additional embodiments relate to compounds of Formula (I). Such specific substituents may be used, where appropriate, with any of the definitions, claims or embodiments defined hereinbefore or hereinafter.

A

In one aspect, **A** may be N.

In another aspect, **A** may be CH.

D

In one aspect, **D** may be N.

In another aspect, **D** may be CH.

A and D

In one aspect, **A** may be N; and
D may be CH.

In another aspect, **A** may be CH; and
D may be N.

E, G, R⁸, and R⁹

In one aspect, **E** and **G** may each be O; and
R⁸ and **R⁹** may each be H.

In another aspect, **E** may be NH;
G may be selected from O and S; and
R⁸ and **R⁹** may together form =O;

In still another aspect, **E** may be NH;
G may be S; and
R⁸ and **R⁹** may together form =O.

In yet another aspect, **E** may be NH;
G may be O; and
R⁸ and **R⁹** may together form =O.

J and M

In one aspect, **J** may be N-R⁵;
M may be CH₂;
R⁵ may be selected from C₁₋₆alkyl, carbocyclyl, and -SO₂R^{5b}, wherein said C₁₋₆alkyl and carbocyclyl may be optionally substituted with one or more R⁵⁰;
R^{5b} may be C₁₋₆alkyl; and
R⁵⁰ in each occurrence may be selected from hydroxy and C₂₋₆alkenyl.

In another aspect, **J** may be N-R⁵;
M may be CH₂;
R⁵ may be selected from methyl, ethyl, propyl, cyclopropyl and methanesulfonyl, wherein said methyl, ethyl, propyl, and cyclopropyl may be optionally substituted with one or more R⁵⁰; and
R⁵⁰ in each occurrence may be selected from hydroxy and ethenyl.

In still another aspect, **J** may be N-R⁵;

M may be CH₂;

R⁵ may be selected from methyl, cyclopropyl, allyl, hydroxypropyl, and methylsulfonyl.

In yet another aspect, **J** may be C-R⁴;

M may be CH;

R⁴ may be C₁₋₆alkyl.

In a further aspect, **J** may be C-R⁴;

M may be CH; and

R⁴ may be methyl.

R¹

In one aspect, **R**¹ may be H.

R²

In one aspect, **R**² may be selected from halo, cyano, and -OR^{2a}; and

R^{2a} may be C₁₋₆alkyl.

In another aspect, **R**² may be selected from fluoro, cyano, and methoxy.

In still another aspect, **R**² may be halo.

In yet another aspect, **R**² may be -OR^{2a}; and

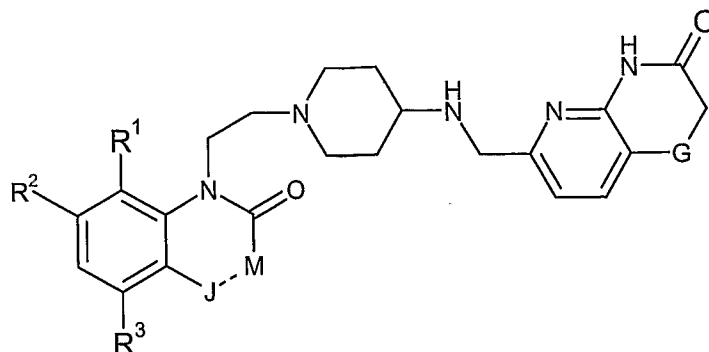
R^{2a} may be C₁₋₆alkyl.

In yet another aspect, **R**² may be cyano.

R³

In one aspect, **R**³ may be H.

In one aspect, the compound of Formula (I), may be a compound of Formula (Ia):



Formula (Ia)

or a pharmaceutically acceptable salt thereof, wherein **R¹**, **R²**, **R³**, **G**, **J**, and **M** are as defined hereinabove.

In a further aspect of the compound of Formula (Ia), or a pharmaceutically acceptable salt thereof,

G may be selected from O and S;

J may be selected from C-R⁴ and N-R⁵;

M may be selected from CH and CH₂;

wherein at least one of **J** and **M** is carbon, and wherein:

- i) if **J** is carbon, the J-M bond is a double bond, and
- ii) if **J** is nitrogen, the J-M bond is a single bond and **M** is CH₂;

R¹ may be H;

R² may be selected from halo, cyano, and -OR^{2a};

R^{2a} may be C₁₋₆alkyl;

R³ may be H;

R⁴ may be C₁₋₆alkyl;

R⁵ may be selected from C₁₋₆alkyl, carbocyclyl, and -SO₂R^{5b}, wherein said C₁₋₆alkyl and carbocyclyl may be optionally substituted with one or more R⁵⁰;

R^{5b} may be C₁₋₆alkyl; and

R⁵⁰ in each occurrence may be selected from hydroxy and C₂₋₆alkenyl.

In still a further aspect of the compound of Formula (Ia), or a pharmaceutically acceptable salt thereof,

G may be selected from O and S;

J may be selected from C-R⁴ and N-R⁵;

M may be selected from CH and CH₂;

wherein at least one of J and M is carbon, and wherein:

- i) if J is carbon, the J-M bond is a double bond, and
- ii) if J is nitrogen, the J-M bond is a single bond and M is CH₂;

R¹ may be H;

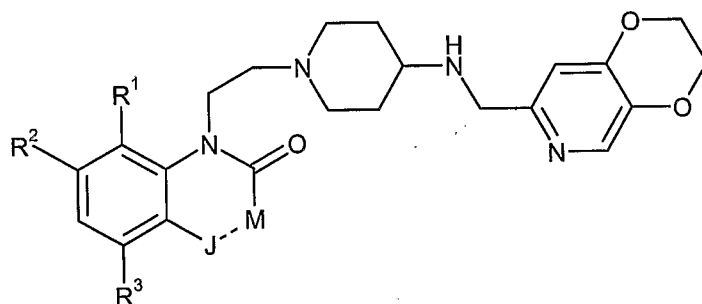
R² may be selected from fluoro, cyano, and methoxy;

R³ may be H;

R⁴ may be methyl;

R⁵ may be selected from methyl, cyclopropyl, allyl, hydroxypropyl, and methylsulfonyl.

In another aspect, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, may be of Formula (Ib):



Formula (Ib)

wherein **R**¹, **R**², **R**³, **J**, and **M** are as defined hereinabove.

In a further aspect of the compound of Formula (Ib) or a pharmaceutically acceptable salt thereof,

J may be selected from C-R⁴ and N-R⁵;

M may be selected from CH and CH₂;

wherein at least one of J and M is carbon, and wherein:

- i) if J is carbon, the J-M bond is a double bond, and
- ii) if J is nitrogen, the J-M bond is a single bond and M is CH₂;

R¹ may be H;

R² may be selected from halo, cyano, and -OR^{2a};

R^{2a} may be C_{1-6} alkyl;

R^3 may be H;

R^4 may be C_{1-6} alkyl;

R^5 may be selected from C_{1-6} alkyl, carbocyclyl, and $-SO_2R^{5b}$, wherein said C_{1-6} alkyl and carbocyclyl may be optionally substituted with one or more R^{50} ;

R^{5b} may be C_{1-6} alkyl; and

R^{50} in each occurrence may be selected from hydroxy and C_{2-6} alkenyl.

In still a further aspect of the compound of Formula (Ib), or a pharmaceutically acceptable salt thereof,

J may be selected from C- R^4 and N- R^5 ;

M may be selected from CH and CH_2 ;

wherein at least one of J and M is carbon, and wherein:

- i) if J is carbon, the J-M bond is a double bond, and
- ii) if J is nitrogen, the J-M bond is a single bond and M is CH_2 ;

R^1 may be H;

R^2 may be selected from fluoro, cyano, and methoxy;

R^3 may be H;

R^4 may be methyl;

R^5 may be selected from methyl, cyclopropyl, allyl, hydroxypropyl, and methylsulfonyl.

In another aspect, the present invention provides compounds of Formulas (I) as illustrated by the Examples, each of which provides a further independent aspect of the invention.

Biological Activity

The compounds of Formula (I) are of interest due to their antibacterial effects. The ability of the invention compounds disclosed herein to achieve an antibacterial effect may be demonstrated by the following test.

Bacterial Susceptibility Testing Methods

Compounds were tested for antimicrobial activity by susceptibility testing in liquid media in a 96 well format. Compounds were dissolved in dimethylsulfoxide and tested in 10 doubling dilutions in the susceptibility assays. The organisms used in the assay were grown overnight

on suitable agar media and then suspended in a liquid medium appropriate for the growth of the organism. The suspension was a 0.5 McFarland and a further 1 in 10 dilution was made into the same liquid medium to prepare the final organism suspension in 100 μ L. Plates were incubated under appropriate conditions at 37 °C for 24 hours prior to reading. The Minimum Inhibitory Concentration (MIC) was determined as the lowest drug concentration able to reduce growth by 80% or more.

Compounds were evaluated against a panel of Gram-positive species, including *Staphylococcus aureus*, *Streptococcus pneumoniae*, *Streptococcus pyogenes*, and *Enterococcus faecium*. In addition, compounds were evaluated against a panel of Gram-negative species including *Haemophilus influenzae*, *Escherichia coli* and *Moraxella catarrhalis*. Compounds of the present invention have MIC's less than or equal to 8 μ g/ml versus one or more of the organisms named above.

The compound of Example 13 had an MIC of 0.13 (mg/L) against *Staphylococcus aureus* and an MIC of 0.5 (mg/L) against *Escherichia coli*.

Thus, in one aspect there is provided a compound of Formula (I), or a pharmaceutically acceptable salt thereof, for use as a medicament.

In still another aspect, there is provided the use a compound of Formula (I), or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for use in the treatment of a bacterial infection in a warm-blooded animal such as man.

In still another aspect, there is provided the use a compound of Formula (I), or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for use in the treatment of a bacterial infection in a warm-blooded animal such as man.

In yet another aspect, there is provided the use of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for use in the treatment of a bacterial infection caused by one or more pathogenic organisms such as *Acinetobacter baumannii*, *Aeromonas hydrophila*, *Bacillus anthracis*, *Bacteroides fragilis*, *Bordetella pertussis*, *Burkholderia cepacia*, *Chlamydia pneumoniae*, *Citrobacter freundii*,

Clostridium difficile, *Enterobacter cloacae*, *Enterococcus faecalis*, *Enterococcus faecium*, *Enterobacter aerogenes*, *Escherichia coli*, *Fusobacterium necrophorum*, *Haemophilus influenzae*, *Haemophilus parainfluenzae*, *Haemophilus somnus*, *Klebsiella oxytoca*, *Klebsiella pneumoniae*, *Legionella pneumophila*, *Listeria monocytogenes*, *Moraxella catarrhalis*, *Morganella morganii*, *Mycoplasma pneumoniae*, *Neisseria gonorrhoeae*, *Neisseria meningitidis*, *Pasteurella multocida*, *Proteus mirabilis*, *Proteus vulgaris*, *Pseudomonas aeruginosa*, *Salmonella typhi*, *Salmonella typhimurium*, *Serratia marcesens*, *Shigella flexneria*, *Shigella dysenteriae*, *Staphylococcus aureus*, *Staphylococcus epidermidis*, *Staphylococcus haemolyticus*, *Staphylococcus intermedius*, *Staphylococcus saprophyticus*, *Stenotrophomonas maltophilia*, *Streptococcus agalactiae*, *Streptococcus mutans*, *Streptococcus pneumoniae*, and *Streptococcus pyogenes*, in a warm-blooded animal such as man.

In a further aspect, there is provided the use of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for use in the treatment of an infection such as bronchitis, *C. difficile* colitis, cervicitis, endocarditis, gonococcal urethritis, inhalation Anthrax, intra-abdominal infections, meningitis, osteomyelitis, otitis media, pharyngitis, pneumonia, prostatitis, septicemia, sinusitis, skin and soft tissue infections, and urinary tract infections, in a warm-blooded animal such as man.

In still a further aspect, there is provided the use of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for use in the treatment of a bacterial infection, wherein the bacteria is of a genus selected from *Aeromonas*, *Acinetobacter*, *Bacillus*, *Bacteroides*, *Bordetella*, *Burkholderia*, *Chlamydophila*, *Citrobacter*, *Clostridium*, *Enterobacter*, *Enterococcus*, *Escherichia*, *Flavobacterium*, *Fusobacterium*, *Haemophilus*, *Klebsiella*, *Legionella*, *Listeria*, *Morganella*, *Moraxella*, *Mycoplasma*, *Neisseria*, *Pasteurella*, *Peptococci*, *Peptostreptococci*, *Prevotella*, *Proteus*, *Salmonella*, *Pseudomonas*, *Serratia*, *Shigella*, *Stenotrophomonas*, *Streptococcus*, and *Staphylococcus*, in a warm-blooded animal such as man.

In another aspect, there is provided a method for treating a bacterial infection in a warm-blooded animal such as man, said method comprising administering to said animal an effective amount of a compound of formula (I), or a pharmaceutically acceptable salt thereof.

In still another aspect, there is provided a method for treating a bacterial infection caused by one or more pathogenic organisms such as *Acinetobacter baumannii*, *Aeromonas hydrophila*, *Bacillus anthracis*, *Bacteroides fragilis*, *Bordetella pertussis*, *Burkholderia cepacia*, *Chlamydia pneumoniae*, *Citrobacter freundii*, *Clostridium difficile*, *Enterobacter cloacae*, *Enterococcus faecalis*, *Enterococcus faecium*, *Enterobacter aerogenes*, *Escherichia coli*, *Fusobacterium necrophorum*, *Haemophilus influenzae*, *Haemophilus parainfluenzae*, *Haemophilus somnus*, *Klebsiella oxytoca*, *Klebsiella pneumoniae*, *Legionella pneumophila*, *Listeria monocytogenes*, *Moraxella catarrhalis*, *Morganella morganii*, *Mycoplasma pneumoniae*, *Neisseria gonorrhoeae*, *Neisseria meningitidis*, *Pasteurella multocida*, *Proteus mirabilis*, *Proteus vulgaris*, *Pseudomonas aeruginosa*, *Salmonella typhi*, *Salmonella typhimurium*, *Serratia marcescens*, *Shigella flexneria*, *Shigella dysenteriae*, *Staphylococcus aureus*, *Staphylococcus epidermidis*, *Staphylococcus haemolyticus*, *Staphylococcus intermedius*, *Staphylococcus saprophyticus*, *Stenotrophomonas maltophilia*, *Streptococcus agalactiae*, *Streptococcus mutans*, *Streptococcus pneumoniae*, and *Streptococcus pyogenes*, in a warm-blooded animal such as man, said method comprising administering to said animal an effective amount of a compound of Formula (I), or a pharmaceutically acceptable salt thereof.

In yet another aspect, there is provided a method for treating a bacterial infection such as bronchitis, *C. difficile* colitis, cervicitis, endocarditis, gonococcal urethritis, inhalation Anthrax, intra-abdominal infections, meningitis, osteomyelitis, otitis media, pharyngitis, pneumonia, prostatitis, septicemia, sinusitis, skin and soft tissue infections, and urinary tract infections, in a warm-blooded animal such as man, said method comprising administering to said animal an effective amount of a compound of Formula (I), or a pharmaceutically acceptable salt thereof.

In a further aspect, there is provided a method for treating a bacterial infection, wherein the bacteria is of a genus selected from *Aeromonas*, *Acinetobacter*, *Bacillus*, *Bacteroides*, *Bordetella*, *Burkholderia*, *Chlamydia*, *Citrobacter*, *Clostridium*, *Enterobacter*, *Enterococcus*, *Escherichia*, *Flavobacterium*, *Fusobacterium*, *Haemophilus*, *Klebsiella*, *Legionella*, *Listeria*, *Morganella*, *Moraxella*, *Mycoplasma*, *Neisseria*, *Pasteurella*, *Peptococci*, *Peptostreptococci*, *Prevotella*, *Proteus*, *Salmonella*, *Pseudomonas*, *Serratia*,

Shigella, *Stenotrophomonas*, *Streptococcus*, and *Staphylococcus*, in a warm-blooded animal such as man, said method comprising administering to said animal an effective amount of a compound of Formula (I), or a pharmaceutically acceptable salt thereof.

In still a further aspect, there is provided a compound of Formula (I), or a pharmaceutically acceptable salt thereof, for use in treating a bacterial infection in a warm-blooded animal, such as man.

In another aspect, there is provided a compound of Formula (I), or a pharmaceutically acceptable salt thereof, for use in treating a bacterial infection caused by one or more pathogenic organisms such as *Acinetobacter baumannii*, *Aeromonas hydrophila*, *Bacillus anthracis*, *Bacteroides fragilis*, *Bordetella pertussis*, *Burkholderia cepacia*, *Chlamydia pneumoniae*, *Citrobacter freundii*, *Clostridium difficile*, *Enterobacter cloacae*, *Enterococcus faecalis*, *Enterococcus faecium*, *Enterobacter aerogenes*, *Escherichia coli*, *Fusobacterium necrophorum*, *Haemophilus influenzae*, *Haemophilus parainfluenzae*, *Haemophilus somnus*, *Klebsiella oxytoca*, *Klebsiella pneumoniae*, *Legionella pneumophila*, *Listeria monocytogenes*, *Moraxella catarrhalis*, *Morganella morganii*, *Mycoplasma pneumoniae*, *Neisseria gonorrhoeae*, *Neisseria meningitidis*, *Pasteurella multocida*, *Proteus mirabilis*, *Proteus vulgaris*, *Pseudomonas aeruginosa*, *Salmonella typhi*, *Salmonella typhimurium*, *Serratia marcescens*, *Shigella flexneria*, *Shigella dysenteriae*, *Staphylococcus aureus*, *Staphylococcus epidermidis*, *Staphylococcus haemolyticus*, *Staphylococcus intermedius*, *Staphylococcus saprophyticus*, *Stenotrophomonas maltophilia*, *Streptococcus agalactiae*, *Streptococcus mutans*, *Streptococcus pneumoniae*, and *Streptococcus pyogenes*, in a warm-blooded animal such as man.

In still another aspect, there is provided a compound of Formula (I), or a pharmaceutically acceptable salt thereof, for use in treating infections such as bronchitis, *C. difficile* colitis, cervicitis, endocarditis, gonococcal urethritis, inhalation Anthrax, intra-abdominal infections, meningitis, osteomyelitis, otitis media, pharyngitis, pneumonia, prostatitis, septicemia, sinusitis, skin and soft tissue infections, and urinary tract infections, in a warm-blooded animal such as man.

In yet another aspect, there is provided a compound of Formula (I), or a pharmaceutically acceptable salt thereof, for use in treating a bacterial infection, wherein the bacteria is of a genus selected from *Aeromonas*, *Acinetobacter*, *Bacillus*, *Bacteroides*, *Bordetella*, *Burkholderia*, *Chlamydophila*, *Citrobacter*, *Clostridium*, *Enterobacter*, *Enterococcus*, *Escherichia*, *Flavobacterium*, *Fusobacterium*, *Haemophilus*, *Klebsiella*, *Legionella*, *Listeria*, *Morganella*, *Moraxella*, *Mycoplasma*, *Neisseria*, *Pasteurella*, *Peptococci*, *Peptostreptococci*, *Prevotella*, *Proteus*, *Salmonella*, *Pseudomonas*, *Serratia*, *Shigella*, *Stenotrophomonas*, *Streptococcus*, and *Staphylococcus*, and *Munnheimia*, in a warm-blooded animal such as man.

In one aspect, the terms "infection" and "bacterial infection" may refer to a bacterial infection caused by *Acinetobacter baumannii*. In another aspect, the terms "infection" and "bacterial infection" may refer to a bacterial infection caused by *Aeromonas hydrophila*. In still another aspect, the terms "infection" and "bacterial infection" may refer to a bacterial infection caused by *Bacillus anthracis*. In yet another aspect, the terms "infection" and "bacterial infection" may refer to a bacterial infection caused by *Bacteroides fragilis*. In a further aspect, the terms "infection" and "bacterial infection" may refer to a bacterial infection caused by *Bordetella pertussis*. In still a further aspect, the terms "infection" and "bacterial infection" may refer to a bacterial infection caused by *Burkholderia cepacia*. In yet a further aspect, the terms "infection" and "bacterial infection" may refer to a bacterial infection caused by *Chlamydia pneumoniae*. In one aspect, the terms "infection" and "bacterial infection" may refer to a bacterial infection caused by *Citrobacter freundii*. In another aspect, the terms "infection" and "bacterial infection" may refer to a bacterial infection caused by *Clostridium difficile*. In still another aspect, the terms "infection" and "bacterial infection" may refer to a bacterial infection caused by *Enterobacter cloacae*. In yet another aspect, the terms "infection" and "bacterial infection" may refer to a bacterial infection caused by *Enterococcus faecalis*. In a further aspect, the terms "infection" and "bacterial infection" may refer to a bacterial infection caused by *Enterococcus faecium*. In still a further aspect, the terms "infection" and "bacterial infection" may refer to a bacterial infection caused by *Enterobacter aerogenes*. In yet a further aspect, the terms "infection" and "bacterial infection" may refer to a bacterial infection caused by *Escherichia coli*. In one aspect, the terms "infection" and "bacterial infection" may refer to a bacterial infection caused by *Fusobacterium necrophorum*. In another aspect, the terms "infection" and "bacterial infection" may refer to a bacterial infection caused by

Haemophilus influenzae. In still another aspect, the terms “infection” and “bacterial infection” may refer to a bacterial infection caused by *Haemophilus parainfluenzae*. In yet another aspect, the terms “infection” and “bacterial infection” may refer to a bacterial infection caused by *Haemophilus somnus*. In a further aspect, the terms “infection” and “bacterial infection” may refer to a bacterial infection caused by *Klebsiella oxytoca*. In still a further aspect, the terms “infection” and “bacterial infection” may refer to a bacterial infection caused by *Klebsiella pneumoniae*. In yet a further aspect, the terms “infection” and “bacterial infection” may refer to a bacterial infection caused by *Legionella pneumophila*. In one aspect, the terms “infection” and “bacterial infection” may refer to a bacterial infection caused by *Listeria monocytogenes*. In another aspect, the terms “infection” and “bacterial infection” may refer to a bacterial infection caused by *Moraxella catarrhalis*. In still another aspect, the terms “infection” and “bacterial infection” may refer to a bacterial infection caused by *Morganella morganii*. In yet another aspect, the terms “infection” and “bacterial infection” may refer to a bacterial infection caused by *Mycoplasma pneumoniae*. In a further aspect, the terms “infection” and “bacterial infection” may refer to a bacterial infection caused by *Neisseria gonorrhoeae*. In still a further aspect, the terms “infection” and “bacterial infection” may refer to a bacterial infection caused by *Neisseria meningitidis*. In yet a further aspect, the terms “infection” and “bacterial infection” may refer to a bacterial infection caused by *Pasteurella multocida*. In one aspect, the terms “infection” and “bacterial infection” may refer to a bacterial infection caused by *Proteus mirabilis*. In another aspect, the terms “infection” and “bacterial infection” may refer to a bacterial infection caused by *Proteus vulgaris*. In still another aspect, the terms “infection” and “bacterial infection” may refer to a bacterial infection caused by *Pseudomonas aeruginosa*. In yet another aspect, the terms “infection” and “bacterial infection” may refer to a bacterial infection caused by *Salmonella typhi*. In a further aspect, the terms “infection” and “bacterial infection” may refer to a bacterial infection caused by *Salmonella typhimurium*. In still a further aspect, the terms “infection” and “bacterial infection” may refer to a bacterial infection caused by *Serratia marcesens*. In yet a further aspect, the terms “infection” and “bacterial infection” may refer to a bacterial infection caused by *Shigella flexneria*. In one aspect, the terms “infection” and “bacterial infection” may refer to a bacterial infection caused by *Shigella dysenteriae*. In another aspect, the terms “infection” and “bacterial infection” may refer to a bacterial infection caused by *Staphylococcus aureus*. In still another aspect, the terms “infection” and “bacterial infection” may refer to a bacterial infection caused by *Staphylococcus epidermidis*.

In yet another aspect, the terms “infection” and “bacterial infection” may refer to a bacterial infection caused by *Staphylococcus haemolyticus*. In a further aspect, the terms “infection” and “bacterial infection” may refer to a bacterial infection caused by *Staphylococcus intermedius*. In still a further aspect, the terms “infection” and “bacterial infection” may refer to a bacterial infection caused by *Staphylococcus saprophyticus*. In yet a further aspect, the terms “infection” and “bacterial infection” may refer to a bacterial infection caused by *Stenotrophomonas maltophilia*. In one aspect, the terms “infection” and “bacterial infection” may refer to a bacterial infection caused by *Streptococcus agalactiae*. In another aspect, the terms “infection” and “bacterial infection” may refer to a bacterial infection caused by *Streptococcus mutans*. In a still another aspect, the terms “infection” and “bacterial infection” may refer to a bacterial infection caused by *Streptococcus pneumoniae*. In yet another aspect, the terms “infection” and “bacterial infection” may refer to a bacterial infection caused by *Streptococcus pyogenes*.

In one aspect, the terms “infection and “bacterial infection” may refer to a bacterial infection caused by a bacteria of the genus *Aeromonas*. In another aspect, the terms “infection and “bacterial infection” may refer to a bacterial infection caused by a bacteria of the genus *Acinetobacter*. In still another aspect, the terms “infection and “bacterial infection” may refer to a bacterial infection caused by a bacteria of the genus *Bacillus*. In yet another aspect, the terms “infection and “bacterial infection” may refer to a bacterial infection caused by a bacteria of the genus *Bacteroides*. In a further aspect, the terms “infection and “bacterial infection” may refer to a bacterial infection caused by a bacteria of the genus *Bordetella*. In still a further aspect, the terms “infection and “bacterial infection” may refer to a bacterial infection caused by a bacteria of the genus *Burkholderia*. In yet a further aspect, the terms “infection and “bacterial infection” may refer to a bacterial infection caused by a bacteria of the genus *Chlamydophila*. In one aspect, the terms “infection and “bacterial infection” may refer to a bacterial infection caused by a bacteria of the genus *Citrobacter*. In another aspect, the terms “infection and “bacterial infection” may refer to a bacterial infection caused by a bacteria of the genus *Clostridium*. In still another aspect, the terms “infection and “bacterial infection” may refer to a bacterial infection caused by a bacteria of the genus *Enterobacter*. In yet another aspect, the terms “infection and “bacterial infection” may refer to a bacterial infection caused by a bacteria of the genus *Enterococcus*. In a further aspect, the terms “infection and “bacterial infection” may refer to a bacterial infection caused by a bacteria of

the genus *Escherichia*. In still a further aspect, the terms “infection and “bacterial infection” may refer to a bacterial infection caused by a bacteria of the genus *Flavobacterium*. In yet a further aspect, the terms “infection and “bacterial infection” may refer to a bacterial infection caused by a bacteria of the genus *Fusobacterium*. In one aspect, the terms “infection and “bacterial infection” may refer to a bacterial infection caused by a bacteria of the genus *Haemophilus*. In one aspect, the terms “infection and “bacterial infection” may refer to a bacterial infection caused by a bacteria of the genus *Klebsiella*. In another aspect, the terms “infection and “bacterial infection” may refer to a bacterial infection caused by a bacteria of the genus *Legionella*. In still another aspect, the terms “infection and “bacterial infection” may refer to a bacterial infection caused by a bacteria of the genus *Listeria*. In yet another aspect, the terms “infection and “bacterial infection” may refer to a bacterial infection caused by a bacteria of the genus *Morganella*. In a further aspect, the terms “infection and “bacterial infection” may refer to a bacterial infection caused by a bacteria of the genus *Moraxella*. In still a further aspect, the terms “infection and “bacterial infection” may refer to a bacterial infection caused by a bacteria of the genus *Mycoplasma*. In yet a further aspect, the terms “infection and “bacterial infection” may refer to a bacterial infection caused by a bacteria of the genus *Neisseria*. In one aspect, the terms “infection and “bacterial infection” may refer to a bacterial infection caused by a bacteria of the genus *Pasteurella*. In another aspect, the terms “infection and “bacterial infection” may refer to a bacterial infection caused by a bacteria of the genus *Peptococci*. In still another aspect, the terms “infection and “bacterial infection” may refer to a bacterial infection caused by a bacteria of the genus *Peptostreptococci*. In yet another aspect, the terms “infection and “bacterial infection” may refer to a bacterial infection caused by a bacteria of the genus *Prevotella*. In a further aspect, the terms “infection and “bacterial infection” may refer to a bacterial infection caused by a bacteria of the genus *Proteus*. In still a further aspect, the terms “infection and “bacterial infection” may refer to a bacterial infection caused by a bacteria of the genus *Pseudomonas*. In still another aspect, the terms “infection and “bacterial infection” may refer to a bacterial infection caused by a bacteria of the genus *Salmonella*. In yet a further aspect, the terms “infection and “bacterial infection” may refer to a bacterial infection caused by a bacteria of the genus *Serratia*. In one aspect, the terms “infection and “bacterial infection” may refer to a bacterial infection caused by a bacteria of the genus *Shigella*. In yet another aspect, the terms “infection and “bacterial infection” may refer to a bacterial infection caused by a bacteria of the genus *Staphylococcus*. In another aspect, the terms “infection and “bacterial infection”

may refer to a bacterial infection caused by a bacteria of the genus *Stenotrophomonas*. In still another aspect, the terms “infection” and “bacterial infection” may refer to a bacterial infection caused by a bacteria of the genus *Streptococcus*.

In one aspect, the terms “infection” and “bacterial infection” may refer to a gynecological infection. In another aspect the terms “infection” and “bacterial infection” may refer to a respiratory tract infection (RTI). In still another, the terms “infection” and “bacterial infection” may refer to a sexually transmitted disease. In yet another aspect, the terms “infection” and “bacterial infection” may refer to a urinary tract infection. In a further aspect, the terms “infection” and “bacterial infection” may refer to acute exacerbation of chronic bronchitis (ACEB). In yet a further aspect, the terms “infection” and “bacterial infection” may refer to acute otitis media. In one aspect, the terms “infection” and “bacterial infection” may refer to acute sinusitis. In another aspect, the terms “infection” and “bacterial infection” may refer to an infection caused by drug resistant bacteria. In still another aspect, the terms “infection” and “bacterial infection” may refer to catheter-related sepsis. In yet another aspect, the terms “infection” and “bacterial infection” may refer to chancroid. In a further aspect, the terms “infection” and “bacterial infection” may refer to chlamydia. In still a further aspect, the terms “infection” and “bacterial infection” may refer to community-acquired pneumonia (CAP). In yet a further aspect, the terms “infection” and “bacterial infection” may refer to complicated skin and skin structure infection. In one aspect, the terms “infection” and “bacterial infection” may refer to uncomplicated skin and skin structure infection. In another aspect, the terms “infection” and “bacterial infection” may refer to endocarditis. In still another aspect, the terms “infection” and “bacterial infection” may refer to febrile neutropenia. In yet another aspect, the terms “infection” and “bacterial infection” may refer to gonococcal cervicitis. In a further aspect, the terms “infection” and “bacterial infection” may refer to gonococcal urethritis. In still a further aspect, the terms “infection” and “bacterial infection” may refer to hospital-acquired pneumonia (HAP). In yet another aspect, the terms “infection” and “bacterial infection” may refer to osteomyelitis. In a further aspect, the terms “infection” and “bacterial infection” may refer to sepsis. In still a further aspect, the terms “infection” and “bacterial infection” may refer to syphilis.

In a further aspect, there is provided a pharmaceutical composition comprising a compound of Formula (I), or a pharmaceutically acceptable salt thereof, and at least one pharmaceutically acceptable carrier, diluent, or excipient

The compositions of the invention may be in a form suitable for oral use (for example as tablets, lozenges, hard or soft capsules, aqueous or oily suspensions, emulsions, dispersible powders or granules, syrups or elixirs), for topical use (for example as creams, ointments, gels, or aqueous or oily solutions or suspensions), for administration by inhalation (for example as a finely divided powder or a liquid aerosol), for administration by insufflation (for example as a finely divided powder) or for parenteral administration (for example as a sterile aqueous or oily solution for intravenous, subcutaneous, intramuscular or intramuscular dosing or as a suppository for rectal dosing).

The compositions of the invention may be obtained by conventional procedures using conventional pharmaceutical excipients well known in the art. Thus, compositions intended for oral use may contain, for example, one or more coloring, sweetening, flavoring and/or preservative agents.

Suitable pharmaceutically acceptable excipients for a tablet formulation include, for example, inert diluents such as lactose, sodium carbonate, calcium phosphate or calcium carbonate; granulating and disintegrating agents such as corn starch or algenic acid; binding agents such as starch; lubricating agents such as magnesium stearate, stearic acid or talc; preservative agents such as ethyl or propyl *p*-hydroxybenzoate; and anti-oxidants, such as ascorbic acid. Tablet formulations may be uncoated or coated either to modify their disintegration and the subsequent absorption of the active ingredient within the gastrointestinal tract, or to improve their stability and/or appearance, in either case, using conventional coating agents and procedures well known in the art.

Compositions for oral use may be in the form of hard gelatin capsules in which the active ingredient is mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate or kaolin, or as soft gelatin capsules in which the active ingredient is mixed with water or an oil such as peanut oil, liquid paraffin, or olive oil.

Aqueous suspensions generally contain the active ingredient in finely powdered form or in the form of nano or micronized particles together with one or more suspending agents, such as sodium carboxymethylcellulose, methylcellulose, hydroxypropylmethylcellulose, sodium alginate, polyvinyl-pyrrolidone, gum tragacanth and gum acacia; dispersing or wetting agents such as lecithin or condensation products of an alkylene oxide with fatty acids (for example polyoxyethylene stearate), or condensation products of ethylene oxide with long chain aliphatic alcohols, for example heptadecaethyleneoxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol such as polyoxyethylene sorbitol monooleate, or condensation products of ethylene oxide with long chain aliphatic alcohols, for example heptadecaethyleneoxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol such as polyoxyethylene sorbitol monooleate, or condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol anhydrides, for example polyethylene sorbitan monooleate. The aqueous suspensions may also contain one or more preservatives such as ethyl or propyl p-hydroxybenzoate; anti-oxidants such as ascorbic acid); coloring agents; flavoring agents; and/or sweetening agents such as sucrose, saccharine or aspartame.

Oily suspensions may be formulated by suspending the active ingredient in a vegetable oil such as arachis oil, olive oil, sesame oil or coconut oil or in a mineral oil such as liquid paraffin. The oily suspensions may also contain a thickening agent such as beeswax, hard paraffin or cetyl alcohol. Sweetening agents such as those set out above, and flavoring agents may be added to provide a palatable oral preparation. These compositions may be preserved by the addition of an anti-oxidant such as ascorbic acid.

Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water generally contain the active ingredient together with a dispersing or wetting agent, suspending agent and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified by those already mentioned above. Additional excipients such as sweetening, flavoring and coloring agents, may also be present.

The pharmaceutical compositions of the invention may also be in the form of oil-in-water emulsions. The oily phase may be a vegetable oil, such as olive oil or arachis oil, or a mineral oil, such as for example liquid paraffin or a mixture of any of these. Suitable

emulsifying agents may be, for example, naturally-occurring gums such as gum acacia or gum tragacanth, naturally-occurring phosphatides such as soya bean, lecithin, an esters or partial esters derived from fatty acids and hexitol anhydrides (for example sorbitan monooleate) and condensation products of the said partial esters with ethylene oxide such as polyoxyethylene sorbitan monooleate. The emulsions may also contain sweetening, flavoring and preservative agents.

Syrups and elixirs may be formulated with sweetening agents such as glycerol, propylene glycol, sorbitol, aspartame or sucrose, and may also contain a demulcent, preservative, flavoring and/or coloring agent.

The pharmaceutical compositions may also be in the form of a sterile injectable aqueous or oily suspension, which may be formulated according to known procedures using one or more of the appropriate dispersing or wetting agents and suspending agents, which have been mentioned above. A sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally-acceptable diluent or solvent, for example a solution in 1,3-butanediol.

Compositions for administration by inhalation may be in the form of a conventional pressurized aerosol arranged to dispense the active ingredient either as an aerosol containing finely divided solid or liquid droplets. Conventional aerosol propellants such as volatile fluorinated hydrocarbons or hydrocarbons may be used and the aerosol device is conveniently arranged to dispense a metered quantity of active ingredient.

For further information on formulation the reader is referred to Chapter 25.2 in Volume 5 of Comprehensive Medicinal Chemistry (Corwin Hansch; Chairman of Editorial Board), Pergamon Press 1990.

The amount of active ingredient that is combined with one or more excipients to produce a single dosage form will necessarily vary depending upon the host treated and the particular route of administration. For example, a formulation intended for oral administration to humans will generally contain, for example, from 0.5 mg to 4 g of active agent compounded with an appropriate and convenient amount of excipients which may vary from about 5 to

about 98 percent by weight of the total composition. Dosage unit forms will generally contain about 1 mg to about 500 mg of an active ingredient. For further information on Routes of Administration and Dosage Regimes the reader is referred to Chapter 25.3 in Volume 5 of Comprehensive Medicinal Chemistry (Corwin Hansch; Chairman of Editorial Board), Pergamon Press 1990.

In addition to the compounds of the present invention, the pharmaceutical composition of this invention may also contain or be co-administered (simultaneously, sequentially or separately) with one or more known drugs selected from other clinically useful classes of antibacterial agents (for example, macrolides, quinolones, β -lactams or aminoglycosides) and/or other anti-infective agents (for example, an antifungal triazole or amphotericin). These may include carbapenems, for example meropenem or imipenem, to broaden the therapeutic effectiveness. Compounds of this invention may also contain or be co-administered with bactericidal/permeability-increasing protein (BPI) products or efflux pump inhibitors to improve activity against gram negative bacteria and bacteria resistant to antimicrobial agents.

As stated above the size of the dose required for the therapeutic or prophylactic treatment of a particular disease state will necessarily be varied depending on the host treated, the route of administration and the severity of the illness being treated. Preferably a daily dose in the range of 1-50 mg/kg is employed. Accordingly, the optimum dosage may be determined by the practitioner who is treating any particular patient.

In addition to its use in therapeutic medicine, the compound of Formulas (I) and its pharmaceutically acceptable salts are also useful as pharmacological tools in the development and standardization of *in vitro* and *in vivo* test systems for the evaluation of antibacterial effects in laboratory animals such as cats, dogs, rabbits, monkeys, rats and mice, as part of the search for new therapeutic agents.

In any of the above-mentioned pharmaceutical composition, process, method, use, medicament, and manufacturing features of the instant invention, any of the alternate embodiments of the compounds of the invention described herein also apply.

Process

If not commercially available, the necessary starting materials for the procedures such as those described herein may be made by procedures which are selected from standard organic chemical techniques, techniques which are analogous to the synthesis of known, structurally similar compounds, or techniques which are analogous to the described procedure or the procedures described in the Examples.

It is noted that many of the starting materials for synthetic methods as described herein are commercially available and/or widely reported in the scientific literature, or could be made from commercially available compounds using adaptations of processes reported in the scientific literature. The reader is further referred to *Advanced Organic Chemistry*, 5th Edition, by Jerry March and Michael Smith, published by John Wiley & Sons **2001**, for general guidance on reaction conditions and reagents.

It will also be appreciated that in some of the reactions mentioned herein it may be necessary/desirable to protect any sensitive groups in compounds. The instances where protection is necessary or desirable are known to those skilled in the art, as are suitable methods for such protection. Conventional protecting groups may be used in accordance with standard practice (for illustration see T.W. Greene, *Protective Groups in Organic Synthesis*, published by John Wiley and Sons, **1991**).

Examples of suitable protecting groups for a hydroxy group are, for example, an acyl group, for example an alkanoyl group such as acetyl, an aroyl group, for example benzoyl, a silyl group such as trimethylsilyl or an arylmethyl group, for example benzyl. The deprotection conditions for the above protecting groups will necessarily vary with the choice of protecting group. Thus, for example, an acyl group such as an alkanoyl or an aroyl group may be removed, for example, by hydrolysis with a suitable base such as an alkali metal hydroxide, for example lithium or sodium hydroxide. Alternatively a silyl group such as trimethylsilyl may be removed, for example, by fluoride or by aqueous acid; or an arylmethyl group such as a benzyl group may be removed, for example, by hydrogenation in the presence of a catalyst such as palladium-on-carbon.

A suitable protecting group for an amino group is, for example, an acyl group, for example an alkanoyl group such as acetyl, an alkoxycarbonyl group, for example a methoxycarbonyl, ethoxycarbonyl or *t*-butoxycarbonyl group, an arylmethoxycarbonyl group, for example benzyloxycarbonyl, or an aroyl group, for example benzoyl. The deprotection conditions for the above protecting groups necessarily vary with the choice of protecting group. Thus, for example, an acyl group such as an alkanoyl or alkoxycarbonyl group or an aroyl group may be removed for example, by hydrolysis with a suitable base such as an alkali metal hydroxide, for example lithium or sodium hydroxide. Alternatively an acyl group such as a *t*-butoxycarbonyl group may be removed, for example, by treatment with a suitable acid as hydrochloric, sulfuric, phosphoric acid or trifluoroacetic acid and an arylmethoxycarbonyl group such as a benzyloxycarbonyl group may be removed, for example, by hydrogenation over a catalyst such as palladium-on-carbon, or by treatment with a Lewis acid, for example boron *tris*(trifluoroacetate). A suitable alternative protecting group for a primary amino group is, for example, a phthaloyl group, which may be removed by treatment with an alkylamine, for example dimethylaminopropylamine or 2-hydroxyethylamine, or with hydrazine. Another suitable protecting group for an amine is, for example, a cyclic ether such as tetrahydrofuran, which may be removed by treatment with a suitable acid such as trifluoroacetic acid.

The protecting groups may be removed at any convenient stage in the synthesis using conventional techniques well known in the chemical art, or they may be removed during a later reaction step or work-up.

Thus, the present invention also provides that the compounds of the invention and pharmaceutically-acceptable salts and *in vivo* hydrolysable esters thereof, can be prepared by a process (a) to (j); and thereafter if necessary:

- i) removing any protecting groups;
- ii) forming a pro-drug (for example an *in-vivo* hydrolysable ester); and/or
- iii) forming a pharmaceutically-acceptable salt;

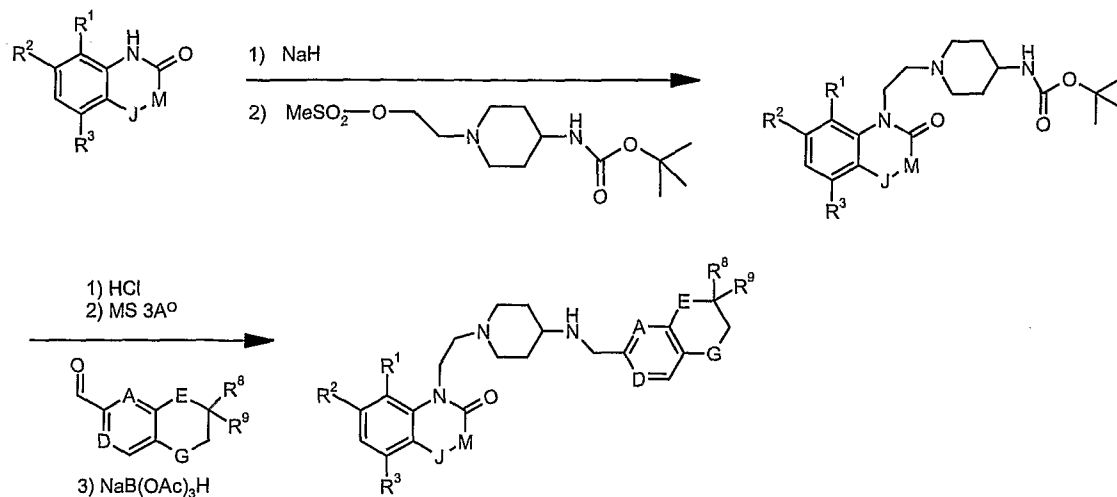
wherein said processes (a) to (j) are as follows (wherein the variables are as defined hereinabove unless otherwise stated):

- a) By modifying a substituent in, or introducing a substituent into another compound of

the invention by using standard chemistry (see for example, Comprehensive Organic Functional Group Transformations (Pergamon), Katritzky, Meth-Cohn & Rees). For example:

- a hydroxy group may be converted into a fluoro group, an acyloxy group (for instance an acetoxy group), an alkoxy group, an amino group, a heterocyclyl group linked through nitrogen (optionally substituted on a carbon other than a carbon atom adjacent to the linking nitrogen ring atom—for instance an optionally substituted amino group). The skilled artisan understands that such reactions of the hydroxy group take place directly (for instance by acylation or Mitsunobu reaction) or through the intermediacy of one or more derivatives (for instance a mesylate or an azide);
 - an acyloxy group may be converted into a hydroxy group or into the groups that may be obtained from a hydroxy group (either directly or through the intermediacy of a hydroxy group); an alkyl halide group may be converted to a hydroxyl group, an amino group, a thioalkyl group or a heterocyclyl group linked through nitrogen; a keto group may be reduced to a hydroxyl group or an saturated alkyl group;
 - A suitable leaving group like bromo or triflate on an aromatic system may be converted into a cyano group by reaction with copper (I) cyanate or by reaction with cyanide ions in the presence of a palladium catalyst;
- b) as depicted for example in Scheme 1, by alkylation of a suitable bicyclic ring system containing a NH group in the ring with a suitable alkylating reagent containing a leaving group (such as an O-mesylate, chloro, bromo or iodo) in the presence of a base. Alkylation may be followed by functional group manipulations and/or further alkylations or reductive aminations;

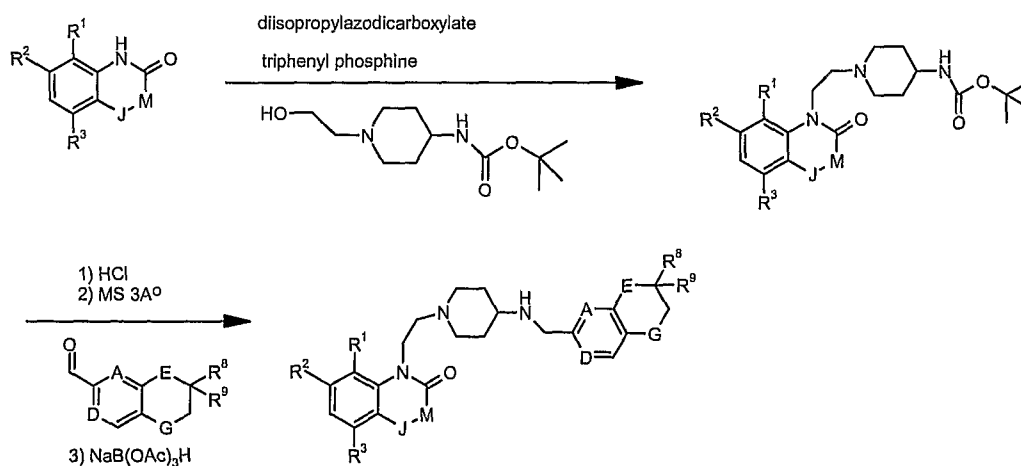
Scheme 1



The aldehydes for the reductive amination steps may be obtained by procedures described in the patent literature, such as PCT Pub. No. WO 2004/048144;

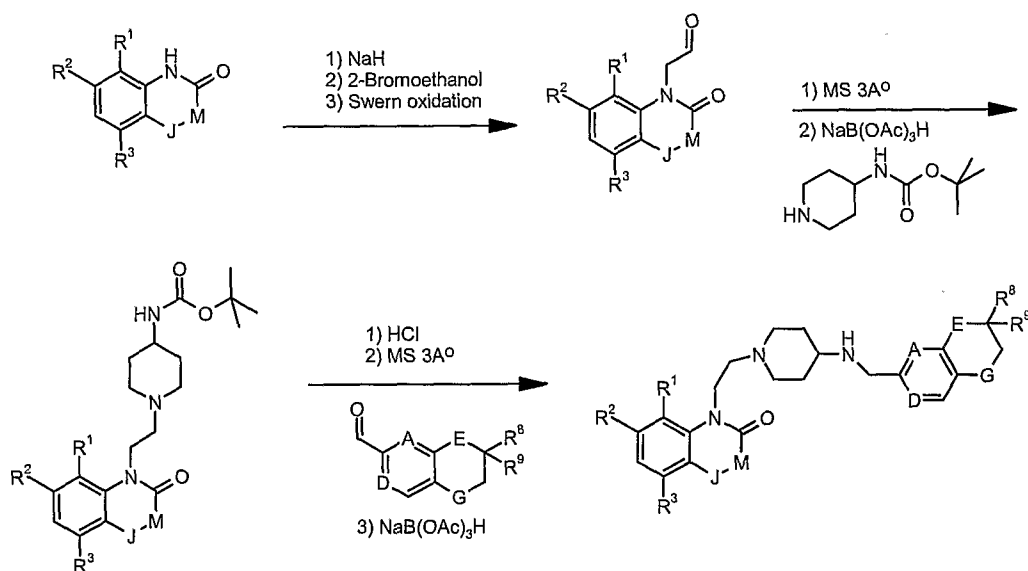
- c) As depicted for example in Scheme 2, by reaction of a suitable bicyclic ring system containing an acidic NH group in the ring with a suitable alcohol under Mitsunobu conditions, followed by deprotection and reductive amination with an aldehyde. This sequence may be followed by functional group manipulations and/or further alkylations or reductive aminations;

Scheme 2

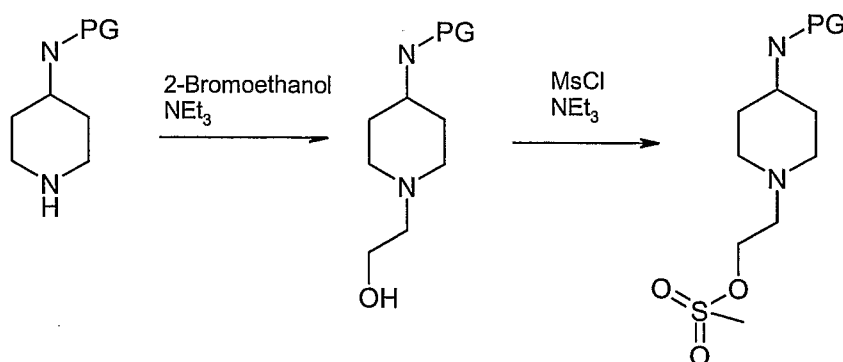


- d) As depicted for example in Scheme 3, by alkylation of a suitable bicyclic ring system containing a NH group in the ring with bromo- or chloroethanol or bromo- or chloroacetaldehyde or with a protected derivative thereof, followed by deprotection and oxidation in case of an alcohol derivative to the aldehyde. The aldehyde may then be subjected to reductive amination, followed by deprotection of the amino group and a second reductive amination step;

Scheme 3

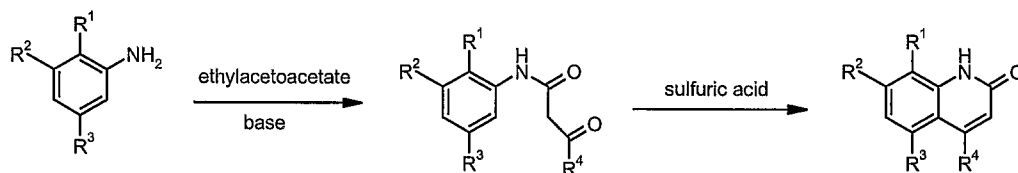


- e) An O-mesylate alkylating reagent may be prepared by alkylation of a suitable protected 4-aminopiperidine derivative with bromoethanol or a derivative thereof in the presence of a base, followed by reaction of the alcohol intermediate with mesyl chloride, in the presence of a base, such as a trialkyl amine or an immobilized version thereof on a resin, as depicted in Scheme 4. It is understood, that such an alkylating reagent is potentially unstable, may represent a mixture with the corresponding chloride (arising from attack of chloride on the mesyl group) and needs to be prepared fresh under careful controlled conditions;

Scheme 4

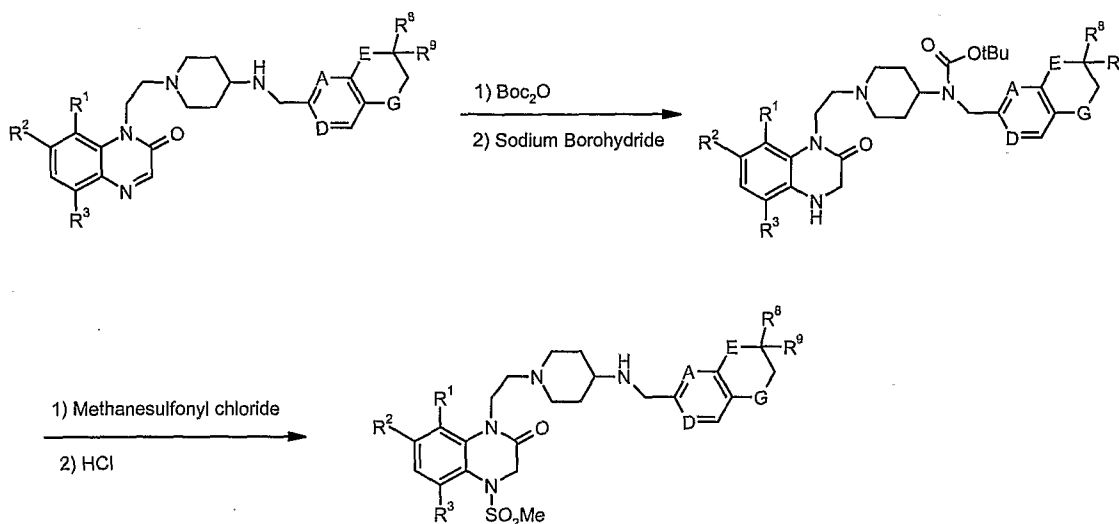
PG= protecting group

- f) 4-Substituted quinolin-2(1*H*)-one derivatives suitable for alkylation as outlined under b) - d) may be prepared by acylation of anilines with ethyl acetoacetate or derivatives thereof, in the presence of base, followed by cyclization under acidic conditions, as depicted for example in Scheme 5;

Scheme 5

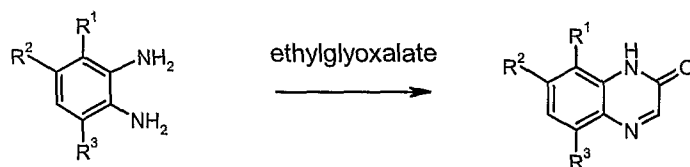
- g) 4-Substituted 2-oxo-3,4-dihydroquinoxalin derivatives may be prepared from quinoxalin-2(1*H*)-ones, which are accessible through the processes described under b)-d). For example, as depicted in Scheme 6, a quinoxalinone derivative may be protected at the secondary amine functionality, then reduced with a suitable reducing agent, such as sodium borohydride and then alkylated, for example with mesyl chloride, followed by deprotection. Alternatively, the 4-substituent may be further functionalized after the alkylation step;

Scheme 6



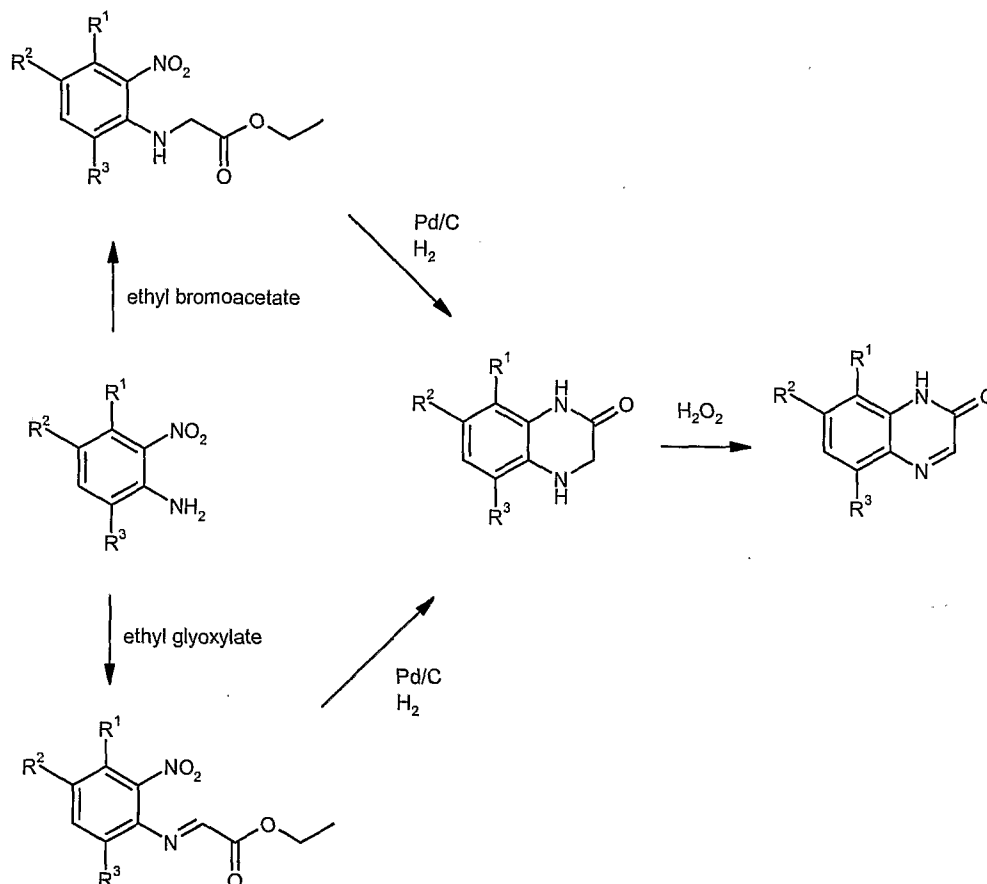
g) Quinoxalin-2(1*H*)-ones derivatives needed for process g) may be obtained by condensation of 1,2-diaminoarenes with ethylglyoxalate, as depicted in Scheme 7.

Scheme 7



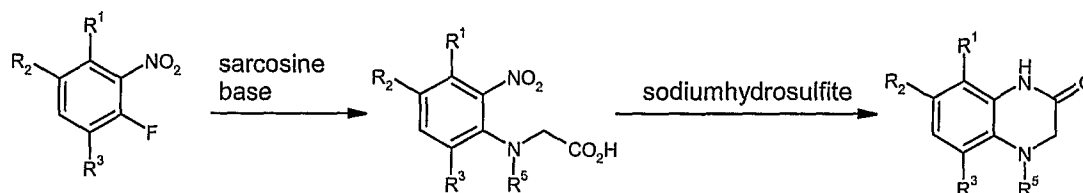
i) Alternatively, quinoxalin-2(1*H*)-ones may be obtained by oxidation of 3,4-dihydroquinoxalin-2(1*H*)-ones with oxidants such as hydrogenperoxide. The 3,4-dihydroquinoxaline-2(1*H*)-ones may be prepared by reaction of a nitroaniline derivative with bromoacetic acid esters or with ethylglyoxylate, followed by cyclization under reducing conditions, as for example depicted in Scheme 8.

Scheme 8



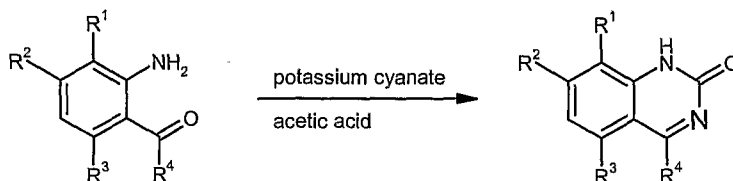
Alternatively, a substituent may be introduced into the 4-position of 3,4-dihydroquinoxalin-2(1H)-ones earlier in the process, and processes described under b)-d) may be employed to arrive at final products. For example, as depicted in Scheme 9, 2-fluoronitroanilines may be reacted with sarcosine and base to provide the arylated N-R⁵ glycine derivatives, which may be reduced and cyclized with a reducing agents such as sodium hydrosulfite.

Scheme 9



- j) 4-Substituted quinazolin-2(1*H*)-ones may be prepared by reaction of 2-amino acetophenone derivatives with potassium cyanide followed by condensation, as depicted for example in Scheme 10.

Scheme 10



With respect to (a)-(j) and Schemes 1-10 above, the removal of any protecting groups, formation of pharmaceutically-acceptable salts and/or formation of in-vivo hydrolysable esters or amides are within the skill of an ordinary organic chemist using standard techniques. Furthermore, details regarding these transformations; for example, the preparation of in-vivo hydrolysable ester prodrugs has been described in the section above on such esters.

When an optically active form of a compound of the invention is required, it may be obtained by carrying out one of the above procedures using a pure enantiomer as a starting material, or by resolution of a mixture of the enantiomers or diastereomers of the final products or chiral intermediates using a standard procedure. The resolution of enantiomers may be achieved by chromatography on a chiral stationary phase, such as a Chiralpak AD column. Consideration has to be given to solubility as well as resolution. Alternatively, resolution may be obtained by preparation and selective crystallization of a diastereomeric salt of a chiral intermediate or chiral product with a chiral acid, such as camphersulfonic acid. Alternatively, a method of stereoselective synthesis may be employed, for example by using a chiral variant of a protection group, a chiral catalyst or a chiral reagent where appropriate in the reaction sequence.

Enzymatic techniques may also be useful for the preparation of optically active compounds and/or intermediates.

Similarly, when a pure regioisomer of a compound of the invention is required, it may be obtained by carrying out one of the above procedures using a pure regioisomer as a starting material, or by resolution of a mixture of the regioisomers or intermediates using a standard procedure.

The skilled organic chemist will be able to use and adapt the information contained and referenced within the above references, and accompanying Examples therein and also the Examples herein, to obtain necessary starting materials and products.

Examples

The invention is now illustrated by but not limited to the following Examples, for which, unless otherwise stated:

- (i) evaporations were carried out by rotary evaporation *in vacuo* and work-up procedures were carried out after removal of residual solids by filtration;
- (ii) temperatures are quoted as °C; operations were carried out at room temperature, that is typically in the range 18-26 °C and without the exclusion of air unless otherwise stated, or unless the skilled person would otherwise work under an inert atmosphere;
- (iii) column chromatography (by the flash procedure) was used to purify compounds and was performed on Merck Kieselgel silica (Art. 9385) unless otherwise stated;
- (iv) in general, the course of reactions was followed by TLC, HPLC, or LC/MS and reaction times are given for illustration only; yields are given for illustration only and are not necessarily the maximum attainable;
- (v) the structure of the end-products of the invention was generally confirmed by NMR and mass spectral techniques. Proton magnetic resonance spectra were generally determined in DMSO-d₆ unless otherwise stated, using a Bruker DRX-300 spectrometer or a Bruker DRX-400 spectrometer, operating at a field strength of 300 MHz, or 400 MHz, respectively. In cases where the NMR spectrum is complex, only diagnostic signals are reported. Chemical shifts are reported in parts per million downfield from tetramethylsilane as an internal standard (δ scale) and peak multiplicities are shown thus: s, singlet; d, doublet; dd, doublet of doublets; dt, doublet of triplets; dm, doublet of multiplets; t, triplet; m, multiplet; br, broad. Fast-atom bombardment (FAB) mass spectral data were generally obtained using a Platform spectrometer (supplied by Micromass) run in electrospray and, where appropriate, either positive ion data or negative ion data were collected or using Agilent 1100 series LC/MSD

equipped with Sedex 75ELSD, and where appropriate, either positive ion data or negative ion data were collected. The lowest mass major ion is reported for molecules where isotope splitting results in multiple mass spectral peaks (for example when chlorine is present). Reverse Phase HPLC was carried out using YMC Pack ODS-AQ (100x20 mmID, S-5 μ particle size, 12 nm pore size) on Agilent instruments;

- (vi) each intermediate was purified to the standard required for the subsequent stage and was characterized in sufficient detail to confirm that the assigned structure was correct; purity was assessed by HPLC, TLC, or NMR and identity was determined by infra-red spectroscopy (IR), mass spectroscopy or NMR spectroscopy as appropriate; and
- (vii) the following abbreviations may be used:

TLC is thin layer chromatography; HPLC is high pressure liquid chromatography; MPLC is medium pressure liquid chromatography; NMR is nuclear magnetic resonance spectroscopy; DMSO is dimethylsulfoxide; CDCl₃ is deuterated chloroform; MeOD is deuterated methanol, i.e. D₃COD; MS is mass spectroscopy; ESP (or ES) is electrospray; EI is electron impact; APCI is atmospheric pressure chemical ionization; THF is tetrahydrofuran; DCM is dichloromethane; MeOH is methanol; DMF is dimethylformamide; EtOAc is ethyl acetate; LC/MS is liquid chromatography/mass spectrometry; h is hour(s); min is minute(s); d is day(s); MTBD is N-methyl-1,5,7-triazabicyclo[4.4.0]dec-5-ene; TFA is trifluoroacetic acid; v/v is ratio of volume/volume; Boc denotes t-butoxycarbonyl; Cbz denotes benzyloxycarbonyl; Bz denotes benzoyl; atm denotes atmospheric pressure; rt denotes room temperature; mg denotes milligram; g denotes gram; μ L denotes microliter; mL denotes milliliter; L denotes liter; μ M denotes micromolar; mM denotes millimolar; M denotes molar; N denotes normal; nm denotes nanometer.

Intermediate 1

tert-Butyl [1-(2-hydroxyethyl)piperidin-4-yl]carbamate

A mixture of *tert*-butyl piperidin-4-ylcarbamate (5 g, 25 mmol), 2-bromoethanol (1.77 mL, 25 mmol) and triethylamine (3.86 mL, 27.5 mmol) in acetonitrile (20 mL) was heated in a sealed tube at 50°C for 16 hours. The solvent was removed under reduced pressure, and the residue was taken up in ethyl acetate (300 mL) and washed with saturated aqueous sodium hydrogen carbonate solution (100 mL). The aqueous phase was back-extracted once with ethyl acetate (100 mL) and the combined organic phases were dried over sodium sulfate and concentrated under reduced pressure. Chromatography on silica gel with dichloromethane/ methanol (4:1)

gave 4.04 g (66% yield) of product as a colourless solid, mp 66°C.

MS (ES): 245.28 (MH⁺) for C₁₂H₂₄N₂O₃

¹H-NMR (DMSO-d₆) δ: 1.33 (m, 2H); 1.36 (s, 9H); 1.62 (m, 2H); 1.92 (t, 2H); 2.32 (t, 2H); 2.77 (m, 2H); 3.17 (m, 1H); 3.43 (m, 2H); 4.34 (t, 1H); 6.73 (d, 1H).

Intermediate 2

2-{4-[(*tert*-Butoxycarbonyl)amino]piperidin-1-yl}ethyl methanesulfonate

A mixture of *tert*-butyl [1-(2-hydroxyethyl)piperidin-4-yl]carbamate (**Intermediate 1**, 1.7 g, 7 mmol) in dry dichloromethane (20 mL) and triethyl amine (1.4 mL, 9.8 mmol) was treated at 0°C with methanesulfonyl chloride (0.65 mL, 8.4 mmol). After 45 minutes the reaction was complete by TLC (chloroform/methanol 6:1, *r_f* ~0.54). Potassium phosphate buffer (pH 7, 1M, 50 mL) was added, dichloromethane was removed under reduced pressure and it was extracted with ice cold ethyl acetate (2 x 100 mL) and dried over sodium sulfate. The solvent was removed under reduced pressure and the crude preparation of the mesylate was used without delay for the next step.

MS (ES): 323.18 (MH⁺) for C₁₃H₂₆N₂O₅S.

Intermediate 3

N-(4-Cyano-2-nitrophenyl)-*N*-methylglycine

A mixture of 4-fluoro-3-nitrobenzonitrile (3.0 g) and sarcosine (2.53 g) with sodium hydrogen carbonate (2.39 g) in water (15 mL) and ethanol (15 mL) was heated at 80°C. After 2 hours, the reaction was concentrated to half its volume and poured into 1M HCl (50 mL). The aqueous solution was extracted with ethyl acetate and then with chloroform. The combined organic phases were dried over sodium sulfate and concentrated under reduced pressure. The residue was suspended in a minimum of dichloromethane and filtered yielding 3.74 g of product.

MS (ES): 236 (MH⁺) for C₁₀H₉N₃O₄

¹H NMR (DMSO-D₆) δ: 2.87 (s, 3H); 4.19 (s, 2H); 7.13 (d, 1H); 7.82 (dd, 1H); 8.29 (d, 1H); 13.03 (s, 1H).

Intermediate 4

1-Methyl-3-oxo-1,2,3,4-tetrahydroquinoxaline-6-carbonitrile

To a solution of sodium hydrosulfite (18.3 g) in water (100 mL) was added a solution of *N*-(4-

cyano-2-nitrophenyl)-*N*-methylglycine (**Intermediate 3**, 3.74 g) in water with potassium carbonate (2.3 g). Additional sodium hydrosulfite (6 g in three portions) was added until the reaction was no longer red. The mixture was neutralized with 1N HCl and extracted with ethyl acetate (four times). The combined organic solution was washed with brine, dried over sodium sulfate and concentrated. When the solvent was reduced to approximately ¼ of its original volume, the precipitate was filtered and washed with ethyl acetate yielding 1.56 g of product.

MS (ES): 188 (MH⁺) for C₁₀H₉N₃O

¹H NMR (DMSO-D₆) δ: 2.86 (s, 3H); 3.89 (s, 2H); 6.77 (d, 1H); 7.00 (s, 1H); 7.32 (dd, 1H); 10.70 (s, 1H).

Intermediate 5

tert-Butyl {1-[2-(7-cyano-4-methyl-2-oxo-3,4-dihydroquinoxalin-1(2*H*)-yl)ethyl]piperidin-4-yl} carbamate

A slurry of 1-methyl-3-oxo-1,2,3,4-tetrahydroquinoxaline-6-carbonitrile (**Intermediate 4**, 1.56 g) in dry dimethylformamide (DMF) (30 mL) was treated at 0 °C with sodium hydride (0.50 g, 60% in oil). The cooling bath was removed and the mixture was stirred for 30 minutes at room temperature. A solution of 2-{4-[(*tert*-butoxycarbonyl)amino]piperidin-1-yl}ethyl methanesulfonate in DMF (**Intermediate 2**, 1 equivalent) was then added and the resulting mixture was stirred over night at room temperature. The solution was diluted with water and ethyl acetate. The organic solution was washed with saturated aqueous sodium hydrogencarbonate solution and brine, dried over sodium sulfate, filtered and concentrated under reduced pressure. Chromatography on silica gel eluting with a gradient of methylene chloride to 4% methanol in methylene chloride gave 3.41 g of the product as a colorless hard foam.

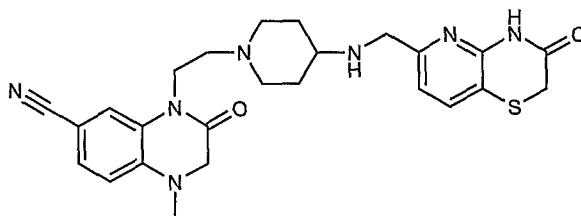
MS (ES): 414 (MH⁺) for C₂₂H₃₁N₅O₃

¹H NMR (CDCl₃) δ: 1.36-1.51 (m, 11H); 1.88-1.99 (m, 2H); 2.15-2.28 (m, 2H); 2.58 (t, 2H); 2.84-2.90 (m, 2H); 2.92 (s, 3H); 3.40-3.57 (m, 1H); 3.89 (s, 2H); 4.04 (t, 2H); 4.45 (s, 1H); 6.67 (d, 1H); 7.31 (dd, 1H); 7.36 (s, 1H).

Intermediate 64-[2-(4-Aminopiperidin-1-yl)ethyl]-1-methyl-3-oxo-1,2,3,4-tetrahydroquinoxaline-6-carbonitrile

A solution of *tert*-butyl {1-[2-(7-cyano-4-methyl-2-oxo-3,4-dihydroquinoxalin-1(2*H*)-yl)ethyl]piperidin-4-yl}carbamate (**Intermediate 5**, 3.41 g) in CH₂Cl₂ (15 mL) was treated at room temperature with TFA (10 mL). After 30 minutes, the reaction mixture was diluted with saturated aqueous sodium hydrogencarbonate solution. The aqueous phase was extracted three times with chloroform and the combined organic phases were dried over sodium sulfate and concentrated under reduced pressure to give 2.90 g of the crude product.

MS (ES): 314 (MH⁺) for C₁₇H₂₃N₅O.

Example 11-Methyl-3-oxo-4-[2-(4-{[(3-oxo-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]thiazin-6-yl)methyl]amino}piperidin-1-yl)ethyl]-1,2,3,4-tetrahydroquinoxaline-6-carbonitrile

A solution of 4-[2-(4-aminopiperidin-1-yl)ethyl]-1-methyl-3-oxo-1,2,3,4-tetrahydroquinoxaline-6-carbonitrile (**Intermediate 6**, 960 mg) and 3-oxo-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]thiazine-6-carbaldehyde (WO 2004/058144) (660 mg) in methanol (15 mL) was heated over 3 Å molecular sieves at 80 °C for 1 hour. The reaction mixture was cooled to 0 °C, and sodium triacetoxy borohydride (1.0 g) was added. The resulting reaction mixture was allowed to warm to room temperature overnight. The mixture was filtered through a 0.45 µm membrane and concentrated to dryness under reduced pressure. The residue was dissolved in ethyl acetate, washed with saturated aqueous sodium hydrogencarbonate solution and brine, dried over sodium sulfate, filtered and concentrated under reduced pressure. Chromatography on silica gel with a gradient of dichloromethane to 20% methanol in dichloromethane. Fractions containing product were collected, concentrated *in vacuo*, dissolved in a minimum of dichloromethane, and precipitated with diethyl ether to yield a colourless solid (175 mg).

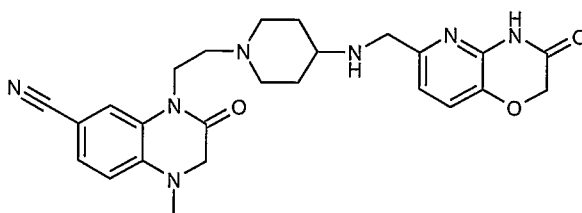
MS (ES): 492 (MH⁺) for C₂₅H₂₉N₇O₂S

¹H NMR (400 MHz, DMSO-D₆) δ: 1.22-1.33 (m, 2H); 1.73-1.84 (m, 2H); 1.95-2.05 (m,

2H); 2.44 (t, 4H); 2.83-2.91 (m, 4H); 3.27-3.32 (m, 1H); 3.53 (s, 2H); 3.76 (s, 2H); 3.91 (s, 2H); 4.03 (t, 2H); 6.83 (d, 1H); 7.10 (d, 1H); 7.42 (dd, 1H); 7.49 (d, 1H); 7.74 (d, 1H); 10.88 (s, 1H).

Example 2

1-Methyl-3-oxo-4-[2-(4-{[(3-oxo-3,4-dihydro-2H-pyrido[3,2-b][1,4]oxazin-6-yl)methyl]amino}piperidin-1-yl)ethyl]-1,2,3,4-tetrahydroquinoxaline-6-carbonitrile



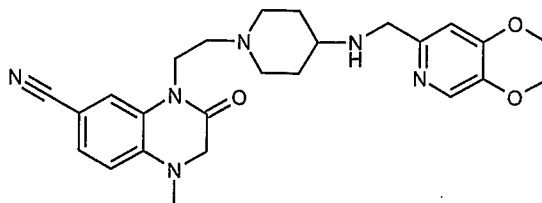
4-[2-(4-Aminopiperidin-1-yl)ethyl]-1-methyl-3-oxo-1,2,3,4-tetrahydroquinoxaline-6-carbonitrile (**Intermediate 6**, 960 mg), 3-oxo-3,4-dihydro-2H-pyrido[3,2-b][1,4]oxazine-6-carbaldehyde (WO 2004/058144) (598 mg) and sodium triacetoxy borohydride (1.0 g) were reacted using a procedure analogous to that described for the synthesis of **Example 1** to give the product a colourless hard foam (572 mg) after chromatography.

MS (ES): 476 (MH⁺) for C₂₅H₂₉N₇O₃

¹H NMR (DMSO-D₆) δ: 1.19-1.30 (m, 2H); 1.77 (d, 2H); 1.99 (t, 2H); 2.42 (t, 3H); 2.82-2.86 (m, 2H); 2.87 (s, 3H); 3.29-3.32 (m, 1H); 3.68 (s, 2H); 3.91 (s, 2H); 4.02 (t, 2H); 4.61 (s, 2H); 6.83 (d, 1H); 7.02 (d, 1H); 7.30 (d, 1H); 7.42 (dd, 1H); 7.50 (d, 1H); 11.17 (s, 1H).

Example 3

4-(2-{4-[(2,3-Dihydro[1,4]dioxino[2,3-c]pyridin-7-yl)methyl]amino}piperidin-1-yl}ethyl)-1-methyl-3-oxo-1,2,3,4-tetrahydroquinoxaline-6-carbonitrile



4-[2-(4-Aminopiperidin-1-yl)ethyl]-1-methyl-3-oxo-1,2,3,4-tetrahydroquinoxaline-6-carbonitrile (**Intermediate 6**, 960 mg), 2,3-dihydro[1,4]dioxino[2,3-c]pyridine-7-

carbaldehyde (560 mg) (WO 2004/058144) and sodium triacetoxy borohydride (1.0 g) were reacted using a procedure analogous to that described for the synthesis of **Example 1** to give the product as a colourless solid (354 mg).

MS (ES): 463 (MH^+) for $C_{25}H_{30}N_6O_3$

1H NMR ($CDCl_3$) δ : 1.39-1.53 (m, 2H); 1.86-1.93 (m, 2H); 2.14 (t, 2H); 2.50-2.60 (m, 3H); 2.88-2.98 (m, 5H); 3.81 (s, 2H); 3.89 (s, 2H); 4.06 (t, 2H); 4.23-4.31 (m, 2H); 4.31-4.34 (m, 2H); 6.66 (d, 1H); 6.83 (s, 1H); 7.27-7.33 (m, 2H); 8.10 (s, 1H).

Intermediate 7

N-(4-Fluoro-2-nitrophenyl)-N-methylglycine

2,5-Difluoro-nitrobenzene (1.65 g), sarcosine (1.40 g) and sodium hydrogen carbonate (1.95 g) were reacted using a procedure analogous to that described for the synthesis of **Intermediate 3** to give 1.86 g of product.

MS (ES): 229 (MH^+) for $C_9H_9FN_2O_4$

1H NMR ($CDCl_3$) δ : 2.95 (s, 3H); 3.87 (s, 2H); 7.15-7.25 (m, 2H); 7.54 (dd, 1H).

Intermediate 8

7-Fluoro-4-methyl-3,4-dihydroquinoxalin-2(1H)-one

To a solution of sodium hydrosulfite (8.8 g) in water (50 mL) was added a solution of *N*-(4-fluoro-2-nitrophenyl)-*N*-methylglycine (**Intermediate 7**, 1.86 g) in water (25 mL) with potassium carbonate (1.2 g). Additional sodium hydrosulfite (8 g, in four portions) until the reaction was no longer red. The mixture was extracted with ethyl acetate (twice). The combined organic solution was washed with brine, dried with sodium sulfated, filtered and concentrated yielding 0.67 g of product.

MS (ES): 181 (MH^+) for $C_9H_9FN_2O$

1H NMR ($DMSO-D_6$) δ : 2.74 (s, 3H); 3.61 (s, 2H); 6.62-6.68 (m, 2H); 6.70-6.75 (m, 1H); 10.51 (s, 1H).

Intermediate 9

tert-Butyl {1-[2-(7-fluoro-4-methyl-2-oxo-3,4-dihydroquinoxalin-1(2H)-yl)ethyl]piperidin-4-yl} carbamate

7-Fluoro-4-methyl-3,4-dihydroquinoxalin-2(1H)-one (**Intermediate 8**, 0.67 g) was reacted with sodium hydride (0.25 g, 60% in oil) and 2-{4-[(*tert*-butoxycarbonyl)amino]piperidin-1-

yl}ethyl methanesulfonate in DMF (**Intermediate 2**, 1 equivalent) using a procedure analogous to that described for the synthesis of **Intermediate 5** to give 1.52 g of the product as a colorless hard foam.

MS (ES): 407 (MH^+) for $C_{21}H_{31}FN_4O_3$

1H NMR ($CDCl_3$) δ : 1.39-1.49 (m, 11H); 1.88 – 1.97 (m, 2H); 2.22 (t, 2H); 2.55 – 2.63 (m, 2H); 2.80 (s, 3H); 2.90 – 2.94 (m, 2H); 3.42 – 3.52 (m, 1H); 3.67 (s, 2H); 3.96 – 4.05 (m, 2H); 4.38 – 4.49 (m, 1H); 6.60 (dd, 1H); 6.73 (td, 1H); 6.81 – 6.89 (m, 1H).

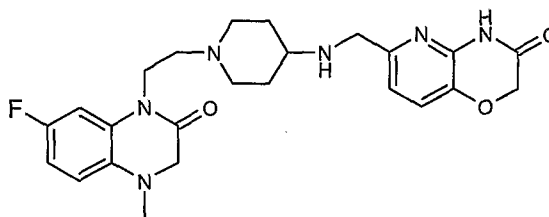
Intermediate 10

1-[2-(4-Aminopiperidin-1-yl)ethyl]-7-fluoro-4-methyl-3,4-dihydroquinoxalin-2(1H)-one
tert-Butyl {1-[2-(7-fluoro-4-methyl-2-oxo-3,4-dihydroquinoxalin-1(2H)-yl)ethyl]piperidin-4-yl}carbamate (**Intermediate 9**, 1.52 g) was treated with TFA (5 mL) using a procedure analogous to that described for the synthesis of **Intermediate 6** to give 1.13 g of the crude product.

MS (ES): 307 (MH^+) for $C_{16}H_{23}FN_4O$

Example 4

6-[(1-[2-(7-Fluoro-4-methyl-2-oxo-3,4-dihydroquinoxalin-1(2H)-yl)ethyl]piperidin-4-yl)amino)methyl]-2H-pyrido[3,2-*b*][1,4]oxazin-3(4H)-one



1-[2-(4-Aminopiperidin-1-yl)ethyl]-7-fluoro-4-methyl-3,4-dihydroquinoxalin-2(1H)-one (**Intermediate 10**, 380 mg), 3-oxo-3,4-dihydro-2H-pyrido[3,2-*b*][1,4]oxazine-6-carbaldehyde (WO 2004/058144) (249 mg) and sodium triacetoxy borohydride (400 mg) were reacted using a procedure analogous to that described for the synthesis of **Example 1** to give the product a colourless hard foam (39 mg) after chromatography.

MS (ES): 469 (MH^+) for $C_{24}H_{29}FN_6O_3$

1H NMR ($CDCl_3$) δ : 1.51-1.66 (m, 2H); 1.90-1.99 (m, 2H); 2.05 (m, 5H); 2.21 (t, 1H); 2.60-2.67 (m, 2H); 2.79 (s, 3H); 3.01-3.08 (m, 2H); 3.67 (s, 2H); 3.86 (s, 2H); 4.03-4.10 (m, 2H); 6.60 (dd, 1H); 6.69-6.77 (m, 1H); 6.87 (dd, 1H); 6.93 (d, 1H); 7.19-7.23 (m, 1H).

Intermediate 11**7-Methoxy-4-methylquinazolin-2(1H)-one**

To a solution of 2-amino-4-methoxyacetophenone (1.07 g) in acetic acid (20 mL) was added potassium cyanate (1.19 g). After stirring overnight, the reaction was poured into water and neutralized with sodium hydrogen carbonate (solid). The mixture was extracted with ethyl acetate and then chloroform. The combined organic phases were washed with brine, dried over sodium sulfated and concentrated under reduced pressure. Chromatography on silica gel with a gradient of methylene chloride to 10% methanol in methylene chloride gave 0.79 g of the product.

MS (ES): 191 (MH^+) for $C_{10}H_{10}N_2O_2$

1H NMR (DMSO- D_6) δ : 2.59 (s, 3H); 3.85 (s, 3H); 6.70 (d, 1H); 6.82 (dd, 1H); 7.87 (d, 1H).

Intermediate 12**tert-Butyl {1-[2-(7-methoxy-4-methyl-2-oxoquinazolin-1(2H)-yl)ethyl]piperidin-4-yl} carbamate**

7-Methoxy-4-methylquinazolin-2(1H)-one (**Intermediate 11**, 0.79 g) was reacted with sodium hydride (0.26 g, 60% in oil) and 2-{4-[(*tert*-butoxycarbonyl)amino]piperidin-1-yl}ethyl methanesulfonate in DMF (**Intermediate 2**, 1 equivalent) using a procedure analogous to that described for the synthesis of **Intermediate 5**. Reverse phase HPLC on a 19 X 100 mm ODO AQ C18 column eluting with a gradient of 0.1% TFA/water to 0.1% TFA/acetonitrile gave 0.60 g of product.

MS (ES): 417 (MH^+) for $C_{22}H_{32}N_4O_4$

1H NMR (CDCl₃) δ : 1.36-1.43 (m, 2H); 1.37-1.47 (m, 9H); 1.89-1.98 (m, 2H); 2.21-2.31 (m, 2H); 2.66-2.70 (m, 2H); 2.71 (s, 2H); 2.87-2.97 (m, 2H); 3.47 (s, 1H); 3.94 (s, 3H); 4.28-4.37 (m, 2H); 4.43 (s, 1H); 6.78 (d, 1H); 6.82 (dd, 1H); 7.80 (d, 1H).

Intermediate 13**1-[2-(4-Aminopiperidin-1-yl)ethyl]-7-methoxy-4-methylquinazolin-2(1H)-one**

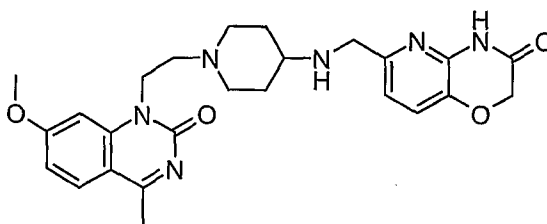
A solution of *tert*-butyl {1-[2-(7-methoxy-4-methyl-2-oxoquinazolin-1(2H)-yl)ethyl]piperidin-4-yl} carbamate (**Intermediate 12**, 0.45 g) was treated with TFA using a procedure analogous to that described for the synthesis of **Intermediate 6** to give 0.33 g of the crude product.

MS (ES): 317 (MH^+) for $C_{17}H_{24}N_4O_2$

1H NMR ($CDCl_3$) δ : 1.36-1.46 (m, 2H); 1.80-1.88 (m, 2H); 2.21 (td, 2H); 2.67-2.76 (m, 6H); 2.98 (d, 2H); 3.95 (s, 3H); 4.30-4.38 (m, 2H); 6.80-6.85 (m, 2H); 7.77-7.83 (m, 1H).

Example 5

6-[(1-[2-(7-Methoxy-4-methyl-2-oxoquinazolin-1(2H)-yl)ethyl]piperidin-4-yl)amino)methyl]-2H-pyrido[3,2-b][1,4]oxazin-3(4H)-one



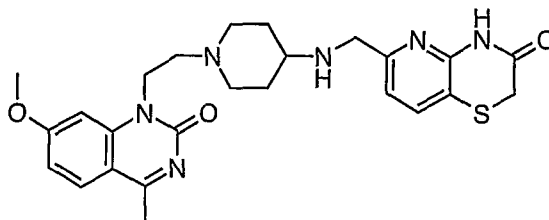
1-[2-(4-Aminopiperidin-1-yl)ethyl]-7-methoxy-4-methylquinazolin-2(1H)-one (**Intermediate 13**, 110 mg), 3-oxo-3,4-dihydro-2H-pyrido[3,2-b][1,4]oxazine-6-carbaldehyde (WO 2004/058144) (71 mg) and sodium triacetoxy borohydride (100 mg) were reacted using a procedure analogous to that described for the synthesis of **Example 1**. Purification of the crude product was performed by reverse phase HPLC on a 19 X 100 mm ODO AQ C18 column eluting with a gradient of 0.1% TFA/water to 0.1% TFA/acetonitrile. The free base was taken up in methanol and 1M HCl in ether (2 mL) was added. The colorless precipitate was collected by filtration and gave 87 mg of the bis-hydrochloride salt of the product.

MS (ES): 479 (MH^+) for $C_{25}H_{30}N_6O_4$

1H NMR ($DMSO-D_6$) δ : 2.03-2.15 (m, 2H); 2.37-2.45 (m, 2H); 2.76-2.85 (m, 3H); 3.09-3.20 (m, 2H); 3.32-3.44 (m, 2H); 3.77-3.87 (m, 3H); 4.03-4.12 (m, 3H); 4.13-4.21 (m, 2H); 4.66-4.77 (m, 4H); 7.08 (d, 1H); 7.21-7.28 (m, 2H); 7.45 (d, 1H); 8.13-8.21 (m, 1H); 9.72 (s, 2H); 11.35 (s, 1H); 11.38 (s, 1H).

Example 6

6-[(1-[2-(7-Methoxy-4-methyl-2-oxoquinazolin-1(2H)-yl)ethyl]piperidin-4-yl)amino)methyl]-2H-pyrido[3,2-b][1,4]thiazin-3(4H)-one



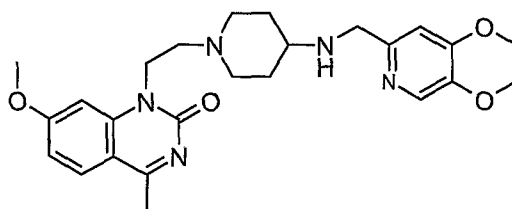
1-[2-(4-Aminopiperidin-1-yl)ethyl]-7-methoxy-4-methylquinazolin-2(1*H*)-one (**Intermediate 13**, 110 mg), 3-oxo-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]thiazine-6-carbaldehyde (WO 2004/058144) (77 mg) and sodium triacetoxo borohydride (100 mg) were reacted using a procedure analogous to that described for the synthesis of **Example 1** to give 107 mg of the bis-hydrochloride salt of the product.

MS (ES): 495 (MH^+) for $C_{25}H_{30}N_6SO_3$

1H NMR (DMSO- D_6) δ : 2.02-2.14 (m, 2H); 2.37-2.48 (m, 2H); 2.74-2.80 (m, 3H); 3.08-3.19 (m, 2H); 3.31-3.38 (m, 2H); 3.41-3.50 (m, 1H); 3.61 (s, 2H); 3.78-3.87 (m, 2H); 4.03-4.12 (m, 3H); 4.19-4.27 (m, 2H); 4.69 (t, 2H); 7.03-7.11 (m, 1H); 7.20 (s, 1H); 7.24-7.33 (m, 1H); 7.91 (d, 1H); 8.11-8.18 (m, 1H); 9.73 (s, 2H); 11.03-11.11 (m, 1H); 11.20 (s, 1H).

Example 7

1-(2-{4-[(2,3-dihydro[1,4]dioxino[2,3-*c*]pyridin-7-ylmethyl)amino]piperidin-1-yl}ethyl)-7-methoxy-4-methylquinazolin-2(1*H*)-one



1-[2-(4-Aminopiperidin-1-yl)ethyl]-7-methoxy-4-methylquinazolin-2(1*H*)-one (**Intermediate 13**, 110 mg), 2,3-dihydro[1,4]dioxino[2,3-*c*]pyridine-7-carbaldehyde (67 mg) and sodium triacetoxo borohydride (100 mg) were reacted using a procedure analogous to that described for the synthesis of **Example 1** to give 107 mg of the bis-hydrochloride salt of the product.

MS (ES): 466 (MH^+) for $C_{25}H_{31}N_5O_4$

1H NMR (DMSO- D_6) δ : 2.03-2.14 (m, 2H); 2.31-2.42 (m, 2H); 2.82 (s, 3H); 3.07-3.14 (m, 2H); 3.32-3.44 (m, 2H); 3.77-3.86 (m, 2H); 4.07-4.15 (m, 3H); 4.22-4.33 (m, 2H); 4.34-4.40 (m, 2H); 4.41-4.47 (m, 2H); 4.67-4.77 (m, 2H); 7.11 (d, 1H); 7.22 (s, 1H); 7.37 (s, 1H); 8.19 (d, 1H); 8.29 (s, 1H); 9.81 (s, 1H); 11.28 (s, 1H).

Intermediate 14

N-Allyl-N-(4-cyano-2-nitrophenyl)glycine

4-Fluoro-3-nitrobenzonitrile (4.0 g), N-allylglycine hydrochloride (5.0 g) and sodium hydrogen carbonate (4.5 g) were reacted using a procedure analogous to that described for the synthesis of **Intermediate 3** to give 5.12 g of product.

MS (ES): 262 (MH^+) for $\text{C}_{12}\text{H}_{11}\text{N}_3\text{O}_4$

^1H NMR (CDCl_3) δ : 3.99 (d, 2H); 4.02 (s, 2H); 5.26-5.36 (m, 2H); 5.80-5.90 (m, 1H); 7.11 (d, 1H); 7.64 (dd, 1H); 8.07 (d, 1H).

Intermediate 15

1-Allyl-3-oxo-1,2,3,4-tetrahydroquinoxaline-6-carbonitrile

To a solution of sodium hydrosulfite (25 g) in water (150 mL) was added a solution of *N*-allyl-*N*-(4-cyano-2-nitrophenyl)glycine (**Intermediate 14**, 4.39 g) in water (80 mL) with potassium carbonate (3.4 g). Additional sodium hydrosulfite (30 g, in six portions) was added until the reaction was no longer red. The mixture was neutralized 1N HCl and extracted with ethyl acetate (four times). The combined organic solution was washed with brine, dried over sodium sulfate and concentrated under reduced pressure to give 1.74 g of product.

MS (ES): 214 (MH^+) for $\text{C}_{12}\text{H}_{11}\text{N}_3\text{O}$

^1H NMR (CDCl_3) δ : 3.93 (d, 2H); 4.00 (s, 2H); 5.24-5.38 (m, 2H); 5.76-5.90 (m, 1H); 6.69 (d, 1H); 6.98 (d, 1H); 7.23-7.26 (m, 1H); 9.01 (s, 1H).

Intermediate 16

tert-Butyl {1-[2-(4-allyl-7-cyano-2-oxo-3,4-dihydroquinoxalin-1(2*H*)-yl)ethyl]piperidin-4-yl} carbamate

1-Allyl-3-oxo-1,2,3,4-tetrahydroquinoxaline-6-carbonitrile (**Intermediate 15**, 1.74 g) was reacted with sodium hydride (0.51 g, 60% in oil) and 2-{4-[(*tert*-butoxycarbonyl)amino]piperidin-1-yl}ethyl methanesulfonate in DMF (**Intermediate 2**, 1 equivalent) using a procedure analogous to that described for the synthesis of **Intermediate 5**. The residue obtained after aqueous workup was triturated in diethylether and filtered to yield 2.59 g of product.

MS (ES): 440 (MH^+) for $\text{C}_{24}\text{H}_{33}\text{N}_5\text{O}_3$

^1H NMR (CDCl_3) δ : 1.38-1.49 (m, 11H); 1.90-1.98 (m, 2H); 2.16-2.25 (m, 2H); 2.58 (t, 2H); 2.84-2.93 (m, 2H); 3.42-3.53 (m, 1H); 3.90 (d, 2H); 3.92 (s, 2H); 4.04 (t, 2H); 4.38-4.50 (m, 1H); 5.28 (dd, 1H); 5.34 (dd, 1H); 5.77-5.87 (m, 1H); 6.72 (d, 1H); 7.28 (d, 1H); 7.37 (s, 1H).

Intermediate 17

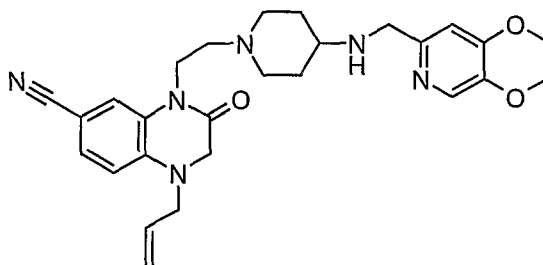
1-Allyl-4-[2-(4-aminopiperidin-1-yl)ethyl]-3-oxo-1,2,3,4-tetrahydroquinoxaline-6-carbonitrile *tert*-Butyl {1-[2-(4-allyl-7-cyano-2-oxo-3,4-dihydroquinoxalin-1(2*H*)-yl)ethyl]piperidin-4-yl} carbamate (**Intermediate 16**, 2.59 g) was treated with TFA using a procedure analogous to that described for the synthesis of **Intermediate 6** to give 2.41 g of the crude product.

MS (ES): 340 (MH⁺) for C₁₉H₂₅N₅O

¹H NMR (CDCl₃) δ: 1.32-1.45 (m, 2H); 1.75-1.89 (m, 2H); 2.08-2.21 (m, 2H); 2.52-2.61 (m, 2H); 2.62-2.74 (m, 1H); 2.87-2.97 (m, 2H); 3.87-3.95 (m, 4H); 4.02-4.11 (m, 2H); 5.22-5.37 (m, 2H); 5.75-5.90 (m, 1H); 6.72 (d, 1H); 7.28 (d, 1H); 7.35 (d, 1H).

Example 8

1-Allyl-4-(2-{4-[(2,3-dihydro[1,4]dioxino[2,3-*c*]pyridin-7-yl)methyl]amino}piperidin-1-yl)ethyl)-3-oxo-1,2,3,4-tetrahydroquinoxaline-6-carbonitrile



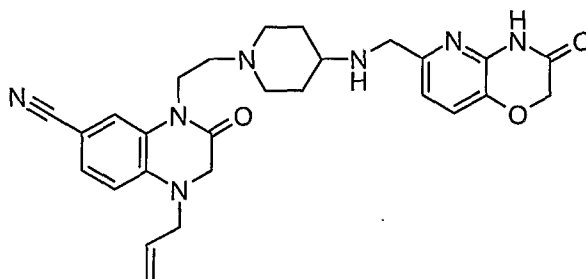
1-Allyl-4-[2-(4-aminopiperidin-1-yl)ethyl]-3-oxo-1,2,3,4-tetrahydroquinoxaline-6-carbonitrile (**Intermediate 17**, 1.20 g), 2,3-dihydro[1,4]dioxino[2,3-*c*]pyridine-7-carbaldehyde (550 mg) (WO 2004/058144) and sodium triacetoxo borohydride (1.0 g) were reacted using a procedure analogous to that described for the synthesis of **Example 1** to give the product as a colourless solid (1.22 g).

MS (ES): 489 (MH⁺) for C₂₇H₃₂N₆O₃

¹H NMR (CDCl₃) δ: 1.40-1.51 (m, 2H); 1.91 (d, 2H); 2.10-2.19 (m, 2H); 2.47-2.54 (m, 1H); 2.54-2.60 (m, 2H); 2.94 (d, 2H); 3.80 (s, 2H); 3.90 (d, 2H); 3.92 (s, 2H); 4.02-4.10 (m, 2H); 4.25-4.30 (m, 2H); 4.30-4.34 (m, 2H); 5.25-5.35 (m, 2H); 5.77-5.87 (m, 1H); 6.71 (d, 1H); 6.83 (s, 1H); 7.25-7.30 (m, 2H); 8.10 (s, 1H).

Example 9

1-Allyl-3-oxo-4-[2-(4-[(3-oxo-3,4-dihydro-2H-pyrido[3,2-b][1,4]oxazin-6-yl)methyl]amino}piperidin-1-yl)ethyl]-1,2,3,4-tetrahydroquinoxaline-6-carbonitrile



1-Allyl-4-[2-(4-aminopiperidin-1-yl)ethyl]-3-oxo-1,2,3,4-tetrahydroquinoxaline-6-carbonitrile (**Intermediate 17**, 1.20 g), 3-oxo-3,4-dihydro-2H-pyrido[3,2-b][1,4]oxazine-6-carbaldehyde (WO 2004/058144) (600 mg) and sodium triacetoxy borohydride (1 g) were reacted using a procedure analogous to that described for the synthesis of **Example 1** to give 1.05 g of the product.

MS (ES): 502 (MH^+) for $C_{27}H_{31}N_7O_3$

1H NMR ($CDCl_3$) δ : 1.40-1.53 (m, 2H); 1.87-1.96 (m, 2H); 2.10-2.21 (m, 2H); 2.48-2.56 (m, 1H); 2.59 (t, 2H); 2.96 (d, 2H); 3.82 (s, 2H); 3.90 (d, 2H); 3.92 (s, 2H); 4.06 (t, 2H); 4.60-4.65 (m, 2H); 5.23-5.38 (m, 2H); 5.74-5.90 (m, 1H); 6.71 (d, 1H); 6.94 (d, 1H); 7.20 (d, 1H); 7.25-7.30 (m, 1H); 7.35 (d, 1H).

Intermediate 18

tert-Butyl {1-[2-(4-allyl-7-cyano-2-oxo-3,4-dihydroquinoxalin-1(2H)-yl)ethyl]piperidin-4-yl}(2,3-dihydro[1,4]dioxino[2,3-c]pyridin-7-ylmethyl)carbamate

To a mixture of 1-allyl-4-(2-{4-[(2,3-dihydro[1,4]dioxino[2,3-c]pyridin-7-ylmethyl)amino]piperidin-1-yl}ethyl)-3-oxo-1,2,3,4-tetrahydroquinoxaline-6-carbonitrile (**Example 8**, 1.12 g) in dichloromethane (20 mL) was added triethylamine (0.50 mL) and di-*tert* butyl dicarbonate (0.63 g). After 3 hours at room temperature, the reaction was diluted with dichloromethane, washed with saturated solution and brine, dried over sodium sulfate and concentrated under reduced pressure to give 1.18 g of product.

MS (ES): 589 (MH^+) for $C_{32}H_{40}N_6O_5$

1H NMR ($CDCl_3$) δ : 1.33 - 1.43 (m, 6 H); 1.58 - 1.77 (m, 9 H); 2.03 - 2.26 (m, 2 H); 2.53 (t, 2 H); 2.97 (d, 2 H); 3.87 - 3.94 (m, 4 H); 4.01 (q, 2 H); 4.23 - 4.41 (m, 6 H); 5.21 - 5.38 (m, 2 H); 5.73 - 5.91 (m, 1 H); 6.67 - 6.76 (m, 2 H); 7.17 - 7.26 (m, 1 H); 8.02 - 8.08 (m, 1

H).

Intermediate 19

tert-Butyl (1-{2-[7-cyano-4-(3-hydroxypropyl)-2-oxo-3,4-dihydroquinoxalin-1(2*H*)-yl]ethyl}piperidin-4-yl)(2,3-dihydro[1,4]dioxino[2,3-*c*]pyridin-7-ylmethyl)carbamate

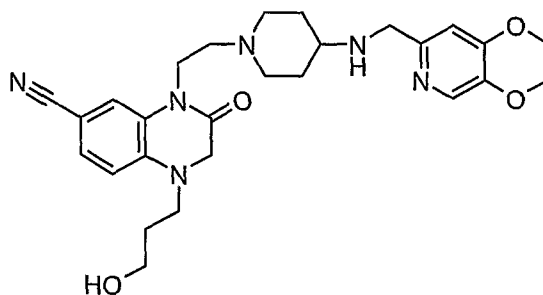
A mixture of *tert*-butyl {1-[2-(4-allyl-7-cyano-2-oxo-3,4-dihydroquinoxalin-1(2*H*)-yl)ethyl]piperidin-4-yl}(2,3-dihydro[1,4]dioxino[2,3-*c*]pyridin-7-ylmethyl)carbamate (**Intermediate 18**, 0.21 g) in THF (3 mL) was added 9-borabicyclo[3.3.1]nonane (9-BBN) (1.4 mL). After 1 hour and again after 4 hours, additional 9-BBN (1.4 mL) was added. After 7 hours, the reaction was cooled with an ice bath and water (0.50 mL) was added. After 10 minutes, 3 N NaOH (0.50 mL) and 30% hydrogen peroxide (0.50 mL) were added. After 30 minutes, the reaction was diluted with ethyl acetate and washed with NaHCO₃ (saturated solution) and brine, dried over sodium sulfate and concentrated under reduced pressure. Chromatography on silica gel with a gradient from methylene chloride to 5% methanol in methylene chloride gave 53 mg of product.

MS (ES): 607 (MH⁺) for C₃₂H₄₂N₆O₆

¹H NMR (CDCl₃) δ: 1.36-1.44 (m, 7H); 1.44-1.56 (m, 9H); 1.87-1.96 (m, 2H); 2.52 (t, 2H); 2.83-2.91 (m, 2H); 3.46 (t, 2H); 3.76 (t, 2H); 3.98 (s, 2H); 4.10 (t, 2H); 4.26-4.33 (m, 2H); 4.33-4.42 (m, 4H); 6.73-6.81 (m, 2H); 7.16 (s, 1H); 7.26-7.27 (m, 1H); 8.02 (s, 1H).

Example 10

4-(2-{4-[(2,3-dihydro[1,4]dioxino[2,3-*c*]pyridin-7-ylmethyl)amino]piperidin-1-yl}ethyl)-1-(3-hydroxypropyl)-3-oxo-1,2,3,4-tetrahydroquinoxaline-6-carbonitrile



To a solution of *tert*-butyl (1-{2-[7-cyano-4-(3-hydroxypropyl)-2-oxo-3,4-dihydroquinoxalin-1(2*H*)-yl]ethyl}piperidin-4-yl)(2,3-dihydro[1,4]dioxino[2,3-*c*]pyridin-7-ylmethyl)carbamate (**Intermediate 19**, 53 mg) in dichloromethane (1 mL) was added HCl in dioxane (4M, 1 mL). After 15 minutes, the resulting precipitate was collected by filtration, dissolved in methanol

and concentrated to dryness. The residue was dissolved in a minimum of methanol and precipitated with diethylether. The solid was collected by filtration, washed with diethylether and dried (65 °C, 1 h, *in vacuo*) to give 53 mg of product as bis-HCl salt.

MS (ES): 507 (MH^+) for $C_{27}H_{34}N_6O_4$

1H NMR (DMSO- D_6) δ : 1.65-1.75 (m, 2H); 2.01-2.13 (m, 2H); 2.29-2.39 (m, 2H); 3.02-3.13 (m, 2H); 3.21-3.32 (m, 3H); 3.36-3.44 (m, 2H); 3.44-3.52 (m, 2H); 3.77 (d, 2H); 4.02-4.11 (m, 2H); 4.17-4.28 (m, 2H); 4.29-4.39 (m, 4H); 4.39-4.44 (m, 2H); 6.90 (d, 1H); 7.29 (s, 1H); 7.43 (dd, 1H); 7.55 (d, 1H); 8.24 (s, 1H); 9.73 (s, 2H); 10.68 (s, 1H).

Intermediate 20

Ethyl [(4-methoxy-2-nitrophenyl)imino]acetate

A solution of 4-methoxy-2-nitroaniline (1 kg, 5.95 mol) and ethyl glyoxylate (1180 mL, 50 wt% in toluene, 5.95 mol) in toluene (10 L) was refluxed in a Dean-Stark apparatus for 48 hours and evaporated under reduced pressure to give the crude product as a dark brown oil.

Intermediate 21

Ethyl N-(4-methoxy-2-nitrophenyl)glycinate

A mixture of 4-methoxy-2-nitroaniline (25.0 g, 0.15 mol), ethyl bromoacetate (200 mL, 1.8 mol) and potassium carbonate (31.1 g, 0.23 mol) was heated at 150 °C for 4.5 hours. After cooling to room temperature aqueous sodium hydroxide solution (1M, 600 mL) was added. This mixture was extracted with ethyl acetate (2 x 500 mL). The combined organic phases were dried over magnesium sulfate and concentrated to dryness. Chromatography on silica gel with 25-50% acetone in hexanes gave 22.1 g of the crude product as a red solid. 1H NMR revealed the presence of ~20% dialkylated product. This material was used without further purification.

1H NMR (DMSO- D_6) δ : 1.18-1.23 (t, 3H); 3.74 (s, 3H); 4.12-4.18 (q, 2H); 4.23-4.25 (d, 2H); 6.90-6.93 (d, 1H); 7.25-7.29 (dd, 1H); 7.51-7.52 (d, 1H); 8.23-8.27 (t, 1H).

Intermediate 22:

7-Methoxy-3,4-dihydroquinoxalin-2(1H)-one

In a 18-L Parr apparatus a suspension of ethyl [(4-methoxy-2-nitrophenyl)imino]acetate (**Intermediate 20**) (crude, as obtained below) was hydrogenated at 55 psi in the presence of 20 wt% Pd/C (100 g, containing ~ 50 wt% water) until no hydrogen was consumed. (Note:

The reaction was strongly exothermic and the temperature should be controlled at around 60 °C by adjusting the rate of recharging hydrogen and by a cooling system). The reaction mixture was discharged, filtered over a celite cake, and evaporated under reduced pressure to give a crude solid that was triturated with MTBE (6 L) to give the product as a tan solid (400 g).

MS (ESP): 179 (MH⁺) for C₉H₁₀N₂O₂

Alternative procedure for **Intermediate 22**:

Ethyl *N*-(4-methoxy-2-nitrophenyl)glycinate (**Intermediate 21**, 15.8 g crude) was taken up in 200 mL of 1:1 methanol/acetic acid, treated with 10% palladium on carbon (2 g), and stirred in an atmosphere of hydrogen overnight. The reaction mixture was filtered through celite and the filtrate was concentrated to dryness giving 10.6 g of the crude product as a tan solid. This was used without further purification.

MS (ESP): 179 (MH⁺) for C₉H₁₀N₂O₂

Intermediate 23

7-Methoxyquinoxalin-2(1*H*)-one

To a solution of 8% aqueous sodium hydroxide (1.32 L) was added 7-methoxy-3,4-dihydroquinoxalin-2(1*H*)-one (**Intermediate 22**) (100 g) followed by a solution of 3 wt% hydrogen peroxide in water (1.17 L). The reaction mixture was slowly heated to 80 °C and maintained at this temperature for 4 hours. Then the heating source was removed and acetic acid (150 mL) was added dropwise. The suspension was stirred overnight at room temperature and the precipitated solid was collected by filtration to afford the product as a tan solid (90 g).

MS (ES): 177 (MH⁺) for C₉H₈N₂O₂

¹H-NMR (DMSO-*d*₆) δ: 3.83 (s, 3H); 6.76 (d, 1H); 6.90 (dd, 1H); 7.67 (d, 1H); 7.97 (s, 1H); 12.32 (brs, 1H).

Intermediate 24

tert-Butyl {1-[2-(7-methoxy-2-oxoquinoxalin-1(2*H*)-yl)ethyl]piperidin-4-yl}carbamate

7-Methoxyquinoxalin-2(1*H*)-one (**Intermediate 23**, 300 mg, 1.70 mmol) was treated with sodium hydride (100 mg, 60% in oil, 2.56 mmol) and alkylated with 2-{4-[(*tert*-butoxycarbonyl)amino]piperidin-1-yl}ethyl methanesulfonate (**Intermediate 2**) (~3.4 mmol)

using a procedure analogous to that described for the synthesis of **Intermediate 5**. Chromatography on silica gel with 25% acetone in hexanes gave 200 mg (29%) of the product as a colourless solid.

MS (ES): 403 (MH^+) for $C_{21}H_{30}N_4O_4$

1H NMR (DMSO- D_6) δ ppm 1.26 - 1.40 (m, 11H); 1.57 - 1.72 (m, 2H); 1.97 - 2.11 (m, 2H); 2.51 - 2.61 (m, 2H); 2.85 - 2.98 (m, 2H); 3.19 (s, 1H); 3.92 (s, 3H); 4.32 (t, 2H); 6.76 (d, 1H); 6.95 - 7.04 (m, 2H); 7.70 - 7.78 (m, 1H); 8.04 (s, 1 H).

Intermediate 25

1-[2-(4-Aminopiperidin-1-yl)ethyl]-7-methoxyquinoxalin-2(1H)-one

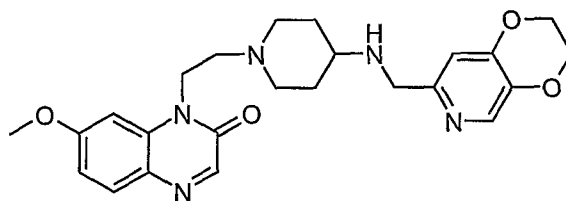
tert-Butyl {1-[2-(7-methoxy-2-oxoquinoxalin-1(2H)-yl)ethyl]piperidin-4-yl}

carbamate (**Intermediate 24**, 190 mg, 0.47 mmol) was reacted with trifluoroacetic acid in dichloromethane using a procedure analogous to that described for the synthesis of **Intermediate 6** to give 110 mg of the crude product as an oil.

MS (ES): 303 (MH^+) for $C_{16}H_{22}N_4O_2$

Intermediate 26

1-(2-{4-[(2,3-Dihydro[1,4]dioxino[2,3-*c*]pyridin-7-ylmethyl)amino]piperidin-1-yl}ethyl)-7-methoxyquinoxalin-2(1H)-one



1-[2-(4-Aminopiperidin-1-yl)ethyl]-7-methoxyquinoxalin-2(1H)-one (**Intermediate 25**, 60 mg crude, 0.20 mmol), 2,3-dihydro[1,4]dioxino[2,3-*c*]pyridine-7-carbaldehyde (WO 2004/058144) (33 mg, 0.20 mmol), and sodium triacetoxy borohydride (130 mg, 0.60 mmol) were reacted using a procedure analogous to that described for the synthesis of **Example 1**. The free base obtained after chromatography was taken up in isopropanol and treated with 4.0M HCl in dioxane (~3 eq). Solvent was removed under reduced pressure to give 28 mg (27% yield) of the bis-hydrochloride salt of the product.

MS (ES): 452 (MH^+) for $C_{24}H_{29}N_5O_4$

1H NMR (D_2O) δ ppm 1.86 - 2.02 (m, 2H); 2.36 - 2.49 (m, 2H); 3.09 - 3.23 (m, 2H); 3.52 (t, 2H); 3.56 - 3.68 (m, 1H); 3.82 - 3.95 (m, 5H); 4.32 - 4.40 (m, 4H); 4.43 - 4.50 (m, 2H);

4.61 (t, 2H); 6.82 (d, 1H); 7.03 (dd, 1H); 7.29 (s, 1H); 7.71 (d, 1H); 7.97 (s, 1H); 8.22 (s, 1H).

Intermediate 27:

tert-Butyl (2,3-dihydro[1,4]dioxino[2,3-*c*]pyridin-7-ylmethyl){1-[2-(7-methoxy-2-oxoquinoxalin-1(2*H*)-yl)ethyl]piperidin-4-yl}carbamate

To a mixture of 1-(2-{4-[(2,3-Dihydro[1,4]dioxino[2,3-*c*]pyridin-7-ylmethyl)amino]piperidin-1-yl}ethyl)-7-methoxyquinoxalin-2(1*H*)-one (**Intermediate 26**) (2.03 g) in dichloromethane (40 mL) was added triethylamine (1.2 mL) and di-*tert* butyl dicarbonate (1.30 g). After 4 hours at room temperature, the reaction was diluted with dichloromethane, washed with NaHCO₃ (saturated solution) and brine, dried over sodium sulfate and concentrated under reduced pressure. The residue was triturated in methanol and filtered yielding 2.23 g of product.

MS (ES): 552 (MH⁺) for C₂₉H₃₇N₅O₆

¹H NMR (CDCl₃) δ: 1.36-1.54 (m, 9H); 1.64-1.70 (m, 2H); 2.11-2.23 (m, 2H); 2.63 (t, 2H); 2.97-3.05 (m, 2H); 3.91 (s, 3H); 4.26-4.38 (m, 7H); 6.73 (s, 1H); 6.82 (d, 1H); 6.92 (dd, 1H); 7.78 (d, 1H); 8.05 (s, 1H); 8.11 (s, 1H).

Intermediate 28

tert-Butyl (2,3-dihydro[1,4]dioxino[2,3-*c*]pyridin-7-ylmethyl){1-[2-(7-methoxy-2-oxo-3,4-dihydroquinoxalin-1(2*H*)-yl)ethyl]piperidin-4-yl}carbamate

To a solution of *tert*-butyl (2,3-dihydro[1,4]dioxino[2,3-*c*]pyridin-7-ylmethyl){1-[2-(7-methoxy-2-oxoquinoxalin-1(2*H*)-yl)ethyl]piperidin-4-yl}carbamate (**Intermediate 27**, 0.60 g) in THF (10 mL) and methanol (1 mL) was added sodium borohydride (0.10 g). After 3 hours, additional sodium borohydride (0.10 g) was added. After stirring overnight, the reaction was diluted with ethyl acetate, washed with NaHCO₃ (saturated solution) and brine, dried over sodium sulfate and concentrated under reduced pressure yielding 0.58 g of crude product.

MS (ES): 554 (MH⁺) for C₂₉H₃₉N₅O₆

¹H NMR (CDCl₃) δ: 1.44-1.54 (m, 2H); 1.61 (s, 11H); 2.08-2.20 (m, 1H); 2.55 (t, 2H); 2.99 (d, 2H); 3.58-3.66 (m, 1H); 3.75 (m, 4H); 3.85 (s, 2H); 3.98 (t, 2H); 4.23-4.38 (m, 6H); 6.47 (dd, 1H); 6.60-6.66 (m, 2H); 6.72 (s, 1H); 8.05 (s, 1H).

Intermediate 29

tert-Butyl (2,3-dihydro[1,4]dioxino[2,3-*c*]pyridin-7-ylmethyl)(1-{2-[7-methoxy-4-(methylsulfonyl)-2-oxo-3,4-dihydroquinoxalin-1(2*H*)-yl]ethyl}piperidin-4-yl)carbamate

To a solution of *tert*-butyl (2,3-dihydro[1,4]dioxino[2,3-*c*]pyridin-7-ylmethyl){1-[2-(7-methoxy-2-oxo-3,4-dihydroquinoxalin-1(2*H*)-yl)ethyl]piperidin-4-yl}carbamate

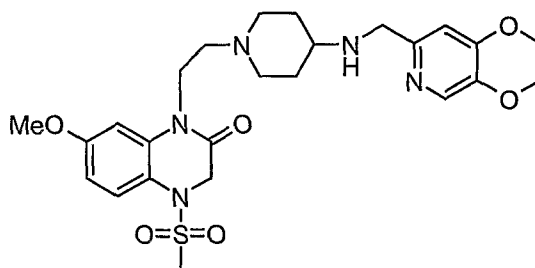
(**Intermediate 28**, 0.29 g) in THF (5 mL) were added diisopropylethylamine (0.10 mL) and methanesulfonyl chloride (0.050 mL). After 4 hours, the reaction was diluted with ethyl acetate and washed with saturated aqueous NaHCO₃ solution and brine, dried over sodium sulfate and concentrated under reduced pressure. Chromatography on silica gel with a gradient from methylene chloride to 5% methanol in methylene chloride yielded 200 mg of product.

MS (ES): 632 (MH⁺) for C₃₀H₄₁N₅O₈S

¹H NMR (CDCl₃) δ : 1.37-1.49 (m, 11H); 1.96-2.08 (m, 2H); 2.52 (t, 2H); 2.77 (s, 3H); 2.94 (d, 2H); 3.04 (d, 1H); 3.82 (s, 3H); 4.06 (m, 3H); 4.26-4.37 (m, 9H); 6.64-6.75 (m, 3H); 7.51 (d, 1H); 8.05 (s, 1H).

Example 11

1-(2-{4-[(2,3-Dihydro[1,4]dioxino[2,3-*c*]pyridin-7-ylmethyl)amino]piperidin-1-yl}ethyl)-7-methoxy-4-(methylsulfonyl)-3,4-dihydroquinoxalin-2(1*H*)-one



To a solution of *tert*-butyl (2,3-dihydro[1,4]dioxino[2,3-*c*]pyridin-7-ylmethyl)(1-{2-[7-methoxy-4-(methylsulfonyl)-2-oxo-3,4-dihydroquinoxalin-1(2*H*)-yl]ethyl}piperidin-4-yl)carbamate (**Intermediate 29**, 200 mg) in dichloromethane (2 mL) was added TFA (1 mL). After 1 hour, the reaction was diluted with chloroform and washed with saturated aqueous sodium carbonate solution. The organic phase was dried over sodium sulfate and concentrated under reduced pressure. Chromatography on silica gel with a gradient from methylene chloride to 20% methanol in methylene chloride yielded 123 mg of product.

MS (ES): 532 (MH⁺) for C₂₅H₃₃N₅O₆S

^1H NMR (CDCl_3) δ : 1.27-1.38 (m, 2H); 1.89 (m, 2H); 2.05 (t, 2H); 2.48-2.59 (m, 3H); 2.79 (s, 3H); 2.86-2.94 (m, 2H); 3.05 (d, 1H); 3.79 (s, 2H); 3.84 (s, 3H); 4.11 (t, 2H); 4.25-4.30 (m, 2H); 4.30-4.33 (m, 2H); 4.34 (s, 2H); 6.66 (dd, 1H); 6.71 (s, 1H); 6.80 (s, 1H); 7.52 (d, 1H); 8.09 (s, 1H).

Intermediate 30

tert-Butyl {1-[2-(7-cyano-4-methyl-2-oxoquinolin-1(2*H*)-yl)ethyl]piperidin-4-yl}carbamate

A slurry of 4-methyl-2-oxo-1,2-dihydroquinoline-7-carbonitrile (C. Charitos, C. Tzougraki and G. Kokotos, *J. Peptide Res.* **56**, 373-381 (2000)) (320 mg, 1.7 mmol) was treated with sodium hydride (96 mg, 60% in oil) and alkylated with 2-{4-[(*tert*-butoxycarbonyl)amino]piperidin-1-yl}ethyl methanesulfonate in DMF (**Intermediate 2**, 1 equivalent) using a procedure analogous to that described for the synthesis of **Intermediate 5**. Chromatography on silica gel eluting with a gradient of 5-7% methanol in methylene chloride gave 635 mg of the product as a yellow solid.

MS (ESP): 411 (MH^+) for $\text{C}_{23}\text{H}_{30}\text{N}_4\text{O}_3$

Intermediate 31

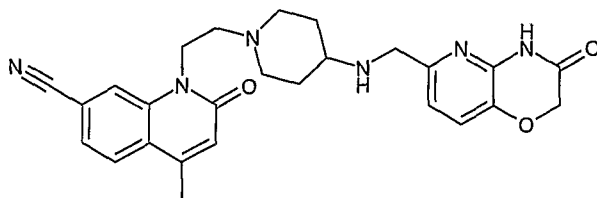
1-[2-(4-Aminopiperidin-1-yl)ethyl]-4-methyl-2-oxo-1,2-dihydroquinoline-7-carbonitrile

tert-Butyl {1-[2-(7-cyano-4-methyl-2-oxoquinolin-1(2*H*)-yl)ethyl]piperidin-4-yl}carbamate (**Intermediate 30**) (630 mg) was reacted with trifluoroacetic acid in dichloromethane using a procedure analogous to that described for the synthesis of **Intermediate 6** to give the crude product as an oil, which was used without further purification.

MS (ESP): 311 (MH^+) for $\text{C}_{18}\text{H}_{22}\text{N}_4\text{O}$

Example 12

4-Methyl-2-oxo-1-[2-(4-{[(3-oxo-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]oxazin-6-yl)methyl]amino}piperidin-1-yl)ethyl]-1,2-dihydroquinoline-7-carbonitrile



A solution of 1-[2-(4-aminopiperidin-1-yl)ethyl]-4-methyl-2-oxo-1,2-dihydroquinoline-7-

carbonitrile TFA salt (**Intermediate 31**, 630 mg, 1.54mmol), 3-oxo-3,4-dihydro-2H-pyrido[3,2-b][1,4]oxazine-6-carbaldehyde (WO 2004/058144) (410 mg, 2.30 mmol) and diisopropylethylamine (1.5 equivalent) in a 1:1 mixture of methanol/ dichloroethane (12 mL/12 mL) was heated over 3 Å molecular sieves at 60 °C for 6 hours. The reaction mixture was cooled to 0 °C, and sodium cyano borohydride (5.0 mmol) was added. The resulting reaction mixture was allowed to warm to room temperature overnight. The mixture was diluted with chloroform and washed with saturated aqueous sodium hydrogencarbonate solution and brine, dried over magnesium sulfate and concentrated under reduced pressure. Reverse Phase HPLC purification was performed with a gradient of acetonitrile /water 5 to 50%. Fractions containing product were collected, concentrated *in vacuo*, and lyophilization to yield a colourless solid (96 mg, 13%).

MS (ESP): 473 (MH⁺) for C₂₆H₂₈N₆O₃

¹H-NMR (DMSO-d₆) δ: 1.22 (m, 1H); 1.78 (m, 2H); 2.35 (m, 2H); 3.07 (m, 2H); 3.36 (s, br, 4H); 3.83 (m, 4H); 4.23 (s, br, 2H); 4.58 (t, 2H); 4.70 (s, 2H); 6.76 (s, 1H); 7.14 (d, 1H); 7.47 (d, 1H); 7.77 (d, 1H); 8.02 (d, 1H); 8.10 (s, 1H); 9.25 (s, br, 2H); 11.35 (s, br, 1H).

Intermediate 32

tert-butyl {1-[2-(7-methoxy-4-methyl-2-oxoquinolin-1(2*H*)-yl)ethyl]piperidin-4-yl} carbamate

7-Methoxy-4-methylquinolin-2(1*H*)-one (V. N. Gogte, S.B. Kulkarni and B.D. Tilak, *Indian Journal of Chemistry*, **15B**, 769-773 (1977)) (1.01 g, 5.34 mmol) was reacted with sodium hydride (320 mg, 60% in oil) and 2-{4-[(*tert*-butoxycarbonyl)amino]piperidin-1-yl}ethyl methanesulfonate in DMF (**Intermediate 2**, 1.1 equivalent) using a procedure analogous to that described for the synthesis of **Intermediate 30** to give 2.95 g of the product as a light brown oil.

MS (ESP): 416 (MH⁺) for C₂₃H₃₃N₃O₄

Intermediate 33

1-[2-(4-Aminopiperidin-1-yl)ethyl]-7-methoxy-4-methylquinolin-2(1*H*)-one

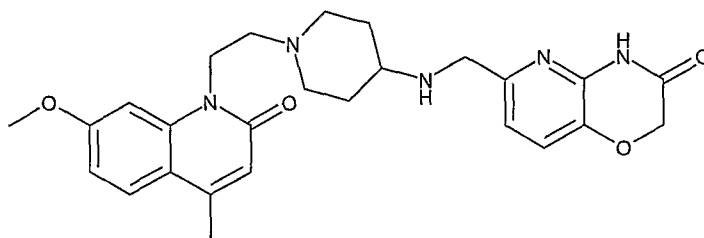
tert-butyl {1-[2-(7-methoxy-4-methyl-2-oxoquinolin-1(2*H*)-yl)ethyl]piperidin-4-yl} carbamate (**Intermediate 32**) (500 mg, 1.2 mmol) was treated with TFA using a procedure

analogous to that described for the synthesis of **Intermediate 31** to give the product as an oil (quant.), which was used without further purification.

MS (ESP): 316(MH⁺) for C₁₈H₂₅N₃O₂

Example 13

6-[(1-[2-(7-Methoxy-4-methyl-2-oxoquinolin-1(2H)-yl)ethyl]piperidin-4-yl)amino)methyl]-2H-pyrido[3,2-b][1,4]oxazin-3(4H)-one



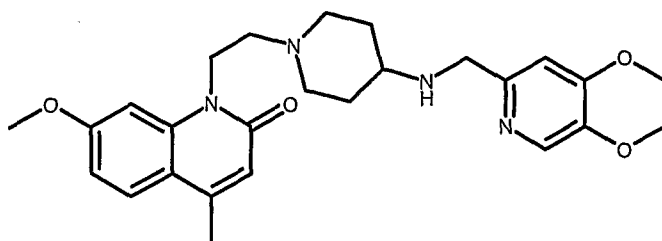
1-[2-(4-Aminopiperidin-1-yl)ethyl]-7-methoxy-4-methylquinolin-2(1H)-one (**Intermediate 33**, 1.2 mmol), 3-oxo-3,4-dihydro-2H-pyrido[3,2-b][1,4]oxazine-6-carbaldehyde (WO 2004/058144) (410 mg, 2.30 mmol), diisopropylethylamine (1.5 equivalent) and sodium cyano borohydride (5.0 mmol) were reacted using a procedure analogous to that described for the synthesis of **Example 12** to give the product as a colourless solid, 96 mg (13%).

MS (ESP): 478 (MH⁺) for C₂₆H₃₁N₅O₄

¹H-NMR (DMSO-d₆) δ: 1.83 (d, br, 2H); 2.41 (s, 3H); 3.09 (m, br, 2H); 3.34 (s, br, 5H); 3.53 (s, br, 2H); 3.91 (s, 3H); 4.23 (s, 2H); 4.57 (s, 2H); 4.70 (s, 2H); 6.40 (s, 1H); 6.97 (m, 2H); 7.14 (d, 1H); 7.44 (d, 1H); 7.75 (d, 1H); 9.31 (s, br, 2H); 11.36 (s, br, 1H).

Example 14

1-[2-(4-[(2,3-Dihydro[1,4]dioxino[2,3-c]pyridin-7-yl)methyl]amino)piperidin-1-yl}ethyl]-7-methoxy-4-methylquinolin-2(1H)-one



1-[2-(4-Aminopiperidin-1-yl)ethyl]-7-methoxy-4-methylquinolin-2(1H)-one (**Intermediate 33**, 0.96 mmol), 2,3-dihydro[1,4]dioxino[2,3-c]pyridine-7-carbaldehyde (174 mg, 1.1

equivalent) (WO 2004/058144) and sodium cyanoborohydride (120 mg, 2 equivalents) were reacted using a procedure analogous to that described for the synthesis of **Example 12** to give the TFA salt of the product as a colourless solid, 26 mg (6%).

MS (ESP): 465 (MH^+) for $C_{26}H_{32}N_4O_4$

1H -NMR (DMSO- d_6) δ : 2.35 (s, 3H); 3.79 (s, 3H); 6.20 (s, 1H); 6.80 (m, 2H); 7.58 (d, 1H); 11.44 (s, br, 1H).

Intermediate 34

benzyl *N*-[(benzyloxy)carbonyl]-*N*-cyclopropylglycinate

To a solution of benzyl cyclopropylcarbamate (US 2004186127) (6.40 g) in DMF (100 mL) at 0 °C was added sodium hydride (1.40 g, 60% in oil). After stirring for 30 minutes, a solution of benzyl 2-bromoacetate (6 mL) in DMF (100 mL) was added to the solution. After stirring overnight, the reaction was diluted with water and ethyl acetate. The organic solution was collected, washed with brine, dried over sodium sulfate, filtered and concentrated under reduced pressure. Chromatography on silica gel eluting with a gradient of hexane to 25% ethyl acetate in hexane gave 1.30 g of the product as a colourless oil.

MS (ES): 362 (MNa^+) for $C_{20}H_{21}NO_4$

1H -NMR (CDCl₃) δ : 0.63 - 0.71 (m, 2H); 0.71 - 0.81 (m, 2H); 2.79 (ddd, 1H); 4.03 (s, 1H); 4.08 (s, 1H); 5.09 (d, 2H); 5.19 (d, 2H); 7.27 - 7.38 (m, 8H).

Intermediate 35

N-(4-cyano-2-nitrophenyl)-*N*-cyclopropylglycine

A solution of benzyl *N*-[(benzyloxy)carbonyl]-*N*-cyclopropylglycinate (**Intermediate 34**, 1.30 g) in ethanol (30 mL) was hydrogenated over 10% Pd/C (140 mg) at 50 psi for 2 hours. The solution was treated with celite and filtered. Sodium hydrogencarbonate (0.84 g) and 4-fluoro-3-nitrobenzonitrile (0.59 g) were added. After stirring overnight at room temperature, the reaction was heated at 80°C for one hour. The reaction was concentrated and the residue was dissolved in ethyl acetate and water. The aqueous solution was collected, the pH adjusted with HCl (concentrated) to pH = 3, and then extracted with ethyl acetate. The organic solution was collected, dried over sodium sulfate, filtered and concentrated under reduced pressure yielding a white solid (0.58 g).

MS (ES): 260 ($M-H^-$) for $C_{12}H_{11}N_3O_4$

1H -NMR (CDCl₃) δ : 0.67 (ddd, 2H); 0.78 - 0.84 (m, 2H); 2.92 - 3.02 (m, 1H); 4.20 (s, 2H);

7.19 (d, 1H); 7.62 (dd, 1H); 8.02 (d, 1H).

Intermediate 36

1-Cyclopropyl-3-oxo-1,2,3,4-tetrahydroquinoxaline-6-carbonitrile

To a solution of sodium hydrosulfite (12 g) in water (50 mL) was added a solution of *N*-(4-cyano-2-nitrophenyl)-*N*-cyclopropylglycine (**Intermediate 35**, 2.31 g) in a saturated solution of sodium carbonate (25 mL). After stirring for 1 hour, the reaction was extracted with ethyl acetate (twice). The organic solution was collected, washed with brine, dried over sodium sulfate, filtered and concentrated under reduced pressure yielding a colourless solid (1.0 g).

MS (ES): 214 (MH⁺) for C₁₂H₁₁N₃O

¹H-NMR (CDCl₃) δ : 0.57 (ddd, 2H); 0.82 - 0.91 (m, 2H); 2.42 (ddd, 1H); 3.86 (s, 2H); 7.03 (d, 1H); 7.14 (d, 1H); 7.36 (dd, 1H); 10.66 (s, 1H).

Intermediate 37

***tert*-Butyl {1-[2-(7-cyano-4-cyclopropyl-2-oxo-3,4-dihydroquinoxalin-1(2*H*)-yl)ethyl]piperidin-4-yl}carbamate**

A slurry of 1-cyclopropyl-3-oxo-1,2,3,4-tetrahydroquinoxaline-6-carbonitrile (**Intermediate 36**, 1.0 g) in dry dimethylformamide (DMF) (20 mL) was treated at 0 °C with sodium hydride (0.33 g, 60% in oil) using a procedure analogous to that described for the synthesis of **Intermediate 5**. Chromatography on silica gel eluting with a gradient of methylene chloride to 5% methanol in methylene chloride gave 1.86 g of the product as a colourless foam.

MS (ES): 440 (MH⁺) for C₂₄H₃₃N₅O₃

¹H-NMR (CDCl₃) δ : 0.61 - 0.70 (m, 2H); 0.87 - 0.97 (m, 2H); 1.39 - 1.49 (m, 11H); 1.69 (s, 2H); 1.89 - 1.98 (m, 2H); 2.21 (t, 2H); 2.35 (ddd, 1H); 2.57 (t, 2H); 3.47 (s, 1 H); 3.91 (s, 2H); 3.99 (t, 2H); 4.45 (s, 1H); 7.19 (d, 1H); 7.32 (dd, 1H); 7.39 (s, 1H).

Intermediate 38

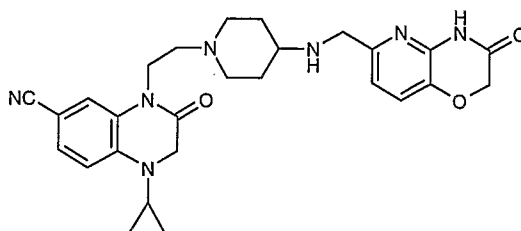
4-[2-(4-Aminopiperidin-1-yl)ethyl]-1-cyclopropyl-3-oxo-1,2,3,4-tetrahydroquinoxaline-6-carbonitrile

A solution of *tert*-butyl {1-[2-(7-cyano-4-cyclopropyl-2-oxo-3,4-dihydroquinoxalin-1(2*H*)-yl)ethyl]piperidin-4-yl}carbamate (**Intermediate 37**, 0.50 g) was reacted with trifluoroacetic acid in dichloromethane using a procedure analogous to that described for the synthesis of **Intermediate 6** to give 0.48 g of the crude product.

MS (ES): 340 (MH^+) for $C_{19}H_{25}N_5O$

Example 15

1-Cyclopropyl-3-oxo-4-[2-(4-{[(3-oxo-3,4-dihydro-2H-pyrido[3,2-b][1,4]oxazin-6-yl)methyl]amino}piperidin-1-yl)ethyl]-1,2,3,4-tetrahydroquinoxaline-6-carbonitrile



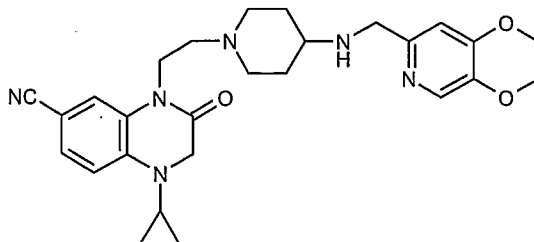
4-[2-(4-Aminopiperidin-1-yl)ethyl]-1-cyclopropyl-3-oxo-1,2,3,4-tetrahydroquinoxaline-6-carbonitrile (**Intermediate 38**, 240 mg), 3-oxo-3,4-dihydro-2H-pyrido[3,2-b][1,4]oxazine-6-carbaldehyde (200 mg) and sodium triacetoxyborohydride (240 mg) were reacted using a procedure analogous to that described for the synthesis of **Example 1**. The residue was purified by reverse phase HPLC on a 19 X 100 mm ODO AQ C18 column eluting with a gradient of 0.1% TFA/water to 0.1% TFA/acetonitrile. The desired fractions were collected, concentrated *in vacuo* to remove the acetonitrile. The aqueous solution was neutralized with Na_2CO_3 (solid) and extracted with chloroform (three times). The combined organic solution was dried (Na_2SO_4), filtered and concentrated. The oil was dissolved in diethyl ether and treated with 1M HCl/diethyl ether (2 mL). The solution was concentrated to dryness, dissolved in methanol, and precipitated with diethyl ether. The solid was collected, washed with diethyl ether, and dried under vacuum with heat (60 °C) to yield the product as a colourless solid (36 mg).

MS (ES): 502 (MH^+) for $C_{27}H_{31}N_7O_3$

1H NMR ($CDCl_3$) δ : 0.57 (m, 2H); 0.90 (m, 2H); 2.00 - 2.12 (m, 2H); 2.31 - 2.43 (m, 2H); 3.02 - 3.14 (m, 2H); 3.21 - 3.29 (m, 2H); 3.71 - 3.82 (m, 2H); 3.99 (s, 2H); 4.16 - 4.25 (m, 2H); 4.27 - 4.37 (m, 2H); 4.71 (s, 2H); 7.25 (dd, 2H); 7.46 (d, 1H); 7.53 (d, 1H); 7.62 (s, 1H); 9.58 (s, 2H); 10.68 (s, 1H); 11.36 (s, 1H).

Example 16

1-Cyclopropyl-4-(2-{4-[(2,3-dihydro[1,4]dioxino[2,3-*c*]pyridin-7-ylmethyl)amino]piperidin-1-yl}ethyl)-3-oxo-1,2,3,4-tetrahydroquinoxaline-6-carbonitrile



4-[2-(4-Aminopiperidin-1-yl)ethyl]-1-cyclopropyl-3-oxo-1,2,3,4-tetrahydroquinoxaline-6-carbonitrile (**Intermediate 38**, 240 mg) and 2,3-dihydro[1,4]dioxino[2,3-*c*]pyridine-7-carbaldehyde (190 mg) and sodium triacetoxy borohydride (240 mg) were reacted using a procedure analogous to that described for the synthesis of **Example 15** to give the product as a colourless solid (39 mg).

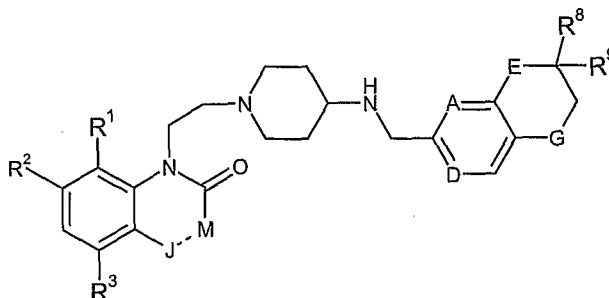
MS (ES): 489 (MH^+) for $C_{27}H_{32}N_6O_3$

1H -NMR ($CDCl_3$) δ : 0.59 (m, 2H); 0.90 (m, 2H); 2.00 - 2.12 (m, 2H); 2.29 - 2.37 (m, 2H); 2.44 - 2.49 (m, 2H); 3.01 - 3.13 (m, 2H); 3.20 - 3.32 (m, 2H); 3.68 - 3.79 (m, 2H); 3.99 (s, 2H); 4.16 - 4.25 (m, 2H); 4.25 - 4.32 (m, 2H); 4.35 (dd, 2H); 4.38 - 4.45 (m, 2H); 7.19 - 7.28 (m, 2H); 7.52 (dd, 1H); 7.58 - 7.64 (m, 1H); 8.22 (s, 1H); 9.62 (s, 2H); 10.68 (s, 1H).

Claims

What is claimed is:

1. A compound of Formula (I):



Formula (I)

or a pharmaceutically acceptable salt thereof, wherein

A is selected from CH and N;

D is selected from C-R⁷ and N;

wherein at least one of **A** and **D** is carbon;

E is selected from O, NH, and S,

wherein:

- i. **E** is NH if R⁸ and R⁹ together form =O; and
- ii. **E** is O or S if R⁸ and R⁹ are each H;

G is selected from O and S;

J is selected from C-R⁴ and N-R⁵;

M is selected from CH, N, and CH₂;

wherein at least one of **J** and **M** is carbon, and wherein:

- i) if **J** is carbon, the J-M bond is a double bond, and
- ii) if **J** is nitrogen, the J-M bond is a single bond and **M** is CH₂;

R^1 is selected from H, halo, cyano, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, $-OR^{1a}$, and $-N(R^{1a})_2$, wherein said C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl are optionally substituted with one or more R^{10} ;

R^{1a} in each occurrence is independently selected from H and C_{1-6} alkyl, wherein said C_{1-6} alkyl is optionally substituted with one or more R^{10} ;

R^2 is selected from H, halo, cyano, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, $-OR^{2a}$, and $-N(R^{2a})_2$, wherein said C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl are optionally substituted with one or more R^{20} ;

R^{2a} in each occurrence is independently selected from H and C_{1-6} alkyl, wherein said C_{1-6} alkyl is optionally substituted with one or more R^{20} ;

R^3 is selected from H, halo, cyano, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, $-OR^{3a}$, and $-N(R^{3a})_2$, wherein said C_{1-6} alkyl is optionally substituted with one or more R^{30} ;

R^{3a} is selected from H and C_{1-6} alkyl, wherein said C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl are optionally substituted with one or more R^{30} ;

R^4 is selected from halo, cyano, $-CO_2H$, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, carbocyclyl, heterocyclyl, $-OR^{4a}$, $-N(R^{4a})_2$, and $-S(O)_2R^{4b}$, wherein said C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, carbocyclyl, and heterocyclyl are optionally substituted with one or more R^{40} ;

R^{4a} in each occurrence is independently selected from H and C_{1-6} alkyl, wherein said C_{1-6} alkyl is optionally substituted with one or more R^{40} ;

R^{4b} is C_{1-6} alkyl, wherein said C_{1-6} alkyl may be optionally substituted with one or more R^{40} ;

R^5 is selected from C_{1-6} alkyl, carbocyclyl, heterocyclyl, and $-SO_2R^{5b}$, wherein said

C₁₋₆alkyl, carbocyclyl, and heterocyclyl are optionally substituted with one or more R⁵⁰;

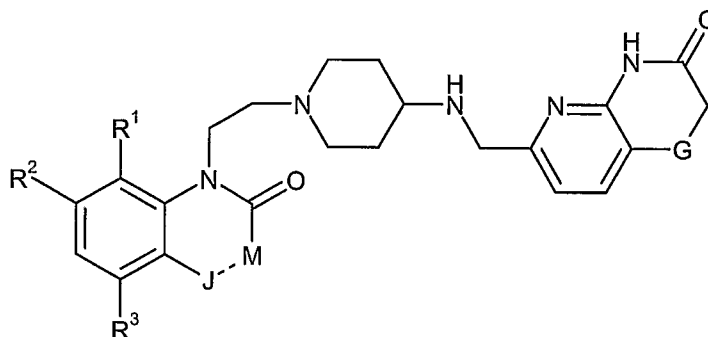
R^{5b} is C₁₋₆alkyl, wherein said C₁₋₆alkyl is optionally substituted with one or more R⁵⁰;

R⁷ is selected from H, halo, cyano, C₁₋₆alkyl, C₂₋₆alkenyl, and C₂₋₆alkynyl, wherein said C₁₋₆alkyl, C₂₋₆alkenyl, and C₂₋₆alkynyl are optionally substituted with one or more R⁷⁰;

R⁸ and R⁹ are each hydrogen, or R⁸ and R⁹ together form =O; and

R¹⁰, R²⁰, R³⁰, R⁴⁰, R⁵⁰, and R⁷⁰ in each occurrence are each, independently, selected from halo, hydroxy, cyano, -CO₂H, C₁₋₆alkoxy, C₁₋₆alkyl, C₂₋₆alkenyl, and C₂₋₆alkynyl.

2. The compound of Formula (I), or a pharmaceutically acceptable salt thereof, as claimed in claim 1, wherein the compound is a compound of Formula (Ia):



Formula (Ia)

wherein R¹, R², R³, G, J, and M are as defined in claim 1.

3. The compound of Formula (I), or a pharmaceutically acceptable salt thereof, as claimed in any one of claims 1 and 2, wherein:

J is selected from C-R⁴ and N-R⁵;

M is selected from CH and CH₂;

wherein at least one of J and M is carbon, and wherein:

- i) if J is carbon, the J-M bond is a double bond, and

ii) if J is nitrogen, the J-M bond is a single bond and M is CH₂;

R⁴ is C₁₋₆alkyl;

R⁵ is selected from C₁₋₆alkyl, carbocyclyl, and -SO₂R^{5b}, wherein said C₁₋₆alkyl and carbocyclyl are optionally substituted with one or more R⁵⁰;

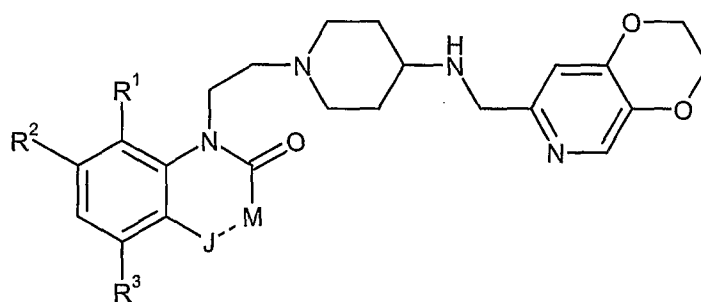
R^{5b} is C₁₋₆alkyl; and

R⁵⁰ in each occurrence is selected from hydroxy and C₂₋₆alkenyl.

4. The compound of Formula (I), or a pharmaceutically acceptable salt thereof, as claimed in any one of claims 1 to 3, wherein R¹ is H.
5. The compound of Formula (I), or a pharmaceutically acceptable salt thereof, as claimed in any one of claims 1 to 4, wherein:

R² is selected from halo, cyano, and -OR^{2a}; and

R^{2a} is C₁₋₆alkyl.
6. The compound of Formula (I), or a pharmaceutically acceptable salt thereof, as claimed in any one of claims 1 to 5, wherein R³ is H.
7. The compound of Formula (I), or a pharmaceutically acceptable salt thereof, as claimed in claim 1, wherein the compound is a compound of Formula (Ib):



Formula (Ib)

wherein R¹, R², R³, J, and M are as defined in claim 1.

8. The compound of Formula (I), or a pharmaceutically acceptable salt thereof, as claimed in any one of claims 1 and 7, wherein:

J is selected from C-R⁴ and N-R⁵;

M is selected from CH and CH₂;

wherein at least one of **J** and **M** is carbon, and wherein:

- i) if **J** is carbon, the J-M bond is a double bond, and
- ii) if **J** is nitrogen, the J-M bond is a single bond and **M** is CH₂;

R⁴ is C₁₋₆alkyl;

R⁵ is selected from C₁₋₆alkyl, carbocyclyl, and -SO₂R^{5b}, wherein said C₁₋₆alkyl and carbocyclyl are optionally substituted with one or more R⁵⁰;

R^{5b} is C₁₋₆alkyl; and

R⁵⁰ in each occurrence is selected from hydroxy and C₂₋₆alkenyl.

9. The compound of Formula (I), or a pharmaceutically acceptable salt thereof, as claimed in any one of claims 1, 7, and 8 wherein **R**¹ is H.
10. The compound of Formula (I), or a pharmaceutically acceptable salt thereof, as claimed in any one of claims 1, and 7 to 9, wherein:

R² is selected from halo, cyano, and -OR^{2a}; and

R^{2a} is C₁₋₆alkyl.
11. The compound of Formula (I), or a pharmaceutically acceptable salt thereof, as claimed in any one of claims 1, and 7 to 10, wherein **R**³ is H.
12. A compound of Formula (I), or a pharmaceutically acceptable salt thereof, as claimed in any one of claims 1 to 11, for use as a medicament.
13. The use of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, as claimed in any one of claims 1 to 11, in the manufacture of a medicament for the treatment of a bacterial infection in a warm-blooded animal such as man.
14. The use of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, as claimed in any one of claims 1 to 11, in the manufacture of a medicament for the treatment of a bacterial infection caused by one or more pathogenic organisms such as

Acinetobacter baumannii, *Aeromonas hydrophila*, *Bacillus anthracis*, *Bacteroides fragilis*, *Bordetella pertussis*, *Burkholderia cepacia*, *Chlamydia pneumoniae*, *Citrobacter freundii*, *Clostridium difficile*, *Enterobacter cloacae*, *Enterococcus faecalis*, *Enterococcus faecium*, *Enterobacter aerogenes*, *Escherichia coli*, *Fusobacterium necrophorum*, *Haemophilus influenzae*, *Haemophilus parainfluenzae*, *Haemophilus somnus*, *Klebsiella oxytoca*, *Klebsiella pneumoniae*, *Legionella pneumophila*, *Listeria monocytogenes*, *Moraxella catarrhalis*, *Morganella morganii*, *Mycoplasma pneumoniae*, *Neisseria gonorrhoeae*, *Neisseria meningitidis*, *Pasteurella multocida*, *Proteus mirabilis*, *Proteus vulgaris*, *Pseudomonas aeruginosa*, *Salmonella typhi*, *Salmonella typhimurium*, *Serratia marcescens*, *Shigella flexneria*, *Shigella dysenteriae*, *Staphylococcus aureus*, *Staphylococcus epidermidis*, *Staphylococcus haemolyticus*, *Staphylococcus intermedius*, *Staphylococcus saprophyticus*, *Stenotrophomonas maltophilia*, *Streptococcus agalactiae*, *Streptococcus mutans*, *Streptococcus pneumoniae*, and *Streptococcus pyogenes*, in a warm-blooded animal such as man.

15. The use of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, as claimed in any one of claims 1 to 11, in the manufacture of a medicament for the treatment of an infection such as bronchitis, *C. difficile* colitis, cervicitis, endocarditis, gonococcal urethritis, inhalation Anthrax, intra-abdominal infections, meningitis, osteomyelitis, otitis media, pharyngitis, pneumonia, prostatitis, septicemia, sinusitis, skin and soft tissue infections, and urinary tract infections, in a warm-blooded animal such as man.
16. The use of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, as claimed in any one of claims 1 to 11, in the manufacture of a medicament for the treatment of a bacterial infection, wherein the bacteria is of a genus selected from *Aeromonas*, *Acinetobacter*, *Bacillus*, *Bacteroides*, *Bordetella*, *Burkholderia*, *Chlamydia*, *Citrobacter*, *Clostridium*, *Enterobacter*, *Enterococcus*, *Escherichia*, *Flavobacterium*, *Fusobacterium*, *Haemophilus*, *Klebsiella*, *Legionella*, *Listeria*, *Morganella*, *Moraxella*, *Mycoplasma*, *Neisseria*, *Pasteurella*, *Peptococci*, *Peptostreptococci*, *Prevotella*, *Proteus*, *Salmonella*, *Pseudomonas*, *Serratia*, *Shigella*, *Stenotrophomonas*, *Streptococcus*, and *Staphylococcus*, in a warm-blooded animal such as man.

17. A method for treating a bacterial infection in a warm-blooded animal such as man, said method comprising administering to said animal an effective amount of a compound of formula (I), as claimed in any one of claims 1 to 11, or a pharmaceutically acceptable salt thereof.
18. A method for treating a bacterial infection caused by one or more pathogenic organisms such as *Acinetobacter baumannii*, *Aeromonas hydrophila*, *Bacillus anthracis*, *Bacteroides fragilis*, *Bordetella pertussis*, *Burkholderia cepacia*, *Chlamydia pneumoniae*, *Citrobacter freundii*, *Clostridium difficile*, *Enterobacter cloacae*, *Enterococcus faecalis*, *Enterococcus faecium*, *Enterobacter aerogenes*, *Escherichia coli*, *Fusobacterium necrophorum*, *Haemophilus influenzae*, *Haemophilus parainfluenzae*, *Haemophilus somnus*, *Klebsiella oxytoca*, *Klebsiella pneumoniae*, *Legionella pneumophila*, *Listeria monocytogenes*, *Moraxella catarrhalis*, *Morganella morganii*, *Mycoplasma pneumoniae*, *Neisseria gonorrhoeae*, *Neisseria meningitidis*, *Pasteurella multocida*, *Proteus mirabilis*, *Proteus vulgaris*, *Pseudomonas aeruginosa*, *Salmonella typhi*, *Salmonella typhimurium*, *Serratia marcescens*, *Shigella flexneria*, *Shigella dysenteriae*, *Staphylococcus aureus*, *Staphylococcus epidermidis*, *Staphylococcus haemolyticus*, *Staphylococcus intermedius*, *Staphylococcus saprophyticus*, *Stenotrophomonas maltophilia*, *Streptococcus agalactiae*, *Streptococcus mutans*, *Streptococcus pneumoniae*, and *Streptococcus pyogenes*, in a warm-blooded animal such as man, said method comprising administering to said animal an effective amount of a compound of Formula (I), as claimed in any one of claims 1 to 11, or a pharmaceutically acceptable salt thereof.
19. A method for treating a bacterial infection such as bronchitis, *C. difficile* colitis, cervicitis, endocarditis, gonococcal urethritis, inhalation Anthrax, intra-abdominal infections, meningitis, osteomyelitis, otitis media, pharyngitis, pneumonia, prostatitis, septicemia, sinusitis, skin and soft tissue infections, and urinary tract infections, in a warm-blooded animal such as man, said method comprising administering to said animal an effective amount of a compound of Formula (I), as claimed in any one of claims 1 to 11, or a pharmaceutically acceptable salt thereof.

20. A method for treating a bacterial infection, wherein the bacteria is of a genus selected from *Aeromonas*, *Acinetobacter*, *Bacillus*, *Bacteroides*, *Bordetella*, *Burkholderia*, *Chlamydophila*, *Citrobacter*, *Clostridium*, *Enterobacter*, *Enterococcus*, *Escherichia*, *Flavobacterium*, *Fusobacterium*, *Haemophilus*, *Klebsiella*, *Legionella*, *Listeria*, *Morganella*, *Moraxella*, *Mycoplasma*, *Neisseria*, *Pasteurella*, *Peptococci*, *Peptostreptococci*, *Prevotella*, *Proteus*, *Salmonella*, *Pseudomonas*, *Serratia*, *Shigella*, *Stenotrophomonas*, *Streptococcus*, and *Staphylococcus*, in a warm-blooded animal such as man, said method comprising administering to said animal an effective amount of a compound of Formula (I), as claimed in any one of claims 1 to 11, or a pharmaceutically acceptable salt thereof.
21. A compound of Formula (I), or a pharmaceutically acceptable salt thereof, as claimed in any one of claims 1 to 11, for use in treating a bacterial infection in a warm-blooded animal, such as man.
22. A compound of Formula (I), or a pharmaceutically acceptable salt thereof, as claimed in any one of claims 1 to 11, for use in treating a bacterial infection caused by one or more pathogenic organisms such as *Acinetobacter baumannii*, *Aeromonas hydrophila*, *Bacillus anthracis*, *Bacteroides fragilis*, *Bordetella pertussis*, *Burkholderia cepacia*, *Chlamydia pneumoniae*, *Citrobacter freundii*, *Clostridium difficile*, *Enterobacter cloacae*, *Enterococcus faecalis*, *Enterococcus faecium*, *Enterobacter aerogenes*, *Escherichia coli*, *Fusobacterium necrophorum*, *Haemophilus influenzae*, *Haemophilus parainfluenzae*, *Haemophilus somnus*, *Klebsiella oxytoca*, *Klebsiella pneumoniae*, *Legionella pneumophila*, *Listeria monocytogenes*, *Moraxella catarrhalis*, *Morganella morganii*, *Mycoplasma pneumoniae*, *Neisseria gonorrhoeae*, *Neisseria meningitidis*, *Pasteurella multocida*, *Proteus mirabilis*, *Proteus vulgaris*, *Pseudomonas aeruginosa*, *Salmonella typhi*, *Salmonella typhimurium*, *Serratia marcescens*, *Shigella flexneria*, *Shigella dysenteriae*, *Staphylococcus aureus*, *Staphylococcus epidermidis*, *Staphylococcus haemolyticus*, *Staphylococcus intermedius*, *Staphylococcus saprophyticus*, *Stenotrophomonas maltophilia*, *Streptococcus agalactiae*, *Streptococcus mutans*, *Streptococcus pneumoniae*, and *Streptococcus pyogenes*, in a warm-blooded animal such as man.

23. A compound of Formula (I), or a pharmaceutically acceptable salt thereof, as claimed in any one of claims 1 to 11, for use in treating infections such as bronchitis, *C. difficile* colitis, cervicitis, endocarditis, gonococcal urethritis, inhalation Anthrax, intra-abdominal infections, meningitis, osteomyelitis, otitis media, pharyngitis, pneumonia, prostatitis, septicemia, sinusitis, skin and soft tissue infections, and urinary tract infections, in a warm-blooded animal such as man.
24. A compound of Formula (I), or a pharmaceutically acceptable salt thereof, as claimed in any one of claims 1 to 11, for use in treating a bacterial infection, wherein the bacteria is of a genus selected from *Aeromonas*, *Acinetobacter*, *Bacillus*, *Bacteroides*, *Bordetella*, *Burkholderia*, *Chlamydophila*, *Citrobacter*, *Clostridium*, *Enterobacter*, *Enterococcus*, *Escherichia*, *Flavobacterium*, *Fusobacterium*, *Haemophilus*, *Klebsiella*, *Legionella*, *Listeria*, *Morganella*, *Moraxella*, *Mycoplasma*, *Neisseria*, *Pasteurella*, *Peptococci*, *Peptostreptococci*, *Prevotella*, *Proteus*, *Salmonella*, *Pseudomonas*, *Serratia*, *Shigella*, *Stenotrophomonas*, *Streptococcus*, and *Staphylococcus*, and *Munnheimia*, in a warm-blooded animal such as man.
25. A pharmaceutical composition comprising a compound of Formula (I), or a pharmaceutically acceptable salt thereof, as claimed in any one of claims 1 to 11, and at least one pharmaceutically acceptable carrier, diluent, or excipient.

INTERNATIONAL SEARCH REPORT

International application No
PCT/GB2007/004794

A. CLASSIFICATION OF SUBJECT MATTER

INV. C07D493/04 C07D498/04 C07D513/04

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2004/002490 A (GLAXO GROUP LTD [GB]; AXTEN JEFFREY MICHAEL [US]; DAINES ROBERT A [US]) 8 January 2004 (2004-01-08) page 64, line 10 - line 20 -----	1,12-25
E	WO 2008/009700 A1 (GLAXO GROUP LIMITED, UK) 24 January 2008 (2008-01-24) claims 1-23 -----	1-25
P,X	WO 2006/137485 A1 (TOYAMA CHEMICAL CO., LTD., JAPAN; TAISHO PHARMACEUTICAL CO., LTD.) 28 December 2006 (2006-12-28) page 21 -----	1-25
P,X	WO 2006/134378 A (ASTRAZENECA AB [SE]; ASTRAZENECA UK LTD [GB]; BREAUULT GLORIA [US]; EYE) 21 December 2006 (2006-12-21) claims 1-20 -----	1-25



Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents:

A document defining the general state of the art which is not considered to be of particular relevance

E earlier document but published on or after the international filing date

L document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

O document referring to an oral disclosure, use, exhibition or other means

P document published prior to the international filing date but later than the priority date claimed

T later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

X document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

Y document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

Z document member of the same patent family

Date of the actual completion of the international search

26 February 2008

Date of mailing of the International search report

05/03/2008

Name and mailing address of the ISA/

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Authorized officer

Bader, Karl Günther

INTERNATIONAL SEARCH REPORT

International application No.
PCT/GB2007/004794

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 Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: —
because they relate to subject matter not required to be searched by this Authority, namely:
see FURTHER INFORMATION sheet PCT/ISA/210
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 6.4(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 allsearchable 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 reportcovers 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.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box II.1

Although claims 17-20 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

Continuation of Box II.1

Claims Nos.: -

Rule 39.1(iv) PCT - Method for treatment of the human or animal body by therapy

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/GB2007/004794

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
WO 2004002490	A	08-01-2004	AU 2003238054 A1	19-01-2004
			EP 1583537 A2	12-10-2005
			JP 2006505505 T	16-02-2006
			US 2006058287 A1	16-03-2006
WO 2008009700	A1	24-01-2008	NONE	
WO 2006137485	A1	28-12-2006	NONE	
WO 2006134378	A	21-12-2006	AR 054781 A1	18-07-2007
			AU 2006258879 A1	21-12-2006
			UY 29608 A1	31-01-2007