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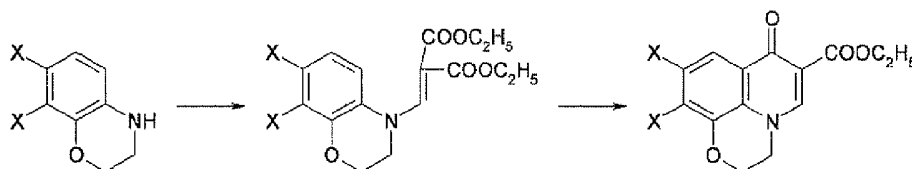
(54) Title: REDOX DRUG DERIVATIVES

(57) Abstract: The present invention provides redox drug derivatives. In particular, 9-fluoro-2,3-dihydro-3-methyl-10-(4-methyl-1-piperazinyl)-7-oxo-7H-pyrido[1,2,3-de]-1,4-benzoxazine-6-carboxylic acid, 1-ethyl-6-fluoro-1,4-dihydro-7-(4-methyl-1-piperazinyl)-4-oxo-3-quinolincarboxylic acid, (3R, 4R, 5S)-4-(acetylamino)-5-amino-3-(1-ethylpropoxy)-1-cyclohexene-1-carboxylic acid ethyl ester, (3S)-3-(aminomethyl)-5-methylhexanoic acid, (3S)-1-[2-(2,3-dihydro-5-benzofuranyl)ethyl]- α - α -diphenyl-3-pyrrolidineacetamide, (1S,2S,3S,4R)-3-[(1S)-1-acetamido-2-ethyl-butyl]-4-(diaminomethylideneamino)-2-hydroxy-cyclopentane-1-carboxylic acid and (2R,3R,4S)-4-[(diaminomethylideneamino)-3-acetamido-2-[(1R,2R)-1,2,3-trihydroxypropyl]-3,4-dihydro-2H-pyran-6-carboxylic acid redox derivatives.

Redox Drug Derivatives

The present invention relates to redox drug derivatives. In particular, the present invention relates to 9-fluoro-2,3-dihydro-3-methyl-10-(4-methyl-1-piperazinyl)-7-oxo-7H-pyrido[1,2,3-de]-1,4-benzoxazine-6-carboxylic acid (ofloxacin), 1-ethyl-6-fluoro-1,4-dihydro-7-(4-methyl-1-piperazinyl)-4-oxo-3-quinolinecarboxylic acid (pefloxacin), (3R, 4R, 5S)-4-(acetylamino)-5-amino-3-(1-ethylpropoxy)-1-cyclohexene-1-carboxylic acid ethyl ester (oseltamivir), (3S)-3-(aminomethyl)-5-methylhexanoic acid (pregabalin), (3S)-1-[2-(2,3-dihydro-5-benzofuranyl)ethyl]- α - α -diphenyl-3-pyrrolidineacetamide (darifenacin), (1S,2S,3S,4R)-3-[(1S)-1-acetamido-2-ethyl-butyl]-4-(diaminomethylideneamino)-2-hydroxy-cyclopentane-1-carboxylic acid (peramivir) and (2R,3R,4S)-4-[[diaminomethylidene)amino]-3-acetamido-2-[(1R,2R)-1,2,3-trihydroxypropyl]-3,4-dihydro-2H-pyran-6-carboxylic acid (zanamivir) redox derivatives.

Ofloxacin was first disclosed in EP 0 047 005 and US 4,382,892. This disclosure included a racemic mixture of the two enantiomers of ofloxacin. The optically active enantiomer was disclosed in EP 0 206 283. Pefloxacin was first disclosed in DE 2840910 and US 4,292,317. An essential feature of the compounds disclosed in each of these documents is the substitution at the 6-position by a carboxylic acid and at the 7-position by an oxo group. Thus, it is considered that the specific substitution at the 6- and 7-positions of the ring is central to providing the desired antibacterial activity properties of the compounds. Moreover the synthetic route for ofloxacin disclosed in EP 0 047 005 involves the conversion of a 4-aza-chromane compound to the below illustrated di-ester compound which is subsequently ring-closed to form an ofloxacin precursor:



Thus, in addition to being considered essential to providing the desired antibacterial activity properties of the compounds, this specific substitution results from the synthesis of the active compound.

Oseltamivir was first disclosed in US 5,763,483. It appears that the combination of (i) an ester group at the double bond on the cyclohexene ring, and (ii) an amine group para to the ester are essential in obtaining an active compound.

5 Pregabalin was first disclosed in US 5,563,175 in which its use, amongst other 3-alkyl-4-aminobutyric acid analogues, as an anticonvulsant was also disclosed. In addition to this document, US 6,001,876 and US 6,127,418 disclose a series of 3-alkyl-4-aminobutyric acid analogues which are useful in the treatment of pain and in preventing and treating gastrointestinal damage respectively. The essential features of the
10 compounds disclosed in each of the above documents are the terminal amine group and the opposing terminal carboxylic acid group. Thus, it is considered that these features are essential for providing the desired GABA regulating activity of the compounds which is believed to be responsible for the useful effects of these compounds.

15 Darifenacin, and its activity as a muscarinic receptor antagonist, was first disclosed in US 5,096,890. This document discloses, in particular, compounds having an amide group adjacent to the two phenyl rings. There are also disclosed compounds having a nitrile group adjacent to the two phenyl rings, the nitrile moiety being in place of the amide moiety. However, it is considered that the presence of the amide group is
20 essential in imparting the antagonistic activity of these compounds as it is disclosed that the analogous nitrile compound is useful as a synthetic intermediate but has low activity as a muscarinic receptor antagonists.

Zanamivir was first disclosed in US 5,360,817. It appears that the combination of (i) a
25 carboxylic acid group at the double bond on the cyclohexene ring, and (ii) an amine group para to the carboxylic acid group are essential in obtaining an active compound.

The acid forms of the parent compounds, for example ofloxacin, pefloxacin and pregabalin, may suffer problems in terms of stability over an extended period of time.
30 For example, ofloxacin and pefloxacin may undergo decarboxylation of the terminal acid. This represents a significant problem during manufacture of an active principal or during extended storage of the same in a pharmacy. Similarly, the unprotected amide form of darifenacin is subject to hydrolysis to the carboxylic acid derivative. The resulting decomposition products may have reduced activity and potentially increased
35 toxicity when compared with the parent active.

It is therefore an aim of the present invention to provide reduced or oxidised derivatives of active compounds which are able to demonstrate similar to or better than the parent active compound. It is also an aim of the present invention to provide compounds which have an IC50 value comparable to or better than that of the parent active. Ideally, these
5 reduced or oxidised derivatives will have good stability and bioavailability relative to the parent active compound. It is thus an aim to provide reduced or oxidised derivatives having improved stability. Ideally, the reduced or oxidised derivatives will have an extended shelf-life. It is thus an aim of the present invention to provide further
10 compounds having improved bioavailability.

This invention provides compounds that achieve one or more of the above aims. The compounds may be active in their own right or may metabolise or react in aqueous media to yield a parent active compound.

15 According to a first aspect, the present invention provides a method of preparing an oxidised or reduced pharmaceutical active derivative, comprising:

- (i) obtaining a parent pharmaceutical active;
- (ii) oxidising the parent pharmaceutical active to provide an oxidised pharmaceutical active derivative which is in an oxidation state one or
20 more oxidation states higher than the parent pharmaceutical active; or reducing the parent pharmaceutical active to provide a reduced pharmaceutical active derivative which is in an oxidation state one or more oxidation states lower than the parent pharmaceutical active; and
- (iii) isolating the oxidised or reduced pharmaceutical active derivative.

25 The term derivative in this context means a compound that is identical to a target active compound (which may be an approved drug compound or a known active structural compound of the same class as an approved drug compound) in terms of its structure except that one or more functional groups in the compound have been oxidised or
30 reduced.

This approach is novel and the finding of activity for compounds of the invention is contrary to normal expectations in the pharmaceutical industry. Whilst, it is may be conventional in the industry to aim to provide prodrugs of certain compounds, the
35 industry has been very wary of modifying active compounds to any significant degree. In addition, there is a concern in the industry that compounds such as aldehydes could be

potentially problematic in terms of their effects. Thus aldehydes, acetal, hemi-acetals and related compounds in the same oxidation state as these have been avoided since it is expected that they will not be viable development candidates. Surprisingly, we have found that we can provide active compounds or compounds that metabolise to active
5 compounds by modifying the oxidation state of certain key functional groups in known active compounds. This effect is surprising given that the modification of the oxidation state of one or more functional groups in a known active will inevitably have an effect on the electronic distribution and hence binding of a molecule. Similarly, the overall stereochemistry is likely to be affected which will also affect binding of a molecule at the
10 target receptor site. Thus the finding of activity in the compounds of the invention is both unpredictable and unexpected.

For a compound to qualify as a parent pharmaceutical active drug compound that is suitable for synthetic modification according to the invention, the parent must contain
15 one or more oxidisable or reducible functional groups. Another requirement of the parent compound is that it must have existing pharmaceutical activity against a particular target. The parent compound is preferably an approved drug. Preferably, the oxidisable or reducible functional group is selected from the group comprising: hydroxyl, carbonyl, carboxylate, amine, amide, imine, and ester. The compound according to the
20 invention will, in one embodiment, thus contain at least one functional group that can be obtained by or has been obtained by reducing or oxidising (as chemically appropriate) one or more groups in the parent active compound selected from the group comprising: hydroxyl, carbonyl, carboxylate, amine, amide, imine, and ester. Most preferred are compounds of the invention derived from a parent having one or more of: hydroxyl,
25 carbonyl, and carboxylate groups.

The efficacy of the compounds of the invention against a particular target can be demonstrated for example by *in silico* modelling, or by conventional *in vitro* or *in vivo* testing. The *in silico* modelling provides a good proof of efficacy of the compounds of
30 the invention.

In an embodiment, step (ii) of the method comprises oxidising the parent pharmaceutical active to provide an oxidised pharmaceutical active derivative.

35 In an embodiment, step (ii) of the method comprises reducing the parent pharmaceutical active to provide a reduced pharmaceutical active derivative.

Processes for the manufacture of parent pharmaceutical active are disclosed in EP 0 206 283, US 4,292,317, US 5,763,483, US 5,563,175 and 5,096,890 and, in particular, in the examples of these documents. The disclosures of EP 0 206 283, US 4,292,317,
5 US 5,763,483, US 5,563,175, 5,096,890 and US 5,360,817 insofar as the synthetic procedures are concerned form part of the disclosure of the present invention. In the interests of brevity, the details of these synthetic procedures are not reproduced here but it is intended that this subject matter is specifically incorporated into the disclosure of these documents by reference.

10

Each of the compounds of the present invention may be used as a medicament.

The compounds of the present invention may be used in the treatment of treatment of bacterial infections. For example, diseases such as pneumonia, urinary tract infections,
15 acute bacterial sinusitis, acute bacterial exacerbation of chronic bronchitis, anthrax, various skin infections, chronic bacterial prostatitis, acute pyelonephritis.

The compounds of the present invention may also be used in the treatment of conditions treatable by neuraminidase inhibition. For example, the compounds of the present
20 invention may be used to treat viral infections, in particular, infections caused by the influenza virus.

The compounds of the present invention may also be used in treating conditions treatable by modulating GABA turnover and, in particular, in the treatment of neuropathic
25 pain such as neuropathic pain from diabetic neuropathy or post herpetic neuralgia. The compounds of the present invention may also be used in the treatment of seizures. The compounds of the present invention may also be used in various anxiety disorders, such as bipolar disorder or generalised depression.

30 The compounds of the present invention may also be used in conditions treatable by blocking the M₃-muscarinic acetylcholine receptor. In particular, the compounds of the present invention may also be used in the treatment of urinary incontinence, oesophageal achalasia, irritable bowel syndrome and chronic obstructive airways disease.

35

The skilled man will appreciate that adaptation of methods known in the art could be applied in the manufacture of the compounds of the present invention.

For example, the skilled person will be immediately familiar with standard textbooks such as "Comprehensive Organic Transformations - A Guide to Functional Group Transformations", RC Larock, Wiley-VCH (1999 or later editions), "March's Advanced Organic Chemistry - Reactions, Mechanisms and Structure", MB Smith, J. March, Wiley, (5th edition or later) "Advanced Organic Chemistry, Part B, Reactions and Synthesis", FA Carey, RJ Sundberg, Kluwer Academic/Plenum Publications, (2001 or later editions), "Organic Synthesis - The Disconnection Approach", S Warren (Wiley), (1982 or later editions), "Designing Organic Syntheses" S Warren (Wiley) (1983 or later editions), "Guidebook To Organic Synthesis" RK Mackie and DM Smith (Longman) (1982 or later editions), etc., and the references therein as a guide.

The skilled chemist will exercise his judgement and skill as to the most efficient sequence of reactions for synthesis of a given target compound and will employ protecting groups as necessary. This will depend *inter alia* on factors such as the nature of other functional groups present in a particular substrate. Clearly, the type of chemistry involved will influence the choice of reagent that is used in the said synthetic steps, the need, and type, of protecting groups that are employed, and the sequence for accomplishing the protection / deprotection steps. These and other reaction parameters will be evident to the skilled person by reference to standard textbooks and to the examples provided herein.

Sensitive functional groups may need to be protected and deprotected during synthesis of a compound of the invention. This may be achieved by conventional methods, for example as described in "Protective Groups in Organic Synthesis" by TW Greene and PGM Wuts, John Wiley & Sons Inc (1999), and references therein.

Compounds of the invention intended for pharmaceutical use may be administered as crystalline or amorphous products. They may be obtained, for example, as solid plugs, powders, or films by methods such as precipitation, crystallization, freeze drying, or spray drying, or evaporative drying. Microwave or radio frequency drying may be used for this purpose.

Compounds of the invention containing one or more asymmetric carbon atoms can exist as two or more stereoisomers. Where a compound of the invention contains a double bond such as a C=C or C=N group, geometric cis/trans (or Z/E) isomers are possible. Where structural isomers are interconvertible via a low energy barrier, tautomeric isomerism ('tautomerism') can occur. This can take the form of proton tautomerism in compounds of the invention containing, for example, an imino, keto, or oxime group, or so-called valence tautomerism in compounds which contain an aromatic moiety. It follows that a single compound may exhibit more than one type of isomerism.

Included within the scope of the present invention are all stereoisomers, geometric isomers and tautomeric forms of the compounds of the invention, including compounds exhibiting more than one type of isomerism, and mixtures of one or more thereof. Also included are acid addition or base salts wherein the counter ion is optically active, for example, d-lactate or l-lysine, or racemic, for example, dl-tartrate or dl-arginine.

Cis/trans isomers may be separated by conventional techniques well known to those skilled in the art, for example, chromatography and fractional crystallisation.

Conventional techniques for the preparation/isolation of individual enantiomers when necessary include chiral synthesis from a suitable optically pure precursor or resolution of the racemate (or the racemate of a salt or derivative) using, for example, chiral high pressure liquid chromatography (HPLC).

Alternatively, the racemate (or a racemic precursor) may be reacted with a suitable optically active compound, for example, an alcohol, or, in the case where the compound of the invention contains an acidic or basic moiety, a base or acid such as 1-phenylethylamine or tartaric acid. The resulting diastereomeric mixture may be separated by chromatography and/or fractional crystallization and one or both of the diastereoisomers converted to the corresponding pure enantiomer(s) by means well known to a skilled person.

Chiral compounds of the invention (and chiral precursors thereof) may be obtained in enantiomerically-enriched form using chromatography, typically HPLC, on an asymmetric resin with a mobile phase consisting of a hydrocarbon, typically heptane or hexane, containing from 0 to 50% by volume of isopropanol, typically from 2% to 20%, and from 0

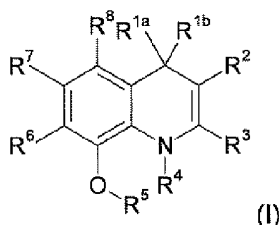
to 5% by volume of an alkylamine, typically 0.1% diethylamine. Concentration of the eluate affords the enriched mixture.

When any racemate crystallises, crystals of two different types are possible. The first type
 5 is the racemic compound (true racemate) referred to above wherein one homogeneous form of crystal is produced containing both enantiomers in equimolar amounts. The second type is the racemic mixture or conglomerate wherein two forms of crystal are produced in equimolar amounts each comprising a single enantiomer.

10 While both of the crystal forms present in a racemic mixture have identical physical properties, they may have different physical properties compared to the true racemate. Racemic mixtures may be separated by conventional techniques known to those skilled in the art - see, for example, "Stereochemistry of Organic Compounds" by E. L. Eliel and S. H. Wilen (Wiley, 1994).

15

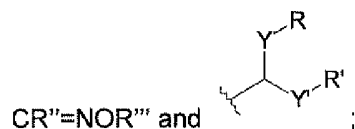
According to a second aspect, the present invention provides a compound of formula I:



wherein:

R^{1a} and R^{1b} are together selected from the group comprising: oxo and =NOR''; or
 20 R^{1a} is -H and R^{1b} is -OR''; and

R^2 is selected from the group comprising: -COOR'', -CR''O, -CR''R''OR'', -



wherein

-Y- is selected from the group comprising: =N-, -O- and -S-;

25 -Y'- is selected from the group comprising: -O- and -S-;

each R, R' and R'' is independently selected from the group comprising: -H and C₁₋₄ alkyl; or each R'' is independently selected from the group comprising: -H and C₁₋₄ alkyl, and R and R' join to form a 5 to 8 membered ring together with the atoms to which they are bonded; and

R^{'''} is selected from the group comprising: H, C₁₋₄ alkyl and -(CR^{'''}R^{'''})_n-aryl; wherein each R^{'''} is independently selected from the group comprising: H and aryl and wherein n is from 1 to 4;

5 R³, R⁷ and R⁸ are each independently selected from the group comprising: H, substituted or unsubstituted C₁₋₄alkyl and halogen;

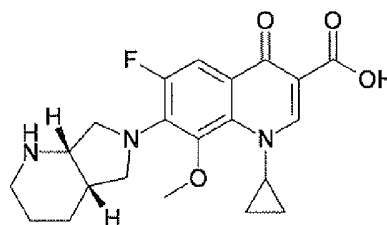
R⁴ and R⁵ are each independently substituted or unsubstituted C₁₋₄alkyl; or R⁴ and R⁵ join to form a 6 membered ring together with the atoms to which they are bonded;

10 R⁶ is a substituted or unsubstituted N-heterocycloalkyl group comprising from 5 to 10 ring atoms and at least one nitrogen atom;

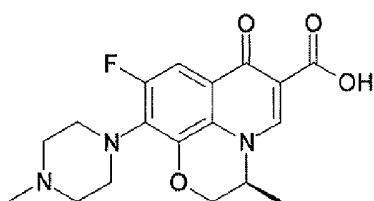
wherein, where chemically possible, each alkyl and each aryl may be independently substituted with up to 5 substituents independently selected from the group comprising:

15 F, Cl, Br, CN, NO₂, OR^{''} or OH; and

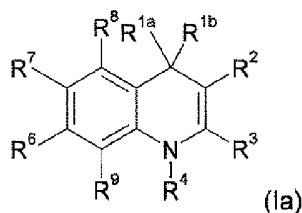
provided that the compound is not



or



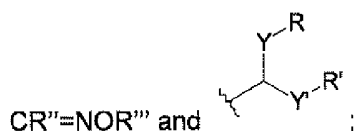
20 According to a third aspect, the present invention provides a compound of formula (Ia):



wherein:

R^{1a} and R^{1b} are together selected from the group comprising: oxo and =NOR^{''}; or R^{1a} is -H and R^{1b} is -OR^{''}; and

R^2 is selected from the group comprising: $-\text{COOR}''$, $-\text{CR}''\text{O}$, $-\text{CR}''\text{R}''\text{OR}''$, -



wherein

$-\text{Y}-$ is selected from the group comprising: $=\text{N}-$, $-\text{O}-$ and $-\text{S}-$;

5 $-\text{Y}'-$ is selected from the group comprising: $-\text{O}-$ and $-\text{S}-$;

each R , R' and R'' is independently selected from the group comprising: $-\text{H}$ and C_{1-4} alkyl; or each R'' is independently selected from the group comprising: $-\text{H}$ and C_{1-4} alkyl, and R and R' join to form a 5 to 8 membered ring together with the atoms to which they are bonded; and

10 R''' is selected from the group comprising: H , C_{1-4} alkyl and $-(\text{CR}''''\text{R}''''))_n-$ aryl; wherein R'''' is selected from the group comprising: H and aryl;

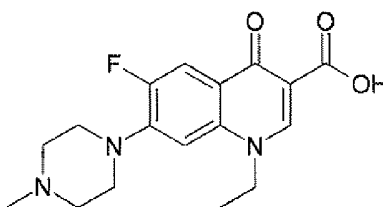
R^3 , R^7 , R^8 and R^9 are each independently selected from the group comprising: H , substituted or unsubstituted C_{1-4} alkyl and halogen;

15 R^4 is a substituted or unsubstituted C_{1-4} alkyl;

R^6 is a substituted or unsubstituted N-heterocycloalkyl group comprising from 5 to 10 ring atoms and at least one nitrogen atom;

wherein, where chemically possible, each alkyl and each aryl may be independently substituted with up to 5 substituents independently selected from the group comprising: F , Cl , Br , CN , NO_2 , OR'' or OH ; and

20



provided that the compound is not

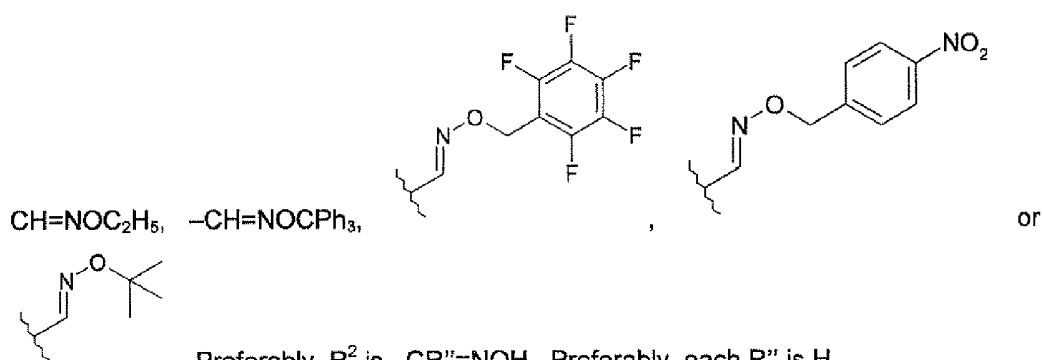
The following embodiments apply to the compounds of the above second and third aspects.

25

In an embodiment, when R^{1a} and R^{1b} together are oxo, R^2 is not $-\text{COOH}$.

In an embodiment, R^{1a} and R^{1b} are together oxo. In an alternative embodiment, R^{1a} and R^{1b} are together =NOR". Preferably, R^{1a} and R^{1b} are together =NOH. In an alternative embodiment, R^{1a} is H and R^{1b} is -OR". Preferably, R^{1a} is H and R^{1b} is -OH.

- 5 In an embodiment, R^2 is selected from the group comprising: -COOR", -CR"O and -CR"R"OR". Preferably, R^2 is selected from the group comprising: -COOH, -CR"O and -CR"R"OH. In an alternative embodiment, R^2 is -CR"=NOR", e.g. -CH=NOCH₂Ph, -



10

In an embodiment, R^3 is H.

In an embodiment, R^4 is substituted or unsubstituted C₁₋₃alkyl. In an embodiment, R^4 is substituted or unsubstituted cyclopropyl, preferably unsubstituted cyclopropyl.

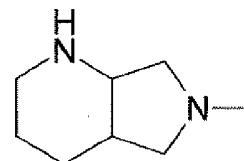
- 15 In an alternative embodiment, R^4 is substituted or unsubstituted ethyl.

In an embodiment, R^5 is substituted or unsubstituted C₁₋₃alkyl. In an embodiment, R^5 is methyl.

- 20 In an embodiment, R^4 is ethyl and R^5 is methyl and R^4 and R^5 join to form a 6 membered ring together with the atoms to which they are bonded.

In an embodiment, R^6 is a substituted or unsubstituted N-heterocycloalkyl group comprising from 5, 6, 7, 8, 9 or 10 ring atoms and at least one nitrogen atom.

- 25 Preferably, the N-heterocycloalkyl group comprises at least two nitrogen atoms. In an embodiment, R^6 is substituted or unsubstituted piperazine, preferably N-methyl piperazine.



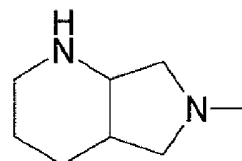
In an embodiment, R^6 is substituted or unsubstituted group of preferably unsubstituted.

In an embodiment, R^7 is halogen. Preferably, R^7 is fluoro.

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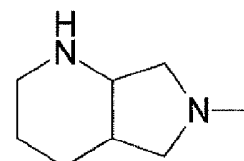
In an embodiment, R^8 is hydrogen.

In an embodiment, R^3 is H, R^7 is fluoro and R^8 is hydrogen.



10 In an embodiment, R^4 is cyclopropyl, R^5 is methyl and R^6 is

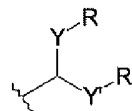
In an embodiment, R^4 is ethyl, R^5 is methyl, and R^4 and R^5 join to form a 6 membered ring together with the atoms to which they are bonded, and R^6 is N-methyl piperazine.

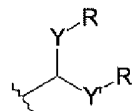


15 In an embodiment, R^3 is H, R^4 is cyclopropyl, R^5 is methyl, R^6 is R^7 is fluoro and R^8 is hydrogen.

In an embodiment, R^3 is H, R^4 is ethyl, R^5 is methyl, and R^4 and R^5 join to form a 6 membered ring together with the atoms to which they are bonded, R^6 is N-methyl
20 piperazine, R^7 is fluoro and R^8 is hydrogen.

In an embodiment, R'' is H.



In an embodiment, the ring formed by the R and R' in  is a 5 to 7 membered ring, preferably a 5 or 6 membered ring.

In an embodiment, Y and Y' are each -O-. In an alternative embodiment, Y and Y' are each -S-. In a further alternative embodiment, Y is -O- and Y' is -S-. In another embodiment, Y is =N- and Y' is -O-. In another embodiment, Y is =N- and Y' is -S-.

In an embodiment, R is H. In an embodiment, R' is H. In an alternative embodiment, R and R' are each C₁₋₃alkyl, e.g. methyl, ethyl or propyl. In an alternative embodiment, one of R and R' is H and the other is C₁₋₃alkyl, e.g. methyl, ethyl or propyl.

In an embodiment, Y, Y', R and R' are selected from the following table:

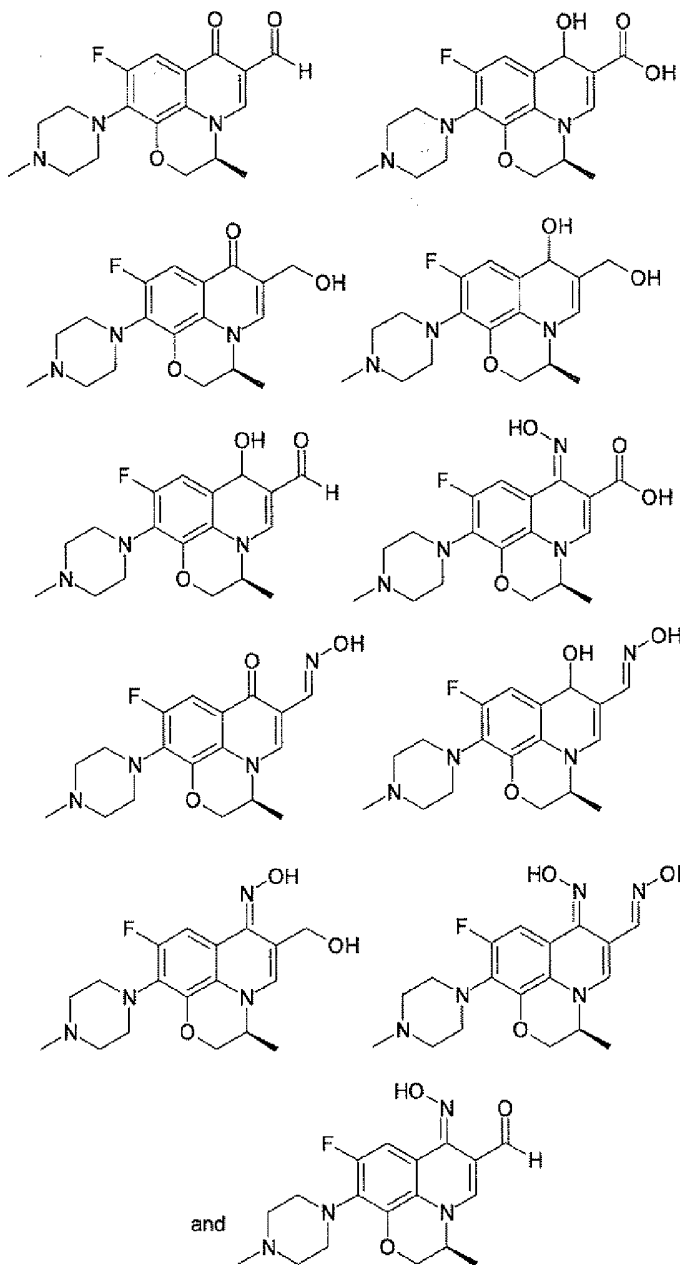
Y	Y'	R	R'
-O-	-O-	H	H
-S-	-O-	H	H
-S-	-S-	H	H
=N-	-O-	H	H
=N-	-S-	H	H
-O-	-O-	Methyl	H
-O-	-O-	Ethyl	H
-O-	-O-	Propyl	H
-S-	-O-	Methyl	H
-S-	-O-	Ethyl	H
-S-	-O-	Propyl	H
=N-	-O-	Methyl	H
=N-	-O-	Ethyl	H
=N-	-O-	Propyl	H
-O-	-S-	Methyl	H
-O-	-S-	Ethyl	H
-O-	-S-	Propyl	H
-S-	-S-	Methyl	H

-S-	-S-	Ethyl	H
-S-	-S-	Propyl	H
=N-	-S-	Methyl	H
=N-	-S-	Ethyl	H
=N-	-S-	Propyl	H
-O-	-O-	Methyl	C ₁₋₃ alkyl
-O-	-O-	Ethyl	C ₁₋₃ alkyl
-O-	-O-	Propyl	C ₁₋₃ alkyl
-S-	-O-	Methyl	C ₁₋₃ alkyl
-S-	-O-	Ethyl	C ₁₋₃ alkyl
-S-	-O-	Propyl	C ₁₋₃ alkyl
=N-	-O-	Methyl	C ₁₋₃ alkyl
=N-	-O-	Ethyl	C ₁₋₃ alkyl
=N-	-O-	Propyl	C ₁₋₃ alkyl
-O-	-S-	Methyl	C ₁₋₃ alkyl
-O-	-S-	Ethyl	C ₁₋₃ alkyl
-O-	-S-	Propyl	C ₁₋₃ alkyl
-S-	-S-	Methyl	C ₁₋₃ alkyl
-S-	-S-	Ethyl	C ₁₋₃ alkyl
-S-	-S-	Propyl	C ₁₋₃ alkyl
=N-	-S-	Methyl	C ₁₋₃ alkyl
=N-	-S-	Ethyl	C ₁₋₃ alkyl
=N-	-S-	Propyl	C ₁₋₃ alkyl

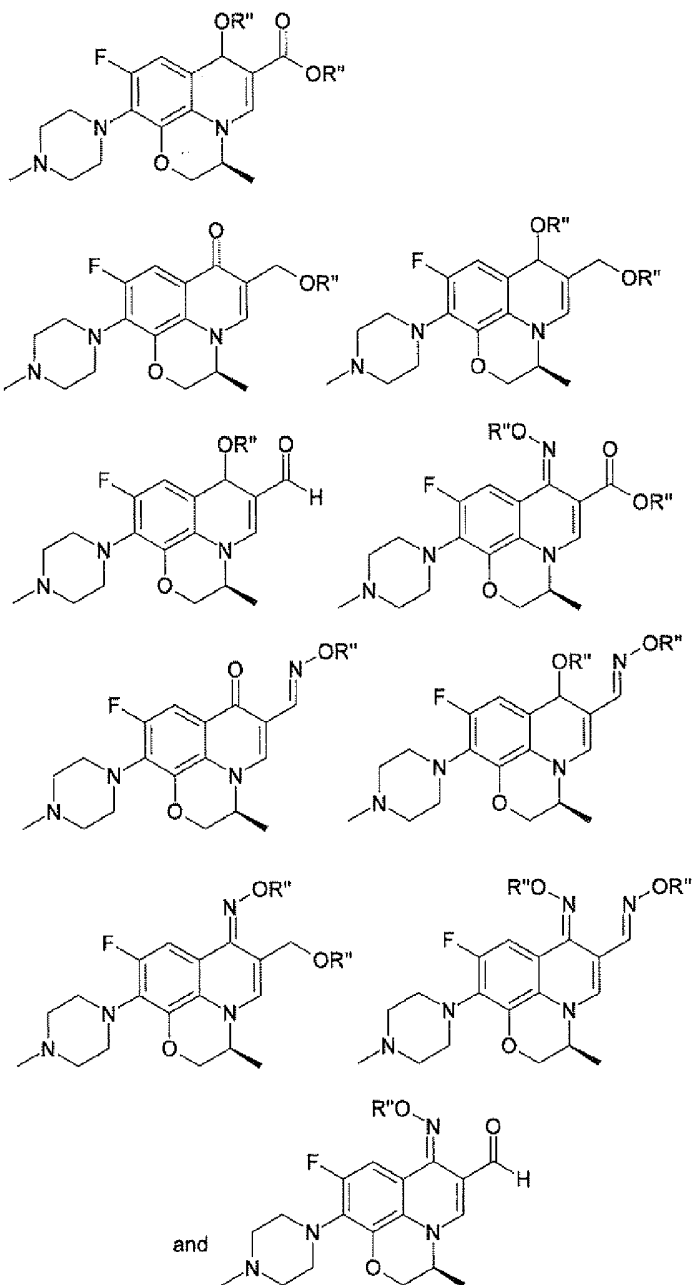
wherein C₁₋₃alkyl includes methyl, ethyl and propyl.

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In an embodiment, the compound of formula I is selected the group comprising:



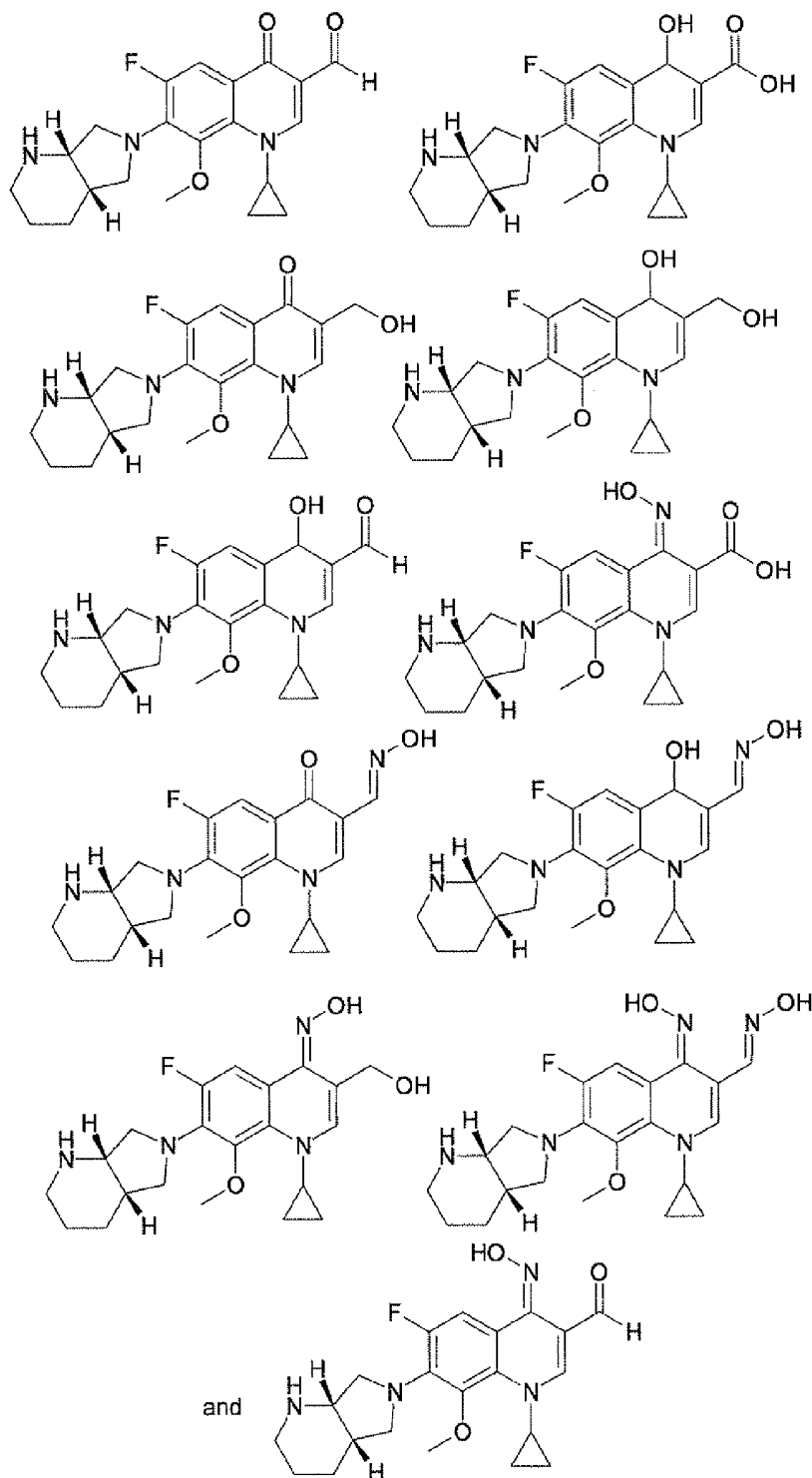
In an embodiment, the compound of formula I is selected the group comprising:



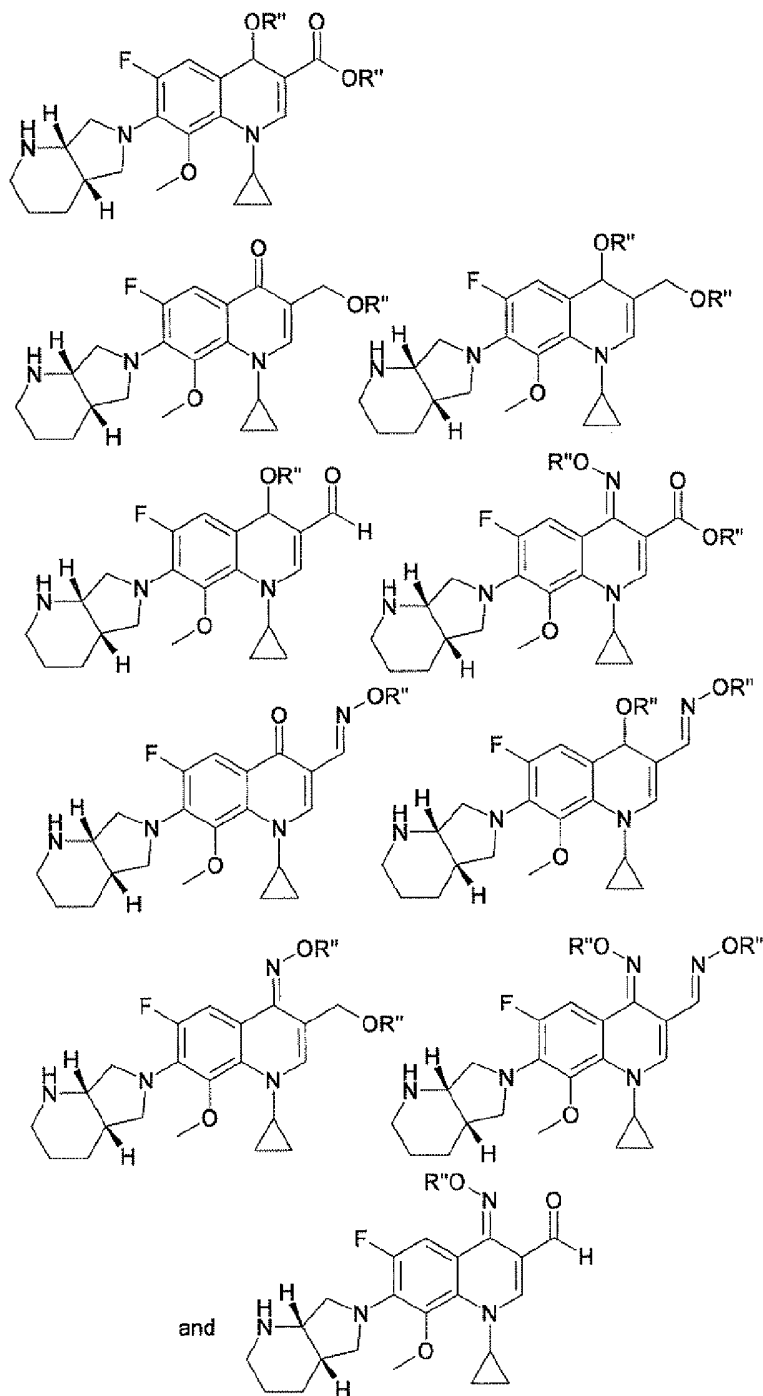
, wherein R'' is as defined

above.

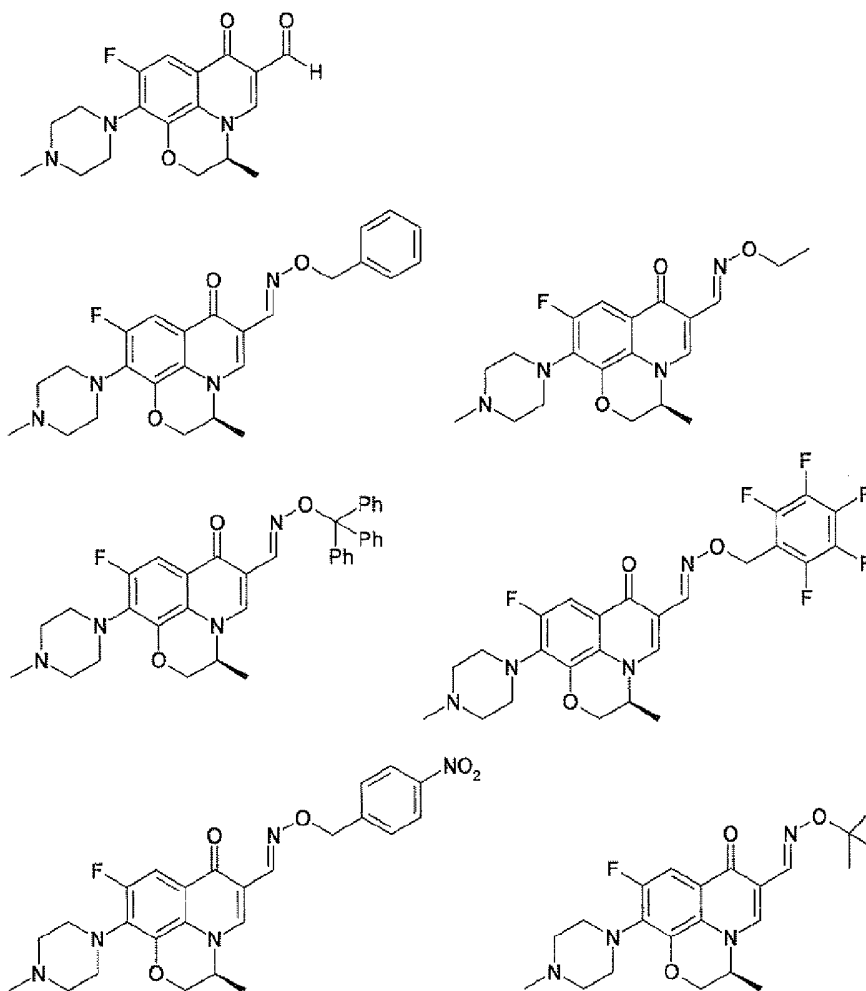
In an embodiment, the compound of formula I is selected the group comprising:



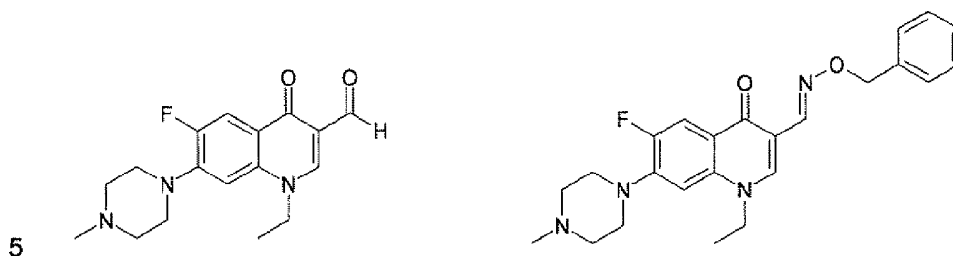
In an embodiment, the compound of formula I is selected the group comprising:



In an embodiment, the compound of formula I is selected the group comprising:

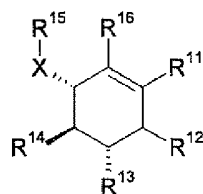


In an embodiment, the compound of formula Ia is selected the group comprising:



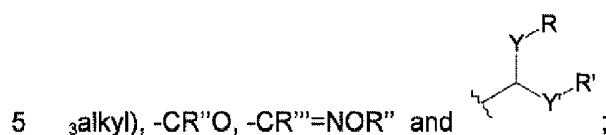
20

According to a fourth aspect, the present invention provides a compound of formula II:



wherein:

R^{11} is selected from the group comprising: $-C(O)NR''R'''$, $-CR''R''OR''$, $-COO(C_{1-3}alkyl)$, $-CR''O$, $-CR'''=NOR''$ and



5 $-CR''O$, $-CR'''=NOR''$ and

wherein

$-Y-$ is selected from the group comprising: $=N-$, $-O-$ and $-S-$;

$-Y'-$ is selected from the group comprising: $-O-$ and $-S-$; and

10 each R , R' and R'' is independently selected from the group comprising: $-H$, C_{1-4} alkyl and $-(CH_2)_n-aryl$; or each R'' is independently selected from the group comprising: $-H$, C_{1-4} alkyl and $-(CH_2)_n-aryl$, and R and R' join to form a 5 to 8 membered ring together with the atoms to which they are bonded, wherein n is from 1 to 4;

15 each R''' is selected from the group comprising: H , C_{1-4} alkyl, OR'' and SR'' ; and

each R'''' is selected from the group comprising: H , OH and SH ;

20 R^{12} and R^{16} are each independently selected from the group comprising: H , substituted or unsubstituted $C_{1-4}alkyl$ and halogen;

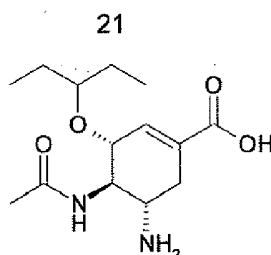
R^{13} is selected from the group comprising: $-OR''$, $-NR''R''$ and $-(CR''R'')_mNR''R''$, wherein m is 1 or 2;

R^{14} is selected from the group comprising: $-NR''CO(C_{1-3}alkyl)$ and $-N=CR''(C_{1-3}alkyl)$;

25 R^{15} is substituted or unsubstituted $C_{1-8}alkyl$;

X is O or S ;

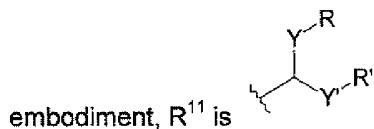
30 wherein, where chemically possible, each alkyl may be substituted with up to 5 substituents independently selected from the group comprising: F , Cl , Br , CN , NO_2 , OR'' or OH ; and



provided that the compound is not

In an embodiment, when R^{11} is $-\text{COOEt}$, R^{14} is not $-\text{NHCOMe}$.

- 5 In an embodiment, R^{11} is $-\text{COO}(\text{C}_{1-3}\text{alkyl})$. In an embodiment, the $\text{C}_{1-3}\text{alkyl}$ is unsubstituted. Preferably, the $\text{C}_{1-3}\text{alkyl}$ is methyl or ethyl, more preferably ethyl. In an alternative embodiment, R^{11} is $-\text{CR}''\text{O}$. Preferably R'' is H. In another alternative embodiment, R^{11} is $-\text{CH}_2\text{OH}$. In another alternative embodiment, R^{11} is $-\text{CR}'''=\text{NOR}''$. Preferably R''' is H. Preferably, R^{11} is $-\text{CSR}'''=\text{NOR}''$. Preferably, R^{11} is $-\text{COR}'''=\text{NOR}''$.
- 10 Preferably, R^{11} is $-\text{CR}'''=\text{NOH}$. Preferably R''' is H. In an another alternative



In an embodiment, R^{12} is H.

- 15 In an embodiment, R^{13} is $-\text{NR}''\text{R}''$. In an embodiment, R^{13} is $-\text{NH}_2$.

In an embodiment, R^{14} is $-\text{NR}''\text{CO}(\text{C}_{1-3}\text{alkyl})$. In an alternative embodiment, R^{14} is $-\text{N}=\text{CR}''(\text{C}_{1-3}\text{alkyl})$. Preferably, the $\text{C}_{1-3}\text{alkyl}$ is methyl or ethyl, preferably methyl.

- 20 In an embodiment, when R^{14} is $-\text{NHCOMe}$, R^{11} is not a group having an acidic hydrogen atom. In this context, an acidic hydrogen is a hydrogen that can be removed by a base yielding an anion or its corresponding salt or solvate more specifically R^{11} is a group having a pKa of more than 10.
- 25 In an embodiment, R^{15} is substituted or unsubstituted $\text{C}_{1-6}\text{alkyl}$. In an embodiment, R^{15} is methyl, ethyl, propyl, butyl, pentyl or hexyl. Preferably, R^{15} is 3-pentyl.

In an embodiment, R^{16} is H.

- 30 In an embodiment, R'' is H.

In an embodiment, R¹¹ is -OH or -SH. In an alternative embodiment, R¹¹ is H.

In an embodiment, X is O. In an embodiment, X is S.

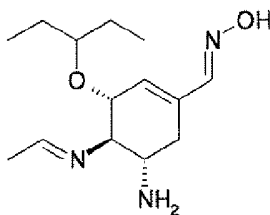
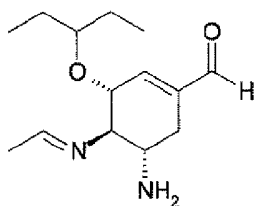
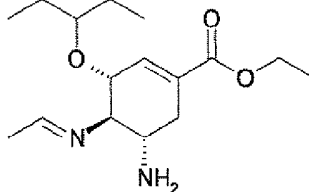
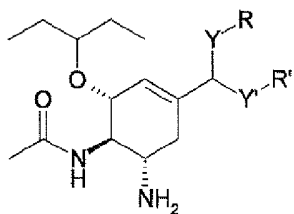
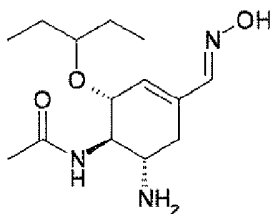
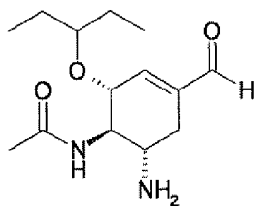
5

In an embodiment, R¹² is H, R¹³ is -NH₂, R¹⁵ is 3-pentyl, R¹⁶ is H and X is O.

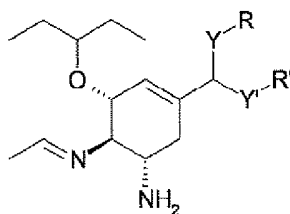
In an embodiment, Y, Y', R and R' are each as defined as in the embodiments of the second aspect for formula I.

10

In an embodiment, the compound of formula II is selected from the group comprising:

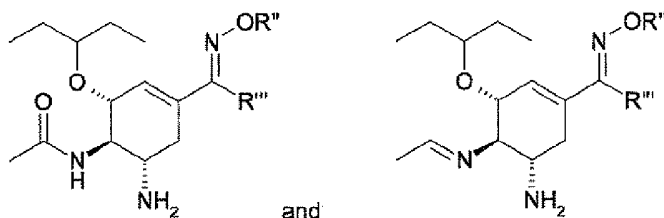


and



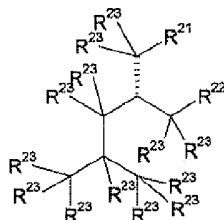
23

In an embodiment, the compound of formula II is selected from the group comprising:



and

According to a fifth aspect, the present invention provides a compound of formula III:



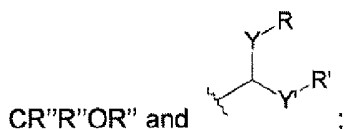
5

wherein:

each R^{23} is independently selected from the group comprising: -H, -Cl, -F and C_{1-3} alkyl;

R^{21} is $-NRR'$; and

10 R^{22} is selected from the group comprising: $-CR''O$, $-CR''=NOR'''$, $-N(=NR'')R''$,



wherein:

-Y- is selected from the group comprising: =N-, -O- and -S-;

15 -Y'- is selected from the group comprising: -O- and -S-;

each R, R' and R'' is independently selected from the group comprising: -H and C_{1-4} alkyl; or each R'' is independently selected from the group comprising: -H and C_{1-4} alkyl, and R and R' join to form a 5 to 8 membered ring together with the atom(s) to which they are bonded; and

20 R''' is selected from the group comprising: H, C_{1-4} alkyl and $-(CR''''R''''')_n$ -aryl; wherein R'''' is selected from the group comprising: H and aryl and wherein n is from 1 to 4;

or

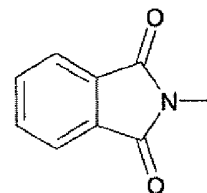
25 wherein R^{21} is $-N=$ and R^{22} is $-CR''=$ and R^{21} and R^{22} join to form a 5 membered ring together with the atoms to which they are bonded; or

wherein R^{21} is $-NR''$ - and R^{22} is $-C(O)-$ and R^{21} and R^{22} join to form a 5 membered ring together with the atoms to which they are bonded.

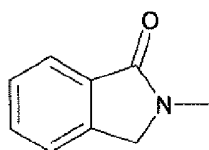
- 5 In an embodiment when R^{21} and R^{22} join to form a 5 membered ring together with the atoms to which they are bonded, the ring may be saturated or unsaturated.

In an embodiment, R^{21} is $-N=$ and R^{22} is $-CR''=$ and R^{21} and R^{22} join to form a 5 membered ring together with the atoms to which they are bonded. Preferably, R'' is H.

10



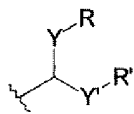
In an embodiment, R^{21} is $-NH_2$. In an embodiment, R^{21} is $-N-$. In an



embodiment, R^{21} is $-NH-$.

- 15 In an embodiment, R^{22} is $-CR''O$, preferably R^{22} is $-CHO$. In an alternative embodiment, R^{22} is $-CR''=NOR''$. Preferably, R^{22} is $-CR''=NOH$, and further preferably R^{22} is $-CH=NOH$. In an alternative embodiment, R^{22} is $CR''R''OH$. In an alternative

embodiment, R^{22} is $-C(Y)R$. In an alternative embodiment, R^{22} is $-N(=NH)R''$.

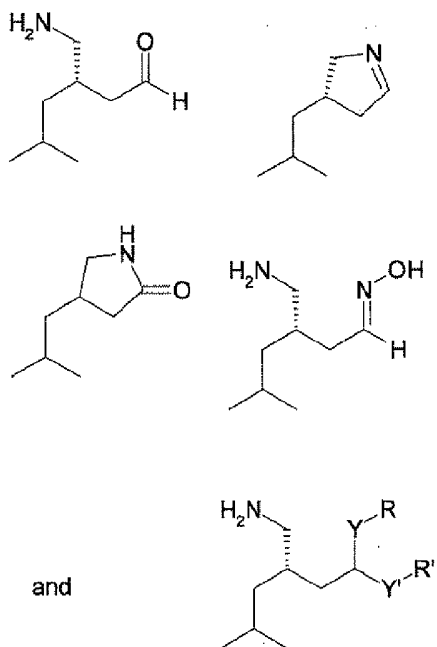


- 20 In an embodiment, each R^{23} is H.

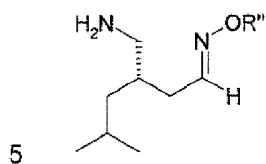
In an embodiment, each R^{23} is independently selected from the group comprising: $-H$ and $-C_{1-3}$ alkyl, e.g. methyl, ethyl or propyl.

- 25 In an embodiment, Y , Y' , R and R' are each as defined as in the embodiments of the second aspect for the compounds of formula I.

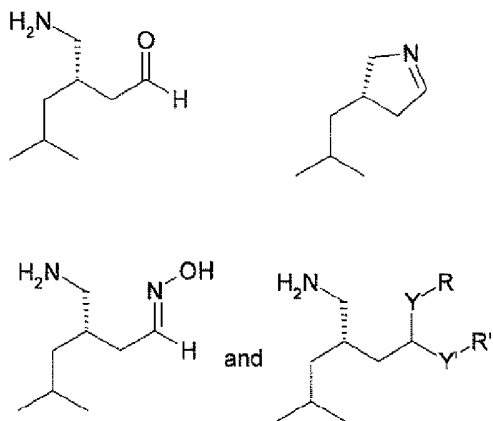
In an embodiment, the compound of formula III is selected from the group comprising:



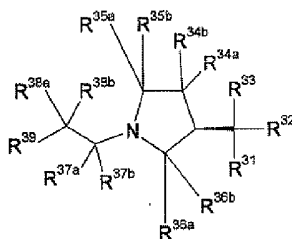
In an embodiment, the compound of formula III is:



In an embodiment, the compound of formula III is selected from the group comprising:

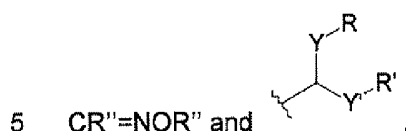


According to a sixth aspect, the present invention provides a compound of formula IV:



wherein:

R³¹ is selected from the group comprising: -CR''R''OR'', -CR''O, -CR''=NR'', -



wherein

-Y- is selected from the group comprising: =N-, -O- and -S-;

-Y'- is selected from the group comprising: -O- and -S-; and

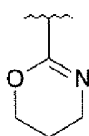
10 each R, R' and R'' is independently selected from the group comprising: -H and C₁₋₄ alkyl; or each R'' is independently selected from the group comprising: -H and C₁₋₄ alkyl, and R and R' join to form a 5 to 8 membered ring together with the atoms to which they are bonded;

15 R³² and R³³ are each independently selected from the group comprising: substituted or unsubstituted phenyl and substituted or unsubstituted pyridinyl;

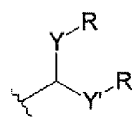
R^{34a}, R^{34b}, R^{35a}, R^{35b}, R^{36a}, R^{36b}, R^{37a}, R^{37b}, R^{38a} and R^{38b} are each independently selected from the group comprising: -H, C₁₋₄alkyl and halo;

20 R³⁹ is selected from the group comprising: substituted or unsubstituted aryl and substituted or unsubstituted heteroaryl.

In an embodiment, R³¹ is -CHO. In an alternative embodiment, R³¹ is -CR''=NH, preferably -CH=NH. In a further alternative embodiment, R³¹ is -CR''NOH. Preferably, R³¹ is -CH=NOR'', more preferably, R³¹ is -CH=NOH. In a further alternative
25 embodiment, R³¹ is -CR''R''OH. In a further alternative embodiment, R³¹ is



. In a further alternative embodiment, R³¹ is



In an embodiment, R^{32} is phenyl.

In an embodiment, R^{33} is phenyl.

5 In an embodiment, R^{32} and R^{33} are each phenyl.

In an embodiment, R^{34a} , R^{34b} , R^{35a} , R^{35b} , R^{36a} and R^{36b} are each selected from the group comprising: -H, -Me and -F. In an embodiment, R^{34a} , R^{34b} , R^{35a} , R^{35b} , R^{36a} and R^{36b} are each -H.

10

In an embodiment, R^{37a} , R^{37b} , R^{38a} and R^{38b} are each selected from the group comprising: -H, -Me and -F. In an embodiment, R^{37a} , R^{37b} , R^{38a} and R^{38b} are each -H.

15 In an embodiment, R^{32} and R^{33} are each phenyl and R^{34a} , R^{34b} , R^{35a} , R^{35b} , R^{36a} , R^{36b} , R^{37a} , R^{37b} , R^{38a} and R^{38b} are each -H.

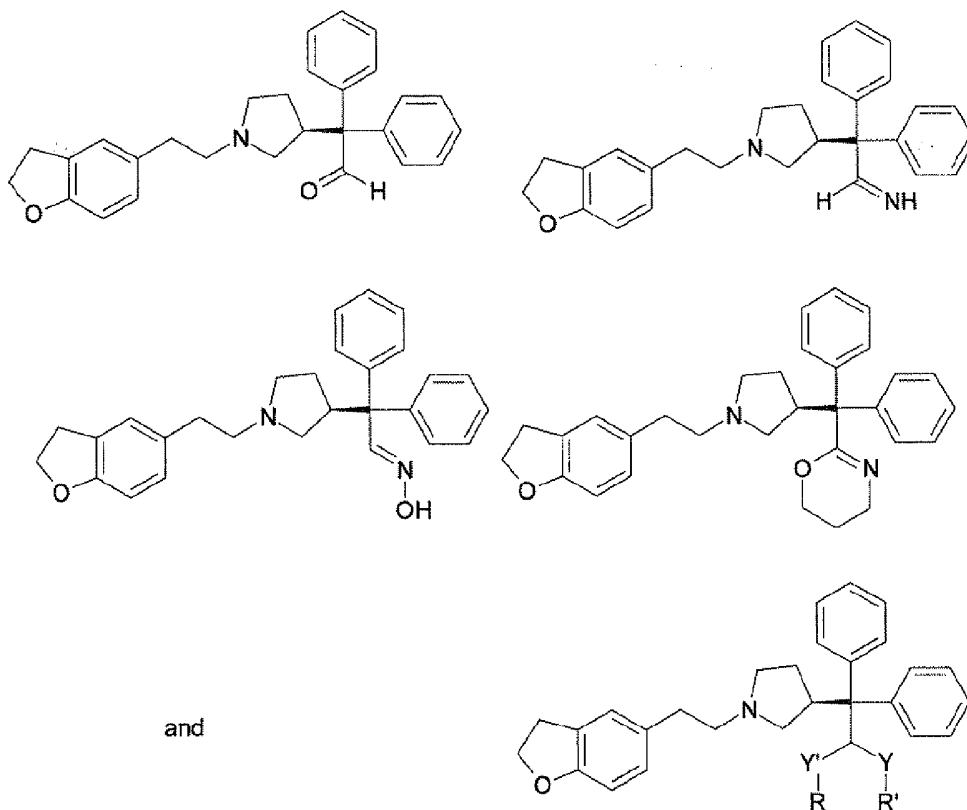
In an embodiment, R^{39} is a substituted phenyl ring or bicyclic ring system comprising a fused phenyl ring. In an embodiment, R^{39} is 5-benzo[b]-oxolanyl.

20 In an embodiment, R^{32} and R^{33} are each phenyl, R^{34a} , R^{34b} , R^{35a} , R^{35b} , R^{36a} , R^{36b} , R^{37a} , R^{37b} , R^{38a} and R^{38b} are each -H and R^{39} is 5-benzo[b]-oxolanyl.

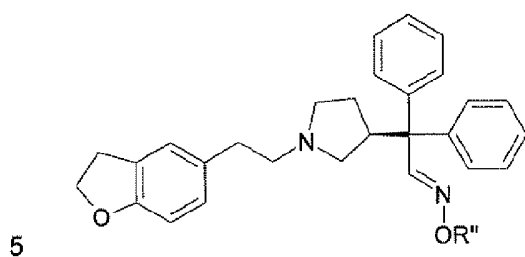
In an embodiment, Y, Y', R and R' are each as defined as in the embodiments of the second aspect for the compounds of formula I.

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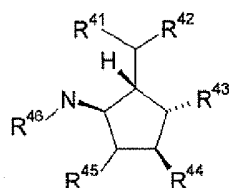
In an embodiment, the compound of formula IV is selected from the group comprising:



In an embodiment, the compound of formula IV is selected from the group comprising:



According to a seventh aspect, the present invention provides a compound of formula V:



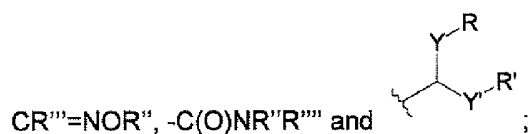
10 wherein:

R⁴¹ is selected from the group comprising: -NR''CO(C₁₋₃alkyl) and -N=CR''(C₁₋₃alkyl);

R⁴² is substituted or unsubstituted C₁₋₈ alkyl;

R⁴³ is selected from the group comprising: -OR'', -NR''R'', -(CR''R'')_mOR'' and -
5 (CR''R'')_mNR''R'', wherein m is 1 or 2;

R⁴⁴ is selected from the group comprising: -COOR'', -CR''O, -CR''R''OR'', -



wherein

-Y- is selected from the group comprising: =N-, -O- and -S-;

-Y'- is selected from the group comprising: -O- and -S-;

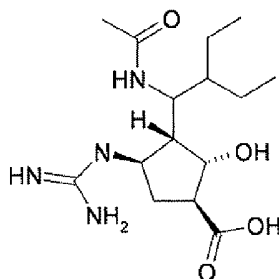
each R, R' and R'' is independently selected from the group comprising: -
H and C₁₋₄ alkyl; or each R'' is independently selected from the group comprising:
-H and C₁₋₄ alkyl, and R and R' join to form a 5 to 8 membered ring together with
the atoms to which they are bonded;

each R''' is selected from the group comprising: H, C₁₋₄ alkyl, OR'' and
SR''; and

each R'''' is selected from the group comprising: H, OH and SH;

R⁴⁵ is selected from the group comprising: H, substituted or unsubstituted C₁₋₄
20 alkyl and halogen; and

R⁴⁶ is selected from the group comprising: -C(=NR'')NR''R'', -C(=O)NR''R'' and -
C(=O)OR'';



provided that the compound is not

25

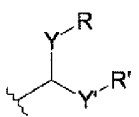
In an embodiment, when R⁴¹ is -NHCOMe, R⁴⁴ is not -COOH.

In an embodiment, R⁴¹ is -NR''CO(C₁₋₃alkyl). In an alternative embodiment, R⁴¹ is -
N=CR''(C₁₋₃alkyl). Preferably, the C₁₋₃alkyl is methyl. Preferably, R'' is H.

In an embodiment, R^{42} is C_{1-6} alkyl. Preferably, R^{42} is C_{3-6} alkyl. More preferably, R^{42} is 3-pentyl.

5 In an embodiment, R^{43} is $-OR''$. Preferably, R^{43} is $-OH$.

In an embodiment, R^{44} is $-COOR''$. Preferably R^{44} is $-COOH$. In an alternative embodiment, R^{44} is $-CR''O$, preferably, $-CHO$. In an alternative embodiment, R^{44} is $-CR''R''OH$. In an alternative embodiment, R^{44} is $-CR'''=NOR''$. Preferably, R''' is H.
 10 Preferably, R^{44} is $-CSR''=NOR''$. Preferably, R^{44} is $-COR''=NOR''$. Preferably, R^{44} is $-CR'''=NOH$, more preferably $-CH=NOH$. Preferably, R'' is H. In an alternative

embodiment, R^{44} is  .

In an embodiment, R^{45} is H.

15

In an embodiment, R^{46} $-C(=NR'')NR''R''$, preferably $-C(=NH)NH_2$.

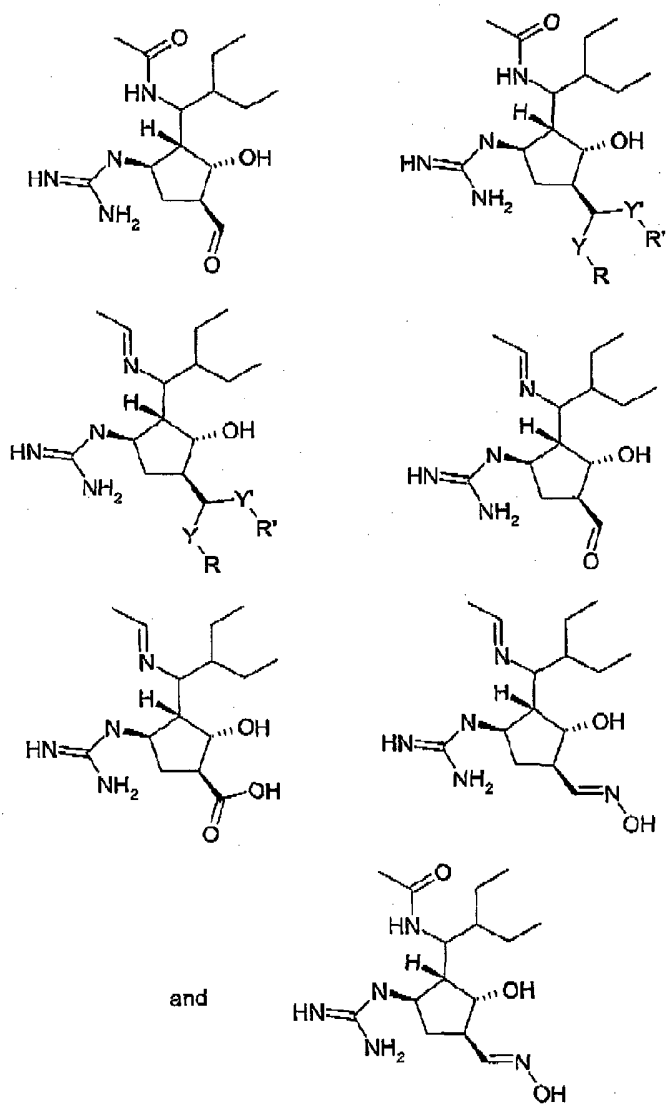
In an embodiment, R^{42} is 3-pentyl, R^{43} is $-OH$, R^{45} is H and R^{46} $-C(=NH)NH_2$.

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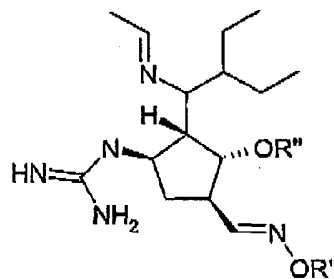
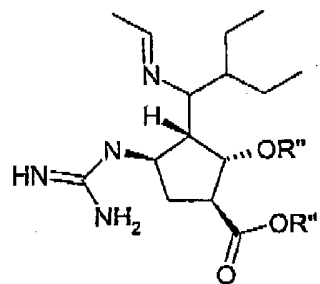
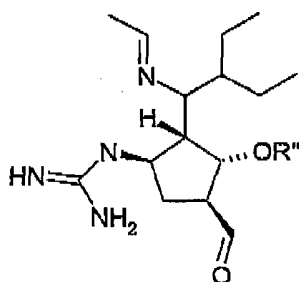
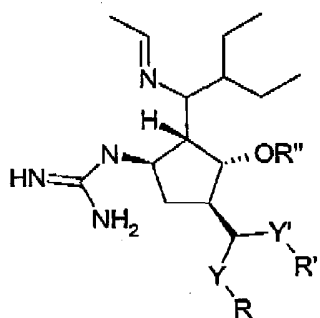
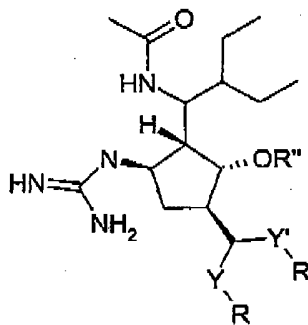
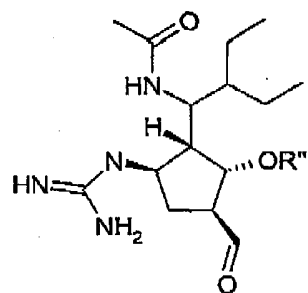
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In an embodiment, the compound of formula V is selected from the group comprising:

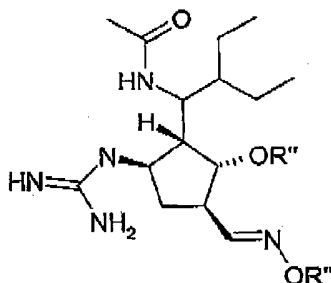


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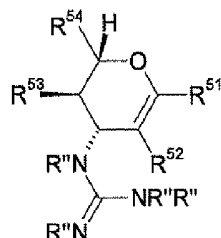
In an embodiment, the compound of formula V is selected from the group comprising:



and

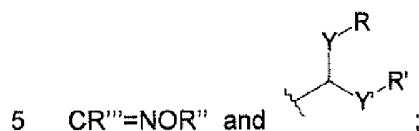


According to an eighth aspect, the present invention provides a compound of formula VI:



wherein

R⁵¹ is selected from the group comprising: -C(O)NR''R''', -COOR'', -CR''O, -



wherein

-Y- is selected from the group comprising: =N-, -O- and -S-;

-Y'- is selected from the group comprising: -O- and -S-;

10 each R, R' and R'' is independently selected from the group comprising: -H and C₁₋₄ alkyl; or each R'' is independently selected from the group comprising: -H and C₁₋₄ alkyl, and R and R' join to form a 5 to 8 membered ring together with the atoms to which they are bonded;

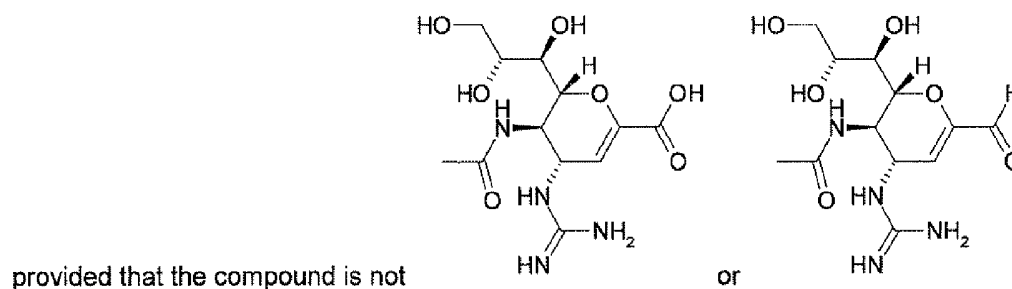
each R''' is selected from the group comprising: H, C₁₋₄ alkyl, OR'' and SR''; and

15 each R'''' is selected from the group comprising: H, OH and SH;

R⁵² is selected from the group comprising: H, substituted or unsubstituted C₁₋₄alkyl and halogen;

R⁵³ is selected from the group comprising: -NR''C(=O)R'' and -N=CR''(C₁₋₃alkyl);

20 R⁵⁴ is a substituted or unsubstituted C₁₋₆alkyl;

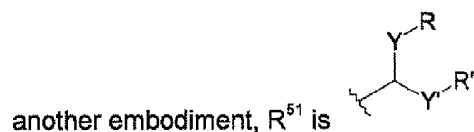


In an embodiment, when R⁵³ is -NHR(=O)Me, R⁵⁴ is not -COOH or -CHO.

In an embodiment, R^{51} is $-\text{COOR}''$. Preferably, R^{51} is $-\text{COOH}$. In another embodiment, R^{51} is $-\text{CR}''\text{O}$, preferably $-\text{CHO}$. In another embodiment, R^{51} is $-\text{CR}''=\text{NOR}''$.

Preferably, R''' is H. Preferably, R^{51} is $-\text{CSR}''=\text{NOR}''$. Preferably, R^{51} is $-\text{COR}''=\text{NOR}''$.

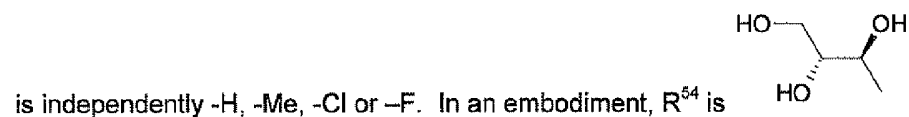
- 5 Preferably, R'' is H. Preferably, R^{51} is $-\text{CR}''=\text{NOH}$, more preferably $-\text{CH}=\text{NOH}$. In



In an embodiment, R^{52} is H.

- 10 In an embodiment, R^{53} is $-\text{NR}''\text{C}(=\text{O})\text{R}''$, preferably $-\text{NHC}(=\text{O})\text{Me}$. In another embodiment, R^{53} is $-\text{N}=\text{CR}''(\text{C}_{1-3}\text{alkyl})$, preferably $-\text{N}=\text{CH}(\text{C}_{1-3}\text{alkyl})$. Preferably the $\text{C}_{1-3}\text{alkyl}$ is methyl.

- In an embodiment, R^{54} is a $\text{C}_{1-6}\text{alkyl}$ substituted with hydroxy. In an embodiment, R^{54} is -
 15 $\text{CHY}''\text{R}''-\text{CHY}''\text{R}''-\text{CH}_2\text{Y}''\text{R}''$ wherein each Y' is independently S or O and wherein each R''



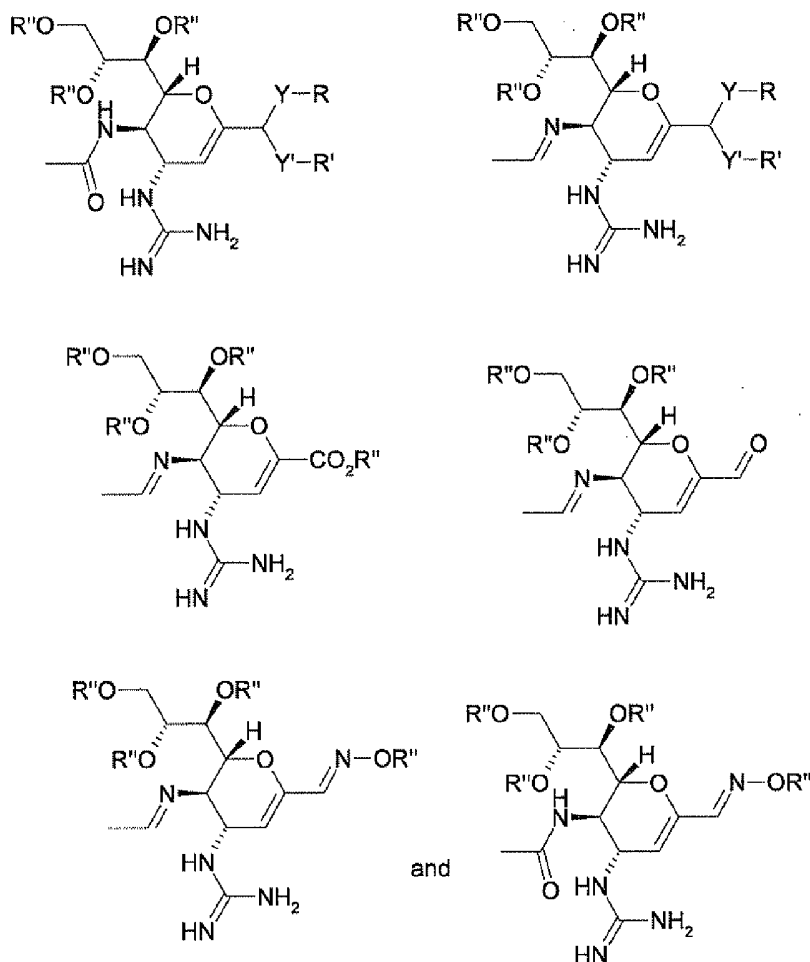
In an embodiment, Y, Y', R and R' are each as defined as in the embodiments of the second aspect for the compounds of formula I.

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In an embodiment, the compound of formula VI is selected from the group comprising:



- 5 The present invention also includes the synthesis of all pharmaceutically acceptable isotopically-labelled compounds of formulae (I) to (VI) wherein one or more atoms are replaced by atoms having the same atomic number, but an atomic mass or mass number different from the atomic mass or mass number usually found in nature.
- 10 Examples of isotopes suitable for inclusion in the compounds of the invention include isotopes of hydrogen, such as ²H and ³H, carbon, such as ¹¹C, ¹³C and ¹⁴C, chlorine, such as ³⁶Cl, fluorine, such as ¹⁸F, iodine, such as ¹²³I and ¹²⁵I, nitrogen, such as ¹³N and ¹⁵N, oxygen, such as ¹⁵O, ¹⁷O and ¹⁸O, phosphorus, such as ³²P, and sulphur, such as ³⁵S.

Certain isotopically-labelled compounds, for example, those incorporating a radioactive isotope, are useful in drug and/or substrate tissue distribution studies. The radioactive isotopes tritium, i.e. ^3H , and carbon-14, i.e. ^{14}C , are particularly useful for this purpose in view of their ease of incorporation and ready means of detection.

5

Substitution with heavier isotopes such as deuterium, i.e. ^2H , may afford certain therapeutic advantages resulting from greater metabolic stability, for example, increased *in vivo* half-life or reduced dosage requirements, and hence may be preferred in some circumstances.

10

Substitution with positron emitting isotopes, such as ^{11}C , ^{18}F , ^{15}O and ^{13}N , can be useful in Positron Emission Topography (PET) studies for examining substrate receptor occupancy.

15

Isotopically-labelled compounds can generally be prepared by conventional techniques known to those skilled in the art or by processes analogous to those described using an appropriate isotopically-labelled reagent in place of the non-labelled reagent previously employed.

20

Throughout the description and claims of this specification, the words "comprise" and "contain" and variations of the words, for example "comprising" and "comprises", means "including but not limited to", and is not intended to (and does not) exclude other moieties, additives, components, integers or steps.

25

Throughout the description and claims of this specification, the singular encompasses the plural unless the context otherwise requires. In particular, where the indefinite article is used, the specification is to be understood as contemplating plurality as well as singularity, unless the context requires otherwise.

30

Features, integers, characteristics, compounds, chemical moieties or groups described in conjunction with a particular aspect, embodiment or example of the invention are to be understood to be applicable to any other aspect, embodiment or example described herein unless incompatible therewith.

The invention will now be illustrated by the following Examples which are intended to demonstrate specific embodiments of the invention but which are not to be construed as limiting.

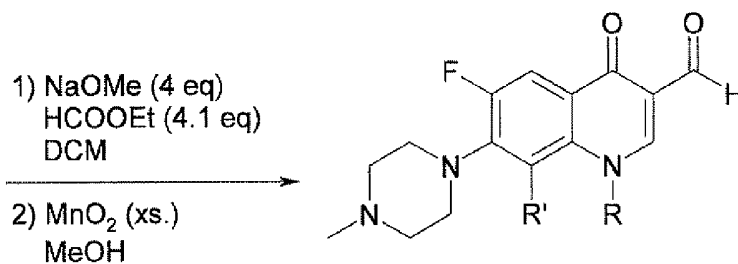
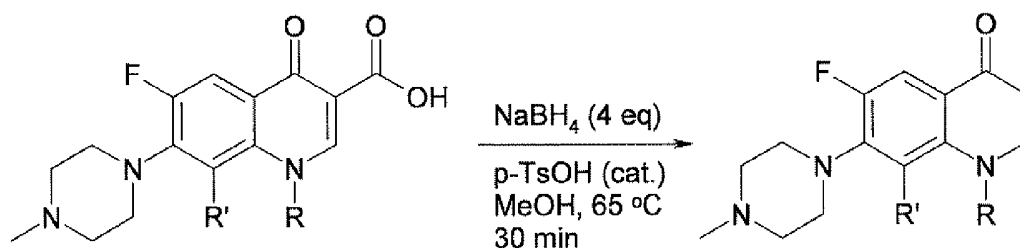
- 5 The known active drug compounds, and their derivatives in unoxidised or reduced form, can be prepared by known methods described in the literature and patent literature relative to those compounds. The novel oxidised or reduced forms of the present invention may generally be prepared from the prior art compounds by conventional synthetic procedures for conducting oxidation and reduction reactions, using protecting or masking groups where necessary. Standard texts referring to such procedures are
- 10 mentioned above. Examples of the synthetic routes for preparing a number of compounds according to the invention are illustrated below (for NMR, coupling constants are quoted in Hz).

15 EXAMPLE 1 – FLUOROQUINOLONE DERIVATIVES

Formation of fluoroquinolone aldehyde derivatives have been undertaken by modifying a reduction/ decarboxylation/ Claisen addition/ oxidation protocol reported by Kondo *et al.* (Kondo, H.; Sakamoto, F.; Kawakami, K.; Tsukamoto, G. *J. Med. Chem.*, **1988**, 31, 221.)

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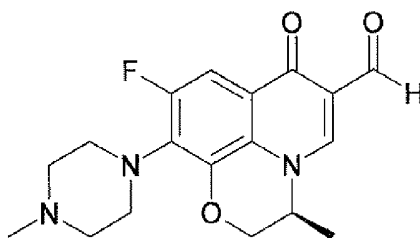
Fluoroquinolone Aldehyde Synthesis



To a 0 °C stirring solution of fluoroquinolone in anhydrous methanol under inert atmosphere was added solid sodium borohydride (4.5 eq.) slowly over 30 minutes. The mixture was allowed to warm to room temperature and *p*-toluene sulfonic acid (0.1 eq.) was added. After heating at reflux for 3.5 hours, the mixture was allowed to cool and the solvent removed *in vacuo*. The crude solid was washed with hot chloroform and water and then extracted with chloroform (× 3). The combined organic extracts were dried (magnesium sulfate), filtered and concentrated under reduced pressure. The crude mixture was subjected to flash column chromatography (20 % methanol/ chloroform) to afford the intermediate.

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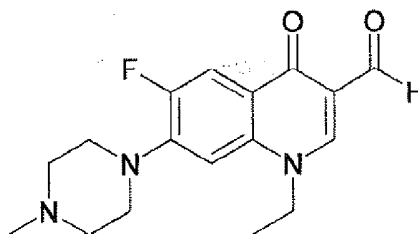
To a room temperature stirring solution of fluoroquinolone intermediate in anhydrous dichloromethane under inert atmosphere was added sodium methoxide (3.9 eq.) and ethyl formate (3.94 eq.). After eighteen hours, the mixture was quenched with ice-water. After separation, the organic layer was washed with 3 M sodium hydroxide (× 2). The aqueous washings were acidified to pH 6 with concentrated hydrochloric acid and then extracted with dichloromethane (× 3). The combined organic extracts were dried (magnesium sulfate), filtered and concentrated under reduced pressure. The crude mixture was dissolved in anhydrous methanol and manganese dioxide was added (excess). After stirring at room temperature for eighteen hours, the mixture washed filtered through Celite®. After flushing the filter cake with methanol and dichloromethane, the solvent was removed *in vacuo* and the crude solid subjected to flash column chromatography (20 % methanol/ chloroform) to afford the desired fluoroquinolone aldehyde.

25 **Levofloxacin Aldehyde**

Title compound was formed as a yellow solid in 46 %.

30 ¹H NMR, 400MHz (CDCl₃) δ 10.39 (1H, s), 8.15 (1H, s), 7.75 (1H, d, J = 12.4), 4.42 – 4.30 (3H, m), 3.36 (4H, m), 2.55 (4H, m), 2.37 (3H, s) and 1.59 (3H, d, J = 7.2).

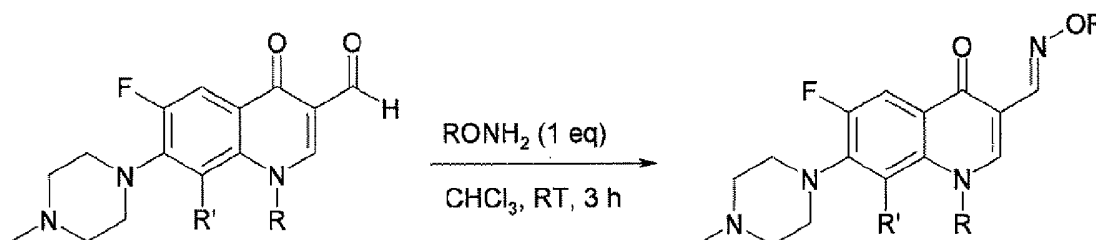
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Pefloxacin Aldehyde

Title compound was formed as an off-white solid in 50 %.

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$^1\text{H NMR}$, 400MHz (CDCl_3) δ 10.39 (1H, s), 8.25 (1H, s), 8.08 (1H, d, $J = 12.8$), 6.78 (1H, d, $J = 6.8$), 4.23 (2H, q, $J = 7.2$), 3.30 (4H, t, $J = 4.8$), 2.64 (4H, t, $J = 4.8$), 2.39 (3H, s) and 1.56 (3H, t, $J = 7.6$).

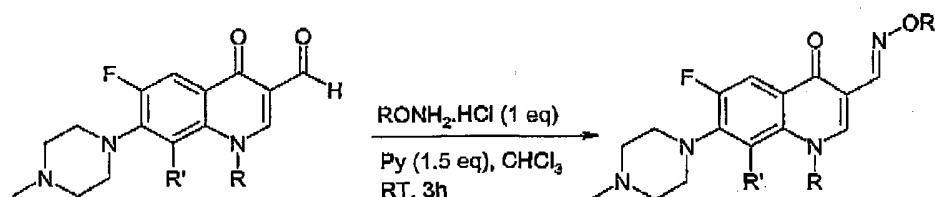
10 **Procedure for Oxime Formation**

- 15 To a room temperature stirring solution of fluoroquinolone aldehyde in anhydrous chloroform under inert atmosphere was added *o*-substituted hydroxylamine (1 eq.). After three hours, the mixture was partitioned between chloroform/ water and extracted with chloroform ($\times 2$). The combined organic extracts were dried (magnesium sulfate), filtered and concentrated under reduced pressure. The crude mixture was subjected to flash
- 20 column chromatography (5 % methanol/ chloroform) to afford the product as an off-white solid.

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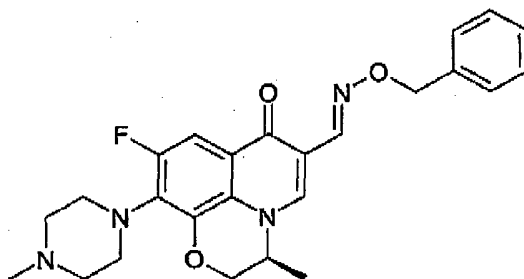
41

Procedure for Oxime Formation (from *o*-substituted hydroxylamine Hydrochloride Salt)



- 5 To a room temperature stirring solution of fluoroquinolone aldehyde in anhydrous chloroform under inert atmosphere was added *o*-substituted hydroxylamine hydrochloride salt (1 eq.), followed by anhydrous pyridine (1.5 eq.). After three hours, the mixture was partitioned between chloroform/ water and extracted with chloroform ($\times 2$). The combined organic extracts were dried (magnesium sulfate), filtered and
- 10 concentrated under reduced pressure. The crude mixture was subjected to flash column chromatography (5 % methanol/ chloroform) to afford the product as an off-white solid.

Levofloxacin Aldehyde Benzyl Oxime



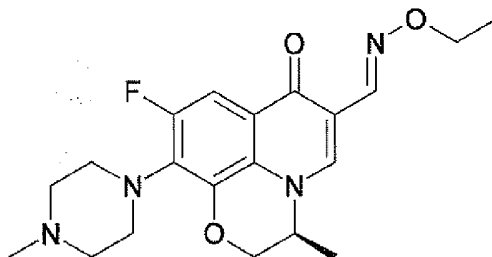
15

Title compound was formed as a yellow solid in 46 %.

- ^1H NMR, 400MHz (CDCl_3) δ 8.54 (1H, s), 7.93 (1H, s), 7.55 (1H, d, $J = 12.4$), 7.42-7.27 (5H, m, Ph), 5.17 (2H, s), 4.35 – 4.28 (2H, m), 4.18 (1H, m, $J = 2.4$), 3.31 (4H, m), 2.56 (4H, m), 2.37 (3H, s) and 1.49 (3H, d, $J = 6.8$).
- 20

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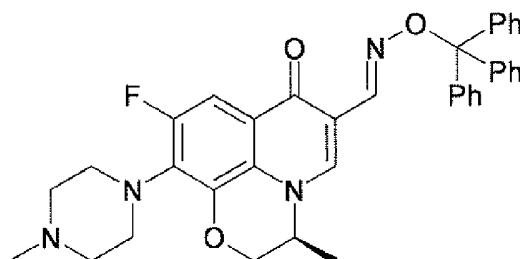
42

Levofloxacin Aldehyde Ethyl Oxime

5 Title compound was formed as a yellow solid in 36 %.

^1H NMR, 400MHz (CDCl_3) δ 8.46 (1H, s), 8.00 (1H, s), 7.60 (1H, d, $J = 12.4$), 4.40 – 4.23 (3H, m), 4.17 (2H, q, $J = 6.8$), 3.39-3.31 (4H, m), 2.56 (4H, m), 2.37 (3H, s), 1.55 (3H, d, $J = 6.8$) and 1.36 (3H, t, $J = 6.8$).

10

Levofloxacin Aldehyde Trityl Oxime

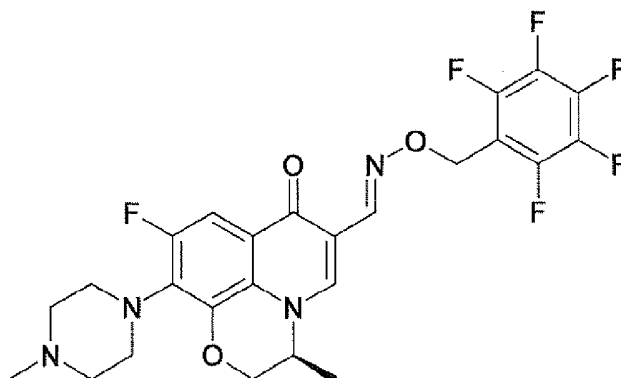
15 Title compound was formed as a yellow solid in 57 %.

^1H NMR, 400MHz (CDCl_3) δ 8.59 (1H, s), 7.47 (1H, d, $J = 12.4$), 7.36 (1H, s), 7.36-7.14 (15H, m, 3 \times Ph), 4.14 (2H, m), 3.82 (1H, m), 3.26 (4H, t, $J = 4.4$), 2.47 (4H, t, $J = 4.4$), 2.29 (3H, s) and 1.27 (3H, d, $J = 6.8$).

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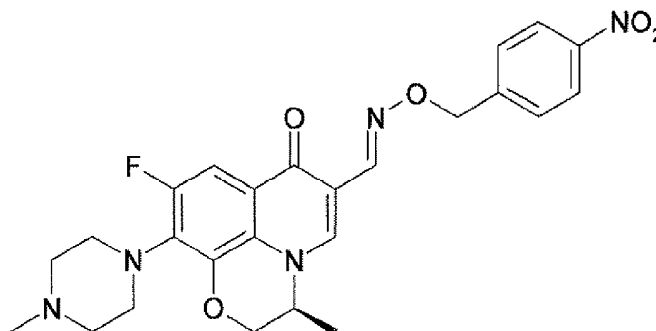
43

Levofloxacin Aldehyde Pentafluorobenzyl Oxime

Title compound was formed as a yellow solid in 58 %.

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$^1\text{H NMR}$, 400MHz (CDCl_3) δ 8.44 (1H, s), 7.96 (1H, s), 7.57 (1H, d, $J = 12.4$), 5.20 (2H, s), 4.35 – 4.28 (2H, m), 4.18 (1H, m, $J = 2.4$), 3.31 (4H, m), 2.56 (4H, m), 2.37 (3H, s) and 1.49 (3H, d, $J = 6.8$).

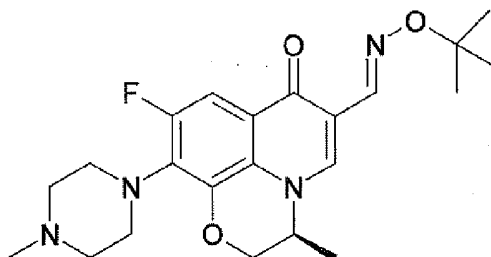
10 Levofloxacin Aldehyde *para*-Nitrobenzyl Oxime

Title compound was formed in 52 %.

15 $^1\text{H NMR}$, 400MHz (CDCl_3) δ 8.59 (1H, s), 8.20 (2H, d, $J = 8.7$), 7.96 (1H, s), 7.62 (1H, d, $J = 12.4$), 7.53 (2H, d, $J = 8.7$), 5.20 (2H, s), 4.40-4.29 (3H, m), 3.40-3.30 (4H, m), 2.58-2.54 (4H, m), 2.37 (3H, s) and 1.56 (3H, d, $J = 7.2$).

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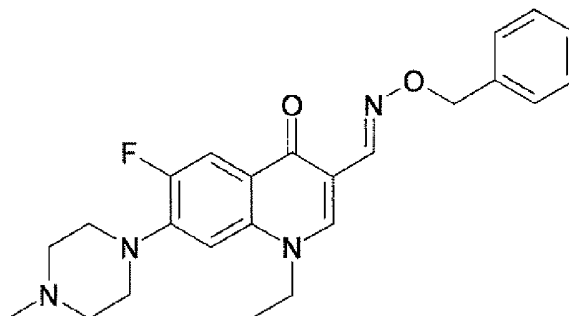
44

Levofloxacin Aldehyde tert-Butyl Oxime

Title compound was formed in 100 %.

5

$^1\text{H NMR}$, 400MHz (CDCl_3) δ 8.46 (1H, s), 8.02 (1H, s), 7.69 (1H, d, $J = 12.4$), 4.38 – 4.29 (3H, m), 3.45 (4H, m), 2.75 (4H, m), 2.50 (3H, s), 1.57 (3H, d, $J = 6.8$) and 1.34 (9H, s).

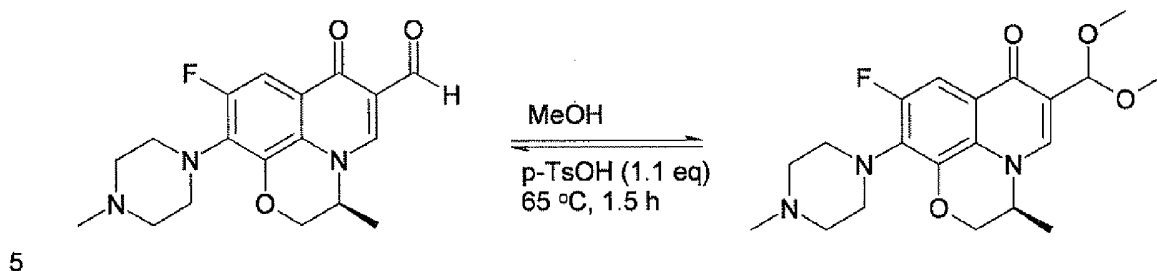
Pefloxacin Aldehyde Benzyl Oxime

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Title compound was formed as a white solid in 47 %.

$^1\text{H NMR}$, 400MHz (CDCl_3) δ 8.57 (1H, s), 8.07 (1H, s), 7.98 (1H, d, $J = 13.2$), 7.42-7.27 (5H, m, Ph), 6.69 (1H, d, $J = 7.2$), 5.17 (2H, s), 4.12 (2H, q, $J = 7.2$), 3.26 (4H, t, $J = 4.8$), 2.63 (4H, t, $J = 4.8$), 2.38 (3H, s) and 1.48 (3H, d, $J = 7.2$).

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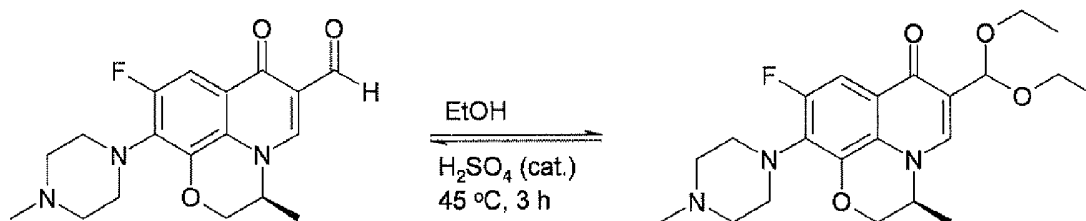
Acetal Formations**Levofloxacin Aldehyde Dimethoxy Acetal**

To a room temperature stirring solution of levofloxacin aldehyde (0.100 g, 0.26 mmol) in anhydrous methanol (20 mL) under inert atmosphere was added *p*-toluene sulfonic acid (0.050 g, 1.1 eq.). The mixture was heated at reflux for 1.5 hours. After allowing the mixture to cool to room temperature, the mixture was quenched with saturated sodium hydrogen carbonate solution (20 mL) and extracted with dichloromethane (3 × 20 mL). The combined organic extracts were dried (magnesium sulfate), filtered and concentrated under reduced pressure to afford the product as a white solid (94 %).

15 ¹H NMR, 400MHz (CDCl₃) δ 7.69 (1H, s), 7.68 (1H, d, J = 12.8), 5.68 (1H, s), 4.34 (1H, m), 4.27-4.23 (2H, m), 3.47 (6H, s), 3.35 (4H, m), 2.55 (4H, m), 2.36 (3H, s) and 1.52 (3H, d, J = 7.2).

Levofloxacin Aldehyde Diethoxy Acetal

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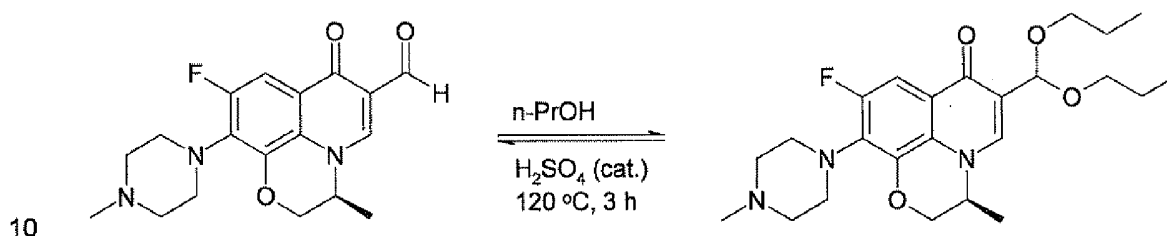
To a room temperature stirring solution of levofloxacin aldehyde dimethoxy acetal (0.100 g, 0.24 mmol) in anhydrous ethanol (20 mL) under inert atmosphere was added 4 Å molecular sieves and 6 drops of concentrated sulfuric acid. The mixture was heated at 45 °C for three hours. After allowing the mixture to cool to room temperature, the mixture was quenched with saturated sodium hydrogen carbonate solution (20 mL) and extracted with dichloromethane (3 × 20 mL). The combined organic extracts were dried

25

(magnesium sulfate), filtered and concentrated under reduced pressure. The crude mixture was subjected to flash column chromatography (10 % methanol/ dichloromethane) to afford the product as a yellow oil in quantitative yield.

- 5 ^1H NMR, 400MHz (CDCl_3) δ 7.76 (1H, s), 7.67 (1H, d, $J = 12.8$), 5.81 (1H, s), 4.36 (1H, m), 4.25-4.22 (2H, m), 3.84-3.76 (2H, m), 3.69-3.63 (2H, m), 3.34 (4H, m), 2.55 (4H, m), 2.36 (3H, s), 1.52 (3H, d, $J = 6.8$), 1.254 (3H, t, $J = 7.2$) and 1.252 (3H, t, $J = 7.2$).

Levofloxacin Aldehyde Di-*n*-propoxy Acetal

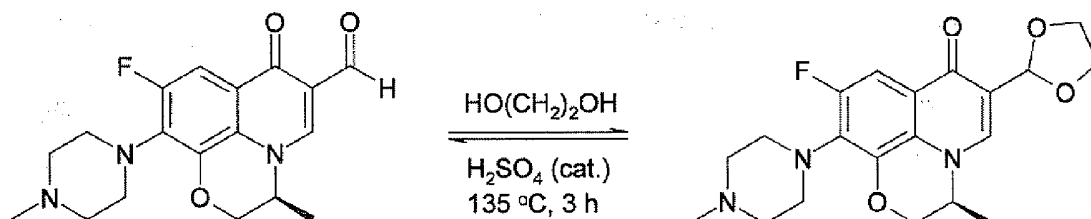


To a room temperature stirring solution of levofloxacin aldehyde (0.100 g, 0.22 mmol) in anhydrous *n*-propanol (20 mL) under inert atmosphere was added 4 Å molecular sieves and 3 drops of concentrated sulfuric acid. The mixture was heated at 120 °C for three
 15 hours. After allowing the mixture to cool to room temperature, the mixture was quenched with saturated sodium hydrogen carbonate solution (20 mL) and extracted with dichloromethane (3×20 mL). The combined organic extracts were dried (magnesium sulfate), filtered and concentrated under reduced pressure. The crude mixture was subjected to flash column chromatography (10 % methanol/ dichloromethane) to afford
 20 the product as a yellow oil (57 %).

^1H NMR, 400MHz (CDCl_3) δ 7.75 (1H, s), 7.67 (1H, d, $J = 12.4$), 5.79 (1H, s), 4.35 (1H, m), 4.27-4.24 (2H, m), 3.71-3.67 (2H, m), 3.56-3.51 (2H, m), 3.38 (4H, m), 2.60 (4H, m), 2.39 (3H, s), 1.68-1.62 (4H, m), 1.52 (3H, d, $J = 7.2$) and 0.95 (6H, t, $J = 7.2$).

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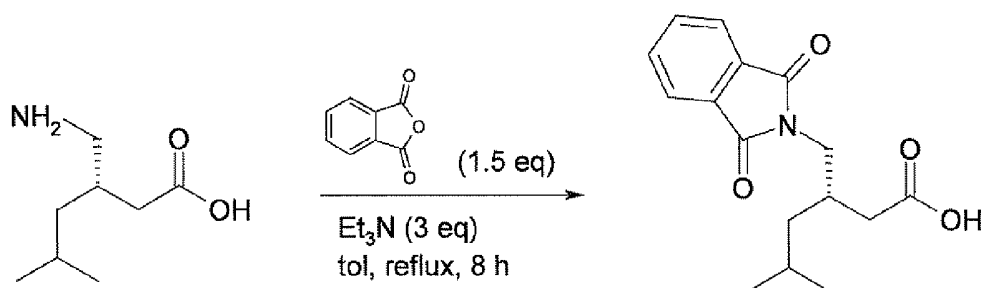
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Levofloxacin Aldehyde Dioxolano Acetal

- 5 To a room temperature stirring solution of levofloxacin aldehyde (0.100 g, 0.22 mmol) in anhydrous ethylene glycol (20 mL) under inert atmosphere was added 4 Å molecular sieves and 6 drops of concentrated sulfuric acid. The mixture was heated at 135 °C for three hours. After allowing the mixture to cool to room temperature, the mixture was quenched with saturated sodium hydrogen carbonate solution (20 mL) and extracted
- 10 with dichloromethane (3 × 20 mL). The combined organic extracts were dried (magnesium sulfate), filtered and concentrated under reduced pressure. The crude mixture was subjected to flash column chromatography (15 % methanol/ dichloromethane) to afford the product as a yellow oil (30 %).
- 15 ¹H NMR, 400MHz (CDCl₃) δ 7.72 (1H, s), 7.62 (1H, d, J = 12.4), 6.08 (1H, s), 4.39 (1H, m), 4.36-4.29 (2H, m), 4.15 (2H, m), 4.06 (2H, m), 3.36 (4H, m), 2.60 (4H, m), 2.40 (3H, s) and 1.51 (3H, d, J = 7.2).

EXAMPLE 2 – PREGABALIN DERIVATIVES

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Pregabalin Phthalic Imide

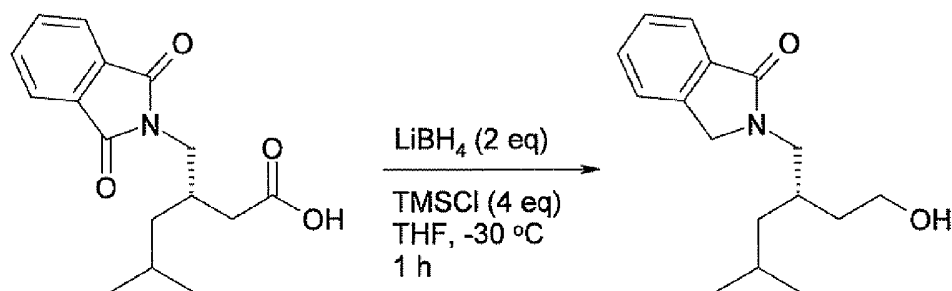
- 25 To a room temperature stirring solution of pregabalin (1.5 g, 9.43 mmol) in anhydrous toluene (45 mL) under inert atmosphere was added triethylamine (3.9 mL, 3 eq.) and phthalic anhydride (2.0 g, 1.5 eq.). The mixture was heated at reflux for eight hours.

After allowing the mixture to cool to 0 °C, the mixture was acidified to pH 2 and extracted with ethyl acetate (× 3). The combined organic extracts were dried (magnesium sulfate), filtered and concentrated under reduced pressure. The crude mixture was subjected to flash column chromatography (40 % ethyl acetate/ hexane) to afford the product as a white solid (2.4 g, 88 %).

¹H NMR, 400MHz (CDCl₃) δ 7.83 (2H, d, J = 8.0), 7.72 (2H, d, J = 8.0), 3.71 (1H, dd, J = 14.0, 4.0), 3.62 (1H, dd, J = 14.0, 8.0), 2.44-2.24 (3H, m), 1.75 (1H, sep, J = 6.8), 1.23 (2H, m), 0.95 (3H, d, J = 6.4) and 0.90 (3H, d, J = 6.4).

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Pregabalin Phthalimidine Alcohol

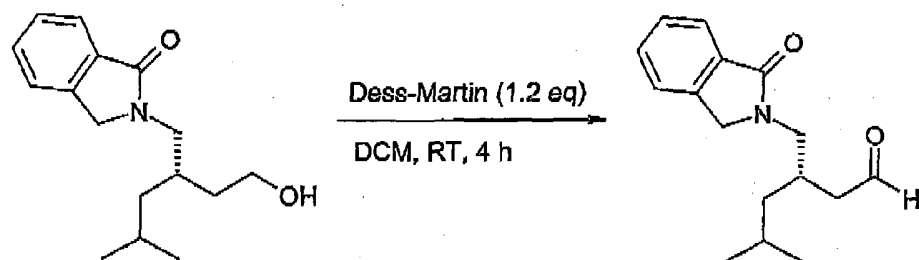


To a -30 °C stirring solution of pregabalin phthalic imide (2.4 g, 8.30 mmol) in anhydrous tetrahydrofuran (80 mL) under inert atmosphere was added lithium borohydride (8.3 mL, 2.0 eq.). After one hour, the mixture was allowed to warm to 0 °C, quenched with aqueous ammonium chloride solution and extracted with dichloromethane (× 3). The combined organic extracts were dried (magnesium sulfate), filtered and concentrated under reduced pressure. The crude mixture was subjected to flash column chromatography (50 % ethyl acetate/ hexane) to afford the product as a white solid (1.2 g, 54 %).

¹H NMR, 400MHz (CDCl₃) δ 7.84 (1H, d, J = 7.6), 7.54-7.44 (3H, m), 4.48 (1H, d, J = 16.8), 4.38 (1H, d, J = 17.2), 3.76 (2H, m), 3.46 (1H, m), 2.60 (1H, br s), 1.71 (2H, m), 1.59 (2H, m), 1.26 (2H, m), 0.95 (3H, d, J = 6.8) and 0.90 (3H, d, J = 6.8).

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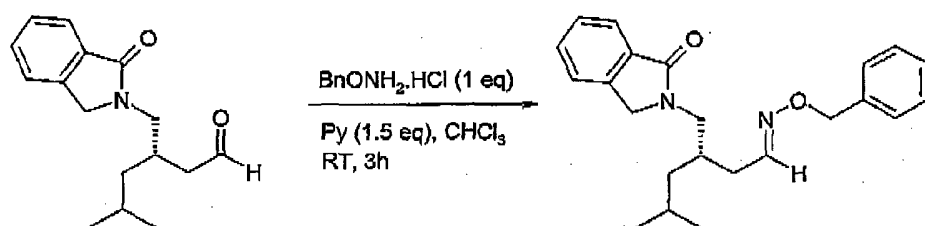
Pregabalin Phthalimidine Aldehyde

To a room temperature stirring solution of pregabalin phthalic imide (0.58 g, 2.11 mmol) in anhydrous dichloromethane (50 mL) under inert atmosphere was added Dess-Martin periodinane (1.07 g, 1.2 eq.). After four hours, the mixture was partitioned between diethyl ether (50 mL) and 1 M sodium hydroxide solution (50 mL). The organic phase was dried (magnesium sulfate), filtered and concentrated under reduced pressure. The crude mixture was subjected to flash column chromatography (50 % ethyl acetate/hexane) to afford the product as a yellow oil (1.2 g, 54 %).

10

$^1\text{H NMR}$, 400MHz (CDCl_3) δ 9.73 (1H, s, CHO), 7.83 (1H, d, $J = 7.6$), 7.56-7.44 (3H, m), 4.45 (1H, d, $J = 16.8$), 4.33 (1H, d, $J = 17.2$), 3.62 (1H, dd, $J = 14.0, 8.4$), 3.45 (1H, dd, $J = 14.0, 5.2$), 2.59-2.53 (2H, m), 2.43 (1H, m), 1.66 (1H, sep, $J = 6.4$), 1.26 (2H, m), 0.95 (3H, d, $J = 6.8$) and 0.90 (3H, d, $J = 6.4$).

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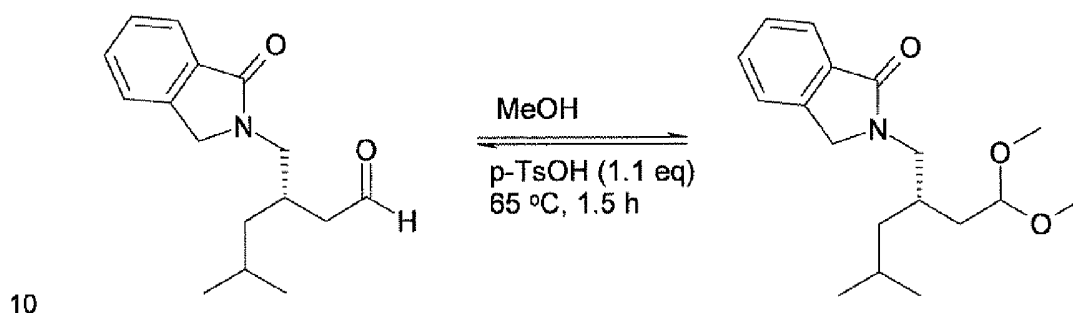
Pregabalin Phthalimidine Aldehyde Benzyl Oxime

To a room temperature stirring solution of pregabalin phthalic imide aldehyde (0.103 g, 0.38 mmol) in anhydrous chloroform (5 mL) under inert atmosphere was added *o*-benzylhydroxylamine hydrochloride salt (0.060 g, 1 eq.), followed by anhydrous pyridine (0.05 mL, 1.5 eq.). After three hours, the mixture was partitioned between chloroform/water and extracted with chloroform ($\times 2$). The combined organic extracts were dried (magnesium sulfate), filtered and concentrated under reduced pressure. The crude

mixture was subjected to flash column chromatography (5 % methanol/ chloroform) to afford the product as a yellow oil (49 %).

¹H NMR, 400MHz (CDCl₃) δ 7.83 (2H, d, J = 11.6), 7.52-7.45 (3H, m), 7.36-7.25 (5H, m), 6.76 (1H, t, J = 5.6), 5.06 (2H, s), 5.00 (s, minor isomer), 4.33-4.24 (2H, m), 3.53-3.47 (2H, m), 2.35 (1H, m), 2.21 (1H, m), 1.70 (1H, m), 1.28-1.19 (2H, m), 0.90 (3H, d, J = 6.4) and 0.87 (3H, d, J = 6.8).

Pregabalin Phthalimidine Aldehyde Dimethoxy Acetal



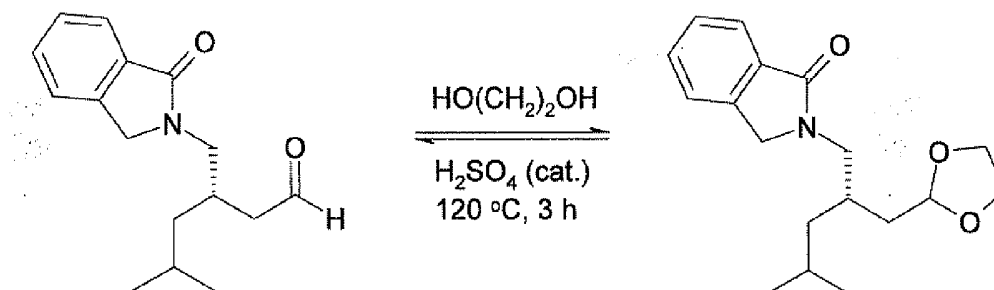
To a room temperature stirring solution of pregabalin phthalic imide aldehyde (0.101 g, 0.37 mmol) in anhydrous methanol (20 mL) under inert atmosphere was added *p*-toluene sulfonic acid (0.070 g, 1.1 eq.). The mixture was heated at 40 °C for two hours, followed by heating at reflux for a further three hours. After allowing the mixture to cool to room temperature, the mixture was quenched with saturated sodium hydrogen carbonate solution (20 mL) and extracted with dichloromethane (3 × 20 mL). The combined organic extracts were dried (magnesium sulfate), filtered and concentrated under reduced pressure. The crude mixture was subjected to flash column chromatography (1/ 3 ethyl acetate/ hexane) to afford the product as a yellow oil (63 %).

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¹H NMR, 400MHz (CDCl₃) δ 7.85 (1H, d, J = 7.6), 7.55-7.43 (3H, m), 4.47 (1H, t, J = 5.6), 4.42 (1H, d, J = 16.8), 4.39 (1H, d, J = 16.8), 3.58 (1H, dd, J = 14.0, 7.6), 3.51 (1H, dd, J = 14.0, 6.8), 3.29 (3H, s), 3.27 (3H, s), 2.02 (1H, m), 1.72 (1H, m), 1.68-1.59 (2H, m), 1.27-1.17 (2H, m), 0.91 (3H, d, J = 6.4) and 0.88 (3H, d, J = 6.4).

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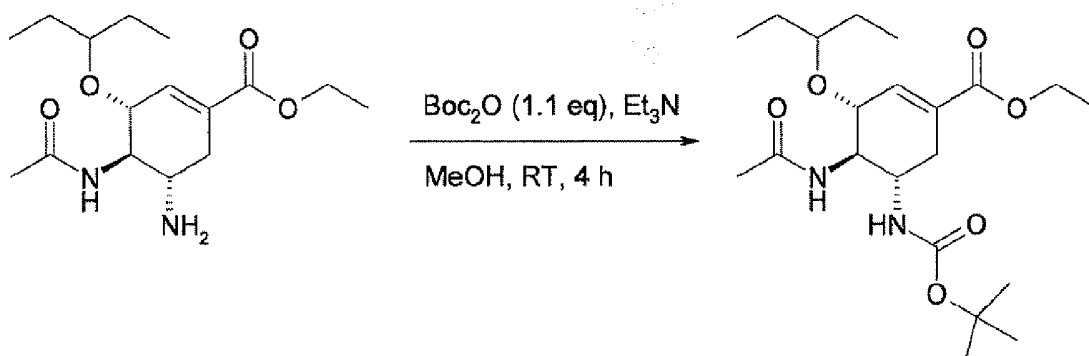
Pregabalin Phthalimidine Aldehyde Dioxolano Acetal

To a room temperature stirring solution of pregabalin phthalic imide aldehyde (0.987 g, 0.36 mmol) in anhydrous ethylene glycol (20 mL) under inert atmosphere was added 6 drops of concentrated sulfuric acid. The mixture was heated at 120 °C for three hours. After allowing the mixture to cool to room temperature, the mixture was quenched with saturated sodium hydrogen carbonate solution (20 mL) and extracted with dichloromethane (3 × 20 mL). The combined organic extracts were dried (magnesium sulfate), filtered and concentrated under reduced pressure. The crude mixture was subjected to flash column chromatography (1/ 3 ethyl acetate/ hexane) to afford the product as a yellow oil (62 %).

¹H NMR, 400MHz (CDCl₃) δ 7.85 (1H, d, J = 7.2), 7.53-7.43 (3H, m), 4.94 (1H, t, J = 4.8), 4.44 (1H, d, J = 16.8), 4.36 (1H, d, J = 16.8), 3.92 (2H, m), 3.81 (2H, m), 3.62 (1H, dd, J = 14.0, 6.4), 3.55 (1H, dd, J = 13.6, 6.8), 2.11 (1H, m), 1.73-1.65 (3H, m), 1.31-1.20 (2H, m), 0.91 (3H, d, J = 6.8) and 0.87 (3H, d, J = 6.4).

Supplementary Information

Phthalimidine protecting group may be removed by oxidizing to the corresponding phthalimide using 2,2'-bipyridinium chlorochromate (2 eq.) and *meta*-chloroperoxybenzoic acid (5 eq.) in the presence of Celite® with dichloromethane as the solvent (Luzzio, F. A.; Zacherl, D. P.; Figg, W. D. *Tetrahedron Lett.*, **1999**, 11, 2087). Following this, the phthalimido group may be removed by reacting the compound with hydrazine in refluxing methanol (Lagu, B.; Tian, D.; Jeon, Y.; Li, C.; Wetzel, J. M.; Nagarathnam, D.; Shen, Q.; Forray, C.; Chang, R. S. L.; Broten, T. P.; Ransom, R. W.; Chan, T-B.; O'Malley, S. S.; Schorn, T. W.; Rodrigues, A. D.; Kassahun, K.; Pettibone, D. J.; Freidinger, R.; Gluchowski, C. *J. Med. Chem.*, **2000**, 43, 2775).

EXAMPLE 3 – OSELTAMIVIR DERIVATIVES**Oseltamivir Boc-Amide**

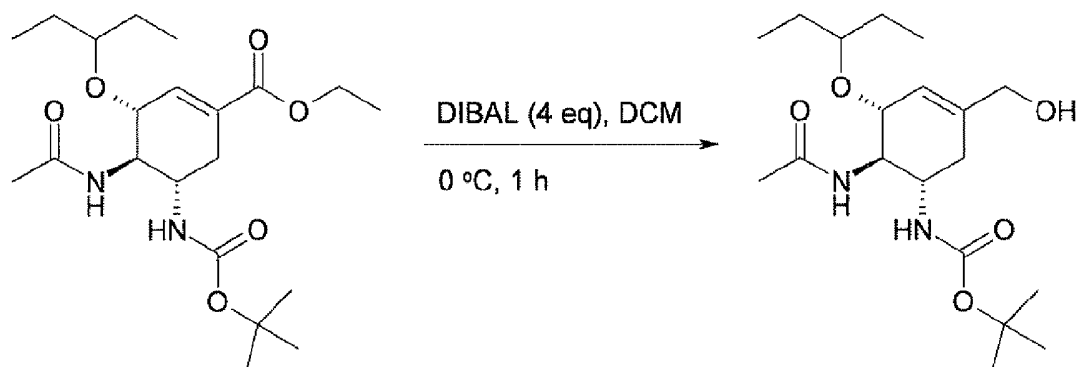
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To a room temperature stirring solution of oseltamivir (1.5 g, 4.81 mmol) in anhydrous methanol (50 mL) under inert atmosphere was added di-*tert*-butyl dicarbonate (1.15 g, 1.1 eq.) and triethylamine (2 mL). After four hours, the crude mixture was concentrated under reduced pressure and subjected to flash column chromatography (30 % methanol/

10 dichloromethane) to afford the product as a white solid (1.6 g, 90 %).

$^1\text{H NMR}$, 400MHz (CDCl_3) δ 6.80 (1H, s), 5.72 (1H, d, $J = 9.2$), 5.07 (1H, d, $J = 9.1$), 4.21 (2H, dq, $J = 6.7, 1.7$), 4.08 (1H, q, $J = 9.1$), 3.95 (1H, m), 3.80 (1H, m), 3.35 (1H, m), 2.74 (1H, dd, $J = 17.8, 5.1$), 2.29 (1H, m), 1.99 (3H, s), 1.51 (4H, m), 1.42 (9H, s),

15 1.29 (3H, t, $J = 7.2$) and 0.89 (6H, d, $J = 7.4$).

Oseltamivir Boc-Amide Alcohol

20 To a 0 °C stirring solution of oseltamivir Boc-amide (1.33 g, 3.23 mmol) in anhydrous dichloromethane (100 mL) under inert atmosphere was added di-*iso*-butyl aluminium hydride (12.92 mL, 1.2 eq.). After one hour, the mixture was partitioned between

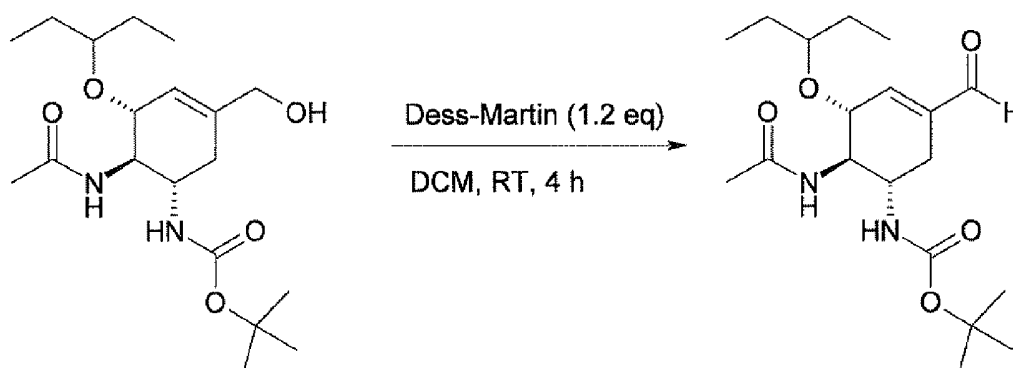
dichloromethane (50 mL) and 1 M sodium hydroxide solution (50 mL). The organic phase was dried (magnesium sulfate), filtered and concentrated under reduced pressure. The crude mixture was subjected to flash column chromatography (5 % methanol/ dichloromethane) to afford the product (0.34 g, 34 %).

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^1H NMR, 400MHz (CDCl_3) δ 6.22 (1H, d, $J = 9.2$), 5.66 (1H, s), 5.33 (1H, d, $J = 9.3$), 4.09-4.05 (2H, m), 3.91 (1H, m), 3.88 (1H, m), 3.33 (1H, quin, $J = 5.6$), 2.53 (1H, br s), 2.34 (1H, dd, $J = 7.2, 5.1$), 2.11 (1H, m), 1.99 (3H, s), 1.52-1.45 (4H, m), 1.42 (9H, s) and 0.90-0.85 (6H, m).

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Oseltamivir Boc-Amide Aldehyde



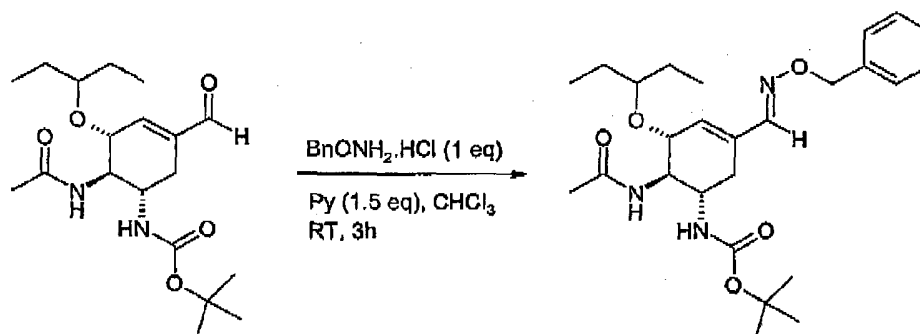
To a room temperature stirring solution of oseltamivir Boc-amide alcohol (1.57 g, 4.24 mmol) in anhydrous dichloromethane (150 mL) under inert atmosphere was added Dess-Martin periodinane (2.15 g, 1.2 eq.). After four hours, the mixture was partitioned between dichloromethane (50 mL) and 1 M sodium hydroxide solution (50 mL). The organic phase was dried (magnesium sulfate), filtered and concentrated under reduced pressure. The crude mixture was subjected to flash column chromatography (5 % methanol/ dichloromethane) to afford the product as yellow oil (1.2 g, 54 %).

20

^1H NMR, 400MHz (CDCl_3) δ 9.50 (1H, s), 6.61 (1H, s), 5.83 (1H, d, $J = 8.7$), 4.96 (1H, d, $J = 9.1$), 4.16-4.07 (2H, m), 3.80 (1H, m), 3.38 (1H, quin, $J = 5.6$), 2.74 (1H, dd, $J = 17.9, 5.2$), 2.13 (1H, m), 2.00 (3H, s), 1.58-1.48 (4H, m), 1.43 (9H, s), 0.95-0.87 (6H, m).

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Oseltamivir Boc-Amide Aldehyde Benzyl Oxime

To a room temperature stirring solution of oseltamivir Boc-amide aldehyde (0.153 g, 0.41 mmol) in anhydrous chloroform (5 mL) under inert atmosphere was added o-benzylhydroxylamine hydrochloride salt (0.067 g, 1 eq.), followed by anhydrous pyridine (0.051 mL, 1.5 eq.). After three hours, the mixture was partitioned between chloroform/

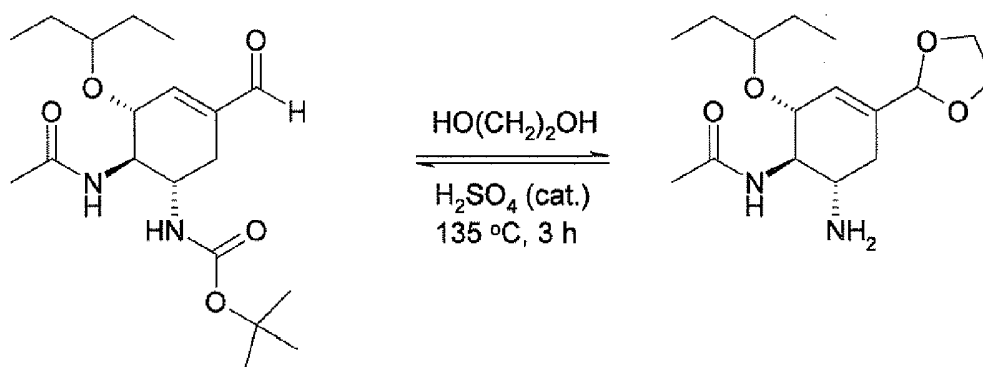
5 benzylhydroxylamine hydrochloride salt (0.067 g, 1 eq.), followed by anhydrous pyridine (0.051 mL, 1.5 eq.). After three hours, the mixture was partitioned between chloroform/ water and extracted with chloroform (× 2). The combined organic extracts were dried (magnesium sulfate), filtered and concentrated under reduced pressure. The crude mixture was subjected to flash column chromatography (5 % methanol/ chloroform) to

10 afford the product as an off-white foam (69 %).

¹H NMR, 400MHz (CDCl₃) δ 7.68 (1H, s), 7.37-7.30 (5H, m), 6.02 (1H, d, J = 9.2), 5.80 (1H, s), 5.13 (1H, d, J = 9.2), 5.09 (2H, s), 4.07 (1H, m), 3.96 (1H, m), 3.80 (1H, m), 3.31 (1H, quin, J = 5.6), 2.75 (1H, dd), 2.25 (1H, m), 1.98 (3H, s), 1.52-1.46 (4H, m), 1.45

15 (9H, s), 0.89-0.85 (6H, m).

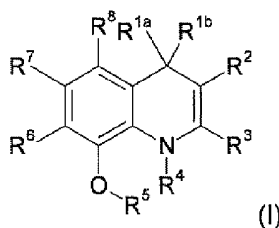
Oseltamivir Aldehyde Dioxolano Acetal (NB. Conditions have also removed the Boc Protecting Group)



- 5 To a room temperature stirring solution of oseltamivir Boc-amide aldehyde (0.2 g, 0.54 mmol) in anhydrous ethylene glycol (30 mL) under inert atmosphere was added 6 drops of concentrated sulfuric acid. The mixture was heated at 135 °C for three hours. After allowing the mixture to cool to room temperature, the mixture was quenched with saturated sodium hydrogen carbonate solution (20 mL) and extracted with
- 10 dichloromethane (3 × 20 mL). The combined organic extracts were dried (magnesium sulfate), filtered and concentrated under reduced pressure. The crude mixture was subjected to flash column chromatography (5 % methanol/ chloroform) to afford the product as a yellow oil.
- 15 ¹H NMR, 400MHz (CDCl₃) δ 6.38 (1H, m), 5.91 (1H, s), 5.16 (1H, s), 4.08 (1H, m), 3.98-3.96 (2H, m), 3.92-3.90 (2H, m), 3.36 (1H, quin), 2.92 (1H, m), 2.55 (1H, m), 2.05-1.97 (5H, m), 1.99 (3H, s), 1.56-1.49 (4H, m), 0.95-0.87 (6H, m).

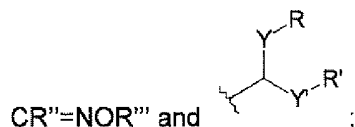
CLAIMS:

1. A method of preparing an oxidised or reduced pharmaceutical active derivative, comprising:
- 5 (iv) obtaining a parent pharmaceutical active;
- (v) oxidising the parent pharmaceutical active to provide an oxidised pharmaceutical active derivative which is in an oxidation state one or more oxidation states higher than the parent pharmaceutical active; or reducing the parent pharmaceutical active to provide a reduced pharmaceutical active derivative which is in an oxidation state one or
- 10 more oxidation states lower than the parent pharmaceutical active; and
- (vi) isolating the oxidised or reduced pharmaceutical active derivative.
2. The method of claim 1 wherein step (ii) of the method comprises oxidising the
- 15 parent pharmaceutical active to provide an oxidised pharmaceutical active derivative.
3. The method of claim 1 wherein step (ii) of the method comprises reducing the parent pharmaceutical active to provide a reduced pharmaceutical active derivative.
- 20 4. A compound of formula I:



wherein:

- R^{1a} and R^{1b} are together selected from the group comprising: oxo and =NOR''; or
- R^{1a} is -H and R^{1b} is -OR''; and
- 25 R^2 is selected from the group comprising: -COOR'', -CR''O, -CR''R''OR'', -



wherein

- Y- is selected from the group comprising: =N-, -O- and -S-;
- Y'- is selected from the group comprising: -O- and -S-;
- 30 each R, R' and R'' is independently selected from the group comprising: -H and C₁₋₄ alkyl; or each R'' is independently selected from the group comprising:

-H and C₁₋₄ alkyl, and R and R' join to form a 5 to 8 membered ring together with the atoms to which they are bonded; and

R^{'''} is selected from the group comprising: H, C₁₋₄ alkyl and -(CR^{'''}R^{'''})_n-aryl; wherein each R^{'''} is independently selected from the group comprising: H and aryl and wherein n is from 1 to 4;

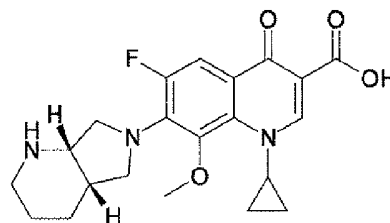
R³, R⁷ and R⁸ are each independently selected from the group comprising: H, substituted or unsubstituted C₁₋₄alkyl and halogen;

R⁴ and R⁵ are each independently substituted or unsubstituted C₁₋₄alkyl; or R⁴ and R⁵ join to form a 6 membered ring together with the atoms to which they are bonded;

R⁶ is a substituted or unsubstituted N-heterocycloalkyl group comprising from 5 to 10 ring atoms and at least one nitrogen atom;

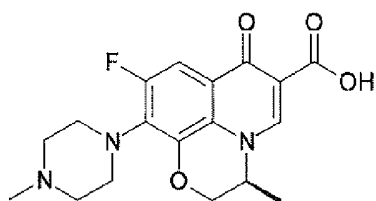
wherein, where chemically possible, each alkyl and each aryl may be independently substituted with up to 5 substituents independently selected from the group comprising: F, Cl, Br, CN, NO₂, OR'' or OH; and

provided that the compound is not



or

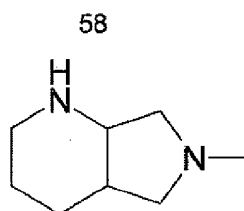
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5. The compound of claim 4 wherein:

R³ is H;

R⁴ is unsubstituted cyclopropyl and R⁵ is methyl; or R⁴ is ethyl and R⁵ is methyl and R⁴ and R⁵ join to form a 6 membered ring together with the atoms to which they are bonded;

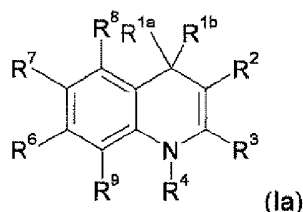


R^6 is N-methyl piperazine or

R^7 is fluoro; and

R^8 is hydrogen.

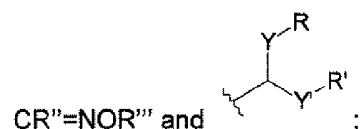
- 5 6. A compound of formula (Ia):



wherein:

R^{1a} and R^{1b} are together selected from the group comprising: oxo and =NOR''; or
 R^{1a} is -H and R^{1b} is -OR''; and

- 10 R^2 is selected from the group comprising: -COOR'', -CR''O, -CR''R''OR'', -



wherein

-Y- is selected from the group comprising: =N-, -O- and -S-;

-Y'- is selected from the group comprising: -O- and -S-;

- 15 each R, R' and R'' is independently selected from the group comprising: -H and C₁₋₄ alkyl; or each R'' is independently selected from the group comprising: -H and C₁₋₄ alkyl, and R and R' join to form a 5 to 8 membered ring together with the atoms to which they are bonded; and

- 20 R''' is selected from the group comprising: H, C₁₋₄ alkyl and -(CR''''R''''_n)-aryl; wherein R'''' is selected from the group comprising: H and aryl;

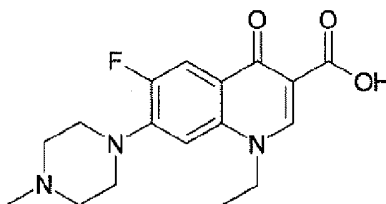
R^3 , R^7 , R^8 and R^9 are each independently selected from the group comprising: H, substituted or unsubstituted C₁₋₄alkyl and halogen;

R^4 is a substituted or unsubstituted C₁₋₄alkyl;

- 25 R^6 is a substituted or unsubstituted N-heterocycloalkyl group comprising from 5 to 10 ring atoms and at least one nitrogen atom;

wherein, where chemically possible, each alkyl and each aryl may be independently substituted with up to 5 substituents independently selected from the group comprising: F, Cl, Br, CN, NO₂, OR'' or OH; and

5 provided that the compound is not



7. The compound of claim 6 wherein:

R³ is H;

R⁴ is ethyl;

10 R⁶ is N-methyl piperazine;

R⁷ is fluoro; and

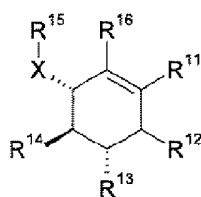
R⁸ is hydrogen.

8. The compound of any of claims 4 to 7, wherein R^{1a} and R^{1b} are together oxo.

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9. The compound of any of claims 4 to 8, wherein R² is selected from the group comprising: -COOH, -CHO, -CH₂OH and CH=NOH.

10. A compound of formula II:

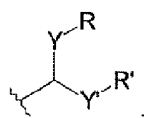


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wherein:

R¹¹ is selected from the group comprising: -C(O)NR''R''', -CR''R''OR'', -COO(C₁-

alkyl), -CR''O, -CR'''=NOR'' and



wherein

25

-Y- is selected from the group comprising: =N-, -O- and -S-;

-Y'- is selected from the group comprising: -O- and -S-; and

each R, R' and R'' is independently selected from the group comprising: -H, C₁₋₄ alkyl and -(CH₂)_n-aryl; or each R'' is independently selected from the group comprising: -H, C₁₋₄ alkyl and -(CH₂)_n-aryl, and R and R' join to form a 5 to 8 membered ring together with the atoms to which they are bonded, wherein n is from 1 to 4;

each R''' is selected from the group comprising: H, C₁₋₄ alkyl, OR'' and SR''; and

each R'''' is selected from the group comprising: H, OH and SH;

R¹² and R¹⁶ are each independently selected from the group comprising: H, substituted or unsubstituted C₁₋₄alkyl and halogen;

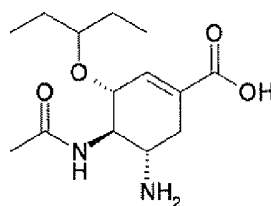
R¹³ is selected from the group comprising: -OR'', -NR''R'' and -(CR''R'')_mNR''R'', wherein m is 1 or 2;

R¹⁴ is selected from the group comprising: -NR''CO(C₁₋₃alkyl) and -N=CR''(C₁₋₃alkyl);

R¹⁵ is substituted or unsubstituted C₁₋₈alkyl;

X is O or S;

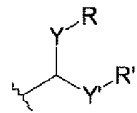
wherein, where chemically possible, each alkyl may be substituted with up to 5 substituents independently selected from the group comprising: F, Cl, Br, CN, NO₂, OR'' or OH; and



provided that the compound is not

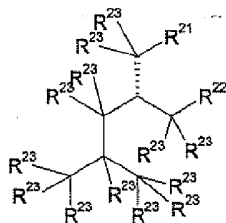
11. The compound according to claim 10 wherein R¹² is H, R¹³ is -NH₂, R¹⁴ is -NHCOCH₃, R¹⁵ is 3-pentyl, R¹⁶ is H and X is O.

12. The compounds according to claim 10 or claim 11 wherein R¹¹ is -CHO, -

CH₂OH, -CH=NOH, -CSH=NOH, -COH=NOH or 

61

13. A compound of formula III:

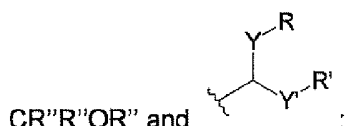


wherein:

each R^{23} is independently selected from the group comprising: -H, -Cl, -F and C_{1-3} alkyl;

R^{21} is $-NRR'$; and

R^{22} is selected from the group comprising: $-CR''O$, $-CR''=NOR'''$, $-N(=NR'')R''$,



wherein:

10

-Y- is selected from the group comprising: =N-, -O- and -S-;

-Y'- is selected from the group comprising: -O- and -S-;

each R, R' and R'' is independently selected from the group comprising: -H and C_{1-4} alkyl; or each R'' is independently selected from the group comprising: -H and C_{1-4} alkyl, and R and R' join to form a 5 to 8 membered ring together with the atom(s) to which they are bonded; and

15

R''' is selected from the group comprising: H, C_{1-4} alkyl and $-(CR''''R''''')_n$ -aryl; wherein R'''' is selected from the group comprising: H and aryl and wherein n is from 1 to 4;

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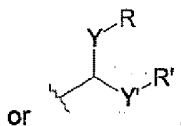
or

wherein R^{21} is $-N=$ and R^{22} is $-CR''=$ and R^{21} and R^{22} join to form a 5 membered ring together with the atoms to which they are bonded; or

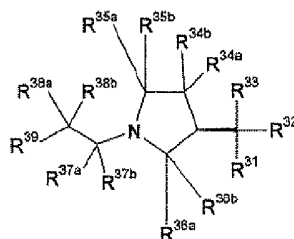
25 wherein R^{21} is $-NR''-$ and R^{22} is $-C(O)-$ and R^{21} and R^{22} join to form a 5 membered ring together with the atoms to which they are bonded.

14. The compound of claim 13, wherein R^{21} is $-NH_2$ and each R^{23} is H.

15. The compound of claim 13 or claim 14, wherein R²² is -CHO, -CH=NOH, CH₂OH



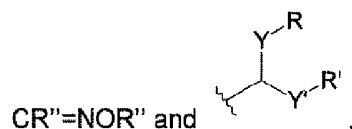
16. A compound of formula IV:



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wherein:

R³¹ is selected from the group comprising: -CR''R''OR'', -CR''O, -CR''=NR'', -



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wherein

-Y- is selected from the group comprising: =N-, -O- and -S-;

-Y'- is selected from the group comprising: -O- and -S-; and

each R, R' and R'' is independently selected from the group comprising: -

H and C₁₋₄ alkyl; or each R'' is independently selected from the group comprising:

15

-H and C₁₋₄ alkyl, and R and R' join to form a 5 to 8 membered ring together with the atoms to which they are bonded;

R³² and R³³ are each independently selected from the group comprising: substituted or unsubstituted phenyl and substituted or unsubstituted pyridinyl;

20

R^{34a}, R^{34b}, R^{35a}, R^{35b}, R^{36a}, R^{36b}, R^{37a}, R^{37b}, R^{38a} and R^{38b} are each independently selected from the group comprising: -H, C₁₋₄alkyl and halo;

R³⁹ is selected from the group comprising: substituted or unsubstituted aryl and substituted or unsubstituted heteroaryl.

25

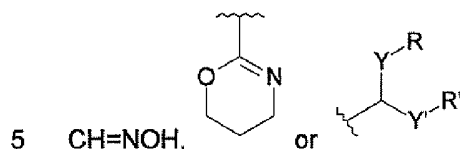
17. The compound of claim 16 wherein:

R³² is phenyl;

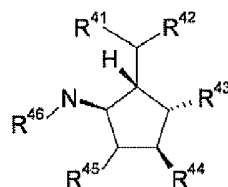
R³³ is phenyl;

R^{34a} , R^{34b} , R^{35a} , R^{35b} , R^{36a} , R^{36b} , R^{37a} , R^{37b} , R^{38a} and R^{38b} are each -H; and R^{39} is 5-benzo[b]-oxolanyl.

18. The compound of claim 17 or claim 18 wherein R^{31} is -CHO, -CH=NH, -



19. A compound of formula V:



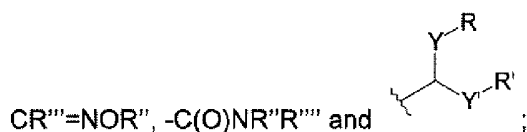
10 wherein:

R^{41} is selected from the group comprising: -NR''CO(C₁₋₃alkyl) and -N=CR''(C₁₋₃alkyl);

R^{42} is substituted or unsubstituted C₁₋₈ alkyl;

15 R^{43} is selected from the group comprising: -OR'', -NR''R'', -(CR''R'')_mOR'' and -(CR''R'')_mNR''R'', wherein m is 1 or 2;

R^{44} is selected from the group comprising: -COOR'', -CR''O, -CR''R''OR'', -



wherein

20 -Y- is selected from the group comprising: =N-, -O- and -S-;

-Y'- is selected from the group comprising: -O- and -S-;

each R, R' and R'' is independently selected from the group comprising: -H and C₁₋₄ alkyl; or each R'' is independently selected from the group comprising: -H and C₁₋₄ alkyl, and R and R' join to form a 5 to 8 membered ring together with the atoms to which they are bonded;

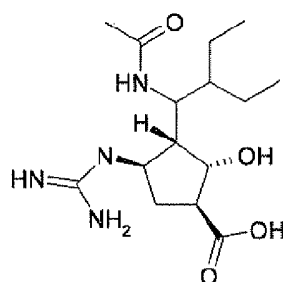
25 each R''' is selected from the group comprising: H, C₁₋₄ alkyl, OR'' and SR''; and

each R'''' is selected from the group comprising: H, OH and SH;

R⁴⁵ is selected from the group comprising: H, substituted or unsubstituted C₁₋₄alkyl and halogen; and

R⁴⁶ is selected from the group comprising: -C(=NR'')NR''R'', -C(=O)NR''R'' and -C(=O)OR'';

5

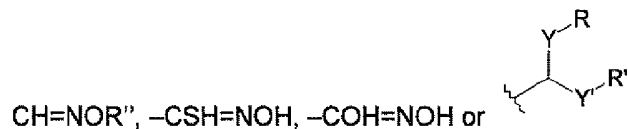


provided that the compound is not

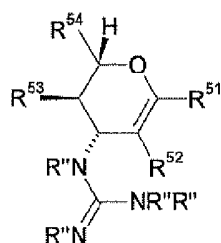
20. The compound of claim 19, wherein R⁴¹ is -NH-C(=O)Me, R⁴² is 3-pentyl, R⁴³ is -OH, R⁴⁵ is H and R⁴⁶ -C(=NH)NH₂

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21. The compound of claim 19 or claim 20 wherein R⁴⁴ is -COOH, -CHO, -CH₂OH, -



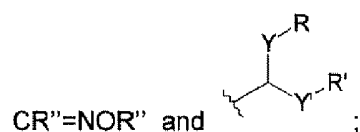
22. A compound of formula VI:



15

wherein

R⁵¹ is selected from the group comprising: -C(O)NR''R''', -COOR'', -CR''O, -



wherein

20

-Y- is selected from the group comprising: =N-, -O- and -S-;

-Y'- is selected from the group comprising: -O- and -S-;

each R, R' and R'' is independently selected from the group comprising: -H and C₁₋₄ alkyl; or each R'' is independently selected from the group comprising: -H and C₁₋₄ alkyl, and R and R' join to form a 5 to 8 membered ring together with the atoms to which they are bonded;

5 each R''' is selected from the group comprising: H, C₁₋₄ alkyl, OR'' and SR''; and

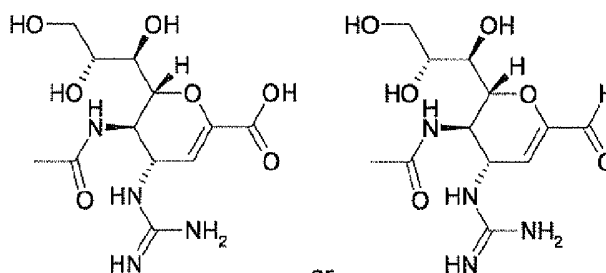
each R'''' is selected from the group comprising: H, OH and SH;

R⁵² is selected from the group comprising: H, substituted or unsubstituted C₁₋₄ alkyl and halogen;

R⁵³ is selected from the group comprising: -NR''C(=O)R'' and -N=CR''(C₁₋₃alkyl);

R⁵⁴ is a substituted or unsubstituted C₁₋₆alkyl;

10



provided that the compound is not

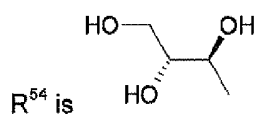
or

15

23. The compound of claim 22, wherein:

R⁵² is H;

R⁵³ is -NHC(=O)Me or -N=CHMe;



20

24. The compound of claim 22 or claim 23 wherein -COOH, -CHO, -CH=NOH, -

