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(54) Title: COMPOUNDS AND METHODS FOR TREATING DISEASES OR CONDITIONS ASSOCIATED WITH THE CENTRAL NERVOUS SYSTEM AND/OR NEURITE OUTGROWTH

(57) Abstract: The present disclosure relates to quinoline compounds of formula I, compositions comprising them and methods and uses for the treatment of central nervous system disorders, such as mood disorders (eg. depression), anxiety disorders, and neurodegenerative diseases. Additionally, the disclosure relates to methods of enhancing neurite outgrowth and the treatment of diseases/conditions associated with neurite outgrowth (eg. multiple sclerosis).

**COMPOUNDS AND METHODS FOR TREATING DISEASES OR CONDITIONS  
ASSOCIATED WITH THE CENTRAL NERVOUS SYSTEM AND/OR NEURITE  
OUTGROWTH**

**Field**

The present disclosure relates generally compounds useful for the treatment of central nervous system disorders, such as mood disorders (e.g., depression), anxiety disorders, and neurodegenerative diseases. The subject disclosure enables the manufacture of medicaments as well as compositions containing same for use in methods of therapy and prophylaxis of central nervous system disorders.

**Background of the Invention**

A neurite is any projection or outgrowth emanating from the cell body of a neuron or nerve cell. Neurons are the core components of the nervous system, which includes the brain, spinal cord, and peripheral ganglia. Compounds inducing neurite outgrowth have neuroprotective properties and the induction of neurite outgrowth is a surrogate of the ability of a compound to induce neurogenesis.

Neurotrophins are critical mediators of neuronal survival during development and are involved in the regulation of neurogenesis (axonal and dendritic outgrowth), synapse formation and function, cell migration and cell proliferation, plasticity, survival and differentiation in adult neurons and glia. Although the majority of neurons in the mammalian brain are formed prenatally, parts of the adult brain retain the ability to grow new neurons from neural stem cells in a process known as neurogenesis.

Neurotrophins are highly specific ligands for Trk (tropomyosin receptor-kinase) receptors, the most common of which are TrkB, TrkA, and TrkC. Each type of neurotrophin has a different binding affinity toward its corresponding Trk receptor. TrkA is a signaling receptor for nerve growth factor (NGF), TrkB is a signaling receptor for the related neurotrophin brain-derived neurotrophic factor (BDNF), neurotrophin 4/5 and, with lower

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affinity, for neurotrophin-3, and TrkC is a receptor for neurotrophin-3 (NT3). The activation of Trk receptors by the binding of specific neurotrophins triggers receptor dimerization and consequent trans-phosphorylation of tyrosine residues of the tyrosine kinase domain. Phosphorylated receptors undergo conformational changes which promote the recruitment of intracellular substrates such SHC1, PI-3 kinase and PLC $\gamma$ -1 to activate signaling cascades. For example, the recruitment and tyrosine phosphorylation of PLC $\gamma$ -1 activates this enzyme and catalyzes the breakdown of lipids to diacyl glycerol and inositol(1,4,5)triphosphate (IP3). Binding of IP3 to specific receptors promotes release of calcium from intracellular stores, while diacyl glycerol allows maximal activation of several protein kinase C isoforms. In addition, the phospholipase pathway can indirectly activate MAP kinases and phosphatidylinositol 30-kinase (PI3 kinase) by changes in intracellular calcium. These intracellular signal cascades may result in neurogenesis, promotion of neuronal survival during development and following injuries, neuronal differentiation and maintenance, control short-term and long-term synaptic activity and other functional regulation of cells.

Antidepressants (*e.g.*, SSRIs and tricyclics) and mood stabilisers (sodium valproate, lithium) have been found to exhibit neurotrophic properties. These effects are not directly mediated through Trk receptors but occur via activation of neurotrophic signalling pathways that trigger biological events within the cell to modulate neuronal function. Activation of G-protein coupled receptors, for example, initiates signalling from many downstream effector proteins, such as phospholipases and ion channels, thus permitting the release of second messenger molecules within the cell, such as IP3 or calcium ions to promote neurogenesis.

Neurodegenerative diseases are characterised by a loss of neurons from specific regions of the central nervous system. Current research has provided evidence that neurogenesis is impaired in neurodegenerative diseases such as Parkinson's disease, Lewy body disease, and Huntington's disease, and amyotrophic lateral sclerosis, and that stimulation of neurogenesis is associated with restored function in animal models of these diseases, suggesting that neurogenesis is functionally important.

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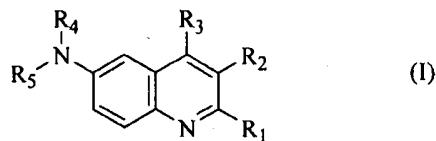
From the above it can be observed that neurite outgrowth is a critical event in neuronal development, the formation and remodelling of synapses, response to injury, and regeneration. Changes in the pattern of neurite outgrowth have been implicated in neurodegenerative disorders including traumatic brain injury. The discovery of new compounds that can positively affect neurite outgrowth by directly modulating neurotrophic pathways is important for the development of new therapeutic agents for treating certain central nervous system disorders (including mood disorders, such as depression, anxiety disorders, neurodegenerative diseases, and brain injury).

### **Summary**

The instant disclosure teaches that compounds of formula (I) act as effective enhancers of neurite outgrowth in animals including mammals (such as human) and are therefore therapeutically useful in the prophylaxis and treatment of certain central nervous system (CNS) disorders, such as mood disorders (*e.g.*, depression) and neurodegenerative diseases, such as, for instance, multiple sclerosis.

The term "disorder" includes an adverse condition, trauma or other adverse manifestation of the CNS.

Accordingly, provided herein are methods of enhancing neurite outgrowth in a subject in need thereof, the method comprising the step of administering an effective amount of a compound of formula (I) or pharmaceutically acceptable salt thereof:



wherein

R<sub>1</sub> represents hydrogen, or optionally substituted C<sub>1</sub>-C<sub>6</sub> alkyl;

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R<sub>2</sub> represents -C(O)NR'R'' (where R' is -H or optionally substituted C<sub>1</sub>-C<sub>6</sub> alkyl and R'' is optionally substituted C<sub>1</sub>-C<sub>6</sub> alkyl, -OH or -CN, or R' and R'' together form an optionally substituted heterocyclyl), -C(O)OR' (where R' is -H or optionally substituted C<sub>1</sub>-C<sub>6</sub> alkyl), -C(O)NHSO<sub>2</sub>R''' (where R''' is optionally substituted aryl or optionally substituted C<sub>1</sub>-C<sub>6</sub> alkyl), -S(O)<sub>2</sub>NHR'''' (where R'''' is -H, optionally substituted C<sub>1</sub>-C<sub>6</sub> alkyl, or optionally substituted aryl), optionally substituted heteroaryl or optionally substituted heterocyclyl;

R<sub>3</sub> represents optionally substituted aryl or optionally substituted heteroaryl;

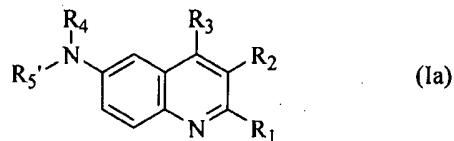
R<sub>4</sub> represents H, optionally substituted alkyl, optionally substituted aryl, optionally substituted cycloalkyl, optionally substituted cycloalkenyl, optionally substituted acyl, optionally substituted alkenyl, optionally substituted heterocyclyl, optionally substituted heteroaryl, optionally substituted oxysulfinyl, optionally substituted oxysulfonyl, optionally substituted sulfinyl, or optionally substituted sulfonyl; and

R<sub>5</sub> represents H, optionally substituted cycloalkyl, optionally substituted cycloalkenyl, optionally substituted acyl, optionally substituted aryl, optionally substituted arylalkyl, optionally substituted heteroaryl, optionally substituted heteroarylalkyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted cycloalkylalkyl, -S(O)<sub>2</sub>-optionally substituted C<sub>1</sub>-C<sub>6</sub> alkyl, or -C(O)NR'R' (wherein each R' is independently H, optionally substituted C<sub>1</sub>-C<sub>6</sub> alkyl or optionally substituted aryl).

In some embodiments, the compound of formula (I) is not 6-(2,3-dihydro-1H-inden-2-ylamino)-2-methyl-4-phenylquinoline-3-carboxylic acid.

The present invention also provides methods for treating central nervous system disorders, such as anxiety disorders, mood disorders (e.g., depression), and/or neurodegenerative diseases (e.g., multiple sclerosis) comprising the step of administering to a patient in need thereof a compound of formula (Ia) or a pharmaceutically acceptable salt thereof;

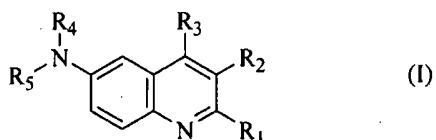
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wherein R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub>, and R<sub>4</sub> are as described herein; and

R<sub>5</sub>' represents H, optionally substituted acyl, optionally substituted aryl, optionally substituted arylalkyl, optionally substituted heteroaryl, optionally substituted heteroarylalkyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted cycloalkylalkyl, -S(O)<sub>2</sub>-optionally substituted C<sub>1</sub>-C<sub>6</sub> alkyl, or -C(O)NR'R' (wherein each R' is independently H, optionally substituted C<sub>1</sub>-C<sub>6</sub> alkyl or optionally substituted aryl).

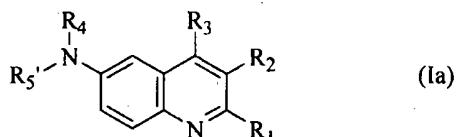
The present invention also provides the use of a compound of formula (I) or a salt thereof:



wherein R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub>, R<sub>4</sub>, and R<sub>5</sub> are as described herein,

in the manufacture of a medicament for enhancing neurite outgrowth in a subject in need thereof.

The present invention also provides the use of a compound of formula (Ia) or a salt thereof:



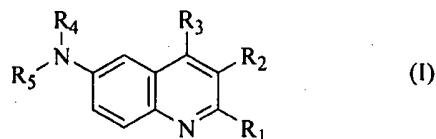
wherein R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub>, and R<sub>4</sub> are as described herein; and

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$R_5$  represents H, optionally substituted acyl, optionally substituted aryl, optionally substituted arylalkyl, optionally substituted heteroaryl, optionally substituted heteroarylalkyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted cycloalkylalkyl,  $-S(O)_2$ -optionally substituted C<sub>1</sub>-C<sub>6</sub> alkyl, or  $-C(O)NR'R'$  (wherein each R' is independently H, optionally substituted C<sub>1</sub>-C<sub>6</sub> alkyl or optionally substituted aryl),

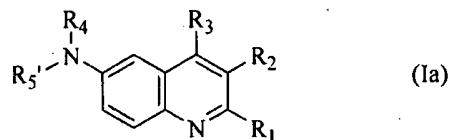
in the manufacture of a medicament for the treatment of central nervous system disorders, such as anxiety disorders and/or depression.

The present invention also provides the use of a compound of formula (I) or a salt thereof:



wherein R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub>, R<sub>4</sub>, and R<sub>5</sub> are as described herein, for enhancing neurite outgrowth in a subject in need thereof.

The present invention also provides the use of a compound of formula (Ia) or a salt thereof:



wherein R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub>, and R<sub>4</sub> are as described herein, and

$R_5$  represents H, optionally substituted acyl, optionally substituted aryl, optionally substituted arylalkyl, optionally substituted heteroaryl, optionally substituted heteroarylalkyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted cycloalkylalkyl,  $-S(O)_2$ -optionally substituted C<sub>1</sub>-C<sub>6</sub> alkyl, or  $-C(O)NR'R'$  (wherein each R' is independently H, optionally substituted C<sub>1</sub>-C<sub>6</sub> alkyl or optionally substituted aryl),

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for the treatment of central nervous system disorders, such as anxiety disorders, mood disorders (*e.g.*, depression), and/or neurodegenerative diseases (*e.g.*, multiple sclerosis).

### **Detailed Description of the Invention**

The present disclosure contemplates the treatment or prophylaxis of a disease of the central nervous system, such as mood disorders (*e.g.*, depression), anxiety disorders, and neurodegenerative diseases. The term neurodegenerative disease encompasses a condition leading to the progressive loss of structure or function of neurons, including death of neurons. Examples of neurodegenerative diseases contemplated herein include AIDS dementia complex, adrenoleukodystrophy, alexander disease, Alpers' disease, amyotrophic lateral sclerosis, ataxia telangiectasia, Batten disease, bovine spongiform encephalopathy, Canavan disease, corticobasal degeneration, Creutzfeldt–Jakob disease, dementia with Lewy bodies, fatal familial insomnia, frontotemporal lobar degeneration, Huntington's disease, infantile Refsum disease, Kennedy's disease, Krabbe disease, Lyme disease, Machado–Joseph disease, monomelic amyotrophy, multiple sclerosis, multiple system atrophy, neuroacanthocytosis, Niemann–Pick disease, neurodegeneration with brain iron accumulation, opsoclonus myoclonus, Parkinson's disease, Pick's disease, primary lateral sclerosis, progranulin, progressive multifocal leukoencephalopathy, progressive supranuclear palsy, protein aggregation, Refsum disease, Sandhoff disease, diffuse myelinoclastic sclerosis, Shy–Drager syndrome, spinocerebellar ataxia, subacute combined degeneration of spinal cord, Tabes dorsalis, Tay–Sachs disease, toxic encephalopathy, transmissible spongiform encephalopathy, and Wobbly hedgehog syndrome.

It is proposed herein that the compounds of formula (I) treat, ameliorate the symptoms of, prevent, or otherwise delay the onset or development of the CNS disease, disorder, or condition.

The invention is also based on the discovery that the compounds of the general formula (Ia) as described herein have useful properties as possible ligands for biological receptors

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and biological targets that elicit an effect on the central nervous system. Such compounds have significant potential for the treatment of a variety of disorders of the central nervous system, and in particular disorders such as anxiety and depression.

"Alkyl" refers to a saturated monovalent hydrocarbon radical which may be straight chained or branched and preferably have from 1 to 10 carbon atoms or more preferably 1 to 6 carbon atoms or 1 to 9 carbon atoms (i.e., C<sub>1</sub>-C<sub>4</sub> alkyl). Examples of such alkyl groups include methyl, ethyl, *n*-propyl, *iso*-propyl, *n*-butyl, *iso*-butyl, *n*-hexyl, and the like.

"Alkylene" refers to divalent alkyl groups preferably having from 1 to 10 carbon atoms and more preferably 1 to 6 carbon atoms. Examples of such alkylene groups include methylene (-CH<sub>2</sub>), ethylene (-CH<sub>2</sub>CH<sub>2</sub>-), and the propylene isomers (e.g., -CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>- and -CH(CH<sub>3</sub>)CH<sub>2</sub>-), and the like.

"Aryl" refers to an unsaturated aromatic carbocyclic group having a single ring (eg. phenyl) or multiple condensed rings (eg. naphthyl or anthryl), preferably having from 6 to 14 carbon atoms. Examples of aryl groups include phenyl, naphthyl and the like.

"Aryloxy" refers to the group aryl-O- wherein the aryl group is as described above.

"Arylalkyl" refers to -alkylene-aryl groups preferably having from 1 to 10 carbon atoms in the alkylene moiety and from 6 to 10 carbon atoms in the aryl moiety. Such arylalkyl groups are exemplified by benzyl, phenethyl and the like.

"Arylalkoxy" refers to the group arylalkyl-O- wherein the arylalkyl group are as described above. Such arylalkoxy groups are exemplified by benzyloxy and the like.

"Alkoxy" refers to the group alkyl-O- where the alkyl group is as described above. Examples include, methoxy, ethoxy, *n*-propoxy, *iso*-propoxy, *n*-butoxy, *tert*-butoxy, *sec*-butoxy, *n*-pentoxy, *n*-hexoxy, 1,2-dimethylbutoxy, and the like.

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"Alkenyl" refers to a monovalent hydrocarbon radical with at least one site of unsaturation, *i.e.*, a carbon-carbon,  $sp^2$  double bond, which may be straight chained or branched and preferably have from 2 to 10 carbon atoms and more preferably 2 to 6 carbon atoms and have at least 1 and preferably from 1-2, carbon to carbon, double bonds. An alkenyl radical includes radicals having "cis" and "trans" orientations, or alternatively, "E" and "Z" orientations. Examples include ethenyl (-CH=CH<sub>2</sub>), *n*-propenyl (-CH<sub>2</sub>CH=CH<sub>2</sub>), *iso*-propenyl (-C(CH<sub>3</sub>)=CH<sub>2</sub>), but-2-enyl (-CH<sub>2</sub>CH=CHCH<sub>3</sub>), and the like.

"Alkenyloxy" refers to the group alkenyl-O- wherein the alkenyl group is as described above.

"Alkynyl" refers to a linear or branched monovalent hydrocarbon radical with at least one site of unsaturation, *i.e.*, a carbon-carbon sp triple bond, preferably having from 2 to 10 carbon atoms and more preferably 2 to 6 carbon atoms and having at least 1, and preferably from 1-2, carbon to carbon, triple bonds. Examples of alkynyl groups include ethynyl (-C≡CH), propargyl (-CH<sub>2</sub>C≡CH), pent-2-ynyl (-CH<sub>2</sub>C≡CCH<sub>2</sub>-CH<sub>3</sub>), and the like.

"Alkynyloxy" refers to the group alkynyl-O- wherein the alkynyl groups is as described above.

"Acyl" refers to groups H-C(O)-, alkyl-C(O)-, cycloalkyl-C(O)-, aryl-C(O)-, heteroaryl-C(O)- and heterocycl-C(O)-, where alkyl, cycloalkyl, aryl, heteroaryl and heterocycl are as described herein.

"Oxyacyl" refers to groups HO-C(O)-, alkyl-OC(O)-, cycloalkyl-OC(O)-, aryl-OC(O)-, heteroaryl-OC(O)-, and heterocycl-OC(O)-, where alkyl, cycloalkyl, aryl, heteroaryl and heterocycl are as described herein.

"Amino" refers to the group -NR<sup>A</sup>R<sup>A</sup> where each R<sup>A</sup> is independently hydrogen, alkyl, cycloalkyl, aryl, heteroaryl, and heterocycl and where each of alkyl, cycloalkyl, aryl, heteroaryl and heterocycl is as described herein.

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"Aminoacyl" refers to the group  $-C(O)NR^A R^A$  where each  $R^A$  is independently hydrogen, alkyl, cycloalkyl, aryl, heteroaryl, and heterocyclyl and where each of alkyl, cycloalkyl, aryl, heteroaryl and heterocyclyl is as described herein.

"Acylamino" refers to the group  $-NR^A C(O)R^A$  where each  $R^A$  is independently hydrogen, alkyl, cycloalkyl, aryl, heteroaryl and heterocyclyl and where each of alkyl, cycloalkyl, aryl, heteroaryl, and heterocyclyl are as described herein.

"Acyloxy" refers to the groups  $-OC(O)$ -alkyl,  $-OC(O)$ -aryl,  $-C(O)O$ -heteroaryl, and  $-C(O)O$ -heterocyclyl where alkyl, aryl, heteroaryl and heterocyclyl are as described herein.

"Aminoacyloxy" refers to the groups  $-OC(O)NR^A$ -alkyl,  $-OC(O)NR^A$ -aryl,  $-OC(O)NR^A$ -heteroaryl, and  $-OC(O)NR^A$ -heterocyclyl where  $R^A$  is independently hydrogen, alkyl, cycloalkyl, aryl, heteroaryl, and heterocyclyl and where each of alkyl, cycloalkyl, aryl, heteroaryl and heterocyclyl is as described herein.

"Oxyacylamino" refers to the groups  $-NR^A C(O)O$ -alkyl,  $-NR^A C(O)O$ -aryl,  $-NR^A C(O)O$ -heteroaryl, and  $NR^A C(O)O$ -heterocyclyl where  $R^A$  is independently hydrogen, alkyl, cycloalkyl, aryl, heteroaryl, and heterocyclyl and where each of alkyl, cycloalkyl, aryl, heteroaryl and heterocyclyl is as described herein.

"Oxyacyloxy" refers to the groups  $-OC(O)O$ -alkyl,  $-O-C(O)O$ -aryl,  $-OC(O)O$ -heteroaryl, and  $-OC(O)O$ -heterocyclyl where alkyl, cycloalkyl, aryl, heteroaryl, and heterocyclyl are as described herein.

"Acylimino" refers to the groups  $-C(NR^A)-R^A$  where each  $R^A$  is independently hydrogen, alkyl, cycloalkyl, aryl, heteroaryl and heterocyclyl and where each of alkyl, cycloalkyl, aryl, heteroaryl, and heterocyclyl are as described herein.

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"Acyliminoxy" refers to the groups  $-\text{O}-\text{C}(\text{NR}^A)-\text{R}^A$  where each  $\text{R}^A$  is independently hydrogen, alkyl, cycloalkyl, aryl, heteroaryl and heterocyclyl and where each of alkyl, cycloalkyl, aryl, heteroaryl, and heterocyclyl are as described herein.

"Oxyacylimino" refers to the groups  $-\text{C}(\text{NR}^A)-\text{OR}^A$  where each  $\text{R}^A$  is independently hydrogen, alkyl, cycloalkyl, aryl, heteroaryl and heterocyclyl and where each of alkyl, cycloalkyl, aryl, heteroaryl, and heterocyclyl are as described herein.

"Cycloalkyl" refers to cyclic alkyl groups having a single cyclic ring or multiple condensed rings, preferably incorporating 3 to 11 carbon atoms. Such cycloalkyl groups include, by way of example, single ring structures such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cyclooctyl, and the like. The term also includes polycyclic ring systems where the cycloalkyl ring is fused with one or more aromatic or non-aromatic carbocyclic or heterocyclic rings, such as adamantanyl, indanyl, 1,2,3,4-tetrahydronaphthalenyl and the like. It will also be understood by one skilled in the art that a cycloalkyl may be attached via an alkylene moiety to form a "cycloalkylalkyl" group. In some embodiments, the alkylene moiety of a cycloalkylalkyl group contains between 1 and 10 carbon atoms. In certain embodiments, the alkylene moiety of a cycloalkylalkyl group contains between 1 and 3 carbon atoms. In some embodiments, a cycloalkylalkyl group is optionally substituted on the alkylene moiety and/or on the cycloalkyl.

"Cycloalkenyl" refers to cyclic alkenyl groups having a single cyclic ring or multiple condensed rings, and at least one point of internal unsaturation, preferably incorporating 4 to 11 carbon atoms. Examples of suitable cycloalkenyl groups include, for instance, cyclobut-2-enyl, cyclopent-3-enyl, cyclohex-4-enyl, cyclooct-3-enyl, indenyl and the like.

"Halo" or "halogen" refers to fluoro, chloro, bromo and iodo.

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"Heteroaryl" refers to a monovalent aromatic heterocyclic group which fulfills the Hückel criteria for aromaticity (ie. contains  $4n + 2 \pi$  electrons) and preferably has from 2 to 10 carbon atoms and 1 to 4 heteroatoms selected from oxygen, nitrogen, selenium, and sulfur within the ring (and includes oxides of sulfur, selenium and nitrogen). Such heteroaryl groups can have a single ring (eg. pyridyl, pyrrolyl or N-oxides thereof or furyl) or multiple condensed rings (eg. indolizinyl, benzoimidazolyl, coumarinyl, quinolinyl, isoquinolinyl or benzothienyl). It will be understood that where, for instance, R<sub>2</sub> is an optionally substituted heteroaryl which has one or more ring heteroatoms, the heteroaryl group can be connected to the core molecule of the compounds of the present invention, through a C-C or C-heteroatom bond, in particular a C-N bond. It will also be understood by one skilled in the art that a heteroaryl may be attached via an alkylene moiety to form a "heteroarylalkyl" group. In some embodiments, the alkylene moiety of a heteroarylalkyl group contains between 1 and 10 carbon atoms. In certain embodiments, the alkylene moiety of a heteroarylalkyl group contains between 1 and 3 carbon atoms. In some embodiments, a heteroarylalkyl group is optionally substituted on the alkylene moiety and/or on the heteroaryl.

"Heterocycl" refers to a monovalent saturated or unsaturated group having a single ring or multiple condensed rings, preferably from 1 to 8 carbon atoms and from 1 to 4 hetero atoms selected from nitrogen, sulfur, oxygen, selenium or phosphorous within the ring. In some embodiments, the heteroatom is nitrogen. It will be understood that where, for instance, R<sub>2</sub> is an optionally substituted heterocycl which has one or more ring heteroatoms, the heterocycl group can be connected to the core molecule of the compounds of the present invention, through a C-C or C-heteroatom bond, in particular a C-N bond. It will also be understood by one skilled in the art that a heterocycl may be attached via an alkylene moiety to form a "heterocyclalkyl" group. In some embodiments, the alkylene moiety of a heterocyclalkyl group contains between 1 and 10 carbon atoms. In certain embodiments, the alkylene moiety of a heterocyclalkyl group contains between 1 and 3 carbon atoms. In some embodiments, a heterocyclalkyl group is optionally substituted on the alkylene moiety and/or on the heterocycl.

Examples of heterocyclyl and heteroaryl groups include, but are not limited to, oxazole, pyrrole, imidazole, pyrazole, pyridine, pyrazine, pyrimidine, pyridazine, indolizine, isoindole, indole, indazole, purine, quinolizine, isoquinoline, quinoline, phthalazine, naphthylpyridine, quinoxaline, quinazoline, cinnoline, pteridine, carbazole, carboline, phenanthridine, acridine, phenanthroline, isothiazole, phenazine, isoxazole, isothiazole, phenoxazine, phenothiazine, imidazolidine, imidazoline, piperidine, piperazine, indoline, phthalimide, 1,2,3,4-tetrahydroisoquinoline, 4,5,6,7-tetrahydrobenzo[b]thiophene, thiazole, thiadiazoles, oxadiazole, oxatriazole, tetrazole, thiazolidine, thiophene, benzo[b]thiophene, morpholino, piperidinyl, pyrrolidine, tetrahydrofuranyl, triazole, and the like.

"Thio" refers to groups H-S-, alkyl-S-, cycloalkyl-S-, aryl-S-, heteroaryl-S-, and heterocyclyl-S-, where alkyl, cycloalkyl, aryl, heteroaryl and heterocyclyl are as described herein.

"Thioacyl" refers to groups H-C(S)-, alkyl-C(S)-, cycloalkyl-C(S)-, aryl-C(S)-, heteroaryl-C(S)-, and heterocyclyl-C(S)-, where alkyl, cycloalkyl, aryl, heteroaryl and heterocyclyl are as described herein.

"Oxythioacyl" refers to groups HO-C(S)-, alkylO-C(S)-, cycloalkylO-C(S)-, arylO-C(S)-, heteroarylO-C(S)-, and heterocyclylO-C(S)-, where alkyl, cycloalkyl, aryl, heteroaryl and heterocyclyl are as described herein.

"Oxythioacyloxy" refers to groups HO-C(S)-O-, alkylO-C(S)-O-, cycloalkylO-C(S)-O-, arylO-C(S)-O-, heteroarylO-C(S)-O-, and heterocyclylO-C(S)-O-, where alkyl, cycloalkyl, aryl, heteroaryl and heterocyclyl are as described herein.

"Phosphorylamino" refers to the groups  $-NR^A-P(O)(R^B)(OR^C)$  where  $R^A$  represents H, alkyl, cycloalkyl, alkenyl, or aryl,  $R^B$  represents  $OR^C$  or is hydroxy or amino and  $R^C$  is alkyl, cycloalkyl, aryl or arylalkyl, where alkyl, amino, alkenyl, aryl, cycloalkyl, and arylalkyl are as described herein.

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"Thioacyloxy" refers to groups H-C(S)-O-, alkyl-C(S)-O-, cycloalkyl-C(S)-O-, aryl-C(S)-O-, heteroaryl-C(S)-O-, and heterocyclyl-C(S)-O-, where alkyl, cycloalkyl, aryl, heteroaryl, and heterocyclyl are as described herein.

"Sulfinyl" refers to groups H-S(O)-, alkyl-S(O)-, cycloalkyl-S(O)-, aryl-S(O)-, heteroaryl-S(O)-, and heterocyclyl-S(O)-, where alkyl, cycloalkyl, aryl, heteroaryl and heterocyclyl are as described herein.

"Sulfonyl" refers to groups H-S(O)<sub>2</sub>-, alkyl-S(O)<sub>2</sub>-, cycloalkyl-S(O)<sub>2</sub>-, aryl-S(O)<sub>2</sub>-, heteroaryl-S(O)<sub>2</sub>-, and heterocyclyl-S(O)<sub>2</sub>-, where alkyl, cycloalkyl, aryl, heteroaryl and heterocyclyl are as described herein.

"Sulfinylamino" refers to groups H-S(O)-NR<sup>A</sup>-, alkyl-S(O)-NR<sup>A</sup>-, cycloalkyl-S(O)-NR<sup>A</sup>-, aryl-S(O)-NR<sup>A</sup>-, heteroaryl-S(O)-NR<sup>A</sup>-, and heterocyclyl-S(O)-NR<sup>A</sup>-, where R<sup>A</sup> is independently hydrogen, alkyl, cycloalkyl, aryl, heteroaryl, and heterocyclyl and where each of alkyl, cycloalkyl, aryl, heteroaryl and heterocyclyl is as described herein.

"Sulfonylamino" refers to groups H-S(O)<sub>2</sub>-NR<sup>A</sup>-, alkyl-S(O)<sub>2</sub>-NR<sup>A</sup>-, cycloalkyl-S(O)<sub>2</sub>-NR<sup>A</sup>-, aryl-S(O)<sub>2</sub>-NR<sup>A</sup>-, heteroaryl-S(O)<sub>2</sub>-NR<sup>A</sup>-, and heterocyclyl-S(O)<sub>2</sub>-NR<sup>A</sup>-, where R<sup>A</sup> is independently hydrogen, alkyl, cycloalkyl, aryl, heteroaryl, and heterocyclyl and where each of alkyl, cycloalkyl, aryl, heteroaryl and heterocyclyl is as described herein.

"Oxysulfinylamino" refers to groups HO-S(O)-NR<sup>A</sup>-, alkylO-S(O)-NR<sup>A</sup>-, cycloalkylO-S(O)-NR<sup>A</sup>-, arylO-S(O)-NR<sup>A</sup>-, heteroarylO-S(O)-NR<sup>A</sup>-, and heterocyclylO-S(O)-NR<sup>A</sup>-, where R<sup>A</sup> is independently hydrogen, alkyl, cycloalkyl, aryl, heteroaryl, and heterocyclyl and where each of alkyl, cycloalkyl, aryl, heteroaryl and heterocyclyl is as described herein.

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"Oxysulfonylamino" refers to groups HO-S(O)<sub>2</sub>-NR<sup>A</sup>-, alkylO-S(O)<sub>2</sub>-NR<sup>A</sup>-, cycloalkylO-S(O)<sub>2</sub>-NR<sup>A</sup>-, arylO-S(O)<sub>2</sub>-NR<sup>A</sup>-, heteroarylO-S(O)<sub>2</sub>-NR<sup>A</sup>-, and heterocyclylO-S(O)<sub>2</sub>-NR<sup>A</sup>-, where R<sup>A</sup> is independently hydrogen, alkyl, cycloalkyl, aryl, heteroaryl, and heterocyclyl and where each of alkyl, cycloalkyl, aryl, heteroaryl and heterocyclyl is as described herein.

"Aminothioacyl" refers to groups R<sup>A</sup>R<sup>A</sup>N-C(S)-, where each R<sup>A</sup> is independently hydrogen, alkyl, cycloalkyl, aryl, heteroaryl, and heterocyclic and where each of alkyl, cycloalkyl, aryl, heteroaryl and heterocyclyl is as described herein.

"Thioacylamino" refers to groups H-C(S)-NR<sup>A</sup>-, alkyl-C(S)-NR<sup>A</sup>-, cycloalkyl-C(S)-NR<sup>A</sup>-, aryl-C(S)-NR<sup>A</sup>-, heteroaryl-C(S)-NR<sup>A</sup>-, and heterocyclyl-C(S)-NR<sup>A</sup>-, where R<sup>A</sup> is independently hydrogen, alkyl, cycloalkyl, aryl, heteroaryl, and heterocyclyl and where each of alkyl, cycloalkyl, aryl, heteroaryl and heterocyclyl is as described herein.

"Aminosulfinyl" refers to groups R<sup>A</sup>R<sup>A</sup>N-S(O)-, where each R<sup>A</sup> is independently hydrogen, alkyl, cycloalkyl, aryl, heteroaryl, and heterocyclic and where each of alkyl, cycloalkyl, aryl, heteroaryl and heterocyclyl is as described herein.

"Aminosulfonyl" refers to groups R<sup>A</sup>R<sup>A</sup>N-S(O)<sub>2</sub>-, where each R<sup>A</sup> is independently hydrogen, alkyl, cycloalkyl, aryl, heteroaryl, and heterocyclic and where each of alkyl, cycloalkyl, aryl, heteroaryl and heterocyclyl is as described herein.

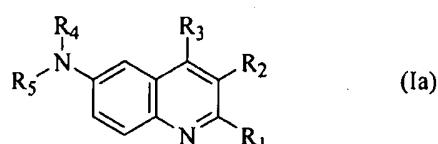
In this specification "optionally substituted" is taken to mean that a group may or may not be further substituted or fused (so as to form a condensed polycyclic group) with one or more groups selected from hydroxyl, acyl, alkyl, alkoxy, alkenyl, alkenyloxy, alkynyl, alkynyloxy, amino, aminoacyl, thio, arylalkyl, arylalkoxy, aryl, aryloxy, carboxyl, acylamino, cyano, halogen, nitro, phosphono, sulfo, phosphorylamino, phosphinyl, heteroaryl, heteroaryloxy, heterocyclyl, heterocyclyloxy, oxyacyl, oxime, oxime ether, hydrazone, oxyacylamino, oxysulfonylamino, aminoacyloxy, trihalomethyl,

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trialkylsilyl, pentafluoroethyl, trifluoromethoxy, difluoromethoxy, trifluoromethanethio, trifluoroethyl, mono- and di-alkylamino, mono-and di-(substituted alkyl)amino, mono- and di-arylamino, mono- and di-heteroaryl amino, mono- and di-heterocyclyl amino, and unsymmetric di-substituted amines having different substituents selected from alkyl, aryl, heteroaryl and heterocyclyl, and the like, and may also include a bond to a solid support material, (for example, substituted onto a polymer resin). For instance, an "optionally substituted amino" group may include amino acid and peptide residues.

In an embodiment the "optionally substituted" group is selected from halo (e.g., chloro, fluoro or bromo), -CN, -NO<sub>2</sub>, -CO<sub>2</sub>H, -CO<sub>2</sub>C<sub>1-6</sub>alkyl, -CONH<sub>2</sub>, -CONH(C<sub>1-6</sub>alkyl), -CONH(C<sub>1-6</sub>alkyl)<sub>2</sub>, -OH, hydroxyC<sub>1-6</sub>alkyl, C<sub>1-6</sub>alkoxy, C<sub>1-6</sub>alkyl, C<sub>1-6</sub>acyl, carboxyC<sub>1-6</sub>alkyl, acetyl, trifluoromethyl, benzyloxy, phenyl, phenoxy, -NH<sub>2</sub>, -NH(C<sub>1-6</sub>alkyl) or -N(C<sub>1-6</sub>alkyl)<sub>2</sub>.

The present invention also provides compounds of formula (Ia) and salts thereof,



wherein

R<sub>1</sub> represents hydrogen, or optionally substituted C<sub>1</sub>-C<sub>6</sub> alkyl;

R<sub>2</sub> represents -C(O)NR'R'' (where R' is -H or optionally substituted C<sub>1</sub>-C<sub>6</sub> alkyl and R'' is optionally substituted C<sub>1</sub>-C<sub>6</sub> alkyl, -OH or -CN, or R' and R'' together form an optionally substituted heterocyclyl), -C(O)OR' (where R' is -H or optionally substituted C<sub>1</sub>-C<sub>6</sub> alkyl), -C(O)NHSO<sub>2</sub>R''' (where R''' is optionally substituted aryl or optionally substituted C<sub>1</sub>-C<sub>6</sub> alkyl), -S(O)<sub>2</sub>NHR'''' (where R'''' is -H, optionally substituted C<sub>1</sub>-C<sub>6</sub> alkyl, or optionally substituted aryl), optionally substituted heteroaryl or optionally substituted heterocyclyl;

R<sub>3</sub> represents optionally substituted aryl or optionally substituted heteroaryl;

R<sub>4</sub> represents H, optionally substituted alkyl, optionally substituted aryl, optionally substituted cycloalkyl, optionally substituted cycloalkenyl, optionally substituted acyl, optionally substituted alkenyl, optionally substituted heterocyclyl, optionally substituted heteroaryl, optionally substituted oxysulfinyl, optionally substituted oxysulfonyl, optionally substituted sulfinyl, or optionally substituted sulfonyl; and

R<sub>5</sub> represents H, optionally substituted cycloalkyl, optionally substituted cycloalkenyl, optionally substituted acyl, optionally substituted aryl, optionally substituted arylalkyl, optionally substituted heteroaryl, optionally substituted heteroarylalkyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted cycloalkylalkyl, -S(O)<sub>2</sub>-optionally substituted C<sub>1</sub>-C<sub>6</sub> alkyl, or -C(O)NR'R' (wherein each R' is independently H, optionally substituted C<sub>1</sub>-C<sub>6</sub> alkyl or optionally substituted aryl).

In certain embodiments, and in respect of compounds of formula (Ia), or salts thereof, when R<sub>3</sub> is optionally substituted phenyl, R<sub>5</sub> is not optionally substituted cycloalkyl or optionally substituted cycloalkenyl.

In certain embodiments, for a compound of formula (Ia),

R<sub>1</sub> represents H and C<sub>1</sub>-C<sub>4</sub> alkyl;

R<sub>2</sub> represents -C(O)NR'R" (where R' is H or C<sub>1</sub>-C<sub>4</sub> alkyl and R" is C<sub>1</sub>-C<sub>4</sub> alkyl, OH or CN), -C(O)OR' (where R' is H or C<sub>1</sub>-C<sub>4</sub> alkyl), -C(O)NHSO<sub>2</sub>R''' (where R''' is aryl or C<sub>1</sub>-C<sub>3</sub> alkyl), -S(O)<sub>2</sub>NHR''' (where R''' is H, C<sub>1</sub>-C<sub>3</sub> alkyl, or aryl), optionally substituted heteroaryl or optionally substituted heterocyclyl;

R<sub>3</sub> represents optionally substituted heteroaryl;

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R<sub>4</sub> represents H, optionally substituted alkyl, optionally substituted aryl, optionally substituted cycloalkyl, optionally substituted cycloalkenyl, optionally substituted acyl, optionally substituted alkenyl, optionally substituted heterocycl, optionally substituted heteroaryl, optionally substituted oxysulfinyl, optionally substituted oxysulfonyl, optionally substituted sulfinyl, or optionally substituted sulfonyl; and

R<sub>5</sub> represents H, optionally substituted cycloalkyl, optionally substituted cycloalkenyl, optionally substituted acyl, optionally substituted aryl, optionally substituted arylalkyl, optionally substituted heteroaryl, optionally substituted heteroarylalkyl, optionally substituted heterocycl, optionally substituted heterocyclalkyl, optionally substituted cycloalkylalkyl, -S(O)<sub>2</sub>-optionally substituted C<sub>1</sub>-C<sub>6</sub> alkyl, or -C(O)NR'R' (wherein each R' is independently H, optionally substituted C<sub>1</sub>-C<sub>6</sub> alkyl or optionally substituted aryl).

In certain embodiments, for a compound of formula (Ia),

R<sub>1</sub> represents H and C<sub>1</sub>-C<sub>4</sub> alkyl;

R<sub>2</sub> represents -C(O)NR'R" (where R' is H or C<sub>1</sub>-C<sub>4</sub> alkyl and R" is C<sub>1</sub>-C<sub>4</sub> alkyl, OH or CN), -C(O)OR' (where R' is H or C<sub>1</sub>-C<sub>4</sub> alkyl), -C(O)NHSO<sub>2</sub>R''' (where R''' is aryl or C<sub>1</sub>-C<sub>3</sub> alkyl), -S(O)<sub>2</sub>NHR'''' (where R'''' is H, C<sub>1</sub>-C<sub>3</sub> alkyl, or aryl), optionally substituted heteroaryl or optionally substituted heterocycl;

R<sub>3</sub> represents optionally substituted aryl;

R<sub>4</sub> represents H, optionally substituted alkyl, optionally substituted aryl, optionally substituted cycloalkyl, optionally substituted cycloalkenyl, optionally substituted acyl, optionally substituted alkenyl, optionally substituted heterocycl, optionally substituted heteroaryl, optionally substituted oxysulfinyl, optionally substituted oxysulfonyl, optionally substituted sulfinyl, or optionally substituted sulfonyl; and

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R<sub>5</sub> is R<sub>5</sub> and represents H, optionally substituted acyl, optionally substituted aryl, optionally substituted arylalkyl, optionally substituted heteroaryl, optionally substituted heteroarylalkyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted cycloalkylalkyl, -S(O)<sub>2</sub>-optionally substituted C<sub>1</sub>-C<sub>6</sub> alkyl, or -C(O)NR'R' (wherein each R' is independently H, optionally substituted C<sub>1</sub>-C<sub>6</sub> alkyl or optionally substituted aryl).

In certain embodiments, for a compound of formula (Ia),

R<sub>1</sub> represents C<sub>1</sub>-C<sub>4</sub> alkyl;

R<sub>2</sub> represents -C(O)NR'R" (where R' is H or C<sub>1</sub>-C<sub>4</sub> alkyl and R" is C<sub>1</sub>-C<sub>4</sub> alkyl, OH or CN), -C(O)OR' (where R' is H or C<sub>1</sub>-C<sub>4</sub> alkyl), -C(O)NHSO<sub>2</sub>R'" (where R''' is aryl or C<sub>1</sub>-C<sub>3</sub> alkyl), -S(O)<sub>2</sub>NHR"" (where R"" is H, C<sub>1</sub>-C<sub>3</sub> alkyl, or aryl), optionally substituted heteroaryl or optionally substituted heterocyclyl;

R<sub>3</sub> represents optionally substituted heteroaryl;

R<sub>4</sub> represents H, optionally substituted alkyl, optionally substituted aryl, optionally substituted cycloalkyl, optionally substituted cycloalkenyl, optionally substituted acyl, optionally substituted alkenyl, optionally substituted heterocyclyl, optionally substituted heteroaryl, optionally substituted oxysulfinyl, optionally substituted oxysulfonyl, optionally substituted sulfinyl, or optionally substituted sulfonyl; and

R<sub>5</sub> represents H, optionally substituted cycloalkyl, optionally substituted cycloalkenyl, optionally substituted acyl, optionally substituted aryl, optionally substituted arylalkyl, optionally substituted heteroaryl, optionally substituted heteroarylalkyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted cycloalkylalkyl, -S(O)<sub>2</sub>-optionally substituted C<sub>1</sub>-C<sub>6</sub> alkyl, or -C(O)NR'R' (wherein each R' is independently H, optionally substituted C<sub>1</sub>-C<sub>6</sub> alkyl or optionally substituted aryl).

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In certain embodiments, for a compound of formula (Ia),

R<sub>1</sub> represents C<sub>1</sub>-C<sub>4</sub> alkyl;

R<sub>2</sub> represents -C(O)NR'R'' (where R' is H or C<sub>1</sub>-C<sub>4</sub> alkyl and R'' is C<sub>1</sub>-C<sub>4</sub> alkyl, OH or CN), -C(O)OR' (where R' is H or C<sub>1</sub>-C<sub>4</sub> alkyl), -C(O)NHSO<sub>2</sub>R''' (where R''' is aryl or C<sub>1</sub>-C<sub>3</sub> alkyl), -S(O)<sub>2</sub>NHR'''' (where R'''' is H, C<sub>1</sub>-C<sub>3</sub> alkyl, or aryl), optionally substituted heteroaryl or optionally substituted heterocyclyl;

R<sub>3</sub> represents optionally substituted aryl;

R<sub>4</sub> represents H, optionally substituted alkyl, optionally substituted aryl, optionally substituted cycloalkyl, optionally substituted cycloalkenyl, optionally substituted acyl, optionally substituted alkenyl, optionally substituted heterocyclyl, optionally substituted heteroaryl, optionally substituted oxysulfinyl, optionally substituted oxysulfonyl, optionally substituted sulfinyl, or optionally substituted sulfonyl; and

R<sub>5</sub> is R<sub>5'</sub> and represents H, optionally substituted acyl, optionally substituted aryl, optionally substituted arylalkyl, optionally substituted heteroaryl, optionally substituted heteroarylalkyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted cycloalkylalkyl, -S(O)<sub>2</sub>-optionally substituted C<sub>1</sub>-C<sub>6</sub> alkyl, or -C(O)NR'R' (wherein each R' is independently H, optionally substituted C<sub>1</sub>-C<sub>6</sub> alkyl or optionally substituted aryl).

In some embodiments, R<sub>1</sub> is C<sub>1</sub>-C<sub>4</sub> alkyl. In some embodiments, R<sub>1</sub> is methyl, ethyl, isopropyl, n-propyl, or butyl. In certain embodiments, R<sub>1</sub> is C<sub>1</sub>-C<sub>2</sub> alkyl. In certain embodiments, R<sub>1</sub> is methyl. In certain embodiments, R<sub>1</sub> is ethyl.

In certain embodiments, R<sub>2</sub> represents -C(O)NR'R'' (where R' is -H or optionally substituted C<sub>1</sub>-C<sub>6</sub> alkyl and R'' is optionally substituted C<sub>1</sub>-C<sub>6</sub> alkyl, -OH or -CN, or R' and R'' together form an optionally substituted heterocyclyl), -C(O)OH, -C(O)NHSO<sub>2</sub>R'''

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(where R''' is optionally substituted aryl or optionally substituted C<sub>1</sub>-C<sub>6</sub> alkyl), -S(O)<sub>2</sub>NHR''' (where R''' is -H, optionally substituted C<sub>1</sub>-C<sub>6</sub> alkyl, or optionally substituted aryl), optionally substituted heteroaryl or optionally substituted heterocyclyl.

In some embodiments, R<sub>2</sub> is -C(O)NR'R'', wherein R' is H or C<sub>1</sub>-C<sub>4</sub> alkyl, and R'' is C<sub>1</sub>-C<sub>4</sub> alkyl, -OH, or -CN. In certain embodiments, R<sub>2</sub> is -C(O)NR'R'', wherein R' is H and R'' is -OH or -CN. In certain embodiments, R<sub>2</sub> is -C(O)NHOH. In certain embodiments, R<sub>2</sub> is -C(O)NHCN. In certain embodiments, R<sub>2</sub> is -C(O)NH(C<sub>1</sub>-C<sub>4</sub> alkyl). In certain embodiments, R<sub>2</sub> is -C(O)NHMe or -C(O)NHEt.

In some embodiments, R<sub>2</sub> is -C(O)NR'R'', wherein R' and R'' taken together form an optionally substituted heterocyclyl. In certain embodiments, R' and R'' taken together form a 5-7 membered heterocyclyl having 1-2 heteroatoms selected from nitrogen, oxygen, and sulfur. In certain embodiments, R' and R'' taken together form a 5-membered heterocyclyl having 1-2 heteroatoms selected from nitrogen, oxygen, and sulfur. In certain embodiments, R' and R'' taken together form a 6-membered heterocyclyl having 1-2 heteroatoms selected from nitrogen, oxygen, and sulfur. In certain embodiments, R' and R'' taken together form a 5-membered heterocyclyl having one heteroatom selected from nitrogen, oxygen, and sulfur. In certain embodiments, R' and R'' taken together form a 6-membered heterocyclyl having one heteroatom selected from nitrogen, oxygen, and sulfur. In certain embodiments, R' and R'' taken together form a 6-membered heterocyclyl having two heteroatoms selected from nitrogen, oxygen, and sulfur. In certain embodiments, R' and R'' taken together form a morpholine ring.

In certain embodiments, R<sub>2</sub> is -C(O)OR', wherein R' is hydrogen or optionally substituted C<sub>1</sub>-C<sub>6</sub> alkyl. In certain embodiments, R<sub>2</sub> is -C(O)OR', wherein R' is C<sub>1</sub>-C<sub>3</sub> alkyl. In certain embodiments, R<sub>2</sub> is -CO<sub>2</sub>Me or -CO<sub>2</sub>Et.

In certain embodiments, R<sub>2</sub> is -C(O)OH.

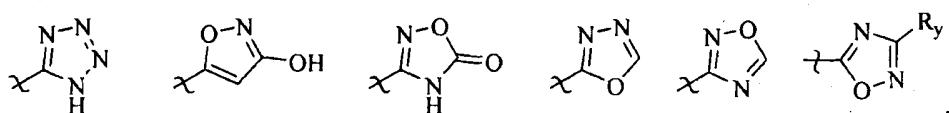
In some embodiments, R<sub>2</sub> is -C(O)NHSO<sub>2</sub>R'', wherein R''' is aryl or C<sub>1</sub>-C<sub>3</sub> alkyl. In certain

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embodiments, R<sub>2</sub> is -C(O)NHSO<sub>2</sub>(phenyl). In certain embodiments, R<sub>2</sub> is -C(O)NHSO<sub>2</sub>(C<sub>1</sub>-C<sub>3</sub> alkyl). In certain embodiments, R<sub>2</sub> is -C(O)NHSO<sub>2</sub>Me, -C(O)NHSO<sub>2</sub>Et, or -C(O)NHSO<sub>2</sub>iPr.

In some embodiments, R<sub>2</sub> is -S(O)<sub>2</sub>NHR<sup>'''</sup>, wherein R<sup>'''</sup> is H, C<sub>1</sub>-C<sub>3</sub> alkyl, or aryl. In certain embodiments, R<sub>2</sub> is -S(O)<sub>2</sub>NH<sub>2</sub>. In certain embodiments, R<sub>2</sub> is -S(O)<sub>2</sub>NH(C<sub>1</sub>-C<sub>3</sub> alkyl). In certain embodiments, R<sub>2</sub> is -S(O)<sub>2</sub>NHMe, -S(O)<sub>2</sub>NHET, or -S(O)<sub>2</sub>NHiPr. In certain embodiments, R<sub>2</sub> is -S(O)<sub>2</sub>NH(aryl).

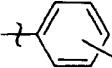
In some embodiments, R<sub>2</sub> is optionally substituted heteroaryl or optionally substituted heterocyclyl. In some embodiments, R<sub>2</sub> is substituted or unsubstituted 5-6 membered heteroaryl having 1-3 heteroatoms selected from nitrogen, oxygen, and sulfur. In some embodiments, R<sub>2</sub> is a substituted or unsubstituted 5-membered heteroaryl having 1-3 heteroatoms selected from nitrogen, oxygen, and sulfur. In certain embodiments, R<sub>2</sub> is a substituted or unsubstituted 6-membered heteroaryl having 1-3 nitrogens. In some embodiments, R<sub>2</sub> is a substituted or unsubstituted 4-7 membered heterocycle having 1-3 heteroatoms selected from nitrogen, oxygen, and sulfur. In certain embodiments, R<sub>2</sub> is a substituted or unsubstituted 4-membered heterocycle having one heteroatom selected from nitrogen, oxygen, and sulfur. In certain embodiments, R<sub>2</sub> is a substituted or unsubstituted 5-membered heterocycle having one heteroatom selected from nitrogen, oxygen, and sulfur. In certain embodiments, R<sub>2</sub> is a substituted or unsubstituted 6-membered heterocycle having 1-2 heteroatoms selected from nitrogen, oxygen, and sulfur. In certain embodiments, R<sub>2</sub> is a substituted or unsubstituted 7-membered heterocycle having 1-2 heteroatoms selected from nitrogen, oxygen, and sulfur. In certain embodiments, R<sub>2</sub> is one of the following:



where R<sub>y</sub> is H or C<sub>1-6</sub> alkyl.

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In some embodiments, R<sub>3</sub> represents optionally substituted phenyl.

In some embodiments, R<sub>3</sub> represents  (R<sub>6</sub>)<sub>n</sub>,

wherein R<sub>6</sub> is selected from carboxyl, cyano, dihalomethoxy, halogen, hydroxy, nitro, pentahaloethyl, phosphono, phosphorylamino, phosphinyl, sulfo, trihaloethenyl, trihalomethanethio, trihalomethyl, trihalomethoxy, optionally substituted acyl, optionally substituted acylamino, optionally substituted acylimino, optionally substituted acyliminoxy, optionally substituted acyloxy, optionally substituted arylalkyl, optionally substituted arylalkoxy, optionally substituted alkenyl, optionally substituted alkenyloxy, optionally substituted alkoxy, optionally substituted alkyl, optionally substituted alkynyl, optionally substituted alkynyoxy, optionally substituted amino, optionally substituted aminoacyl, optionally substituted aminoacyloxy, optionally substituted aminosulfonyl, optionally substituted aminothioacyl, optionally substituted aryl, optionally substituted arylamino, optionally substituted aryloxy, optionally substituted cycloalkenyl, optionally substituted cycloalkyl, optionally substituted heteroaryl, optionally substituted heterocyclyl, optionally substituted oxyacyl, optionally substituted oxyacylimino, optionally substituted oxyacyloxy, optionally substituted oxyacylimino, optionally substituted oxysulfinylamino, optionally substituted oxysulfonylamino, optionally substituted oxythioacyl, optionally substituted oxythioacyloxy, optionally substituted sulfanyl, optionally substituted sulfinylamino, optionally substituted sulfonyl, optionally substituted sulphonylamino, optionally substituted thio, optionally substituted thioacyl, or optionally substituted thioacylamino; and

n is 0 or an integer of 1 to 4, inclusive.

In some embodiments, n is 0. In other embodiments, n is an integer from 1 to 4, inclusive. In certain embodiments, n is 1. In certain embodiments, n is 2. In certain embodiments, n is 3. In certain embodiments, n is 4.

In the above embodiments R<sub>6</sub>, when present, includes the following groups:

In some embodiments, R<sub>6</sub> is halogen, cyano, nitro, or amino. In certain embodiments, R<sub>6</sub> is bromo or chloro. In some embodiments, R<sub>6</sub> is fluoro.

In some embodiments, R<sub>6</sub> is an optionally substituted alkyl group. In certain embodiments, R<sub>6</sub> is an unsubstituted alkyl group. In certain embodiments, R<sub>6</sub> is a substituted alkyl group. In certain embodiments, R<sub>6</sub> is optionally substituted C<sub>1</sub>-C<sub>6</sub> alkyl. In certain embodiments, R<sub>6</sub> is optionally substituted C<sub>1</sub>-C<sub>3</sub> alkyl. In certain embodiments, R<sub>6</sub> is methyl or ethyl. In certain embodiments, R<sub>6</sub> is 1-hydroxyethyl, 1-thioethyl, methoxyiminomethyl, ethoxyiminomethyl, 1-(hydroxyimino)ethyl, 1-(hydroxyimino)propyl, 1-hydrazinoethyl, 1-hydrazinopropyl, hydroxyiminomethyl, 2-oxopropyl, 2-oxobutyl, 3-oxobutyl, 3-oxopentyl, nitromethyl, 1-nitromethyl, or 2-nitroethyl. In certain embodiments, R<sub>6</sub> is trihalomethyl. In certain embodiments, R<sub>6</sub> is trifluoromethyl. In certain embodiments, R<sub>6</sub> is pentahaloethyl.

In some embodiments, R<sub>6</sub> is an optionally substituted aryl group. In certain embodiments, R<sub>6</sub> is unsubstituted aryl. In certain embodiments, R<sub>6</sub> is phenyl or napthyl. In certain embodiments, R<sub>6</sub> is substituted aryl. In certain embodiments, R<sub>6</sub> is halophenyl (for instance, fluorophenyl), aminophenyl, carboxyphenyl, hydroxyphenyl, cyanophenyl, nitrophenyl, trihaloalkylphenyl, or alkylphenyl.

In some embodiments, R<sub>6</sub> is an optionally substituted acyl group. In certain embodiments, R<sub>6</sub> is unsubstituted acyl. In certain embodiments, R<sub>6</sub> is substituted acyl. In certain embodiments, R<sub>6</sub> is formyl, acetyl, propionyl, or benzoyl. In certain embodiments, R<sub>6</sub> is formyl, acetyl, propionyl, or benzoyl, optionally substituted with methyl, methoxy, halogen, nitro, trifluoromethyl, or cyano.

In some embodiments, R<sub>6</sub> is a substituted or unsubstituted alkoxy group. In certain embodiments, R<sub>6</sub> is C<sub>1</sub>-C<sub>6</sub> alkoxy. In certain embodiments, R<sub>6</sub> is C<sub>1</sub>-C<sub>3</sub> alkoxy. In certain embodiments, R<sub>6</sub> is methoxy or ethoxy. In certain embodiments, R<sub>6</sub> is dihalomethoxy. In

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certain embodiments, R<sub>6</sub> is trihalomethoxy. In certain embodiments, R<sub>6</sub> is trifluoromethoxy.

In some embodiments, R<sub>6</sub> is a substituted or unsubstituted oxyacyl group. In certain embodiments, R<sub>6</sub> is C<sub>1</sub>-C<sub>6</sub> alkoxy carbonyl. In certain embodiments, R<sub>6</sub> is methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, butyloxycarbonyl, or isobutyloxycarbonyl.

In some embodiments, R<sub>6</sub> is a substituted or unsubstituted acyloxy group. In certain embodiments, R<sub>6</sub> is C<sub>1</sub>-C<sub>6</sub> acyloxy. In certain embodiments, R<sub>6</sub> is acetoxy or propioxy.

In some embodiments, R<sub>6</sub> is an optionally substituted arylalkyl group. In certain embodiments, R<sub>6</sub> is an unsubstituted arylalkyl group. In certain embodiments, R<sub>6</sub> is benzyl. In certain embodiments, R<sub>6</sub> is a substituted arylalkyl group. In certain embodiments, R<sub>6</sub> is 1-hydroxybenzyl or 1-thiobenzyl.

In some embodiments, R<sub>6</sub> is an optionally substituted sulfinyl group. In certain embodiments, R<sub>6</sub> is alkylsulfinyl or arylsulfinyl. In certain embodiments, R<sub>6</sub> is alkoxy sulfinyl. In certain embodiments, R<sub>6</sub> is methylsulfinyl, ethylsulfinyl, benzene sulfinyl, methoxysulfinyl, or ethoxysulfinyl. In certain embodiments, R<sub>6</sub> is benzene sulfinyl, optionally substituted with methyl, methoxy, halogen, nitro, trifluoromethyl, or cyano.

In some embodiments, R<sub>6</sub> is an optionally substituted sulfonyl\* group. In certain embodiments, R<sub>6</sub> is alkylsulfonyl or arylsulfonyl. In certain embodiments, R<sub>6</sub> is methylsulfonyl, ethylsulfonyl, or benzenesulfonyl (optionally substituted with methyl, methoxy, halogen, nitro, trifluoromethyl, or cyano).

In some embodiments, R<sub>6</sub> is an optionally substituted oxyacylamino group. In certain embodiments, R<sub>6</sub> is C<sub>1</sub>-C<sub>6</sub> alkoxy carbonylamido. In certain embodiments, R<sub>6</sub> is methoxycarbonylamido or ethoxycarbonylamido.

In some embodiments, R<sub>6</sub> is an optionally substituted oxythioacyl group. In certain embodiments, R<sub>6</sub> is C<sub>1</sub>-C<sub>6</sub> alkoxythiocarbonyl. In certain embodiments, R<sub>6</sub> is methoxythiocarbonyl or ethoxythiocarbonyl. In some embodiments, R<sub>6</sub> is an optionally substituted thioacyloxy group. In certain embodiments, R<sub>6</sub> is thionoacetoxy or thionopropionoxy.

In some embodiments, R<sub>6</sub> is an optionally substituted sulphinylamino group. In certain embodiments, R<sub>6</sub> is alkylsulfinylamino or arylsulfinylamino. In certain embodiments, R<sub>6</sub> is methylsulfinylamino, ethylsulfinylamino, or benzenesulfinylamino. In certain embodiments, R<sub>6</sub> is benzenesulfinylamino optionally substituted with methyl, methoxy, halogen, nitro, trifluoromethyl, or cyano.

In some embodiments, R<sub>6</sub> is an amino group. In certain embodiments, R<sub>6</sub> is alkylamino or dialkylamino. In certain embodiments, R<sub>6</sub> is N-methylamino or N,N'-dimethylamino. In certain embodiments, R<sub>6</sub> is a substituted amino group, such as a residue of L-valine, D-valine, L-alanine, D-alanine, aspartic acid, or alanylserine.

In certain embodiments, R<sub>6</sub> is an optionally substituted sulphonylamino group. In certain embodiments, R<sub>6</sub> is alkylsulfonylamino or arylsulfonylamino. In certain embodiments, R<sub>6</sub> is C<sub>1</sub>-C<sub>6</sub> alkylsulfonylamino. In certain embodiments, R<sub>6</sub> is methylsulfonylamino, ethylsulfonylamino, or benzenesulfonylamino. In certain embodiments, R<sub>6</sub> is benzenesulfonylamino optionally substituted with methyl, methoxy, halogen, nitro, trifluoromethyl, or cyano.

In some embodiments, R<sub>6</sub> is an optionally substituted thio group. In certain embodiments, R<sub>6</sub> is a substituted thio group. In certain embodiments, R<sub>6</sub> is alkylthio. In certain embodiments, R<sub>6</sub> is C<sub>1</sub>-C<sub>6</sub> alkylthio. In certain embodiments, R<sub>6</sub> is thiomethyl or thioethyl. In certain embodiments, R<sub>6</sub> is trihalomethanethio.

In some embodiments, R<sub>6</sub> is an optionally substituted oxysulfinylamino group. In certain embodiments, R<sub>6</sub> is alkoxyoxysulfinylamino. In certain embodiments, R<sub>6</sub> is methoxyoxysulfinylamino or ethoxyoxysulfinylamino.

In some embodiments, R<sub>6</sub> is an optionally substituted oxysulfonylamino group. In certain embodiments, R<sub>6</sub> is alkoxyoxysulfonylamino. In certain embodiments, R<sub>6</sub> is methoxyoxysulfonylamino or ethoxyoxysulfonylamino.

In some embodiments, R<sub>6</sub> is an optionally substituted alkenyl group. In some embodiments, R<sub>6</sub> is unsubstituted alkenyl. In some embodiments, R<sub>6</sub> is substituted alkenyl. In certain embodiments, R<sub>6</sub> is 1-propenyl, vinyl, nitrovinyl, cyano vinyl, or trifluorovinyl, or styryl. In certain embodiments R<sub>6</sub> is styryl optionally substituted with methyl, methoxy, halogen, nitro, trifluoromethyl, or cyano. In certain embodiments, R<sub>6</sub> is trihaloethenyl.

In some embodiments, R<sub>6</sub> is an optionally substituted alkynyl group. In some embodiments, R<sub>6</sub> is substituted C<sub>1</sub>-C<sub>6</sub> alkynyl. In some embodiments, R<sub>6</sub> is unsubstituted C<sub>1</sub>-C<sub>6</sub> alkynyl. In certain embodiments, R<sub>6</sub> is 1-propynyl, ethynyl, or trimethylsilylethynyl.

In certain embodiments, n is 1 and R<sub>6</sub> is selected from halogen, -CN, -CF<sub>3</sub>, -CHF<sub>2</sub>, -CH<sub>2</sub>F, amino, hydroxyl, -NHC<sub>1</sub>-C<sub>3</sub> alkyl, -N(C<sub>1</sub>-C<sub>3</sub> alkyl)<sub>2</sub>, -COOH, -COO(C<sub>1</sub>-C<sub>3</sub> alkyl), phenyl, benzyl, C<sub>1</sub>-C<sub>3</sub> alkyl, or C<sub>1</sub>-C<sub>3</sub> alkoxy.

In certain embodiments, n is 2 and each R<sub>6</sub> is independently selected from halogen, -CN, -CF<sub>3</sub>, -CHF<sub>2</sub>, -CH<sub>2</sub>F, amino, hydroxyl, -NHC<sub>1</sub>-C<sub>3</sub> alkyl, -N(C<sub>1</sub>-C<sub>3</sub> alkyl)<sub>2</sub>, -COOH, -COO(C<sub>1</sub>-C<sub>3</sub> alkyl), phenyl, benzyl, C<sub>1</sub>-C<sub>3</sub> alkyl, or C<sub>1</sub>-C<sub>3</sub> alkoxy.

In certain embodiments, n is 3 and each R<sub>6</sub> is independently selected from halogen, -CN, -CF<sub>3</sub>, -CHF<sub>2</sub>, -CH<sub>2</sub>F, amino, hydroxyl, -NHC<sub>1</sub>-C<sub>3</sub> alkyl, -N(C<sub>1</sub>-C<sub>3</sub> alkyl)<sub>2</sub>, -COOH, -COO(C<sub>1</sub>-C<sub>3</sub> alkyl), phenyl, benzyl, C<sub>1</sub>-C<sub>3</sub> alkyl, or C<sub>1</sub>-C<sub>3</sub> alkoxy.

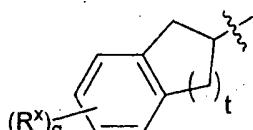
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In certain embodiments, R<sub>4</sub> is C<sub>1</sub>-C<sub>3</sub> alkyl or H. In certain embodiments, R<sub>4</sub> is H. In certain embodiments, R<sub>4</sub> is methyl, ethyl, n-propyl, or isopropyl.

In certain embodiments, R<sub>2</sub> is -COOH, and R<sub>4</sub> is H.

In certain embodiments, R<sub>5</sub> is a benzofused C<sub>5</sub>-C<sub>7</sub> cycloalkyl (wherein the benzene ring may be optionally substituted). In certain embodiments, R<sub>5</sub> is an optionally substituted indanyl or optionally substituted 1,2,3,4-tetrahydronaphthalenyl. In certain embodiments, R<sub>5</sub> is unsubstituted indanyl or 1,2,3,4-tetrahydronaphthalenyl. In certain embodiments, R<sub>5</sub> is an optionally substituted benzofused C<sub>5</sub>-C<sub>7</sub> cycloalkyl, such as indanyl or 1,2,3,4-tetrahydronaphthalenyl, wherein the optional substitutents are independently selected from the group consisting of halo (e.g., chloro, fluoro, or bromo), -CN, -NO<sub>2</sub>, -CO<sub>2</sub>H, -CO<sub>2</sub>C<sub>1-6</sub>alkyl, -CONH<sub>2</sub>, -CONH(C<sub>1-6</sub>alkyl), -CONH(C<sub>1-6</sub>alkyl)<sub>2</sub>, -OH, hydroxyalkyl, alkoxy, alkyl, acyl, carboxyalkyl, acetyl, trifluoromethyl, benzyloxy, phenoxy, -NH<sub>2</sub>, -NH(C<sub>1-6</sub>alkyl), or -N(C<sub>1-6</sub>alkyl)<sub>2</sub>.

In certain embodiments, R<sub>5</sub> is:

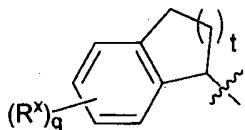


, wherein t is 1, 2, or 3; q is 1, 2, 3, or 4; and R<sup>x</sup> is halo (e.g., chloro, fluoro or bromo), -CN, -NO<sub>2</sub>, -CO<sub>2</sub>H, -CO<sub>2</sub>C<sub>1-6</sub>alkyl, -CONH<sub>2</sub>, -CONH(C<sub>1-6</sub>alkyl), -CONH(C<sub>1-6</sub>alkyl)<sub>2</sub>, -OH, hydroxyalkyl, alkoxy, alkyl, acyl, carboxyalkyl, acetyl, trifluoromethyl, benzyloxy, phenoxy, -NH<sub>2</sub>, -NH(C<sub>1-6</sub>alkyl) or -N(C<sub>1-6</sub>alkyl)<sub>2</sub>.

In some embodiments, t is 1. In some embodiments, t is 2. In some embodiments, t is 3. In some embodiments, q is 1. In some embodiments, q is 2. In some embodiments, q is 3. In some embodiments, q is 4. In certain embodiments, t is 1 and q is 1.

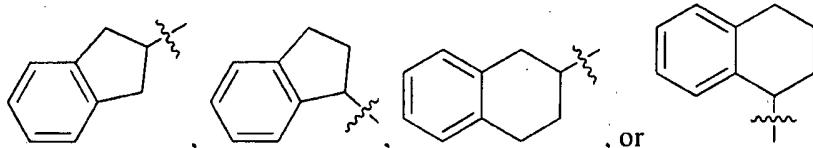
In certain embodiments, R<sub>5</sub> is:

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, wherein t is 1, 2, or 3; q is 1, 2, 3, or 4; and R<sup>x</sup> is halo (e.g., chloro, fluoro or bromo), -CN, -NO<sub>2</sub>, -CO<sub>2</sub>H, -CO<sub>2</sub>C<sub>1-6</sub>alkyl, -CONH<sub>2</sub>, -CONH(C<sub>1-6</sub>alkyl), -CONH(C<sub>1-6</sub>alkyl)<sub>2</sub>, -OH, hydroxyalkyl, alkoxy, alkyl, acyl, carboxyalkyl, acetyl, trifluoromethyl, benzyloxy, phenoxy, -NH<sub>2</sub>, -NH(C<sub>1-6</sub>alkyl) or -N(C<sub>1-6</sub>alkyl)<sub>2</sub>.

In certain embodiments, R<sub>5</sub> is:



In certain embodiments, R<sub>5</sub> is a benzofused C<sub>5</sub>-C<sub>7</sub> cycloalkenyl (wherein the benzene ring may be optionally substituted). In certain embodiments, R<sub>5</sub> is optionally substituted indenyl. In certain embodiments, R<sub>5</sub> is unsubstituted indenyl.

In certain embodiments, R<sub>5</sub> or R<sub>5'</sub> is H, optionally substituted acyl, optionally substituted aryl, -(CH<sub>2</sub>)<sub>m</sub>-optionally substituted aryl, optionally substituted heteroaryl, -(CH<sub>2</sub>)<sub>m</sub>-optionally substituted heteroaryl, optionally substituted heterocyclyl, -(CH<sub>2</sub>)<sub>m</sub>-optionally substituted heterocyclyl, -(CH<sub>2</sub>)<sub>m</sub>-optionally substituted cycloalkyl, -S(O)<sub>2</sub>-optionally substituted C<sub>1</sub>-C<sub>6</sub> alkyl, or -C(O)NR'R' (wherein each R' is independently H, optionally substituted C<sub>1</sub>-C<sub>6</sub> alkyl, or optionally substituted aryl); wherein m is 1, 2, or 3.

In certain embodiments, R<sub>5</sub> or R<sub>5'</sub> is:

optionally substituted acyl, selected from -C(O)-optionally substituted heteroaryl, -C(O)-optionally substituted alkyl, -C(O)-optionally substituted aryl, -C(O)-optionally substituted heterocyclyl or -C(O)-optionally substituted cycloalkyl.

In certain embodiments, R<sub>5</sub> or R<sub>5'</sub> is selected from -C(O)-heteroaryl, -C(O)-alkyl, -C(O)-aryl, -C(O)-heterocyclyl or -C(O)-cycloalkyl, optionally substituted 1 or 2 times by halo (e.g., chloro, fluoro or bromo), -CN, -NO<sub>2</sub>, -CO<sub>2</sub>H, -CO<sub>2</sub>C<sub>1-6</sub>alkyl, -CONH<sub>2</sub>, -CONH(C<sub>1-6</sub>alkyl), -CONH(C<sub>1-6</sub>alkyl)<sub>2</sub>, -OH, hydroxyalkyl, alkoxy, alkyl, acyl, carboxyalkyl, acetyl, trifluoromethyl, benzyloxy, phenoxy, -NH<sub>2</sub>, -NH(C<sub>1-6</sub>alkyl) or -N(C<sub>1-6</sub>alkyl)<sub>2</sub>.

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$\text{C}_{1-6}\text{alkyl}$ ),  $-\text{CON}(\text{C}_{1-6}\text{alkyl})_2$ ,  $-\text{OH}$ , hydroxyalkyl, alkoxy, alkyl, acyl, carboxyalkyl, acetyl, trifluoromethyl, benzyloxy, phenoxy,  $-\text{NH}_2$ ,  $-\text{NH}(\text{C}_{1-6}\text{alkyl})$  or  $-\text{N}(\text{C}_{1-6}\text{alkyl})_2$ .

In certain embodiments,  $R_5$  or  $R_{5'}$  is optionally substituted arylalkyl, optionally substituted heteroarylalkyl, optionally substituted heterocyclalkyl, or optionally substituted cycloalkylalkyl.

In certain embodiments,  $R_5$  or  $R_{5'}$  is  $-(\text{CH}_2)_m$ -optionally substituted aryl,  $-(\text{CH}_2)_m$ -optionally substituted heteroaryl,  $-(\text{CH}_2)_m$ -optionally substituted heterocycl, or  $-(\text{CH}_2)_m$ -optionally substituted cycloalkyl; and  $m$  is an integer of 1 to 3.

In certain embodiments,  $R_5$  or  $R_{5'}$  is  $-(\text{CH}_2)_m$ -optionally substituted heteroaryl wherein  $m$  is 1 or 2.

In certain embodiments,  $R_5$  or  $R_{5'}$  is  $-(\text{CH}_2)_m$ -optionally substituted heteroaryl wherein  $m$  is 1.

In certain embodiments,  $R_5$  or  $R_{5'}$  is  $-(\text{CH}_2)_m$ -heteroaryl, optionally substituted 1 or 2 times by halo (*e.g.*, chloro, fluoro or bromo),  $-\text{CN}$ ,  $-\text{NO}_2$ ,  $-\text{CO}_2\text{H}$ ,  $-\text{CO}_2\text{C}_{1-6}\text{alkyl}$ ,  $-\text{CONH}_2$ ,  $-\text{CONH}(\text{C}_{1-6}\text{alkyl})$ ,  $-\text{CON}(\text{C}_{1-6}\text{alkyl})_2$ ,  $-\text{OH}$ , hydroxyalkyl, alkoxy, alkyl, acyl, carboxyalkyl, acetyl, trifluoromethyl, benzyloxy, phenoxy,  $-\text{NH}_2$ ,  $-\text{NH}(\text{C}_{1-6}\text{alkyl})$  or  $-\text{N}(\text{C}_{1-6}\text{alkyl})_2$ .

In certain embodiments,  $R_5$  or  $R_{5'}$  is  $-\text{S}(\text{O}_2)\text{-C}_{1-6}$  alkyl.

In certain embodiments,  $R_5$  or  $R_{5'}$  is  $-\text{C}(\text{O})\text{-NH}$ -optionally substituted phenyl.

In certain embodiments,  $R_5$  or  $R_{5'}$  is H.

In certain embodiments of the methods for enhancing neurite outgrowth,  $R_4$  is hydrogen, and  $R_5$  is a benzofused  $\text{C}_5\text{-C}_7$  cycloalkyl. In certain embodiments,  $R_4$  is  $\text{C}_1\text{-C}_3$  alkyl, and  $R_5$  is a benzofused  $\text{C}_5\text{-C}_7$  cycloalkyl. In certain embodiments,  $R_4$  is hydrogen, and  $R_5$  is a

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benzofused C<sub>5</sub>-C<sub>7</sub> cycloalkenyl. In certain embodiments, R<sub>4</sub> is C<sub>1</sub>-C<sub>3</sub> alkyl, and R<sub>5</sub> is a benzofused C<sub>5</sub>-C<sub>7</sub> cycloalkenyl. In certain embodiments, R<sub>4</sub> is hydrogen, and R<sub>5</sub> is indanyl. In certain embodiments, R<sub>4</sub> is methyl, and R<sub>5</sub> is indanyl. In certain embodiments, R<sub>4</sub> is hydrogen, and R<sub>5</sub> is indenyl. In certain embodiments, R<sub>4</sub> is methyl, and R<sub>5</sub> is indenyl. In certain embodiments, R<sub>4</sub> is hydrogen, and R<sub>5</sub> is 1,2,3,4-tetrahydronaphthalenyl. In certain embodiments, R<sub>4</sub> is methyl, and R<sub>5</sub> is 1,2,3,4-tetrahydronaphthalenyl.

In certain embodiments of the methods and compounds of the present invention, R<sub>4</sub> is hydrogen, and R<sub>5</sub> or R<sub>5'</sub> is optionally substituted acyl. In certain embodiments, R<sub>4</sub> is C<sub>1</sub>-C<sub>3</sub> alkyl, and R<sub>5</sub> or R<sub>5'</sub> is optionally substituted acyl. In certain embodiments, R<sub>4</sub> is hydrogen, and R<sub>5</sub> or R<sub>5'</sub> is -C(O)-optionally substituted heteroaryl. In certain embodiments, R<sub>4</sub> is C<sub>1</sub>-C<sub>3</sub> alkyl, and R<sub>5</sub> or R<sub>5'</sub> is -C(O)-optionally substituted heteroaryl. In certain embodiments, R<sub>4</sub> is hydrogen, and R<sub>5</sub> or R<sub>5'</sub> is -C(O)-optionally substituted alkyl. In certain embodiments, R<sub>4</sub> is methyl, and R<sub>5</sub> or R<sub>5'</sub> is -C(O)-optionally substituted alkyl. In certain embodiments, R<sub>4</sub> is hydrogen, and R<sub>5</sub> or R<sub>5'</sub> is -C(O)-optionally substituted aryl. In certain embodiments, R<sub>4</sub> is methyl, and R<sub>5</sub> or R<sub>5'</sub> is -C(O)-optionally substituted aryl. In certain embodiments, R<sub>4</sub> is hydrogen, and R<sub>5</sub> or R<sub>5'</sub> is -C(O)-optionally substituted phenyl. In certain embodiments, R<sub>4</sub> is methyl, and R<sub>5</sub> or R<sub>5'</sub> is -C(O)-optionally substituted phenyl. In certain embodiments, R<sub>4</sub> is hydrogen, and R<sub>5</sub> or R<sub>5'</sub> is -C(O)-unsubstituted phenyl. In certain embodiments, R<sub>4</sub> is methyl, and R<sub>5</sub> or R<sub>5'</sub> is -C(O)-unsubstituted phenyl. In certain embodiments, R<sub>4</sub> is hydrogen, and R<sub>5</sub> or R<sub>5'</sub> is -C(O)-optionally substituted pyridyl. In certain embodiments, R<sub>4</sub> is methyl, and R<sub>5</sub> or R<sub>5'</sub> is -C(O)-unsubstituted pyridyl. In certain embodiments, R<sub>4</sub> is hydrogen, and R<sub>5</sub> or R<sub>5'</sub> is -C(O)-unsubstituted pyridyl. In certain embodiments, R<sub>4</sub> is methyl, and R<sub>5</sub> or R<sub>5'</sub> is -C(O)-unsubstituted pyridyl. In certain embodiments, R<sub>4</sub> is hydrogen and R<sub>5</sub> or R<sub>5'</sub> is -S(O<sub>2</sub>)-C<sub>1-6</sub> alkyl. In certain embodiments, R<sub>4</sub> is methyl and R<sub>5</sub> or R<sub>5'</sub> is -S(O<sub>2</sub>)-C<sub>1-6</sub> alkyl. In certain embodiments, R<sub>4</sub> is hydrogen and R<sub>5</sub> or R<sub>5'</sub> is -C(O)-NH-optionally substituted phenyl. In certain embodiments, R<sub>4</sub> is methyl and R<sub>5</sub> or R<sub>5'</sub> is -C(O)-NH-optionally substituted phenyl.

In the above embodiments the aryl, heteroaryl, alkyl, or phenyl groups are, in some embodiments, optionally substituted 1 or 2 times by halo (e.g., chloro, fluoro or bromo), -

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CN, -NO<sub>2</sub>, -CO<sub>2</sub>H, -CO<sub>2</sub>C<sub>1-6</sub>alkyl, -CONH<sub>2</sub>, -CONH(C<sub>1-6</sub>alkyl), -CON(C<sub>1-6</sub>alkyl)<sub>2</sub>, -OH, hydroxyalkyl, alkoxy, alkyl, acyl, carboxyalkyl, acetyl, trifluoromethyl, benzyloxy, phenoxy, -NH<sub>2</sub>, -NH(C<sub>1-6</sub>alkyl), or -N(C<sub>1-6</sub>alkyl)<sub>2</sub>.

In certain embodiments, the following definitions for a compound of formula (Ia) apply:

n is 0 or 1;

R<sub>1</sub> is C<sub>1</sub>-C<sub>2</sub> alkyl;

R<sub>2</sub> is -C(O)OH, -C(O)OCH<sub>3</sub>, -C(O)OCH<sub>2</sub>CH<sub>3</sub>, -C(O)OCH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>, or -C(O)NR'R" (where R' and R" together form an optionally substituted morpholinyl);

R<sub>3</sub> is phenyl optionally substituted 1 or 2 times by a substituent independently selected from the group consisting of halogen, -CN, -CF<sub>3</sub>, amino, hydroxyl, -NHC<sub>1</sub>-C<sub>3</sub> alkyl, -N(C<sub>1</sub>-C<sub>3</sub> alkyl)<sub>2</sub>, -COO(C<sub>1</sub>-C<sub>3</sub> alkyl), phenyl, benzyl, C<sub>1</sub>-C<sub>3</sub> alkyl or C<sub>1</sub>-C<sub>3</sub> alkoxy;

R<sub>4</sub> is H or C<sub>1</sub>-C<sub>3</sub> alkyl; and .

R<sub>5</sub> is R<sub>5'</sub> and represents H, optionally substituted acyl, optionally substituted aryl, optionally substituted arylalkyl, optionally substituted heteroaryl, optionally substituted heteroarylalkyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted cycloalkylalkyl, -S(O)<sub>2</sub>- optionally substituted C<sub>1</sub>-C<sub>6</sub> alkyl, or -C(O)NR'R' (wherein each R' is independently H, optionally substituted C<sub>1</sub>-C<sub>6</sub> alkyl or optionally substituted aryl).

In certain embodiments, the following definitions for a compound of formula (Ia) apply:

n is 0 or 1;

R<sub>1</sub> is C<sub>1</sub>-C<sub>2</sub> alkyl;

R<sub>2</sub> is -COOR' (where R' is H or C<sub>1</sub>-C<sub>4</sub> alkyl);

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R<sub>3</sub> is phenyl optionally substituted 1 or 2 times by a substituent independently selected from the group consisting of halogen, -CN, -CF<sub>3</sub>, amino, hydroxyl, -NHC<sub>1</sub>-C<sub>3</sub> alkyl, -N(C<sub>1</sub>-C<sub>3</sub> alkyl)<sub>2</sub>, -COO(C<sub>1</sub>-C<sub>3</sub> alkyl), phenyl, benzyl, C<sub>1</sub>-C<sub>3</sub> alkyl or C<sub>1</sub>-C<sub>3</sub> alkoxy;

R<sub>4</sub> is H or C<sub>1</sub>-C<sub>3</sub> alkyl; and

R<sub>5</sub> is R<sub>5'</sub> and represents H, optionally substituted acyl, optionally substituted aryl, optionally substituted arylalkyl, optionally substituted heteroaryl, optionally substituted heteroarylalkyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted cycloalkylalkyl, -S(O)<sub>2</sub>-optionally substituted C<sub>1</sub>-C<sub>6</sub> alkyl, or -C(O)NR'R' (wherein each R' is independently H, optionally substituted C<sub>1</sub>-C<sub>6</sub> alkyl or optionally substituted aryl).

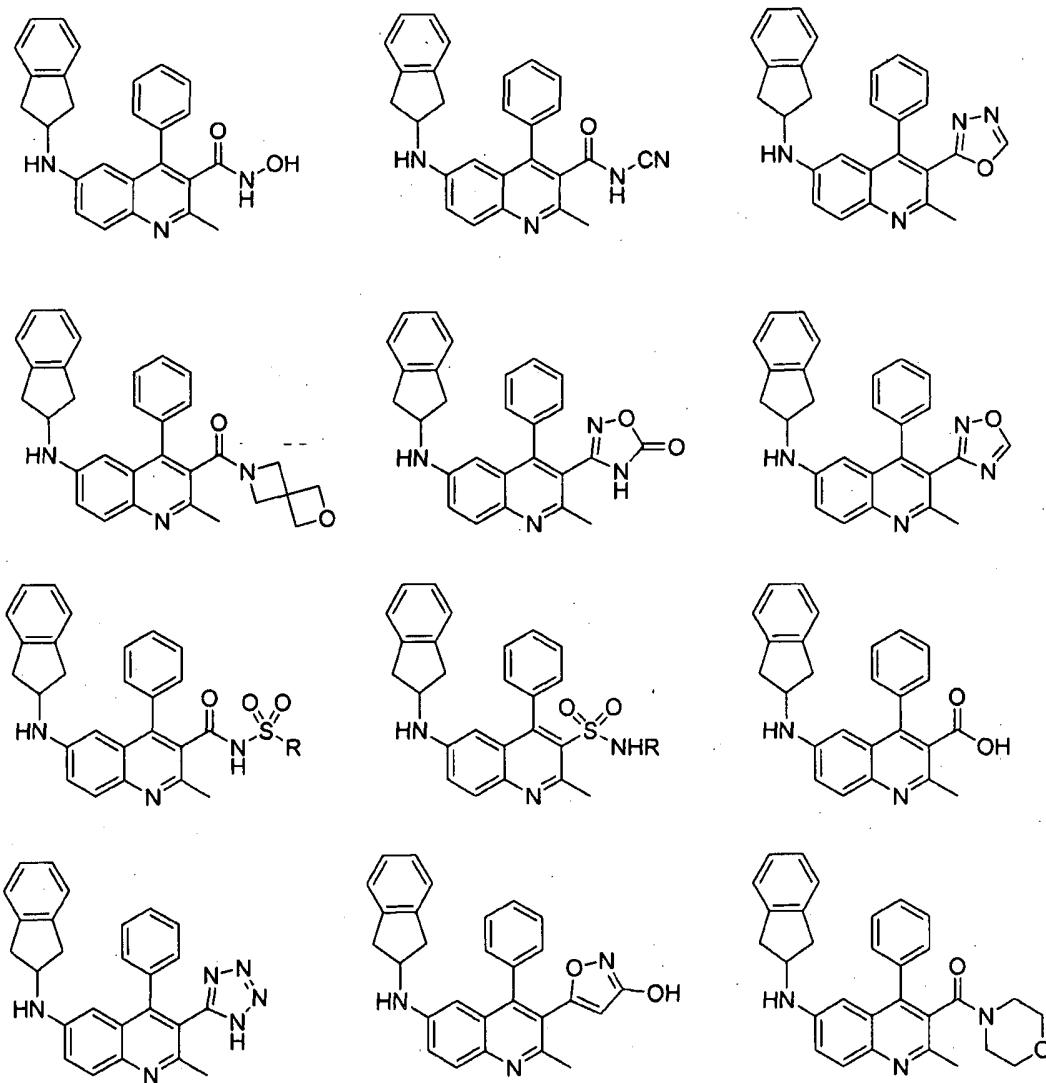
In certain embodiments, the invention provides compounds of formula (Ia) or salts thereof, wherein R<sub>1</sub> is methyl, R<sub>2</sub> is -C(O)OH, -C(O)OCH<sub>3</sub>, -C(O)OCH<sub>2</sub>CH<sub>3</sub>, R<sub>4</sub> is H, and R<sub>5</sub> is R<sub>5'</sub> and is -C(O)-optionally substituted heteroaryl (in particular pyridyl, -C(O)-C<sub>1</sub>-C<sub>4</sub>alkyl, or -C(O)-optionally substituted phenyl).

In certain embodiments the invention provides compounds of formula (Ia), or salts thereof, provided that the compounds wherein R<sub>3</sub> is optionally substituted phenyl, one of R<sub>4</sub> and R<sub>5</sub> is H, and the other of R<sub>4</sub> and R<sub>5</sub> is optionally substituted bicyclic cycloalkyl or optionally substituted bicyclic cycloalkenyl, are specifically excluded.

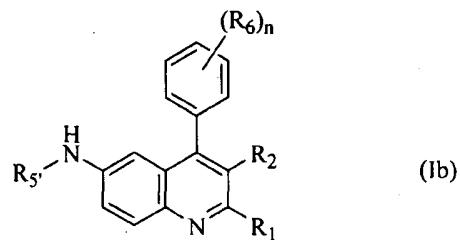
In certain embodiments the invention provides compounds of formula (Ia), or salts thereof, provided that the compounds wherein R<sub>3</sub> is optionally substituted phenyl, one of R<sub>4</sub> and R<sub>5</sub> is H, and the other of R<sub>4</sub> and R<sub>5</sub> is indanyl, are specifically excluded.

In certain embodiments the invention provides compounds of formula (Ia), provided that the following compounds, and pharmaceutically acceptable salts thereof, are specifically excluded:

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In certain embodiments, the present invention provides compounds of formula (Ib) or salts thereof:



wherein  $\text{R}_1$ ,  $\text{R}_2$ ,  $\text{R}_6$ ,  $\text{R}_5'$  and  $n$  are as described herein.

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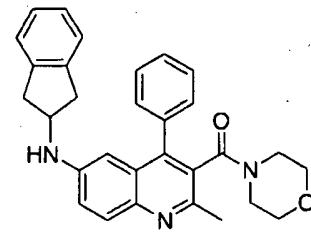
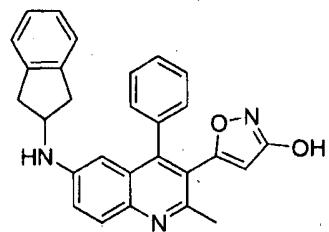
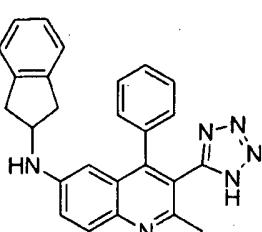
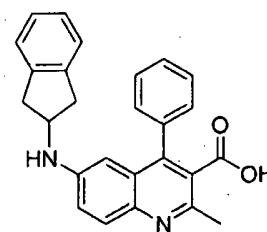
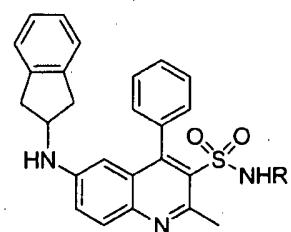
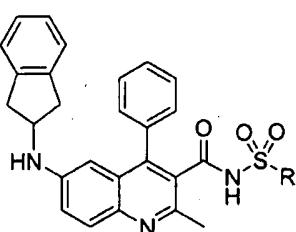
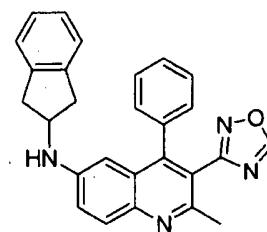
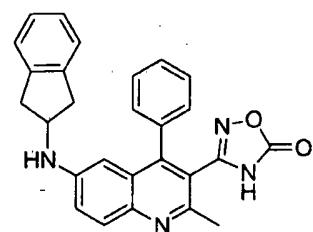
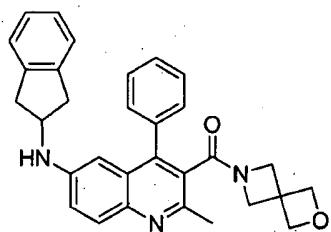
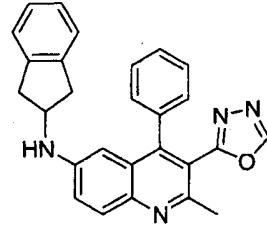
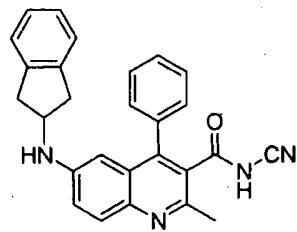
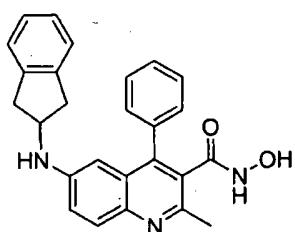
In some embodiments, one or more of the following definitions apply:

- (a) n is 0,
- (b) R<sub>1</sub> is methyl,
- (c) R<sub>2</sub> is -C(O)OH, -C(O)OCH<sub>3</sub>, or -C(O)OCH<sub>2</sub>CH<sub>3</sub>,
- (d) R<sub>4</sub> is H, and
- (e) R<sub>5</sub> represents optionally substituted acyl, -(CH<sub>2</sub>)<sub>m</sub>-optionally substituted aryl, -(CH<sub>2</sub>)<sub>m</sub>-optionally substituted heteroaryl, -(CH<sub>2</sub>)<sub>m</sub>-optionally substituted heterocyclyl, or -(CH<sub>2</sub>)<sub>m</sub>-optionally substituted cycloalkyl, wherein m is an integer of 1 to 3, inclusive.

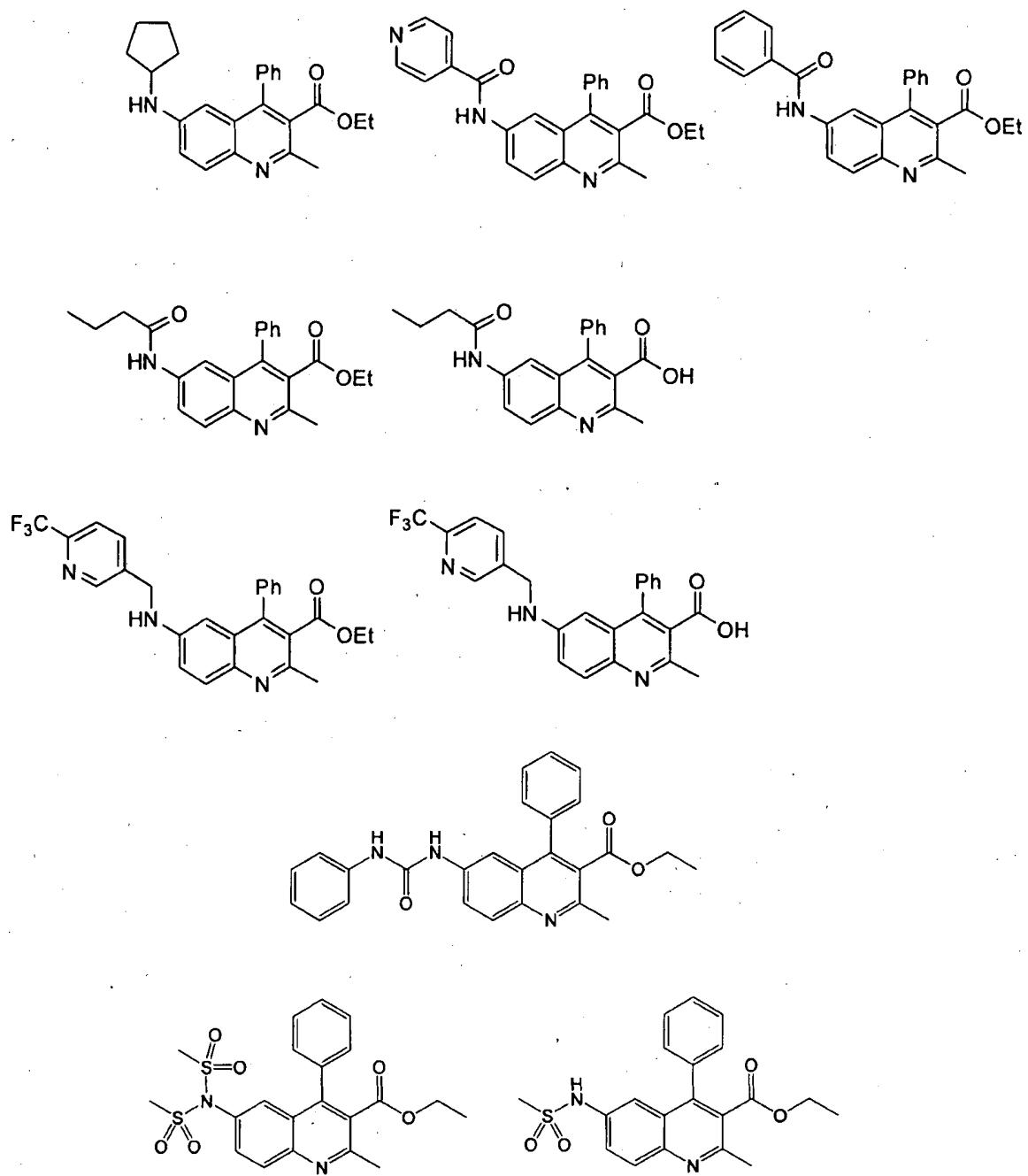
The present invention also provides pharmaceutical compositions comprising a compound of formula (Ia) or (Ib), or a salt thereof, and optionally a pharmaceutically acceptable excipient.

Representative compounds of the present invention and compounds which can be used in the methods of the present invention include:

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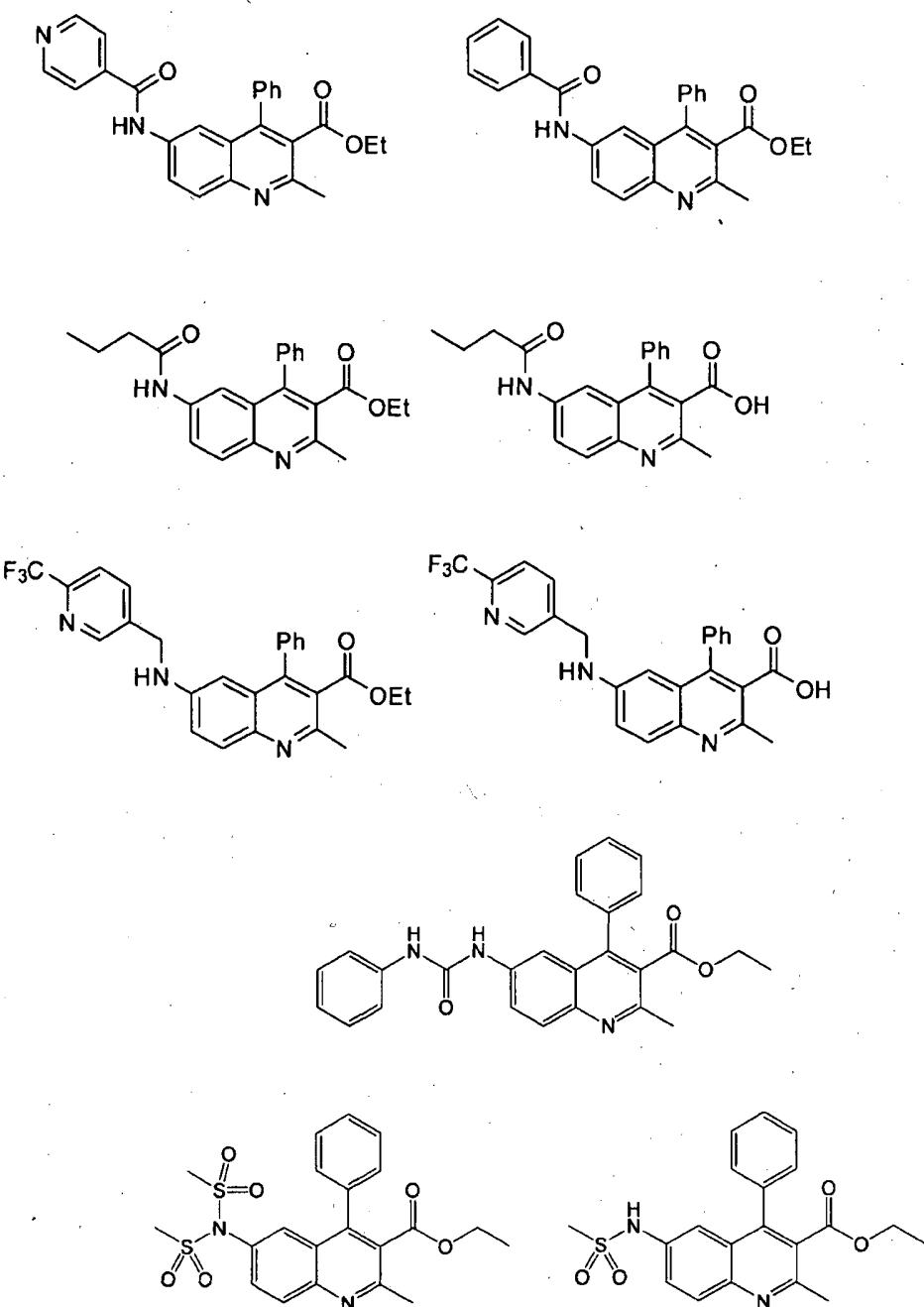
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In certain embodiments, R is H, aryl, or C<sub>1-3</sub> alkyl.

Representative compounds of the present invention include:

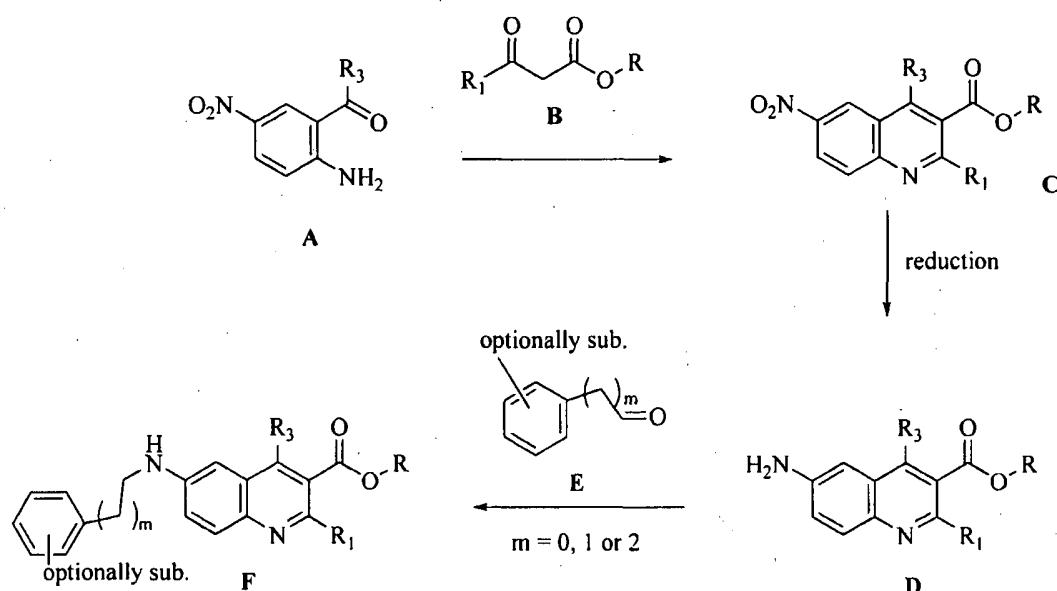
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The compounds of the present invention can be prepared according to Schemes 1 to 8 below:

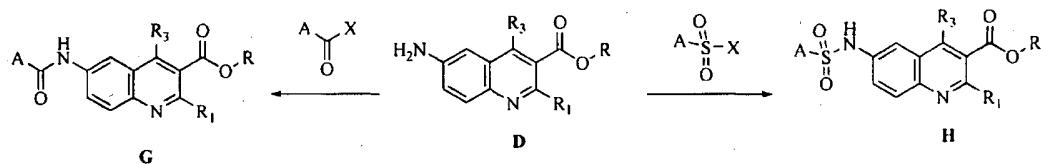
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**Scheme 1**



Compounds of formula **F** (where R is alkyl,) of the invention may be prepared by initially reacting 2-amino-5-nitrobenzophenone of formula **A** with an alkyl acetoacetate of formula **B** to afford quinolines **C**. Reduction of the nitro group may afford **D** which can subsequently be coupled to carbonyl substrates of formula **E** to prepare compounds of formula **F**.

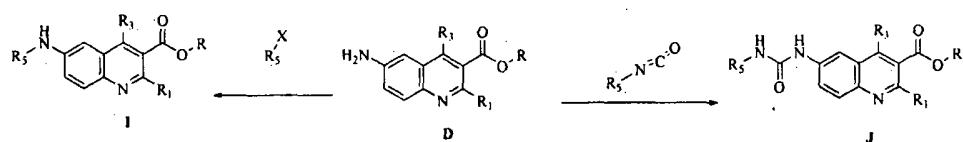
**Scheme 2**



According to Scheme 2, compounds of formula **D** (where R is alkyl) can be reacted with activated carboxyl or sulfonic acids to give the compounds of formula **G** and **H** where A is optionally substituted alkyl, cycloalkyl, aryl, heteroaryl, or heterocyclyl.

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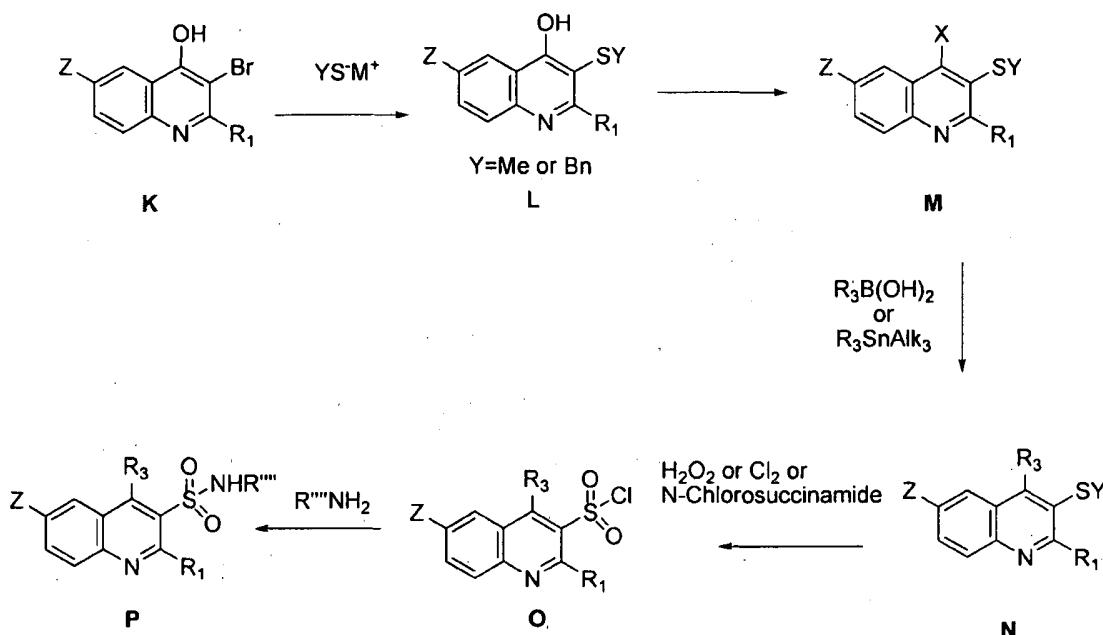
**Scheme 3**



According to Scheme 3, the compounds of formula **I** (where  $R_5$  is optionally substituted aryl or heteroaryl) can be prepared by reacting compounds of formula **D** using Buchwald or Ullmann coupling conditions. Also, the compounds of formula **J** (where  $R_5$  is optionally substituted aryl or heteroaryl) can be prepared by reacting compounds of formula **D** with alkyl isocyanates. Alternatively, the anilines of formula **D** can be converted to corresponding isocyanates that can be further reacted with primary or secondary amines. Persons skilled in the art will understand that esters of formula **F** to **J** can be further converted to their corresponding acids (where  $R$  is H) using methods such as alkali metal hydroxide mediated hydrolysis. The compounds of formula **F** to **J** (where  $R$  is H) can be further modified to give the corresponding primary, secondary, or tertiary amides by one skilled in the art.

**Scheme 4**

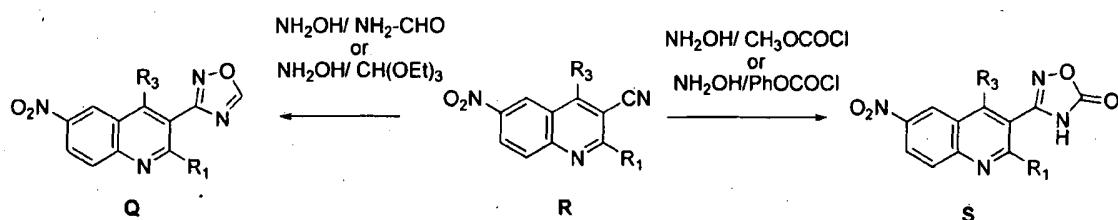
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According to Scheme 4, 3-bromo-quinolin-4-ol derivatives of formula **K** ( $Z=NR_4R_5$  or  $\text{NO}_2$ ) can be reacted with alkali- (e.g., sodium metal) or alkaline-earth metal salts of methyl or benzyl thiol to provide compounds of formula **L** (e.g., Bioorg. Med. Chem. Lett., 2001, 9, 1141; Heterocycles 2007, 71, 1975). 3-Bromo-quinolin-4-ol derivatives of formula **K** are known (e.g., 3-bromo-6-(*N,N'*-dimethylamino)-2-(trifluoromethyl)-quinolin-4-ol: J. Chem. Info. Comp. Sci. 2001, 41, 1316) or can be synthesized from commercially available 3-bromo-quinolin-4-ol by conventional methods such as nitration with nitric acid. Conversion of compounds of formula **L** to **M** can be achieved by known halogenation methods with suitable halogenating reagents (e.g.,  $\text{POCl}_3$ ,  $\text{SOCl}_2$ ,  $\text{PCl}_5$ , or  $\text{PBr}_3$ ). Compounds of formula **N** can be prepared by reacting compounds of formula **M** with aryl boronic acids according to Suzuki coupling conditions, any modification of Suzuki coupling conditions or Stille coupling conditions. Conversion of 4-aryl-3-sulfide-quinoline derivative of formula **N** to **O** can be achieved by known oxidative methods (e.g., Heterocycles, 1994, 38, 1317; Heterocycles 2007, 71, 1975). 3-Sulfonylchloride derivative of quinoline of formula **O** can be reacted with a suitable amine to provide a compound of formula **P**. For compound of formula **P** where  $Z=\text{NO}_2$ , the nitro group can be reduced to an amine by known methods and further derivatized according to Schemes 1-3.

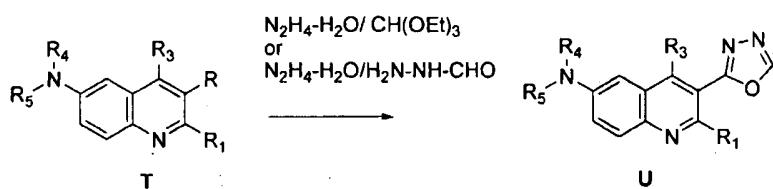
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**Scheme 5**



According to Scheme 5, 3-(1,2,4-oxadiazole)-quinoline derivative of formula **Q** can be synthesized by reacting 3-cyano-quinoline derivative of formula **R** (prepared according to Scheme 8) with hydroxylamine and formamide (e.g., J. Org. Chem., 1979, 44, 1695) or hydroxyl amine and triethyl orthoformate (e.g., WO2005/097750). 3-cyano-quinoline derivative of formula **R** can be reacted with hydroxyl amine and a suitable ester of chloroformic acid (e.g., methyl ester: J. Med. Chem., 2001, 44, 1560; phenyl ester: WO2007/039172) to form a compound of formula **S**. The nitro group of compounds of the formula **Q** or **S** can be reduced to an amine by known methods and further derivatized according to Schemes 1-3.

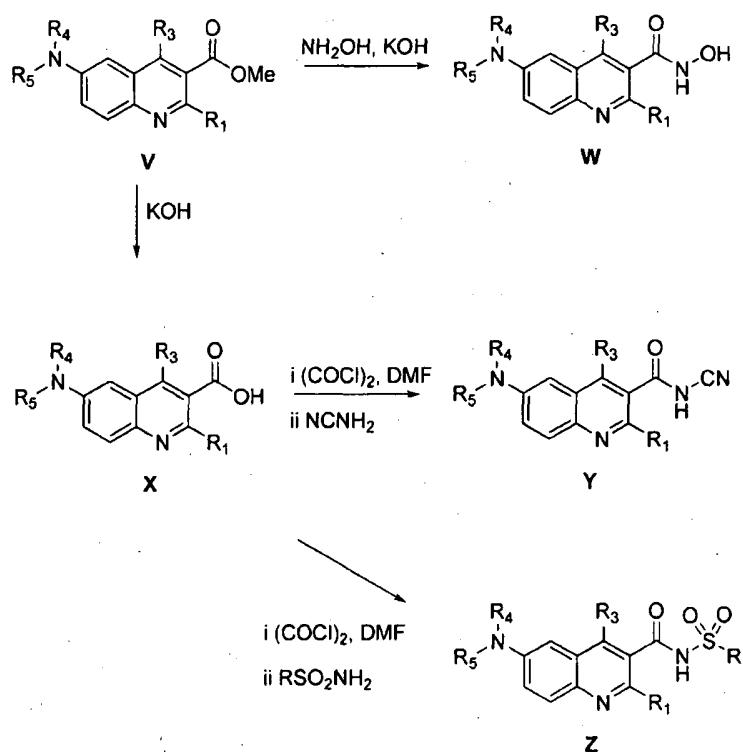
**Scheme 6**



As shown in Scheme 6, 3-(1,3,4-oxadiazole)-quinoline derivatives of formula **U** can be prepared by reacting a suitable acid ( $\text{R}=\text{COOH}$ ) or ester ( $\text{R}=\text{COOMe}$ ) of formula **T** with hydrazine-hydrate and triethyl orthoformate (e.g. WO2010/135360) or with hydrazine-hydrate and hydrazide of formic acid (e.g., Tetrahedron Letters, 2009, 65, 9989).

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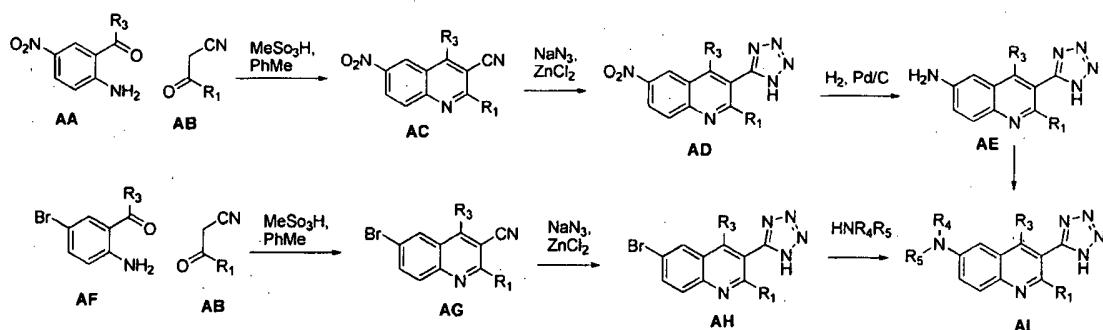
**Scheme 7**



As shown in Scheme 7, compounds of the formula **W** can be prepared by reacting esters of formula **V** with hydroxylamine and potassium hydroxide. Compounds of the formula **Y** can be prepared by converting compounds of the formula **X** to the corresponding acid chloride, for example, with oxalyl chloride and dimethylformamide, then by treatment with cyanoamide (NCNH<sub>2</sub>). Compounds of the formula **Z** can be formed by treating these acid chlorides with a primary sulphonamide.

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**Scheme 8**



Compounds of the formula **AI** can be prepared by the route shown in Scheme 8 (e.g., Bioorg. Med. Chem. Lett. 2011, 19 (15) 4482). Reaction of 2-aminobenzophenones **AA** or **AF** with alpha-cyanoketones can form 3-cyanoquinolines **AC** or **AG** respectively. Compounds **AC** or **AG** can be reacted with sodium azide to give tetrazoles **AD** or **AH**. 6-Nitro-3-tetrazolylquinolines of the formula **AD** can be reduced, for example, by hydrogenation, to give the 6-aminoquinolines **AE**. Either one or two successive reductive aminations of compounds of the formula **AE** with aldehydes or ketones can give compounds of the formula **AI**. Alternatively compounds of the formula **AH** can undergo Buchwald coupling with amines to give compounds of the formula **AI**.

Other compounds of formula (I) can be prepared by the addition, removal or modification of existing substituents. This could be achieved by using standard techniques for functional group inter-conversion that are well known in the industry, such as those described in "Comprehensive organic transformations: a guide to functional group preparations" by Larock R. C., New York, VCH Publishers, Inc. 1989.

Examples of functional group inter-conversions are:  $-\text{C}(\text{O})\text{NR}^*\text{R}^{**}$  from  $-\text{CO}_2\text{CH}_3$  by heating with or without catalytic metal cyanide, e.g.,  $\text{NaCN}$ , and  $\text{HNR}^*\text{R}^{**}$  in  $\text{CH}_3\text{OH}$ ;  $-\text{OC}(\text{O})\text{R}$  from  $-\text{OH}$  with, e.g.,  $\text{ClC}(\text{O})\text{R}$  in pyridine;  $-\text{NC(S)}\text{NR}^*\text{R}^{**}$  from  $-\text{NHR}$  with an alkylisothiocyanate or thiocyanic acid;  $-\text{NRC(O)OR}^*$  from  $-\text{NHR}$  with alkyl chloroformate;  $-\text{NRC(O)NR}^*\text{R}^{**}$  from  $-\text{NHR}$  by treatment with an isocyanate, e.g.,  $\text{HN=C=O}$  or  $\text{RN=C=O}$ ;  $-\text{NRC(O)R}^*$  from  $-\text{NHR}$  by treatment with  $\text{ClC}(\text{O})\text{R}^*$  in pyridine;  $-\text{C}=\text{NR})\text{NR}^*\text{R}^{**}$  from  $-\text{C}(\text{NR}^*\text{R}^{**})\text{SR}$  with  $\text{H}_3\text{NR}^+\text{OAc}^-$  by heating in alcohol; -

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C(NR<sup>\*</sup>R<sup>\*\*</sup>)SR from -C(S)NR<sup>\*</sup>R<sup>\*\*</sup> with R-I in an inert solvent, e.g., acetone; -C(S)NR<sup>\*</sup>R<sup>\*\*</sup> (where R<sup>\*</sup> or R<sup>\*\*</sup> is not hydrogen) from -C(S)NH<sub>2</sub> with HNR<sup>\*</sup>R<sup>\*\*</sup>; -C(=NCN)-NR<sup>\*</sup>R<sup>\*\*</sup> from -C(=NR<sup>\*</sup>R<sup>\*\*</sup>)-SR with NH<sub>2</sub>CN by heating in anhydrous alcohol, alternatively from -C(=NH)-NR<sup>\*</sup>R<sup>\*\*</sup> by treatment with BrCN and NaOEt in EtOH; -NR-C(=NCN)SR from -NHR<sup>\*</sup> by treatment with (RS)<sub>2</sub>C=NCN; -NR<sup>\*\*</sup>SO<sub>2</sub>R from -NHR<sup>\*</sup> by treatment with ClSO<sub>2</sub>R by heating in pyridine; -NR<sup>\*</sup>C(S)R from -NR<sup>\*</sup>C(O)R by treatment with Lawesson's reagent [2,4-bis(4-methoxyphenyl)-1,3,2,4-dithiadiphosphetane-2,4-disulfide]; -NRSO<sub>2</sub>CF<sub>3</sub> from -NHR with triflic anhydride and base, -CH(NH<sub>2</sub>)CHO from -CH(NH<sub>2</sub>)C(O)OR<sup>\*</sup> with Na(Hg) and HCl/EtOH; -CH<sub>2</sub>C(O)OH from -C(O)OH by treatment with SOCl<sub>2</sub> then CH<sub>2</sub>N<sub>2</sub> then H<sub>2</sub>O/Ag<sub>2</sub>O; -C(O)OH from -CH<sub>2</sub>C(O)OCH<sub>3</sub> by treatment with PhMgX/HX then acetic anhydride then CrO<sub>3</sub>; R-OC(O)R<sup>\*</sup> from RC(O)R<sup>\*</sup> by R<sup>\*\*</sup>CO<sub>3</sub>H; -CCH<sub>2</sub>OH from -C(O)OR<sup>\*</sup> with Na / R<sup>\*</sup>OH; -CHCH<sub>2</sub> from -CH<sub>2</sub>CH<sub>2</sub>OH by the Chugaev reaction; -NH<sub>2</sub> from -C(O)OH by the Curtius reaction; -NH<sub>2</sub> from -C(O)NHOH with TsCl/base then H<sub>2</sub>O; -CHC(O)CHR from -CHCHOHCHR by using the Dess-Martin Periodinane reagent or CrO<sub>3</sub> / aqH<sub>2</sub>SO<sub>4</sub> / acetone; -C<sub>6</sub>H<sub>5</sub>CHO from -C<sub>6</sub>H<sub>5</sub>CH<sub>3</sub> with CrO<sub>2</sub>Cl<sub>2</sub>; -CHO from -CN with SnCl<sub>2</sub> / HCl; -CN from -C(O)NHR with PCl<sub>5</sub>; -CH<sub>2</sub>R from -C(O)R with N<sub>2</sub>H<sub>4</sub> / KOH.

One of ordinary skill in the art will appreciate that the synthetic methods, as described herein, may necessitate a variety of protecting groups. By the term "protecting group", as used herein, it is meant that a particular functional moiety, e.g., O, S, or N, is temporarily blocked so that a reaction can be carried out selectively at another reactive site in a multifunctional compound. In certain embodiments, a protecting group reacts selectively in good yield to give a protected substrate that is stable to the projected reactions; the protecting group should be selectively removable in good yield by readily available, preferably non-toxic reagents that do not attack the other functional groups; the protecting group forms an easily separable derivative (more preferably without the generation of new stereogenic centers); and the protecting group has a minimum of additional functionality to avoid further sites of reaction. As detailed herein, oxygen, sulfur, nitrogen, and carbon protecting groups may be utilized. Oxygen protecting groups include methyl, methoxymethyl (MOM), methylthiomethyl (MTM), t-butylthiomethyl,

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(phenyldimethylsilyl)methoxymethyl (SMOM), benzyloxymethyl (BOM), p-methoxybenzyloxymethyl (PMBM), (4-methoxyphenoxy)methyl (p-AOM), guaiacolmethyl (GUM), t-butoxymethyl, 4-pentenyloxymethyl (POM), siloxymethyl, 2-methoxyethoxymethyl (MEM), 2,2,2-trichloroethoxymethyl, bis(2-chloroethoxy)methyl, 2-(trimethylsilyl)ethoxymethyl (SEMOR), tetrahydropyranyl (THP), 3-bromotetrahydropyranyl, tetrahydrothiopyranyl, 1-methoxycyclohexyl, 4-methoxytetrahydropyranyl (MTHP), 4-methoxytetrahydrothiopyranyl, 4-methoxytetrahydrothiopyranyl S,S-dioxide, 1-[(2-chloro-4-methyl)phenyl]-4-methoxypiperidin-4-yl (CTMP), 1,4-dioxan-2-yl, tetrahydrofuranyl, tetrahydrothiofuranyl, 2,3,3a,4,5,6,7,7a-octahydro-7,8,8-trimethyl-4,7-methanobenzofuran-2-yl, 1-ethoxyethyl, 1-(2-chloroethoxy)ethyl, 1-methyl-1-methoxyethyl, 1-methyl-1-benzyloxyethyl, 1-methyl-1-benzyloxy-2-fluoroethyl, 2,2,2-trichloroethyl, 2-trimethylsilylethyl, 2-(phenylselenyl)ethyl, t-butyl, allyl, p-chlorophenyl, p-methoxyphenyl, 2,4-dinitrophenyl, benzyl, p-methoxybenzyl, 3,4-dimethoxybenzyl, o-nitrobenzyl, p-nitrobenzyl, p-halobenzyl, 2,6-dichlorobenzyl, p-cyanobenzyl, p-phenylbenzyl, 2-picoly, 4-picoly, 3-methyl-2-picoly N-oxido, diphenylmethyl, p,p'-dinitrobenzhydryl, 5-dibenzosuberyl, triphenylmethyl,  $\alpha$ -naphthyldiphenylmethyl, p-methoxyphenyldiphenylmethyl, di(p-methoxyphenyl)phenylmethyl, tri(p-methoxyphenyl)methyl, 4-(4'-bromophenacyloxyphenyl)diphenylmethyl, 4,4',4''-tris(4,5-dichlorophthalimidophenyl)methyl, 4,4',4''-tris(levulinoyloxyphenyl)methyl, 4,4',4''-tris(benzoyloxyphenyl)methyl, 3-(imidazol-1-yl)bis(4',4''-dimethoxyphenyl)methyl, 1,1-bis(4-methoxyphenyl)-1'-pyrenylmethyl, 9-anthryl, 9-(9-phenyl)xanthenyl, 9-(9-phenyl-10-oxo)anthryl, 1,3-benzodithiolan-2-yl, benzisothiazolyl S,S-dioxido, trimethylsilyl (TMS), triethylsilyl (TES), triisopropylsilyl (TIPS), dimethylisopropylsilyl (IPDMS), diethylisopropylsilyl (DEIPS), dimethylhexylsilyl, t-butyldimethylsilyl (TBDMS), t-butyldiphenylsilyl (TBDPS), tribenzylsilyl, tri-p-xylylsilyl, triphenylsilyl, diphenylmethylsilyl (DPMS), t-butylmethoxyphenylsilyl (TBMPS), formate, benzoylformate, acetate, chloroacetate, dichloroacetate, trichloroacetate, trifluoroacetate, methoxyacetate, triphenylmethoxyacetate, phenoxyacetate, p-chlorophenoxyacetate, 3-phenylpropionate, 4-oxopentanoate (levulinic acid), 4,4-(ethylenedithio)pentanoate (levulinoyldithioacetal), pivaloate, adamantoate, crotonate, 4-methoxycrotonate, benzoate,

p-phenylbenzoate, 2,4,6-trimethylbenzoate (mesitoate), alkyl methyl carbonate, 9-fluorenylmethyl carbonate (Fmoc), alkyl ethyl carbonate, alkyl 2,2,2-trichloroethyl carbonate (Troc), 2-(trimethylsilyl)ethyl carbonate (TMSEC), 2-(phenylsulfonyl) ethyl carbonate (Psec), 2-(triphenylphosphonio) ethyl carbonate (Peoc), alkyl isobutyl carbonate, alkyl vinyl carbonate alkyl allyl carbonate, alkyl p-nitrophenyl carbonate, alkyl benzyl carbonate, alkyl p-methoxybenzyl carbonate, alkyl 3,4-dimethoxybenzyl carbonate, alkyl o-nitrobenzyl carbonate, alkyl p-nitrobenzyl carbonate, alkyl S-benzyl thiocarbonate, 4-ethoxy-1-naphthyl carbonate, methyl dithiocarbonate, 2-iodobenzoate, 4-azidobutyrate, 4-nitro-4-methylpentanoate, o-(dibromomethyl)benzoate, 2-formylbenzenesulfonate, 2-(methylthiomethoxy)ethyl, 4-(methylthiomethoxy)butyrate, 2-(methylthiomethoxymethyl)benzoate, 2,6-dichloro-4-methylphenoxyacetate, 2,6-dichloro-4-(1,1,3,3-tetramethylbutyl)phenoxyacetate, 2,4-bis(1,1-dimethylpropyl)phenoxyacetate, chlorodiphenylacetate, isobutyrate, monosuccinate, (E)-2-methyl-2-butenoate, o-(methoxycarbonyl)benzoate,  $\alpha$ -naphthoate, nitrate, alkyl N,N,N',N'-tetramethylphosphorodiamide, alkyl N-phenylcarbamate, borate, dimethylphosphinothioyl, alkyl 2,4-dinitrophenylsulfenate, sulfate, methanesulfonate (mesylate), benzylsulfonate, and tosylate (Ts). For protecting 1,2- or 1,3-diols, the protecting groups include methylene acetal, ethylidene acetal, 1-t-butylethylidene ketal, 1-phenylethylidene ketal, (4-methoxyphenyl)ethylidene acetal, 2,2,2-trichloroethylidene acetal, acetonide, cyclopentylidene ketal, cyclohexylidene ketal, cycloheptylidene ketal, benzylidene acetal, p-methoxybenzylidene acetal, 2,4-dimethoxybenzylidene ketal, 3,4-dimethoxybenzylidene acetal, 2-nitrobenzylidene acetal, methoxymethylene acetal, ethoxymethylene acetal, dimethoxymethylene ortho ester, 1-methoxyethylidene ortho ester, 1-ethoxyethylidene ortho ester, 1,2-dimethoxyethylidene ortho ester,  $\alpha$ -methoxybenzylidene ortho ester, 1-(N,N-dimethylamino)ethylidene derivative,  $\alpha$ -(N,N'-dimethylamino)benzylidene derivative, 2-oxacyclopentylidene ortho ester, di-t-butylsilylene group (DTBS), 1,3-(1,1,3,3-tetraisopropylsiloxyanylidene) derivative (TIPDS), tetra-t-butoxydisiloxane-1,3-diylidene derivative (TBDS), cyclic carbonates, cyclic boronates, ethyl boronate, and phenyl boronate. Amino-protecting groups include methyl carbamate, ethyl carbamate, 9-fluorenylmethyl carbamate (Fmoc), 9-(2-sulfo)fluorenylmethyl carbamate, 9-(2,7-dibromo)fluoroenylmethyl carbamate, 2,7-di-t-

butyl-[9-(10,10-dioxo-10,10,10,10-tetrahydrothioxanthyl)]methyl carbamate (DBD-Tmoc), 4-methoxyphenacyl carbamate (Phenoc), 2,2,2-trichloroethyl carbamate (Troc), 2-trimethylsilylethyl carbamate (Teoc), 2-phenylethyl carbamate (hZ), 1-(1-adamantyl)-1-methylethyl carbamate (Adpoc), 1,1-dimethyl-2-haloethyl carbamate, 1,1-dimethyl-2,2-dibromoethyl carbamate (DB-t-BOC), 1,1-dimethyl-2,2,2-trichloroethyl carbamate (TCBOC), 1-methyl-1-(4-biphenylyl)ethyl carbamate (Bpoc), 1-(3,5-di-t-butylphenyl)-1-methylethyl carbamate (t-Bumeoc), 2-(2'- and 4'-pyridyl)ethyl carbamate (Pyoc), 2-(N,N-dicyclohexylcarboxamido)ethyl carbamate, t-butyl carbamate (BOC), 1-adamantyl carbamate (Adoc), vinyl carbamate (Voc), allyl carbamate (Alloc), 1-isopropylallyl carbamate (Ipaoc), cinnamyl carbamate (Coc), 4-nitrocinnamyl carbamate (Noc), 8-quinolyl carbamate, N-hydroxypiperidinyl carbamate, alkyldithio carbamate, benzyl carbamate (Cbz), p-methoxybenzyl carbamate (Moz), p-nitobenzyl carbamate, p-bromobenzyl carbamate, p-chlorobenzyl carbamate, 2,4-dichlorobenzyl carbamate, 4-methylsulfinylbenzyl carbamate (Msz), 9-anthrylmethyl carbamate, diphenylmethyl carbamate, 2-methylthioethyl carbamate, 2-methylsulfonylethyl carbamate, 2-(p-toluenesulfonyl)ethyl carbamate, [2-(1,3-dithianyl)]methyl carbamate (Dmoc), 4-methylthiophenyl carbamate (Mtpc), 2,4-dimethylthiophenyl carbamate (Bmpc), 2-phosphonioethyl carbamate (Peoc), 2-triphenylphosphonioisopropyl carbamate (Ppoc), 1,1-dimethyl-2-cyanoethyl carbamate, m-chloro-p-acyloxybenzyl carbamate, p-(dihydroxyboryl)benzyl carbamate, 5-benzisoxazolylmethyl carbamate, 2-(trifluoromethyl)-6-chromonylmethyl carbamate (Troc), m-nitrophenyl carbamate, 3,5-dimethoxybenzyl carbamate, o-nitrobenzyl carbamate, 3,4-dimethoxy-6-nitrobenzyl carbamate, phenyl(o-nitrophenyl)methyl carbamate, phenothiazinyl-(10)-carbonyl derivative, N'-p-toluenesulfonylaminocarbonyl derivative, N'-phenylaminothiocarbonyl derivative, t-amyl carbamate, S-benzyl thiocarbamate, p-cyanobenzyl carbamate, cyclobutyl carbamate, cyclohexyl carbamate, cyclopentyl carbamate, cyclopropylmethyl carbamate, p-decyloxybenzyl carbamate, 2,2-dimethoxycarbonylvinyl carbamate, o-(N,N-dimethylcarboxamido)benzyl carbamate, 1,1-dimethyl-3-(N,N-dimethylcarboxamido)propyl carbamate, 1,1-dimethylpropynyl carbamate, di(2-pyridyl)methyl carbamate, 2-furanylmethyl carbamate, 2-iodoethyl carbamate, isoborynl carbamate, isobutyl carbamate, isonicotinyl carbamate, p-(p'-methoxyphenylazo)benzyl

carbamate, 1-methylcyclobutyl carbamate, 1-methylcyclohexyl carbamate, 1-methyl-1-cyclopropylmethyl carbamate, 1-methyl-1-(3,5-dimethoxyphenyl)ethyl carbamate, 1-methyl-1-(p-phenylazophenyl)ethyl carbamate, 1-methyl-1-phenylethyl carbamate, 1-methyl-1-(4-pyridyl)ethyl carbamate, phenyl carbamate, p-(phenylazo)benzyl carbamate, 2,4,6-tri-t-butylphenyl carbamate, 4-(trimethylammonium)benzyl carbamate, 2,4,6-trimethylbenzyl carbamate, formamide, acetamide, chloroacetamide, trichloroacetamide, trifluoroacetamide, phenylacetamide, 3-phenylpropanamide, picolinamide, 3-pyridylcarboxamide, N-benzoylphenylalanyl derivative, benzamide, p-phenylbenzamide, o-nitrophenylacetamide, o-nitrophenoxyacetamide, acetoacetamide, (N'-dithiobenzylloxycarbonylamino)acetamide, 3-(p-hydroxyphenyl)propanamide, 3-(o-nitrophenyl)propanamide, 2-methyl-2-(o-nitrophenoxy)propanamide, 2-methyl-2-(o-phenylazophenoxy)propanamide, 4-chlorobutanamide, 3-methyl-3-nitrobutanamide, o-nitrocinnamide, N-acetylmethionine derivative, o-nitrobenzamide, o-(benzoyloxymethyl)benzamide, 4,5-diphenyl-3-oxazolin-2-one, N-phthalimide, N-dithiasuccinimide (Dts), N-2,3-diphenylmaleimide, N-2,5-dimethylpyrrole, N-1,1,4,4-tetramethylsilylazacyclopentane adduct (STABASE), 5-substituted 1,3-dimethyl-1,3,5-triazacyclohexan-2-one, 5-substituted 1,3-dibenzyl-1,3,5-triazacyclohexan-2-one, 1-substituted 3,5-dinitro-4-pyridone, N-methylamine, N-allylamine, N-[2-(trimethylsilyl)ethoxy]methylamine (SEM), N-3-acetoxypropylamine, N-(1-isopropyl-4-nitro-2-oxo-3-pyroolin-3-yl)amine, quaternary ammonium salts, N-benzylamine, N-di(4-methoxyphenyl)methylamine, N-5-dibenzosuberylamine, N-triphenylmethylamine (Tr), N-[(4-methoxyphenyl)diphenylmethyl]amine (MMTr), N-9-phenylfluorenylamine (PhF), N-2,7-dichloro-9-fluorenylmethyleneamine, N-ferrocenylmethylamino (Fcm), N-2-picolylamino N'-oxide, N-1,1-dimethylthiomethyleneamine, N-benzylideneamine, N-pmethoxybenzylideneamine, N-diphenylmethyleneamine, N-[(2-pyridyl)mesityl]methyleneamine, N-(N',N'-dimethylaminomethylene)amine, N,N'-isopropylidenediamine, N-p-nitrobenzylideneamine, N-salicylideneamine, N-5-chlorosalicylideneamine, N-(5-chloro-2-hydroxyphenyl)phenylmethylenamine, N-cyclohexylideneamine, N-(5,5-dimethyl-3-oxo-1-cyclohexenyl)amine, N-borane derivative, N-diphenylborinic acid derivative, N-[phenyl(pentacarbonylchromium- or tungsten)carbonyl]amine, N-copper chelate, N-zinc chelate, N-nitroamine, N-nitrosoamine,

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amine N-oxide, diphenylphosphinamide (Dpp), dimethylthiophosphinamide (Mpt), diphenylthiophosphinamide (Ppt), dialkyl phosphoramidates, dibenzyl phosphoramidate, diphenyl phosphoramidate, benzenesulfenamide, o-nitrobenzenesulfenamide (Nps), 2,4-dinitrobenzenesulfenamide, pentachlorobenzenesulfenamide, 2-nitro-4-methoxybenzenesulfenamide, triphenylmethylsulfenamide, 3-nitropyridinesulfenamide (Npys), p-toluenesulfonamide (Ts), benzenesulfonamide, 2,3,6-trimethyl-4-methoxybenzenesulfonamide (Mtr), 2,4,6-trimethoxybenzenesulfonamide (Mt<sub>b</sub>), 2,6-dimethyl-4-methoxybenzenesulfonamide (Pme), 2,3,5,6-tetramethyl-4-methoxybenzenesulfonamide (Mte), 4-methoxybenzenesulfonamide (Mbs), 2,4,6-trimethylbenzenesulfonamide (Mts), 2,6-dimethoxy-4-methylbenzenesulfonamide (iMds), 2,2,5,7,8-pentamethylchroman-6-sulfonamide (Pmc), methanesulfonamide (Ms),  $\beta$ -trimethylsilylethanesulfonamide (SES), 9-anthracesulfonamide, 4-(4',8'-dimethoxynaphthylmethyl)benzenesulfonamide (DNMBS), benzylsulfonamide, trifluoromethylsulfonamide, and phenacylsulfonamide. Exemplary protecting groups are detailed herein, however, it will be appreciated that the present invention is not intended to be limited to these protecting groups; rather, a variety of additional equivalent protecting groups can be readily identified using the above criteria and utilized in the method of the present invention. Additionally, a variety of protecting groups are described in *Protective Groups in Organic Synthesis*, Third Ed. Greene, T.W. and Wuts, P.G., Eds., John Wiley & Sons, New York: 1999, the entire contents of which are hereby incorporated by reference.

In studies conducted by the inventors it has been demonstrated that compounds disclosed herein enhance neurite outgrowth in primary cortical neurons. In certain embodiments, a compound that enhances neurite outgrowth is a compound that increases neurite outgrowth by at least 5% (e.g., at least 10%, at least 20%, at least 50%, or more in comparison to a control) in a neurite outgrowth assay, for example, a neurite outgrowth assay described herein. In certain embodiments, it has been demonstrated that compounds disclosed herein enhance neurite outgrowth in primary cortical neurons which contain TrkB but do not appear to have any significant effect in PC12 cells which lack the TrkB receptor. The expression of TrkB and its ligand BDNF in limbic brain regions including the hippocampus have a critical role in the pathology of mood (affective) disorders and

neurodegeneration. There are several lines of evidence to support a role for BDNF, the most abundant neurotrophin in the brain, in the action of antidepressant compounds. Exposure to stress, which is associated with the onset of many mood disorders, has consistently been shown to decrease hippocampal neurotrophin expression, in particular BDNF, while chronic antidepressant administration and /or electro-convulsive therapy, increases the expression of BDNF and its receptor TrkB, in the brain. Recent studies have also demonstrated that infusion of BDNF directly into the hippocampus produces an antidepressant-like effect in animal behavioural models of depression. In relation to the antidepressant effects of the compounds this was confirmed by the rat forced swim test (Porsolt et al, 1978, Eur J. Pharma, 47, 379-391). Furthermore, several lines of research have directly linked the depression and neurogenesis. Decreased hippocampal neurogenesis has been observed in the brains of depressed patients in post mortem studies. In addition, it has been demonstrated that when hippocampal neurogenesis is prevented, using irradiation techniques, for example, antidepressants such as SSRI's and SNRI's are no longer active. The time taken for neurogenesis to occur has been proposed to account for the delay of about 2-4 weeks that occurs before the beneficial effects of current antidepressant therapies are experienced.

Evidence is accumulating for the neurotrophic and neuroprotective effects of other psychotropic agents such as mood stabilizers, antidepressants, and antipsychotics. They also promote neurogenesis and are protective in models of neurodegenerative disease and ischemia. These effects are achieved by activation of particular intracellular signaling pathways and up-regulation of the expression of neurotrophic/neuroprotective molecules such as BDNF, NGF, Bcl-2, and AKT.

Taught herein, therefore, is the use of a compound of formula (I), (Ia) or (Ib), or an embodiment thereof described herein, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating or preventing central nervous system disorders, such as mood disorders (e.g., depression), anxiety disorders, or neurodegenerative diseases, in a subject in need thereof.

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Also provided herein are methods of treating or preventing central nervous system disorders, such as mood disorders (e.g., depression), anxiety disorders, or neurodegenerative diseases comprising the administration of an effective amount of at least one compound of formulae (I), (Ia), (Ib) or an embodiment thereof described herein, or a pharmaceutically acceptable salt thereof, to a subject in need thereof.

As used herein mood disorders are broadly recognized and clearly defined by the relevant DSM-IV-TR (Diagnostic and Statistical Manual of Mental Disorders, 4<sup>th</sup> Edition, Text Revision) criteria. Thus, there are depressive disorders, of which the best known and most researched is major depressive disorder (MDD) commonly called clinical depression or major depression, and bipolar disorder (BD), formerly known as manic depression and characterized by intermittent episodes of mania or hypomania, usually interlaced with depressive episodes. Other depressive disorders include: atypical depression, melancholic depression, psychotic major depression, catatonic depression, postpartum depression, seasonal affective disorder), dysthymia, depressive disorder not otherwise specified (DD-NOS) (e.g., recurrent brief depression, minor depressive disorder), substance induced mood disorders (e.g., alcohol induced mood disorders, benzodiazepine induced mood disorders, interferon-alpha induced mood disorders).

Persons of skill in the art will be familiar with the lag period of traditional antidepressant medications, and with the heightened anxiety produced by the newer generation antidepressants, including SSRI's, SNRI's and NRI's in the early stages of treatment before the antidepressant effects are seen (within 2-4 weeks). Thus, in certain embodiments, the compounds described herein can be administered to a subject in need thereof as a substitute or replacement for traditional antidepressant medication. In other embodiments, compounds described herein can be administered to a subject in need thereof as a supplement to traditional antidepressant medication. In other embodiments, there is provided a method for treating or preventing depression in a subject, the method including the step of administering to said subject a compound of formula (I), (Ia), or (Ib), or an embodiment thereof described herein, or a pharmaceutically acceptable salt thereof, in the absence of adjunct antidepressant therapy.

Replacing traditional antidepressant medication with the present compounds can be advantageous, particularly where the traditional medication is associated with one or more adverse effects (*e.g.*, anxiety, nausea, headaches, erectile dysfunction, early-onset suicidal tendencies, *etc*). Examples of traditional antidepressant medication would be known to those skilled in the art and include, but are not limited to, selective serotonin re-uptake inhibitors (SSRI), serotonin/noradrenalin re-uptake inhibitors, selective noradrenalin re-uptake inhibitors, monoamine oxidase inhibitors, tricyclic antidepressants, lithium and other mood stabilisers, atypical antidepressants, and hormones such as estrogen or progestogen.

In other embodiments, the present compounds are administered to a subject in need thereof, together with traditional antidepressants for a period of about 2-4 weeks, to address the symptoms of depression, with the option of discontinuing treatment with the present compounds whilst continuing with the traditional therapy. In other embodiments, the subject is treated with both a present compound and one or more traditional antidepressant medications (administered sequentially or in combination) for the duration of the treatment period. Such combination therapy may be particularly useful, for example, where the combination of a present compound and one or more traditional antidepressant medications provides relief from depression in the acute lag phase of the treatment period and/or where an additive or synergistic antidepressant therapeutic effect is desired.

In some embodiments, a subject according to the methods of the present invention does not suffer from an anxiety disorder. In certain embodiments, a subject does not suffer from a phobia. In certain embodiments, a subject does not suffer from one or more of agoraphobia, agoraphobia without history of panic disorder, animal phobia, and social phobia. In certain embodiments, a subject does not suffer from one or more of obsessive-compulsive disorder, stress disorders including post-traumatic and acute stress disorder, and substance-induced anxiety disorder. In certain embodiments, a subject does not suffer from generalized anxiety disorder. In certain embodiments, a subject does not suffer from

social anxiety disorder.

In some embodiments, a subject according to the methods of the present invention does not suffer from one or more of neuroses, convulsions, migraine, depressive disorder, bipolar disorder, psychotic disorder, neurodegeneration arising from cerebral ischemia, attention deficit hyperactivity disorder, Tourette's syndrome, speech disorder, and disorders of circadian rhythm. In certain embodiments, a subject does not suffer from one or more of single-episode or recurrent major depressive disorder, dysthymic disorder, bipolar I or bipolar II manic disorder, and cyclothymic disorder. In certain embodiments, a subject does not suffer from schizophrenia. In certain embodiments, a subject does not suffer from stuttering.

In some embodiments, a subject according to the methods of the present invention does not suffer from one or more of pain or nociception, emesis, eating disorder, premenstrual syndrome, muscle spasm or spasticity, hearing disorder, urinary incontinence, and the effects of substance abuse or dependency. In certain embodiments, a subject does not suffer from one or more of acute emesis, delayed emesis, anticipatory emesis, emesis induced by chemotherapy or radiation, motion sickness, and post-operative nausea and vomiting. In certain embodiments, a subject does not suffer from anorexia nervosa or bulimia nervosa. In certain embodiments, a subject does not suffer from tinnitus or age-related hearing impairment. In certain embodiments, a subject does not suffer from alcohol withdrawal. In some embodiments, a subject does not suffer from Alzheimer's disease.

In some embodiments, a subject according to the methods of the present invention does not display one or more symptoms, *e.g.*, one, two, three, four, five, six, seven, eight, nine, or ten symptoms of one or more of the following diseases or conditions: anxiety disorders, such as panic disorder with or without agoraphobia, agoraphobia without history of panic disorder, animal and other phobias including social phobias, obsessive-compulsive disorder, stress disorders including post-traumatic and acute stress disorder, and generalized or substance-induced anxiety disorder; neuroses; convulsions; migraine;

depressive or bipolar disorders, for example single-episode or recurrent major depressive disorder, dysthymic disorder, bipolar I and bipolar II manic disorders, and cyclothymic disorder; psychotic disorders including schizophrenia; neurodegeneration arising from cerebral ischemia; attention deficit hyperactivity disorder; Tourette's syndrome; speech disorders, including stuttering; and disorders of circadian rhythm, e.g. in subjects suffering from the effects of jet lag or shift work; pain and nociception; emesis, including acute, delayed and anticipatory emesis, in particular emesis induced by chemotherapy or radiation, as well as motion sickness, and post-operative nausea and vomiting; eating disorders including anorexia nervosa and bulimia nervosa; premenstrual syndrome; muscle spasm or spasticity, e.g., in paraplegic patients; hearing disorders, including tinnitus and age-related hearing impairment; urinary incontinence; and the effects of substance abuse or dependency, including alcohol withdrawal; dementing conditions; and Alzheimer's disease.

Depression relapse can also occur in patients treated with traditional antidepressant medication. Many such compounds are administered for anywhere from months to years and a reduction in efficacy is often seen with such long-term use, leading to significant continuing depression and dysfunction. Depression relapse may be sudden onset for some patients, while for others it might be evident as a gradual decline in mood and function, which diminishes over time as the patient approaches the state of relapse. Thus, patients who experience sudden onset of depression relapse or a gradual depression relapse would benefit from the methods disclosed herein, as the present compounds of formula (I) or (Ia), or a subformula thereof described herein, can offset the diminishing effect of traditional antidepressant therapy. Thus, the use of the present compounds may prevent or partly alleviate depression relapse often seen in patients taking traditional antidepressant medication.

Thus, in an embodiment, there is provided a method for treating or preventing relapse in a subject receiving antidepressant therapy, the method including the step of administering to said subject a compound of formula (I), (Ia), or (Ib), or an embodiment thereof described herein, or a pharmaceutically acceptable salt thereof.

The traditional antidepressant therapies that are associated with potential depression relapse in a subject would be known to those skilled in the art. Examples include, but are not limited to, dosage increases, alternative SSRIs or SNRIs, and non-SSRI antidepressants such as noradrenaline re-uptake inhibitors, monoamine oxidase inhibitors, tricyclic antidepressants, lithium and other mood stabilisers, atypical antidepressants and hormones such as estrogen and progestogen, also referred to herein as "second antidepressant compounds".

"Treat", "treating" or "treatment" with regard to a disorder or disease refers to alleviating or abrogating the cause and/or the effects of the disorder or disease. As used herein, the terms "treat", "treatment" and "treating" refer to the reduction or amelioration of the progression, severity and/or duration of condition, or the amelioration of one or more symptoms (*e.g.*, one or more discernable symptoms) of said condition (*i.e.*, "managing" without "curing" the condition), resulting from the administration of one or more therapies (*e.g.*, one or more therapeutic agents such as a compound or composition of the invention). In specific embodiments, the terms "treat"; "treatment" and "treating" refer to the amelioration of at least one measurable physical parameter of a condition described herein. In other embodiments the terms "treat", "treatment" and "treating" refer to the inhibition of the progression of a condition described herein, either physically by, *e.g.*, stabilization of a discernable symptom or physiologically by, *e.g.*, stabilization of a physical parameter, or both.

The desired therapeutic activity, or effect, will typically depend on the condition being treated. For example, where the subject is being treated for depression, the therapeutic effect may be a reduction in at least one clinical symptom of depression, including, but not limited to, cognitive impairment, loss of appetite, mood, and/or inactivity.

The term "preventing" as used herein refers to administering a medicament beforehand to avert or forestall the appearance of one or more symptoms of a disease or disorder. The person of ordinary skill in the medical art recognizes that the term "prevent" is not an absolute term. In the medical art it is understood to refer to the prophylactic administration

of a drug to substantially diminish the likelihood or seriousness of a condition, or symptom of the condition and this is the sense intended in this disclosure. The Physician's Desk Reference, a standard text in the field, uses the term "prevent" hundreds of times. As used therein, the terms "prevent", "preventing" and "prevention" with regard to a disorder or disease, refer to averting the cause, effects, symptoms or progression of a disease or disorder prior to the disease or disorder fully manifesting itself.

In certain embodiments, the present compounds of formula (I) or (Ia), or an embodiment thereof described herein, or a pharmaceutically acceptable salt thereof, are administered to said subject sequentially (*i.e.*, before or after) or in combination with a second antidepressant compound (*e.g.*, with existing antidepressant therapy).

In certain embodiments, the present compounds have the further added advantage over traditional therapy in that they exhibit reduced sedative side effects which may adversely affect a patient's quality of life. In certain embodiments, the present compounds are free of measurable sedative side effects.

Sudden discontinuation of antidepressant medication may produce withdrawal effects caused by physical dependence on the drug. Compounds can be evaluated for physical dependence in a simple animal model where, following a period of chronic dosing (*e.g.*, for 14-20 days), the study drug is stopped and measurements of food intake, body weight and body temperature are taken over the next 5 days. The symptoms of abrupt discontinuation of the drug are manifest as significantly reduced appetite, weight loss, and drop in body temperature. This model is suitable for detecting the effects across a broad range of drug classes including opiates, antidepressants, and benzodiazepines. Abrupt withdrawal of the present compounds tested did not produce any changes in these parameters indicating that the compounds do not produce physical dependence and supporting their suitability for chronic use to treat mood disorders such as depression. The compounds encompassed herein may also be used as a combination therapy, *e.g.*, combining the treatment with other antidepressants such as benzodiazepines (*e.g.*, alprazolam, diazepam, lorazepam, clonazepam), selective serotonin re-uptake inhibitors

(SSRI) (e.g., citalopram, dapoxetine, escitalopram, fluoxetine, fluvoxamine, indalpine, paroxetine, sertraline, zimelidine, vilaxodone), serotonin norepinephrine reuptake inhibitors (SNRI) (e.g., venlafaxine, duloxetine, desvenlafaxine, milnacipran), monoamine oxidase inhibitors (e.g., phenelzine, moclobemide), tricyclic antidepressants (e.g., trimipramine, imipramine), tetracyclic antidepressants (e.g., mertazepine, maprotiline), mood stabilisers (e.g. lithium, sodium valproate, valproic acid), atypical antidepressants (e.g., bupropion), acetylcholinesterase inhibitors (e.g., donepezil, galantamine, rivastigmine), atypical antipsychotics (e.g., risperidone, aripiprazole, quetiapine, olanzapine), and hormones such as estrogen and progestogen.

It will thus be understood that the compounds herein can be used in the treatment of any disease state, disorder, or condition which may be ameliorated by enhancement of neurite outgrowth. Such diseases, disorders, and conditions are referred to herein as "neurite outgrowth-responsive."

In certain embodiments, the neurite outgrowth-responsive disease is a neurodegenerative disease.

In a certain preferred embodiment, the neurodegenerative disease is multiple sclerosis or Parkinsonian related disorders.

In a further preferred embodiment the neurodegenerative disease is multiple sclerosis.

In a further embodiment the neurodegenerative disease may involve a condition which involves neural damage including wound healing, spinal cord injury, peripheral nerve disorders.

Also contemplated herein is a sub-threshold disease, condition, state, disorder or trauma. In an embodiment, the disease, condition, state, disorder, or trauma is defined by its symptoms. Hence, the compounds contemplated herein are useful in ameliorating the symptoms of a disease, condition, state, disorder, or trauma of the CNS. By "trauma" this

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includes stroke, brain haemorrhage, or another condition or event of the systemic vasculature which affects the CNS. The symptoms of a disease, condition, state, disorder, or trauma of the CNS would be familiar to those skilled in the art. Examples of such symptoms include mood disorders, such as depression. Thus, in certain embodiments, the compounds herein are used in the treatment of depression attributed to (or associated with) a neurodegenerative disease in the subject.

The compounds encompassed herein may also be used as therapy, e.g., combining the treatment with other neurodegenerative treatments, such as acetylcholinesterase inhibitors (e.g., Aricept, Exelon), and treatments for multiple sclerosis (e.g., Avonex, Betaseron, Copaxone, Tysabri, Gilenya).

In an embodiment, the neurodegenerative disease is not Alzheimer's disease. In another embodiment, the neurodegenerative disease is not a neurodegenerative disease arising from cerebral ischemia.

In certain embodiments, the neurodegenerative disease is not Alzheimer's disease, Pick's disease, Lewy body dementia, Basal ganglia Huntington's disease, Parkinson's disease, Brainstem & cerebellum atrophy, Freidrich's ataxia, multiple system atrophy, types 1, 2, 3, 6, 7 spinocerebellar atrophy, Motor amyotrophic lateral sclerosis, familial spastic paraparesis, spinal muscular atrophy, or spinal & bulbar muscular atrophy.

In a further embodiment there is also provided a method of treatment of disorders of the central nervous system comprising the administration of an effective amount of at least one compound of formula (Ia) or (Ib), or a salt thereof, to a subject in need thereof.

It will be understood that the compounds of formula (Ia) or (Ib) as described herein can be used in the treatment of anxiety or conditions/disease states associated with anxiety such as irritable bowel syndrome and fibromyalgia.

In certain embodiments, an anxiety disorder is classified as one of the following:

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- panic disorder,
- obsessive-compulsive disorder (OCD),
- post-traumatic stress disorder (PTSD),
- social phobia (or social anxiety disorder - SAD),
- specific phobias,
- generalized anxiety disorder (GAD),
- substance-induced anxiety disorder, and
- acute stress disorder (ASD).

In an embodiment the compounds of formula (Ia) or (Ib) as described herein may be used in the treatment of a panic disorder.

In an embodiment the compounds of formula (Ia) or (Ib) as described herein may be used in the treatment of obsessive-compulsive disorder (OCD).

In an embodiment the compounds of formula (Ia) or (Ib) as described herein may be used in the treatment of post-traumatic stress disorder (PTSD).

In an embodiment the compounds of formula (Ia) or (Ib) as described herein may be used in the treatment of social phobia (or social anxiety disorder - SAD).

In an embodiment the compounds of formula (Ia) or (Ib) as described herein may be used in the treatment of specific phobias.

In an embodiment the compounds of formula (Ia) or (Ib) as described herein may be used in the treatment of substance-induced anxiety disorder.

In an embodiment the compounds of formula (Ia) or (Ib) as described herein may be used in the treatment of acute stress disorder (ASD).

In an embodiment the compounds of formula (Ia) or (Ib) as described herein may be used

in the treatment of generalized anxiety disorder (GAD).

Generalised anxiety disorder criteria include:

- (i) At least 6 months of "excessive anxiety and worry" about a variety of events and situations. Generally, "excessive" can be interpreted as more than would be expected for a particular situation or event. Most people become anxious over certain things, but the intensity of the anxiety typically corresponds to the situation.
- (ii) There is significant difficulty in controlling the anxiety and worry. If someone has a very difficult struggle to regain control, relax, or cope with the anxiety and worry, then this requirement is met.
- (iii) The presence for most days over the previous six months of 3 or more (only 1 for children) of the following symptoms:
  - 1. Feeling wound-up, tense, or restless
  - 2. Easily becoming fatigued or worn-out
  - 3. Concentration problems
  - 4. Irritability
  - 5. Significant tension in muscles
  - 6. Difficulty with sleep
- (iv) The symptoms are not part of another mental disorder.
- (v) The symptoms cause "clinically significant distress" or problems functioning in daily life. "Clinically significant" is the part that relies on the perspective of the treatment provider. Some people can have many of the aforementioned symptoms and cope with them well enough to maintain a high level of functioning.
- (vi) The condition is not due to a substance or medical issue.

In certain embodiments, a subject to be treated with a compound of formula (Ia) or (Ib) as described herein may be identified by one or more of the above criteria for generalized anxiety disorder.

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In another embodiment the compounds of formula (Ia) or (Ib) as described herein may be used to treat or prevent one or more symptoms associated with an anxiety disorder.

Each anxiety disorder has different symptoms, but all the symptoms cluster around excessive, irrational fear and dread.

In another embodiment the compounds of formula (Ia) or (Ib) as described herein may be used in the treatment of depression, for instance, major depressive disorder.

Major depressive disorder criteria include:

- (i) At least five of the following symptoms have been present during the same 2-week period and represent a change from previous functioning: at least one of the symptoms is either
  - 1) depressed mood or
  - 2) loss of interest or pleasure.
- (ii) Depressed mood most of the day, nearly every day, as indicated either by subjective report (e.g., feels sad or empty) or observation made by others (e.g., appears tearful).
- (iii) Markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day (as indicated either by subjective account or observation made by others).
- (iv) Significant weight loss when not dieting or weight gain (e.g., a change of more than 5% of body weight in a month), or decrease or increase in appetite nearly every day.
- (v) Insomnia or hypersomnia nearly every day.
- (vi) Psychomotor agitation or retardation nearly every day (observable by others, not merely subjective feelings of restlessness or being slowed down).
- (vii) Fatigue or loss of energy nearly every day.
- (viii) Feelings of worthlessness or excessive or inappropriate guilt (which may be delusional) nearly every day (not merely self-reproach or guilt about being sick).
- (ix) Diminished ability to think or concentrate, or indecisiveness, nearly every day (either by subjective account or as observed by others).

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- (x) Recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation without a specific plan, or a suicide attempt or specific plan for committing suicide
- (xi) The symptoms do not meet criteria for a mixed episode.
- (xii) The symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.
- (xiii) The symptoms are not due to the direct physiological effects of a substance (e.g. a drug of abuse, a medication) or a general medical condition (e.g., hypothyroidism).
- (xiv) The symptoms are not better accounted for by bereavement, i.e., after the loss of a loved one, the symptoms persist for longer than 2 months or are characterized by marked functional impairment, morbid preoccupation with worthlessness, suicidal ideation, psychotic symptoms, or psychomotor retardation.

The above criteria have been sourced from the American Psychiatric Association (2000) Diagnostic and Statistical Manual of Mental Disorders (4th Ed., Text Revision). Washington DC: American Psychiatric Association.

In certain embodiments, a subject to be treated with a compound of formula (Ia) or (Ib) as described herein may be identified by one or more of the above criteria for major depressive disorder.

In another embodiment the compounds of formula (Ia) or (Ib) as described herein may be used to treat or prevent one or more symptoms associated with depression.

Further disorders for which compounds of formula (Ia) or (Ib) as described herein may be of benefit include pain and nociception; emesis, including acute, delayed and anticipatory emesis, in particular emesis induced by chemotherapy or radiation, as well as motion sickness, and post-operative nausea and vomiting; eating disorders including anorexia nervosa and bulimia nervosa; premenstrual syndrome; muscle spasm or spasticity, e.g. in paraplegic patients; hearing disorders, including tinnitus and age-related hearing impairment; urinary incontinence; and the effects of substance abuse or dependency, including alcohol withdrawal.

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In an embodiment the compounds of formula (Ia) or (Ib) as described herein may be used in the treatment of cerebral ischemia.

In an embodiment the compounds of formula (Ia) or (Ib) as described herein may be used in the treatment of disorders of the circadian rhythm.

In an embodiment the compounds of formula (Ia) or (Ib) as described herein may be used in the treatment of pain and nociception.

In an embodiment the compounds of formula (Ia) or (Ib) as described herein may be used in the treatment of Alzheimer's disease.

The compounds enclosed herein are administered to the subject in a treatment effective amount. In some embodiments, a treatment effective amount is a therapeutically effective amount or a prophylactically effective amount. The term "therapeutically effective amount" as used herein means that amount of active compound or pharmaceutical agent that elicits the biological or medicinal response in a tissue, system, animal or human that is being sought by a researcher, veterinarian, medical doctor, or other clinician. The therapeutically effective amount of the compound to be administered will be governed by such considerations, and is the minimum amount necessary to ameliorate, cure, or treat the disease or disorder or one or more of its symptoms. The term "prophylactically effective amount" refers to an amount effective in preventing or substantially lessening the chances of acquiring a disease or disorder or in reducing the severity of the disease or disorder before it is acquired or reducing the severity of one or more of its symptoms before the symptoms develop. Roughly, prophylactic measures are divided between primary prophylaxis (to prevent the development of a disease or symptom) and secondary prophylaxis (whereby the disease or symptom has already developed and the patient is protected against worsening of this process).

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As used herein, the term "effective amount" relates to an amount of compound which, when administered according to a desired dosing regimen, provides the desired therapeutic activity. Dosing may occur at intervals of minutes, hours, days, weeks, months or years or continuously over any one of these periods. Suitable dosages lie within the range of about 0.1 ng per kg of body weight to 1 g per kg of body weight per dosage. The dosage may be in the range of 1 µg to 1 g per kg of body weight per dosage, such as is in the range of 1 mg to 1 g per kg of body weight per dosage. In one embodiment, the dosage may be in the range of 1 mg to 500 mg per kg of body weight per dosage. In another embodiment, the dosage may be in the range of 1 mg to 250 mg per kg of body weight per dosage. In yet another embodiment, the dosage may be in the range of 1 mg to 100 mg per kg of body weight per dosage, such as up to 50 mg per body weight per dosage.

In an embodiment, the method comprises administering to a subject in need thereof the present compound in a dosage to provide an effective amount *in vivo* that will enhance neurite outgrowth (neurogenesis), including, but not limited to the acute stages of treatment (e.g., within 1, 2, 3, or 4 weeks from the commencement of treatment). In an embodiment, an effective amount *in vivo* has an *in vitro* equivalent concentration that is sufficient to increase neurite outgrowth by at least 5%, at least 10%, at least 20%, or at least 50% in a neurite outgrowth assay, for example, a neurite outgrowth assay described herein. Methods of determining an *in vitro* equivalent concentration of the present compounds would be familiar to the skilled artisan. For example, at from about 10 minutes to about 60 minutes after administration of the present compounds to a subject, a blood sample is taken and assayed by HPLC, ELISA, gas chromatography, or by other suitable assay to determine the concentration per ml of blood. An equivalent effective concentration can then be used in an *in vitro* assay once factors such as the weight of the subject, the appropriate blood volume of the subject and the appropriate rate of diffusion of the present compound across the blood-brain barrier are taken into account. In another embodiment, when the present compound is found to stimulate neurite outgrowth *in vitro* (as compared to a control), an approximate *in vivo* effective amount can be determined for a subject by extrapolating the *in vitro* concentration to an *in vivo* equivalent. Factors such as the weight of the subject, the appropriate blood volume of the subject and the

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appropriate rate of diffusion of the present compound across the blood-brain barrier may be used to extrapolate an *in vivo* effective amount and hence the appropriate dosage amount that would give rise to said *in vivo* effective amount.

Thereafter, treatment with the present compounds may be continued throughout the treatment period or it may be ceased or replaced with traditional therapeutic compounds. Methods of determining the effective amount of the present compounds that is required for enhancing neurite outgrowth (neurogenesis) *in vivo* would be familiar to those skilled in the art. For example, enhancement of neurogenesis can be determined by measuring a symptom of the CNS disorder including, but not limited to, cognitive impairment, degree and frequency of seizures or tremors, motordysfunction, headaches and mood (e.g., degree of happiness).

The terms "administer", "administering" or "administration" in reference to a compound, composition or formulation of the invention means introducing the compound into the system of the animal in need of treatment. When a compound of the invention is provided in combination with one or more other active agents, "administration" and its variants are each understood to include concurrent and/or sequential introduction of the compound and the other active agents.

In certain embodiments, an effective amount of a compound for administration one or more times a day to a 70 kg adult human may comprise about 0.0001 mg to about 3000 mg, about 0.0001 mg to about 2000 mg, about 0.0001 mg to about 1000 mg, about 0.001 mg to about 1000 mg, about 0.01 mg to about 1000 mg, about 0.1 mg to about 1000 mg, about 1 mg to about 1000 mg, about 1 mg to about 100 mg, about 10 mg to about 1000 mg, or about 100 mg to about 1000 mg, of a compound per unit dosage form.

In certain embodiments, the compounds of the invention may be at dosage levels sufficient to deliver from about 0.001 mg/kg to about 100 mg/kg, from about 0.01 mg/kg to about 50 mg/kg, from about 0.1 mg/kg to about 40 mg/kg, from about 0.5 mg/kg to about 30 mg/kg, from about 0.01 mg/kg to about 10 mg/kg, from about 0.1 mg/kg to about 10 mg/kg, and

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from about 1 mg/kg to about 25 mg/kg, of subject body weight per day, one or more times a day, to obtain the desired therapeutic effect.

Suitable dosage amounts and dosing regimens can be determined by the attending physician and may depend on the particular condition being treated, the severity of the condition as well as the general age, health and weight of the subject. It will be appreciated that dose ranges as described herein provide guidance for the administration of provided pharmaceutical compositions to an adult. The amount to be administered to, for example, a child or an adolescent can be determined by a medical practitioner or person skilled in the art and can be lower or the same as that administered to an adult.

The active ingredient may be administered in a single dose or a series of doses. While it is possible for the active ingredient to be administered alone, it is preferable to present it as a composition, preferably as a pharmaceutical composition. The formulation of such compositions is well known to those skilled in the art. The composition may contain any suitable carriers, diluents or excipients. These include all conventional solvents, dispersion media, fillers, solid carriers, coatings, antifungal and antibacterial agents, dermal penetration agents, surfactants, isotonic and absorption agents and the like. It will be understood that the compositions of the invention may also include other supplementary physiologically active agents.

The compounds and pharmaceutical compositions described herein can be used in combination therapy with one or more additional therapeutic agents. For combination treatment with more than one active agent, where the active agents are in separate dosage formulations, the active agents may be administered separately or in conjunction. In addition, the administration of one element may be prior to, concurrent to, or subsequent to the administration of the other agent.

When co-administered with other agents, e.g., when co-administered with another anti-anxiety or anti-depressant medication, an "effective amount" of the second agent will depend on the type of drug used. Suitable dosages are known for approved agents and can

be adjusted by the skilled artisan according to the condition of the subject, the type of condition(s) being treated and the amount of a compound described herein being used. In cases where no amount is expressly noted, an effective amount should be assumed. For example, compounds described herein can be administered to a subject in a dosage range from between about 0.01 to about 10,000 mg/kg body weight/day, about 0.01 to about 5000 mg/kg body weight/day, about 0.01 to about 3000 mg/kg body weight/day, about 0.01 to about 1000 mg/kg body weight/day, about 0.01 to about 500 mg/kg body weight/day, about 0.01 to about 300 mg/kg body weight/day, about 0.01 to about 100 mg/kg body weight/day.

When "combination therapy" is employed, an effective amount can be achieved using a first amount of a compound of Formula (I), (Ia), or (Ib) or a pharmaceutically acceptable salt thereof, and a second amount of an additional suitable therapeutic agent.

In certain embodiments, the compound of formula (I), (Ia), or (Ib) as described herein, or a pharmaceutically acceptable salt thereof, and the additional therapeutic agent are each administered in an effective amount (*i.e.*, each in an amount which would be therapeutically effective if administered alone). In other embodiments, the compound of formula (I), (Ia), or (Ib) as described herein, or a pharmaceutically acceptable salt thereof, and the additional therapeutic agent are each administered in an amount which alone does not provide a therapeutic effect (a sub-therapeutic dose). In yet other embodiments, the compound of formula (I), (Ia), or (Ib) as described herein, or a pharmaceutically acceptable salt thereof can be administered in an effective amount, while the additional therapeutic agent is administered in a sub-therapeutic dose. In still other embodiments, the compound of formula (I), (Ia), or (Ib) as described herein, or a pharmaceutically acceptable salt thereof, can be administered in a sub-therapeutic dose, while the additional therapeutic agent is administered in an effective amount.

As used herein, the terms "in combination" or "co-administration" can be used interchangeably to refer to the use of more than one therapy (*e.g.*, one or more prophylactic and/or therapeutic agents). The use of the terms does not restrict the order in which

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therapies (*e.g.*, prophylactic and/or therapeutic agents) are administered to a subject.

Co-administration encompasses administration of the first and second amounts of the compounds in an essentially simultaneous manner, such as in a single pharmaceutical composition, for example, capsule or tablet having a fixed ratio of first and second amounts, or in multiple, separate capsules or tablets for each. In addition, such co-administration also encompasses use of each compound in a sequential manner in either order. When co-administration involves the separate administration of the first amount of a compound of formula (I), (Ia), or (Ib) as described herein, or a pharmaceutically acceptable salt thereof, and a second amount of an additional therapeutic agent, the compounds are administered sufficiently close in time to have the desired therapeutic effect. For example, the period of time between each administration which can result in the desired therapeutic effect, can range from minutes to hours and can be determined taking into account the properties of each compound such as potency, solubility, bioavailability, plasma half-life, and kinetic profile. For example, a compound of formula (I), (Ia), or (Ib) as described herein, or a pharmaceutically acceptable salt thereof, and the second therapeutic agent can be administered in any order within about 24 hours of each other, within about 16 hours of each other, within about 8 hours of each other, within about 4 hours of each other, within about 1 hour of each other or within about 30 minutes of each other.

More, specifically, a first therapy (*e.g.*, a prophylactic or therapeutic agent such as a compound described herein) can be administered prior to (*e.g.*, 5 minutes, 15 minutes, 30 minutes, 45 minutes, 1 hour, 2 hours, 4 hours, 6 hours, 12 hours, 24 hours, 48 hours, 72 hours, 96 hours, 1 week, 2 weeks, 3 weeks, 4 weeks, 5 weeks, 6 weeks, 8 weeks, or 12 weeks before), concomitantly with, or subsequent to (*e.g.*, 5 minutes, 15 minutes, 30 minutes, 45 minutes, 1 hour, 2 hours, 4 hours, 6 hours, 12 hours, 24 hours, 48 hours, 72 hours, 96 hours, 1 week, 2 weeks, 3 weeks, 4 weeks, 5 weeks, 6 weeks, 8 weeks, or 12 weeks after) the administration of a second therapy to a subject.

Examples of therapeutic agents that may be combined with a compound of this disclosure,

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either administered separately or in the same pharmaceutical composition, include, but are not limited to, muscle relaxants, anticonvulsants, hypnotics, anaesthetics, analgesics, cholinergics, antidepressants, mood stabilisers, anxiolytics, etc.

In an embodiment, the second therapeutic agent is a SSRI selected from the following:

citalopram (Celexa, Cipramil, Cipram, Dalsan, Recital, Emocal, Sepram, Seropram, Citox, Cital)  
dapoxetine (Priligy)  
escitalopram (Lexapro, Cipralex, Seroplex, Esertia)  
fluoxetine (Prozac, Fontex, Seromex, Seronil, Sarafem, Ladose, Motivest, Flutop, Fluctin (EUR), Fluox (NZ), Depress (UZB), Lovan (AUS), Prodep (IND))  
fluvoxamine (Luvox, Favarin, Faverin, Dumyrox, Favoxil, Movox)  
paroxetine (Paxil, Seroxat, Sereupin, Aropax, Deroxat, Divarius, Rexetin, Xetanor, Paroxat, Loxamine, Deparoc)  
sertraline (Zoloft, Lustral, Serlain, Asentra)  
vilazodone (Viibryd)

In another embodiment the second therapeutic agent is a tetracyclic antidepressant (TeCA) selected from the group consisting of:

Amoxapine (Amokisan, Asendin, Asendis, Defanyl, Demolox, Moxadil)  
Maprotiline (Deprilept, Ludiomil, Psymion)  
Mazindol (Mazanor, Sanorex)  
Mianserin (Bolvidon, Depnon, Norval, Tolvon)  
Mirtazapine (Remeron, Avanza, Zispin, Miro)  
Setiptiline (Tecipul)

In another embodiment the second therapeutic agent is a serotonin-noradrenaline reuptake inhibitor (SNRI) selected from the group consisting of:

Desvenlafaxine (Pristiq)  
Duloxetine (Cymbalta, Ariclaim, Xeristar, Yentreve, Duzela)

Milnacipran (Ixel, Savella, Dalcipran, Toledomin)

Venlafaxine (Effexor, Efexor)

In another embodiment the second therapeutic agent is a Noradrenaline reuptake inhibitor (NRI) selected from the group consisting of:

Atomoxetine (Tomoxetine, Strattera, Attentin)

Mazindol (Mazanor, Sanorex)

Reboxetine (Edronax, Norebox, Prolift, Solvex, Davedax, Vestra)

Viloxazine (Vivalan, Emovit, Vivarint, Vicilan)

In another embodiment the second therapeutic agent is a monoamine oxidase inhibitor (MAOI) selected from the group consisting of:

Benmoxin (Nerusil, Neuralex)

Hydralazine (Apresoline)

Iproclozide (Sursum)

Iproniazid (Marsilid, Iprozid, Ipronid, Rivivot, Propilniazida)

Isocarboxazid (Marplan)

Isoniazid (Laniazid, Nydrazid)

Mebanazine (Actomol)

Nialamide (Niamic)

Octamoxin (Ximaol, Nimaol)

Phenelzine (Nardil, Nardelzine)

Pheniprazine (Catron)

Phenoxypropazine (Drazine)

Pivalylbenzhydrazine (Tersavid)

Procarbazine (Matulane, Natulan, Indicarb)

Caroxazone (Surodil, Timostenil)

Echinopsidine (Adepren)

Furazolidone (Furoxone, Dependal-M)

Linezolid (Zyvox, Zyvoxam, Zyvoxid)

Tranylcypromine (Parnate, Jatrosom)

Brofaromine (Consonar)  
Metralindole (Inkazan)  
Minaprine (Cantor)  
Moclobemide (Aurorix, Manerix)  
Pirlindole (Pirazidol)  
Toloxatone (Humoryl)  
Lazabemide (Pakio, Tempium)  
Pargyline (Eutonyl)  
Rasagiline (Azilect)  
Selegiline (Deprenyl, Eldepryl, Emsam)

In another embodiment the second therapeutic agent is a tricyclic antidepressant (TCA) selected from the group consisting of:

Amitriptyline (Tryptomer, Elavil, Tryptizol, Laroxyl, Sarotex, Lentizol)  
Butriptyline (Evadene, Evadyne, Evasidol, Centrolese)  
Clomipramine (Anafranil)  
Desipramine (Norpramin, Pertofrane)  
Doseulepin (Prothiaden, Dothep, Thaden and Dopress)  
Doxepin (Aponal, Adapine, Doxal, Deptran, Sinquan, Sinequan, Zonalon, Xepin, Silenor)  
Imipramine (Antideprin, Deprimin, Deprinol, Depsol, Depsonil, Dynaprin, Eupramin, Imipramil, Irmin, Janimine, Melipramin, Surplix, Tofranil)  
Lofepramine (Gamanil, Tymelyt, Lomont)  
Nortriptyline (Sensoval, Aventyl, Pamelor, Norpress, Allegron, Noritren, Nortrilen)  
Protriptyline (Vivactil)  
Trimipramine (Surmontil, Rhotrimine, Stangyl)

The compounds and compositions provided herein can be administered by any route, including enteral (e.g., oral), parenteral, intravenous, intramuscular, intra-arterial, intramedullary, intrathecal, subcutaneous, intraventricular, transdermal, interdermal, rectal, intravaginal, intraperitoneal, topical (as by powders, ointments, creams, and/or drops),

mucosal, nasal, bucal, sublingual; by intratracheal instillation, bronchial instillation, and/or inhalation; and/or as an oral spray, nasal spray, and/or aerosol. Specifically contemplated routes are oral administration, intravenous administration (e.g., systemic intravenous injection), regional administration via blood and/or lymph supply, and/or direct administration to an affected site. In general, the most appropriate route of administration will depend upon a variety of factors including the nature of the agent (e.g., its stability in the environment of the gastrointestinal tract), and/or the condition of the subject (e.g., whether the subject is able to tolerate oral administration).

The exact amount of a compound required to achieve an effective amount will vary from subject to subject, depending, for example, on species, age, and general condition of a subject, severity of the side effects or disorder, identity of the particular compound(s), mode of administration, and the like. The desired dosage can be delivered three times a day, two times a day, once a day, every other day, every third day, every week, every two weeks, every three weeks, or every four weeks. In certain embodiments, the desired dosage can be delivered using multiple administrations (e.g., two, three, four, five, six, seven, eight, nine, ten, eleven, twelve, thirteen, fourteen, or more administrations).

The carrier must be pharmaceutically "acceptable" in the sense of being compatible with the other ingredients of the composition and not injurious to the subject. Compositions include those suitable for oral, rectal, nasal, topical (including buccal and sublingual), vaginal or parenteral (including subcutaneous, intramuscular, intravenous, and intradermal) administration. The compositions may conveniently be presented in unit dosage form and may be prepared by any methods well known in the art of pharmacy. Such methods include the step of bringing into association the active ingredient with the carrier which constitutes one or more accessory ingredients. In general, the compositions are prepared by uniformly and intimately bringing into association the active ingredient with liquid carriers or finely divided solid carriers or both, and then if necessary shaping the product.

Pharmaceutically acceptable excipients include any and all solvents, diluents, or other liquid vehicles, dispersions, suspension aids, surface active agents, isotonic agents,

thickening or emulsifying agents, preservatives, solid binders, lubricants, and the like, as suited to the particular dosage form desired. General considerations in formulation and/or manufacture of pharmaceutical compositions agents can be found, for example, in *Remington's Pharmaceutical Sciences*, Sixteenth Edition, E. W. Martin (Mack Publishing Co., Easton, Pa., 1980), and *Remington: The Science and Practice of Pharmacy*, 21st Edition (Lippincott Williams & Wilkins, 2005).

Pharmaceutical compositions described herein can be prepared by any method known in the art of pharmacology. In general, such preparatory methods include the steps of bringing the compound of the present invention (the "active ingredient") into association with a carrier and/or one or more other accessory ingredients, and then, if necessary and/or desirable, shaping and/or packaging the product into a desired single- or multi-dose unit.

Pharmaceutical compositions can be prepared, packaged, and/or sold in bulk, as a single unit dose, and/or as a plurality of single unit doses. As used herein, a "unit dose" is discrete amount of the pharmaceutical composition comprising a predetermined amount of the active ingredient. The amount of the active ingredient is generally equal to the dosage of the active ingredient which would be administered to a subject and/or a convenient fraction of such a dosage such as, for example, one-half or one-third of such a dosage.

Relative amounts of the active ingredient, the pharmaceutically acceptable excipient, and/or any additional ingredients in a pharmaceutical composition of the invention will vary, depending upon the identity, size, and/or condition of the subject treated and further depending upon the route by which the composition is to be administered. By way of example, the composition may comprise between 0.1% and 100% (w/w) active ingredient.

Pharmaceutically acceptable excipients used in the manufacture of provided pharmaceutical compositions include inert diluents, dispersing and/or granulating agents, surface active agents and/or emulsifiers, disintegrating agents, binding agents, preservatives, buffering agents, lubricating agents, and/or oils. Excipients such as cocoa

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butter and suppository waxes, coloring agents, coating agents, sweetening, flavoring, and perfuming agents may also be present in the composition.

Exemplary diluents include calcium carbonate, sodium carbonate, calcium phosphate, dicalcium phosphate, calcium sulfate, calcium hydrogen phosphate, sodium phosphate lactose, sucrose, cellulose, microcrystalline cellulose, kaolin, mannitol, sorbitol, inositol, sodium chloride, dry starch, cornstarch, powdered sugar, and mixtures thereof.

Exemplary granulating and/or dispersing agents include potato starch, corn starch, tapioca starch, sodium starch glycolate, clays, alginic acid, guar gum, citrus pulp, agar, bentonite, cellulose and wood products, natural sponge, cation-exchange resins, calcium carbonate, silicates, sodium carbonate, cross-linked poly(vinyl-pyrrolidone) (crospovidone), sodium carboxymethyl starch (sodium starch glycolate), carboxymethyl cellulose, cross-linked sodium carboxymethyl cellulose (croscarmellose), methylcellulose, pregelatinized starch (starch 1500), microcrystalline starch, water insoluble starch, calcium carboxymethyl cellulose, magnesium aluminum silicate (Veegum), sodium lauryl sulfate, quaternary ammonium compounds, and mixtures thereof.

Exemplary surface active agents and/or emulsifiers include natural emulsifiers (e.g., acacia, agar, alginic acid, sodium alginate, tragacanth, chondrus, cholesterol, xanthan, pectin, gelatin, egg yolk, casein, wool fat, cholesterol, wax, and lecithin), colloidal clays (e.g., bentonite (aluminum silicate) and Veegum (magnesium aluminum silicate)), long chain amino acid derivatives, high molecular weight alcohols (e.g., stearyl alcohol, cetyl alcohol, oleyl alcohol, triacetin monostearate, ethylene glycol distearate, glyceryl monostearate, and propylene glycol monostearate, polyvinyl alcohol), carbomers (e.g., carboxy polymethylene, polyacrylic acid, acrylic acid polymer, and carboxyvinyl polymer), carrageenan, cellulosic derivatives (e.g., carboxymethylcellulose sodium, powdered cellulose, hydroxymethyl cellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, methylcellulose), sorbitan fatty acid esters (e.g., polyoxyethylene sorbitan monolaurate (Tween 20), polyoxyethylene sorbitan (Tween 60), polyoxyethylene sorbitan monooleate (Tween 80), sorbitan monopalmitate (Span 40), sorbitan monostearate (Span

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60], sorbitan tristearate (Span 65), glyceryl monooleate, sorbitan monooleate (Span 80)), polyoxyethylene esters (e.g., polyoxyethylene monostearate (Myrj 45), polyoxyethylene hydrogenated castor oil, polyethoxylated castor oil, polyoxymethylene stearate, and Solutol), sucrose fatty acid esters, polyethylene glycol fatty acid esters (e.g., Cremophor<sup>TM</sup>), polyoxyethylene ethers, (e.g., polyoxyethylene lauryl ether (Brij 30)), poly(vinyl-pyrrolidone), diethylene glycol monolaurate, triethanolamine oleate, sodium oleate, potassium oleate, ethyl oleate, oleic acid, ethyl laurate, sodium lauryl sulfate, Pluronic F68, Poloxamer 188, cetrimonium bromide, cetylpyridinium chloride, benzalkonium chloride, docusate sodium, and/or mixtures thereof.

Exemplary binding agents include starch (e.g., cornstarch and starch paste), gelatin, sugars (e.g., sucrose, glucose, dextrose, dextrin, molasses, lactose, lactitol, mannitol, etc.), natural and synthetic gums (e.g., acacia, sodium alginate, extract of Irish moss, panwar gum, ghatti gum, mucilage of isapol husks, carboxymethylcellulose, methylcellulose, ethylcellulose, hydroxyethylcellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, microcrystalline cellulose, cellulose acetate, poly(vinyl-pyrrolidone), magnesium aluminum silicate (Veegum), and larch arabogalactan), alginates, polyethylene oxide, polyethylene glycol, inorganic calcium salts, silicic acid, polymethacrylates, waxes, water, alcohol, and/or mixtures thereof.

Exemplary preservatives include antioxidants, chelating agents, antimicrobial preservatives, antifungal preservatives, alcohol preservatives, acidic preservatives, and other preservatives.

Exemplary antioxidants include alpha tocopherol, ascorbic acid, acorbyl palmitate, butylated hydroxyanisole, butylated hydroxytoluene, monothioglycerol, potassium metabisulfite, propionic acid, propyl gallate, sodium ascorbate, sodium bisulfite, sodium metabisulfite, and sodium sulfite.

Exemplary chelating agents include ethylenediaminetetraacetic acid (EDTA) and salts and hydrates thereof (e.g., sodium edetate, disodium edetate, trisodium edetate, calcium

disodium edetate, dipotassium edetate, and the like), citric acid and salts and hydrates thereof (e.g., citric acid monohydrate), fumaric acid and salts and hydrates thereof, malic acid and salts and hydrates thereof, phosphoric acid and salts and hydrates thereof, and tartaric acid and salts and hydrates thereof. Exemplary antimicrobial preservatives include benzalkonium chloride, benzethonium chloride, benzyl alcohol, bronopol, cetrimide, cetylpyridinium chloride, chlorhexidine, chlorobutanol, chlorocresol, chloroxylenol, cresol, ethyl alcohol, glycerin, hexetidine, imidurea, phenol, phenoxyethanol, phenylethyl alcohol, phenylmercuric nitrate, propylene glycol, and thimerosal.

Exemplary antifungal preservatives include butyl paraben, methyl paraben, ethyl paraben, propyl paraben, benzoic acid, hydroxybenzoic acid, potassium benzoate, potassium sorbate, sodium benzoate, sodium propionate, and sorbic acid.

Exemplary alcohol preservatives include ethanol, polyethylene glycol, phenol, phenolic compounds, bisphenol, chlorobutanol, hydroxybenzoate, and phenylethyl alcohol.

Exemplary acidic preservatives include vitamin A, vitamin C, vitamin E, beta-carotene, citric acid, acetic acid, dehydroacetic acid, ascorbic acid, sorbic acid, and phytic acid.

Other preservatives include tocopherol, tocopherol acetate, detersoxime mesylate, cetrimide, butylated hydroxyanisol (BHA), butylated hydroxytoluened (BHT), ethylenediamine, sodium lauryl sulfate (SLS), sodium lauryl ether sulfate (SLES), sodium bisulfite, sodium metabisulfite, potassium sulfite, potassium metabisulfite, Glydant Plus, Phenonip, methylparaben, Germall 115, Germaben II, Neolone, Kathon, and Euxyl. In certain embodiments, the preservative is an anti-oxidant. In other embodiments, the preservative is a chelating agent.

Exemplary buffering agents include citrate buffer solutions, acetate buffer solutions, phosphate buffer solutions, ammonium chloride, calcium carbonate, calcium chloride, calcium citrate, calcium glubionate, calcium gluceptate, calcium gluconate, D-gluconic acid, calcium glycerophosphate, calcium lactate, propanoic acid, calcium levulinate,

pentanoic acid, dibasic calcium phosphate, phosphoric acid, tribasic calcium phosphate, calcium hydroxide phosphate, potassium acetate, potassium chloride, potassium gluconate, potassium mixtures, dibasic potassium phosphate, monobasic potassium phosphate, potassium phosphate mixtures, sodium acetate, sodium bicarbonate, sodium chloride, sodium citrate, sodium lactate, dibasic sodium phosphate, monobasic sodium phosphate, sodium phosphate mixtures, tromethamine, magnesium hydroxide, aluminum hydroxide, alginic acid, pyrogen-free water, isotonic saline, Ringer's solution, ethyl alcohol, and mixtures thereof.

Exemplary lubricating agents include magnesium stearate, calcium stearate, stearic acid, silica, talc, malt, glyceryl behanate, hydrogenated vegetable oils, polyethylene glycol, sodium benzoate, sodium acetate, sodium chloride, leucine, magnesium lauryl sulfate, sodium lauryl sulfate, and mixtures thereof.

Exemplary natural oils include almond, apricot kernel, avocado, babassu, bergamot, black current seed, borage, cade, camomile, canola, caraway, carnauba, castor, cinnamon, cocoa butter, coconut, cod liver, coffee, corn, cotton seed, emu, eucalyptus, evening primrose, fish, flaxseed, geraniol, gourd, grape seed, hazel nut, hyssop, isopropyl myristate, jojoba, kukui nut, lavandin, lavender, lemon, litsea cubeba, macadamia nut, mallow, mango seed, meadowfoam seed, mink, nutmeg, olive, orange, orange roughy, palm, palm kernel, peach kernel, peanut, poppy seed, pumpkin seed, rapeseed, rice bran, rosemary, safflower, sandalwood, sasquana, savoury, sea buckthorn, sesame, shea butter, silicone, soybean, sunflower, tea tree, thistle, tsubaki, vetiver, walnut, and wheat germ oils. Exemplary synthetic oils include, but are not limited to, butyl stearate, caprylic triglyceride, capric triglyceride, cyclomethicone, diethyl sebacate, dimethicone 360, isopropyl myristate, mineral oil, octyldodecanol, oleyl alcohol, silicone oil, and mixtures thereof.

Compositions of the present invention suitable for oral administration may be presented as discrete units such as capsules, sachets or tablets each containing a predetermined amount of the active ingredient; as a powder or granules; as a solution or a suspension in an aqueous or non-aqueous liquid; or as an oil-in-water liquid emulsion or a water-in-oil

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liquid emulsion. The active ingredient may also be presented as a bolus, electuary or paste.

A tablet may be made by compression or moulding, optionally with one or more accessory ingredients. Compressed tablets may be prepared by compressing in a suitable machine the active ingredient in a free-flowing form such as a powder or granules, optionally mixed with a binder (e.g., inert diluent, preservative disintegrant (e.g., sodium starch glycolate, cross-linked polyvinyl pyrrolidone, cross-linked sodium carboxymethyl cellulose) surface-active or dispersing agent. Moulded tablets may be made by moulding in a suitable machine a mixture of the powdered compound moistened with an inert liquid diluent. The tablets may optionally be coated or scored and may be formulated so as to provide slow or controlled release of the active ingredient therein using, for example, hydroxypropylmethyl cellulose in varying proportions to provide the desired release profile. Tablets may optionally be provided with an enteric coating, to provide release in parts of the gut other than the stomach.

The active ingredient can be in micro-encapsulated form with one or more excipients. The solid dosage forms of tablets, dragees, capsules, pills; and granules can be prepared with coatings and shells such as enteric coatings, release controlling coatings and other coatings well known in the pharmaceutical formulating art. In such solid dosage forms the active ingredient can be admixed with at least one inert diluent such as sucrose, lactose, or starch. Such dosage forms may comprise, as is normal practice, additional substances other than inert diluents, e.g., tableting lubricants and other tableting aids such as magnesium stearate and microcrystalline cellulose. In the case of capsules, tablets, and pills, the dosage forms may comprise buffering agents. They may optionally comprise opacifying agents and can be of a composition that they release the active ingredient(s) only, or preferentially, in a certain part of the intestinal tract, optionally, in a delayed manner. Examples of embedding compositions which can be used include polymeric substances and waxes.

Liquid dosage forms for oral and parenteral administration include pharmaceutically acceptable emulsions, microemulsions, solutions, suspensions, syrups and elixirs. In

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addition to the active ingredients, the liquid dosage forms may comprise inert diluents commonly used in the art such as, for example, water or other solvents, solubilizing agents and emulsifiers such as ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propylene glycol, 1,3-butylene glycol, dimethylformamide, oils (e.g., cottonseed, groundnut, corn, germ, olive, castor, and sesame oils), glycerol, tetrahydrofurfuryl alcohol, polyethylene glycols and fatty acid esters of sorbitan, and mixtures thereof. Besides inert diluents, the oral compositions can include adjuvants such as wetting agents, emulsifying and suspending agents, sweetening, flavoring, and perfuming agents. In certain embodiments for parenteral administration, the conjugates of the invention are mixed with solubilizing agents such as Cremophor<sup>TM</sup>, alcohols, oils, modified oils, glycols, polysorbates, cyclodextrins, polymers, and mixtures thereof.

Compositions suitable for topical administration in the mouth include lozenges comprising the active ingredient in a flavoured base, usually sucrose and acacia or tragacanth gum; pastilles comprising the active ingredient in an inert basis such as gelatine and glycerin, or sucrose and acacia gum; and mouthwashes comprising the active ingredient in a suitable liquid carrier.

Compositions suitable for topical administration to the skin may comprise the compounds dissolved or suspended in any suitable carrier or base and may be in the form of lotions, gel, creams, pastes, ointments and the like. Suitable carriers include mineral oil, propylene glycol, polyoxyethylene, polyoxypropylene, emulsifying wax, sorbitan monostearate, polysorbate 60, cetyl esters wax, cetaryl alcohol, 2-octyldodecanol, benzyl alcohol, and water. Transdermal patches may also be used to administer the compounds of the invention.

Compositions for rectal administration may be presented as a suppository with a suitable base comprising, for example, cocoa butter, glycerin, gelatine or polyethylene glycol.

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Compositions suitable for vaginal administration may be presented as pessaries, tampons, creams, gels, pastes, foams or spray formulations containing in addition to the active ingredient such carriers as are known in the art to be appropriate.

Compositions suitable for parenteral administration include aqueous and non-aqueous isotonic sterile injection solutions which may contain anti-oxidants, buffers, bactericides and solutes which render the composition isotonic with the blood of the intended recipient; and aqueous and non-aqueous sterile suspensions which may include suspending agents and thickening agents. The compositions may be presented in unit-dose or multi-dose sealed containers, for example, ampoules and vials, and may be stored in a freeze-dried (lyophilised) condition requiring only the addition of the sterile liquid carrier, for example water for injections, immediately prior to use. Extemporaneous injection solutions and suspensions may be prepared from sterile powders, granules and tablets of the kind previously described. An injectable preparation can be a sterile injectable solution, suspension or emulsion in a nontoxic parenterally acceptable diluent or solvent, for example, as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that can be employed are water, Ringer's solution, U.S.P. and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil can be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid are used in the preparation of injectables. The injectable formulations can be sterilized, for example, by filtration through a bacterial-retaining filter, or by incorporating sterilizing agents in the form of sterile solid compositions which can be dissolved or dispersed in sterile water or other sterile injectable medium prior to use.

In certain embodiments, unit dosage compositions are those containing a daily dose or unit, daily sub-dose, as herein above described, or an appropriate fraction thereof, of the active ingredient.

It should be understood that in addition to the active ingredients particularly mentioned above, the compositions of this invention may include other agents conventional in the art

having regard to the type of composition in question, for example, those suitable for oral administration may include such further agents as binders, sweeteners, thickeners, flavouring agents disintegrating agents, coating agents, preservatives, lubricants and/or time delay agents. Suitable sweeteners include sucrose, lactose, glucose, aspartame or saccharine. Suitable disintegrating agents include cornstarch, methylcellulose, polyvinylpyrrolidone, xanthan gum, bentonite, alginic acid or agar. Suitable flavouring agents include peppermint oil, oil of wintergreen, cherry, orange or raspberry flavouring. Suitable coating agents include polymers or copolymers of acrylic acid and/or methacrylic acid and/or their esters, waxes, fatty alcohols, zein, shellac or gluten. Suitable preservatives include sodium benzoate, vitamin E, alpha-tocopherol, ascorbic acid, methyl paraben, propyl paraben or sodium bisulphite. Suitable lubricants include magnesium stearate, stearic acid, sodium oleate, sodium chloride or talc. Suitable time delay agents include glyceryl monostearate or glyceryl distearate.

The phrase "pharmaceutically acceptable salt," as used herein, refers to pharmaceutically acceptable organic or inorganic salts of a provided compound. For use in medicine, the salts of the provided compounds will be pharmaceutically acceptable salts. Other salts may, however, be useful in the preparation of provided compounds or of their pharmaceutically acceptable salts. Pharmaceutically acceptable salts are well known in the art. For example, Berge *et al.*, describe pharmaceutically acceptable salts in detail in *J. Pharm. Sci.* (1977) 66:1-19, incorporated herein by reference in its entirety. A pharmaceutically acceptable salt involves the inclusion of another molecule such as an acetate ion, a succinate ion or other counter ion. The counter ion may be any organic or inorganic moiety that stabilizes the charge on the parent compound. Furthermore, a pharmaceutically acceptable salt may have more than one charged atom in its structure. When multiple charged atoms are present in the parent drug, its pharmaceutically acceptable salts will have multiple counter ions and these can be several instances of the same counter ion or different counter ions. Hence, a pharmaceutically acceptable salt can have one or more charged atoms in the parent compound and/or one or more counter ions.

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Pharmaceutically acceptable salts of the compounds described herein include those derived from suitable inorganic and organic acids and bases. In some embodiments, the salts can be prepared in situ during the final isolation and purification of the compounds. In other embodiments the salts can be prepared from the free form of the compound in a separate synthetic step.

When a provided compound is acidic or contains a sufficiently acidic bioisostere, suitable "pharmaceutically acceptable salts" refers to salts prepared from pharmaceutically acceptable non-toxic bases including inorganic bases and organic bases. Salts derived from inorganic bases include aluminum, ammonium, calcium, copper, ferric, ferrous, lithium, magnesium, manganic salts, manganous, potassium, sodium, zinc and the like. Particular embodiments include ammonium, calcium, magnesium, potassium and sodium salts. Salts derived from pharmaceutically acceptable organic non-toxic bases include salts of primary, secondary and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic amines and basic ion exchange resins, such as arginine, betaine, caffeine, choline, N,N-dibenzylethylenediamine, diethylamine, 2-diethylaminoethanol, 2-dimethylaminoethanol, ethanolamine, ethylenediamine, N-ethylmorpholine, N-ethylpiperidine, glucamine, glucosamine, histidine, hydrabamine, isopropylamine, lysine, methylglucamine, morpholine, piperazine, piperidine, polyamine resins, procaine, purines, theobromine, triethylamine, trimethylamine tripropylamine, tromethamine and the like. Quaternary ammonium salts such as  $N^+(C_{1-4} \text{ alkyl})_4$  are also included.

When a provided compound is basic or contains a sufficiently basic bioisostere, salts may be prepared from pharmaceutically acceptable non-toxic acids, including inorganic and organic acids. Such acids include, but are not limited to, acetic, benzenesulfonic, benzoic, camphorsulfonic, citric, ethanesulfonic, fumaric, gluconic, glutamic, hydrobromic, hydrochloric, isethionic, lactic, maleic, malic, mandelic, methanesulfonic, mucic, nitric, pamoic, pantothenic, phosphoric, succinic, sulfuric, tartaric, carbonic, boric, sulfamic, propionic, butyric, hydroxymaleic, mucic, phenylacetic, sulfanilic, aspartic, edetic, stearic, palmitic, oleic, lauric, ascorbic, valeric, perchloric, malonic, p-toluenesulfonic acid and the like. Particular embodiments include citric, hydrobromic, hydrochloric, maleic,

phosphoric, sulfuric and tartaric acids. Other exemplary salts include, but are not limited to, sulfate, citrate, acetate, oxalate, chloride, bromide, iodide, nitrate, bisulfate, phosphate, acid phosphate, isonicotinate, lactate, salicylate, acid citrate, tartrate, oleate, tannate, pantothenate, bitartrate, ascorbate, succinate, maleate, gentisinate, fumarate, gluconate, glucuronate, saccharate, formate, benzoate, glutamate, methanesulfonate, ethanesulfonate, benzenesulfonate, p-toluenesulfonate, palmoate (*i.e.*, 1,1'-methylene-bis-(2-hydroxy-3-naphthoate)), adipate, alginate, ascorbate, aspartate, cyclopentanepropionate, borate, butyrate, camphorate, digluconate, dodecylsulfate, ethanesulfonate, glucoheptonate, glycerophosphate, hemisulfate, heptanoate, hexanoate, 2-hydroxyethanesulfonate, lactobionate, laurate, lauryl sulphate, malonate, 2-naphthalenesulfonate, nicotinate, pectinate, persulfate, 3-phenylpropionate, picrate, pivalate, propionate, stearate, thiocyanate, undecanoate, and valerate salts.

The preparation of the pharmaceutically acceptable salts described above and other typical pharmaceutically acceptable salts is more fully described by Berge *et al.*, "Pharmaceutical Salts," *J. Pharm. Sci.*, 1977:66:1-19.

Basic nitrogen-containing groups may be quaternised 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 and pharmaceutical formulations described herein may be contained in a kit. The kit may include single or multiple doses of two or more agents, each packaged or formulated individually, or single or multiple doses of two or more agents packaged or formulated in combination. Thus, one or more agents can be present in first container, and the kit can optionally include one or more agents in a second container. The container or containers are placed within a package, and the package can optionally include administration or dosage instructions. A kit can include additional components such as syringes or other means for administering the agents as well as diluents or other means for formulation. Thus, the kits can comprise: a) a pharmaceutical composition comprising a compound described herein and a pharmaceutically acceptable carrier, vehicle or diluent;

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and b) a container or packaging. The kits may optionally comprise instructions describing a method of using the pharmaceutical compositions in one or more of the methods described herein (e.g. preventing or treating one or more of the diseases and disorders described herein). The kit may optionally comprise a second pharmaceutical composition comprising one or more additional agents described herein for co therapy use, a pharmaceutically acceptable carrier, vehicle or diluent. The pharmaceutical composition comprising the compound described herein and the second pharmaceutical composition contained in the kit may be optionally combined in the same pharmaceutical composition.

A kit includes a container or packaging for containing the pharmaceutical compositions and may also include divided containers such as a divided bottle or a divided foil packet. The container can be, for example a paper or cardboard box, a glass or plastic bottle or jar, a re-sealable bag (for example, to hold a "refill" of tablets for placement into a different container), or a blister pack with individual doses for pressing out of the pack according to a therapeutic schedule. It is feasible that more than one container can be used together in a single package to market a single dosage form. For example, tablets may be contained in a bottle which is in turn contained within a box.

An example of a kit is a so-called blister pack. Blister packs are well known in the packaging industry and are being widely used for the packaging of pharmaceutical unit dosage forms (tablets, capsules, and the like). Blister packs generally consist of a sheet of relatively stiff material covered with a foil of a preferably transparent plastic material. During the packaging process, recesses are formed in the plastic foil. The recesses have the size and shape of individual tablets or capsules to be packed or may have the size and shape to accommodate multiple tablets and/or capsules to be packed. Next, the tablets or capsules are placed in the recesses accordingly and the sheet of relatively stiff material is sealed against the plastic foil at the face of the foil which is opposite from the direction in which the recesses were formed. As a result, the tablets or capsules are individually sealed or collectively sealed, as desired, in the recesses between the plastic foil and the sheet. Preferably the strength of the sheet is such that the tablets or capsules can be removed from the blister pack by manually applying pressure on the recesses whereby an opening is

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formed in the sheet at the place of the recess. The tablet or capsule can then be removed via said opening.

It may be desirable to provide written memory aid containing information and/or instructions for the physician, pharmacist or subject regarding when the medication is to be taken. A "daily dose" can be a single tablet or capsule or several tablets or capsules to be taken on a given day. When the kit contains separate compositions, a daily dose of one or more compositions of the kit can consist of one tablet or capsule while a daily dose of another or more compositions of the kit can consist of several tablets or capsules. A kit can take the form of a dispenser designed to dispense the daily doses one at a time in the order of their intended use. The dispenser can be equipped with a memory-aid, so as to further facilitate compliance with the regimen. An example of such a memory-aid is a mechanical counter which indicates the number of daily doses that have been dispensed. Another example of such a memory-aid is a battery-powered micro-chip memory coupled with a liquid crystal readout, or audible reminder signal which, for example, reads out the date that the last daily dose has been taken and/or reminds one when the next dose is to be taken.

It will be appreciated that any compound that is a prodrug of a compound of formula (I) or (I'), or a subformula thereof described herein, is also within the scope and spirit of the invention. The term "pro-drug" is used in its broadest sense and encompasses those derivatives that are converted *in vivo* to the compounds of the invention. Such derivatives would readily occur to those skilled in the art, and include, for example, compounds where a free hydroxy group (for instance at the CR' position) is converted into an ester, such as an acetate or phosphate ester, or where a free amino group is (for instance at the CR' position) converted into an amide (e.g.,  $\alpha$ -aminoacid amide). Procedures for esterifying, e.g., acylating, the compounds of the invention are well known in the art and may include treatment of the compound with an appropriate carboxylic acid, anhydride or chloride in the presence of a suitable catalyst or base.

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The compounds of the invention may be in crystalline form either as the free compounds or as solvates (*e.g.*, hydrates) and it is intended that both forms are within the scope of the present invention. Methods of solvation are generally known within the art.

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 *e.g.*, 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 mixtures may be resolved by conventional methods, *e.g.*, chromatography, or use of a resolving agent.

Furthermore, depending on the substitution pattern the compounds of the present invention may be capable of undergoing tautomerism. Accordingly, all possible tautomers of a compound of the present invention fall within the scope and spirit of the invention.

The synthetic methods and processes described herein to prepare the compounds of the present invention are amenable to solid phase synthetic techniques and/or combinatorial chemistry to produce individual compounds or libraries of compounds.

Those skilled in the art will appreciate that the invention described herein is susceptible to variations and modifications other than those specifically described. It is to be understood that the invention includes all such variations and modifications which fall within the spirit and scope. The invention also includes all of the steps, features, compositions and compounds referred to or indicated in this specification, individually or collectively, and any and all combinations of any two or more of said steps or features.

Throughout this specification and the claims which follow, unless the context requires otherwise, the word "comprise", and variations such as "comprises" and "comprising", will

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be understood to imply the inclusion of a stated integer or step or group of integers or steps but not the exclusion of any other integer or step or group of integers or steps.

The reference in this specification to any prior publication (or information derived from it), or to any matter which is known, is not, and should not be taken as an acknowledgment or admission or any form of suggestion that that prior publication (or information derived from it) or known matter forms part of the common general knowledge in the field of endeavour to which this specification relates.

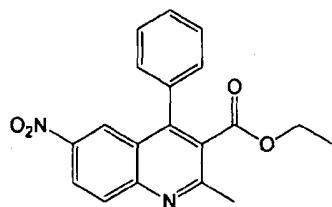
Certain embodiments of the invention will now be described with reference to the following examples which are intended for the purpose of illustration only and are not intended to limit the scope of the generality hereinbefore described.

### Examples

#### Synthetic Protocols

##### Example 1 Preparation of Ethyl 6-amino-2-methyl-4-phenylquinoline-3-carboxylate

###### Step a. Preparation of Ethyl 2-methyl-6-nitro-4-phenylquinoline-3-carboxylate

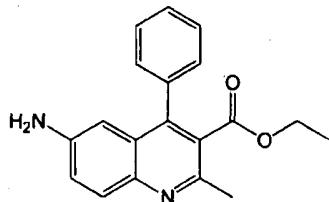


A mixture of 2-amino-5-nitrobenzophenone (1 g, 4.1 mmol), H<sub>2</sub>NSO<sub>3</sub>H (40 mg) and ethyl acetoacetate (1.3 ml, 10.3 mmol) was stirred for 12 h at 120°C under N<sub>2</sub>. After cooling to room temperature, the reaction mixture was diluted with ethyl acetate and washed with water. The organic layer was dried over anhydrous MgSO<sub>4</sub> and concentrated under reduced pressure to give a solid, which was recrystallised from EtOH to give a pale orange solid (1.05 g, 76%). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 8.54 (d, *J* = 2.48 Hz, 1H), 8.48 (dd, *J* = 2.48,

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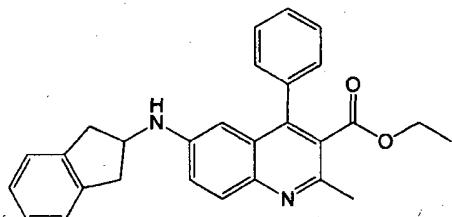
9 Hz, 1H), 8.20 (d, 9 Hz, 1H), 7.56-7.53 (m, 3H), 7.39-7.35 (m, 2H), 4.10 (q,  $J = 7.2$  Hz, 2H), 2.82 (s, 3H), 0.94 (t,  $J = 7.2$  Hz, 3H). LCMS,  $m/z$  337 ( $M + H$ )<sup>+</sup>.

**Step b Preparation of Ethyl 6-amino-2-methyl-4-phenylquinoline-3-carboxylate**



A mixture of ethyl 2-methyl-6-nitro-4-phenylquinoline-3-carboxylate (375.7 mg, 1.12 mmol) and 10% Pd/C (30.1 mg) in EtOAc was degassed under reduced pressure and saturated with H<sub>2</sub> gas. The resulting mixture was stirred overnight under H<sub>2</sub> balloon pressure at room temperature, filtered through a Celite bed and the filtrate evaporated to dryness under reduced pressure. The crude residue was purified by column chromatography (SiO<sub>2</sub>, 0-50% EtOAc/DCM) to give a pale orange solid (261.0 mg, 76%). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 7.88 (d,  $J = 8.7$  Hz, 1H), 7.48-7.44 (m, 3H), 7.36-7.33 (m, 2H), 7.15 (dd,  $J = 2.4, 8.7$  Hz, 1H), 6.63 (d,  $J = 2.4$  Hz, 1H), 4.04 (q,  $J = 7.2$  Hz, 2H), 3.83 (broad s, 2H), 2.71 (s, 3H), 0.94 (q,  $J = 7.2$  Hz, 3H). LCMS,  $m/z$  307 ( $M + H$ )<sup>+</sup>.

**Example 2: Preparation of Ethyl 6-(2,3-dihydro-1H-inden-2-ylamino)-2-methyl-4-phenylquinoline-3-carboxylate**

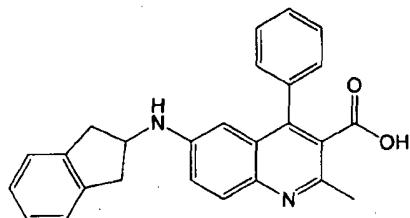


A method of Abdel-Magid et al (J. Org. Chem., 61, 3849, 1996) was used: Glacial AcOH (0.25 ml) was added to a solution of Example 1 (1.46g, 4.4 mmol), 1H-inden-2(3H)-one

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(0.46g, 4.5 mmol) and NaBH(OAc)<sub>3</sub> (1.4g, 6.55 mmol) in anhydrous 1,2-dichloroethane (17 ml). The resulting mixture was stirred overnight at room temperature under N<sub>2</sub> and to it more of NaBH(OAc)<sub>3</sub> (0.4g, 1.9 mmol) was added. After 2 hours of stirring at room temperature, the mixture was quenched by addition of 1N NaOH<sub>aq</sub> (5 ml). This was diluted to 60 ml with Et<sub>2</sub>O and washed with H<sub>2</sub>O and brine. The organic phase was dried over anhydrous MgSO<sub>4</sub>, filtered and filtrate evaporated to dryness under reduced pressure. The residue was purified by flash column chromatography (SiO<sub>2</sub>, CH<sub>2</sub>Cl<sub>2</sub>) to give pure product as a creamy solid (1.4 g, 71%). <sup>1</sup>H NMR (300 MHz, DMSO-d<sub>6</sub>) δ 7.72 (d, *J* = 9.0 Hz, 1H), 7.53-7.41 (m, 3H), 7.31-7.28 (m, 2H), 7.23 (dd, *J* = 2.7, 9.3 Hz, 1H), 7.18-7.13 (m, 2H), 7.11-7.07 (m, 2H), 6.48 (d, *J* = 6 Hz, 1H), 6.32 (d, *J* = 2.4 Hz, 1H), 4.01-3.92 (m, 3H), 3.10 (dd, *J* = 6.9, 15.9 Hz, 2H), 2.74 (dd, *J* = 4.8, 15.9 Hz, 2H), 2.52 (s, 3H), 0.84 (t, *J* = 7.2 Hz, 3H). LCMS, *m/z* 423 (M + H)<sup>+</sup>.

**Example 3: Preparation of 6-(2,3-dihydro-1H-inden-2-ylamino)-2-methyl-4-phenylquinoline-3-carboxylic acid**

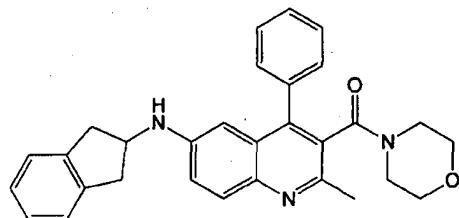


A mixture of **Example 2** (0.98g, 2.4 mmol), 2M KOH aq (3.6 ml, 7.2 ml) and 18-crown-6 ether (0.63g, 0.24 mmol) in EtOH (50 ml) was refluxed for 30 hours under N<sub>2</sub>. After cooling to room temperature the organic solvent was removed under reduced pressure and the residue was diluted to 5 ml with H<sub>2</sub>O, filtered and the filtrate was acidified to pH~5 with 10% aqueous citric acid. The precipitate formed was filtered off, washed with H<sub>2</sub>O, small volume of EtOH, Et<sub>2</sub>O and evaporated under reduced pressure to give pure product as a deep yellow solid (0.89 g, 93%). <sup>1</sup>H NMR (300 MHz, DMSO-d<sub>6</sub>) δ 7.69 (d, *J* = 9.3 Hz, 1H), 7.50-7.38 (m, 3H), 7.35-7.29 (m, 2H), 7.19-7.03 (m, 5H), 6.39 (d, *J* = 5.4 Hz,

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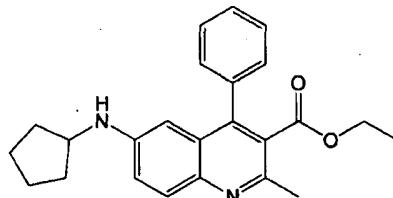
1H), 6.28 (d,  $J = 2.4$  Hz, 1H), 3.93 (m, 1H), 3.09 (dd,  $J = 7.2, 16.2$  Hz, 2H), 2.73 (dd,  $J = 7.2, 16.2$  Hz, 2H), 2.52 (s, 3H). LCMS,  $m/z$  395 ( $M + H$ )<sup>+</sup>.

#### Example 4



Thionyl chloride (1 mL) was added to a suspension of **Example 3** (150 mg, 0.37 mmol) in DCM (5 mL) and the reaction mixture was stirred at room temperature for 1 hour. The solvent was removed under reduced pressure and the resulting residue dissolved in DCM (5 mL). Morpholine (0.32 mL, 3.7 mmol) was added and the solution was stirred for 1 h. The reaction mixture was partitioned over DCM and 10% aqueous citric acid solution. The organics were dried over MgSO<sub>4</sub> and concentrated under reduced pressure to give a yellow residue. The crude residue was purified by column chromatography (SiO<sub>2</sub>, 50% EtOAc/DCM) to give a bright yellow solid (110.0 mg, 65%). <sup>1</sup>H NMR (300 MHz, DMSO-d<sub>6</sub>) δ 7.94 (d,  $J = 9.0$  Hz, 1H), 7.38-7.57 (m, 5H), 6.99-7.20 (m, 5H), 6.57 (d,  $J = 2.4$  Hz, 1H), 4.18-4.26 (m, 2H), 2.67-3.59 (m, 12H), 2.67 (s, 3H). LCMS  $m/z$  464 ( $M + H$ )<sup>+</sup>.

#### Example 5

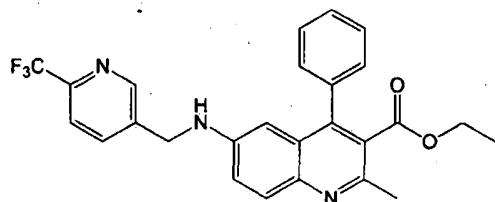


NaBH(OAc)<sub>3</sub> (91.4 mg, 0.43 mmol) was added to a solution of **Example 1** (80.8 mg, 0.26 mmol), cyclopentanone (25 μL, 0.28 mmol) and glacial AcOH (100 μL) in anhydrous 1,2-dichloroethane (3 ml). The resulting mixture was stirred overnight at room temperature under N<sub>2</sub>. The mixture was quenched by addition of sat.NaHCO<sub>3</sub> aq (5 ml) and extracted with EtOAc. The extracts were dried over anhydrous MgSO<sub>4</sub>, filtered and the filtrate

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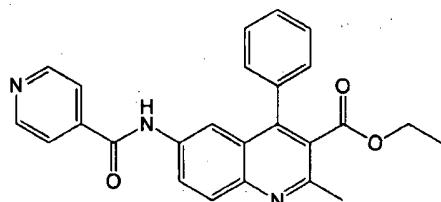
evaporated to dryness under reduced pressure. The residue was purified by column chromatography ( $\text{SiO}_2$ , 10% EtOAc/DCM) (80.0 mg, 81%).  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.84 (d,  $J = 9.0$  Hz, 1H), 7.50-7.43 (m, 3H), 7.37-7.34 (m, 2H), 7.08 (dd,  $J = 2.4, 9.0$  Hz, 1H), 6.42 (d,  $J = 2.4$  Hz, 1H), 4.04 (q,  $J = 7.2$  Hz, 2H), 3.90 (broad s, 1H), 3.63 (quintet,  $J = 6.6$  Hz, 1H), 2.70 (s, 3H), 1.93-1.83 (m, 2H), 1.73-1.50 (m, 4H), 1.46-1.36 (m, 2H), 0.94 (t,  $J = 7.2$  Hz, 3H). LCMS,  $m/z$  375 ( $\text{M} + \text{H}$ ) $^+$ .

#### Example 6



$\text{NaBH(OAc)}_3$  (131.7 mg, 0.62 mmol) was added to a solution of **Example 1** (88.4 mg, 0.29 mmol), 6-(trifluoromethyl)nicotinaldehyde (53.7 mg, 0.31 mmol) and glacial AcOH (100  $\mu\text{L}$ ) in anhydrous 1,2-dichloroethane (3 ml). The resulting mixture was stirred overnight at room temperature under  $\text{N}_2$ . The mixture was quenched by addition of sat. $\text{NaHCO}_3\text{aq}$  (5 ml) and extracted with EtOAc. The extracts were dried over anhydrous  $\text{MgSO}_4$ , filtered and the filtrate evaporated to dryness under reduced pressure. The residue was purified by column chromatography ( $\text{SiO}_2$ , 60-100% Et<sub>2</sub>O/n-hexane) (84.4 mg, 63%).  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  8.55 (s, 1H), 7.93 (d,  $J = 9$  Hz, 1H), 7.69 (d,  $J = 8.1$  Hz, 1H), 7.57 (d,  $J = 8.1$  Hz, 1H), 7.45-7.33 (m, 3H), 7.19-7.11 (m, 3H), 6.24 (d,  $J = 2.7$  Hz, 1H), 4.58 (broad s, 1H), 4.36 (broad s, 2H), 4.01 (q,  $J = 7.2$  Hz, 2H), 2.71 (s, 3H), 0.90 (t,  $J = 7.2$  Hz, 3H). LCMS,  $m/z$  466 ( $\text{M} + \text{H}$ ) $^+$ .

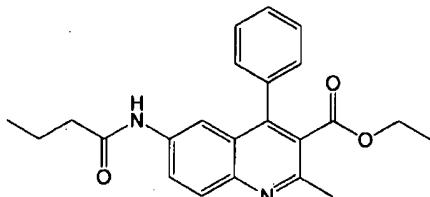
#### Example 7



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Triethylamine (20  $\mu$ L, 0.14 mmol) was added to a solution of **Example 1** (18.8 mg, 0.06 mmol) and isonicotinoyl chloride hydrochloride (11.9 mg, 0.07 mmol) in anhydrous DCM (1 mL). The resulting mixture was stirred overnight at room temperature under  $N_2$ . The mixture was quenched by addition of sat.NaHCO<sub>3</sub>aq (1 ml) and extracted with EtOAc. The extracts were dried over anhydrous MgSO<sub>4</sub>, filtered and the filtrate evaporated to dryness under reduced pressure. The residue was purified by column chromatography (SiO<sub>2</sub>, 20-70% EtOAc/DCM) (22.0 mg, 88%). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)  $\delta$  8.78-8.76 (m, 2H), 8.10-8.04 (m, 3H), 7.77 (s, 1H), 7.68-7.66 (m, 2H), 7.52-7.46 (m, 3H), 7.39-7.36 (m, 2H), 4.07 (q,  $J$  = 6.9 Hz, 2H), 2.78 (s, 3H), 0.96 (t,  $J$  = 6.9 Hz, 3H). LCMS, *m/z* 412 (M + H)<sup>+</sup>.

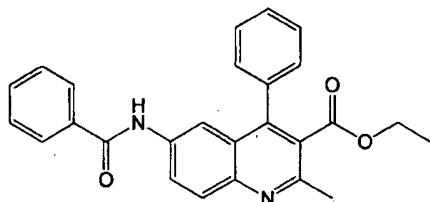
#### Example 8



Triethylamine (55  $\mu$ L, 0.40 mmol) was added to a solution of **Example 1** (72.0 mg, 0.24 mmol) and butyryl chloride (40  $\mu$ L, 0.39 mmol) in anhydrous DCM (1 mL). The resulting mixture was stirred for 1 hour at room temperature under  $N_2$ . The mixture was quenched by addition of sat.NH<sub>4</sub>Cl aq (1 ml) and extracted with EtOAc. The extracts were dried over anhydrous MgSO<sub>4</sub>, filtered and the filtrate evaporated to dryness under reduced pressure. The residue was purified by column chromatography (SiO<sub>2</sub>, 10-30% EtOAc/DCM) (80.9 mg, 91%). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)  $\delta$  8.05-7.99 (m, 2H), 7.62 (d,  $J$  = 1.8, 1H), 7.50-7.45 (m, 3H), 7.38-7.34 (m, 2H), 7.24 (broad s, 1H), 4.05 (q,  $J$  = 6.9 Hz, 2H), 2.76 (s, 3H), 2.31 (t,  $J$  = 7.5 Hz, 2H), 1.73 (sextet,  $J$  = 7.5 Hz, 2H), 1.00-0.93 (m, 6H). LCMS, *m/z* 377 (M + H)<sup>+</sup>.

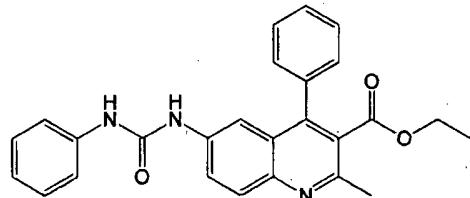
#### Example 9

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Triethylamine (20  $\mu$ L, 0.14 mmol) was added to a solution of **Example 1** (27.8 mg, 0.09 mmol) and benzoyl chloride (15  $\mu$ L, 0.13 mmol) in anhydrous DCM (1 mL). The resulting mixture was stirred for 1 hour at room temperature under  $N_2$ . The mixture was quenched by addition of sat.NH<sub>4</sub>Cl aq (1 ml) and extracted with EtOAc. The extracts were dried over anhydrous MgSO<sub>4</sub>, filtered and the filtrate evaporated to dryness under reduced pressure. The residue was purified by column chromatography (SiO<sub>2</sub>, 80% Et<sub>2</sub>O/n-hexane) (28.2mg, 76%). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)  $\delta$  8.11–8.10 (m, 2H), 7.88 (broad s, 1H), 7.85–7.74 (m, 3H), 7.55–7.38 (m, 8H), 4.07 (q,  $J$  = 7.2 Hz, 2H), 2.78 (s, 3H), 0.96 (t,  $J$  = 7.2 Hz, 3H). LCMS, *m/z* 411 (M + H)<sup>+</sup>.

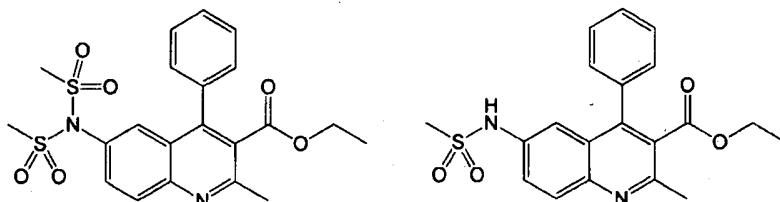
#### Example 10



Phenyl isocyanate (20  $\mu$ L, 0.184 mmol) was added to a solution of **Example 1** (50.1 mg, 0.164 mmol) and triethylamine (30  $\mu$ L, 0.215 mmol) in anhydrous 1,2-dichloroethane (2 mL). The resulting mixture was stirred at 65°C for 18 hours under  $N_2$ . The reaction was evaporated to dryness and the residue purified by column chromatography (SiO<sub>2</sub>, 40-60% Et<sub>2</sub>O/DCM) (23.3mg, 33.4%). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)  $\delta$  7.96 (d,  $J$  = 9.3 Hz, 1H), 7.65–7.57 (m, 2H), 7.64–7.05 (m, 8H), 6.94 (broad s, 1H), 4.04 (q,  $J$  = 7.2 Hz, 2H), 2.74 (s, 3H), 0.94 (t,  $J$  = 7.2 Hz, 3H). LCMS, *m/z* 426 (M + H)<sup>+</sup>.

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**Example 11s & 12**



Example 11

Example 12

Methanesulfonyl chloride (15  $\mu$ L, 0.194 mmol) was added to a solution of **Example 1** (48.0 mg, 0.157 mmol) and triethylamine (30  $\mu$ L, 0.215 mmol) in anhydrous DCM (2 mL). The resulting mixture was stirred for 1 hour at room temperature under N<sub>2</sub>. The mixture was quenched by addition of sat.NaHCO<sub>3aq</sub> (1 ml) and extracted with EtOAc. The extracts were dried over anhydrous MgSO<sub>4</sub>, filtered and the filtrate evaporated to dryness under reduced pressure. The residue was purified by column chromatography. (SiO<sub>2</sub>, 10-40% Et<sub>2</sub>O/DCM) to afford **Example 11** (51.4 mg, 70.8%). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)  $\delta$  8.29 (d, *J* = 8.7 Hz, 1H), 7.70-7.60 (m, 2H), 7.54-7.50 (m, 3H), 7.39-7.36 (m, 2H), 4.07 (q, *J* = 7.2 Hz, 2H), 3.35 (s, 6H), 2.85 (s, 3H), 0.95 (t, *J* = 7.2 Hz, 3H). LCMS, *m/z* 463 (M + H)<sup>+</sup> and **Example 12** (10.7mg, 17.7%) <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)  $\delta$  78.096 (d, *J* = 9.30 Hz, 1H), 7.65-7.57 (mdd, *J* = 2.4, 9.0 Hz, 21H), 7.6451-7.0549 (m, 83H), 7.36-7.33 (m, 2H), 7.276.94 (broad sd, *J* = 2.7 Hz, 1H), 6.48 (broad s, 1H), 4.0704 (q, *J* = 7.2 Hz, 2H), 2.98 (s, 3H), 2.7774 (s, 3H), 0.94 (t, *J* = 7.2 Hz, 3H). LCMS, *m/z* 385426 (M + H)<sup>+</sup>

**Biological Protocols**

**1. Screening of the neurotrophic properties of the compounds in the Neurite Outgrowth assay**

**Cortical neurons culture**

Female rats of 17 days gestation were killed by cervical dislocation and the foetuses were removed from the uterus. Their brains were placed in ice-cold medium of Leibovitz (L15, Gibco, Fisher bioblock, France). Cortex were dissected and meninges were carefully removed. The cortical neurons were dissociated by trypsinization for 30 min at 37°C (trypsin-EDTA Gibco) in presence of 0.1 mg/ml DNase I (Roche, France). The reaction was stopped by addition of Dulbecco's Modified Eagle Medium (DMEM; Gibco) with

10% of fetal bovine serum (FBS ; Gibco). The suspension was triturated with a 10-ml pipette and using a 21G needle and syringe, and centrifuged at 350 x g for 10 min at room temperature. The pellet of dissociated cells was resuspended in medium consisting of Neurobasal (Gibco) supplemented with 2% B27 supplement (Gibco), 0.5 mM L-Glutamine (Gibco), an antibiotic-antimicotic mixture. Viable cells were counted in a Neubauer cytometer using the trypan blue exclusion test (Sigma). Cells were seeded on the basis of 30000 cells per Petri dish ( $\varnothing$  35 mm, Nunc) precoated with poly-L-lysine.

**a. Treatment**

Cells were allowed to adhere 2h and maintained in a humidified incubator at 37°C in 5 % CO<sub>2</sub>-95 % air atmosphere. After neuronal adhesion (2h after the plating), cultures were exposed to the Examples or BDNF for a period of 3 days.

**b. Evaluation of neurite outgrowth**

After the 3 days exposure of the neurons to the test compounds, cultures were washed with phosphate-buffered saline (PBS, Gibco) and fixed using 2.5% glutaraldehyde in PBS. Several pictures (~80) of neurons with neurites without any branching were taken per condition using a digital camera (Coolpix 995; Nikon) mounted on the microscope (Nikon, objective 40x). Neurites were outlined on computer screen using imaging software (Image-Pro Plus, France), which automatically calculates the length.

**c. Statistical analysis**

A global analysis of the data was performed using a one way analysis of variance (ANOVA), followed by Fisher's Protected Least Significant Difference when applicable. The level of significance was set to p < 0.05. All results were expressed as mean±sem. N = ~180 cells

Compounds were tested at 1nM, 10nM and 100nM on two independent cultures comprising 2 Petri dishes per culture and per condition. In parallel, BDNF was tested at 50 ng/ml.

**d. Biological Results**

Examples 1-9 show a significant enhancement in neurite outgrowth in Biological Protocol 1., at concentrations of 100 nM or less.

**2. Screening of the anxiolytic effect****a. Light dark test**

The light dark paradigm is based on a conflict between the innate aversion of rodents to brightly illuminated areas and on the spontaneous exploratory behaviour of the mice. If given a choice between a large brightly compartment versus a small dark compartment they spontaneously prefer the dark part. Anxiolytic compounds have been found to increase the number of entries into the bright compartment and the total time spent there. Anxiogenic compounds were observed to work in the opposite way.

The apparatus consists of two PVC (polyvinylchloride) boxes ( $19 \times 19 \times 15$  cm) covered with Plexiglas. One of these boxes is darkened. The other box is illuminated by 100 W desk lamp placed 15 cm above and providing an illumination of about 4400 Lux. An opaque plastic tunnel ( $5 \times 7 \times 10$  cm) separates the dark box from the illuminated one.

Animals were placed individually in the lit box, with head directed towards the tunnel. The time spent in the lit box and the number of transitions between the two boxes was recorded over a 5 min period after the first entry of the animal in the dark box. The total walked distance in the lit box was also recorded. Animals scored without entry into the lit box were excluded from the analysis.

**b. Test compounds and treatment**

Test compounds may be prepared in aqueous vehicle containing 0.5% w/v hydroxypropylmethyl cellulose, 0.5% v/v benzyl alcohol and 0.4% v/v Tween 80. The compounds may be administrated *per os* 1 hour before the implementation of the test.

N=10-12 mice

### 3. Elevated Plus Maze

The Elevated Plus Maze (EPM) situation rests on the conflict between the innate tendencies of rodents to explore novel environments and avoid open and brightly lit areas. In this task the mouse is placed in the centre of the maze. From here it can walk down any of four runways. Two of the arms are well lit and open, and the other two are enclosed and dimly lit. Mice prefer the closed arms but will venture out into the open arms. The amount of time spent in the open arms and the number of times the mice enter the open arms are recorded. The total walked distance in the open arms is also recorded. "Anxious" mice will spend little time in the open arms and make very few entries into the open arms.

The apparatus is made of polyvinylchloride materials and consists of four equal exploratory arms ( $45 \times 10$  cm) which are all interconnected by a small platform ( $10 \times 10$  cm). Two arms are open and two others are closed with walls (30 cm high). The apparatus is placed 66 cm above the floor. A videotracking system is used to record the test (ViewPoint, France). The video camera is placed at 2.50 m above the equipment and connected to the computer via a video capture card (Pinnacle Systems, France).

A trial consists of placing an animal on the central platform facing a closed arm. The number of entries and the duration spent in open arms are automatically recorded by a videotrack system during an 5 minutes period.

The apparatus is cleaned between each animal using alcohol (70%).

#### a. Test compounds and treatment

Test compounds may be prepared in aqueous vehicle containing 0.5% w/v hydroxypropylmethyl cellulose, 0.5% v/v benzyl alcohol and 0.4% v/v Tween 80. The compounds may be administrated *per os* 1 hour before the implementation of the test.

N=10-12 rats

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#### 4. Marble Burying

The Marble Burying test is used as a model for both anxiety and obsessive compulsive disorders. Mice have a natural tendency to bury marbles under the bedding when placed in a cage with rows of evenly spaced marbles on the floor. Suppression of this spontaneous burying has been used as a measure of anxiolytic drug action. Mice pre-treated with benzodiazepines and different classes of antidepressants bury less marbles when compared to the control mice

The apparatus consists of transparent polycarbonate cages (30 cm x 18 cm x 19 cm) containing a 5 cm layer of fine sawdust bedding and 20 glass marbles (diameter: 1.5 cm) spaced evenly along the walls of the cage. Each animal is placed individually in the cage where it remains for a 20 min test session. On termination of the test session the animals are removed from the cage and the number of marbles at least two-thirds buried in the sawdust is recorded.

##### a. Test compounds and treatment

Test compounds may be prepared in aqueous vehicle containing 0.5% w/v hydroxypropylmethyl cellulose, 0.5% v/v benzyl alcohol and 0.4% v/v Tween 80. The compounds may be administrated *per os* 1 hour before the implementation of the test.

N=10-12 mice

#### 5. Screening of the sedative or stimulating effect of compounds in the modified Open Field

The open field (dark) is used to measure the spontaneous motor activity of mice in a quiet, dark environment. This system is useful for discriminating the sedating or stimulating properties of test compounds on spontaneous locomotion and can thus provide a preliminary indication of potentially adverse effects such as sedation.

The apparatus is an open plexiglass cage (52 x 52 cm) with 40 cm walls. The animal's movements are tracked by a computerised video tracking system, consisting of an overhead camera, diode sensors placed underneath the floor of the cage, computer and

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video analyser software (ViewPoint, France). The video camera is placed at 2.50 m above the cage and connected to the computer via a video capture card (Pinnacle Systems, France). The video tracking system is set in a way that the floor of the OF is divided into nine equal squares. The total number of crossed squares and the total walked distance are recorded.

Each animal is singly placed in a corner of the apparatus and its locomotor activity is automatically recorded over a period of 20 minutes.

The apparatus is cleaned between each animal with alcohol (70%).

**a. Test compounds and treatment**

Test compounds may be prepared in aqueous vehicle containing 0.5% w/v hydroxypropylmethyl cellulose, 0.5% v/v benzyl alcohol and 0.4% v/v Tween 80. The compounds may be administrated *per os* 1 hour before the implementation of the test.

N=10-12 mice

**6. Screening of the antidepressant properties of the compound(s) in the mouse Forced Swim Test**

The forced swim test is the most widely used paradigm for the evaluation of potential antidepressant effect of drugs. Animals placed in a container filled with water show periods of increased swimming activity and periods of relative immobility. Immobile posture reflects a state of tiredness, fatigue, reduced stamina or a lowered mood (hopelessness) similar to the core symptoms observed in depressed patients and in individuals under intense stress. Clinically active anti-depressants have been found to delay the onset of the first phase of immobility and to reduce the total time of relative immobility. The test has some predictive value for anti-depressant drugs. The apparatus consists of a glass cylinder (height 35 cm; diameter 24 cm) filled with water (depth: 25 cm, temperature:  $25 \pm 1$  °C).

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**a. Test compounds and treatment**

Test compounds may be prepared in aqueous vehicle containing 0.5% w/v hydroxypropylmethyl cellulose, 0.5% v/v benzyl alcohol and 0.4% v/v Tween 80. The compounds may be administrated *per os* 1 hour before the implementation of the test.

N=10-12 mice.

Table 1 below depicts the results of compound example 3 in respect of biological protocols 1 to 6.

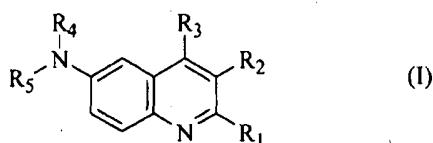
TABLE 1

Example Number	Light Dark Box in mice	Open Field (Dark) in mice	Elevated Plus Maze in rat	Marble Burying in mice	Forced Swim Test in mice	Neurite outgrowth
<b>3</b>	MED 0.1 mg/kg	Tested at 5-100 mg/kg No Sedation at any dose	MED 0.1 mg/kg	MED 0.1 mg/kg	MED 10 mg/kg	Significant effect at concentration s ≤ 100 nM

MED - Minimum Effective Dose

## THE CLAIMS:

1. A method of enhancing neurite outgrowth in a subject in need thereof, the method including the step of administering an effective amount of a compound of formula (I) or pharmaceutically acceptable salt thereof:



wherein

R<sub>1</sub> represents hydrogen, or optionally substituted C<sub>1</sub>-C<sub>6</sub> alkyl;

R<sub>2</sub> represents -C(O)NR'R'' (where R' is -H or optionally substituted C<sub>1</sub>-C<sub>6</sub> alkyl and R'' is optionally substituted C<sub>1</sub>-C<sub>6</sub> alkyl, -OH or -CN, or R' and R'' together form an optionally substituted heterocyclil), -C(O)OR' (where R' is -H or optionally substituted C<sub>1</sub>-C<sub>6</sub> alkyl), -C(O)NHSO<sub>2</sub>R''' (where R''' is optionally substituted aryl or optionally substituted C<sub>1</sub>-C<sub>6</sub> alkyl), -S(O)<sub>2</sub>NHR'''' (where R'''' is -H, optionally substituted C<sub>1</sub>-C<sub>6</sub> alkyl, or optionally substituted aryl), optionally substituted heteroaryl or optionally substituted heterocyclil;

R<sub>3</sub> represents optionally substituted aryl or optionally substituted heteroaryl;

R<sub>4</sub> represents H, optionally substituted alkyl, optionally substituted aryl, optionally substituted cycloalkyl, optionally substituted cycloalkenyl, optionally substituted acyl, optionally substituted alkenyl, optionally substituted heterocyclil, optionally substituted heteroaryl, optionally substituted oxysulfinyl, optionally substituted oxysulfonyl, optionally substituted sulfinyl, or optionally substituted sulfonyl; and

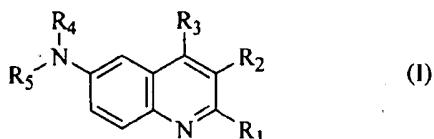
R<sub>5</sub> represents H, optionally substituted cycloalkyl, optionally substituted cycloalkenyl, optionally substituted acyl, optionally substituted aryl, optionally substituted arylalkyl, optionally substituted heteroaryl, optionally substituted heteroarylalkyl, optionally

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substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted cycloalkylalkyl, -S(O)<sub>2</sub>-optionally substituted C<sub>1</sub>-C<sub>6</sub> alkyl, or -C(O)NR'R' (wherein each R' is independently H, optionally substituted C<sub>1</sub>-C<sub>6</sub> alkyl or optionally substituted aryl).

2. A method of claim 1, wherein the compound is not 6-(2,3-dihydro-1H-inden-2-ylamino)-2-methyl-4-phenylquinoline-3-carboxylic acid.

3. A method for treating a neurite outgrowth-responsive disease, condition, or disorder comprising the step of administering to a patient in need thereof an effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof:



wherein

R<sub>1</sub> represents hydrogen, or optionally substituted C<sub>1</sub>-C<sub>6</sub> alkyl;

R<sub>2</sub> represents -C(O)NR'R'' (where R' is -H or optionally substituted C<sub>1</sub>-C<sub>6</sub> alkyl and R'' is optionally substituted C<sub>1</sub>-C<sub>6</sub> alkyl, -OH or -CN, or R' and R'' together form an optionally substituted heterocyclyl), -C(O)OR' (where R' is -H or optionally substituted C<sub>1</sub>-C<sub>6</sub> alkyl), -C(O)NHSO<sub>2</sub>R''' (where R''' is optionally substituted aryl or optionally substituted C<sub>1</sub>-C<sub>6</sub> alkyl), -S(O)<sub>2</sub>NHR''' (where R''' is -H, optionally substituted C<sub>1</sub>-C<sub>6</sub> alkyl, or optionally substituted aryl), optionally substituted heteroaryl or optionally substituted heterocyclyl;

R<sub>3</sub> represents optionally substituted aryl or optionally substituted heteroaryl;

R<sub>4</sub> represents H, optionally substituted alkyl, optionally substituted aryl, optionally substituted cycloalkyl, optionally substituted cycloalkenyl, optionally substituted acyl, optionally substituted alkenyl, optionally substituted heterocyclyl, optionally substituted heteroaryl, optionally substituted oxysulfanyl, optionally substituted oxysulfonyl,

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optionally substituted sulfinyl, or optionally substituted sulfonyl; and

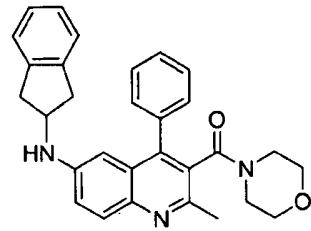
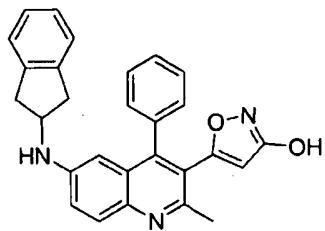
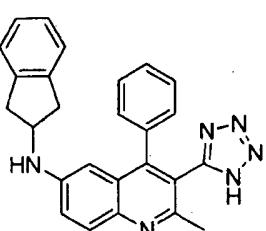
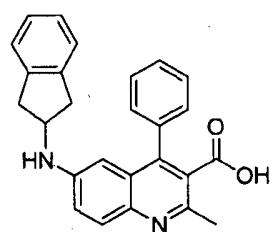
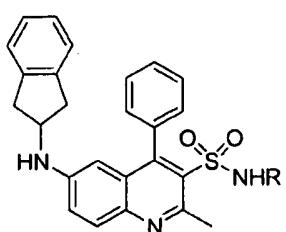
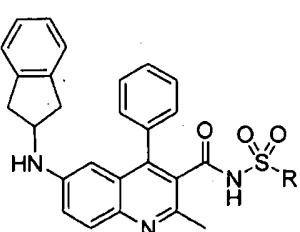
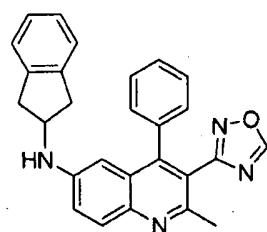
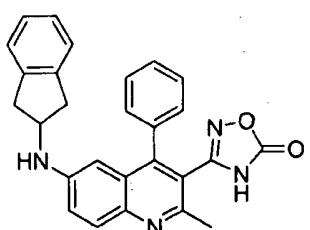
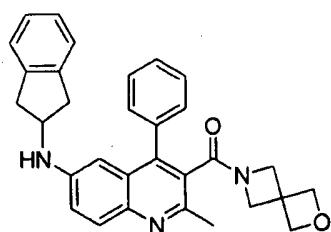
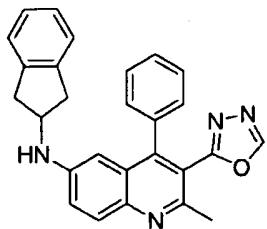
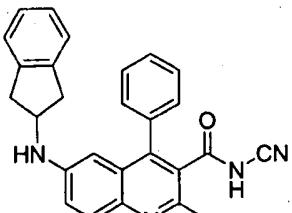
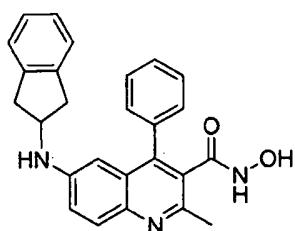
R<sub>5</sub> represents H, optionally substituted cycloalkyl, optionally substituted cycloalkenyl, optionally substituted acyl, optionally substituted aryl, optionally substituted arylalkyl, optionally substituted heteroaryl, optionally substituted heteroarylalkyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted cycloalkylalkyl, -S(O)<sub>2</sub>-optionally substituted C<sub>1</sub>-C<sub>6</sub> alkyl, or -C(O)NR'R' (wherein each R' is independently H, optionally substituted C<sub>1</sub>-C<sub>6</sub> alkyl or optionally substituted aryl).

4. A method of claim 3, wherein the neurite outgrowth-responsive disease, condition, or disorder is multiple sclerosis.

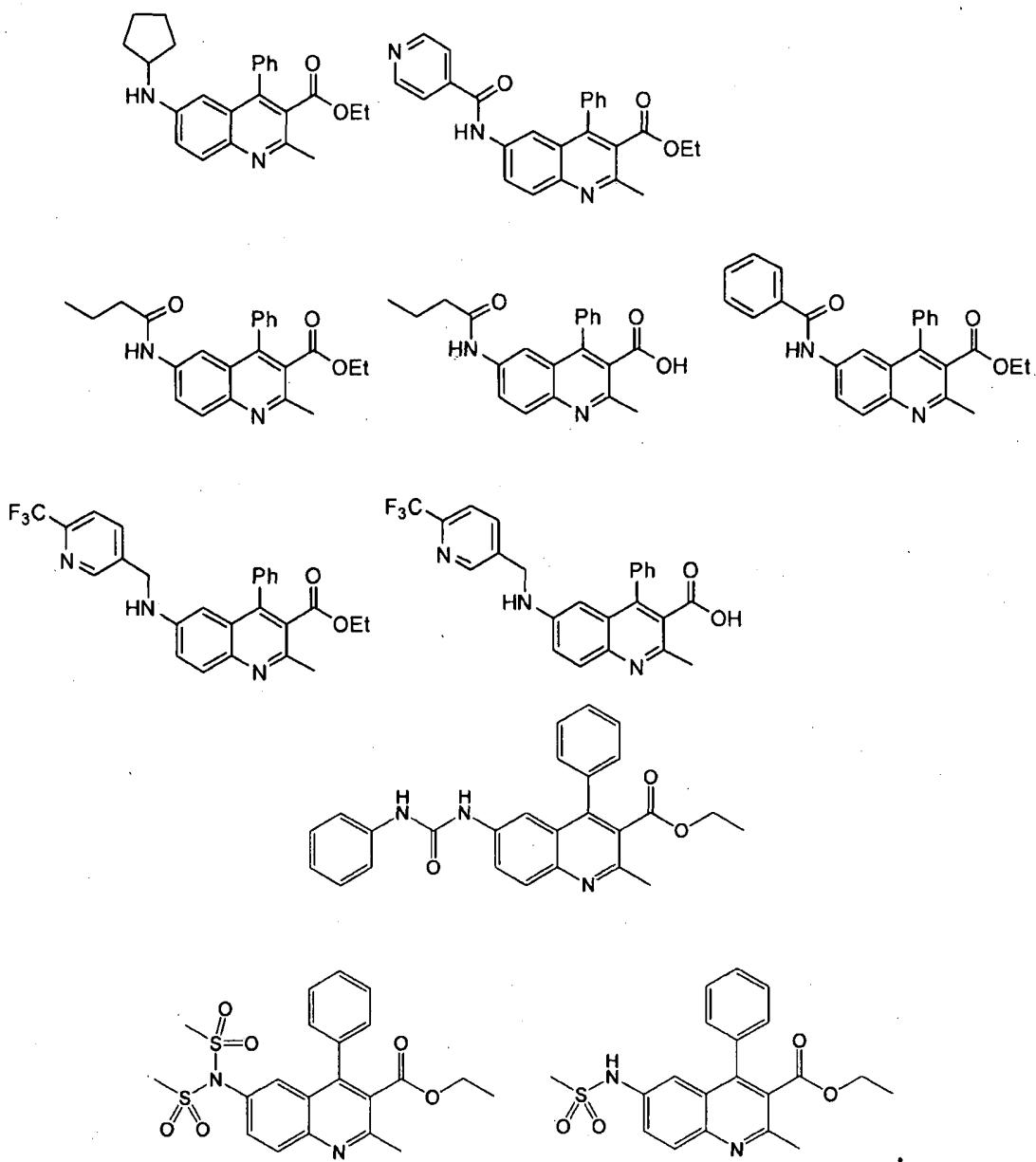
5. A method of claim 3 or 4, wherein the compound is 6-(2,3-dihydro-1H-inden-2-ylamino)-2-methyl-4-phenylquinoline-3-carboxylic acid.

6. A method of any one of claims 1 through 4, wherein the compound is one of the following:

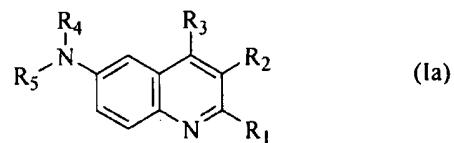
- 105 -



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7. A compound of formula (Ia) or a pharmaceutically acceptable salt thereof:



wherein

R<sub>1</sub> represents hydrogen, or optionally substituted C<sub>1</sub>-C<sub>6</sub> alkyl;

R<sub>2</sub> represents -C(O)NR'R'' (where R' is -H or optionally substituted C<sub>1</sub>-C<sub>6</sub> alkyl and R'' is optionally substituted C<sub>1</sub>-C<sub>6</sub> alkyl, -OH or -CN, or R' and R'' together form an optionally substituted heterocyclyl), -C(O)OR' (where R' is -H or optionally substituted C<sub>1</sub>-C<sub>6</sub> alkyl), -C(O)NHSO<sub>2</sub>R''' (where R''' is optionally substituted aryl or optionally substituted C<sub>1</sub>-C<sub>6</sub> alkyl), -S(O)<sub>2</sub>NHR'''' (where R'''' is -H, optionally substituted C<sub>1</sub>-C<sub>6</sub> alkyl, or optionally substituted aryl), optionally substituted heteroaryl or optionally substituted heterocyclyl;

R<sub>3</sub> represents optionally substituted aryl or optionally substituted heteroaryl;

R<sub>4</sub> represents H, optionally substituted alkyl, optionally substituted aryl, optionally substituted cycloalkyl, optionally substituted cycloalkenyl, optionally substituted acyl, optionally substituted alkenyl, optionally substituted heterocyclyl, optionally substituted heteroaryl, optionally substituted oxysulfinyl, optionally substituted oxysulfonyl, optionally substituted sulfinyl, or optionally substituted sulfonyl; and

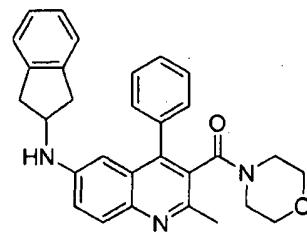
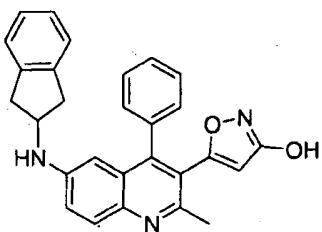
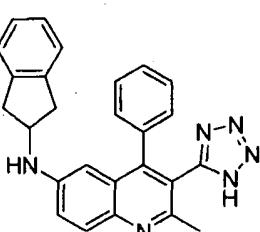
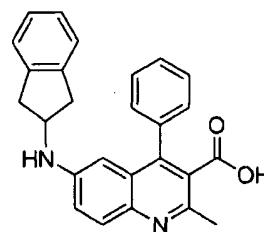
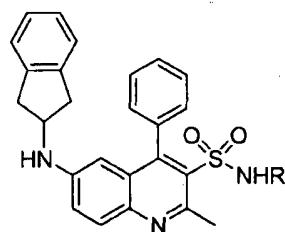
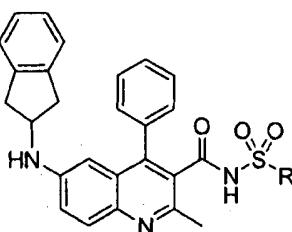
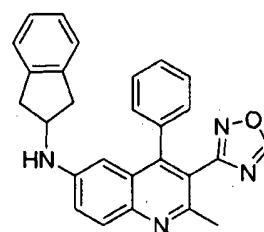
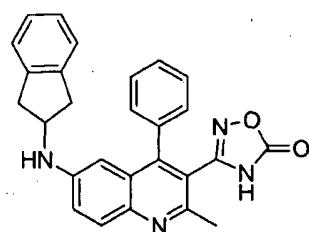
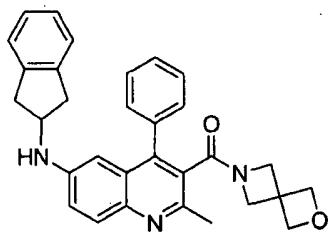
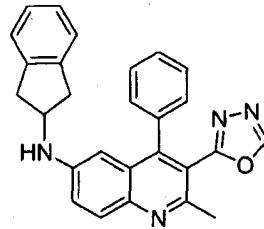
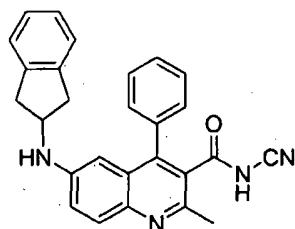
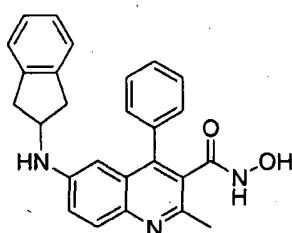
R<sub>5</sub> represents H, optionally substituted cycloalkyl, optionally substituted cycloalkenyl, optionally substituted acyl, optionally substituted aryl, optionally substituted arylalkyl, optionally substituted heteroaryl, optionally substituted heteroarylalkyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted cycloalkylalkyl, -S(O)<sub>2</sub>-optionally substituted C<sub>1</sub>-C<sub>6</sub> alkyl, or -C(O)NR'R' (wherein each R' is independently H, optionally substituted C<sub>1</sub>-C<sub>6</sub> alkyl or optionally substituted aryl).

8. A compound of claim 7, or salts thereof, provided that compounds wherein R<sub>3</sub> is optionally substituted phenyl, one of R<sub>4</sub> and R<sub>5</sub> is H, and the other of R<sub>4</sub> and R<sub>5</sub> is optionally substituted bicyclic cycloalkyl or optionally substituted bicyclic cycloalkenyl, are specifically excluded.

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9. A compound of claim 7, or salts thereof, provided that compounds wherein R<sub>3</sub> is optionally substituted phenyl, one of R<sub>4</sub> and R<sub>5</sub> is H, and the other of R<sub>4</sub> and R<sub>5</sub> is indanyl, are specifically excluded.

10. A compound of claim 7, or salts thereof, provided that the following compounds, and pharmaceutically acceptable salts thereof, are specifically excluded:



11. A compound of claim 7, wherein:

n is 0 or 1;

R<sub>1</sub> is C<sub>1</sub>-C<sub>2</sub> alkyl;

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$R_2$  is  $-C(O)OH$ ,  $-C(O)OCH_3$ ,  $-C(O)OCH_2CH_3$ ,  $-C(O)OCH_2CH_2CH_3$ , or  $-C(O)NR'R''$  (where  $R'$  and  $R''$  together form an optionally substituted morpholinyl);

$R_3$  is phenyl optionally substituted 1 or 2 times by a substituent independently selected from the group consisting of halogen,  $-CN$ ,  $-CF_3$ , amino, hydroxyl,  $-NHC_1-C_3$  alkyl,  $-N(C_1-C_3\text{ alkyl})_2$ ,  $-COO(C_1-C_3\text{ alkyl})$ , phenyl, benzyl,  $C_1-C_3$  alkyl or  $C_1-C_3$  alkoxy;

$R_4$  is H or  $C_1-C_3$  alkyl; and

$R_5$  is  $R_5'$  and represents H, optionally substituted acyl, optionally substituted aryl, optionally substituted arylalkyl, optionally substituted heteroaryl, optionally substituted heteroarylalkyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted cycloalkylalkyl,  $-S(O)_2$ -optionally substituted  $C_1-C_6$  alkyl, or  $-C(O)NR'R'$  (wherein each  $R'$  is independently H, optionally substituted  $C_1-C_6$  alkyl or optionally substituted aryl).

12. A compound of claim 7, wherein one or more of the following definitions apply:

- (a)  $n$  is 0,
- (b)  $R_1$  is methyl,
- (c)  $R_2$  is  $-C(O)OH$ ,  $-C(O)OCH_3$ , or  $-C(O)OCH_2CH_3$ ,
- (d)  $R_4$  is H, and
- (e)  $R_5$  is  $R_5'$  and represents optionally substituted acyl,  $-(CH_2)_m$ -optionally substituted aryl,  $-(CH_2)_m$ -optionally substituted heteroaryl,  $-(CH_2)_m$ -optionally substituted heterocyclyl, or  $-(CH_2)_m$ -optionally substituted cycloalkyl, wherein  $m$  is an integer of 1 to 3, inclusive.

13. A compound of claim 7, wherein:

$n$  is 0 or 1;

$R_1$  is  $C_1-C_2$  alkyl;

$R_2$  is  $-COOR'$  (where  $R'$  is H or  $C_1-C_4$  alkyl);

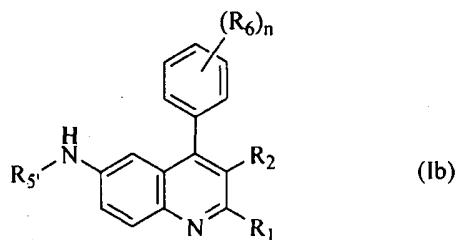
$R_3$  is phenyl optionally substituted 1 or 2 times by a substituent independently selected from the group consisting of halogen,  $-CN$ ,  $-CF_3$ , amino, hydroxyl,  $-NHC_1-C_3$  alkyl,  $-N(C_1-C_3\text{ alkyl})_2$ ,  $-COO(C_1-C_3\text{ alkyl})$ , phenyl, benzyl,  $C_1-C_3$  alkyl or  $C_1-C_3$  alkoxy;

$R_4$  is H or  $C_1-C_3$  alkyl; and

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$R_5$  is  $R_5'$  and represents H, optionally substituted acyl, optionally substituted aryl, optionally substituted arylalkyl, optionally substituted heteroaryl, optionally substituted heteroarylalkyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted cycloalkylalkyl,  $-S(O)_2$ -optionally substituted C<sub>1</sub>-C<sub>6</sub> alkyl, or  $-C(O)NR'R'$  (wherein each R' is independently H, optionally substituted C<sub>1</sub>-C<sub>6</sub> alkyl or optionally substituted aryl).

14. A compound of claim 7, wherein the compound is of formula (Ib):

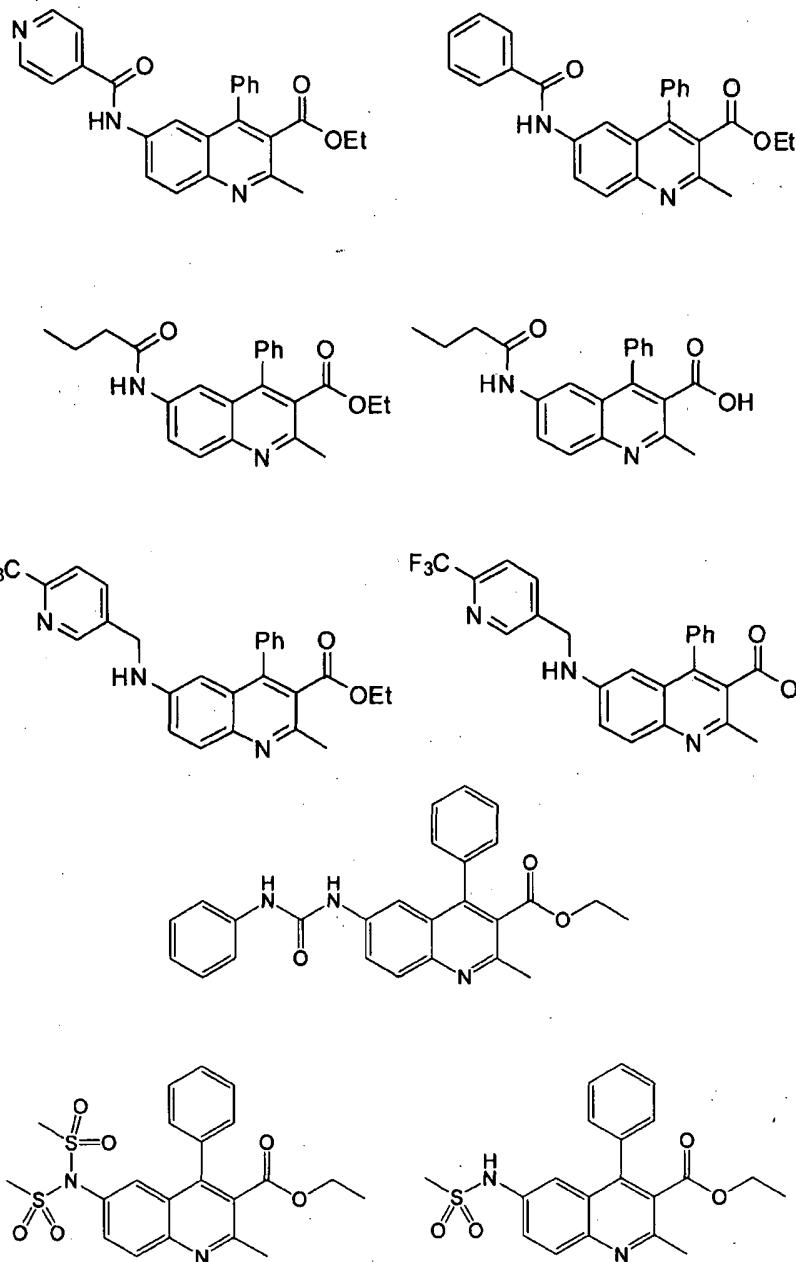


where n is 1 or 2 and each  $R_6$  is independently selected from the group consisting of halogen, -CN, -CF<sub>3</sub>, amino, hydroxyl, -NHC<sub>1</sub>-C<sub>3</sub> alkyl, -N(C<sub>1</sub>-C<sub>3</sub> alkyl)<sub>2</sub>, -COO(C<sub>1</sub>-C<sub>3</sub> alkyl), phenyl, benzyl, C<sub>1</sub>-C<sub>3</sub> alkyl or C<sub>1</sub>-C<sub>3</sub> alkoxy, and  $R_5'$  is

- (i) H, optionally substituted acyl, optionally substituted aryl,  $-(CH_2)_m$ -optionally substituted aryl, optionally substituted heteroaryl,  $-(CH_2)_m$ -optionally substituted heteroaryl, optionally substituted heterocyclyl,  $-(CH_2)_m$ -optionally substituted heterocyclyl,  $-(CH_2)_m$ -optionally substituted cycloalkyl,  $-S(O)_2$ -optionally substituted C<sub>1</sub>-C<sub>6</sub> alkyl, or  $-C(O)NR'R'$  (wherein each R' is independently H, optionally substituted C<sub>1</sub>-C<sub>6</sub> alkyl, or optionally substituted aryl); wherein m is 1, 2, or 3; or
- (ii) optionally substituted acyl, selected from  $-C(O)$ -optionally substituted heteroaryl,  $-C(O)$ -optionally substituted alkyl,  $-C(O)$ -optionally substituted aryl,  $-C(O)$ -optionally substituted heterocyclyl or  $-C(O)$ -optionally substituted cycloalkyl; or
- (iii)  $-C(O)$ -heteroaryl,  $-C(O)$ -alkyl,  $-C(O)$ -aryl,  $-C(O)$ -heterocyclyl or  $-C(O)$ -cycloalkyl, optionally substituted 1 or 2 times by halo, -CN, -NO<sub>2</sub>, -CO<sub>2</sub>H, -CO<sub>2</sub>C<sub>1-6</sub>alkyl, -CONH<sub>2</sub>, -CONH(C<sub>1-6</sub>alkyl), -CON(C<sub>1-6</sub>alkyl)<sub>2</sub>, -OH, hydroxyalkyl, alkoxy, alkyl, acyl, carboxyalkyl, acetyl, trifluoromethyl, benzyloxy, phenoxy, -NH<sub>2</sub>, -NH(C<sub>1-6</sub>alkyl) or  $-N(C_{1-6}alkyl)_2$ .

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15. A compound of claim 7, wherein the compound is one of the following:



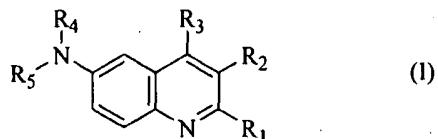
16. A method for treating a central nervous system disorder comprising the step of administering to a patient in need thereof an effective amount of a compound of any one of

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claims 7 through 15.

17. A method of claim 16, wherein the central nervous system disorder is an anxiety disorder, a mood disorder, or a neurodegenerative disorder.

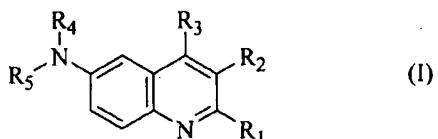
18. Use of a compound of formula (I) or a salt thereof:



wherein R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub>, R<sub>4</sub> and R<sub>5</sub> are as described in any one of claims 1 to 15,

in the manufacture of a medicament for enhancing neurite outgrowth in a subject in need thereof.

19. Use of a compound of formula (I) or a salt thereof:



wherein R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub>, R<sub>4</sub>, and R<sub>5</sub> are as described in any one of claims 1 to 15,

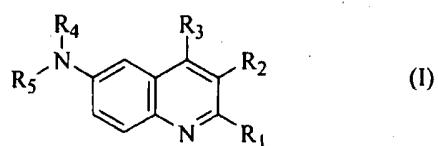
in the manufacture of a medicament for treating a neurite outgrowth-responsive disease, disorder, or condition in a subject in need thereof.

20. Use of a compound of any one of claims 7 through 15 in the manufacture of a medicament for the treatment of a central nervous system disorder.

21. The use of claim 20, wherein the central nervous system disorder is an anxiety disorder, a mood disorder, or a neurodegenerative disorder.

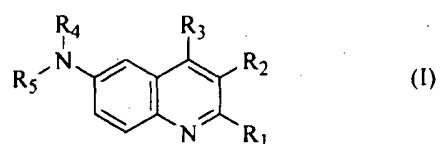
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22. Use of a compound of formula (I) or a salt thereof:



wherein R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub>, R<sub>4</sub>, and R<sub>5</sub> are as described in any one of claims 1 to 15, for enhancing neurite outgrowth in a subject in need thereof.

23. Use of a compound of formula (I) or a salt thereof:



wherein R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub>, R<sub>4</sub>, and R<sub>5</sub> are as described in any one of claims 1 to 15, for treating a neurite outgrowth-responsive disease, disorder, or condition in a subject in need thereof.

24. Use of a compound of any one of claims 7 through 15 for the treatment of a central nervous system disorder.

25. The use of claim 24, wherein the central nervous system disorder is an anxiety disorder, a mood disorder, or a neurodegenerative disease.

## INTERNATIONAL SEARCH REPORT

International application No.

PCT/AU2013/000991

## A. CLASSIFICATION OF SUBJECT MATTER

**A61K 31/47 (2006.01) A61K 31/4709 (2006.01) A61P 25/00 (2006.01) A61P 25/16 (2006.01) A61P 25/22 (2006.01)**  
**A61P 25/24 (2006.01) A61P 25/28 (2006.01) C07D 215/36 (2006.01) C07D 215/54 (2006.01) C07D 413/04 (2006.01)**

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)

STN (CAPLUS): structure search based on formula Ia of claim 7

## 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
"E" earlier application or patent but published on or after the international filing date	"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
"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)	"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
"O" document referring to an oral disclosure, use, exhibition or other means	"&"	document member of the same patent family
"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  
11 October 2013

Date of mailing of the international search report  
11 October 2013

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INTERNATIONAL SEARCH REPORT		International application No.
C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		PCT/AU2013/000991
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2008/046135 A1 (BIONOMICS LIMITED) 24 April 2008 Whole document	
P,X	WO 2012/116415 A1 (BIONOMICS LIMITED) 07 September 2012 abstract; page 26; examples 1-2; claims	1-3,5-7,16-25

<b>INTERNATIONAL SEARCH REPORT</b> Information on patent family members		International application No. <b>PCT/AU2013/000991</b>	
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.			
<b>Patent Document/s Cited in Search Report</b>		<b>Patent Family Member/s</b>	
Publication Number	Publication Date	Publication Number	Publication Date
WO 2008/046135 A1	24 Apr 2008	AU 2007312936 B2 CA 2666219 A1 EP 2074123 A1 EP 2074123 B1 EP 2540722 A1 HK 1132268 A1 JP 2010506829 A NZ 576036 A US 2010105678 A1 US 8293737 B2 US 2013012508 A1 US 2013012509 A1 WO 2008046135 A1	26 Sep 2013 24 Apr 2008 01 Jul 2009 05 Dec 2012 02 Jan 2013 03 May 2013 04 Mar 2010 29 Oct 2010 29 Apr 2010 23 Oct 2012 10 Jan 2013 10 Jan 2013 24 Apr 2008
WO 2012/116415 A1	07 Sep 2012	WO 2012116415 A1	07 Sep 2012
<b>End of Annex</b>			
<small>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 2009)</small>			