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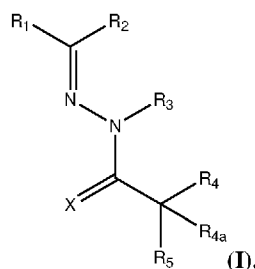
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(54) Title: COMPOUNDS FOR AND METHODS OF TREATING DISEASES



(57) Abstract: The present invention relates to compounds that have zinc and/or iron ionophore activity and their use in treating diseases that are modulated by reducing zinc and/or iron. In particular embodiments, the compounds are compounds of formula (I):



Compounds for and Methods of Treating Diseases

Field of the Invention

The present invention relates to compounds that have zinc and/or iron ionophore activity and their use in treating diseases that are modulated by reducing zinc and/or iron.

Background of the Invention

Zinc and iron are micronutrients involved in a number of biological processes including immune response, metabolism, nucleic acid synthesis and repair, apoptosis and redox homeostasis and can be important in host-pathogen interactions.

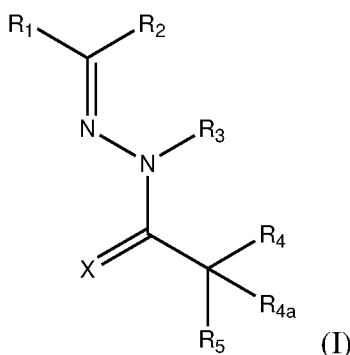
Zinc has been implicated in processes involved in diseases such as cancer and neurological diseases and has been shown to have antiviral, antibiotic and anti-infective activities.

Iron has been implicated in processes involved in neurodegenerative disorders and disorders associated with iron overload.

The ability to chelate zinc and/or iron and transport zinc and/or iron, for example, from the extracellular environment to the intracellular environment has utility in diverse disease processes. There is a need for further zinc and iron ionophores that may be useful in treating or managing disease processes.

Summary of the Invention

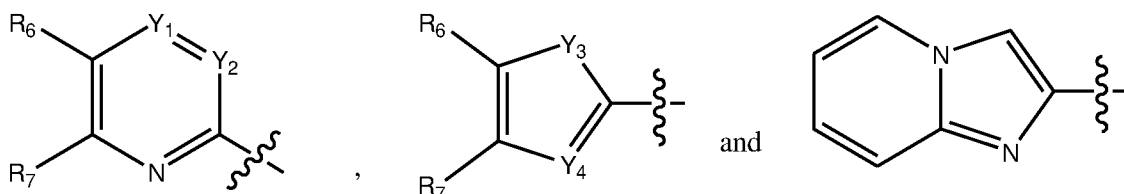
Described herein are compounds of formula (I):



wherein X is O or S;

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R₁ is selected from:



Y₁ is CR₈ or N;

Y₂ is CR₈ or N;

5 provided that both Y₁ and Y₂ are not N;

Y₃ is C(R₈)₂, NR₉ or S;

Y₄ is CR₈ or N;

provided that Y₃ is not C(R₈)₂ when Y₄ is CR₈;

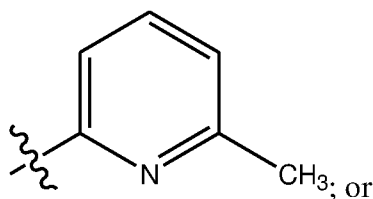
R₆ and R₇ are independently selected from hydrogen, C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, hydroxy, C₁₋₆alkoxy, C₁₋₆haloalkyl, C₁₋₆haloalkoxy, halo, CN, CO₂R₉ and
10 N(R₉)₂; or

R₆ and R₇ taken together with the atoms to which they are attached form an optionally substituted 6 membered aryl or heteroaryl ring;

each R₈ is independently selected from hydrogen, C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, hydroxy, C₁₋₆alkoxy, C₁₋₆haloalkyl, C₁₋₆haloalkoxy, halo, (C(R₁₀)₂)_mCO₂R₉ and
15 (C(R₁₀)₂)_mN(R₉)₂;

each R₉ is independently selected from hydrogen, C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl and C₁₋₆haloalkyl;

R₂ is selected from hydrogen, C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₁₋₆haloalkyl, C₃₋₈
20 cycloalkyl and



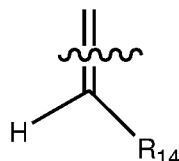
R₁ and R₂ taken together for a 5, 6 or 7 membered cycloalkyl or heterocycloalkyl ring fused with a six-membered nitrogen-containing heteroaryl ring, wherein the cycloalkyl, heterocycloalkyl or heteroaryl ring may be optionally substituted,

25 R₃ is selected from hydrogen, C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl and (C(R₁₀)₂)_mCO₂R₉;

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R_4 and R_{4a} are each independently selected from hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl and C_{1-6} haloalkyl; and R_5 is hydrogen, $(C(R_{10})_2)_m$ aryl or $(C(R_{10})_2)_m$ heteroaryl wherein aryl and heteroaryl are optionally substituted; or

R_{4a} is CN and R_4 and R_5 taken together form:

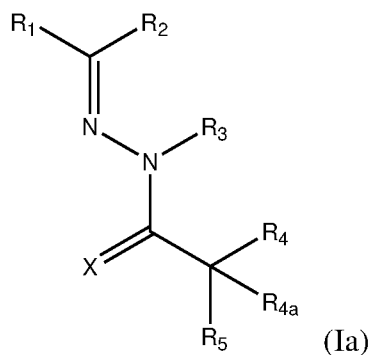


where R_{14} is hydrogen, $(C(R_{10})_2)_m$ aryl or $(C(R_{10})_2)_m$ heteroaryl where aryl and heteroaryl are optionally substituted; or

R_{4a} is absent and R_4 and R_5 taken together form an optionally substituted aryl or optionally substituted heteroaryl group;

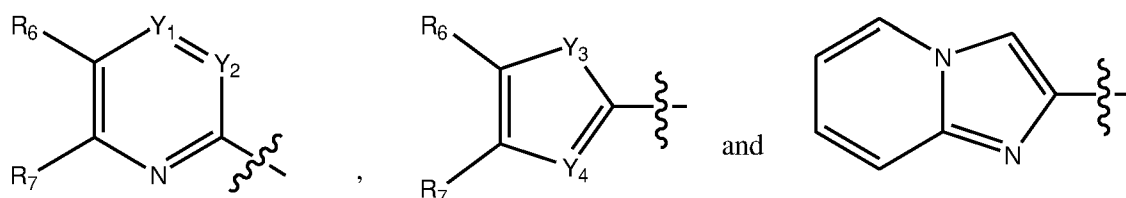
- each R_{10} is independently selected from hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, hydroxy, C_{1-6} alkoxy, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, CN, halo and $N(R_9)_2$;
 m is 0 or an integer of 1 to 6;
 or a pharmaceutically acceptable salt thereof.

Also described herein are compounds of formula (Ia):



wherein X is O or S;

R_1 is selected from:



Y_1 is CR_8 ;

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Y_2 is CR_8 or N;

Y_3 is $C(R_8)_2$, NR_9 or S;

Y_4 is CR_8 or N;

provided that Y_3 is $C(R_8)_2$ then Y_4 is not CR_8 ;

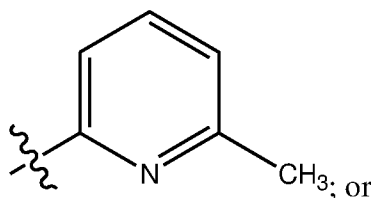
- 5 R_6 and R_7 are independently selected from hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, hydroxy, C_{1-6} alkoxy, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, halo, CN, CO_2R_9 and $N(R_9)_2$; or

R_6 and R_7 taken together with the atoms to which they are attached form an unsubstituted 6 membered aryl or heteroaryl ring;

- 10 each R_8 is independently selected from hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, hydroxy, C_{1-6} alkoxy, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, halo, $(CH_2)_mCO_2R_9$ and $(CH_2)_mN(R_9)_2$;

each R_9 is independently selected from hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl and C_{1-6} haloalkyl;

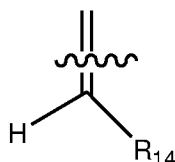
- 15 R_2 is selected from C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{3-8} cycloalkyl and



R_1 and R_2 taken together for a 5, 6 or 7 membered cycloalkyl ring fused with a six membered nitrogen-containing heteroaryl ring, wherein the cycloalkyl or heteroaryl ring may be optionally substituted,

- 20 R_3 is selected from hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl and $C(R_{10})_2CO_2R_9$; R_4 and R_{4a} are each independently selected from hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl and C_{1-6} haloalkyl; and R_5 is $(C(R_{10})_2)_m$ aryl or $(C(R_{10})_2)_m$ heteroaryl where aryl and heteroaryl are optionally substituted; or

- 25 R_{4a} is CN and R_4 and R_5 taken together form:



- 5 -

where R_{14} is hydrogen, $(C(R_{10})_2)_m$ aryl or $(C(R_{10})_2)_m$ heteroaryl wherein aryl and heteroaryl are optionally substituted; or

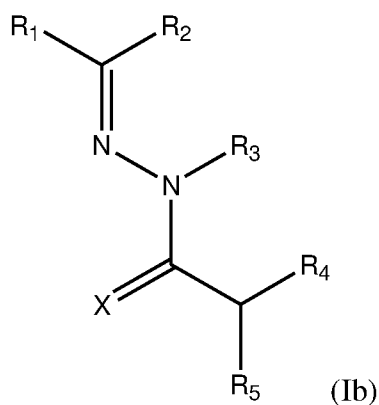
R_{4a} is absent and R_4 and R_5 taken together form an optionally substituted aryl or optionally substituted heteroaryl group;

- 5 each R_{10} is independently selected from hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, hydroxy, C_{1-6} alkoxy, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, CN, halo and $N(R_9)_2$;

m is 0 or an integer of 1 to 6;

or a pharmaceutically acceptable salt thereof.

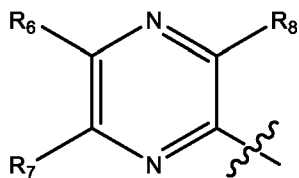
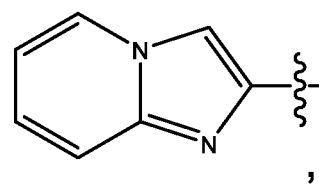
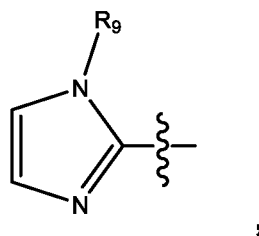
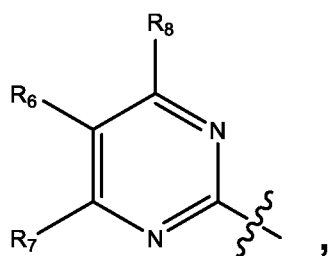
Also described herein are compounds of formula (Ib):



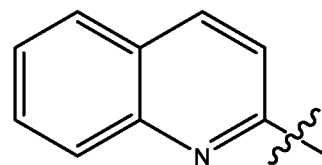
10

wherein X is O;

R_1 is selected from:



and



- 6 -

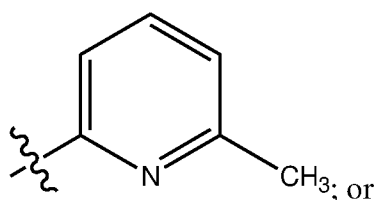
R₆ and R₇ are independently selected from hydrogen, C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, hydroxy, C₁₋₆alkoxy, C₁₋₆haloalkyl, C₁₋₆haloalkoxy, halo, CN, CO₂R₉ and N(R₉)₂; or

5 R₆ and R₇ taken together with the atoms to which they are attached form an optionally substituted 6-membered aryl or heteroaryl ring;

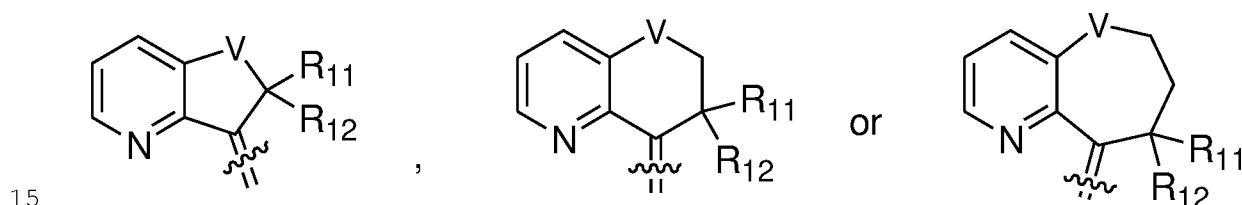
each R₈ is independently selected from hydrogen, C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, hydroxy, C₁₋₆alkoxy, C₁₋₆haloalkyl, C₁₋₆haloalkoxy, halo, (C(R₁₀)₂)_mCO₂R₉ and (C(R₁₀)₂)_mN(R₉)₂;

10 each R₉ is independently selected from hydrogen, C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl and C₁₋₆haloalkyl;

R₂ is selected from hydrogen, C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₁₋₆haloalkyl, C₃₋₈cycloalkyl and



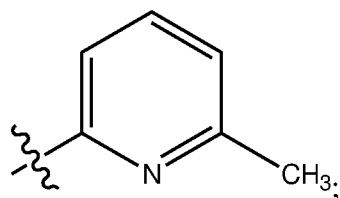
R₁ and R₂ taken together form



wherein V is CH, O or S and R₁₁ and R₁₂ are each independently selected from hydrogen, C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, halo, C₁₋₆haloalkyl, (CH₂)_mC₃₋₈cycloalkyl, (CH₂)_maryl, (CH₂)_mheterocyclyl, (CH₂)_mheteroaryl and COR₁₃ where R₁₃ is selected

20 from OH, OC₁₋₆alkyl, OC₂₋₆alkenyl, OC₂₋₆alkynyl and N(R₉)₂, wherein the cycloalkyl, heterocycloalkyl or heteroaryl ring of the bicyclic structure formed from R₁ and R₂ may be optionally substituted, or

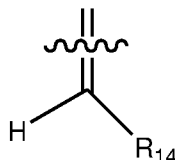
R₁ and R₂ are both:



- 7 -

- R₃ is selected from hydrogen, C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl and (C(R₁₀)₂)_mCO₂R₉; R₄ and R_{4a} are each independently selected from hydrogen, C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl and C₁₋₆haloalkyl; and R₅ is hydrogen, (C(R₁₀)₂)_maryl, (C(R₁₀)₂)_mheteroaryl, O(C(R₁₀)₂)_maryl or O(C(R₁₀)₂)_mheteroaryl wherein the aryl and heteroaryl are optionally substituted; or

R_{4a} is CN and R₄ and R₅ are each hydrogen or are taken together form:



- where R₁₄ is hydrogen, (C(R₁₀)₂)_maryl or (C(R₁₀)₂)_mheteroaryl wherein the aryl and heteroaryl are optionally substituted; or
- R_{4a} is absent and R₄ and R₅ taken together form an optionally substituted aryl or optionally substituted heteroaryl group;
- each R₁₀ is independently selected from hydrogen, C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, hydroxy, C₁₋₆alkoxy, C₁₋₆haloalkyl, C₁₋₆haloalkoxy, CN, halo and N(R₉)₂;
- m is 0 or an integer of 1 to 6;
- or a pharmaceutically acceptable salt thereof.

Detailed Description of the Invention

Definitions

- Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by those of ordinary skill in the art to which the invention belongs. Although any methods and materials similar or equivalent to those described herein can be used in the practice or testing of the present invention, preferred methods and materials are described. For the purposes of the present invention, the following terms are defined below.
- The articles "a" and "an" are used herein to refer to one or to more than one (i.e. to at least one) of the grammatical object of the article. By way of example, "an element" means one element or more than one element.

As used herein, the term "about" refers to a quantity, level, value, dimension, size, or amount that varies by as much as 15% or 10% to a reference quantity, level, value, dimension, size, or amount.

Throughout this specification, unless the context requires otherwise, the words
5 "comprise", "comprises" and "comprising" will be understood to imply the inclusion of a stated step or element or group of steps or elements but not the exclusion of any other step or element or group of steps or elements.

As used herein, the term "alkyl" refers to a straight chain or branched saturated hydrocarbon group having 1 to 10 carbon atoms. Where appropriate, the alkyl group
10 may have a specified number of carbon atoms, for example, C₁₋₆alkyl which includes alkyl groups having 1, 2, 3, 4, 5 or 6 carbon atoms in a linear or branched arrangement. Examples of suitable alkyl groups include, but are not limited to, methyl, ethyl, *n*-propyl, *i*-propyl, *n*-butyl, *i*-butyl, *t*-butyl, *n*-pentyl, 2-methylbutyl, 3-methylbutyl, 4-methylbutyl, *n*-hexyl, 2-methylpentyl, 3-methylpentyl, 4-methylpentyl, 5-methylpentyl,
15 2-ethylbutyl, 3-ethylbutyl, heptyl, octyl, nonyl and decyl.

The term "haloalkyl" as used herein refers to an alkyl group as defined above where one or more hydrogen atoms have been replaced with a halogen atom and includes perhalogenated alkyl groups. Examples of suitable haloalkyl groups include fluoromethyl, difluoromethyl, trifluoromethyl, chloromethyl, dichloromethyl,
20 trichloromethyl, chlorofluoromethyl, difluorochloromethyl, dichlorofluoromethyl, bromomethyl, iodomethyl, 1-fluoroethyl, 2-fluoroethyl, 1-chloroethyl, 2-chloroethyl, 1-bromoethyl, 2-bromoethyl, 1-iodoethyl, 2-iodoethyl, 1-fluoropropyl, 2-fluoropropyl, 3-fluoropropyl, 1-chloropropyl, 2-chloropropyl, 3-chloropropyl, and the like.

As used herein, the term "alkenyl" refers to a straight-chain or branched hydrocarbon
25 group having one or more double bonds between carbon atoms and having 2 to 10 carbon atoms. Where appropriate, the alkenyl group may have a specified number of carbon atoms. For example, C₂₋₆ as in "C₂₋₆alkenyl" includes groups having 2, 3, 4, 5 or 6 carbon atoms in a linear or branched arrangement. Examples of suitable alkenyl groups include, but are not limited to, ethenyl, propenyl, isopropenyl, butenyl,

butadienyl, pentenyl, pentadienyl, hexenyl, hexadienyl, heptenyl, octenyl, nonenyl and decenyl.

As used herein, the term "alkynyl" refers to a straight-chain or branched hydrocarbon group having one or more triple bonds and having 2 to 10 carbon atoms. Where
5 appropriate, the alkynyl group may have a specified number of carbon atoms. For example, C₂₋₆ as in "C₂₋₆alkynyl" includes groups having 2, 3, 4, 5 or 6 carbon atoms in a linear or branched arrangement. Examples of suitable alkynyl groups include, but are not limited to ethynyl, propynyl, butynyl, pentynyl and hexynyl.

As used herein, the term "cycloalkyl" refers to a saturated cyclic hydrocarbon. The
10 cycloalkyl ring may include a specified number of carbon atoms. For example, a 3 to 10 membered cycloalkyl group includes 3, 4, 5, 6, 7, 8, 9 or 10 carbon atoms. Examples of suitable cycloalkyl groups include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, cyclononyl and cyclodecyl.

15 As used herein, the term "aryl" is intended to mean any stable, monocyclic, bicyclic or tricyclic carbon ring system of up to 7 atoms in each ring, wherein at least one ring is aromatic. Examples of such aryl groups include, but are not limited to, phenyl, naphthyl, tetrahydronaphthyl, indanyl, fluorenyl, phenanthrenyl, biphenyl and binaphthyl.

20 As used herein, the term "halogen" or "halo" refers to fluorine (fluoro), chlorine (chloro), bromine (bromo) and iodine (iodo).

As used herein, the terms "alkoxy" and "haloalkyloxy" refer to alkyl and haloalkyl groups defined above respectively when attached to an oxygen. Suitable examples include methoxy, ethoxy, *n*-propoxy, *i*-propoxy, *n*-butoxy, *i*-butoxy, *t*-butoxy, *n*-
25 pentoxy, 2-methylbutoxy, 3-methylbutoxy, 4-methylbutoxy, *n*-hexoxy, 2-methylpentoxy, 3-methylpentoxy, 4-methylpentoxy, 5-methylpentoxy, 2-ethylbutoxy, 3-ethylbutoxy, fluoromethoxy, difluoromethoxy, trifluoromethoxy, chloromethoxy, dichloromethoxy, trichloromethoxy, chlorofluoromethoxy, difluorochloromethoxy, dichlorofluoromethoxy, bromomethoxy, iodomethoxy, 1-fluoroethoxy, 2-fluoroethoxy,

1-chloroethoxy, 2-chloroethoxy, 1-bromoethoxy, 2-bromoethoxy, 1-iodoethoxy, 2-iodoethoxy, 1-fluoropropoxy, 2-fluoropropoxy, 3-fluoropropoxy, 1-chloropropoxy, 2-chloropropoxy and 3-chloropropyl.

The term "heterocyclic" or "heterocyclyl" as used herein, refers to a cyclic hydrocarbon, such as a cycloalkyl group defined above, in which one to four carbon atoms have been replaced by heteroatoms independently selected from the group consisting of N, N(R), S, S(O), S(O)₂ and O. A heterocyclic ring may be saturated or unsaturated but not aromatic. Examples of suitable heterocyclyl groups include azetidine, tetrahydrofuranyl, tetrahydrothiophenyl, pyrrolidinyl, 2-oxopyrrolidinyl, pyrrolinyl, pyranyl, dioxolanyl, piperidinyl, 2-oxopiperidinyl, pyrazolinyl, imidazolinyl, thiazolinyl, dithiolyl, oxathiolyl, dioxanyl, dioxinyl, dioxazolyl, oxathiozolyl, oxazolonyl, piperazinyl, morpholino, thiomorpholinyl, 3-oxomorpholinyl, dithianyl, trithianyl and oxazinyl.

The term "heteroaryl" as used herein, represents a stable monocyclic, bicyclic or tricyclic ring of up to 7 atoms in each ring, wherein at least one ring is aromatic and at least one ring contains from 1 to 4 heteroatoms selected from the group consisting of O, N and S. Heteroaryl groups within the scope of this definition include, but are not limited to, acridinyl, carbazolyl, cinnolinyl, quinoxalinyl, quinazolinyl, pyrazolyl, indolyl, isoindolyl, 1H,3H-1-oxoisoindolyl, benzotriazolyl, furanyl, thienyl, thiophenyl, benzothieryl, 4H-thieno[3,2-c]chromene, benzofuranyl, benzodioxane, benzodioxin, quinolinyl, isoquinolinyl, oxazolyl, isoxazolyl, imidazolyl, pyrazinyl, pyridazinyl, pyridinyl, pyrimidinyl, pyrrolyl, tetrahydroquinolinyl, thiazolyl, isothiazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, 1,2,4-oxadiazolyl, 1,2,4-thiadiazolyl, 1,2,3-thiadiazolyl, 1,3,5-triazinyl, 1,2,4-triazinyl, 1,2,4,5-tetrazinyl and tetrazolyl.

Each alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heterocyclyl and heteroaryl whether an individual entity or as part of a larger entity may be optionally substituted with one or more optional substituents selected from the group consisting of C₁₋₆alkyl, C₂₋₆alkenyl, C₃₋₆cycloalkyl, oxo (=O), -OH, -SH, C₁₋₆alkylO-, C₂₋₆alkenylO-, C₃₋₆cycloalkylO-, C₁₋₆alkylS-, C₂₋₆alkenylS-, C₃₋₆cycloalkylS-, -CO₂H, -CO₂C₁₋₆alkyl, -OC(=O)C₁₋₆alkyl, -NH₂, -NH(C₁₋₆alkyl), -N(C₁₋₆alkyl)₂, -NH(phenyl), -N(phenyl)₂, -C₁₋₆alkylNH₂, -C₁₋₆alkylNH(C₁₋₆alkyl), -C₁₋₆alkylN(C₁₋₆alkyl)₂, -C₁₋₆alkylNH(phenyl), -C₁₋

₆alkylN(phenyl)₂, -OC₁₋₆alkylNH₂, -OC₁₋₆alkylNH(C₁₋₆alkyl), -OC₁₋₆alkylN(C₁₋₆alkyl)₂,
 -OC₁₋₆alkylNH(phenyl), -OC₁₋₆alkylN(phenyl)₂, -CN, -NO₂, -halogen, -CF₃, -OCF₃, -
 SCF₃, -CHF₂, -OCHF₂, -SCHF₂, -phenyl, -heterocyclyl, -heteroaryl, -Oheteroaryl, -
 Oheterocyclyl, -Ophenyl, -OC₁₋₆alkylheteroaryl, -OC₁₋₆alkylheterocyclyl, -OC₁₋₆alkylphenyl, -C(=O)phenyl, -C(=O)C₁₋₆alkyl. Examples of suitable substituents
 include, but are not limited to, methyl, ethyl, propyl, isopropyl, butyl, *sec*-butyl, *tert*-
 butyl, vinyl, methoxy, ethoxy, propoxy, isopropoxy, butoxy, methylthio, ethylthio,
 propylthio, isopropylthio, butylthio, hydroxy, oxo, hydroxymethyl, hydroxyethyl,
 hydroxypropyl, hydroxybutyl, fluoro, chloro, bromo, iodo, cyano, nitro, -CO₂H,
 -CO₂CH₃, -OC(=O)CH₃, trifluoromethyl, trifluoromethoxy, trifluoromethylthio,
 difluoromethyl, difluoromethoxy, difluoromethylthio, morpholino, amino,
 methylamino, dimethylamino, ethylamino, diethylamino, aminoC₁₋₆alkyl,
 methylaminoC₁₋₆alkyl, dimethylaminoC₁₋₆alkyl, ethylaminoC₁₋₆alkyl, diethylaminoC₁₋₆alkyl,
 aminoC₁₋₆alkoxy, methylaminoC₁₋₆alkoxy, dimethylaminoC₁₋₆alkoxy,
 ethylaminoC₁₋₆alkoxy, diethylaminoC₁₋₆alkoxy, phenyl, phenoxy, phenylcarbonyl,
 benzyl, phenylethoxy, phenylmethoxy, phenylpropoxy, pyrrolidinylmethoxy,
 pyrrolidinylethoxy, pyrrolidinylpropoxy, pyridinylmethoxy, pyridinylethoxy,
 pyridinylpropoxy and acetyl.

The compounds of the invention may be in the form of pharmaceutically acceptable
 salts. It will be appreciated however that non-pharmaceutically acceptable salts also
 fall within the scope of the invention since these may be useful as intermediates in the
 preparation of pharmaceutically acceptable salts or may be useful during storage or
 transport. Suitable pharmaceutically acceptable salts include, but are not limited to,
 salts of pharmaceutically acceptable inorganic acids such as hydrochloric, sulphuric,
 phosphoric, nitric, carbonic, boric, sulfamic, and hydrobromic acids, or salts of
 pharmaceutically acceptable organic acids such as formic, acetic, propionic, butyric,
 tartaric, maleic, hydroxymaleic, fumaric, citric, lactic, mucic, malonic, malic (L), lactic
 (DL), mandelic (DL), gluconic, carbonic, benzoic, succinic, oxalic, phenylacetic,
 methanesulphonic, ethanesulphonic, toluenesulphonic, camphorsulphonic,
 benzenesulphonic, salicylic, cinnamic, cyclamic, sulphanilic, aspartic, glutamic,
 glutaric, galactaric, gentisic, hippuric, edetic, stearic, palmitic, oleic, lauric, pantothenic,
 tannic, ascorbic and valeric acids.

Base salts include, but are not limited to, those formed with pharmaceutically acceptable cations, such as sodium, potassium, lithium, calcium, magnesium, aluminium, zinc, lysine, histidine, meglumine, ammonium and alkylammonium.

Basic nitrogen-containing groups may be quaternized with such agents as lower alkyl halide, such as methyl, ethyl, propyl, and butyl chlorides, bromides and iodides; dialkyl sulfates like dimethyl and diethyl sulfate; and others.

The compounds of the invention may also be in the form of solvates, including hydrates. The term “solvate” is used herein to refer to a complex of variable stoichiometry formed by a solute (a compound of formula (I)) and a solvent. Such solvents should not interfere with the biological activity of the solute. Solvents that may be included in a solvate include, but are not limited to, water, ethanol, propanol, and acetic acid. Methods of solvation are generally known within the art.

The term “pro-drug” is used in its broadest sense and encompasses those derivatives that are converted *in vivo* to the compounds of formula (I). Such derivatives would readily occur to those skilled in the art and include, for example, compounds where a free hydroxy group is converted into an ester derivative or a ring nitrogen is converted to an N-oxide. Examples of ester derivatives include alkyl esters, phosphate esters and those formed from amino acids. Conventional procedures for the preparation of suitable prodrugs are described in text books such as “Design of Prodrugs” Ed. H. Bundgaard, Elsevier, 1985.

It will also be recognised that compounds of the invention may possess asymmetric centres and are therefore capable of existing in more than one stereoisomeric form. The invention thus also relates to compounds in substantially pure isomeric form at one or more asymmetric centres eg., greater than about 90% ee, such as about 95% or 97% ee or greater than 99% ee, as well as mixtures, including racemic mixtures, thereof. Such isomers may be prepared by asymmetric synthesis, for example using chiral intermediates, or by chiral resolution. The compounds of the invention may exist as geometric isomers. The invention also relates to compounds in substantially pure *cis* (Z) or *trans* (E) or mixtures thereof.

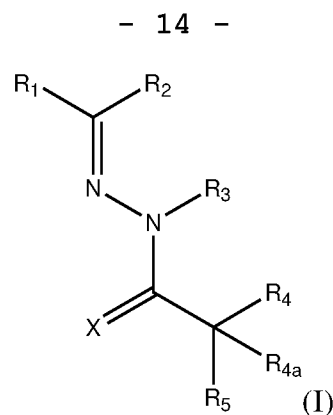
The compounds of the invention may also exist in the form of rotational isomers or conformers where there is restricted or hindered rotation about a single bond.

Any formula or structure given herein, including Formula (I) compounds are also intended to represent unlabelled forms as well as isotopically labelled forms of the compounds for use as medicaments or as a study tool. This may include metabolic studies, reaction kinetic studies, detection or imaging techniques, such as positron emission tomography (PET) or single-photon emission computed tomography (SPECT) including drug or substrate tissue distribution assays or in radioactive treatment of patients. Isotopically labelled compounds have structures depicted by the formulas given herein except that one or more atoms are replaced by an atom having a selected atomic mass or mass number. Examples of isotopes that can be incorporated into compounds of the disclosure include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorous, fluorine and chlorine, such as, but not limited to ^2H (deuterium, D), ^3H (tritium), ^{10}B , ^{11}C , ^{13}C , ^{14}C , ^{15}N , ^{18}F , ^{31}P , ^{32}P , ^{35}S , ^{36}Cl and ^{125}I . Various isotopically labelled compounds of the present disclosure, for example those into which radioactive isotopes such as ^3H , ^{13}C and ^{14}C are incorporated. In addition to use as pharmaceutical treatments, such isotopically labelled compounds may be useful.

Compounds of the Invention

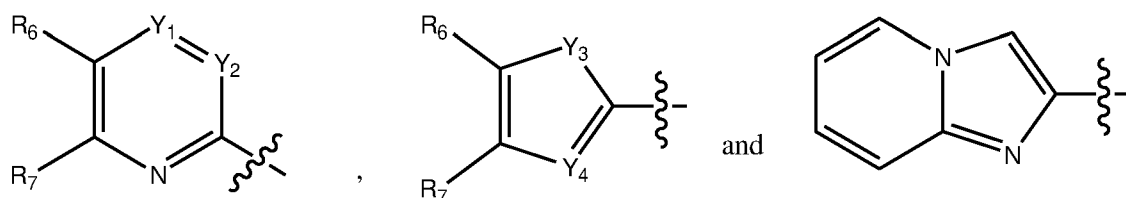
The present invention provides metal ion modulating compounds, particularly zinc and iron selective ionophores. Such ionophores may have one or more of the desirable properties of: orally deliverable; low liver extraction, non-toxicity and the ability to modulate metals, particularly zinc and iron in biological systems. Advantageous metal selectivity, affinity and kinetic stability of the complexes formed may also be provided by particular compounds.

Described herein are compounds of formula (I):



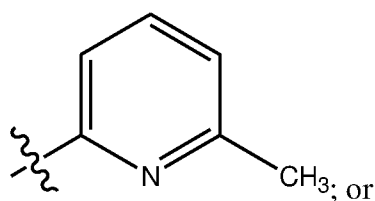
wherein X is O or S;

R_1 is selected from:



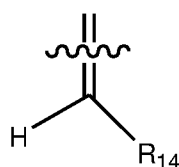
- 5 Y_1 is CR_8 or N;
 Y_2 is CR_8 or N;
 provided that both Y_1 and Y_2 are not N;
 Y_3 is $C(R_8)_2$, NR_9 or S;
 Y_4 is CR_8 or N;
 10 provided that Y_3 is not $C(R_8)_2$ when Y_4 is CR_8 ;
 R_6 and R_7 are independently selected from hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, hydroxy, C_{1-6} alkoxy, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, halo, CN, CO_2R_9 and $N(R_9)_2$; or
 R_6 and R_7 taken together with the atoms to which they are attached form an optionally
 15 substituted 6-membered aryl or heteroaryl ring;
 each R_8 is independently selected from hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, hydroxy, C_{1-6} alkoxy, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, halo, $(C(R_{10})_2)_mCO_2R_9$ and $(C(R_{10})_2)_mN(R_9)_2$;
 each R_9 is independently selected from hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl
 20 and C_{1-6} haloalkyl;
 R_2 is selected from hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{3-8} cycloalkyl and

- 15 -



R₁ and R₂ taken together for a 5, 6 or 7 membered cycloalkyl or heterocycloalkyl ring fused with a six membered nitrogen-containing heteroaryl ring, wherein the cycloalkyl, heterocycloalkyl or heteroaryl ring may be optionally substituted,

- 5 R₃ is selected from hydrogen, C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl and (C(R₁₀)₂)_mCO₂R₉;
 R₄ and R_{4a} are each independently selected from hydrogen, C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl and C₁₋₆haloalkyl; and R₅ is hydrogen, (C(R₁₀)₂)_maryl or (C(R₁₀)₂)_mheteroaryl where aryl and heteroaryl are optionally substituted; or
 R_{4a} is CN and R₄ and R₅ taken together form:



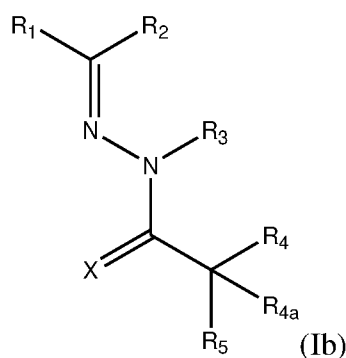
10

where R₁₄ is hydrogen, (C(R₁₀)₂)_maryl or (C(R₁₀)₂)_mheteroaryl where aryl and heteroaryl are optionally substituted; or

R_{4a} is absent and R₄ and R₅ taken together form an optionally substituted aryl or optionally substituted heteroaryl group;

- 15 each R₁₀ is independently selected from hydrogen, C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, hydroxy, C₁₋₆alkoxy, C₁₋₆haloalkyl, C₁₋₆haloalkoxy, CN, halo and N(R₉)₂;
 m is 0 or an integer of 1 to 6;
 or a pharmaceutically acceptable salt thereof.

In a particular embodiment, there is provided a compound of formula (Ib):

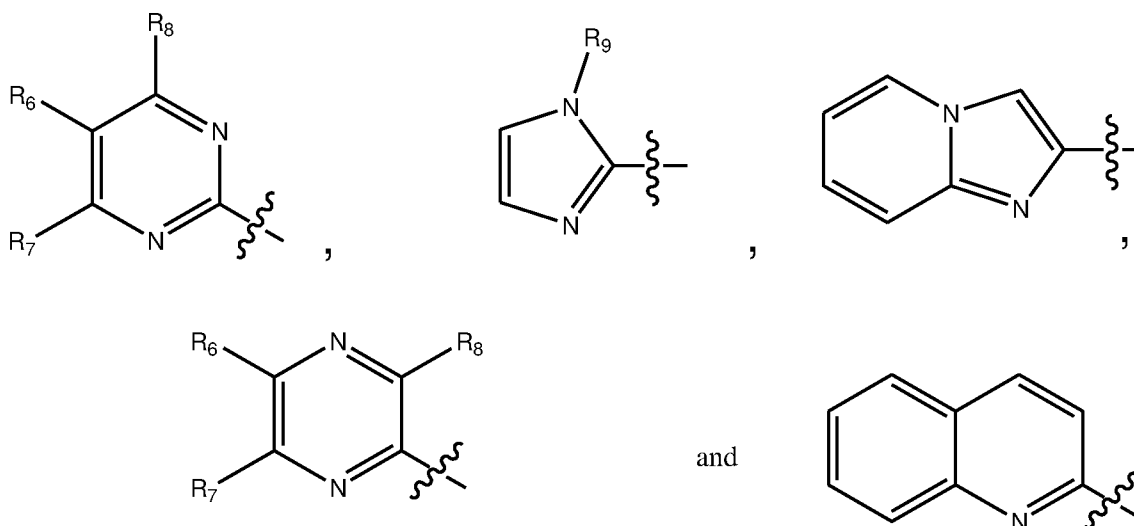


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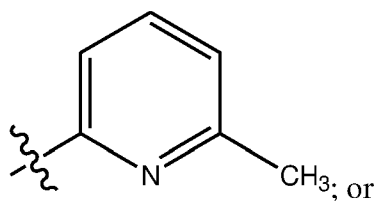
- 16 -

wherein X is O;

R₁ is selected from:

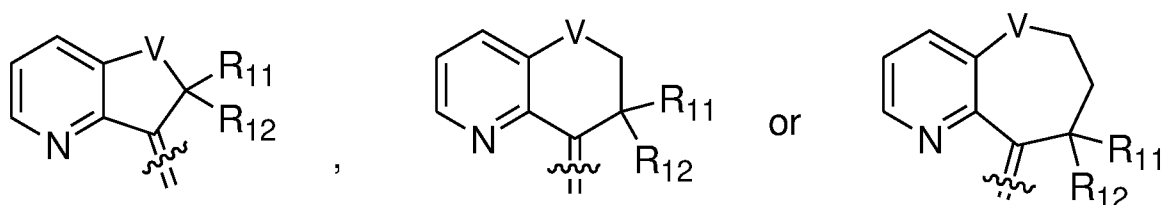


- 5 R₆ and R₇ are independently selected from hydrogen, C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, hydroxy, C₁₋₆alkoxy, C₁₋₆haloalkyl, C₁₋₆haloalkoxy, halo, CN, CO₂R₉ and N(R₉)₂; or
R₆ and R₇ taken together with the atoms to which they are attached form an optionally substituted 6-membered aryl or heteroaryl ring;
- 10 each R₈ is independently selected from hydrogen, C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, hydroxy, C₁₋₆alkoxy, C₁₋₆haloalkyl, C₁₋₆haloalkoxy, halo, (C(R₁₀)₂)_mCO₂R₉ and (C(R₁₀)₂)_mN(R₉)₂;
each R₉ is independently selected from hydrogen, C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl and C₁₋₆haloalkyl;
- 15 R₂ is selected from hydrogen, C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₁₋₆haloalkyl, C₃₋₈cycloalkyl and



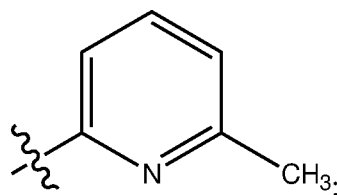
R₁ and R₂ taken together form

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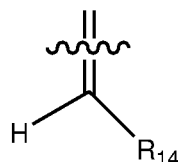
wherein V is CH, O or S and R₁₁ and R₁₂ are each independently selected from hydrogen, C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, halo, C₁₋₆haloalkyl, (CH₂)_mC₃₋₈cycloalkyl, (CH₂)_maryl, (CH₂)_mheterocyclyl, (CH₂)_mheteroaryl and COR₁₃ where R₁₃ is selected from OH, OC₁₋₆alkyl, OC₂₋₆alkenyl, OC₂₋₆alkynyl and N(R₉)₂, wherein the cycloalkyl, heterocycloalkyl or heteroaryl ring of the bicyclic structure formed from R₁ and R₂ may be optionally substituted, or

R₁ and R₂ are both:



R₃ is selected from hydrogen, C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl and (C(R₁₀)₂)_mCO₂R₉; R₄ and R_{4a} are each independently selected from hydrogen, C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl and C₁₋₆haloalkyl; and R₅ is hydrogen, (C(R₁₀)₂)_maryl, (C(R₁₀)₂)_mheteroaryl, O(C(R₁₀)₂)_maryl or O(C(R₁₀)₂)_mheteroaryl wherein the aryl and heteroaryl are optionally substituted; or

R_{4a} is CN and R₄ and R₅ are both hydrogen or taken together form:



where R₁₄ is hydrogen, (C(R₁₀)₂)_maryl or (C(R₁₀)₂)_mheteroaryl where in the aryl and heteroaryl are optionally substituted; or

R_{4a} is absent and R₄ and R₅ taken together form an optionally substituted aryl or optionally substituted heteroaryl group;

each R₁₀ is independently selected from hydrogen, C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, hydroxy, C₁₋₆alkoxy, C₁₋₆haloalkyl, C₁₋₆haloalkoxy, CN, halo and N(R₉)₂;

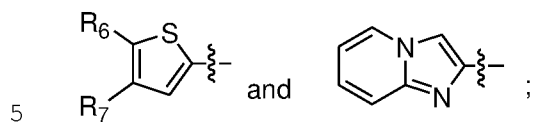
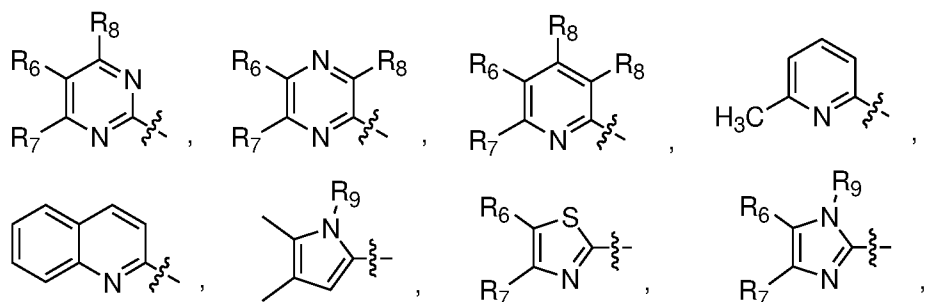
m is 0 or an integer of 1 to 6;

or a pharmaceutically acceptable salt thereof.

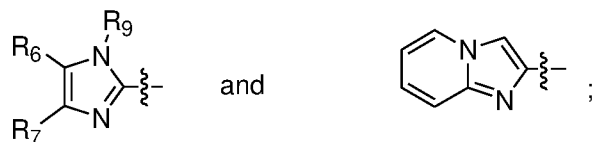
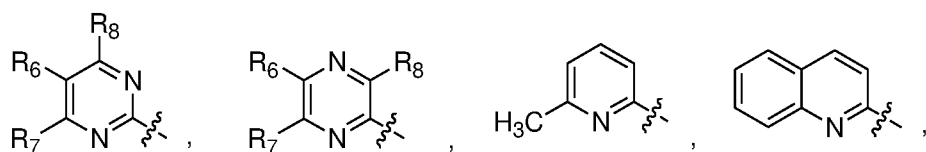
In particular embodiments of the compounds of formula (I), one or more of the following applies:

X is O;

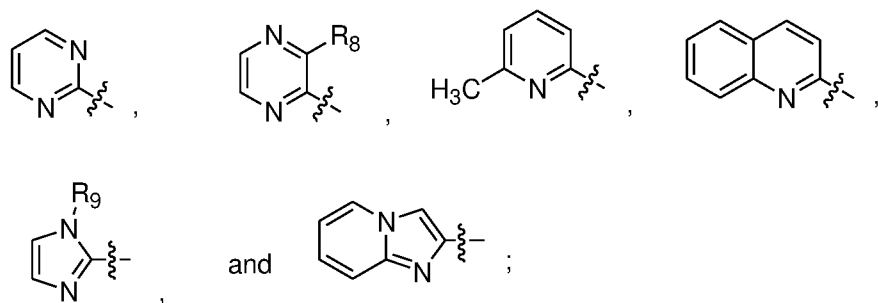
R₁ is selected from:



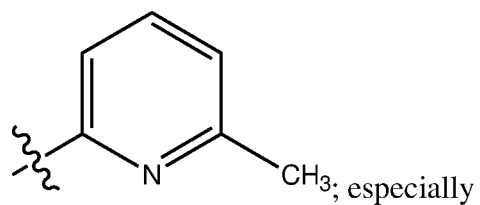
especially



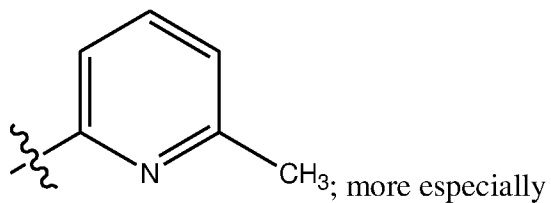
and more especially



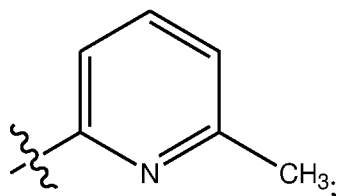
10 R₂ is selected from hydrogen, C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₈ cycloalkyl and



C₁₋₄alkyl, C₂₋₄alkenyl, C₂₋₄alkynyl, C₃₋₆ cycloalkyl and



C₁₋₄alkyl, C₃₋₆ cycloalkyl and

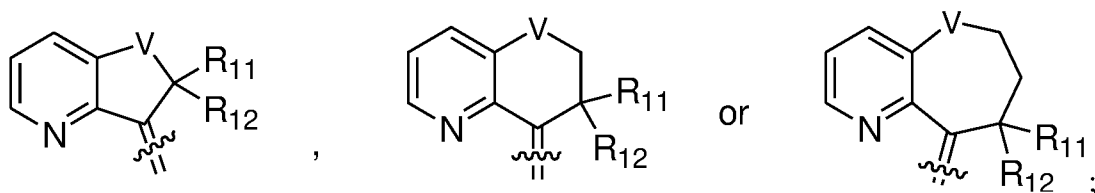


- 5 wherein when R₁ is then R₂ is ; especially where both R₁

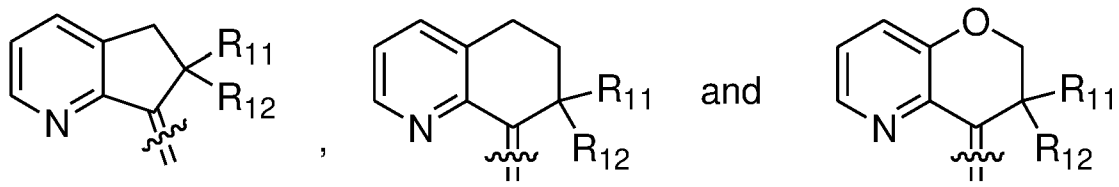
and R₂ are ;

R₂ may be hydrogen when R₁ is , and ; or

- R₁ and R₂ together form a 5 or 6 membered cycloalkyl or heterocycloalkyl ring fused with a six-membered nitrogen-containing heteroaryl ring, wherein the cycloalkyl and
 10 heteroaryl ring may be optionally substituted; especially where R₁ and R₂ together are selected from:



wherein V is CH, O or S, especially CH or O; especially



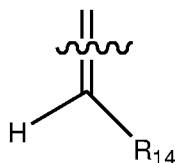
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wherein R₁₁ and R₁₂ are each independently selected from hydrogen, C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, halo, C₁₋₆haloalkyl, (CH₂)_mC₃₋₈cycloalkyl, (CH₂)_maryl,

$(\text{CH}_2)_m$ heterocyclyl, $(\text{CH}_2)_m$ heteroaryl and COR_{13} where R_{13} is selected from OH, OC_{1-6} alkyl, OC_{2-6} alkenyl, OC_{2-6} alkynyl and $\text{N}(\text{R}_9)_2$, especially hydrogen, C_{1-6} alkyl and COR_{13} where R_{13} is selected from OC_{1-6} alkyl and $\text{N}(\text{R}_9)_2$, more especially hydrogen, C_{1-3} alkyl and COOC_{1-3} alkyl;

- 5 R_3 is selected from hydrogen, C_{1-6} alkyl, $(\text{CH}_2)_m\text{CO}_2\text{H}$ and $(\text{CH}_2)_m\text{CO}_2\text{C}_{1-3}$ alkyl, especially hydrogen, C_{1-3} alkyl, $\text{CH}_2\text{CO}_2\text{H}$ and $\text{CH}_2\text{CO}_2\text{CH}_3$, more especially hydrogen; R_4 and R_{4a} are each independently selected from hydrogen, C_{1-3} alkyl, C_{2-3} alkenyl, C_{2-3} alkynyl and C_{1-3} haloalkyl; and R_5 is hydrogen, $(\text{CH}_2)_m$ aryl or $(\text{CH}_2)_m$ heteroaryl where aryl and heteroaryl are optionally substituted; especially where R_4 and R_{4a} are each
- 10 independently hydrogen and R_5 is $(\text{CH}_2)_m$ aryl, $(\text{CH}_2)_m$ heteroaryl or Oaryl; where each aryl or heteroaryl ring are selected from phenyl, pyridinyl, indolyl, thiazolyl, oxazolyl, thiadiazolyl, benzothiophenyl and pyridizynyl, especially phenyl, indolyl and pyridinyl; and especially where each aryl or heteroaryl ring may be unsubstituted or substituted by one or more substituents selected from C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, halo,
- 15 hydroxy, $-\text{OC}_{1-6}$ alkyl, $-\text{OC}_{2-6}$ alkenyl, $-\text{OC}_{2-6}$ alkynyl, $-\text{OC}_{1-6}$ haloalkyl, $\text{N}(\text{R}_9)_2$, $(\text{CH}_2)_q\text{N}(\text{R}_{15})_2$ and $\text{O}(\text{CH}_2)_q\text{N}(\text{R}_{15})_2$, wherein q is an integer of 1 to 6 and each R_{15} is independently selected from hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl and C_{1-6} haloalkyl or two R_{15} taken together with the nitrogen atom to which they are attached form a 5 or 6 membered heterocyclic ring, especially C_{1-3} alkyl, C_{2-3} alkenyl, C_{2-3} alkynyl,
- 20 C_{1-3} haloalkyl, halo, hydroxy, $-\text{OC}_{1-3}$ alkyl, $-\text{OC}_{2-3}$ alkenyl, $-\text{OC}_{2-3}$ alkynyl, $-\text{OC}_{1-3}$ haloalkyl, $\text{N}(\text{C}_{1-3}\text{alkyl})_2$ and $\text{O}(\text{CH}_2)_q\text{N}(\text{R}_{15})_2$, wherein q is an integer from 1 to 3 and each R_{15} is independently selected from hydrogen, C_{1-3} alkyl, C_{2-3} alkenyl, C_{2-3} alkynyl and C_{1-3} haloalkyl or two R_{15} taken together with the nitrogen atom to which they are attached form a 5 or 6 membered heterocyclic ring, more especially methyl, ethyl,
- 25 propyl, isopropyl, chloro, fluoro, trifluoromethyl, methoxy, ethoxy, dimethyl amino, diethyl amino, $-\text{OCH}_2\text{CH}_2\text{N}(\text{CH}_3)_2$, $-\text{OCH}_2\text{CH}_2$ piperidinyl, OCH_2CH_2 pyrrolyl and $-\text{OCH}_2\text{CH}_2\text{CH}_2$ piperidinyl; or

R_{4a} is CN and R_4 and R_5 are each hydrogen or taken together form:

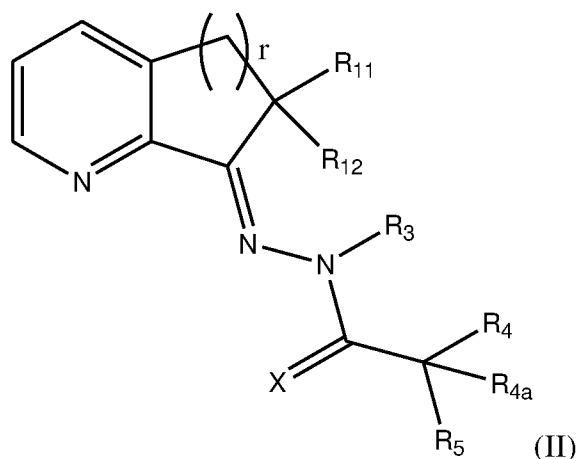


where R_{14} is hydrogen, $(CH_2)_m$ aryl or $(CH_2)_m$ heteroaryl wherein the aryl and heteroaryl are optionally substituted; especially $(CH_2)_m$ aryl or $(CH_2)_m$ heteroaryl; wherein each aryl or heteroaryl ring may be unsubstituted or substituted by one or more substituents selected from C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, halo, hydroxy, $-OC_{1-6}$ alkyl, $-OC_{2-6}$ alkenyl, $-OC_{2-6}$ alkynyl, $-OC_{1-6}$ haloalkyl, $N(R_9)_2$ and $O(CH_2)_qN(R_{15})_2$,
 5 wherein q is an integer of 1 to 6 and each R_{15} is independently selected from hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl and C_{1-6} haloalkyl or two R_{15} taken together with the nitrogen atom to which they are attached form a 5 or 6 membered heterocyclic ring, especially C_{1-3} alkyl, C_{2-3} alkenyl, C_{2-3} alkynyl, C_{1-3} haloalkyl, halo, hydroxy, $-OC_{1-3}$ alkyl,
 10 $-OC_{2-3}$ alkenyl, $-OC_{2-3}$ alkynyl, $-OC_{1-3}$ haloalkyl, $N(C_{1-3}alkyl)_2$, $(CH_2)_qN(R_{15})_2$ and $O(CH_2)_qN(R_{15})_2$, wherein q is an integer from 1 to 3 and each R_{15} is independently selected from hydrogen, C_{1-3} alkyl, C_{2-3} alkenyl, C_{2-3} alkynyl and C_{1-3} haloalkyl or two R_{15} taken together with the nitrogen atom to which they are attached form a 5 or 6 membered heterocyclic ring, more especially methyl, ethyl, propyl, isopropyl, chloro,
 15 fluoro, trifluoromethyl, methoxy, ethoxy, dimethyl amino, diethyl amino, - $OCH_2CH_2N(CH_3)_2$, $-OCH_2CH_2$ piperidinyl, OCH_2CH_2 pyrrolyl and - $OCH_2CH_2CH_2$ piperidinyl; or
 R_{4a} is absent and R_4 and R_5 taken together form an optionally substituted aryl or optionally substituted heteroaryl group; especially where R_4 and R_5 taken together form a phenyl ring, a 2-
 20 pyridinyl ring, 3-pyridinyl ring, 4-pyridinyl ring, 3-pyridazinyl ring, 4-pyridazinyl ring, 2-furanyl, 3-furanyl, 2-thiophenyl ring, 3-thiophenyl ring, 2-thiazolyl ring, 3-thiazolyl ring, 4-thiazolyl ring, 3-isoxazolyl ring, 4-isoxazolyl ring, 5-isoxazolyl ring, 4-(1,2,3-thiadiazolyl) ring, 5-(1,2,3-thiadiazolyl) ring, 4-thiadiazolyl ring, 5-thiadiazolyl ring, 2-benzo[b]thiophenyl, 3-benzothiophenyl ring, 3-(1H)-indolyl ring or a or a 4H-thieno[3,2-c]chromene ring, especially
 25 a phenyl ring, a 2-pyridinyl ring, 3-pyridinyl ring, 4-pyridinyl ring, 3-pyridazinyl ring, 2-furanyl, 2-thiophenyl ring, 3-thiazolyl ring, 3-isoxazolyl ring, 5-(1,2,3-thiadiazolyl) ring, 5-thiadiazolyl ring, 2-benzo[b]thiophenyl ring, 3-(1H)-indolyl ring or a 4H-thieno[3,2-c]chromene ring, where each aryl or heteroaryl ring may be unsubstituted or substituted by one or more substituents selected from C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, halo,
 30 hydroxy, $-OC_{1-6}$ alkyl, $-OC_{2-6}$ alkenyl, $-OC_{2-6}$ alkynyl, $-OC_{1-6}$ haloalkyl, $N(R_9)_2$, $(CH_2)_qN(R_{15})_2$ and $O(CH_2)_qN(R_{15})_2$, wherein q is an integer of 1 to 6 and each R_{15} is independently selected from hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl and C_{1-6} haloalkyl or two R_{15} taken together with the nitrogen atom to which they are attached

- form a 5 or 6 membered heterocyclic ring, especially C₁₋₃alkyl, C₂₋₃alkenyl, C₂₋₃alkynyl, C₁₋₃haloalkyl, halo, hydroxy, -OC₁₋₃alkyl, -OC₂₋₃alkenyl, -OC₂₋₃alkynyl, -OC₁₋₃haloalkyl, N(C₁₋₃alkyl)₂ and O(CH₂)_qN(R₁₅)₂, wherein q is an integer from 1 to 3 and each R₁₅ is independently selected from hydrogen, C₁₋₃alkyl, C₂₋₃alkenyl, C₂₋₃alkynyl and C₁₋₃haloalkyl or two R₁₅ taken together with the nitrogen atom to which they are attached form a 5 or 6 membered heterocyclic ring, more especially methyl, ethyl, propyl, isopropyl, chloro, fluoro, trifluoromethyl, methoxy, ethoxy, dimethyl amino, diethyl amino, -OCH₂CH₂N(CH₃)₂, -OCH₂CH₂piperidinyl, OCH₂CH₂pyrrolyl and -OCH₂CH₂CH₂piperidinyl;
- 10 R₆ and R₇ are independently selected from hydrogen, C₁₋₆alkyl, hydroxy, C₁₋₆alkoxy, C₁₋₆haloalkyl, C₁₋₆haloalkoxy, halo, CN, CO₂H, CO₂C₁₋₃alkyl and N(R₉)₂, especially hydrogen, C₁₋₃alkyl, hydroxy, C₁₋₃alkoxy, C₁₋₃haloalkyl, C₁₋₃haloalkoxy, halo, CN, CO₂H, CO₂CH₃ and N(C₁₋₃alkyl)₂, more especially hydrogen, methyl, ethyl, or CF₃, most especially hydrogen or methyl; or
- 15 R₆ and R₇ taken together with the atoms to which they are attached form an optionally substituted phenyl, more especially an unsubstituted phenyl ring;
- each R₈ is independently selected from hydrogen, C₁₋₆alkyl, hydroxy, C₁₋₆alkoxy, C₁₋₆haloalkyl, C₁₋₆haloalkoxy, halo, (CH₂)₁₋₃CO₂H and (CH₂)₁₋₃N(R₉)₂, especially hydrogen, C₁₋₃alkyl, hydroxy, C₁₋₃alkoxy, C₁₋₃haloalkyl, C₁₋₃haloalkoxy, halo, CH₂CO₂H, CH₂CH₂CO₂H and N(C₁₋₃alkyl)₂, more especially hydrogen, methyl, ethyl, or CF₃, most especially hydrogen or methyl;
- 20 each R₉ is independently selected from hydrogen, C₁₋₆alkyl and C₁₋₆haloalkyl, especially hydrogen, C₁₋₆alkyl, more especially hydrogen, C₁₋₃alkyl, most especially hydrogen and methyl;
- 25 each R₁₀ is independently selected from hydrogen, C₁₋₆alkyl, hydroxy, C₁₋₆alkoxy, C₁₋₆haloalkyl, C₁₋₆haloalkoxy, CN, halo and N(R₉)₂, especially, hydrogen, C₁₋₃alkyl, hydroxy, C₁₋₃alkoxy, C₁₋₃haloalkyl, C₁₋₃haloalkoxy, CN, halo and N(C₁₋₃alkyl)₂, more especially hydrogen, methyl, ethyl, hydroxy, methoxy, ethoxy, trifluoromethyl, trifluoromethoxy, fluoro and chloro;
- 30 m is 0 or an integer 1 to 3, especially where m is 0 or an integer 1 or 2.

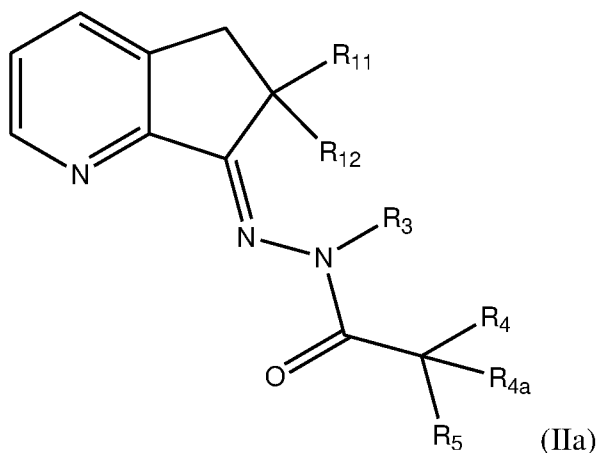
In some embodiments, the compound of formula (I) is a compound of formula (II):

- 23 -



wherein X, R₃, R₄, R_{4a} and R₅ are as defined for formula (I), R₁₁ and R₁₂ are each independently selected from hydrogen, C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, halo, C₁₋₆haloalkyl, (CH₂)_mC₃₋₆ cycloalkyl, (CH₂)_maryl, (CH₂)_mheterocyclyl, (CH₂)_mheteroaryl and COR₁₃ where R₁₃ is selected from OH, OC₁₋₆alkyl, OC₂₋₆alkenyl, OC₂₋₆alkynyl and N(R₉)₂ and r is 1, 2 or 3, or a pharmaceutically acceptable salt thereof.

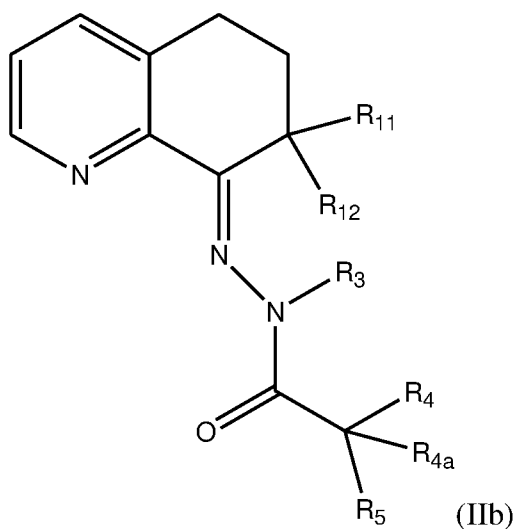
In some embodiments, the compound of formula (II) is a compound of formula (IIa):



wherein R₃, R₄, R_{4a}, R₅, R₁₁ and R₁₂ are as defined for formula (II), or a pharmaceutically acceptable salt thereof.

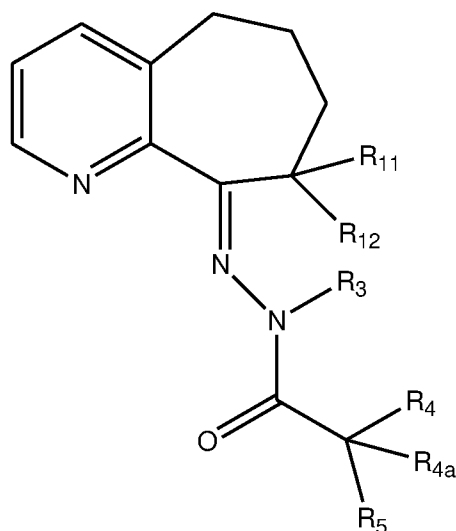
In some embodiments, the compound of formula (II) is a compound of formula (IIb):

- 24 -



wherein R_3 , R_4 , R_{4a} , R_5 , R_{11} and R_{12} are as defined for formula (II), or a pharmaceutically acceptable salt thereof.

In some embodiments, the compound of formula (II) is a compound of formula (IIc):



5

wherein R_3 , R_4 , R_{4a} , R_5 , R_{11} and R_{12} are as defined for formula (II), or a pharmaceutically acceptable salt thereof.

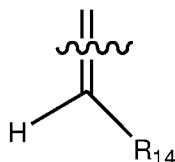
In particular embodiments of the compounds of formula (II), one or more of the following applies:

10 X is O;

R_3 is selected from hydrogen, C_{1-6} alkyl, $(CH_2)_mCO_2H$ and $(CH_2)_mCO_2C_{1-3}$ alkyl, especially hydrogen, C_{1-3} alkyl, CH_2CO_2H and $CH_2CO_2CH_3$, more especially hydrogen;

- 25 -

R_4 and R_{4a} are each independently selected from hydrogen, C_{1-3} alkyl, C_{2-3} alkenyl, C_{2-3} alkynyl and C_{1-3} haloalkyl; and R_5 is hydrogen, $(CH_2)_m$ aryl or $(CH_2)_m$ heteroaryl where aryl and heteroaryl are optionally substituted; especially where R_4 and R_{4a} are each independently hydrogen and R_5 is $(CH_2)_m$ aryl, $O(CH_2)_m$ aryl or $(CH_2)_m$ heteroaryl; where
 5 each aryl or heteroaryl ring are selected from phenyl, pyridinyl, indolyl, thiazolyl, oxazolyl, thiadiazolyl, benzothiophenyl and pyridizynyl, especially phenyl, indolyl and pyridinyl; and especially where each aryl or heteroaryl ring may be unsubstituted or substituted by one or more substituents selected from C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, halo, hydroxy, $-OC_{1-6}$ alkyl, $-OC_{2-6}$ alkenyl, $-OC_{2-6}$ alkynyl, $-OC_{1-6}$ haloalkyl, $N(R_9)_2$,
 10 $(CH_2)_qN(R_{15})_2$ and $O(CH_2)_qN(R_{15})_2$, wherein q is an integer of 1 to 6 and each R_{15} is independently selected from hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl and C_{1-6} haloalkyl or two R_{15} taken together with the nitrogen atom to which they are attached form a 5 or 6 membered heterocyclic ring, especially C_{1-3} alkyl, C_{2-3} alkenyl, C_{2-3} alkynyl, C_{1-3} haloalkyl, halo, hydroxy, $-OC_{1-3}$ alkyl, $-OC_{2-3}$ alkenyl, $-OC_{2-3}$ alkynyl, $-OC_{1-3}$ haloalkyl, $N(C_{1-3}alkyl)_2$ and $O(CH_2)_qN(R_{15})_2$, wherein q is an integer from 1 to 3 and each R_{15} is independently selected from hydrogen, C_{1-3} alkyl, C_{2-3} alkenyl, C_{2-3} alkynyl and C_{1-3} haloalkyl or two R_{15} taken together with the nitrogen atom to which they are attached form a 5 or 6 membered heterocyclic ring, more especially methyl, ethyl, propyl, isopropyl, chloro, fluoro, trifluoromethyl, methoxy, ethoxy, dimethyl amino, diethyl amino, $-OCH_2CH_2N(CH_3)_2$, $-OCH_2CH_2$ piperidinyl, OCH_2CH_2 pyrrolyl and $-OCH_2CH_2CH_2$ piperidinyl; or
 15 R_{4a} is CN and R_4 and R_5 are each hydrogen or taken together form:



where R_{14} is hydrogen, $(CH_2)_m$ aryl or $(CH_2)_m$ heteroaryl where aryl and heteroaryl are
 25 optionally substituted; especially $(CH_2)_m$ aryl or $(CH_2)_m$ heteroaryl; wherein each aryl or heteroaryl ring may be unsubstituted or substituted by one or more substituents selected from C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, halo, hydroxy, $-OC_{1-6}$ alkyl, $-OC_{2-6}$ alkenyl, $-OC_{2-6}$ alkynyl, $-OC_{1-6}$ haloalkyl, $N(R_9)_2$, $(CH_2)_qN(R_{15})_2$ and $O(CH_2)_qN(R_{15})_2$, wherein q is an integer of 1 to 6 and each R_{15} is independently selected from hydrogen,
 30 C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl and C_{1-6} haloalkyl or two R_{15} taken together with the

- nitrogen atom to which they are attached form a 5 or 6 membered heterocyclic ring, especially C₁₋₃alkyl, C₂₋₃alkenyl, C₂₋₃alkynyl, C₁₋₃haloalkyl, halo, hydroxy, -OC₁₋₃alkyl, -OC₂₋₃alkenyl, -OC₂₋₃alkynyl, -OC₁₋₃haloalkyl, N(C₁₋₃alkyl)₂, (CH₂)_qN(R₁₅)₂ and O(CH₂)_qN(R₁₅)₂, wherein q is an integer from 1 to 3 and each R₁₅ is independently
- 5 selected from hydrogen, C₁₋₃alkyl, C₂₋₃alkenyl, C₂₋₃alkynyl and C₁₋₃haloalkyl or two R₁₅ taken together with the nitrogen atom to which they are attached form a 5 or 6 membered heterocyclic ring, more especially methyl, ethyl, propyl, isopropyl, chloro, fluoro, trifluoromethyl, methoxy, ethoxy, dimethyl amino, diethyl amino, -OCH₂CH₂N(CH₃)₂, -OCH₂CH₂piperidinyl, OCH₂CH₂pyrrolyl and -
- 10 OCH₂CH₂CH₂piperidinyl; or
- R_{4a} is absent and R₄ and R₅ taken together form an optionally substituted aryl or optionally substituted heteroaryl group; especially where R₄ and R₅ taken together form a phenyl ring, a 2-pyridinyl ring, 3-pyridinyl ring, 4-pyridinyl ring, 3-pyridazinyl ring, 4-pyridazinyl ring, 2-furanyl, 3-furanyl, 2-thiophenyl ring, 3-thiophenyl ring, 2-
- 15 thiazolyl ring, 3-thiazolyl ring, 4-thiazolyl ring, 3-isoxazolyl ring, 4-isoxazolyl ring, 5-isoxazolyl ring, 4-(1,2,3-thiadiazolyl) ring, 5-(1,2,3-thiadiazolyl) ring, 4-thiadiazolyl ring, 5-thiadiazolyl ring, 2-benzo[b]thiophenyl, 3-benzothiophenyl ring, -3-(1H)-indolyl ring or a 4H-thieno[3,2-c]chromene ring, especially a phenyl ring, a 2-pyridinyl ring, 3-pyridinyl ring, 4-pyridinyl ring, 3-pyridazinyl ring, 2-furanyl, 2-thiophenyl ring, 3-
- 20 thiazolyl ring, 3-isoxazolyl ring, 5-(1,2,3-thiadiazolyl) ring, 5-thiadiazolyl ring, 2-benzo[b]thiophenyl ring, 3-(1H)-indolyl ring or a 4H-thieno[3,2-c]chromene ring, where each aryl or heteroaryl ring may be unsubstituted or substituted by one or more substituents selected from C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₁₋₆haloalkyl, halo, hydroxy, -OC₁₋₆alkyl, -OC₂₋₆alkenyl, -OC₂₋₆alkynyl, -OC₁₋₆haloalkyl, N(R₉)₂,
- 25 (CH₂)_qN(R₁₅)₂ and O(CH₂)_qN(R₁₅)₂, wherein q is an integer of 1 to 6 and each R₁₅ is independently selected from hydrogen, C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl and C₁₋₆haloalkyl or two R₁₅ taken together with the nitrogen atom to which they are attached form a 5 or 6 membered heterocyclic ring, especially C₁₋₃alkyl, C₂₋₃alkenyl, C₂₋₃alkynyl, C₁₋₃haloalkyl, halo, hydroxy, -OC₁₋₃alkyl, -OC₂₋₃alkenyl, -OC₂₋₃alkynyl, -OC₁₋₃haloalkyl, N(C₁₋₃alkyl)₂ and O(CH₂)_qN(R₁₅)₂, wherein q is an integer from 1 to 3 and
- 30 each R₁₅ is independently selected from hydrogen, C₁₋₃alkyl, C₂₋₃alkenyl, C₂₋₃alkynyl and C₁₋₃haloalkyl or two R₁₅ taken together with the nitrogen atom to which they are

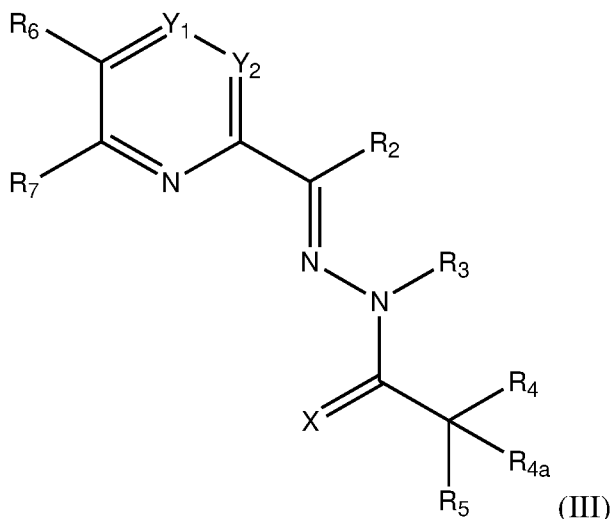
attached form a 5 or 6 membered heterocyclic ring, more especially methyl, ethyl, propyl, isopropyl, chloro, fluoro, trifluoromethyl, methoxy, ethoxy, dimethyl amino, diethyl amino, $-\text{OCH}_2\text{CH}_2\text{N}(\text{CH}_3)_2$, $-\text{OCH}_2\text{CH}_2\text{piperidinyl}$, $\text{OCH}_2\text{CH}_2\text{pyrrolyl}$ and $-\text{OCH}_2\text{CH}_2\text{CH}_2\text{piperidinyl}$;

- 5 R_{11} and R_{12} are each independently selected from hydrogen, C_{1-6} alkyl, halo, C_{1-6} haloalkyl, $(\text{CH}_2)_m\text{C}_{3-8}$ cycloalkyl, $(\text{CH}_2)_m\text{aryl}$, $(\text{CH}_2)_m\text{heterocyclyl}$, $(\text{CH}_2)_m\text{heteroaryl}$ and COR_{13} where R_{13} is selected from OH, OC_{1-6} alkyl, and $\text{N}(\text{R}_9)_2$, especially where R_{11} and R_{12} are independently selected from hydrogen, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{3-8} cycloalkyl, CH_2phenyl , $\text{CH}_2\text{pyridyl}$, and CO C_{1-6} alkyl, more especially where R_{11} and
- 10 R_{12} are independently selected from hydrogen, C_{1-3} alkyl, C_{1-3} haloalkyl, fluoro, C_{3-6} cycloalkyl, CH_2phenyl , $\text{CH}_2\text{pyridyl}$ and COC_{1-3} alkyl, most especially where R_{11} and R_{12} are both hydrogen, both methyl, both ethyl or where one of R_{11} and R_{12} is hydrogen and the other is methyl, ethyl, fluoro, CH_2phenyl , $\text{CH}_2\text{pyridyl}$, CO_2methyl or CO_2ethyl .

Particular compounds of formula II include compounds 1 to 42, 156 to 159 as set out in

15 Tables 1 to 3 and compounds 145, 170, 179 and 180.

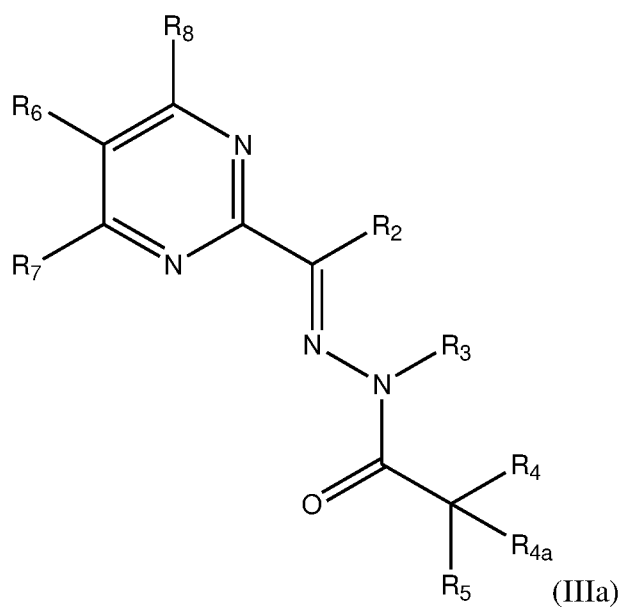
In some embodiments, the compound of formula (I) is a compound of formula (III):



wherein X, Y_1 , Y_2 , R_2 , R_3 , R_4 , R_{4a} , R_5 , R_6 and R_7 are as defined for formula (I), or a pharmaceutically acceptable salt thereof.

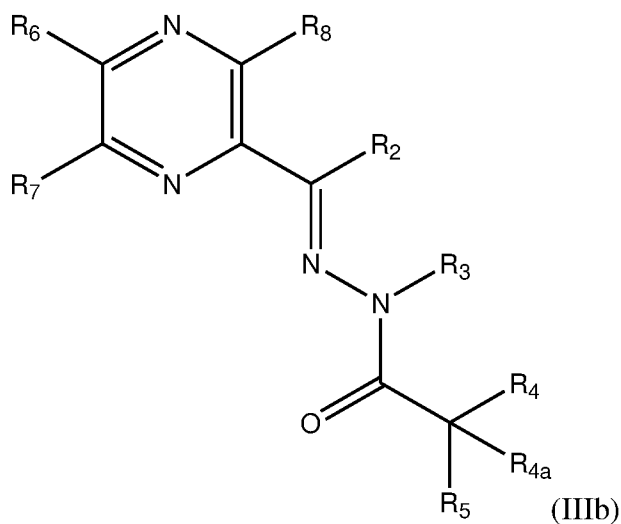
- 20 In some embodiments, the compound of formula (III) is a compound of formula (IIIa):

- 28 -



wherein R₂, R₃, R₄, R_{4a}, R₅, R₆, R₇ and R₈ are as defined for formula (III), or a pharmaceutically acceptable salt thereof.

In some embodiments, the compound of formula (III) is a compound of formula (IIIb):

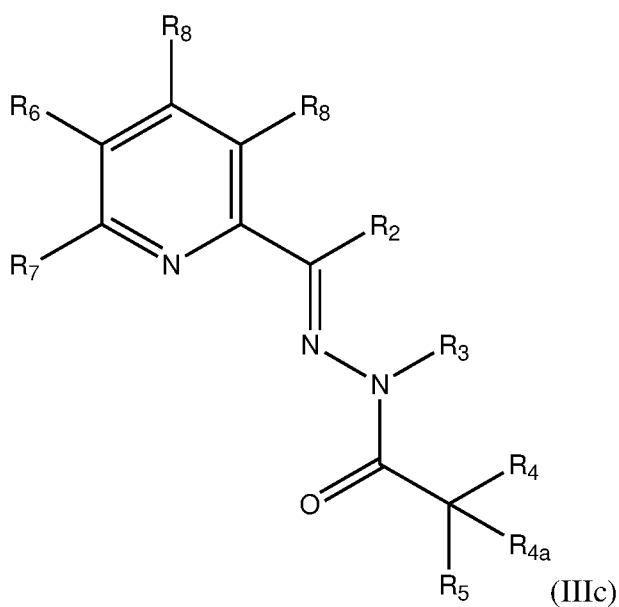


5

wherein R₂, R₃, R₄, R_{4a}, R₅, R₆, R₇ and R₈ are as defined for formula (III), or a pharmaceutically acceptable salt thereof.

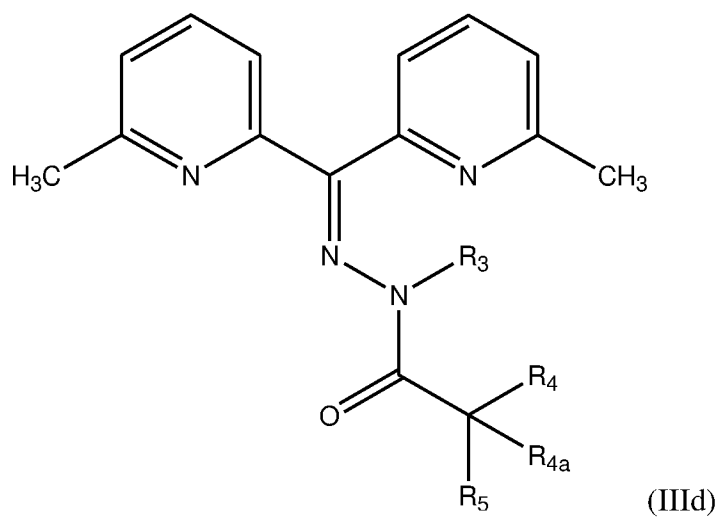
In some embodiments, the compound of formula (III) is a compound of formula (IIIc):

- 29 -



wherein R_2 , R_3 , R_4 , R_{4a} , R_5 , R_6 , R_7 and each R_8 are as defined for formula (III), or a pharmaceutically acceptable salt thereof.

In some embodiments, the compound of formula (III) is a compound of formula (IIIId):



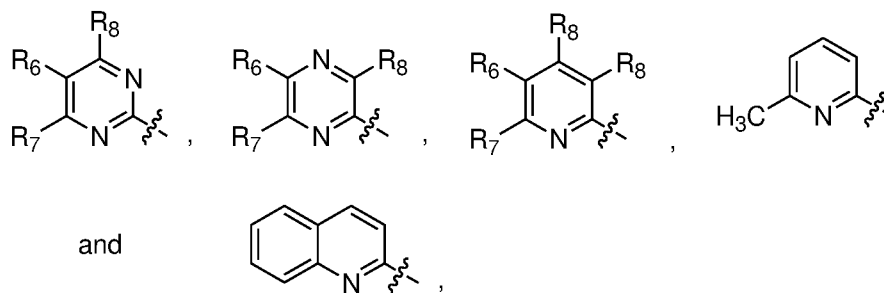
5

wherein R_3 , R_4 , R_{4a} and R_5 are as defined for formula (III), or a pharmaceutically acceptable salt thereof.

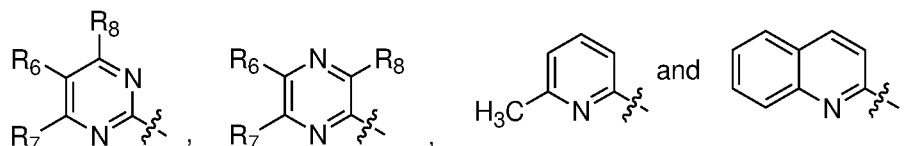
In particular embodiments of the compounds of formula (III), one or more of the following applies:

10 X is O;

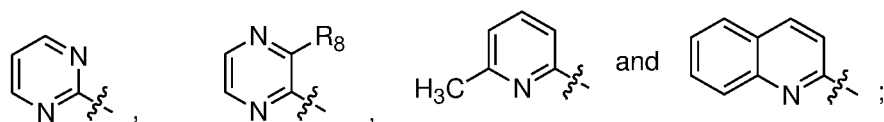
R₁ is selected from:



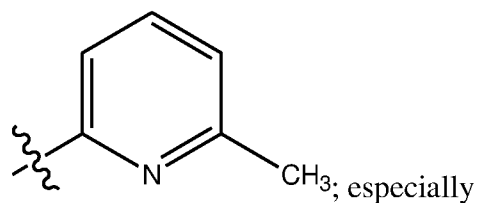
especially



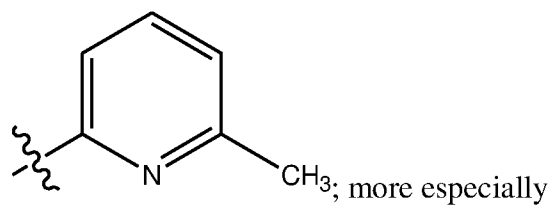
5 More especially



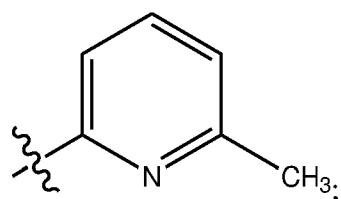
R₂ is selected from hydrogen, C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₈ cycloalkyl and



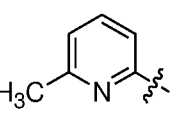
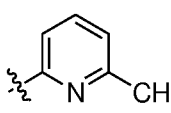
C₁₋₄alkyl, C₂₋₄alkenyl, C₂₋₄alkynyl, C₃₋₆ cycloalkyl and

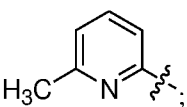


C₁₋₄alkyl, C₃₋₆ cycloalkyl and

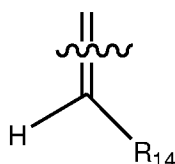


- 31 -

wherein when R_1 is  then R_2 is ; especially where both R_1

and R_2 are ;

- R_3 is selected from hydrogen, C_{1-6} alkyl, $(CH_2)_mCO_2H$ and $(CH_2)_mCO_2C_{1-3}$ alkyl, especially hydrogen, C_{1-3} alkyl, CH_2CO_2H and $CH_2CO_2CH_3$, more especially hydrogen;
- R_4 and R_{4a} are each independently selected from hydrogen, C_{1-3} alkyl, C_{2-3} alkenyl, C_{2-3} alkynyl and C_{1-3} haloalkyl; and R_5 is hydrogen, $(CH_2)_m$ aryl or $(CH_2)_m$ heteroaryl where aryl and heteroaryl are optionally substituted; especially where R_4 and R_{4a} are each independently hydrogen and R_5 is $(CH_2)_m$ aryl, $O(CH_2)_m$ aryl or $(CH_2)_m$ heteroaryl;
- wherein each aryl or heteroaryl ring are selected from phenyl, pyridinyl, indolyl, thiazolyl, oxazolyl, thiadiazolyl, benzothiophenyl and pyridizinyl, especially phenyl, indolyl and pyridinyl; and especially where each aryl or heteroaryl ring may be unsubstituted or substituted by one or more substituents selected from C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, halo, hydroxy, $-OC_{1-6}$ alkyl, $-OC_{2-6}$ alkenyl, $-OC_{2-6}$ alkynyl, $-OC_{1-6}$ haloalkyl, $N(R_9)_2$, $(CH_2)_qN(R_{15})_2$ and $O(CH_2)_qN(R_{15})_2$, wherein q is an integer of 1 to 6 and each R_{15} is independently selected from hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl and C_{1-6} haloalkyl or two R_{15} taken together with the nitrogen atom to which they are attached form a 5 or 6 membered heterocyclic ring, especially C_{1-3} alkyl, C_{2-3} alkenyl, C_{2-3} alkynyl, C_{1-3} haloalkyl, halo, hydroxy, $-OC_{1-3}$ alkyl, $-OC_{2-3}$ alkenyl, $-OC_{2-3}$ alkynyl, $-OC_{1-3}$ haloalkyl, $N(C_{1-3}alkyl)_2$ and $O(CH_2)_qN(R_{15})_2$, wherein q is an integer from 1 to 3 and each R_{15} is independently selected from hydrogen, C_{1-3} alkyl, C_{2-3} alkenyl, C_{2-3} alkynyl and C_{1-3} haloalkyl or two R_{15} taken together with the nitrogen atom to which they are attached form a 5 or 6 membered heterocyclic ring, more especially methyl, ethyl, propyl, isopropyl, chloro, fluoro, trifluoromethyl, methoxy, ethoxy, dimethyl amino, diethyl amino, $-OCH_2CH_2N(CH_3)_2$, $-OCH_2CH_2$ piperidinyl, OCH_2CH_2 pyrrolyl and $-OCH_2CH_2CH_2$ piperidinyl; or R_{4a} is CN and R_4 and R_5 are each hydrogen or taken together form:

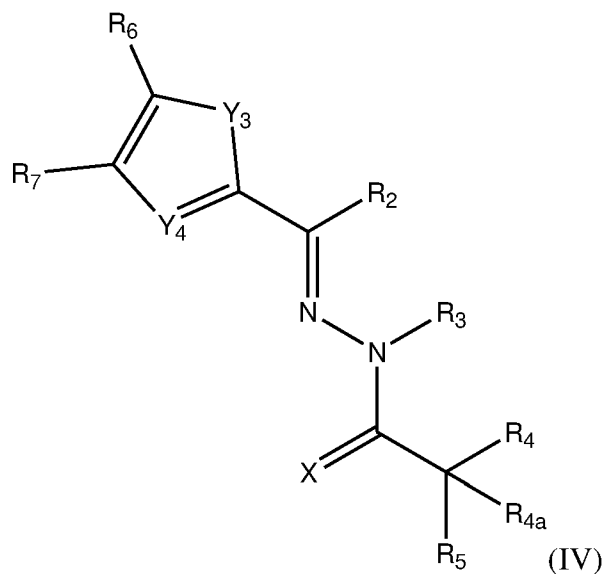


where R_{14} is hydrogen, $(CH_2)_m$ aryl or $(CH_2)_m$ heteroaryl wherein the aryl and heteroaryl are optionally substituted; especially $(CH_2)_m$ aryl or $(CH_2)_m$ heteroaryl; wherein each aryl or heteroaryl ring may be unsubstituted or substituted by one or more substituents selected from C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, halo, hydroxy, $-OC_{1-6}$ alkyl, $-OC_{2-6}$ alkenyl, $-OC_{2-6}$ alkynyl, $-OC_{1-6}$ haloalkyl, $N(R_9)_2$ and $O(CH_2)_qN(R_{15})_2$,
 5 wherein q is an integer of 1 to 6 and each R_{15} is independently selected from hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl and C_{1-6} haloalkyl or two R_{15} taken together with the nitrogen atom to which they are attached form a 5 or 6 membered heterocyclic ring, especially C_{1-3} alkyl, C_{2-3} alkenyl, C_{2-3} alkynyl, C_{1-3} haloalkyl, halo, hydroxy, $-OC_{1-3}$ alkyl,
 10 $-OC_{2-3}$ alkenyl, $-OC_{2-3}$ alkynyl, $-OC_{1-3}$ haloalkyl, $N(C_{1-3}alkyl)_2$, $(CH_2)_qN(R_{15})_2$ and $O(CH_2)_qN(R_{15})_2$, wherein q is an integer from 1 to 3 and each R_{15} is independently selected from hydrogen, C_{1-3} alkyl, C_{2-3} alkenyl, C_{2-3} alkynyl and C_{1-3} haloalkyl or two R_{15} taken together with the nitrogen atom to which they are attached form a 5 or 6 membered heterocyclic ring, more especially methyl, ethyl, propyl, isopropyl, chloro,
 15 fluoro, trifluoromethyl, methoxy, ethoxy, dimethyl amino, diethyl amino, - $OCH_2CH_2N(CH_3)_2$, $-OCH_2CH_2$ piperidinyl, OCH_2CH_2 pyrrolyl and - $OCH_2CH_2CH_2$ piperidinyl; or
 R_{4a} is absent and R_4 and R_5 taken together form an optionally substituted aryl or optionally substituted heteroaryl group; especially where R_4 and R_5 taken together form
 20 a phenyl ring, a 2-pyridinyl ring, 3-pyridinyl ring, 4-pyridinyl ring, 3-pyridazinyl ring, 4-pyridazinyl ring, 2-furanyl, 3-furanyl, 2-thiophenyl ring, 3-thiophenyl ring, 2-thiazolyl ring, 3-thiazolyl ring, 4-thiazolyl ring, 3-isoxazolyl ring, 4-isoxazolyl ring, 5-isoxazolyl ring, 4-(1,2,3-thiadiazolyl) ring, 5-(1,2,3-thiadiazolyl) ring, 4-thiadiazolyl ring, 5-thiadiazolyl ring, 2-benzo[b]thiophenyl, 3-benzothiophenyl ring, -3-(1H)-indolyl
 25 ring or a 4H-thieno[3,2-c]chromene ring, especially a phenyl ring, a 2-pyridinyl ring, 3-pyridinyl ring, 4-pyridinyl ring, 3-pyridazinyl ring, 2-furanyl, 2-thiophenyl ring, 3-thiazolyl ring, 3-isoxazolyl ring, 5-(1,2,3-thiadiazolyl) ring, 5-thiadiazolyl ring, 2-benzo[b]thiophenyl ring, 3-(1H)-indolyl ring or 4H-thieno[3,2-c]chromene ring, where each aryl or heteroaryl ring may be unsubstituted or substituted by one or more
 30 substituents selected from C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, halo, hydroxy, $-OC_{1-6}$ alkyl, $-OC_{2-6}$ alkenyl, $-OC_{2-6}$ alkynyl, $-OC_{1-6}$ haloalkyl, $N(R_9)_2$, $(CH_2)_qN(R_{15})_2$ and $O(CH_2)_qN(R_{15})_2$, wherein q is an integer of 1 to 6 and each R_{15} is

- independently selected from hydrogen, C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl and C₁₋₆haloalkyl or two R₁₅ taken together with the nitrogen atom to which they are attached form a 5 or 6 membered heterocyclic ring, especially C₁₋₃alkyl, C₂₋₃alkenyl, C₂₋₃alkynyl, C₁₋₃haloalkyl, halo, hydroxy, -OC₁₋₃alkyl, -OC₂₋₃alkenyl, -OC₂₋₃alkynyl, -OC₁₋₃haloalkyl, N(C₁₋₃alkyl)₂ and O(CH₂)_qN(R₁₅)₂, wherein q is an integer from 1 to 3 and each R₁₅ is independently selected from hydrogen, C₁₋₃alkyl, C₂₋₃alkenyl, C₂₋₃alkynyl and C₁₋₃haloalkyl or two R₁₅ taken together with the nitrogen atom to which they are attached form a 5 or 6 membered heterocyclic ring, more especially methyl, ethyl, propyl, isopropyl, chloro, fluoro, trifluoromethyl, methoxy, ethoxy, dimethyl amino, diethyl amino, -OCH₂CH₂N(CH₃)₂, -OCH₂CH₂piperidinyl, OCH₂CH₂pyrrolyl and -OCH₂CH₂CH₂piperidinyl;
- R₆ and R₇ are independently selected from hydrogen, C₁₋₆alkyl, hydroxy, C₁₋₆alkoxy, C₁₋₆haloalkyl, C₁₋₆haloalkoxy, halo, CN, CO₂H, CO₂C₁₋₃alkyl and N(R₉)₂, especially hydrogen, C₁₋₃alkyl, hydroxy, C₁₋₃alkoxy, C₁₋₃haloalkyl, C₁₋₃haloalkoxy, halo, CN, CO₂H, CO₂CH₃ and N(C₁₋₃alkyl)₂, more especially hydrogen, methyl, ethyl, or CF₃, most especially hydrogen or methyl; or
- R₆ and R₇ taken together with the atoms to which they are attached form an optionally substituted phenyl, especially an unsubstituted or substituted phenyl ring, more especially an unsubstituted benzene ring;
- each R₈ is independently selected from hydrogen, C₁₋₆alkyl, hydroxy, C₁₋₆alkoxy, C₁₋₆haloalkyl, C₁₋₆haloalkoxy, halo, (CH₂)₁₋₃CO₂H and (CH₂)₁₋₃N(R₉)₂, especially hydrogen, C₁₋₃alkyl, hydroxy, C₁₋₃alkoxy, C₁₋₃haloalkyl, C₁₋₃haloalkoxy, halo, CH₂CO₂H, CH₂CH₂CO₂H and N(C₁₋₃alkyl)₂, more especially hydrogen, methyl, ethyl, or CF₃, most especially hydrogen or methyl;
- each R₉ is independently selected from hydrogen, C₁₋₆alkyl and C₁₋₆haloalkyl, especially hydrogen, C₁₋₆alkyl, more especially hydrogen, C₁₋₃alkyl, most especially hydrogen and methyl.

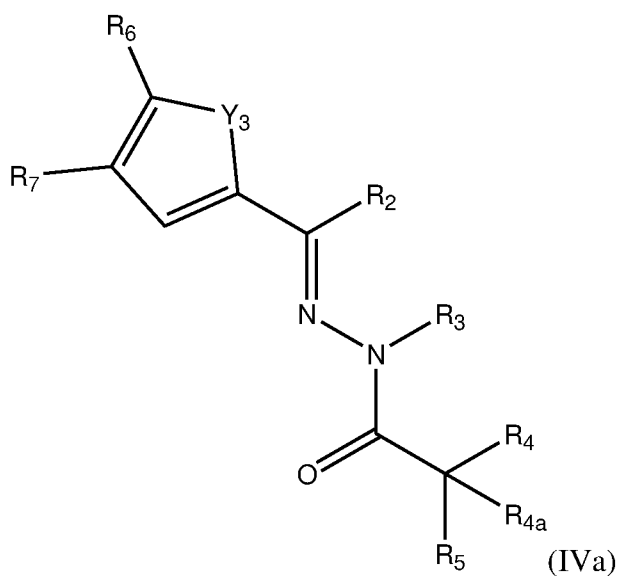
Particular compounds of formula III include compounds 44 to 92 and 160 to 169 as set out in Tables 5 and 6, compounds 122 to 137, 140 to 144, 154, 155 and 181 to 191 as set out in Table 8, compounds 192 to 196 from Table 9 and compounds 146 to 153 as set out in Example 10 and Tables 10 and 11, especially compounds 44 to 54, 56 to 62, 76 to 92, 122 to 137, 140 to 144, 154, 155, 160 to 169, 181 to 183 and 192 to 194.

In some embodiments, the compound of formula (I) is a compound of formula (IV):



wherein X , Y_3 , Y_4 , R_2 , R_3 , R_4 , R_{4a} , R_5 , R_6 and R_7 are as defined for formula (I), or a pharmaceutically acceptable salt thereof.

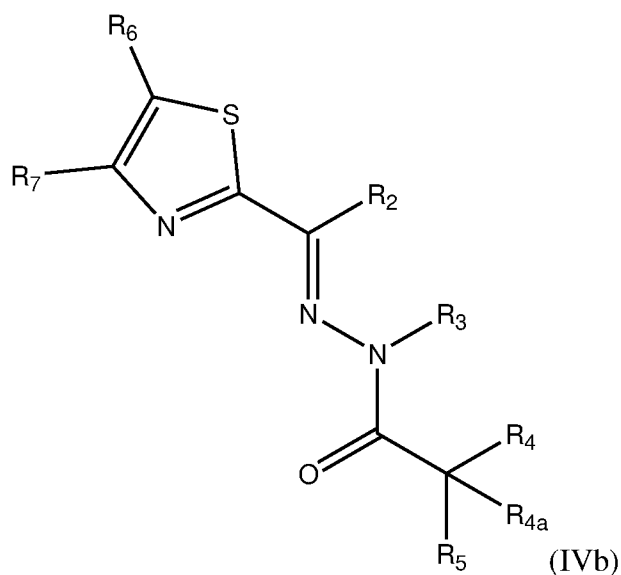
- 5 In some embodiments, the compound of formula (IV) is a compound of formula (IVa):



wherein R_2 , R_3 , R_4 , R_{4a} , R_5 , R_6 , R_7 and R_8 are as defined for formula (IV) and Y_3 is S or NR_9 , or a pharmaceutically acceptable salt thereof.

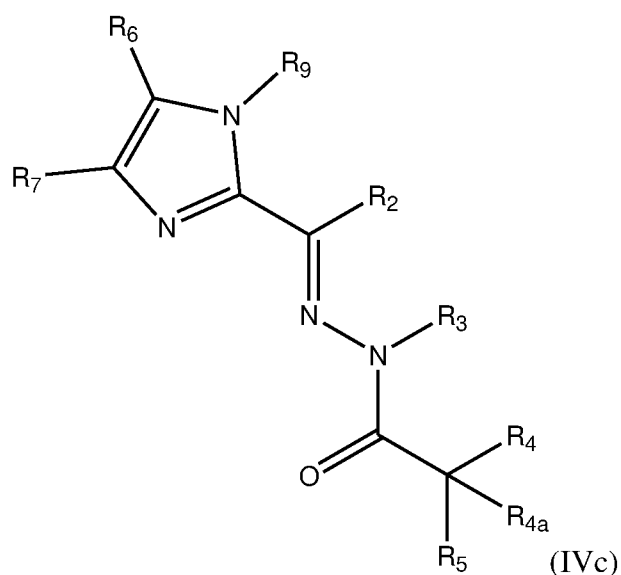
In some embodiments, the compound of formula (IV) is a compound of formula (IVb):

- 35 -



wherein R_2 , R_3 , R_4 , R_{4a} , R_5 , R_6 and R_7 are as defined for formula (IV), or a pharmaceutically acceptable salt thereof.

In some embodiments, the compound of formula (IV) is a compound of formula (IVc):



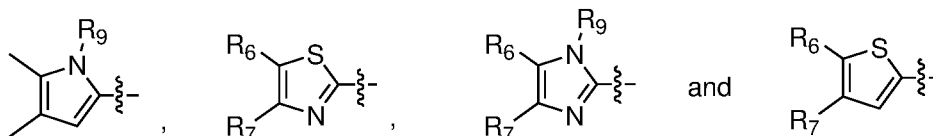
5

wherein R_2 , R_3 , R_4 , R_{4a} , R_5 , R_6 , R_7 and R_8 are as defined for formula (IV), or a pharmaceutically acceptable salt thereof.

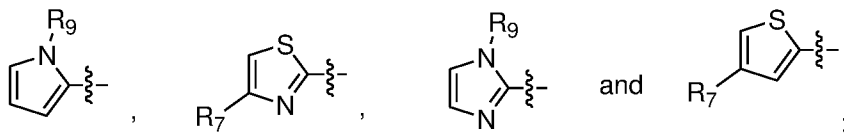
In particular embodiments of the compounds of formula (IV), one or more of the following applies:

10 X is O;

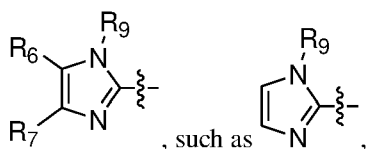
R₁ is selected from:



especially



5 More especially



R₂ is selected from hydrogen, C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, and C₃₋₈ cycloalkyl, especially hydrogen, C₁₋₄alkyl, C₂₋₄alkenyl, C₂₋₄alkynyl and C₃₋₆ cycloalkyl, more especially hydrogen, C₁₋₄alkyl and C₃₋₆ cycloalkyl,

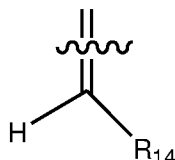
- 10 R₃ is selected from hydrogen, C₁₋₆alkyl, (CH₂)_mCO₂H and (CH₂)_mCO₂C₁₋₃alkyl, especially hydrogen, C₁₋₃alkyl, CH₂CO₂H and CH₂CO₂CH₃, more especially hydrogen;
- R₄ and R_{4a} are each independently selected from hydrogen, C₁₋₃alkyl, C₂₋₃alkenyl, C₂₋₃alkynyl and C₁₋₃haloalkyl; and R₅ is hydrogen, (CH₂)_maryl, O(CH₂)_maryl or (CH₂)_mheteroaryl where aryl and heteroaryl are optionally substituted; especially where
- 15 R₄ and R_{4a} are each independently hydrogen and R₅ is (CH₂)_maryl or (CH₂)_mheteroaryl; where each aryl or heteroaryl ring are selected from phenyl, pyridinyl, indolyl, thiazolyl, oxazolyl, thiadiazolyl, benzothiophenyl and pyridiziny, especially phenyl, indolyl and pyridinyl; and especially where each aryl or heteroaryl ring may be unsubstituted or substituted by one or more substituents selected from C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₁₋₆haloalkyl,
- 20 halo, hydroxy, -OC₁₋₆alkyl, -OC₂₋₆alkenyl, -OC₂₋₆alkynyl, -OC₁₋₆haloalkyl, N(R₉)₂, (CH₂)_qN(R₁₅)₂ and O(CH₂)_qN(R₁₅)₂, wherein q is an integer of 1 to 6 and each R₁₅ is independently selected from hydrogen, C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl and C₁₋₆haloalkyl or two R₁₅ taken together with the nitrogen atom to which they are attached form a 5 or 6 membered heterocyclic ring, especially C₁₋₃alkyl, C₂₋₃alkenyl, C₂₋₃alkynyl,
- 25 C₁₋₃haloalkyl, halo, hydroxy, -OC₁₋₃alkyl, -OC₂₋₃alkenyl, -OC₂₋₃alkynyl, -OC₁₋₃haloalkyl, N(C₁₋₃alkyl)₂ and O(CH₂)_qN(R₁₅)₂, wherein q is an integer from 1 to 3 and each R₁₅ is independently selected from hydrogen, C₁₋₃alkyl, C₂₋₃alkenyl, C₂₋₃alkynyl

- 37 -

and C₁₋₃haloalkyl or two R₁₅ taken together with the nitrogen atom to which they are attached form a 5 or 6 membered heterocyclic ring, more especially methyl, ethyl, propyl, isopropyl, chloro, fluoro, trifluoromethyl, methoxy, ethoxy, dimethyl amino, diethyl amino, -OCH₂CH₂N(CH₃)₂, -OCH₂CH₂piperidinyl, OCH₂CH₂pyrrolyl and -

5 OCH₂CH₂CH₂piperidinyl; or

R_{4a} is CN and R₄ and R₅ are each hydrogen or taken together form:



where R₁₄ is hydrogen, (CH₂)_maryl or (CH₂)_mheteroaryl wherein the aryl and heteroaryl are optionally substituted; especially (CH₂)_maryl or (CH₂)_mheteroaryl; wherein each aryl

10 or heteroaryl ring may be unsubstituted or substituted by one or more substituents

selected from C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₁₋₆haloalkyl, halo, hydroxy, -OC₁₋₆alkyl, -OC₂₋₆alkenyl, -OC₂₋₆alkynyl, -OC₁₋₆haloalkyl, N(R₉)₂ and O(CH₂)_qN(R₁₅)₂,

wherein q is an integer of 1 to 6 and each R₁₅ is independently selected from hydrogen, C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl and C₁₋₆haloalkyl or two R₁₅ taken together with the

15 nitrogen atom to which they are attached form a 5 or 6 membered heterocyclic ring,

especially C₁₋₃alkyl, C₂₋₃alkenyl, C₂₋₃alkynyl, C₁₋₃haloalkyl, halo, hydroxy, -OC₁₋₃alkyl, -OC₂₋₃alkenyl, -OC₂₋₃alkynyl, -OC₁₋₃haloalkyl, N(C₁₋₃alkyl)₂, (CH₂)_qN(R₁₅)₂ and

O(CH₂)_qN(R₁₅)₂, wherein q is an integer from 1 to 3 and each R₁₅ is independently

selected from hydrogen, C₁₋₃alkyl, C₂₋₃alkenyl, C₂₋₃alkynyl and C₁₋₃haloalkyl or two R₁₅

20 taken together with the nitrogen atom to which they are attached form a 5 or 6

membered heterocyclic ring, more especially methyl, ethyl, propyl, isopropyl, chloro, fluoro, trifluoromethyl, methoxy, ethoxy, dimethyl amino, diethyl amino, -

OCH₂CH₂N(CH₃)₂, -OCH₂CH₂piperidinyl, OCH₂CH₂pyrrolyl and -

OCH₂CH₂CH₂piperidinyl; or

25 R_{4a} is absent and R₄ and R₅ taken together form an optionally substituted aryl or

optionally substituted heteroaryl group; especially where R₄ and R₅ taken together form a phenyl ring, a 2-pyridinyl ring, 3-pyridinyl ring, 4-pyridinyl ring, 3-pyridazinyl ring,

4-pyridazinyl ring, 2-furanyl, 3-furanyl, 2-thiophenyl ring, 3-thiophenyl ring, 2-

thiazolyl ring, 3-thiazolyl ring, 4-thiazolyl ring, 3-isoxazolyl ring, 4-isoxazolyl ring, 5-

30 isoxazolyl ring, 4-(1,2,3-thiadiazolyl) ring, 5-(1,2,3-thiadiazolyl) ring, 4-thiadiazolyl

ring, 5-thiadiazolyl ring, 2-benzo[b]thiophenyl, 3-benzothiophenyl ring, -3-(1H)-indolyl ring or 4H-thieno[3,2-c]chromene ring, especially a phenyl ring, a 2-pyridinyl ring, 3-pyridinyl ring, 4-pyridinyl ring, 3-pyridazinyl ring, 2-furanyl, 2-thiophenyl ring, 3-thiazolyl ring, 3-isoxazolyl ring, 5-(1,2,3-thiadiazolyl) ring, 5-thiadiazolyl ring, 2-benzo[b]thiophenyl ring, 3-(1H)-indolyl ring or a 4H-thieno[3,2-c]chromene ring, where each aryl or heteroaryl ring may be unsubstituted or substituted by one or more substituents selected from C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₁₋₆haloalkyl, halo, hydroxy, -OC₁₋₆alkyl, -OC₂₋₆alkenyl, -OC₂₋₆alkynyl, -OC₁₋₆haloalkyl, N(R₉)₂, (CH₂)_qN(R₁₅)₂ and O(CH₂)_qN(R₁₅)₂, wherein q is an integer of 1 to 6 and each R₁₅ is independently selected from hydrogen, C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl and C₁₋₆haloalkyl or two R₁₅ taken together with the nitrogen atom to which they are attached form a 5 or 6 membered heterocyclic ring, especially C₁₋₃alkyl, C₂₋₃alkenyl, C₂₋₃alkynyl, C₁₋₃haloalkyl, halo, hydroxy, -OC₁₋₃alkyl, -OC₂₋₃alkenyl, -OC₂₋₃alkynyl, -OC₁₋₃haloalkyl, N(C₁₋₃alkyl)₂ and O(CH₂)_qN(R₁₅)₂, wherein q is an integer from 1 to 3 and each R₁₅ is independently selected from hydrogen, C₁₋₃alkyl, C₂₋₃alkenyl, C₂₋₃alkynyl and C₁₋₃haloalkyl or two R₁₅ taken together with the nitrogen atom to which they are attached form a 5 or 6 membered heterocyclic ring, more especially methyl, ethyl, propyl, isopropyl, chloro, fluoro, trifluoromethyl, methoxy, ethoxy, dimethyl amino, diethyl amino, -OCH₂CH₂N(CH₃)₂, -OCH₂CH₂piperidinyl, OCH₂CH₂pyrrolyl and -OCH₂CH₂CH₂piperidinyl;

R₆ and R₇ are independently selected from hydrogen, C₁₋₆alkyl, hydroxy, C₁₋₆alkoxy, C₁₋₆haloalkyl, C₁₋₆haloalkoxy, halo, CN, CO₂H, CO₂C₁₋₃alkyl and N(R₉)₂, especially hydrogen, C₁₋₃alkyl, hydroxy, C₁₋₃alkoxy, C₁₋₃haloalkyl, C₁₋₃haloalkoxy, halo, CN, CO₂H, CO₂CH₃ and N(C₁₋₃alkyl)₂, more especially hydrogen, methyl, ethyl, or CF₃, most especially hydrogen or methyl; or

R₆ and R₇ taken together with the atoms to which they are attached form an optionally substituted phenyl, especially an unsubstituted or substituted phenyl ring, more especially an unsubstituted benzene ring;

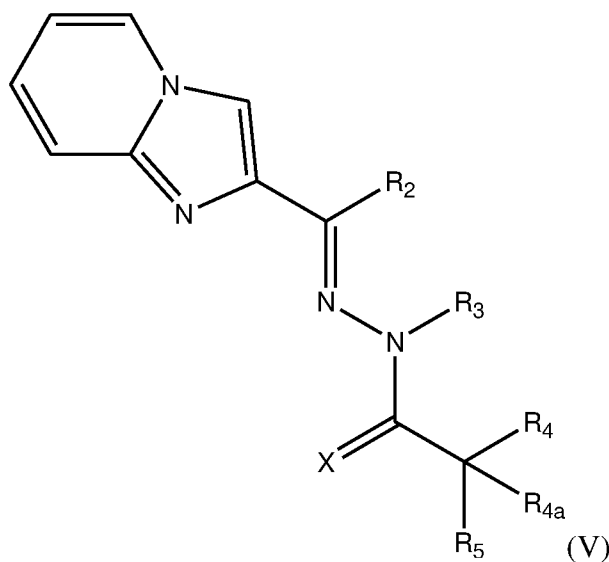
Each R₈ is independently selected from hydrogen, C₁₋₆alkyl, hydroxy, C₁₋₆alkoxy, C₁₋₆haloalkyl, C₁₋₆haloalkoxy, halo, (CH₂)₁₋₃CO₂H and (CH₂)₁₋₃N(R₉)₂, especially hydrogen, C₁₋₃alkyl, hydroxy, C₁₋₃alkoxy, C₁₋₃haloalkyl, C₁₋₃haloalkoxy, halo,

CH₂CO₂H, CH₂CH₂CO₂H and N(C₁₋₃alkyl)₂, more especially hydrogen, methyl, ethyl, or CF₃, most especially hydrogen or methyl;

Each R₉ is independently selected from hydrogen, C₁₋₆alkyl and C₁₋₆haloalkyl, especially hydrogen, C₁₋₆alkyl, more especially hydrogen, C₁₋₃alkyl, most especially
 5 hydrogen and methyl.

Particular compounds of formula (IV) include compounds 93 to 119 and 163 to 169 as set out in Table 6 especially compounds 110 to 113, 116, 117 and 163 to 169.

In some embodiments, the compound of formula (I) is a compound of formula (V):



10 wherein R₂, R₃, R₄, R_{4a} and R₅, are as defined for formula (I).

In particular embodiments of the compounds of formula (V), one or more of the following applies:

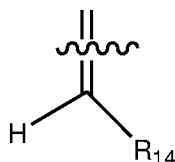
R₂ is selected from hydrogen, C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, and C₃₋₈ cycloalkyl, especially hydrogen, C₁₋₄alkyl, C₂₋₄alkenyl, C₂₋₄alkynyl and C₃₋₆ cycloalkyl, more
 15 especially hydrogen, C₁₋₄alkyl and C₃₋₆ cycloalkyl,

R₃ is selected from hydrogen, C₁₋₆alkyl, (CH₂)_mCO₂H and (CH₂)_mCO₂C₁₋₃alkyl, especially hydrogen, C₁₋₃alkyl, CH₂CO₂H and CH₂CO₂CH₃, more especially hydrogen;

R₄ and R_{4a} are each independently selected from hydrogen, C₁₋₃alkyl, C₂₋₃alkenyl, C₂₋₃alkynyl and C₁₋₃haloalkyl; and R₅ is hydrogen, (CH₂)_maryl, O(CH₂)_maryl or

20 (CH₂)_mheteroaryl where aryl and heteroaryl are optionally substituted; especially where

R_4 and R_{4a} are each independently hydrogen and R_5 is $(CH_2)_m$ aryl or $(CH_2)_m$ heteroaryl; where each aryl or heteroaryl ring are selected from phenyl, pyridinyl, indolyl, thiazolyl, oxazolyl, thiadiazolyl, benzothiophenyl and pyridazinyl, especially phenyl, indolyl and pyridinyl; and especially where each aryl or heteroaryl ring may be unsubstituted or substituted by one or more substituents selected from C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, halo, hydroxy, $-OC_{1-6}$ alkyl, $-OC_{2-6}$ alkenyl, $-OC_{2-6}$ alkynyl, $-OC_{1-6}$ haloalkyl, $N(R_9)_2$, $(CH_2)_qN(R_{15})_2$ and $O(CH_2)_qN(R_{15})_2$, wherein q is an integer of 1 to 6 and each R_{15} is independently selected from hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl and C_{1-6} haloalkyl or two R_{15} taken together with the nitrogen atom to which they are attached form a 5 or 6 membered heterocyclic ring, especially C_{1-3} alkyl, C_{2-3} alkenyl, C_{2-3} alkynyl, C_{1-3} haloalkyl, halo, hydroxy, $-OC_{1-3}$ alkyl, $-OC_{2-3}$ alkenyl, $-OC_{2-3}$ alkynyl, $-OC_{1-3}$ haloalkyl, $N(C_{1-3}alkyl)_2$ and $O(CH_2)_qN(R_{15})_2$, wherein q is an integer from 1 to 3 and each R_{15} is independently selected from hydrogen, C_{1-3} alkyl, C_{2-3} alkenyl, C_{2-3} alkynyl and C_{1-3} haloalkyl or two R_{15} taken together with the nitrogen atom to which they are attached form a 5 or 6 membered heterocyclic ring, more especially methyl, ethyl, propyl, isopropyl, chloro, fluoro, trifluoromethyl, methoxy, ethoxy, dimethyl amino, diethyl amino, $-OCH_2CH_2N(CH_3)_2$, $-OCH_2CH_2$ piperidinyl, OCH_2CH_2 pyrrolyl and $-OCH_2CH_2CH_2$ piperidinyl; or R_{4a} is CN and R_4 and R_5 are each hydrogen or taken together form:



where R_{14} is hydrogen, $(CH_2)_m$ aryl or $(CH_2)_m$ heteroaryl wherein the aryl and heteroaryl are optionally substituted; especially $(CH_2)_m$ aryl or $(CH_2)_m$ heteroaryl; where each aryl or heteroaryl ring may be unsubstituted or substituted by one or more substituents selected from C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, halo, hydroxy, $-OC_{1-6}$ alkyl, $-OC_{2-6}$ alkenyl, $-OC_{2-6}$ alkynyl, $-OC_{1-6}$ haloalkyl, $N(R_9)_2$ and $O(CH_2)_qN(R_{15})_2$, wherein q is an integer of 1 to 6 and each R_{15} is independently selected from hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl and C_{1-6} haloalkyl or two R_{15} taken together with the nitrogen atom to which they are attached form a 5 or 6 membered heterocyclic ring, especially C_{1-3} alkyl, C_{2-3} alkenyl, C_{2-3} alkynyl, C_{1-3} haloalkyl, halo, hydroxy, $-OC_{1-3}$ alkyl, $-OC_{2-3}$ alkenyl, $-OC_{2-3}$ alkynyl, $-OC_{1-3}$ haloalkyl, $N(C_{1-3}alkyl)_2$, $(CH_2)_qN(R_{15})_2$ and

$O(CH_2)_qN(R_{15})_2$, wherein q is an integer from 1 to 3 and each R_{15} is independently selected from hydrogen, C_{1-3} alkyl, C_{2-3} alkenyl, C_{2-3} alkynyl and C_{1-3} haloalkyl or two R_{15} taken together with the nitrogen atom to which they are attached form a 5 or 6 membered heterocyclic ring, more especially methyl, ethyl, propyl, isopropyl, chloro, fluoro, trifluoromethyl, methoxy, ethoxy, dimethyl amino, diethyl amino, -
 5 $OCH_2CH_2N(CH_3)_2$, $-OCH_2CH_2$ piperidinyl, OCH_2CH_2 pyrrolyl and -
 $OCH_2CH_2CH_2$ piperidinyl; or
 R_{4a} is absent and R_4 and R_5 taken together form an optionally substituted aryl or optionally substituted heteroaryl group; especially where R_4 and R_5 taken together form
 10 a phenyl ring, a 2-pyridinyl ring, 3-pyridinyl ring, 4-pyridinyl ring, 3-pyridazinyl ring, 4-pyridazinyl ring, 2-furanyl, 3-furanyl, 2-thiophenyl ring, 3-thiophenyl ring, 2-thiazolyl ring, 3-thiazolyl ring, 4-thiazolyl ring, 3-isoxazolyl ring, 4-isoxazolyl ring, 5-isoxazolyl ring, 4-(1,2,3-thiadiazolyl) ring, 5-(1,2,3-thiadiazolyl) ring, 4-thiadiazolyl ring, 5-thiadiazolyl ring, 2-benzo[b]thiophenyl, 3-benzothiophenyl ring, -3-(1H)-indolyl
 15 ring or a 4H-thieno[3,2-c]chromene ring, especially a phenyl ring, a 2-pyridinyl ring, 3-pyridinyl ring, 4-pyridinyl ring, 3-pyridazinyl ring, 2-furanyl, 2-thiophenyl ring, 3-thiazolyl ring, 3-isoxazolyl ring, 5-(1,2,3-thiadiazolyl) ring, 5-thiadiazolyl ring, 2-benzo[b]thiophenyl ring, 3-(1H)-indolyl ring or a 4H-thieno[3,2-c]chromene ring, where each aryl or heteroaryl ring may be unsubstituted or substituted by one or more
 20 substituents selected from C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, halo, hydroxy, $-OC_{1-6}$ alkyl, $-OC_{2-6}$ alkenyl, $-OC_{2-6}$ alkynyl, $-OC_{1-6}$ haloalkyl, $N(R_9)_2$, $(CH_2)_qN(R_{15})_2$ and $O(CH_2)_qN(R_{15})_2$, wherein q is an integer of 1 to 6 and each R_{15} is independently selected from hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl and C_{1-6} haloalkyl or two R_{15} taken together with the nitrogen atom to which they are attached
 25 form a 5 or 6 membered heterocyclic ring, especially C_{1-3} alkyl, C_{2-3} alkenyl, C_{2-3} alkynyl, C_{1-3} haloalkyl, halo, hydroxy, $-OC_{1-3}$ alkyl, $-OC_{2-3}$ alkenyl, $-OC_{2-3}$ alkynyl, $-OC_{1-3}$ haloalkyl, $N(C_{1-3}alkyl)_2$ and $O(CH_2)_qN(R_{15})_2$, wherein q is an integer from 1 to 3 and each R_{15} is independently selected from hydrogen, C_{1-3} alkyl, C_{2-3} alkenyl, C_{2-3} alkynyl and C_{1-3} haloalkyl or two R_{15} taken together with the nitrogen atom to which they are
 30 attached form a 5 or 6 membered heterocyclic ring, more especially methyl, ethyl, propyl, isopropyl, chloro, fluoro, trifluoromethyl, methoxy, ethoxy, dimethyl amino,

diethyl amino, $-\text{OCH}_2\text{CH}_2\text{N}(\text{CH}_3)_2$, $-\text{OCH}_2\text{CH}_2\text{piperidinyl}$, $\text{OCH}_2\text{CH}_2\text{pyrrolyl}$ and $-\text{OCH}_2\text{CH}_2\text{CH}_2\text{piperidinyl}$;

Each R_8 is independently selected from hydrogen, $\text{C}_{1-6}\text{alkyl}$, hydroxy, $\text{C}_{1-6}\text{alkoxy}$, $\text{C}_{1-6}\text{haloalkyl}$, $\text{C}_{1-6}\text{haloalkoxy}$, halo, $(\text{CH}_2)_{1-3}\text{CO}_2\text{H}$ and $(\text{CH}_2)_{1-3}\text{N}(\text{R}_9)_2$, especially

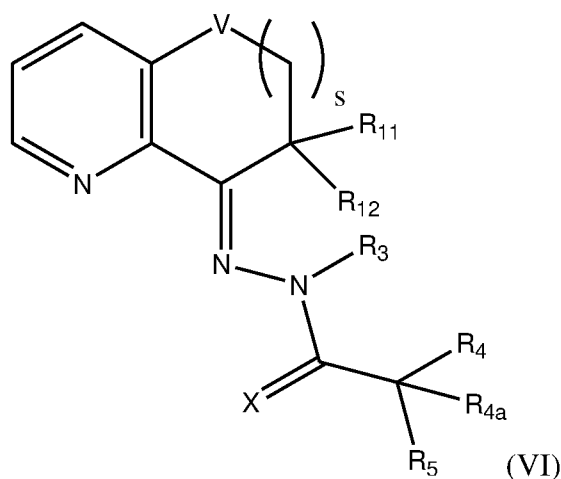
- 5 hydrogen, $\text{C}_{1-3}\text{alkyl}$, hydroxy, $\text{C}_{1-3}\text{alkoxy}$, $\text{C}_{1-3}\text{haloalkyl}$, $\text{C}_{1-3}\text{haloalkoxy}$, halo, $\text{CH}_2\text{CO}_2\text{H}$, $\text{CH}_2\text{CH}_2\text{CO}_2\text{H}$ and $\text{N}(\text{C}_{1-3}\text{alkyl})_2$, more especially hydrogen, methyl, ethyl, or CF_3 , most especially hydrogen or methyl;

Each R_9 is independently selected from hydrogen, $\text{C}_{1-6}\text{alkyl}$ and $\text{C}_{1-6}\text{haloalkyl}$, especially hydrogen, $\text{C}_{1-6}\text{alkyl}$, more especially hydrogen, $\text{C}_{1-3}\text{alkyl}$, most especially

- 10 hydrogen and methyl.

Particular compounds of formula V include compounds 120, 121, 138 and 139 as set out in Table 7.

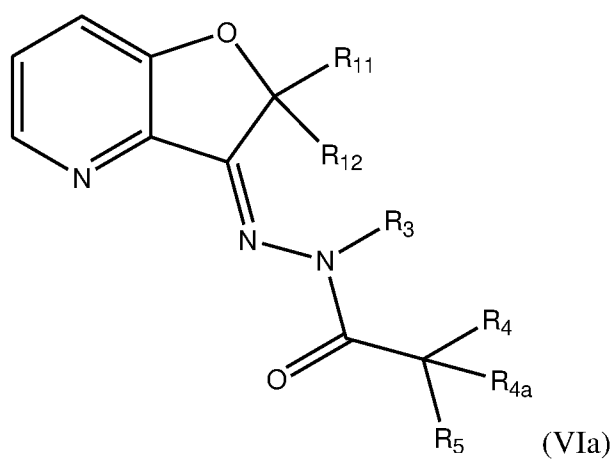
In some embodiments, the compound of formula (I) is a compound of formula (VI):



- 15 wherein X , V , R_3 , R_4 , R_{4a} and R_5 are as defined for formula (I), R_{11} and R_{12} are each independently selected from hydrogen, $\text{C}_{1-6}\text{alkyl}$, $\text{C}_{2-6}\text{alkenyl}$, $\text{C}_{2-6}\text{alkynyl}$, halo, $\text{C}_{1-6}\text{haloalkyl}$, $(\text{CH}_2)_m\text{C}_{3-6}\text{ cycloalkyl}$, $(\text{CH}_2)_m\text{aryl}$, $(\text{CH}_2)_m\text{heterocyclyl}$, $(\text{CH}_2)_m\text{heteroaryl}$ and COR_{13} where R_{13} is selected from OH , $\text{OC}_{1-6}\text{alkyl}$, $\text{OC}_{2-6}\text{alkenyl}$, $\text{OC}_{2-6}\text{alkynyl}$ and $\text{N}(\text{R}_9)_2$ and s is 0, 1 or 2, or a pharmaceutically acceptable salt thereof.

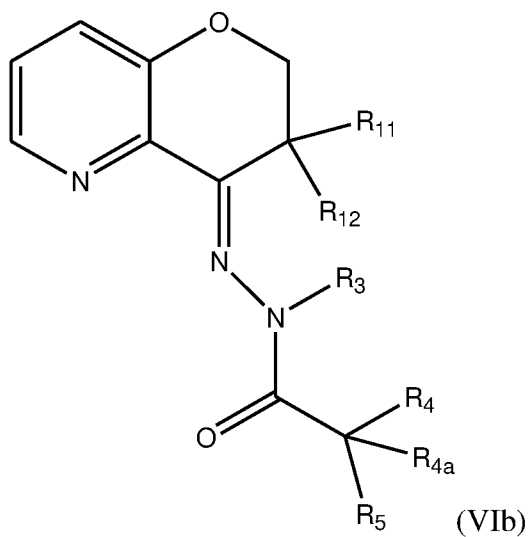
- 20 In some embodiments, the compound of formula (VI) is a compound of formula (VIa):

- 43 -



wherein R₃, R₄, R_{4a}, R₅, R₁₁ and R₁₂ are as defined for formula (VI), or a pharmaceutically acceptable salt thereof.

In some embodiments, the compound of formula (VI) is a compound of formula (VIb):

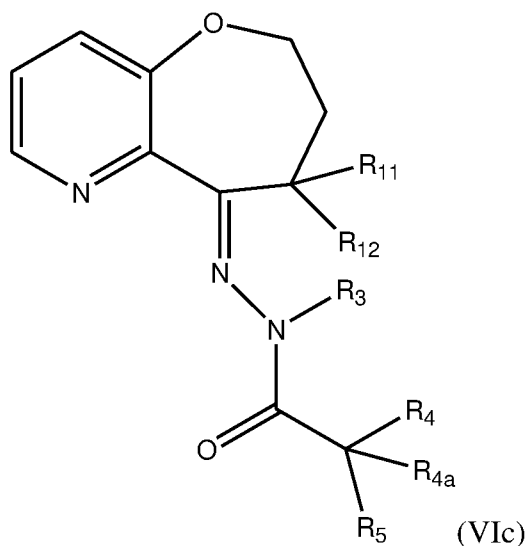


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wherein R₃, R₄, R_{4a}, R₅, R₁₁ and R₁₂ are as defined for formula (VI), or a pharmaceutically acceptable salt thereof.

In some embodiments, the compound of formula (VI) is a compound of formula (VIc):

- 44 -



wherein R_3 , R_4 , R_{4a} , R_5 , R_{11} and R_{12} are as defined for formula (VI) or a pharmaceutically acceptable salt thereof.

In particular embodiments of the compounds of formula (VI), one or more of the following applies:

X is O;

V is O;

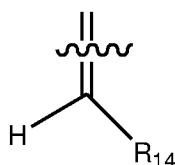
R_3 is selected from hydrogen, C_{1-6} alkyl, $(CH_2)_mCO_2H$ and $(CH_2)_mCO_2C_{1-3}$ alkyl, especially hydrogen, C_{1-3} alkyl, CH_2CO_2H and $CH_2CO_2CH_3$, more especially hydrogen;

R_4 and R_{4a} are each independently selected from hydrogen, C_{1-3} alkyl, C_{2-3} alkenyl, C_{2-3} alkynyl and C_{1-3} haloalkyl; and R_5 is hydrogen, $(CH_2)_m$ aryl, $O(CH_2)_m$ aryl or $(CH_2)_m$ heteroaryl where aryl and heteroaryl are optionally substituted; especially where R_4 and R_{4a} are each independently hydrogen and R_5 is $(CH_2)_m$ aryl or $(CH_2)_m$ heteroaryl; where each aryl or heteroaryl ring are selected from phenyl, pyridinyl, indolyl, thiazolyl, oxazolyl, thiadiazolyl, benzothiophenyl and pyridizinyl, especially phenyl, indolyl and pyridinyl; and especially where each aryl or heteroaryl ring may be unsubstituted or substituted by one or more substituents selected from C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, halo, hydroxy, $-OC_{1-6}$ alkyl, $-OC_{2-6}$ alkenyl, $-OC_{2-6}$ alkynyl, $-OC_{1-6}$ haloalkyl, $N(R_9)_2$, $(CH_2)_qN(R_{15})_2$ and $O(CH_2)_qN(R_{15})_2$, wherein q is an integer of 1 to 6 and each R_{15} is independently selected from hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl and C_{1-6} haloalkyl or two R_{15} taken together with the nitrogen atom to which they are attached form a 5 or 6 membered heterocyclic ring, especially C_{1-3} alkyl, C_{2-3} alkenyl, C_{2-3} alkynyl,

- 45 -

C₁₋₃haloalkyl, halo, hydroxy, -OC₁₋₃alkyl, -OC₂₋₃alkenyl, -OC₂₋₃alkynyl, -OC₁₋₃haloalkyl, N(C₁₋₃alkyl)₂ and O(CH₂)_qN(R₁₅)₂, wherein q is an integer from 1 to 3 and each R₁₅ is independently selected from hydrogen, C₁₋₃alkyl, C₂₋₃alkenyl, C₂₋₃alkynyl and C₁₋₃haloalkyl or two R₁₅ taken together with the nitrogen atom to which they are attached form a 5 or 6 membered heterocyclic ring, more especially methyl, ethyl, propyl, isopropyl, chloro, fluoro, trifluoromethyl, methoxy, ethoxy, dimethyl amino, diethyl amino, -OCH₂CH₂N(CH₃)₂, -OCH₂CH₂piperidinyl, OCH₂CH₂pyrrolyl and -OCH₂CH₂CH₂piperidinyl; or

R_{4a} is CN and R₄ and R₅ are each hydrogen or taken together form:



10

where R₁₄ is hydrogen, (CH₂)_maryl or (CH₂)_mheteroaryl where aryl and heteroaryl are optionally substituted; especially (CH₂)_maryl or (CH₂)_mheteroaryl; where each aryl or heteroaryl ring may be unsubstituted or substituted by one or more substituents selected from C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₁₋₆haloalkyl, halo, hydroxy, -OC₁₋₆alkyl, -OC₂₋₆alkenyl, -OC₂₋₆alkynyl, -OC₁₋₆haloalkyl, N(R₉)₂, (CH₂)_qN(R₁₅)₂ and O(CH₂)_qN(R₁₅)₂, wherein q is an integer of 1 to 6 and each R₁₅ is independently selected from hydrogen, C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl and C₁₋₆haloalkyl or two R₁₅ taken together with the nitrogen atom to which they are attached form a 5 or 6 membered heterocyclic ring, especially C₁₋₃alkyl, C₂₋₃alkenyl, C₂₋₃alkynyl, C₁₋₃haloalkyl, halo, hydroxy, -OC₁₋₃alkyl, -OC₂₋₃alkenyl, -OC₂₋₃alkynyl, -OC₁₋₃haloalkyl, N(C₁₋₃alkyl)₂ and O(CH₂)_qN(R₁₅)₂, wherein q is an integer from 1 to 3 and each R₁₅ is independently selected from hydrogen, C₁₋₃alkyl, C₂₋₃alkenyl, C₂₋₃alkynyl and C₁₋₃haloalkyl or two R₁₅ taken together with the nitrogen atom to which they are attached form a 5 or 6 membered heterocyclic ring, more especially methyl, ethyl, propyl, isopropyl, chloro, fluoro, trifluoromethyl, methoxy, ethoxy, dimethyl amino, diethyl amino, -OCH₂CH₂N(CH₃)₂, -OCH₂CH₂piperidinyl, OCH₂CH₂pyrrolyl and -OCH₂CH₂CH₂piperidinyl; or R_{4a} is absent and R₄ and R₅ taken together form an optionally substituted aryl or optionally substituted heteroaryl group; especially where R₄ and R₅ taken together form a phenyl ring, a 2-pyridinyl ring, 3-pyridinyl ring, 4-pyridinyl ring, 3-pyridazinyl ring, 4-pyridazinyl ring, 2-furanyl, 3-furanyl, 2-thiophenyl ring, 3-thiophenyl ring, 2-

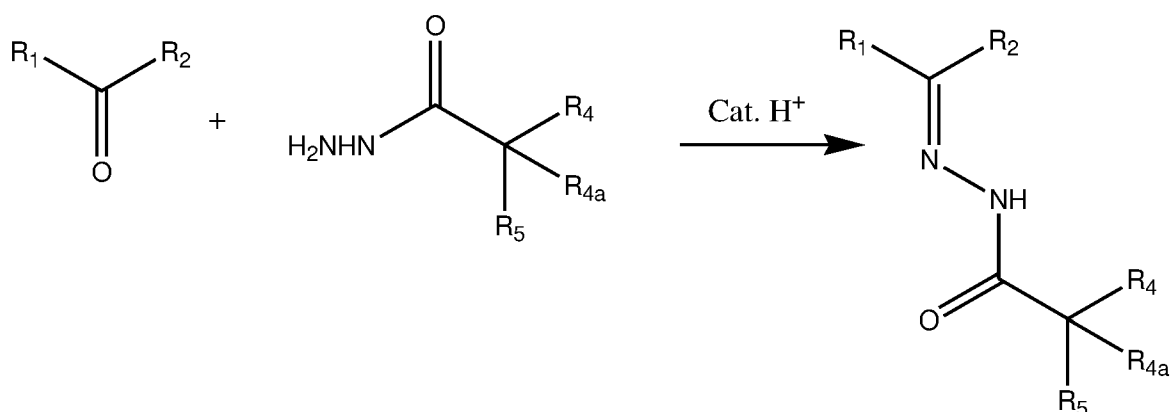
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thiazolyl ring, 3-thiazolyl ring, 4-thiazolyl ring, 3-isoxazolyl ring, 4-isoxazolyl ring, 5-isoxazolyl ring, 4-(1,2,3-thiadiazolyl) ring, 5-(1,2,3-thiadiazolyl) ring, 4-thiadiazolyl ring, 5-thiadiazolyl ring, 2-benzo[b]thiophenyl, 3-benzothiophenyl ring, -3-(1H)-indolyl ring or a 4H-thieno[3,2-c]chromene ring, especially a phenyl ring, a 2-pyridinyl ring, 3-pyridinyl ring, 4-pyridinyl ring, 3-pyridazinyl ring, 2-furanyl, 2-thiophenyl ring, 3-thiazolyl ring, 3-isoxazolyl ring, 5-(1,2,3-thiadiazolyl) ring, 5-thiadiazolyl ring, 2-benzo[b]thiophenyl ring, 3-(1H)-indolyl ring or a 4H-thieno[3,2-c]chromene ring, where each aryl or heteroaryl ring may be unsubstituted or substituted by one or more substituents selected from C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₁₋₆haloalkyl, halo, hydroxy, -OC₁₋₆alkyl, -OC₂₋₆alkenyl, -OC₂₋₆alkynyl, -OC₁₋₆haloalkyl, N(R₉)₂, (CH₂)_qN(R₁₅)₂ and O(CH₂)_qN(R₁₅)₂, wherein q is an integer of 1 to 6 and each R₁₅ is independently selected from hydrogen, C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl and C₁₋₆haloalkyl or two R₁₅ taken together with the nitrogen atom to which they are attached form a 5 or 6 membered heterocyclic ring, especially C₁₋₃alkyl, C₂₋₃alkenyl, C₂₋₃alkynyl, C₁₋₃haloalkyl, halo, hydroxy, -OC₁₋₃alkyl, -OC₂₋₃alkenyl, -OC₂₋₃alkynyl, -OC₁₋₃haloalkyl, N(C₁₋₃alkyl)₂ and O(CH₂)_qN(R₁₅)₂, wherein q is an integer from 1 to 3 and each R₁₅ is independently selected from hydrogen, C₁₋₃alkyl, C₂₋₃alkenyl, C₂₋₃alkynyl and C₁₋₃haloalkyl or two R₁₅ taken together with the nitrogen atom to which they are attached form a 5 or 6 membered heterocyclic ring, more especially methyl, ethyl, propyl, isopropyl, chloro, fluoro, trifluoromethyl, methoxy, ethoxy, dimethyl amino, diethyl amino, -OCH₂CH₂N(CH₃)₂, -OCH₂CH₂piperidinyl, OCH₂CH₂pyrrolyl and -OCH₂CH₂CH₂piperidinyl;

R₁₁ and R₁₂ are each independently selected from hydrogen, C₁₋₆alkyl, halo, C₁₋₆haloalkyl, (CH₂)_mC₃₋₈cycloalkyl, (CH₂)_maryl, (CH₂)_mheterocyclyl, (CH₂)_mheteroaryl and COR₁₃ where R₁₃ is selected from OH, OC₁₋₆alkyl, and N(R₉)₂, especially where R₁₁ and R₁₂ are independently selected from hydrogen, C₁₋₆alkyl, C₁₋₆haloalkyl, C₃₋₈cycloalkyl, CH₂phenyl, CH₂pyridyl, and CO C₁₋₆alkyl, more especially where R₁₁ and R₁₂ are independently selected from hydrogen, C₁₋₃alkyl, C₁₋₃haloalkyl, fluoro, C₃₋₆cycloalkyl, CH₂phenyl, CH₂pyridyl and COC₁₋₃alkyl, most especially where R₁₁ and R₁₂ are both hydrogen, both methyl, both ethyl or where one of R₁₁ and R₁₂ is hydrogen and the other is methyl, ethyl, fluoro, CH₂phenyl, CH₂pyridyl, CO₂methyl or CO₂ethyl.

Particular compounds of formula VI include compounds 171 to 178 in Table 12.

The compounds of the invention may be synthesised from commercially available starting materials using known methods. For example, the hydrazides may be prepared by reacting an appropriate ketone with a carboxylic acid hydrazine in the presence of a catalytic amount of acid.



5

Suitable catalytic acids include concentrated hydrochloric acid or toluene sulphonic acid.

The resulting hydrazides may be further derivatised, for example by alkylation of hydroxy groups or formation of double bonds from ketones and aldehydes. Suitable reactions are provided in the Examples below.

10

EXAMPLES

Abbreviations

ACN	acetonitrile	h	Hour(s)
conc.	concentrated	K ₂ CO ₃	Potassium carbonate
DMF	<i>N,N</i> -Dimethylformamide	MeOH	methanol
EtOH	Ethanol	min	minute
EtOAc	Ethyl Acetate	MS	Mass Spectrometry
THF	Tetrahydrofuran	LiOH	Lithium hydroxide
rt	Room temperature	o/n	Over night

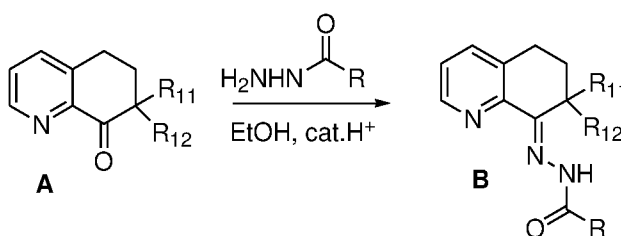
A range of acyl hydrazones can be prepared by the synthetic route depicted in Scheme

1. Heating an equimolar mixture of a dihydroquinolone ketone derivative **A** and

15

substituted acyl hydrazides in ethanol or other suitable solvent, with a catalytic amount of acid, furnished target acyl hydrazone products **B**. Ketone starting materials were available from commercial suppliers or known literature methods. For example, 5,6-dihydro-7,7-dimethylquinolin-8-one could be prepared, as described by Chuang Bing et al, *New Journal of Chemistry* **2016**, 40, 9329-9346. Ethyl 8-oxo-5,6,7,8-tetrahydroquinoline-7-carboxylate starting material is known in the literature (Takashi et al, *Synthesis* **2005**, 10, 1593-1600). The compound could be synthesised by heating 6,7-dihydroquinolin-8(5*H*)-one, sodium hydride and diethyl carbonate at 130°C.

Scheme 1



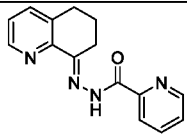
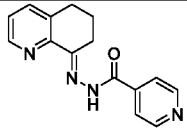
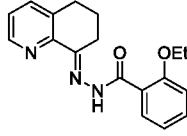
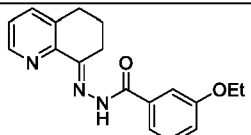
Example: (Table 1)

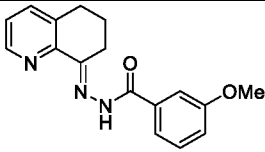
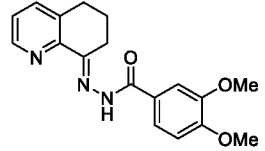
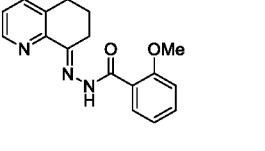
(*E*)-*N'*-(6,7-Dihydroquinolin-8(5*H*)-ylidene)nicotinohydrazide (**1**).

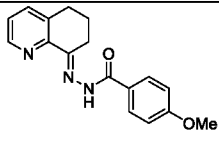
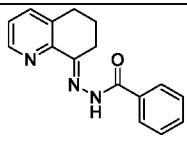
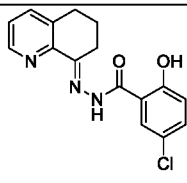
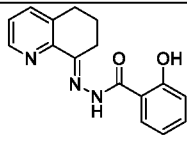
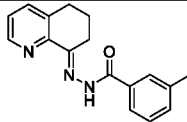
To a solution of 6,7-Dihydroquinolin 8(5*H*)-one (622 mg, 4.22 mmol) in EtOH was added nicotinic acid hydrazide (575 mg, 4.22 mmol) followed by the addition of catalytic *para*-toluene sulphonic acid (7 mg). The reaction was heated to 45°C for 1 h, then left to cool overnight. A cream coloured solid was collected by filtration which was suspended in MeOH. The filtrate was cooled to 4°C overnight. Off-white needles were collected by filtration to afford target compound (*E*)-*N'*-(6,7-dihydroquinolin-8(5*H*)-ylidene)nicotinohydrazide **1** (112 mg). ^1H NMR (600MHz, d_6 -DMSO) δ 1.96 (t, $J=6.0$ Hz, 2H), 2.99 (t, $J=6.0$ Hz, 4H), 7.64 (dd, $J=7.8, 4.8$ Hz, 1H), 7.85 (br s, 1H), 8.38 (d, $J=6.6$ Hz, 2H), 8.68 (d, $J=4.8$ Hz, 1H), 8.81 (d, $J=4.8$ Hz, 1H), 9.13 (s, 1H), 11.64 (s, 1H). MS m/z 267.12 $[M+H]^+$.

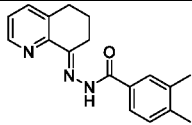
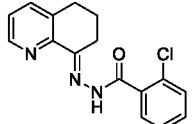
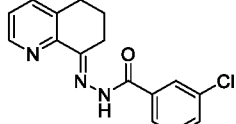
Table 1: Selected Data for Compounds prepared via Scheme 1

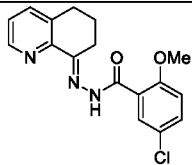
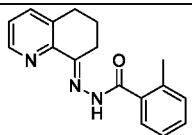
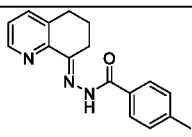
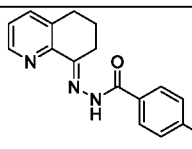
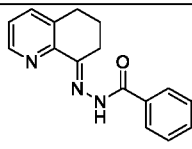
Compound	Structure	NMR	Mass
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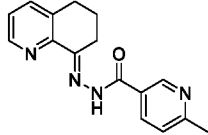
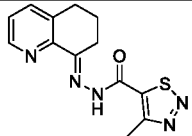
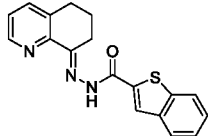
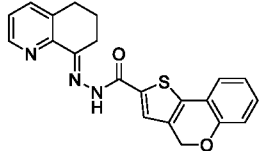
			Spec [M+H] ⁺
2		¹ H NMR (600MHz, d6-DMSO) δ 1.97 (t, <i>J</i> =6.0Hz, 2H), 2.77 (t, <i>J</i> =6.0Hz, 2H), 2.90-2.94 (m, 2H), 7.50 (dd, <i>J</i> =14.0, 6.6Hz, 1H), 7.63-7.66 (m, 1H), 7.86-7.89 (m, 1H), 8.01-8.05 (m, 1H), 8.11-8.14 (m, 1H), 8.71-8.74 (m, 1H), 8.75-8.78 (m, 1H), 16.23 (s, 1H),	<i>m/z</i> 267.12
3		¹ H NMR (600MHz, d6-DMSO) δ 1.96 (t, <i>J</i> =6.0Hz, 2H), 2.77 (t, <i>J</i> =6.0Hz, 2H), 2.93 (t, <i>J</i> =6.0Hz, 2H), 7.55 (dd, <i>J</i> =7.8, 4.8Hz, 1H), 7.80 (dd, <i>J</i> =4.2, 1.2Hz, 2H), 7.92 (d, <i>J</i> =7.8Hz, 1H), 8.77(d, <i>J</i> =4.2 Hz, 1H), 8.82 (dd, <i>J</i> =4.8, 1.2Hz, 2H).	<i>m/z</i> 267.12
4		¹ H NMR (600MHz, d6-DMSO) δ 1.43-1.48 (m, 3H), 1.98 (t, <i>J</i> =6.0Hz, 2H), 2.86 (t, <i>J</i> =6.0Hz, 2H), 2.99 (t, <i>J</i> =6.0Hz, 2H), 4.22-4.27 (m, 2H), 7.13 (t, <i>J</i> =7.8Hz, 1H), 7.25 (d, <i>J</i> =7.8Hz, 1H), 7.56-8.00 (m, 1H), 7.90 (d, <i>J</i> =4.8Hz, 2H), 8.41 (d, <i>J</i> =7.8Hz, 1H), 8.68 (d, <i>J</i> =4.8Hz, 1H).	<i>m/z</i> 310.16
5		¹ H NMR (600MHz, d6-DMSO) δ 1.35 (t, <i>J</i> =6.6Hz, 3H), 1.96 (t, <i>J</i> =6.0Hz, 2H), 2.94-3.02 (m, 4H), 4.10 (q, <i>J</i> =14.4, 6.6Hz, 2H), 7.18 (dd, <i>J</i> =8.4, 2.4Hz, 1H), 7.43-7.46	<i>m/z</i> 310.16

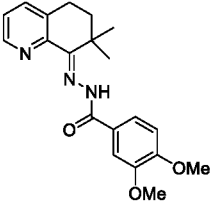
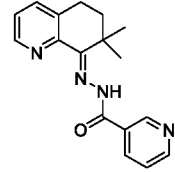
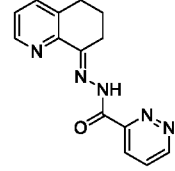
		(m, 2H), 7.51 (d, $J=8.4\text{Hz}$, 1H), 7.26 (dd, $J=6.6$, 1.2Hz, 1H), 8.44 (d, $J=8.4\text{Hz}$, 1H), 8.69 (d, $J=4.8\text{Hz}$, 1H), 11.37 (s, 1H).	
6		^1H NMR (600MHz, d6-DMSO) δ 1.91-1.95 (m, 2H), 2.76 (t, $J=6.0\text{Hz}$, 2H), 2.92 (t, $J=6.0\text{Hz}$, 2H), 3.84 (s, 3H), 7.19 (dd, $J=7.8$, 1.8Hz, 1H), 7.40 (s, 1H), 7.46 (d, $J=7.2\text{Hz}$, 1H), 7.48-7.54 (m, 2H), 7.91 (d, $J=6.0\text{Hz}$, 1H), 8.68 (s, 1H).	m/z 296.14
7		^1H NMR (600MHz, d6-DMSO) δ 1.95 (t, $J=6.0\text{Hz}$, 2H), 2.93-3.01 (m, 4H), 3.84 (s, 3H), 3.86 (s, 3H), 7.09 (d, $J=8.4\text{Hz}$, 1H), 7.51 (s, 1H), 7.61 (dd, $J=8.4$, 1.8Hz, 1H), 7.91 (d, $J=6.6\text{Hz}$, 1H), 8.42 (d, $J=6.6\text{Hz}$, 1H), 8.60 (s, 1H), 11.20 (br s, 1H).	m/z 326.1498
8		^1H NMR (600MHz, d6-DMSO) δ 1.98 (t, $J=6.0\text{Hz}$, 2H), 2.85 (t, $J=6.0\text{Hz}$, 2H), 2.99 (t, $J=6.0\text{Hz}$, 2H), 3.91 (s, 3H), 7.13 (t, $J=7.8\text{Hz}$, 1H), 7.26 (d, $J=7.8\text{Hz}$, 1H), 7.60 (t, $J=7.8\text{Hz}$, 1H), 7.85 (s, 1H), 7.91-7.94 (m, 1H), 8.15 (d, $J=7.8\text{Hz}$, 1H), 8.65 (s, 1H), 11.36 (s, 1H).	m/z 296.14

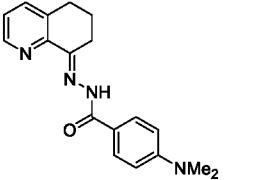
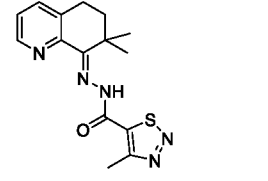
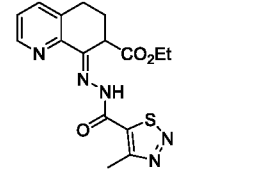
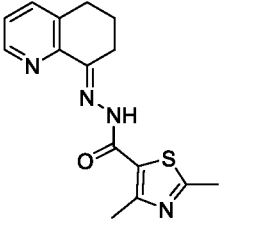
9		¹ H NMR (600MHz, d6-DMSO) δ 1.95 (t, $J=6.6$ Hz, 2H), 2.75 (s, 2H), 2.92 (t, $J=6.6$ Hz, 1H), 3.84 (s, 3H), 7.12 (t, $J=7.8$ Hz, 2H), 7.52 (dd, $J=7.8, 3.6$ Hz, 1H), 7.85-7.91 (m, 3H), 8.74 (d, $J=3.6$ Hz, 1H)	m/z 296.14
10		¹ H NMR (600MHz, d6-DMSO) δ 1.95 (t, $J=5.4$ Hz, 2H), 2.75-2.80 (m, 2H), 2.92 (t, $J=5.4$ Hz, 2H), 7.48-7.52 (m, 1H), 7.57-7.62 (m, 3H), 7.82-7.88 (m, 3H), 8.72 (d, $J=3.0$ Hz, 1H).	m/z 266.13
11		¹ H NMR (600MHz, d6-DMSO) δ 1.99 (t, $J=6.0$ Hz, 2H), 2.79-2.84 (m, 2H), 2.98 (t, $J=6.0$ Hz, 2H), 7.13 (d, $J=7.2$ Hz, 1H), 7.51 (dd, $J=8.4, 2.4$ Hz, 1H), 7.87-7.92 (m, 2H), 8.37 (br s, 1H) 8.68 (s, 1H), 11.65 (br s, 1H), 12.28 (br s, 1H).	m/z 316.08
12		¹ H NMR (600MHz, d6-DMSO) δ 1.95 (m, 2H), 2.82 (br s, 2H), 2.89 (s, 2H), 6.98 (s, 1H), 7.05 (s, 1H), 7.42 (d, $J=7.2$ Hz, 1H), 7.54 (dd, $J=7.8, 4.8$ Hz, 1H), 7.93 (d, $J=7.2$ Hz, 1H), 7.99 (dd, $J=7.8$ Hz, 1.8Hz, 1H), 8.59 (d, $J=3.6$ Hz, 1H), 11.56 (br s, 1H), 11.85 (br s, 1H).	m/z 282.12
13		¹ H NMR (600MHz, d6-DMSO) δ 1.96 (t, $J=6.0$ Hz, 2H), 2.40 (s, 3H), 2.96-3.02 (m, 4H), 7.41-7.46	m/z 280.14

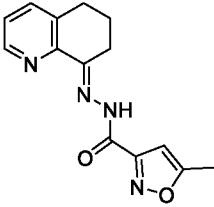
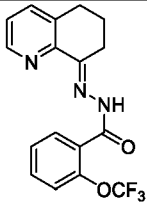
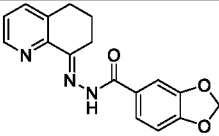
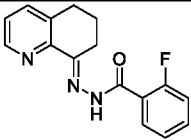
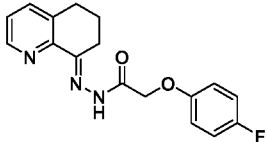
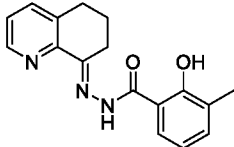
		(m 2H), 7.72-7.77 (m, 2H), 7.94 (dd, $J=7.8, 5.4$ Hz, 1H), 8.46 (d, $J=7.8$ Hz, 1H), 8.69 (d, $J=5.4$ Hz, 1H), 11.40 (s, 1H).	
14		^1H NMR (600MHz, d6-DMSO) δ 1.96 (t, $J=6.0$ Hz, 2H), 2.30 (s, 3H), 2.32 (s, 3H), 2.94-3.01 (m, 4H), 7.30 (d, $J=7.8$ Hz, 1H), 7.68 (d, $J=7.8$ Hz, 1H), 7.74 (s, 1H), 7.92 (t, $J=6.6$ Hz, 1H), 8.44 (d, $J=6.6$ Hz, 1H), 8.68 (d, $J=4.8$ Hz, 1H).	m/z 294.1600
15		^1H NMR (600MHz, d6-DMSO) some peaks not well resolved δ 1.93 (t, $J=6.0$ Hz, 2H), 2.82 (t, $J=6.0$ Hz, 2H), 2.97 (t, $J=6.0$ Hz, 2H), 7.45 (t, $J=7.8$ Hz, 1H), 7.58 (t, $J=7.8$ Hz, 1H), 7.87-7.93 (m, 1H), 7.97-8.02 (m, 2H), 8.39-8.44 (m, 1H), 8.66 (s, 1H), 11.61 (s, 1H)	m/z 300.09
16		^1H NMR (600MHz, d6-DMSO) δ 1.96 (t, $J=6.0$ Hz, 2H), 2.77 (t, $J=6.0$ Hz, 2H), 2.95 (t, $J=6.0$ Hz, 2H), 7.54 (dd, $J=7.8$ Hz, 4.8Hz, 1H), 7.64 (t, $J=7.8$ Hz, 1H), 7.71 (d, $J=7.8$ Hz, 1H), 7.84 (d, $J=7.8$ Hz, 1H), 7.88 (s, 1H), 7.93 (d, $J=7.8$ Hz, 1H), 8.70 (d, $J=4.8$ Hz, 1H).	m/z 300.09

17		¹ H NMR (600MHz, d6-DMSO) δ 1.90 (t, $J=6.0$ Hz, 2H), 2.76-3.01 (m, 4H), 4.00 (s, 3H), 7.28 (d, $J=7.8$ Hz, 1H), 7.30-7.35 (m, 1H), 7.60-7.66 (m, 2H), 7.85 (d, $J=7.8$ Hz, 1H), 8.53 (t, $J=4.2$ Hz, 1H), 10.92 (s, 1H)	m/z 330.10
18		¹ H NMR (600MHz, d6-DMSO) δ 1.91 (t, $J=6.0$ Hz, 2H), 2.34 (s, 3H), 2.94 (t, $J=6.0$ Hz, 2H), 2.95 (s, 2H), 7.27-7.32 (m, 2H), 7.39-7.46 (m, 2H), 7.87 (br s, 1H), 8.34 (s, 1H), 8.63 (s, 1H), 11.41 (s, 1H).	m/z 280.15
19		¹ H NMR (600MHz, d6-DMSO) δ 2.03 (t, $J=6.0$ Hz, 2H), 2.50 (s, 3H), 3.05-3.11 (m, 4H), 7.45 (d, $J=7.8$ Hz, 2H), 7.96 (d, $J=7.8$ Hz, 2H), 8.54 (d, $J=7.8$ Hz, 1H), 8.03 (d, $J=6.0$ Hz, 1H), 8.79 (s, 1H), 11.4 (s, 1H).	m/z 280.15
20		¹ H NMR (600MHz, d6-DMSO) δ 1.95-1.98 (m, 2H), 2.96-3.01 (m, 4H), 7.88-7.93 (m, 3H), 8.10-8.14 (m, 2H), 8.40-8.43 (m, 1H), 8.69 (d, $J=4.8$ Hz, 1H), 11.61 (s, 1H).	m/z 334.12
21		¹ H NMR (600MHz, d6-DMSO) δ 1.96 (t, $J=6.0$ Hz, 2H), 2.76 (t, $J=6.0$ Hz, 2H), 2.93 (t, $J=6.0$ Hz, 2H), 3.86 (s, 3H), 6.94 (d, $J=7.8$ Hz, 1H), 7.37-7.43 (m, 2H),	m/z 312.13

		7.51 (dd, $J=7.8, 4.8\text{Hz}$, 1H), (d, $J=7.8\text{Hz}$, 1H), 8.71 (d, $J=4.8\text{Hz}$, 1H), 9.89 (br s, 1H).	
22		^1H NMR (600MHz, d6-DMSO) δ 1.92-1.99(m, 2H), 2.56 (s, 3H), 2.74-2.79 (m, 2H), 2.88-2.94 (m, 2H), 7.46 (d, $J=7.8\text{Hz}$, 1H), 7.52 (dd, $J=6.6, 4.2\text{Hz}$, 1H), 7.91 (d, $J=7.2\text{Hz}$, 1H), 8.12 (d, $J=7.2\text{Hz}$, 1H), 8.72 (s, 1H), 8.93 (s, 1H)	m/z 281.1392
23		^1H NMR (600MHz, d6-DMSO) δ 1.87 (t, $J=6.0\text{Hz}$, 2H), 2.80-2.84 (m, 4H), 2.97 (s, 3H), 7.36 (dd, $J=7.2, 4.8\text{Hz}$, 1H), 7.66 (d, $J=7.2\text{Hz}$, 1H), 8.68 (d, $J=4.8\text{Hz}$, 1H), 11.62 (s, 1H).	m/z 288.0913
24		^1H NMR (600MHz, d6-DMSO) δ 1.96 (t, $J=6.0\text{Hz}$, 2H), 2.92-2.99 (m, 4H), 7.42-7.58 (m, 2H), 7.72-7.80 (m, 1H), 8.00-8.06 (m, 2H), 8.15-8.26 (m, 1H), 8.51-8.62 (m, 1H), 8.69 (s, 1H), 11.48 (br s, 1H).	m/z 322.1009
25		^1H NMR (600MHz, d6-DMSO) δ 1.97 (quintet, $J=6.0\text{Hz}$, 2H), 2.94-2.99 (m, 4H), 5.32 (s, 2H), 6.97-7.02 (m, 2H), 8.07 (s, 1H), 7.84-7.88 (m, 1H), 7.25 (d, $J=7.2\text{Hz}$, 1H), 7.45 (d, $J=7.2\text{Hz}$, 1H), 8.36 (s, 1H), 8.73 (d, $J=4.8\text{Hz}$, 1H), 11.43 (s, 1H).	m/z 376.11

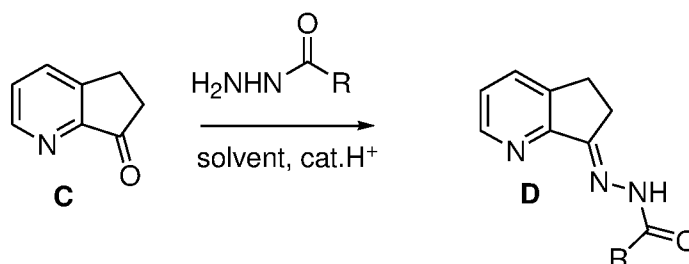
26		¹ H NMR (500MHz, d6-DMSO) δ 1.24 (s, 6H), 1.93 (t, $J=6.5$ Hz, 2H), 2.95 (t, $J=6.5$ Hz, 2H), 3.84 (s, 3H), 3.86 (s, 3H), 7.14 (d, $J=8.5$ Hz, 1H), 7.42 (s, 1H), 7.48-7.52 (m, 2H), 7.90 (d, $J=7.5$ Hz, 1H), 8.71 (d, $J=3.5$ Hz, 1H), 15.98 (s, 1H).	m/z 354.18
27		¹ H NMR (600MHz, d6-DMSO) 3: 1 geometric isomers-major isomer δ 1.25 (s, 6H), 1.84 (t, $J=6.6$ Hz, 2H), 2.96 (t, $J=6.6$ Hz, 2H), 7.52-7.57 (m, 2H), 7.63 (dd, $J=7.8, 4.8$ Hz, 1H), 7.92 (d, $J=7.8$ Hz, 1H), 8.25 (d, $J=7.8$ Hz, 1H), 8.73 (d, $J=3.6$ Hz, 1H), 8.80 (d, $J=4.8$ Hz, 1H), 9.06 (s, 1H), 11.98 (br s, 1H).	m/z 295.1554
28		¹ H NMR (600MHz, d6-DMSO) 1: 1 geometric isomers δ 1.96-2.02 (m, 4H), 2.80 (t, $J=6.0$ Hz, 2H), 2.95 (t, $J=6.0$ Hz, 2H), 2.99-3.05 (m, 4H), 7.52 (dd, $J=7.8, 4.8$ Hz, 1H), 7.90-8.03 (m, 4H), 8.30-8.35 (m, 2H), 8.52 (d, $J=13.8$ Hz, 1H), 8.66 (d, $J=3.0$ Hz, 1H), 8.73 (d, $J=4.8$ Hz, 1H), 9.43-9.46 (m, 1H), 9.51 (d, $J=4.2$ Hz, 1H), 11.32 (br s, 1H).	m/z 268.1196

29		¹ H NMR (600MHz, d6-DMSO) δ 1.93 (t, $J=6.0$ Hz, 2H), 7.72 (t, $J=6.0$ Hz, 2H), 2.89 (t, $J=6.0$ Hz, 2H), 2.91 (s, 3H), 2.93 (s, 3H), 6.79 (d, $J=9.0$ Hz, 1H), 7.48 (d, $J=7.8$ Hz, 1H), 7.74 (d, $J=7.2$ Hz, 2H), 7.86 (d, $J=7.2$ Hz, 1H), 8.72 (d, 3.6Hz, 1H),	m/z 309.17
30		¹ H NMR (500MHz, d6-DMSO) δ 1.35 (s, 6H), 1.85 (t, $J=6.0$ Hz, 2H), 2.96 (t, $J=6.0$ Hz, 2H), 3.31 (s, 3H), 7.57 (dd, $J=8.0, 4.5$ Hz, 1H), 7.93 (d, $J=6.5$ Hz, 1H), 8.50 (d, $J=4.5$ Hz, 1H), 15.62 (s, 1H)	m/z 316.12
31		¹ H NMR (600MHz, d6-DMSO) δ 1.12 (t, $J=7.2$ Hz, 3H), 2.22-2.26 (m, 1H), 2.34-2.38 (m, 2H), 2.84-2.97 (m, 2H), 2.96 (s, 3H), 4.04 (t, $J=6.0$ Hz, 1H), 4.15 (q, $J=7.2, 1.8$ Hz, 2H), 7.56 (dd, $J=7.2, 4.2$ Hz, 1H), 7.93 (d, $J=7.2$ Hz, 1H), 8.73 (d, $J=4.2$ Hz, 1H).	m/z 360.1123
32		¹ H NMR (600MHz, d6-DMSO) δ 1.91-1.97 (m, 2H), 2.61 (s, 3H), 2.66 (s, 3H), 2.88 (t, $J=7.8$ Hz, 2H), 2.98 (t, $J=7.8$ Hz, 2H) 7.95 (app t, $J=7.2$ Hz, 1H), 8.47 (d, $J=9.6$ Hz, 1H), 8.73 (d, $J=7.2$ Hz, 1H), 11.54 (br s, 1H).	m/z 301.1119

33		¹ H NMR (600MHz, d6-DMSO) δ 1.94 (t, $J=6.0$ Hz, 2H), 2.51 (s, 3H), 2.92 (t, $J=6.0$ Hz, 2H), 2.99 (t, $J=6.0$ Hz, 2H), 6.75 (s, 1H), 7.92 (s, 1H), 8.41 (s, 1H), 8.69 (d, $J=4.8$ Hz, 1H), 11.58 (br s, 1H).	m/z 271.1186
156		¹ H NMR (500MHz, d6-DMSO) δ 1.93 (t, $J=5.5$ Hz, 2H), 2.84 (t, $J=5.5$ Hz, 2H), 2.95-2.99 (m, 2H), 7.52-7.56 (m, 2H), 7.67-7.74 (m, 2H), 7.92 (s, 1H), 8.42 (d, $J=6.0$ Hz, 1H), 8.68 (s, 1H), 11.63 (s, 1H)	m/z 350.1113
157			m/z 310.1187
158			m/z 284.1193
159			m/z 314.1301
180		¹ H NMR (400MHz, d6-DMSO) δ 1.98 (t, $J=6.0$ Hz, 2H), 2.48 (s, 3H), 2.78 (t, $J=6.0$ Hz, 2H), 2.94 (t, $J=6.0$ Hz, 2H), 6.95 (t, $J=7.2$ Hz, 1H), 7.39 (d, $J=7.2$ Hz, 1H), 7.54-7.58 (m, 2H), 7.94 (d, $J=7.2$ Hz, 1H), 8.80 (d, $J=4.4$ Hz, 1H).	m/z 296.1392

Similarly, fused cyclopentane derivatives **D** could be synthesised according to **Scheme 2**.

Scheme 2



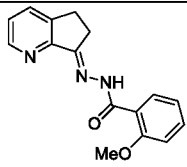
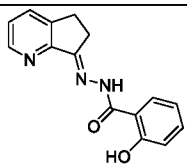
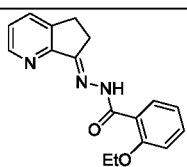
Example 2 (Table 2)

(*E*)-*N'*-(5*H*-Cyclopenta[*b*]pyridin-7(6*H*)-ylidene)-3,4-dimethoxybenzohydrazide (38**)**

To a solution of 5*H*-cyclopenta[*b*]pyridin-7(6*H*)-one (40 mg, 0.30 mmol) in MeOH (8 mL) was added 3,4-dimethoxybenzhydrazide (59 mg, 1 mol eq), followed by one drop of concentrated hydrochloric acid. The reaction was stirred overnight. An off-white solid was collected by filtration to afford the desired (*E*)-*N'*-(5*H*-cyclopenta[*b*]pyridin-7(6*H*)-ylidene)-3,4-dimethoxybenzohydrazide **38** (30 mg). ¹H NMR (600MHz, d6-DMSO) δ 2.95(t, *J*=6.0Hz, 2H), 3.11-3.16 (m, 2H), 3.84 (s, 3H), 3.87 (s, 3H), 7.14 (d, *J*=8.4Hz, 1H), 7.46 (s, 1H), 7.52 (dd, *J*=7.8, 4.8Hz, 2H), 8.02 (d, *J*=7.2Hz, 1H), 8.68 (d, *J*=4.8Hz, 1H). MS *m/z* 312.13[M+H]⁺.

Table 2: Selected data for compounds synthesised by Scheme 2.

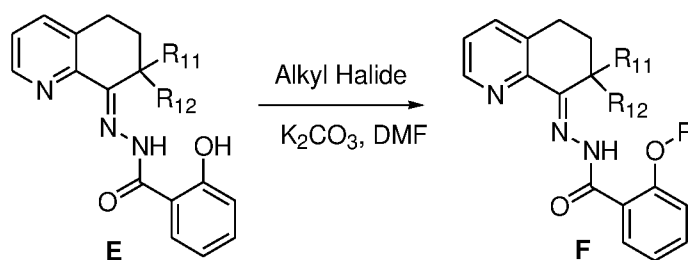
Compound	Structure	Spectral Data
34		¹ H NMR (500MHz, d6-DMSO) δ 2.93-2.96 (m, 2H), 3.15 (t, <i>J</i> =6.0Hz, 2H), 7.52 (dd, <i>J</i> =7.8, 4.8Hz, 1H), 7.56-7.60 (m, 4H), 7.61-7.65 (m, 1H), 7.92 (d, <i>J</i> =7.2Hz, 1H), 8.02 (d, <i>J</i> =7.2Hz, 1H). <i>m/z</i> 252.11 [M+H] ⁺

35		¹ H NMR (600MHz, d6-DMSO) δ 2.92-2.95 (m, 2H), 3.11 (t, <i>J</i> =6.0Hz, 2H), 4.02 (s, 3H), 7.12 (d, <i>J</i> =7.2Hz, 1H), 7.24 (d, <i>J</i> =7.8Hz, 1H), 7.35 (dd, <i>J</i> =7.8, 4.8 Hz, 1H), 7.54-7.58 (m, 1H), 7.84 (d, <i>J</i> =7.8Hz, 1H), 7.93 (dd, <i>J</i> =7.8, 1.2 Hz, 1H), 8.56 (d, <i>J</i> =4.8Hz, 1H).
36		¹ H NMR (600MHz, d6-DMSO) δ 2.92-2.95 (m, 2H), 3.16 (t, <i>J</i> =6.0Hz, 2H), 6.97 (t, <i>J</i> =7.8Hz, 1H), 7.05 (d, <i>J</i> =7.8Hz, 1H), 7.23 (s, 1H), 7.42 (d, <i>J</i> =6.6Hz, 1H), 7.55 (s, 1H), 7.97 (d, <i>J</i> =7.8Hz, 1H), 8.07 (d, <i>J</i> =6.6Hz, 1H), 8.62 (d, <i>J</i> =4.8Hz, 1H), 11.25 (s, 1H), 11.78 (s, 1H).
37		¹ H NMR (600MHz, d6-DMSO) δ 1.49 (t, <i>J</i> =7.2Hz, 3H), 2.92(t, <i>J</i> =6.0Hz, 2H), 3.12 (t, <i>J</i> =6.0Hz, 2H), 4.28 (q, <i>J</i> =7.2Hz, 2H), 7.11 (t, <i>J</i> =7.8Hz, 1H), 7.23 (d, <i>J</i> =7.8Hz, 1H), 7.35 (dd, <i>J</i> =7.8, 4.8Hz, 1H), 7.54 (t, <i>J</i> =7.2Hz, 1H), 7.83 (d, <i>J</i> =7.2Hz, 1H), 7.98 (dd, <i>J</i> =7.8, 1.2Hz, 1H), 8.56 (d, <i>J</i> =4.8Hz, 1H). <i>m/z</i> 296.14 [M+H] ⁺ .

The following 2-*O*-phenol substituted benzohydrazide derivatives were synthesised according to Scheme 3. Phenol intermediate **E**, synthesised using the procedure outlined in Scheme 1, was allowed to react with an alkyl halide in the presence of

5 potassium carbonate to provide the required alkyl amino substituted ethers **F**.

Scheme 3

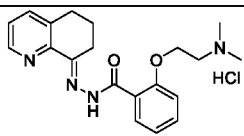
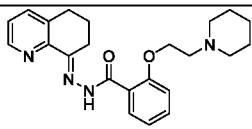
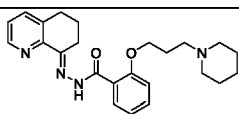


Example 3:

(*E*)-*N'*-(6,7-Dihydroquinolin-8(*5H*)-ylidene)-2-(2-(pyrrolidin-1-yl)ethoxy)benzohydrazide hydrochloride (41**).**

To a suspension of the (*E*)-*N'*-(6,7-dihydroquinolin-8(*5H*)-ylidene)-2-hydroxybenzohydrazide **12** (149 mg, 0.530 mmol) in dry DMF (10 mL) was added K₂CO₃ (246 mg, 1.78 mmol) and the chloroethylpyrrolidine hydrochloride (95 mg, 0.55 mmol). The reaction was heated to 45°C for 2 days, then cooled to rt. The reaction was extracted into EtOAc (x3). Combined organic layers were washed with H₂O, brine, dried over Na₂SO₄, filtered and concentrated to afford a gummy brown solid. The residue was taken up in MeOH (7 mL) and treated with concentrated hydrochloric acid (0.3 mL). Solvent was removed *in vacuo*, the flask was cooled to rt, then ACN (5 mL) was added slowly. The flask was triturated and sonicated to provide (*E*)-*N'*-(6,7-dihydroquinolin-8(*5H*)-ylidene)-2-(2-(pyrrolidin-1-yl)ethoxy)benzohydrazide hydrochloride **41** as a fawn colored solid that was collected by filtration and dried at the pump. Yield 114 mg. ¹H NMR (500 MHz, d₆-DMSO) δ 1.85-1.92 (m, 2H), 1.94-1.99 (m, 4H), 2.95 (t, *J*=6.0 Hz, 2H), 2.99-3.07 (m, 4H), 3.54-3.62 (m, 4H), 4.22-4.26 (m, 2H), 7.16 (t, *J*=7.8 Hz, 1H), 7.24 (d, *J*=7.8 Hz, 1H), 7.58 (t, *J*=7.2 Hz, 1H), 7.83 (s, 1H), 7.89 (s, 1H), 8.41 (br s, 1H), 8.67 (br s, 1H), 11.37 (s, 1H), 11.45 (br s, 1H). MS *m/z* 379.21 [M+H]⁺.

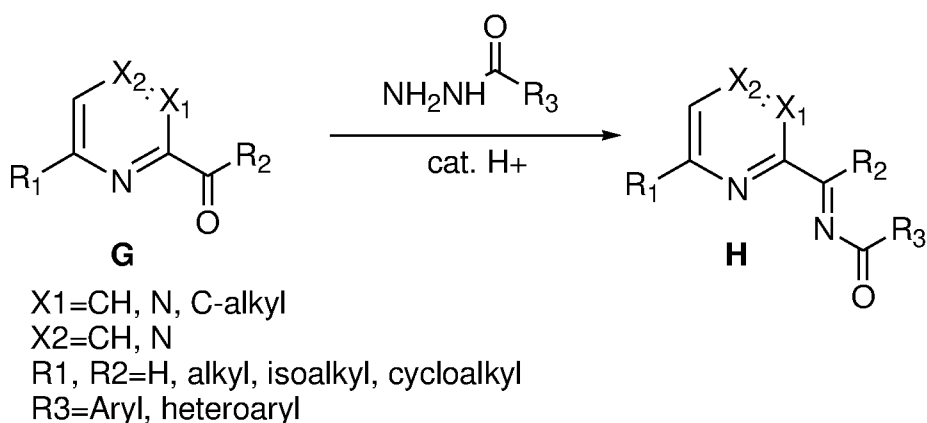
Table 3: Selected data for compounds according to Scheme 3

Compound	Structure	NMR Data	Mass Spec [M+H] ⁺
39		¹ H NMR (600MHz, d6-DMSO) δ 1.97 (t, <i>J</i> =6.0Hz, 2H), 2.80 (s, 3H), 2.81 (s, 3H), 2.89 (t, <i>J</i> =6.0Hz, 2H), 3.00 (t, <i>J</i> =6.0Hz, 2H), 4.55 (s, 2H), 7.14 (t, <i>J</i> =7.8Hz, 1H), 7.26 (<i>J</i> =8.4Hz, 1H), 7.57 (t, <i>J</i> =7.2Hz, 1H), 7.63 (d, <i>J</i> =7.2Hz, 1H), 7.96 (t, <i>J</i> =7.2Hz, 1H), 8.49 (d, <i>J</i> =7.2Hz, 1H), 8.71(d, <i>J</i> =4.2Hz, 1H), 11.20 (br s, 1H), 11.42 (s, 1H).	<i>m/z</i> 353.20
40		¹ H NMR (600MHz, d6-DMSO) δ 1.29-1.35(m, 2H), 1.40-1.45 (m, 4H), 1.89 (t, <i>J</i> =6.0Hz, 2H), 2.63-2.70 (m, 4H), 2.73 (t, <i>J</i> =6.0Hz, 2H), 2.78-2.84 (m, 4H), 4.34(t, <i>J</i> =6.0Hz, 2H), 7.12 (t, <i>J</i> =7.8Hz, 1H), 7.28 (d, <i>J</i> =7.8Hz, 1H), 7.30-7.33 (m, 1H), 7.53 (t, <i>J</i> =8.4Hz, 1H), 7.64 (d, <i>J</i> =6.6Hz, 1H), 7.99 (d, <i>J</i> =6.6Hz, 1H), 8.52 (d, <i>J</i> =3.0Hz, 1H), 10.94 (s, 1H).	<i>m/z</i> 393.10
42		¹ H NMR (600MHz, d6-DMSO) δ 1.28-1.35 (m, 2H), 1.38-1.43 (m, 4H), 1.88 (t, <i>J</i> =6.0Hz, 2H), 1.97 (t, <i>J</i> =6.0Hz, 2H), 2.23-2.28 (m, 4H), 2.36 (t, <i>J</i> =6.6Hz, 2H), 2.70-2.78 (m, 4H), 4.23 (t, <i>J</i> =6.6Hz, 2H),	<i>m/z</i> 407.24

		7.09 (t, $J=7.2\text{Hz}$, 1H), 7.92 (d, $J=7.2\text{Hz}$, 1H), 7.20 (d, $J=8.4\text{Hz}$, 1H), 7.29 (dd, $J=7.8$, 4.8Hz , 1H), 7.52 (t, $J=7.2\text{Hz}$, 1H), 7.62 (d, $J=7.2\text{Hz}$, 1H), 8.50 (d, $J=3.6\text{Hz}$, 1H), 10.83 (s, 1H).	
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- A range of acyl hydrazones can be prepared by the synthetic route depicted in Scheme 4. Heating an equimolar mixture of the 6-membered heterocyclic ketone **G** and the acylhydrazide in ethanol or other suitable solvent in the presence a catalytic amount of acid, furnished target acyl hydrazone compounds **H** (see table 4). The ketone starting materials were available from commercial suppliers or known literature methods.

Scheme 4



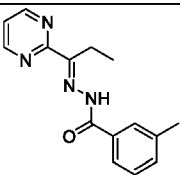
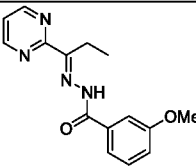
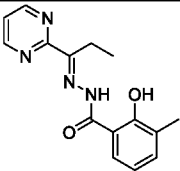
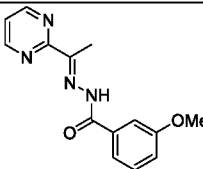
Example 4

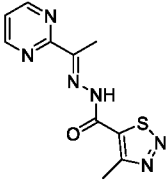
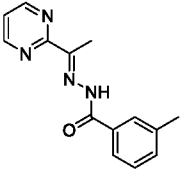
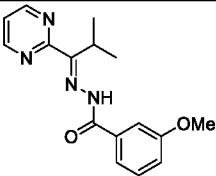
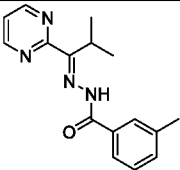
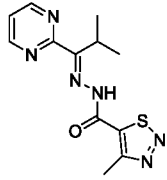
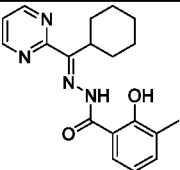
- (E)-4-Methyl-N'-(1-(pyrimidin-2-yl)propylidene)-1,2,3-thiadiazole-5-carbohydrazide (43).**

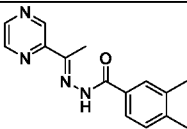
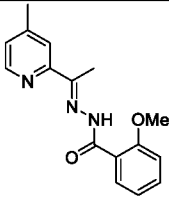
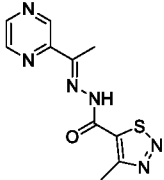
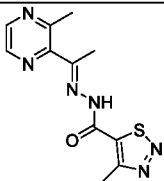
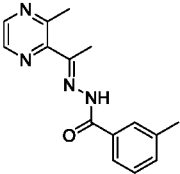
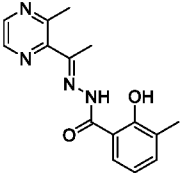
- (Pyrimidin-2-yl)propan-1-one (114 mg) was heated together with 4-methyl-1,2,3-thiadiazole-5-carbohydrazide (132 mg) in EtOH (10 mL) in the presence of concentrated hydrochloric acid (one drop) to 60°C for 30 min. The reaction was cooled to rt, then an off-white solid was collected by filtration. The crude product was further washed with ACN (x2) to generate (E)-4-methyl-N'-(1-(pyrimidin-2-yl)propylidene)-

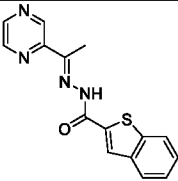
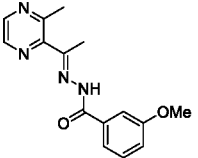
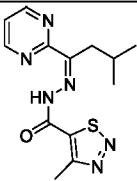
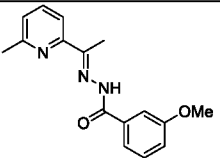
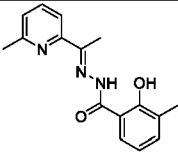
1,2,3-thiadiazole-5-carbohydrazide **43** (60 mg) as a white powder. ^1H NMR (600MHz, $\text{d}_6\text{-DMSO}$) δ 1.07 (t, $J=7.2\text{Hz}$, 3H), 2.97 (s, 3H), 3.06 (q, $J=7.2\text{Hz}$, 2H), 7.57 (t, $J=6.6\text{Hz}$, 1H), 9.01 (d, $J=6.6\text{Hz}$, 2H), 11.96 (s, 1H). MS m/z 277.0865 $[\text{M}+\text{H}]^+$.

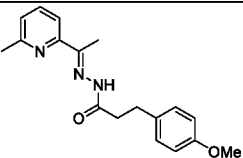
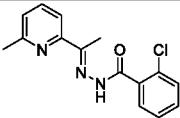
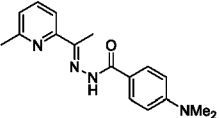
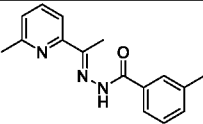
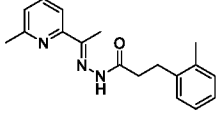
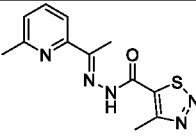
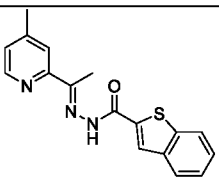
Table 4: MS Data for Compounds synthesised via Scheme 4

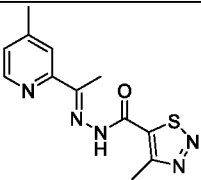
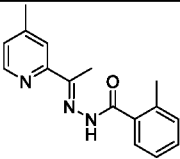
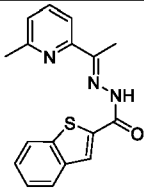
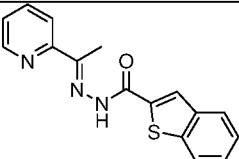
Compound	Structure	Mass Spectrometry $[\text{M}+\text{H}]^+$
44		m/z 269.1397
45		m/z 285.1347
46		m/z 285.1345
47		m/z 271.12

48		m/z 263.07
49		m/z 255.12
50		m/z 299.15
51		m/z 283.15
52		m/z 291.10
53		m/z 306.1399

54		m/z 269.1400
55		m/z 284.1393
56		m/z 276.0193
57		m/z 277.0856
58		m/z 269.1396
59		m/z 285.1354

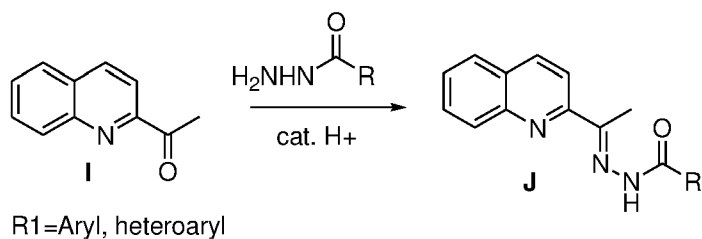
60		m/z 297.0804
61		m/z 285.1344
62		m/z 305.1229
63		m/z 330.1435
64		m/z 284.1963
65		m/z 284.2141

66		m/z 312.2221
67		m/z 288.1760
68		m/z 297.2482
69		m/z 268.1961
70		m/z 296.1758
71		m/z 276.0914
72		m/z 310.0966

73		m/z 276.0913
74		m/z 268.1445
75		m/z 310.1210
197		m/z 296.0460

A range of substituted quinoline acyl hydrazones can be prepared by the synthetic route depicted in Scheme 5. Heating an equimolar mixture of acetyl quinoline **I** and substituted acylhydrazide in ethanol or other suitable solvent with a catalytic amount of acid, provided the target compounds **J**.

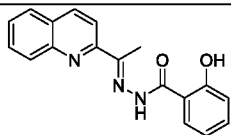
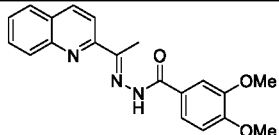
Scheme 5

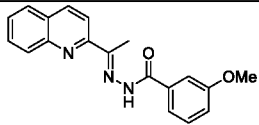
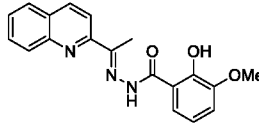
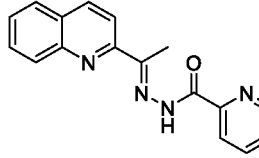


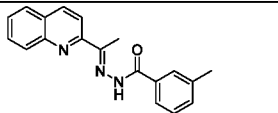
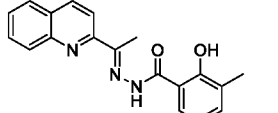
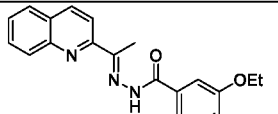
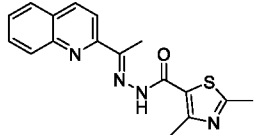
Example 5**(*E*)-*N'*-(1-(Quinolin-2-yl)ethylidene)picolinohydrazide (80).**

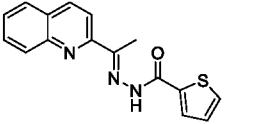
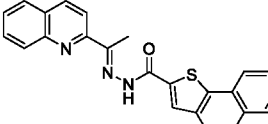
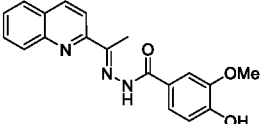
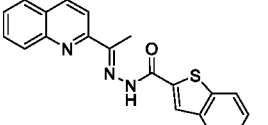
2-Acetylquinoline (162 mg), pyridine-2-carboxylic acid hydrazide (113 mg) were heated together in EtOH (7 mL) at 60°C. One drop of concentrated hydrochloric acid was added and the reaction was stirred for 15 min at which time a precipitate formed. The reaction was cooled and the precipitate was collected by filtration to afford (*E*)-*N'*-(1-(quinolin-2-yl)ethylidene)picolinohydrazide **80** as an off-white powder (50 mg). ¹H NMR (600MHz, d6-DMSO) δ 2.64 (s, 3H), 7.62-7.65 (m, 1H), 7.74-7.77 (m, 1H), 7.80 (t, *J*=8.4Hz, 1H), 8.02 (d, *J*=7.2Hz, 1H), 8.07-8.11 (m, 2H), 8.19 (d, *J*=7.2Hz, 1H), 8.33 (d, *J*=9.0Hz, 1H), 8.43 (d, *J*=9.0Hz, 1H), 8.76 (d, *J*=3.6 Hz, 1H), 11.26 (s, 1H). MS *m/z* 291.1321 [M+H]⁺.

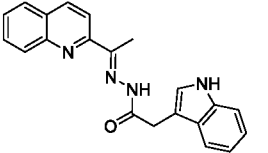
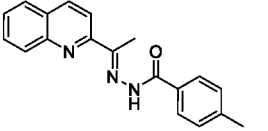
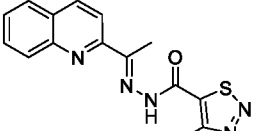
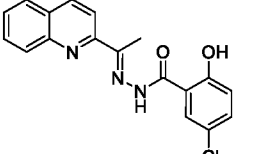
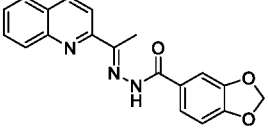
Table 5: Selected data for compounds synthesised according to Scheme 5

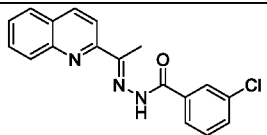
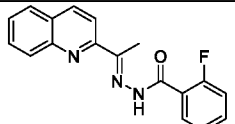
Compound	Structure	NMR	Mass Spec[M+H] ⁺
76		¹ H NMR (600MHz, d6-DMSO) δ 2.56 (s, 3H), 7.00 (t, <i>J</i> =7.2Hz, 1H), 7.11 (d, <i>J</i> = 7.2Hz, 1H), 7.44 (d, <i>J</i> =7.2Hz, 1H) 7.64 (t, <i>J</i> = 7.2Hz, 1H), 7.81 (t, <i>J</i> =7.2 Hz, 1H), 8.02 (d, <i>J</i> =7.8 Hz, 2H), 8.09 (d, <i>J</i> = 8.4Hz, 1H), 8.32 (d, <i>J</i> =8.4Hz, 1H), 8.45 (d, <i>J</i> =8.4Hz, 1H), 11.61 (s, 1H).	<i>m/z</i> 306.1399
77		¹ H NMR (600MHz, d6-DMSO) some peaks are not well resolved δ 2.61 (s, 3H), 3.83 (s, 3H), 3.84 (s, 3H), 7.09 (d, <i>J</i> =8.4Hz, 1H), 7.49 (s, 1H), 7.58 (d, <i>J</i> =7.2Hz,	<i>m/z</i> 350.1635

		1H), 7.61-7.65 (m, 1H), 7.80 (t, $J=7.8\text{Hz}$, 1H), 8.01 (d, $J=7.8\text{Hz}$, 1H), 8.08 (d, $J=8.4\text{Hz}$, 1H), 8.24 (s, 1H), 8.39-8.43 (m, 1H), 10.82 (br s, 1H).	
78		^1H NMR (600MHz, d6-DMSO) δ 2.60 (s, 3H), 3.86 (s, 3H), 7.18 (t, $J=8.4\text{Hz}$, 1H), 7.40-7.49 (m, 3H), 7.64 (t, $J=9.0\text{Hz}$, 1H), 7.80 (t, $J=9.0\text{Hz}$, 1H), 8.00 (d, $J=9.6\text{Hz}$, 1H), 8.09 (d, $J=9.6\text{ Hz}$, 1H), 8.24-8.38 (m, 1H), 8.42 (br s, 1H), 11.00 (s, 1H).	m/z 320.1475
79		^1H NMR (500MHz, d6-DMSO) δ 2.51 (s, 3H), 3.67 (s, 3H), 6.11 (t, $J=8.1\text{Hz}$, 2H), 6.64 (d, $J=7.5\text{Hz}$, 1H), 7.38 (d, $J=8.1\text{ Hz}$, 1H), 7.57 (t, $J=8.4\text{Hz}$, 1H), 7.74 (t, $J=8.4\text{ Hz}$, 1H), 7.95 (d, $J=8.1\text{ Hz}$, 1H), 8.02 (d, $J=8.4\text{ Hz}$, 1H), 8.32 (s, 2H)	m/z 336.1578
80		^1H NMR (600MHz, d6-DMSO) δ 2.64 (s, 3H), 7.62-7.65 (m, 1H), 7.74-7.77 (m, 1H), 7.80 (t, $J=8.4\text{Hz}$, 1H), 8.02 (d, $J=7.2\text{Hz}$, 1H), 8.07-8.11 (m, 2H), 8.19 (d, $J=7.2\text{Hz}$, 1H), 8.33 (d, $J=9.\text{Hz}$, 1H), 8.43 (d, $J=9.0\text{Hz}$, 1H), 8.76 (d, $J=3.6\text{ Hz}$, 1H), 11.26 (s, 1H).	m/z 291.1321

81		¹ H NMR (600MHz, d6-DMSO) δ 2.41 (s, 3H), 2.60 (s, 3H), 7.40-7.44 (m, 2H), 7.62-7.80 (m, 4H), 7.99 (s, 1H), 8.06 (d, <i>J</i> =8.4 Hz, 1H), 8.26-8.34 (m, 1H), 8.40 (s, 1H), 10.98 (br s, 1H).	<i>m/z</i> 304.1445
82		¹ H NMR (600MHz, d6-DMSO) δ 2.24 (s, 3H), 2.63 (s, 3H), 6.91 (t, <i>J</i> =7.2Hz, 1H), 7.38 (d, <i>J</i> =6.6Hz, 1H), 7.65 (t, <i>J</i> =7.2Hz, 1H), 7.81(t, <i>J</i> =7.2Hz, 1H), 7.87 (s, 1H), 8.02 (d, <i>J</i> =7.8Hz, 1H), 8.35 (s, 1H), 8.43 (d, <i>J</i> =7.8Hz, 1H),), 8.81 (d, <i>J</i> =7.8Hz, 1H), 11.39 (s, 1H).	<i>m/z</i> 320.1531
83		¹ H NMR (500MHz, d6-DMSO) δ 1.37 (t, <i>J</i> =7.2Hz, 3H), 2.59 (s, 3H), 4.04 (q, <i>J</i> =7.2Hz, 2H), 7.11-7.16 (m, 1H), 7.38-7.51 (m, 3H), 7.63 (d, <i>J</i> =7.2Hz, 1H), 7.78 (d, <i>J</i> =7.2Hz, 1H), 7.95-8.02 (m, 1H), 8.04-8.09 (m, 1H), 8.17-8.24 (m, 1H), 8.41-8.45 (m, 1H), 11.01 (br s, 1H).	<i>m/z</i> 334.1549
84		¹ H NMR (600MHz, d6-DMSO) δ 2.55 (s, 3H), 2.66 (s, 3H), 2.68 (s, 3H), 7.62-7.65 (m, 1H), 7.77-7.81 (m, 1H), 7.99-8.06 (m, 2H), 8.25 (d, <i>J</i> =8.4Hz, 1H), 8.44 (d, <i>J</i> =8.4Hz, 1H), 11.02 (br s, 1H).	<i>m/z</i> 325.1170

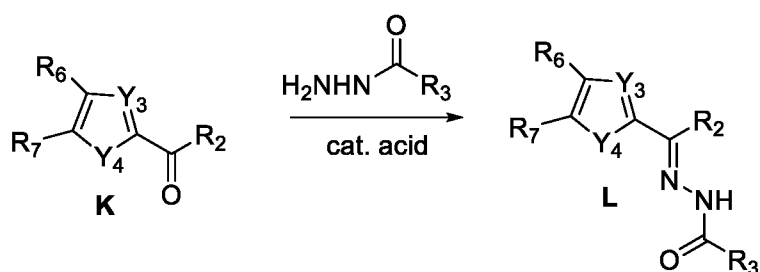
85		¹ H NMR (600MHz, d6-DMSO) δ 2.59 (s, 3H), 7.25 (dd, <i>J</i> =6.6, 4.2Hz, 1H), 7.62-7.65 (m, 1H), 7.77-7.81 (m, 1H), 7.98-8.09 (m, 4H), 8.32-8.36 (m, 1H), 8.41-8.44 (m, 1H), 11.40 (br s, 1H).	<i>m/z</i> 296.0855
86		¹ H NMR (600MHz, d6-DMSO) δ 2.60 (s, 3H), 5.34 (s, 2H), 6.98 (d, <i>J</i> =7.8Hz, 1H), 7.04 (t, <i>J</i> =7.8Hz, 1H), 7.26 (t, <i>J</i> =7.8Hz, 1H), 7.48 (d, <i>J</i> =6.6Hz, 1H), 7.65 (t, <i>J</i> =7.8Hz, 1H), 7.81 (t, <i>J</i> =7.8Hz, 1H), 7.95 (s, 1H), 8.02 (d, <i>J</i> =7.8Hz, 1H), 8.08 (d, <i>J</i> =7.8Hz, 1H), 8.40 (br s, 1H), 8.53 (br s, 1H), 11.22 (br s, 1H).	<i>m/z</i> 400.11
87		¹ H NMR (600MHz, d6-DMSO) δ 2.59 (s, 3H), 3.85 (s, 3H), 6.89 (d, <i>J</i> =7.8Hz, 1H), 7.44-7.48 (m, 2H), 7.64 (d, <i>J</i> =8.4Hz, 1H), 7.89 (d, <i>J</i> =8.4Hz, 1H), 7.99 (d, <i>J</i> =7.2Hz, 1H), 8.06 (d, <i>J</i> =8.4Hz, 1H), 8.22-8.27 (m, 1H), 8.39 (d, <i>J</i> =8.4 Hz, 1H), 10.94 (s, 1H).	<i>m/z</i> 336.1479
88		¹ H NMR (600MHz, d6-DMSO) δ 2.64 (s, 3H), 7.05-7.38 (br m, 2H), 7.44-7.51 (m, 2H), 7.66 (s, 1H), 7.81 (s, 1H), 8.02-8.10 (m, 3H), 8.39-8.47 (m, 2H), 11.37 (br s, 1H).	<i>m/z</i> 346.1009

89		¹ H NMR (600 MHz, d6-DMSO) major regioisomer δ 2.54 (s, 3H), 4.22 (s, 2H), 6.95 (t, <i>J</i> =7.8Hz, 1H), 7.02-7.06 (m, 1H), 7.24 (s, 1H), 7.32-7.36 (m, 1H), 7.58-7.63 (m, 2H), 7.79 (d, <i>J</i> =7.8Hz, 1H), 8.01 (d, <i>J</i> =7.8Hz, 1H), 8.08-8.14 (m, 1H), 8.35 (d, <i>J</i> =7.8Hz, 1H), 8.42 (s, 1H), 10.81 (s, 1H), 10.89 (s, 1H).	<i>m/z</i> 343.1738
90		¹ H NMR (600 MHz, d6-DMSO) δ 2.39 (s, 3H), 2.58 (s, 3H), 7.31- 7.36 (m, 2H), 7.59-7.63 (m, 1H), 7.77-7.91 (m, 3H), 7.95-8.03 (m, 2H), 8.24-8.40 (m, 2H), 10.87 (br s, 1H).	<i>m/z</i> 304.1444
91		¹ H NMR (600 MHz, d6-DMSO) δ 2.61 (s, 3H), 2.99 (s, 3H), 7.67 (d, <i>J</i> =7.2Hz, 1H), 7.81 (s, 1H), 8.02-8.06 (m, 2H), 8.23 (d, <i>J</i> =8.4Hz, 1H), 8.53 (d, <i>J</i> =8.4Hz, 1H), 11.79 (s, 1H).	<i>m/z</i> 312.0914
92			<i>m/z</i> 340.0848
160			<i>m/z</i> 334.1187

161		¹ H NMR (500 MHz, d6-DMSO) δ 2.62 (s, 3H), 7.58 (t, <i>J</i> =8.0Hz, 1H), 7.64 (t, <i>J</i> =7.0Hz 1H), 7.68 (d, <i>J</i> =8.0Hz, 1H), 7.79 (t, <i>J</i> =8.0Hz, 1H), 7.89 (br s, 1H), 7.97 (br s, 1H), 8.00 (br s, 1H), 8.31 (br s, 1H), 8.41 (br s, 1H), 11.08 (s, 1H).	<i>m/z</i> 324.0897
162			<i>m/z</i> 308.1191

A range of fused heterocyclic and heterocyclic substituted acyl hydrazones could be synthesised as outlined in Scheme 6. Starting ketone/aldehyde **K** is defined below in Scheme 6. Heating heterocyclic or fused heterocyclic ketone/aldehyde **K** with an appropriate ketohydrazide in the presence of catalytic acid and a suitable solvent provided the target compounds **L**.

Scheme 6



Y3 is CR8, NR5 or S and

Y4 is CR8 or N, provided both Y3 and Y4 are not CR8.

R6 and R7 taken together with atoms to which they are attached, form a 6 membered aryl or heteroaryl ring.

R2 is selected from hydrogen or alkyl

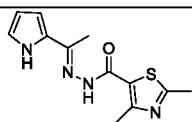
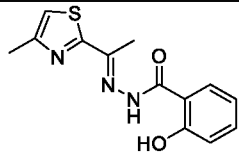
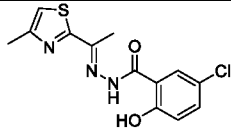
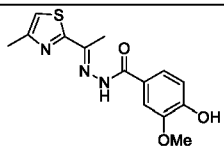
R3 is alkyl, aryl, heteroaryl

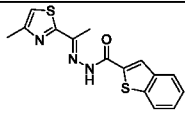
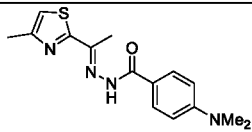
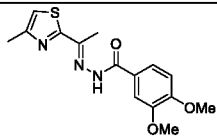
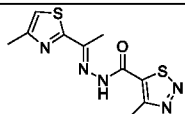
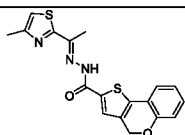
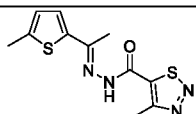
Example 6

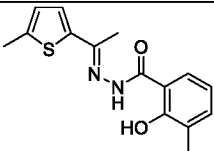
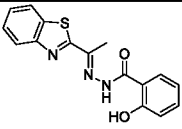
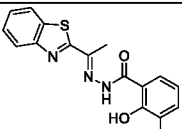
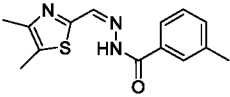
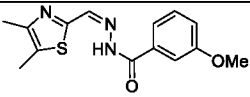
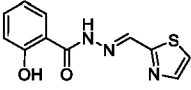
(*E*)-4-Methyl-*N'*-(1-(4-methylthiazol-2-yl)ethylidene)-1,2,3-thiadiazole-5-carbohydrazide (**100**).

- 4-Methyl-2-acetylthiazole (76 mg) was heated together with 4-methyl-1,2,3-thiadiazole-5-carbohydrazide (81mg) in EtOH (7 mL) at 65°C. Concentrated hydrochloric acid (2 drops) were added and the reaction was heated for 1.5 h. After cooling to rt, a pale yellow solid precipitated out of solution and was collected by
- 5 filtration to afford **100** (124mg). ^1H NMR (600MHz, d6-DMSO) δ 2.42 (s, 3H), 2.50 (s, 3H), 2.97 (s, 3H), 7.48 (s, 1H), 11.85 (s, 1H). MS m/z 282.0477[M+H] $^+$.

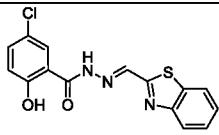
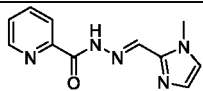
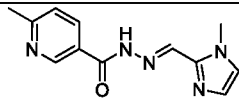
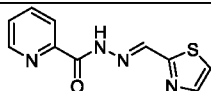
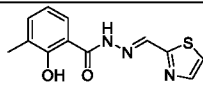
Table 6: Selected data for compounds synthesised according to Scheme 6

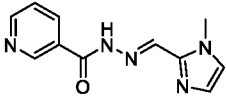
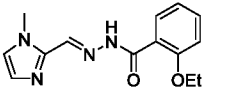
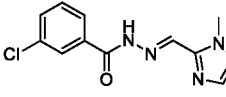
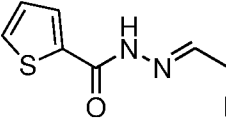
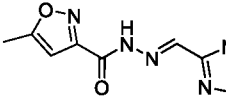
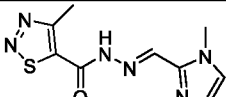
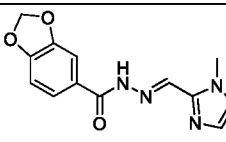
Compound	Structure	NMR	Mass Spec [M+H] $^+$
93		^1H NMR (600MHz, d6-DMSO) δ 2.29 (s, 3H), 2.96 (s, 3H), 6.18 (s, 3H), 6.70 (s, 1H), 7.02 (s, 1H), 10.90 (s, 1H), 11.30 (s, 1H).	m/z 250.0463
94		^1H NMR (600MHz, d6-DMSO) δ 2.40 (s, 3H), 2.43 (s, 3H), 6.99 (s, 1H), 7.07 (d, $J=8.4\text{Hz}$, 1H), 7.36 (s, 1H), 7.44 (s, 1H), 7.98 (d, $J=7.2\text{Hz}$, 1H), 11.46 (s, 1H), 11.85 (s, 1H).	m/z 276.0802
95		^1H NMR (600MHz, d6-DMSO) δ 2.39 (s, 3H), 2.42 (s, 3H), 7.05 (d, $J=9.0\text{Hz}$, 1H), 7.37 (s, 1H), 7.46-7.49 (m, 1H), 7.89 (s, 1H), 11.42 (s, 1H), 12.03 (br s, 1H).	m/z 310.12
96		^1H NMR (600MHz, d6-DMSO) δ 2.44 (s, 3H), 2.55 (s, 3H), 3.86 (s, 3H), 6.94 (d, $J=8.4\text{Hz}$, 1H), 7.30-7.34 (m, 2H), 7.68 (s, 1H), 9.87 (s, 1H).	m/z 306.0906

97		¹ H NMR (600MHz, d6-DMSO) δ 2.37 (s, 3H), 2.41 (s, 3H), 7.38-7.52 (m, 3H), 8.02 (d, <i>J</i> =7.8Hz, 1H), 8.05 (d, <i>J</i> =7.8Hz, 1H), 8.41 (s, 1H).	<i>m/z</i> 316.0591
98		¹ H NMR (600MHz, d6-DMSO) δ 2.41 (s, 3H), 2.48 (s, 3H), 3.00 (s, 6H), 6.80 (d, <i>J</i> =9.0Hz, 2H), 7.67 (s, 1H), 7.77 (d, <i>J</i> =9.0Hz, 2H).	<i>m/z</i> 303.1273
99		¹ H NMR (600MHz, d6-DMSO) δ 2.45 (s, 3H), 2.58 (s, 3H), 3.85 (s, 3H), 3.86 (s, 3H), 7.16 (d, <i>J</i> =8.4Hz, 1H), 7.46 (s, 1H), 7.53 (t, <i>J</i> =8.4Hz, 1H), 7.70 (s, 1H).	<i>m/z</i> 320.1061
100		¹ H NMR (600MHz, d6-DMSO) δ 2.42 (s, 3H), 2.50 (s, 3H), 2.97 (s, 3H), 7.48 (s, 1H), 11.85 (s, 1H).	<i>m/z</i> 282.0477
101		¹ H NMR (600MHz, d6-DMSO) δ 2.40 (s, 3H), 2.44 (s, 3H), 5.31 (s, 2H), 6.97 (dd, <i>J</i> =6.6, 9.6Hz, 1H), 7.03 (dt, <i>J</i> =1.8, 9.0Hz, 1H), 7.24-7.28 (m, 1H), 7.40-7.44 (m, 2H), 7.88 (s, 1H), 10.74 (br s, 1H).	<i>m/z</i> 370.0680
102		¹ H NMR (600MHz, d6-DMSO) δ 2.36 (s, 3H), 2.46 (s, 3H), 2.96 (s, 3H), 6.85 (d, <i>J</i> =3.6Hz, 1H), 7.41 (d, <i>J</i> =3.6Hz, 1H), 11.48 (s, 1H).	<i>m/z</i> 281.05

103		^1H NMR (600MHz, d6-DMSO) δ 2.29 (s, 3H), 2.33 (s, 3H), 2.45 (s, 3H), 6.81-6.86 (m, 2H), 7.32-7.37 (m, 2H), 7.76 (d, $J=9.6\text{Hz}$, 1H), 11.05 (s, 1H), 12.17 (br s, 1H).	m/z 289.1008
104		^1H NMR (600MHz, d6-DMSO) δ 2.52 (s, 3H), 6.99-7.07 (m, 2H), 7.44-7.53 (m, 3H), 7.99-8.12 (m, 3H), 11.62 (s, 1H), 11.81 (s, 1H).	m/z 312.0857
105		^1H NMR (600MHz, d6-DMSO) δ 2.23 (s, 3H), 2.59 (s, 3H), 6.91 (t, $J=7.8\text{ Hz}$, 1H), 7.38 (d, $J=6.6\text{Hz}$, 1H), 7.48-7.56 (m, 2H), 7.82 (s, 1H), 8.05 (d, $J=7.8\text{Hz}$, 1H), 8.12 (d, $J=7.8\text{Hz}$, 1H), 11.47 (s, 1H), 11.58 (br s, 1H).	m/z 326.0958
106		^1H NMR (600MHz, d6-DMSO) δ 2.20 (s, 3H), 2.37 (s, 3H), 2.51 (s, 3H), 7.41 (d, $J=4.2\text{Hz}$, 2H), 7.68-7.72 (m, 2H), 8.55 (s, 1H), 12.08 (s, 1H).	m/z 274.1007
107		^1H NMR (600MHz, d6-DMSO) δ 2.28 (s, 3H), 2.37 (s, 3H), 3.82 (s, 3H), 7.17 (d, $J=7.2\text{Hz}$, 1H), 7.40-7.46 (m, 3H), 8.52 (s, 1H), 12.01 (s, 1H).	m/z 290.0955
108			m/z 248.0517

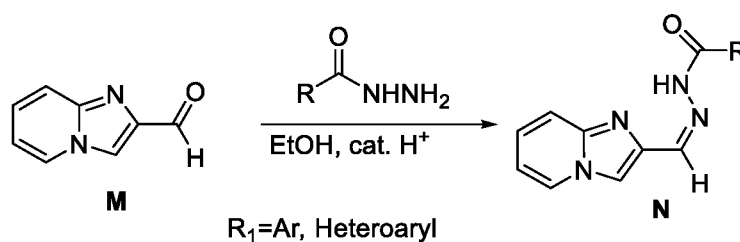
109		^1H NMR (600MHz, d6-DMSO) δ 7.01 (d, $J=8.4\text{Hz}$, 1H), 7.46 (dd, $J=8.4$, 2.4Hz , 1H), 7.81 (d, $J=2.4\text{Hz}$, 1H), 7.87 (s, 1H), 7.98 (d, $J=2.4\text{Hz}$, 1H), 8.65 (s, 1H), 11.55 (br s, 1H), 12.06 (s, 1H).	m/z 282.0982
110		^1H NMR (600MHz, d6-DMSO) δ 3.96 (s, 3H), 6.93 (d, $J=8.4\text{Hz}$, 2H), 6.96 (s, 1H), 7.35 (s, 1H), 7.40-7.45 (m, 1H), 7.84 (d, $J=5.4\text{Hz}$, 1H), 8.41 (s, 1H), 11.92 (s, 1H).	m/z 245.1050
111		^1H NMR (600MHz, d6-DMSO) δ 2.17 (s, 3H), 4.00 (s, 3H), 6.80 (t, $J=7.8\text{Hz}$, 1H), 7.19 (s, 1H), 7.37 (d, $J=7.2\text{Hz}$, 1H), 7.47 (s, 1H), 7.62 (d, $J=7.2\text{Hz}$, 1H), 8.56 (s, 1H).	m/z 259.1179
112		^1H NMR (600MHz, d6-DMSO) δ 2.39 (s, 3H), 4.00 (s, 3H), 7.4 (d, $J=7.8\text{Hz}$, 2H), 7.71 (s, 1H), 7.80-7.85 (m, 3H), 8.80 (s, 1H), 12.88 (br s, 1H).	m/z 243.1241
113		^1H NMR (600MHz, d6-DMSO) δ 3.96 (s, 3H), 6.99 (d, $J=9.0\text{Hz}$, 1H), 7.06 (s, 1H), 7.36 (s, 1H), 7.45 (dd, $J=9.0$, 2.4Hz , 1H), 7.86 (d, $J=2.4\text{ Hz}$, 1H), 8.40 (s, 1H).	m/z 279.0651
114		^1H NMR (600MHz, d6-DMSO) δ 6.96-7.01 (m, 2H), 7.44-7.55 (m, 3H), 7.82 (d, $J=7.2\text{ Hz}$, 1H), 8.05	m/z 298.0686

		(d, $J=7.2\text{Hz}$, 1H), 8.15 (d, $J=7.2\text{Hz}$, 1H), 8.77 (s, 1H), 11.41 (s, 1H), 12.42 (s, 1H).	
115		^1H NMR (600MHz, d6-DMSO) δ 7.03 (d, $J=9.0\text{Hz}$, 1H), 7.47-7.56 (m, 3H), 7.81 (d, $J=3.0\text{Hz}$, 1H), 7.96 (d, $J=7.8\text{Hz}$, 1H), 8.15 (d, $J=7.8\text{Hz}$, 1H), 8.74 (s, 1H), 11.43 (br s, 1H), 12.22 (s, 1H).	m/z 332.0253
116		^1H NMR (600MHz, d6-DMSO) δ 4.02 (s, 3H), 7.70-7.74 (m, 2H), 7.77 (s, 1H), 8.06-8.15 (m, 2H), 8.74 (d, $J=7.2\text{Hz}$, 1H), 8.85 (s, 1H), 12.97 (s, 1H).	m/z 230.1032
117		^1H NMR (600MHz, d6-DMSO) δ 2.58 (s, 3H), 4.02(s, 3H), 7.69 (d, $J=6.6\text{Hz}$, 1H), 7.67 (s, 1H), 7.79 (s, 1H), 8.30 (s, 1H), 8.73 (s, 1H), 9.06 (s, 1H), 12.97 (s, 1H).	m/z 244.1193
118		^1H NMR (600MHz, d6-DMSO) δ 7.68 (t, $J=8.4\text{Hz}$, 1H), 7.85 (s, 1H), 7.95 (s, 1H), 8.06 (t, $J=7.2\text{Hz}$, 1H), 8.13 (d, $J=7.2\text{Hz}$, 1H), 8.72 (d, $J=2.4\text{Hz}$, 1H), 8.88 (s, 1H), 12.62 (s, 1H).	m/z 233.0492
119		^1H NMR (600MHz, d6-DMSO) δ 2.17(s, 3H), 6.87 (t, $J=9.0\text{Hz}$, 1H), 7.39 (d, $J=7.2\text{Hz}$, 1H), 7.88 (dd, $J=13.2, 8.4\text{Hz}$, 1H), 7.98 (s, 1H), 8.80 (s, 1H), 12.39 (br s, 1H), 12.46 (s, 1H).	m/z 262.0646

163			<i>m/z</i> 230.1034
164			<i>m/z</i> 273.1346
165		¹ H NMR (500MHz, d6-DMSO) δ 4.01 (s, 3H), 7.56-7.62 (m, 1H), 7.70-7.74 (m, 2H), 7.83 (br s, 1H), 7.96-8.00 (m, 1H), 8.07 (s, 1H), 8.77 (s, 1H), 13.01 (s, 1H).	<i>m/z</i> 263.0692
166		¹ H NMR (500MHz, d6-DMSO) δ 3.97 (s, 3H), 7.24 (t, <i>J</i> =4.5Hz, 1H), 7.42 (s, 1H), 7.59 (s, 1H), 7.93 (d, <i>J</i> =4.5Hz, 1H), 8.04 (s, 1H), 8.58 (s, 1H), 12.51 (s, 1H).	<i>m/z</i> 235.06
167		¹ H NMR (500MHz, d6-DMSO) δ 2.48 (s, 3H), 3.94 (s, 3H), 6.67 (s, 1H), 7.24 (s, 1H), 7.48 (s, 1H), 8.51 (s, 1H), 12.47 (s, 1H).	<i>m/z</i> 234.10
168			<i>m/z</i> 251.0709
169			<i>m/z</i> 273.0980

Similarly, imidazopyridine derivatives were synthesised according to Scheme 7.

Scheme 7



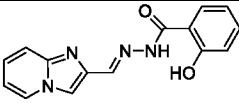
Example 7

5 (Z)-N'-(Imidazo[1,2-a]pyridin-2-ylmethylene)-3-methoxybenzohydrazide (**120**)

Imidazo[1,2-a]pyridine-2-carboxaldehyde (101 mg) and 3-methoxybenzohydrazide (114 mg) were heated to reflux in EtOH (7mL) in the presence of concentrated hydrochloric acid for 2 h. The reaction was allowed to cool and the resulting white precipitate was collected by filtration to afford (Z)-N'-(imidazo[1,2-a]pyridin-2-ylmethylene)-3-methoxybenzohydrazide **120** (61mg) as an off-white solid. ¹H NMR (600MHz, d6-DMSO) δ 3.85 (s, 3H), 7.19 (dd, *J*=8.4, 2.4 Hz, 1H), 7.44-7.48 (m, 2H), 7.56-7.60 (m, 2H), 7.85 (d, *J*=3.0Hz, 1H), 7.93 (t, *J*=7.8Hz, 1H), 8.73 (s, 1H), 8.89 (d, *J*=6.0Hz, 1H), 8.91 (s, 1H), 12.62 (s, 1H). MS *m/z* 295.1191[M+H]⁺.

Table 7: NMR and MS Data for compounds synthesised via Scheme 7.

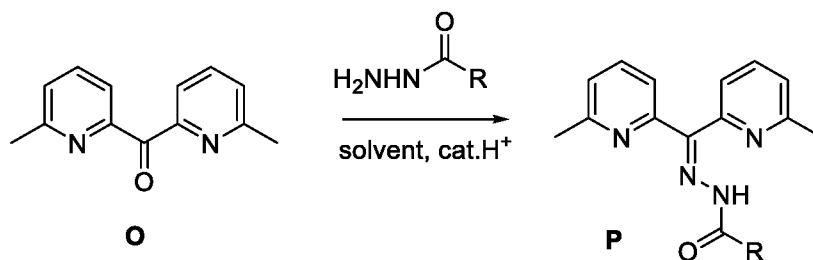
Compound	Structure	NMR	Mass Spec [M+H] ⁺
121		¹ H NMR (600MHz, d6-DMSO) δ 2.39 (s, 3H), 7.42-7.49 (m, 3H), 7.80-7.86 (m, 3H), 7.94 (t, <i>J</i> =7.8Hz, 1H), 8.72-8.76 (m, 2H), 8.91 (d, <i>J</i> =6.6Hz, 1H), 12.56 (s, 1H).	<i>m/z</i> 279.1242
138		¹ H NMR (600MHz, d6-DMSO) δ 7.42-7.53 (m, 3H), 7.86 (br s, 1H),	<i>m/z</i> 321.1164

		7.92 (s, 1H), 8.00-8.08 (m, 2H), 8.46 (s, 1H), 8.74 (s, 1H), 8.90 (d, $J=6.0\text{Hz}$, 1H), 11.98 (br s, 1H), 12.90 (s, 1H).	
139		^1H NMR (600MHz, $\text{d}_6\text{-DMSO}$) δ 6.94-7.03 (m, 3H), 7.35-7.45 (m, 2H), 7.61 (d, $J=9.0\text{ Hz}$, 1H), 7.88 (d, $J=7.2\text{ Hz}$, 1H), 8.41 (s, 1H), 8.54 (s, 1H), 8.61 (d, $J=3.6\text{Hz}$, 1H), 11.81 (s, 1H), 11.96 (s, 1H).	m/z 281.1391

A variety of dipyridyl acyl hydrazones were synthesised according to Scheme 8.

Dimethyldipyridyl ketone **O** was heated together with substituted arylbenzhydrazides to afford target acyl hydrazones **P**.

5 Scheme 8



Example 8

N'-(bis(6-Methylpyridin-2-yl)methylene)-4-hydroxy-3-methoxybenzohydrazide (**130**).

- 10 Bis(6-methylpyridin-2-yl)methanone (227 mg) and vanillic acid hydrazide (195 mg) in EtOH (10 mL) were treated with 2 drops of concentrated hydrochloric acid and the reaction was heated to 60°C for 1 h. The reaction was allowed to cool and a yellow solid was collected by filtration to afford *N'*-(bis(6-methylpyridin-2-yl)methylene)-4-hydroxy-3-methoxybenzohydrazide **130** (248 mg) as a beige solid. ^1H NMR (600MHz,
- 15 $\text{d}_6\text{-DMSO}$) δ 2.61 (s, 3H), 2.70 (s, 3H), 3.84 (s, 3H), 6.98 (d, $J=8.4\text{Hz}$, 1H), 7.31(d,

$J=8.4\text{Hz}$, 1H), 7.41-7.45 (m, 2H), 7.55 (d, $J=7.8\text{Hz}$, 1H), 7.64 (s, 1H), 7.83 (d, $J=7.8\text{Hz}$, 1H), 7.97 (d, $J=7.8\text{Hz}$, 1H), 8.16 (s, 1H), 10.02 (br s, 1H), 15.25 (br s, 1H). MS m/z 377.1611[M+H]⁺.

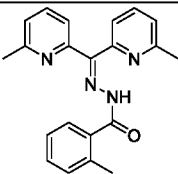
In a further example, a phenolic hydrazone derivative **184** could be converted to the dimethylaminomethyl compound **185** by the action of tetramethylenediamine in refluxing toluene (see example 8a below).

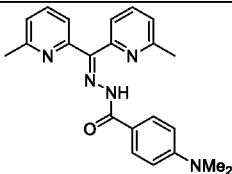
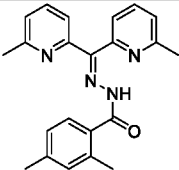
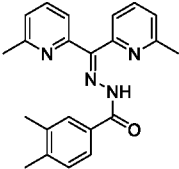
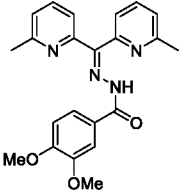
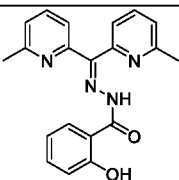
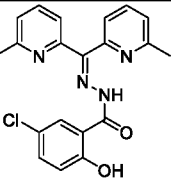
Example 8a

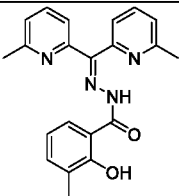
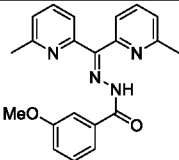
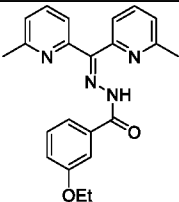
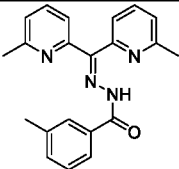
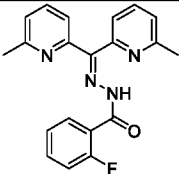
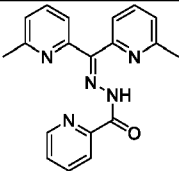
5-chloro-N'-(di(pyridin-2-yl)methylene)-3-((dimethylamino)methyl)-2-hydroxybenzohydrazide (**185**)

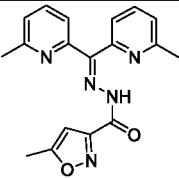
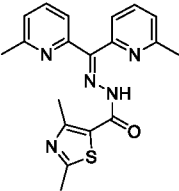
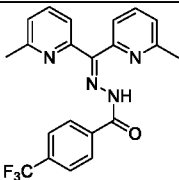
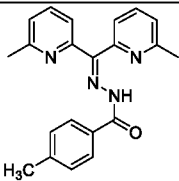
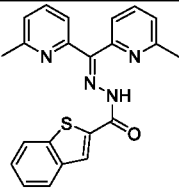
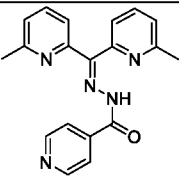
5-chloro-N'-(di(pyridin-2-yl)methylene)-2-hydroxybenzohydrazide **184** (801 mg, 2.27 mmol) was suspended in toluene (95 mL) and treated with *N, N, N, N*-tetramethylenediamine (4 mL). The reaction was heated to reflux for 4h, then allowed to cool to rt o/n. Volatiles were removed *in vacuo* and the resulting residue was taken up in acetonitrile (4 mL) then ether (20 mL) was added slowly. The resulting precipitate was collected by filtration to afford 5-chloro-N'-(di(pyridin-2-yl)methylene)-3-((dimethylamino)methyl)-2-hydroxybenzohydrazide (747mg) as a yellow solid. ¹H NMR (600MHz, d6-DMSO) δ 2.60 (s, 6H), 3.98 (s, 2H), 7.12 (s, 1H), 7.37-7.43 (m, 2H), 7.51 (d, $J=6.0\text{Hz}$, 1H), 7.69 (s, 1H), 7.90-7.94 (m, 2H), 8.14 (d, $J=9.6\text{Hz}$, 1H), 8.46 (s, 1H), 8.76-8.78 (m, 1H), 8.60 (br s, 1H), 8.76 (14.48 (s, 1H). MS m/z 410.2014[M+H]⁺.

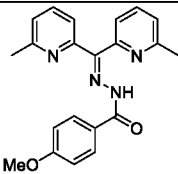
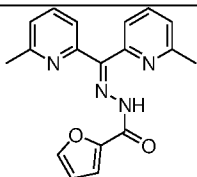
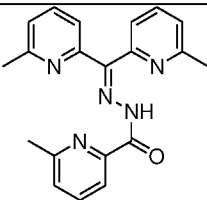
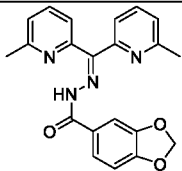
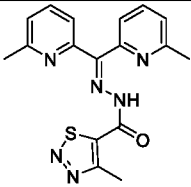
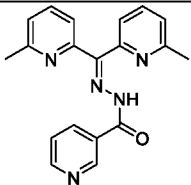
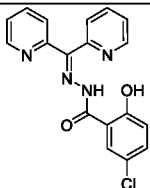
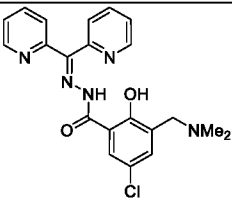
Table 8: MS Data for compounds synthesised according to Scheme 8

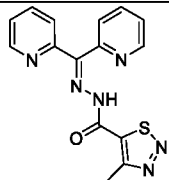
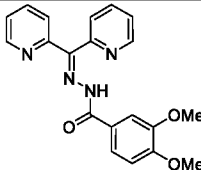
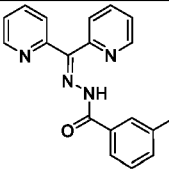
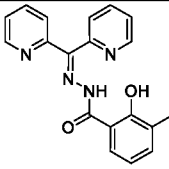
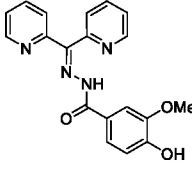
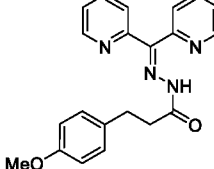
Compound	Structure	Mass Spectrometry [M+H] ⁺
122		m/z 345.1892

123		m/z 374.18
124		m/z 359.27
125		m/z 359.19
126		m/z 391.1913
127		m/z 347.1744
128		m/z 381.1627

129		m/z 361.1789
131		m/z 361.1160
132		m/z 375.1816
133		m/z 345.17
134		m/z 349.1459
135		m/z 332.1506

136		m/z 336.1455
137		m/z 366.1384
140		m/z 399.1429
141		m/z 345.17
142		m/z 387.1275
143		m/z 332.1993

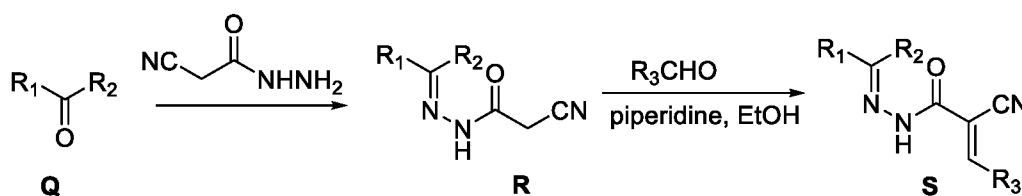
144		m/z 361.1660
154		m/z 321.1346
155		m/z 346.1666
181		m/z 375.1451
182		m/z 353.1181
183		m/z 332.1506
184		m/z 381.1627
185		m/z 410.2014

186		<i>m/z</i> 325.1081
187		<i>m/z</i> 363.1684
188		<i>m/z</i> 317.1400
189		<i>m/z</i> 333.1347
190		<i>m/z</i> 349.1296
191		<i>m/z</i> 361.1661

Acrylonitrile derivatives could be synthesised as outlined in Scheme 9 below

- Quinolone ketone could be converted to the acetocyanohydrazide **Q** by allowing to react with 2-cyanoacetohydrazide under standard conditions. Intermediate **Q** is then
- 5 allowed to react with an aldehyde in the presence of catalytic piperidine to afford the required acrylonitrile derivative **R**.

Scheme 9



R₁,R₂=pyridyl or 2-methylpyridyl

R₁=pyridyl, R₂=H

R₁,R₂=fused quinolone

Synthesis of (*E*)-2-cyano-*N'*-(6,7-dihydroquinolin-8(5*H*)-ylidene)acetohydrazide

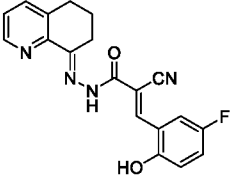
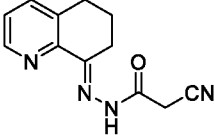
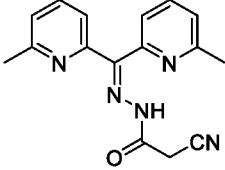
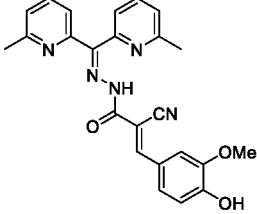
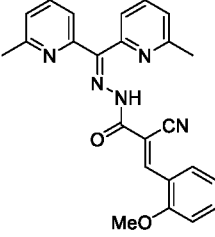
To a mixture of 6,7 dihydroquinolin-8-one (906 mg) **Q** (R₁, R₂ = fused quinoline),
 5 acetocyanohydrazide (712 mg) in EtOH (40 mL) was added conc. hydrochloric acid (3 drops) and the reaction was heated to 50°C for 1 h. After cooling to rt, (*E*)-2-cyano-*N'*-(6,7-dihydroquinolin-8(5*H*)-ylidene)acetohydrazide **R** (R₁, R₂ = fused quinoline) precipitated out of solution as a tan solid. The solid was collected by filtration and dried at the pump to afford 1.2 g of material. MS *m/z* 229.1081 [M+H]⁺.

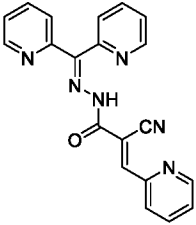
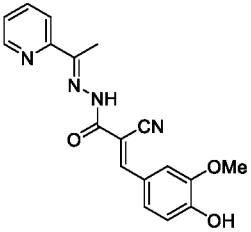
10 Example 9

(2*E,N'E*)-2-Cyano-*N'*-(6,7-dihydroquinolin-8(5*H*)-ylidene)-3-(2-hydroxyphenyl)acrylohydrazide **145**

To a mixture of the (*E*)-2-cyano-*N'*-(6,7-dihydroquinolin-8(5*H*)-ylidene)acetohydrazide (70 mg) **R** (**179**) in EtOH (8 mL) was added salicylaldehyde (110 μL). This was
 15 followed by the addition of a 0.1M solution of piperidine in EtOH (0.2 mL) with vigorous stirring at room temp and gentle heating to get all into solution. After 30 min, a pale yellow solid was collected by filtration and washed with EtOH (x3). After drying 17 mg of (2*E,N'E*)-2-cyano-*N'*-(6,7-dihydroquinolin-8(5*H*)-ylidene)-3-(2-hydroxyphenyl)acrylohydrazide **S** (**145**) was obtained. ¹H NMR (600MHz, d₆-DMSO)
 20 δ 1.89 (t, *J*=6.0Hz, 2H), 2.70 (t, *J*=6.0Hz, 2H), 2.80 (t, *J*=6.0Hz, 2H), 7.24-7.31 (m, 3H), 7.58 (dt, *J*=8.4, 1.2Hz, 1H), 7.62 (d, *J*=8.4Hz, 1H), 7.82 (dd, *J*=7.8, 1.2 Hz, 1H), 8.50 (dd, *J*=4.8, 1.2 Hz, 1H), 8.64 (s, 1H), 9.27 (s, 1H), 13.53 (s, 1H). MS *m/z* 333.1347 [M+H]⁺.

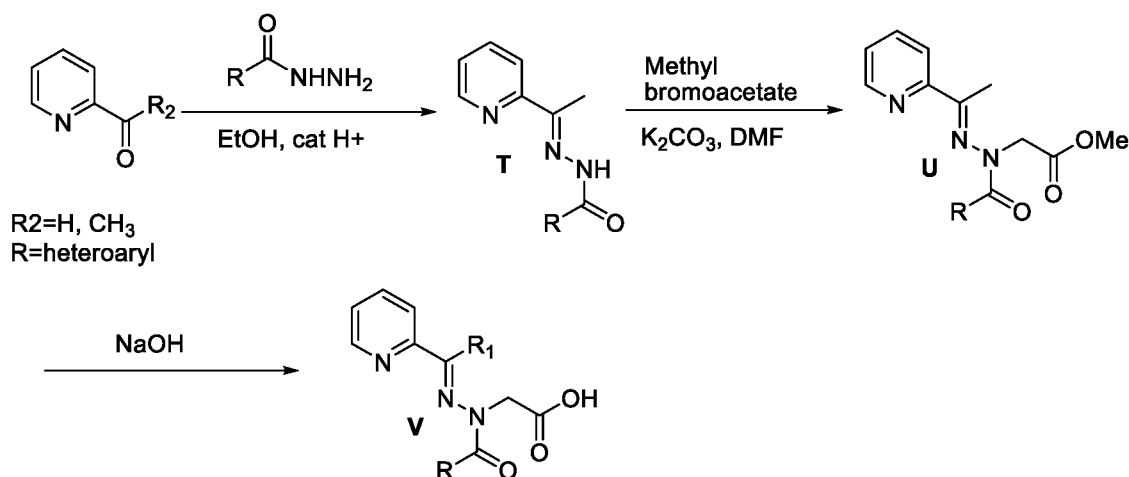
Table 9: Selected data for compounds synthesised according to Scheme 9

Compound	Structure	NMR	Mass Spec[M+H] ⁺
170		¹ H NMR (500MHz, d6-DMSO) δ 1.91 (t, <i>J</i> =6.0Hz, 2H), 2.72 (t, <i>J</i> =6.0Hz, 2H), 2.82 (t, <i>J</i> =6.0Hz, 2H), 7.29-7.34 (m, 2H), 7.45 (dt, <i>J</i> =8.5, 3.0 Hz, 2H), 7.65 (d, <i>J</i> =7.5 Hz, 1H), 7.74 (dd, <i>J</i> =8.5, 3.0Hz), 8.53 (d, <i>J</i> =3.5Hz, 1H), 8.64 (s, 1H), 9.37 (s, 1H), 13.51 (s, 1H).	<i>m/z</i> 351.1251
179 (R)			<i>m/z</i> 229.1081
192			<i>m/z</i> 294.1439
193		¹ H NMR (600MHz, d6-DMSO) δ 2.44 (s, 3H), 2.71 (s, 3H), 3.81 (s, 3H), 4.33 (s, 1H), 6.94 (d, <i>J</i> =8.4Hz, 1H), 7.19 (d, <i>J</i> =7.2Hz, 1H), 7.34 (d, <i>J</i> =7.2Hz, 1H), 7.44 (d, <i>J</i> =7.2Hz, 1H), 7.60-7.64 (m, 2H), 7.75 (s, 1H), 7.82-7.87 (m, 2H), 8.31 (s, 1H).	<i>m/z</i> 428.1271
194		¹ H NMR (600MHz, d6-DMSO) δ 2.47 (s, 3H), 2.71 (s, 3H), 3.92 (s, 3H), 7.15 (t, <i>J</i> =7.8Hz, 1H), 7.23 (t, <i>J</i> =4.2Hz, 2H), 7.37 (d, <i>J</i> =7.8Hz, 1H), 7.47 (d, <i>J</i> =7.8Hz, 1H), 7.61-7.65 (m, 2H), 7.84-7.89 (m, 2H),	<i>m/z</i> 412.1774

		8.65 (s, 1H).	
195		¹ H NMR (600MHz, d6-DMSO) δ 7.51-7.57 (m, 2H), 7.57-7.60 (m, 1H), 7.63-7.66 (m, 1H), 7.92 (d, <i>J</i> =7.8Hz, 1H), 7.96 (d, <i>J</i> =7.8Hz, 1H), 7.99-8.05 (m, 3H), 8.47 (s, 1H), 8.65 (d, <i>J</i> =4.8Hz, 1H), 8.80 (t, <i>J</i> =4.8Hz, 2H).	<i>m/z</i> 355.1303
196		¹ H NMR (600MHz, d6-DMSO) δ 2.50 (s, 3H), 3.83 (s, 3H), 6.95 (d, <i>J</i> =8.4Hz, 1H), 7.59-7.63 (m, 2H), 7.77 (s, 1H), 7.85 (d, <i>J</i> =8.4Hz, 1H), 8.13 (t, <i>J</i> =7.8Hz, 1H), 8.29 (s, 1H), 8.71 (d, <i>J</i> =3.6Hz, 1H), 10.4 (br s, 1H).	<i>m/z</i> 337.1296

In a further example, substitution of the hydrazide group could be achieved by allowing an acyl hydrazone compound to react with a substituted alkyl halide in the presence of potassium carbonate to generate compounds **U** as described in **Scheme 10** below.

- Heating 2-acetylpyridine with a substituted hydrazide afforded acyl hydrazone **T**. Alkylation of **T** by the action of a methyl bromoacetate and potassium carbonate in DMF generated ester **U**. In addition, compound **U** could be readily hydrolysed to a carboxylic acid derivative **V** by reaction with lithium hydroxide in a mixture of THF and water.

**Example 10****(*E*)-*N'*-(1-(Pyridin-2-yl)ethylidene)benzo[*b*]thiophene-2-carbohydrazide (146)**

To a mixture of 2-acetylpyridine (326 mg), benzo[*b*]thiophene-2-carboxylic acid hydrazide (518mg) in EtOH (15mL) at 60°C was added 3 drops of conc. HCl. After heating for 30 min, the reaction was cooled overnight and a white solid precipitated out of solution to provide (*E*)-*N'*-(1-(pyridin-2-yl)ethylidene)benzo[*b*]thiophene-2-carbohydrazide (650 mg). MS m/z 296.0460[M+H]⁺.

Table 10-Hydrazone Intermediates synthesized according to Scheme 10

Compound	Structure	Spectroscopic Data
152		¹ H NMR (600MHz, d6-DMSO) δ 2.45 (s, 3H), 2.97 (s, 3H), 7.47-7.50 (m, 1H), 7.98 (t, <i>J</i> =7.8Hz, 1H), 8.06 (d, <i>J</i> =7.8Hz, 1H), 8.65 (d, <i>J</i> =3.6Hz, 1H), 11.7 (s, 1H). MS m/z 262.0871[M+H] ⁺ .
153		¹ H NMR (600MHz, d6-DMSO) δ 2.97 (s, 3H), 7.69 (dd, <i>J</i> =6.6, 4.8Hz, 1H), 8.01 (s, 1H), 8.11 (d, <i>J</i> =8.4Hz, 1H), 8.25 (s, 1H), 8.66 (d, <i>J</i> =4.2Hz, 1H), 12.59 (s, 1H)

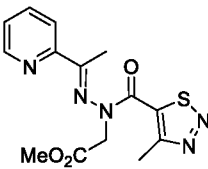
(*E*)-Methyl 2-(1-(benzo[*b*]thiophene-2-carbonyl)-2-(1-(pyridin-2-yl) ethylidene) hydrazinyl) Acetate **147**

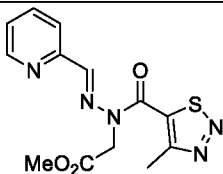
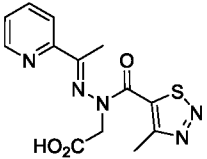
To a solution of (*E*)-*N*-(1-(pyridin-2-yl)ethylidene)benzo[*b*]thiophene-2-carbohydrazone (190 mg) in DMF (8 mL) was added methyl bromoacetate (200 μ L) and
 5 K_2CO_3 (210 mg). The reaction was heated to 50°C for 1.5 h during which time a white precipitate formed. The reaction was cooled, and H_2O (8 mL) was added slowly. After allowing to stand for 30 min, (*E*)-methyl 2-(1-(benzo[*b*]thiophene-2-carbonyl)-2-(1-(pyridin-2-yl) ethylidene)hydrazinyl)acetate precipitated out of solution as a yellow solid (90 mg) **147**. ^1H NMR (d6-DMSO) δ 2.44 (s, 3H), 3.73 (s, 3H), 5.06 (s, 2H), 7.44-
 10 7.49 (m, 2H), 7.53 (d, $J=7.2$ Hz, 1H), 8.00-8.06 (m, 3H), 8.21 (s, 1H), 8.41 (d, $J=7.8$ Hz, 1H), 8.69 (d, $J=3.6$ Hz, 1H). MS m/z 368.1061 $[M+H]^+$.

(*E*)-2-(1-(Benzo[*b*]thiophene-2-carbonyl)-2-(1-(pyridin-2-yl)ethylidene)hydrazinyl) acetic acid **148.**

15 To a solution of (*E*)-methyl 2-(1-(benzo[*b*]thiophene-2-carbonyl)-2-(1-(pyridin-2-yl) ethylidene)hydrazinyl) acetate (64 mg) in THF (7 mL) was added LiOH (65 mg) and H_2O (3 mL). The reaction was heated to 50°C for 2 h and then cooled to rt. THF was removed *in vacuo* and a yellow precipitate formed. The product was collected by filtration to afford (*E*)-2-(1-(benzo[*b*]thiophene-2-carbonyl)-2-(1-(pyridin-2-
 20 yl)ethylidene) hydrazinyl)acetic acid as a yellow powder. MS m/z 354.09 $[M+H]^+$.

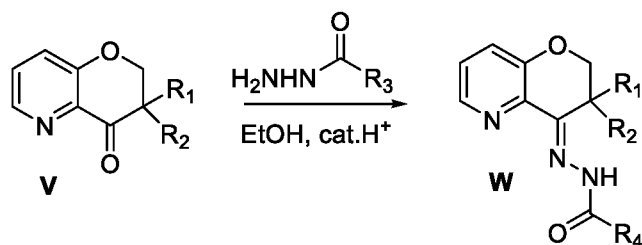
Table 11: Target compounds prepared according to Scheme 10.

Compound	Structure	Spectroscopic Data
149		^1H NMR (600MHz, d6-DMSO) δ 2.50 (s, 3H), 2.99 (s, 3H), 3.74 (s, 3H), 5.14 (s, 2H), 7.55 (dd, $J=7.2$, 4.8Hz, 1H), 8.04 (t, $J=7.8$ Hz, 1H), 8.24 (d, $J=7.8$ Hz, 1H), 8.71 (d, $J=4.8$ Hz, 1H). MS m/z 334.0996 $[M+H]^+$.
150		^1H NMR (600MHz, d6-DMSO) δ 2.98 (s, 3H), 3.77 (s, 3H), 5.15 (s, 2H), 7.48-7.52 (m, 1H), 8.01-8.09 (m, 2H), 8.20 (s, 1H), 8.74-8.78 (m, 1H). MS m/z

		320.0822[M+H] ⁺ .
151		¹ H NMR (600MHz, d6-DMSO) δ 2.51 (s, 3H), 2.98 (s, 3H), 5.05 (s, 2H), 7.54-7.57 (m, 1H), 8.05 (t, J=7.2Hz, 1H), 8.25 (d, J=7.8Hz, 1H), 8.71 (d, J=3.6Hz, 1H). MS m/z 320.08[M+H] ⁺ .

In a further example, a number fused pyridopyrano acyl hydrazones were synthesised according to Scheme 11. ketone **V** was heated together with substituted aryl benzhydrazides in the presence of catalytic acid to afford target acyl hydrazones **W**.

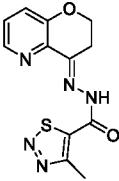
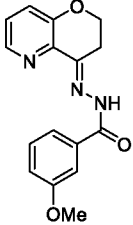
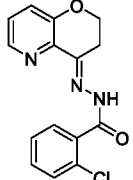
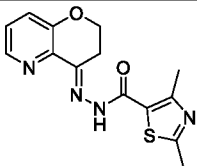
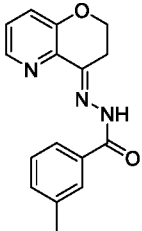
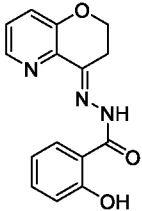
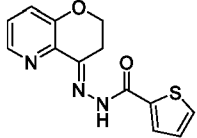
5 Scheme 11



Example 11 (E)-N'-(2,3-dihydro-4H-pyrano[3,2-b]pyridin-4-ylidene)nicotinohydrazide (171)

To a mixture of 2H-pyran[3,2-b]pyridine-4(3H)-one **V** (49mg, 0.33 mmol) in EtOH (6 mL) was added nicotinic acid hydrazide (44 mg, 0.32 mmol) followed by one drop of conc. HCl. The reaction was heated to 55°C for 30 min, then cooled to room temp to afford (E)-N'-(2,3-dihydro-4H-pyrano[3,2-b]pyridin-4-ylidene)nicotinohydrazide **171** as an off-white solid. (34mg). ¹H NMR (500MHz, d6-DMSO) δ 2.96 (t, J=6.0Hz, 2H), 4.47 (t, J=6.0Hz, 2H), 7.56-7.64 (m, 2H), 7.77 (t, J=5.0Hz, 1H), 8.41 (d, J=7.5Hz, 1H), 8.50 (d, J=5Hz, 1H), 8.88 (d, J=5.0Hz, 1H), 9.13 (s, 1H), 15.63 (s, 1H). MS: m/z 269.1033 [M+H]⁺.

Table 12: Compounds synthesized according to Scheme 11

Compound	Structure	Mass Spectrometry [M+H] ⁺
172		<i>m/z</i> 290.0708
173		<i>m/z</i> 298.1189
174		<i>m/z</i> 302.0692
175		<i>m/z</i> 303.0911
176		<i>m/z</i> 282.1236
177		<i>m/z</i> 284.1027
178		<i>m/z</i> 274.0646

Biological Examples

GSK 3b Assay

The phosphorylation of GSK-3 β is enhanced when Zn is imported into a cell by a Zn ionophore. This property was measured for the compounds of the current invention and
5 the data presented relative to the know Zn ionophore PBT2 using the following protocol.

The human neuroblastoma SH-SY5Y cells were obtained from Cell bank Australia (Catalogue number: 94030304). SH-SY5Y cell culture was maintained in DMEM/F12 + 15% FBS inside an incubator at 37°C in the presence of 5% CO₂. The cells were sub-
10 cultured once a week and the media exchanged once during the week. Cells for the assay were plated at a density of 60,000 cells/well.

Stock solutions of the samples were prepared as a 5mM stock in DMSO and a stock solution of 1mM ZnCl₂/3mM Glutamic acid was prepared in water. Immediately before use the compounds were diluted 1:10 with water before being added to Locke's
15 buffer in a treatment tube. Samples were subsequently treated with either distilled water or the ZnCl₂/Glutamic acid solution to yield a treatment solution which has a final concentration of the test compound at 2 μ M +/- ZnCl₂ at 5 μ M.

The culture media was aspirated from the wells and the media replaced with the treatment solution prepared above. In addition to the relative standard (PBT2 +/-
20 ZnCl₂), control wells were also included consisting of +/- ZnCl₂ at 5 μ M with all treatments done in triplicate. The plate was incubated at 37°C with the treatment solution for 2 h after which time the wells were aspirated and washed with sterile PBS.

Measurement of the change of phospho-GSK-3 β was determined using an AlphaScreen® SureFire® Phospho-GSK 3 β (Ser9) Kit with the cells being processed as
25 per the manufacturer's instructions using an initial incubation of 2h/24°C and a final incubation of 16h/24°C.

The fluorescence was measured on an Enspire plate reader. In the absence of the metal, the compounds had no effect on the signal whereas, in the presence of the metal,

positive compounds showed an increased signal which is presented as a % of the positive standard PBT2 + ZnCl₂ set as 100%. Representative data is presented in Table 12 using the following ranges: A <50%, B 50-<100%, C 100-<150%, D >150%.

Table 12: GSK Data for Selected Compounds

Compound	GSK-Zn	Compound	GSK-Zn	Compound	GSK-Zn
1	A	43	C	92	C
2	A	44	B	94	C
3	A	45	C	95	C
4	A	46	C	100	C
6	A	47	C	103	B
7	A	48	C	104	D
8	A	49	B	105	B
9	A	50	C	106	A
10	B	51	B	109	B
11	C	52	B	115	A
12	B	64	B	119	A
15	D	65	B	121	A
16	A	67	C	122	A
17	A	72	C	123	C
18	B	73	C	126	C
20	A	74	B	128	D
21	A	75	C	129	C
23	C	76	C	130	A
24	A	77	C	131	B
25	B	78	C	132	C
26	A	81	C	133	C
38	A	82	C	134	B
39	A	87	C	135	B
41	A	91	C	146	C

Method I: Measurement of Fe efflux from cells

Compounds of the current invention were assessed for their ability to efflux iron (Fe) from a cell using the following protocol.

5 The human neuroblastoma line BE(2)-M17 (M17) cell cultures were acquired from Sigma Aldrich (Catalogue#: 95011816). M17 Cells were maintained in Opti-MEM reduced serum media supplemented with 10% fetal bovine serum (Bovogen, SFBSF) and passaged twice weekly. Cells were cultured at 37°C in the presence of 5% CO₂. Culture supplies were sourced from Thermo Fisher unless otherwise stated.

10 A solution of ⁵⁷Fe cold isotope was prepared by dissolving ⁵⁷Fe metal (>95% enrichment, Trace Sciences International) in concentrated HCl to give a final concentration of 573mM. From this master solution, a 10mM working solution was prepared in sterile water. The working solution was used within two months of preparation.

15 M17 cells were loaded with iron initially by seeding into 48-well plates at a density of 0.15x10⁶ cells per well in 0.5mL media. After 48h, old media was discarded. Fresh media was supplemented with 20μM ⁵⁷Fe isotope, from the 10mM ⁵⁷Fe working solution. Cells received 0.2mL of this ⁵⁷Fe enriched media and were returned to the incubator for 20h. The ability of experimental compounds to efflux iron was determined by the dissolution of compounds in DMSO and diluted in Hanks' Balanced Salt
20 Solution (HBSS) for treatment of M17 cells. After ⁵⁷Fe incubation, cells were rinsed twice with HBSS and treated with 0.15mL trial compound for 2h at a concentration of 20μM. All assays included a relevant vehicle (0.4%-0.8% DMSO) as well as a positive control (20μM). Following the treatment period, 0.1mL of media was collected from cells and the extracellular ⁵⁷Fe content was analysed via inductively coupled mass
25 spectrometry (ICP-MS, Agilent 7700x series instrument).

To perform this protocol the following supplies were purchased from Sigma Aldrich: anhydrous dimethyl sulfoxide (DMSO, Catalogue#: 276855), Hanks' Balanced Salt Solution supplemented with 20mM HEPES and 4.2mM Sodium Bicarbonate (HBSS, pH: 7.4, Catalogue#: H1387).

The ability of the compounds of the invention to efflux Fe from a cell was determined using the above protocol hence cells having been pre-treated with Fe in the media for 24h were subsequently washed and treated with fresh, Fe free media either with or without the compound (20μM). After 2h the Fe levels in the media were measured and the increase determined as a percentage increase relative to the cell media in the absence of the compound.

$$\%Fe\ efflux = \frac{([Fe\ in\ media]_{Compound} - [Fe\ in\ media]_{No\ Compound})}{[Fe\ in\ media]_{No\ Compound}} \times 100$$

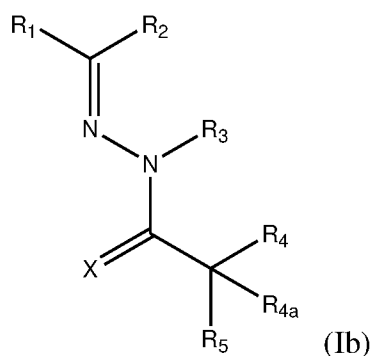
Representative data is provided in Table 13 where the %Fe efflux for the specified compounds of the invention lie in the following ranges: A < 30%, B 30-100%, C 100-150%; D >150%.

Table 13: Fe efflux data for Selected Compounds

Compound	Fe-Efflux	Compound	Fe-Efflux	Compound	Fe-Efflux
1	D	31	B	55	B
2	C	32	C	56	B
3	D	33	D	57	C
4	B	39	D	58	A
6	A	40	D	61	B
7	B	42	D	91	B
8	C	47	B	101	A
9	B	48	D	117	A
10	B	49	D	122	A
15	D	50	A	138	A
23	D	52	B	147	A
171	A	172	C	178	C

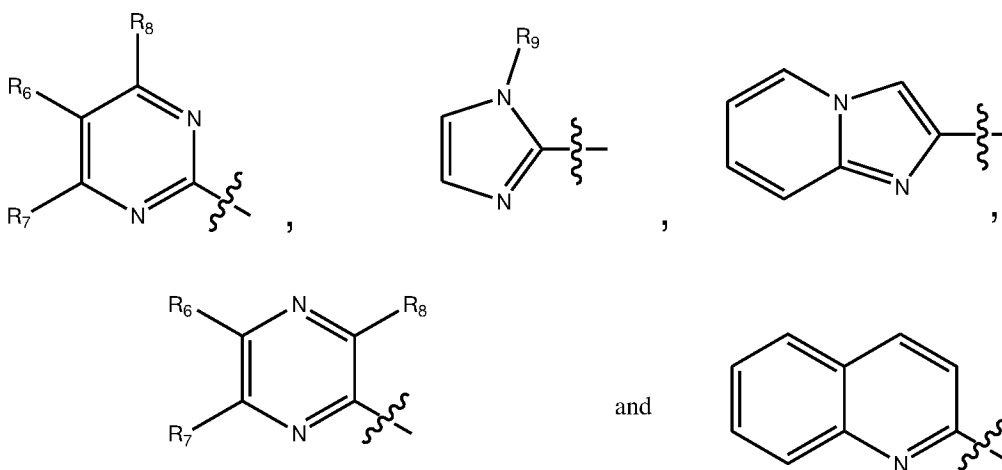
Claims

1. A compound of formula (Ib):



wherein X is O;

- 5 R₁ is selected from:

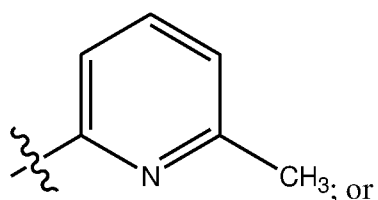


R₆ and R₇ are independently selected from hydrogen, C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, hydroxy, C₁₋₆alkoxy, C₁₋₆haloalkyl, C₁₋₆haloalkoxy, halo, CN, CO₂R₉ and N(R₉)₂; or

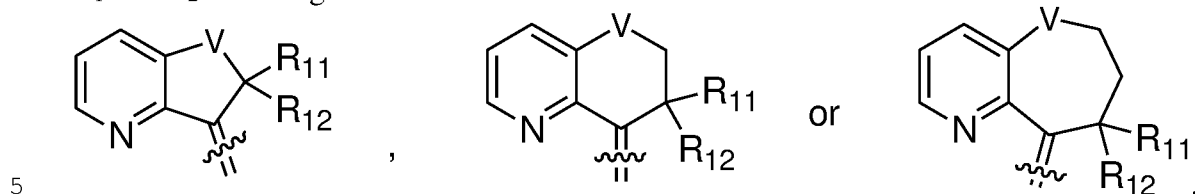
- 10 R₆ and R₇ taken together with the atoms to which they are attached form an unsubstituted 6 membered aryl or heteroaryl ring;
 each R₈ is independently selected from hydrogen, C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, hydroxy, C₁₋₆alkoxy, C₁₋₆haloalkyl, C₁₋₆haloalkoxy, halo, (CH₂)_mCO₂R₉ and (CH₂)_mN(R₉)₂;
 15 each R₉ is independently selected from hydrogen, C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl and C₁₋₆haloalkyl;

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R₂ is selected from hydrogen, C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₁₋₆haloalkyl, C₃₋₈cycloalkyl and



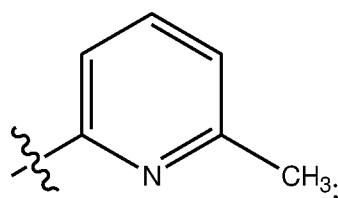
R₁ and R₂ taken together form



wherein V is CH, O or S and R₁₁ and R₁₂ are each independently selected from hydrogen, C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, halo, C₁₋₆haloalkyl, (CH₂)_mC₃₋₈cycloalkyl, (CH₂)_maryl, (CH₂)_mheterocyclyl, (CH₂)_mheteroaryl and COR₁₃ where R₁₃ is selected from OH, OC₁₋₆alkyl, OC₂₋₆alkenyl, OC₂₋₆alkynyl and N(R₉)₂, wherein the cycloalkyl, heterocycloalkyl or heteroaryl ring of the bicyclic structure formed by R₁ and R₂ may be optionally substituted, or

10

R₁ and R₂ are both:

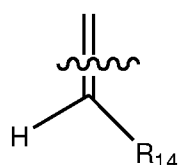


15 ,

R₃ is selected from hydrogen, C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl and C(R₁₀)₂)_mCO₂R₉; R₄ and R_{4a} are each independently selected from hydrogen, C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl and C₁₋₆haloalkyl; and R₅ is hydrogen, (C(R₁₀)₂)_maryl, (C(R₁₀)₂)_mheteroaryl, O(C(R₁₀)₂)_maryl or O(C(R₁₀)₂)_mheteroaryl wherein the aryl and heteroaryl are optionally substituted; or

20

R_{4a} is CN and R₄ and R₅ are both hydrogen or taken together form:



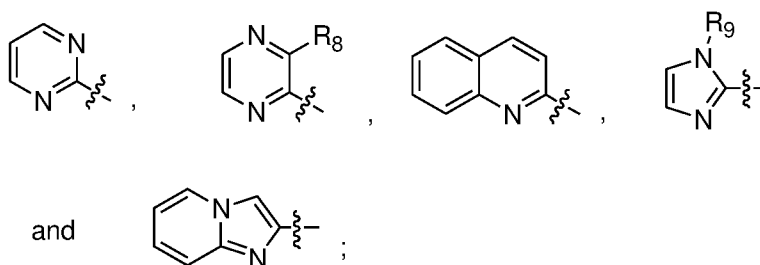
- 102 -

where R_{14} is hydrogen, $(C(R_{10})_2)_m$ aryl or $(C(R_{10})_2)_m$ heteroaryl wherein the aryl and heteroaryl are optionally substituted; or

R_{4a} is absent and R_4 and R_5 taken together form an optionally substituted aryl or optionally substituted heteroaryl group;

- 5 each R_{10} is independently selected from hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, hydroxy, C_{1-6} alkoxy, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, CN, halo and $N(R_9)_2$;
 m is 0 or an integer of 1 to 6;
 or a pharmaceutically acceptable salt thereof.

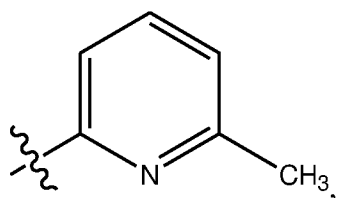
2. The compound according to claim 1 wherein R_1 is selected from the group
 10 consisting of:



or a pharmaceutically acceptable salt thereof.

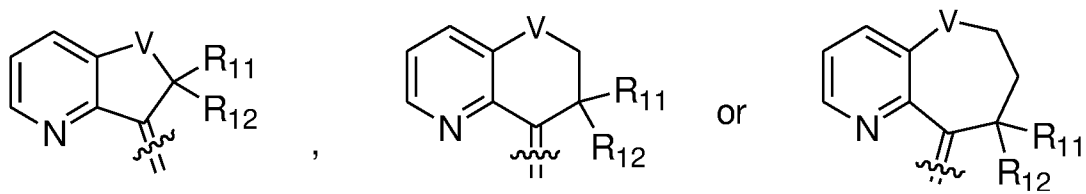
3. The compound according to either one of claims 1 or 2 wherein R_2 is selected from hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-8} cycloalkyl.

- 15 4. The compound according to claim 1 wherein R_1 and R_2 are both



or a pharmaceutically acceptable salt thereof.

5. The compound according to claim 1 wherein R_1 and R_2 together are selected from:



wherein V is CH or O and R₁₁ and R₁₂ are each independently selected from hydrogen, C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₁₋₆haloalkyl, halo, (CH₂)_mC₃₋₈cycloalkyl, (CH₂)_maryl, (CH₂)_mheterocyclyl, (CH₂)_mheteroaryl and COR₁₃ where R₁₃ is selected from OH, OC₁₋₆alkyl, OC₂₋₆alkenyl, OC₂₋₆alkynyl and N(R₉)₂, or a pharmaceutically acceptable salt thereof.

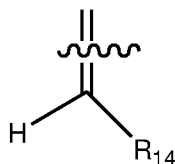
6. The compound according to any one of claims 1 to 5 wherein R₃ is selected from hydrogen, C₁₋₆alkyl, CH₂CO₂H and CH₂CO₂CH₃ or a pharmaceutically acceptable salt thereof.

7. The compound according to any one of claims 1 to 6 wherein R₄ and R_{4a} are each independently selected from hydrogen, C₁₋₃alkyl, C₂₋₃alkenyl, C₂₋₃alkynyl and C₁₋₃haloalkyl; and R₅ is hydrogen, (CH₂)_maryl or (CH₂)_mheteroaryl wherein aryl and heteroaryl are optionally substituted, or a pharmaceutically acceptable salt thereof.

8. The compound according to any one of claims 1 to 6 wherein R_{4a} is absent and R₄ and R₅ taken together form an optionally substituted aryl or optionally substituted heteroaryl group, or a pharmaceutically acceptable salt thereof.

9. The compound according to claim 8 wherein R₄ and R₅ taken together form a phenyl ring, a 2-pyridinyl ring, 3-pyridinyl ring, 4-pyridinyl ring, 3-pyridazinyl ring, 4-pyridazinyl ring, 2-furanyl, 3-furanyl, 2-thiophenyl ring, 3-thiophenyl ring, 2-thiazolyl ring, 3-thiazolyl ring, 4-thiazolyl ring, 3-isoxazolyl ring, 4-isoxazolyl ring, 5-isoxazolyl ring, 4-(1,2,3-thiadiazolyl) ring, 5-(1,2,3-thiadiazolyl) ring, 4-thiadiazolyl ring, 5-thiadiazolyl ring, 2-benzo[b]thiophenyl, 3-benzothiophenyl ring, 3-(1H)-indolyl ring or a 4H-thieno[3,2-c]chromene ring, or a pharmaceutically acceptable salt thereof.

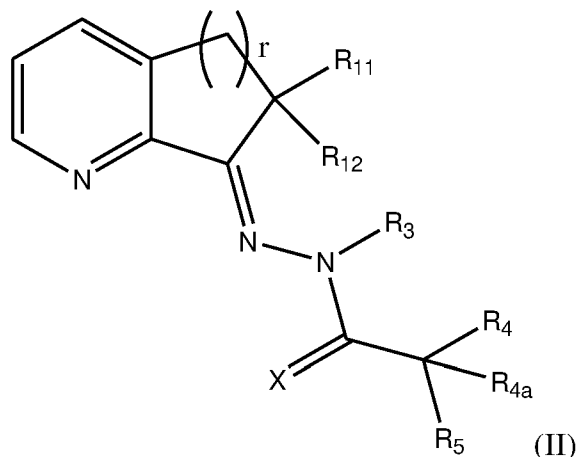
10. The compound according to any one of claims 1 to 6 wherein R_{4a} is CN and R₄ and R₅ taken together form:



where R₁₄ is hydrogen, (C(R₁₀)₂)_maryl or (C(R₁₀)₂)_mheteroaryl wherein aryl and heteroaryl are optionally substituted, or a pharmaceutically acceptable salt thereof.

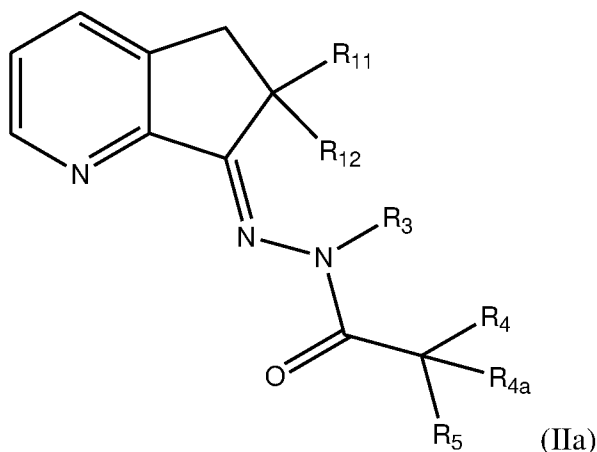
11. The compound according to any one of claims 1 to 6 wherein R_{4a} is CN and R_4 and R_5 are both hydrogen.

12. A compound according to claim 1 which is a compound of formula (II):



5 wherein X, R_3 , R_4 , R_{4a} and R_5 are as defined in claim 1, R_{11} and R_{12} are each independently selected from hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, halo, $(CH_2)_m C_{3-8}$ cycloalkyl, $(CH_2)_m$ aryl, $(CH_2)_m$ heterocyclyl, $(CH_2)_m$ heteroaryl and COR_{13} where R_{13} is selected from OH, OC_{1-6} alkyl, OC_{2-6} alkenyl, OC_{2-6} alkynyl and $N(R_9)_2$ and r is 1, 2 or 3, or a pharmaceutically acceptable salt thereof.

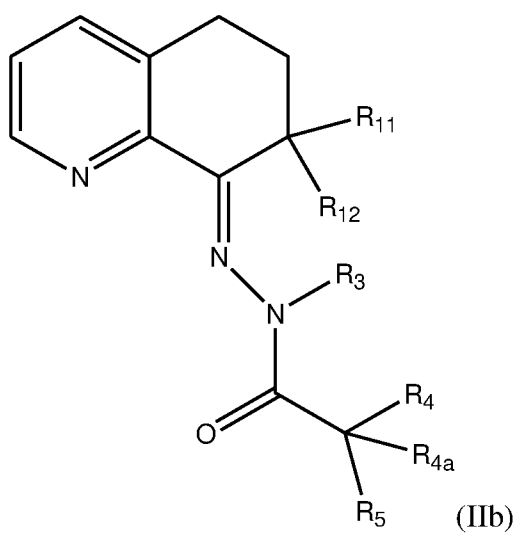
10 13. A compound according to claim 12 which is a compound of formula (IIa):



wherein R_3 , R_4 , R_{4a} , R_5 , R_{11} and R_{12} are as defined for formula (II), or a pharmaceutically acceptable salt thereof.

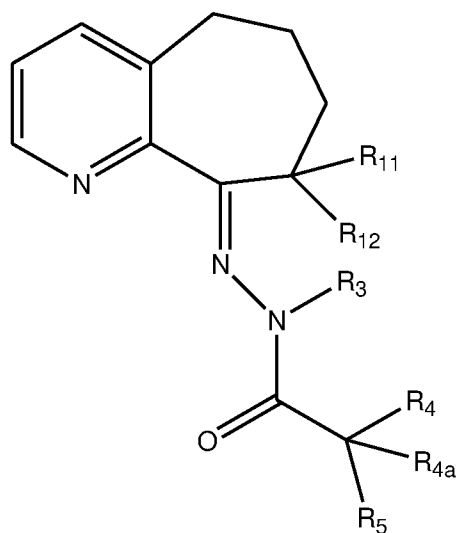
14. A compound according to claim 12 which is a compound of formula (IIb):

- 105 -



wherein R_3 , R_4 , R_{4a} , R_5 , R_{11} and R_{12} are as defined for formula (II), or a pharmaceutically acceptable salt thereof.

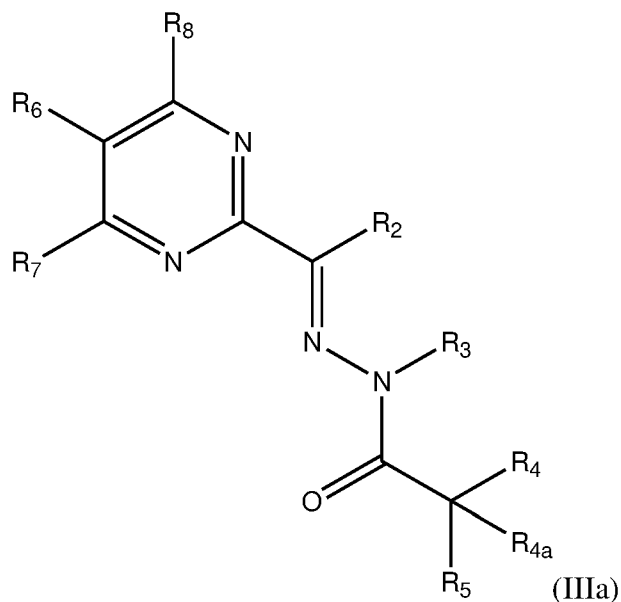
15. A compound according to claim 12 which is a compound of formula (IIc):



5

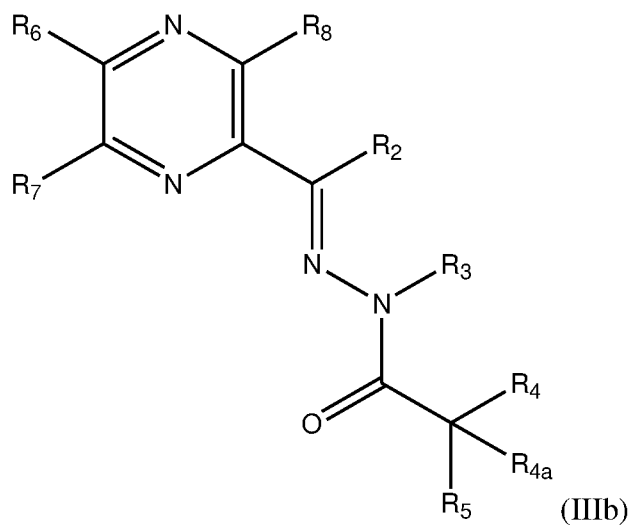
wherein R_3 , R_4 , R_{4a} , R_5 , R_{11} and R_{12} are as defined for formula (II), or a pharmaceutically acceptable salt thereof.

16. A compound according to claim 1 which is a compound of formula (IIIa):



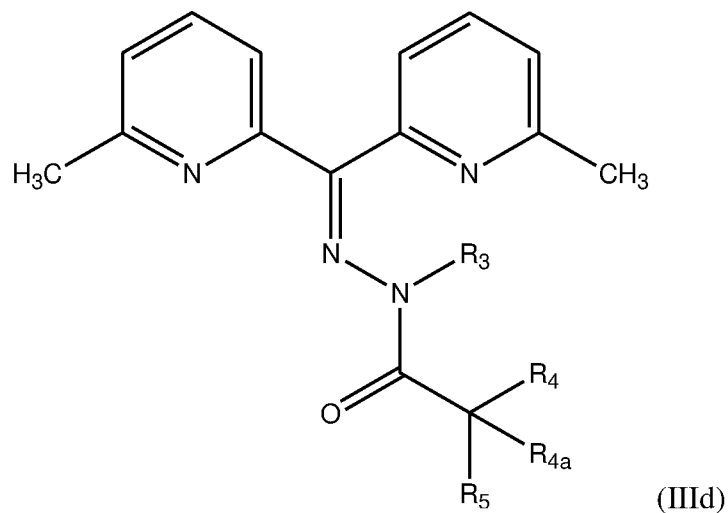
wherein R₂, R₃, R₄, R_{4a}, R₅, R₆, R₇ and R₈ are as defined in claim 1, or a pharmaceutically acceptable salt thereof.

- 5 17. The compound according to claim 1 which is a compound of formula (IIIb):



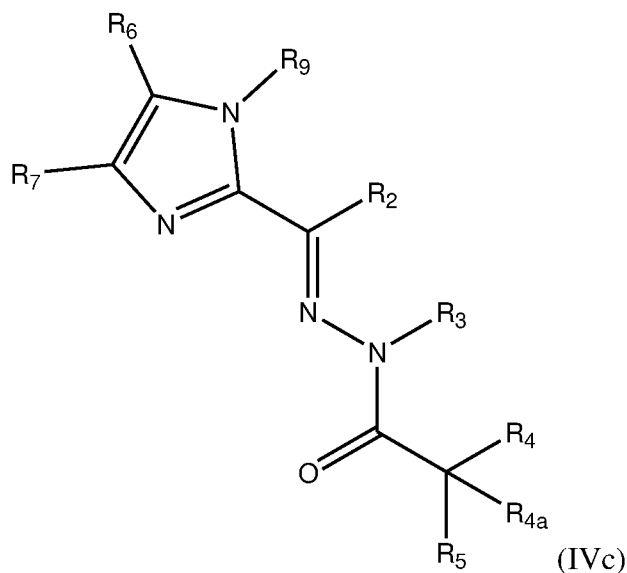
wherein R₂, R₃, R₄, R_{4a}, R₅, R₆, R₇ and R₈ are as defined in claim 1, or a pharmaceutically acceptable salt thereof.

18. The compound according to claim 1 which is a compound of formula (III_d):



wherein R₃, R₄, R_{4a} and R₅ are as defined in claim 1, or a pharmaceutically acceptable salt thereof.

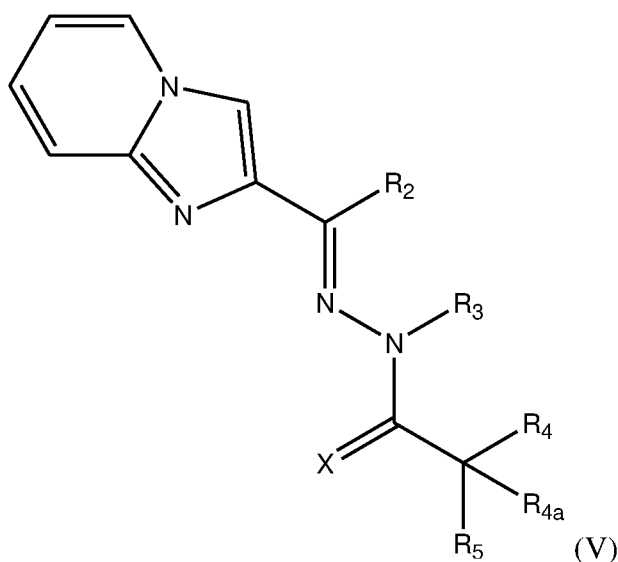
- 5 19. A compound according to claim 1 which is a compound of formula (IV_c):



wherein R₂, R₃, R₄, R_{4a}, R₅, R₆, R₇ and R₈ are as defined in claim 1, or a pharmaceutically acceptable salt thereof.

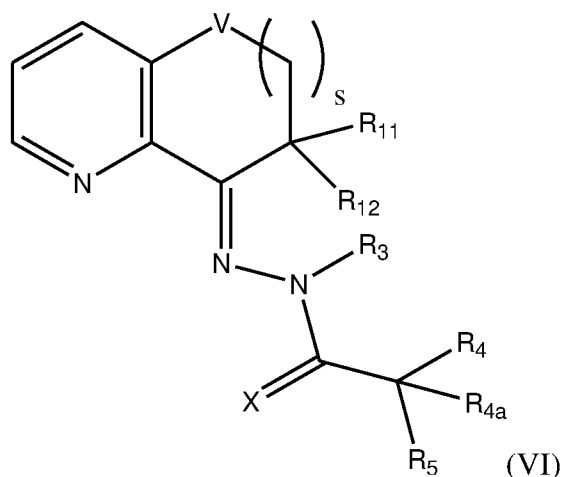
20. A compound according to claim 1 which is a compound of formula (V):

- 108 -



wherein X, R₂, R₃, R₄, R_{4a} and R₅ are as defined in claim 1, or a pharmaceutically acceptable salt thereof.

21. A compound according to claim 1, which is a compound of formula (VI):

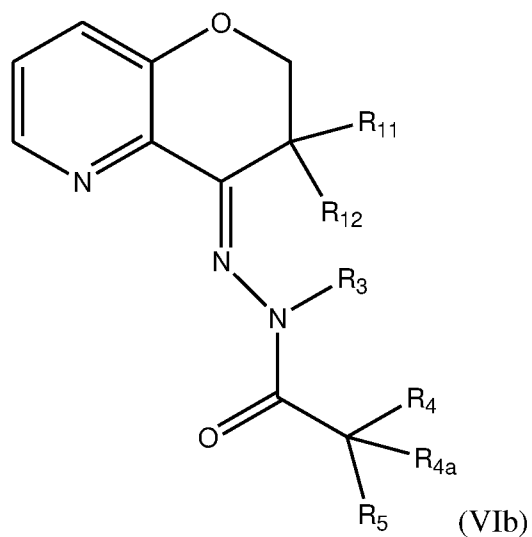


5

wherein X, V, R₃, R₄, R_{4a} and R₅ are as defined for formula (I), R₁₁ and R₁₂ are each independently selected from hydrogen, C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, halo, C₁₋₆haloalkyl, (CH₂)_mC₃₋₆ cycloalkyl, (CH₂)_maryl, (CH₂)_mheterocyclyl, (CH₂)_mheteroaryl and COR₁₃ where R₁₃ is selected from OH, OC₁₋₆alkyl, OC₂₋₆alkenyl, OC₂₋₆alkynyl and
 10 N(R₉)₂ and s is 0, 1 or 2, or a pharmaceutically acceptable salt thereof.

22. A compound according to claim 21, which is a compound of formula (VIb):

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wherein R_3 , R_4 , R_{4a} , R_5 , R_{11} and R_{12} are as defined for formula (VI), or a pharmaceutically acceptable salt thereof.

23. A compound which is one of compounds 1 to 197, or a pharmaceutically acceptable salt thereof.

24. A pharmaceutical composition comprising a compound according to any one of claims 1 to 23 or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/AU2021/050986

A. CLASSIFICATION OF SUBJECT MATTER

[See Supplemental Sheet]

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

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

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

CAPlus & Registry: Structure searches based upon the compounds of formula (Ib) and claim 23.

CAPlus, DOCDB & DWPI: Applicant and inventor search

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
	Documents are listed in the continuation of Box C	

☒ Further documents are listed in the continuation of Box C☒ See patent family annex

* Special categories of cited documents:	
"A" document defining the general state of the art which is not considered to be of particular relevance	"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"D" document cited by the applicant in the international application	"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E" earlier application or patent but published on or after the international filing date	"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&" document member of the same patent family
"O" document referring to an oral disclosure, use, exhibition or other means	
"P" document published prior to the international filing date but later than the priority date claimed	

Date of the actual completion of the international search
6 October 2021Date of mailing of the international search report
06 October 2021

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INTERNATIONAL SEARCH REPORT		International application No.
C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		PCT/AU2021/050986
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	Kalinowski, D. S. et al., 'Structure-activity relationships of novel iron chelators for the treatment of iron overload disease: the methyl pyrazinylketone isonicotinoyl hydrazone series', Journal of Medicinal Chemistry, 2008, 51(2), 331-344 Abstract & figure 1	1-3, 6, 8, 9, 17 & 24
X	WO 89/00992 A1 (THE UPJOHN COMPANY) 09 February 1989 Abstract & Table A	1-3, 6-9, 17 & 24
X	WO 86/05982 A2 (THE UPJOHN COMPANY) 23 October 1986 Abstract & Table A	1-3, 6, 7-9 & 24
X	Laddha, P. R. et al., 'Synthesis, characterization and antimicrobial evaluation of novel schiff bases of aryloxy moiety', Pharmaceutical Resonance, 2019, 2(1), 33-37 Abstract & Table 1	1-3, 6, 7, 19 & 24
X	Hassan, N. W. et al., 'Novel pyrazine based anti-tubercular agents: Design, synthesis, biological evaluation and in silico studies', Bioorganic Chemistry, 2020, 103610pp. Available online 25 January 2020 Abstract & schemes 1 & 2	1-3, 6-8, 11, 17 & 24
X	Cardoso, L. N. F. et al., 'Anti-tuberculosis evaluation and conformational study of N-acylhydrazones containing the thiophene nucleus', Archiv der Pharmazie, 2014, 347(6), 432-448 Abstract & table 1	1-3, 6, 7, 19 & 24
X	Lima, C. H. S. et al., 'Synthesis and antimycobacterial evaluation of N'-(E)-heteroaromaticpyrazine-2-carbohydrazide derivatives', Medicinal Chemistry, 2011, 7(3), 245-249 Abstract & scheme 1	1-3, 6, 8, 19 & 24
X	Sarodnick, G. et al., 'Quinoxalines X [1]. A New and Convenient Synthesis of 1H-Pyrazolo[3,4-b]quinoxalines (Flavazoles)', Journal of Heterocyclic Chemistry, 2001, 38(4), 829-836 Abstract & Scheme 4	1, 3, 6, 8, 9 & 17
X	Nayyar, A. et al., 'Synthesis, anti-tuberculosis activity, and 3D-QSAR study of ring-substituted-2/4-quinolinecarbaldehyde derivatives', Bioorganic & Medicinal Chemistry, 2006, 7302-7310 Abstract & Table 1	1-3, 7 & 24
X	Mahishi, N. B. et al., 'Chlorophenoxyacetic acids and their derivatives as possible tuberculostats', Journal of the Indian Chemical Society, 1965, 42(2), 67-74 Abstract & table 1	1-3, 6 & 24
X	WO 96/29871 A2 (NIHON NOHYAKU CO., LTD.) 03 October 1996 Page 36	23
X	CAS Registry No. 1224623-79-3; Date entered STN 19 May 2010; 2-Pyridinecarboxylic acid, (2E)-2-(2-thiazolylmethylene)hydrazide The compound	23
Form PCT/ISA/210 (fifth sheet) (July 2019)		

INTERNATIONAL SEARCH REPORT Information on patent family members		International application No. PCT/AU2021/050986	
This Annex lists known patent family members relating to the patent documents cited in the above-mentioned international search report. The Australian Patent Office is in no way liable for these particulars which are merely given for the purpose of information.			
Patent Document/s Cited in Search Report		Patent Family Member/s	
Publication Number	Publication Date	Publication Number	Publication Date
WO 89/00992 A1	09 February 1989	WO 8900992 A1	09 Feb 1989
		AU 2314488 A	01 Mar 1989
		EP 0370065 A1	30 May 1990
		JP H03500769 A	21 Feb 1991
		US 5049561 A	17 Sep 1991
WO 86/05982 A2	23 October 1986	WO 8605982 A2	23 Oct 1986
		EP 0218689 A1	22 Apr 1987
		EP 0218689 B1	01 Aug 1990
		EP 0263209 A2	13 Apr 1988
		JP S62502469 A	24 Sep 1987
		US 4870082 A	26 Sep 1989
WO 96/29871 A2	03 October 1996	None	
End of Annex			
Due to data integration issues this family listing may not include 10 digit Australian applications filed since May 2001. Form PCT/ISA/210 (Family Annex)(July 2019)			

INTERNATIONAL SEARCH REPORT

International application No.

PCT/AU2021/050986

Supplemental Box – IPC Marks

*C07D 215/40 (2006.01)**C07D 209/16 (2006.01)**C07D 213/53 (2006.01)**C07D 215/12 (2006.01)**C07D 221/04 (2006.01)**C07D 233/64 (2006.01)**C07D 237/10 (2006.01)**C07D 239/26 (2006.01)**C07D 241/12 (2006.01)**C07D 261/18 (2006.01)**C07D 277/28 (2006.01)**C07D 277/64 (2006.01)**C07D 285/06 (2006.01)**C07D 307/52 (2006.01)**C07D 317/68 (2006.01)**C07D 333/28 (2006.01)**C07D 333/38 (2006.01)**C07D 333/58 (2006.01)**C07D 471/04 (2006.01)**C07D 491/052 (2006.01)**C07D 495/04 (2006.01)**A61P 25/28 (2006.01)*