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(54) Title: PYRIDO [4,3-B] INDOLES AND METHODS OF USE

(57) Abstract: New heterocyclic compounds that may be used to modulate a histamine receptor in an individual are described. Pyrido[4,3-b]indoles are described, as are pharmaceutical compositions comprising the compounds and methods of using the compounds in a variety of therapeutic applications, including the treatment of a cognitive disorder, psychotic disorder, neurotransmitter-mediated disorder and/or a neuronal disorder.



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PYRIDO[4,3-B]INDOLES AND METHODS OF USE

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims priority benefit of Indian Patent Application No. 1136/MUM/2009, filed April 29, 2009, and U.S. Provisional Patent Application No. 61/181,262, filed May 26, 2009, the disclosures of each of which are hereby incorporated herein by reference in their entireties.

STATEMENT OF RIGHTS TO INVENTIONS MADE UNDER FEDERALLY SPONSORED RESEARCH

[0002] Not applicable.

BACKGROUND OF THE INVENTION

[0003] Neurotransmitters such as histamine, serotonin, dopamine and norepinephrine mediate a large number of processes in the central nervous system (CNS) as well as outside the CNS. Abnormal neurotransmitter levels are associated with a wide variety of diseases and conditions including, but not limited to, Alzheimer's disease, Parkinson's Disease, autism, Guillain-Barré syndrome, mild cognitive impairment, schizophrenia (such as cognitive impairment associated with schizophrenia (CIAS), positive symptoms, disorganized symptoms, and negative symptoms of schizophrenia), anxiety, multiple sclerosis, stroke, traumatic brain injury, spinal cord injury, diabetic neuropathy, fibromyalgia, bipolar disorders, psychosis, depression, attention-deficit disorder (ADD), attention-deficit hyperactivity disorder (ADHD) and a variety of allergic diseases. Compounds that modulate these neurotransmitters may be useful therapeutics.

[0004] Histamine receptors belong to the superfamily of G protein-coupled seven transmembrane proteins. G protein-coupled receptors constitute one of the major signal transduction systems in eukaryotic cells. Coding sequences for these receptors, in those regions believed to contribute to the agonist-antagonist binding site, are strongly conserved across mammalian species. Histamine receptors are found in most peripheral tissue and within the central nervous system. Compounds capable of modulating a histamine receptor may find use in therapy, *e.g.*, histamine antagonists may find use as antihistamines.

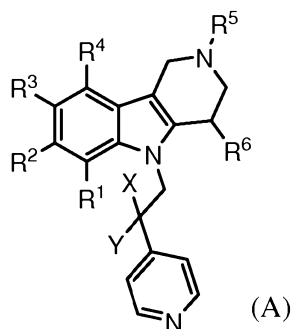
[0005] Dimebon is a known anti-histamine drug that has also been characterized as a neuroprotective agent useful to treat, *inter alia*, neurodegenerative diseases. Dimebon has been shown to inhibit the death of brain cells (neurons) in preclinical models of Alzheimer's disease and Huntington's disease, making it a novel potential treatment for these and other neurodegenerative diseases. In addition, dimebon has been shown to improve the mitochondrial function of cells in the setting of cellular stress with very high potency. For example, dimebon treatment improved mitochondrial function and increased the number of surviving cells after treatment with the cell toxin ionomycin in a dose dependent fashion. Dimebon has also been shown to promote neurite outgrowth and neurogenesis, processes important in the formation of new and/or enhanced neuronal cell connections, and evidence of dimebon's potential for use in additional diseases or conditions. See, *e.g.*, U.S. Patent Nos. 6,187,785 and 7,071,206 and PCT Patent Application Nos. PCT/US2004/041081, PCT/US2007/020483, PCT/US2006/039077, PCT/US2008/077090, PCT/US2007/020516, PCT/US2007/022645, PCT/US2007/002117, PCT/US2008/006667, PCT/US2007/024626, PCT/US2008/009357, PCT/US2007/024623 and PCT/US2008/008121. Hydrogenated pyrido [4,3-b]indoles and uses thereof have been disclosed in PCT Patent Application Nos. PCT/US2008/081390, PCT/US2009/032065, PCT/US2009/038142 and PCT/US2009/062869. All references disclosed herein and throughout, such as publications, patents, patent applications and published patent applications, are incorporated herein by reference in their entireties.

[0006] Although dimebon holds great promise as a drug for the treatment of neurodegenerative diseases and/or diseases in which neurite outgrowth and/or neurogenesis may be implicated in therapy, there remains a need for new and alternative therapies for the treatment of such diseases or conditions. In addition, there remains a need for new and alternative antihistamine drugs, preferably ones in which side-effects such as drowsiness are reduced or eliminated. Compounds that exhibit enhanced and/or more desirable properties than dimebon (*e.g.*, superior safety and efficacy) may find particular use in the treatment of at least those indications for which dimebon is believed to be advantageous. Further, compounds that exhibit a different therapeutic profile than dimebon as determined, *e.g.*, by *in vitro* and/or *in vivo* assays, may find use in additional diseases and conditions.

BRIEF SUMMARY OF THE INVENTION

[0007] Compounds detailed herein are described as histamine receptor modulators. In one aspect, the histamine receptor modulator is a compound that binds to or inhibits binding of a ligand to a histamine (e.g., H₁ and/or H₂ and/or H₃) receptor or mimics an activity of such a histamine receptor. In some embodiments, the histamine receptor modulator inhibits binding of a ligand by at least about or about any one of 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 95% or 100% as determined in the assays described herein. Compositions comprising the compounds are provided, as are kits comprising the compounds as well as methods of using and making the compounds. The compounds provided herein may find use in treating neurodegenerative diseases. Compounds provided may also find use in treating diseases and/or conditions in which modulation of aminergic G protein-coupled receptors and/or neurite outgrowth may be implicated in therapy. Compounds disclosed herein may find use in the methods disclosed herein, including use in treating, preventing, delaying the onset and/or delaying the development of a cognitive disorder, psychotic disorder, neurotransmitter-mediated disorder and/or a neuronal disorder in an individual in need thereof, such as humans.

[0008] Compounds of the formula (A) are provided:



wherein:

R¹, R², R³ and R⁴ are independently H, halo, C₁-C₈ unsubstituted alkyl or C₁-C₈ unsubstituted alkoxy, provided that R³ is other than methyl or chloro when R¹, R² and R⁴ are each H and X is OH and Y is methyl;

R⁵ is unsubstituted C₁-C₈ alkyl or a C₁-C₈ alkyl substituted with a perhaloalkyl moiety;

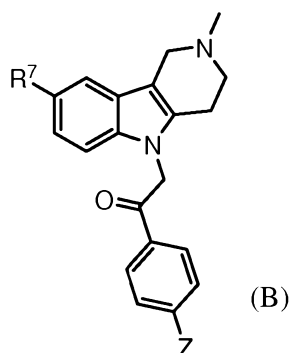
R⁶ is H or an unsubstituted C₁-C₈ alkyl;

X is OH, C₁-C₈ alkyl or is taken together with Y to form a cyclopropyl moiety; and

Y is H, C₁-C₈ alkyl or is taken together with X to form a cyclopropyl moiety,

or a salt thereof, such as a pharmaceutically acceptable salt thereof, or solvate of the foregoing.

[0009] Also provided are compounds of the formula (B):



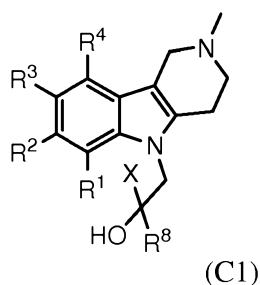
wherein:

R^7 is H, hydroxyl, nitro, cyano, halo, C_1 - C_8 perhaloalkyl, substituted or unsubstituted C_1 - C_8 alkyl, substituted or unsubstituted C_2 - C_8 alkenyl, substituted or unsubstituted C_2 - C_8 alkynyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, C_1 - C_8 perhaloalkoxy, C_1 - C_8 alkoxy, aryloxy, carboxyl, carbonylalkoxy, thiol, substituted or unsubstituted heterocyclcyl, substituted or unsubstituted aralkyl, thioalkyl, substituted or unsubstituted amino, acylamino, aminoacyl, aminocarbonylamino, aminocarbonyloxy, aminosulfonyl, sulfonylamino, sulfonyl, carbonylalkylenealkoxy, alkylsulfonylamino or acyl; and

Z is H, halo or C_1 - C_8 alkyl,

or a salt thereof, such as a pharmaceutically acceptable salt thereof, or solvate of the foregoing.

[0010] Compounds of the formula (C1) are also embraced:



wherein:

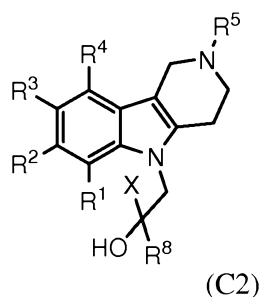
R^1 , R^2 , R^3 and R^4 are independently H, halo, C_1 - C_8 unsubstituted alkyl or C_1 - C_8 unsubstituted alkoxy;

R^8 is a substituted or unsubstituted aryl or a substituted or unsubstituted heteroaryl; and

X is a C₄-C₆ unsubstituted alkyl,
or a salt thereof, such as a pharmaceutically acceptable salt thereof, or solvate of the foregoing.

[0011] In one variation of formula (C1), R¹, R², R³ and R⁴ are as defined for formula (A).

[0012] Compounds of the formula (C2) are also provided:



wherein:

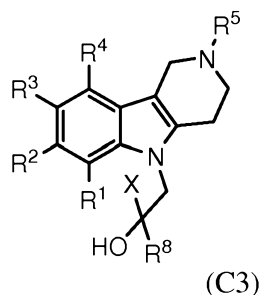
R¹, R², R³ and R⁴ are independently H, halo, C₁-C₈ unsubstituted alkyl or C₁-C₈ unsubstituted alkoxy;

R⁵ is C₁-C₆ unsubstituted alkyl or CF₃;

R⁸ is a substituted or unsubstituted aryl or a substituted or unsubstituted heteroaryl; and

X is a C₄-C₆ unsubstituted n-alkyl or cycloalkyl or a C₃-C₆ unsubstituted branched alkyl,
or a salt thereof, such as a pharmaceutically acceptable salt thereof, or solvate of the foregoing.

[0013] In another embodiment, compounds of the formula (C3) are provided,



wherein:

R¹, R², R³ and R⁴ are independently H, halo, C₁-C₈ unsubstituted alkyl or C₁-C₈ unsubstituted alkoxy;

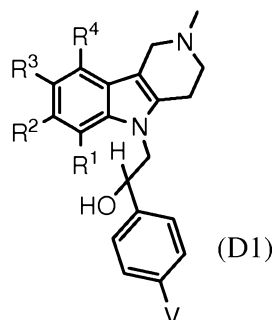
R⁵ is a C₁-C₆ unsubstituted alkyl, or CF₃;

R⁸ is a substituted or unsubstituted aryl or a substituted or unsubstituted heteroaryl; and

X is a C₁-C₆ unsubstituted alkyl,

or a salt thereof, such as a pharmaceutically acceptable salt thereof, or solvate of the foregoing.

[0014] Compounds of the formula (D1) are also provided:



wherein:

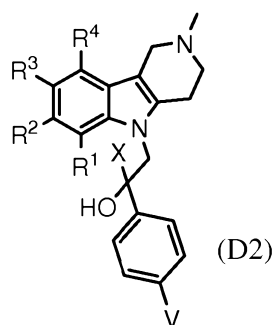
R^1 , R^2 , R^3 and R^4 are independently H, halo, C_1 - C_8 unsubstituted alkyl or C_1 - C_8 unsubstituted alkoxy; and

V is a halo,

or a salt thereof, such as a pharmaceutically acceptable salt thereof, or solvate of the foregoing.

[0015] In one variation of formula (D1), R^1 , R^2 , R^3 and R^4 are as defined for formula (A).

[0016] Compounds of the formula (D2) are also provided:



wherein:

R^1 , R^2 , R^3 and R^4 are independently H, halo, C_1 - C_8 unsubstituted alkyl or C_1 - C_8 unsubstituted alkoxy;

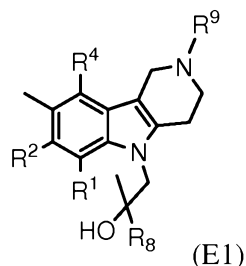
X is H or a C_1 - C_3 unsubstituted alkyl; and

V is a halo,

or a salt thereof, such as a pharmaceutically acceptable salt thereof, or solvate of the foregoing.

[0017] In another embodiment, compounds of the formula (D2) are provided, wherein X is C₁-C₃ unsubstituted alkyl.

[0018] Compounds of the formula (E1) are also detailed herein:



wherein:

R¹, R², R³ and R⁴ are independently H, halo, C₁-C₈ unsubstituted alkyl or C₁-C₈ unsubstituted alkoxy;

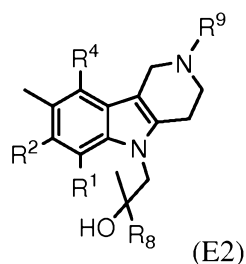
R⁸ is 6-pyrimidyl, 3-methyl-4-pyridyl or a phenyl substituted either: (i) with at least one alkoxy or hydroxyl group or (ii) with at least two halo groups; and

R⁹ is an unsubstituted C₁-C₃ alkyl,

or a salt thereof, such as a pharmaceutically acceptable salt thereof, or solvate of the foregoing.

[0019] In a particular variation of formula (E1), R¹, R², R³ and R⁴ are as defined for formula (A).

[0020] In another embodiment, compounds of the formula (E2) are provided,



wherein:

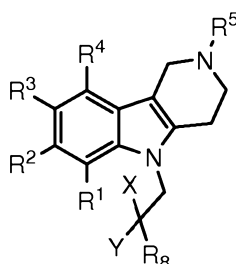
R¹, R², R³ and R⁴ are independently H, halo, C₁-C₈ unsubstituted alkyl or C₁-C₈ unsubstituted alkoxy;

R⁸ is 6-pyrimidyl, 2-pyrazinyl, 3-methyl-4-pyridyl or a phenyl substituted either: (i) with at least one alkoxy or hydroxyl group or (ii) with at least two halo groups; and

R⁹ is an unsubstituted C₁-C₃ alkyl,

or a salt thereof, such as a pharmaceutically acceptable salt thereof, or solvate of the foregoing.

[0021] Also provided are compounds of the formula (F1):



(F1)

wherein:

R^1 , R^2 , R^3 and R^4 are independently H, halo, C_1 - C_8 unsubstituted alkyl or C_1 - C_8 unsubstituted alkoxy;

R^5 is $\text{---CH}_2\text{CH}_2\text{CF}_3$, $\text{---CH}_2\text{CH}_2\text{CN}$ or $\text{---(CH}_2\text{)}_T\text{OH}$ where T is 3 or 4;

X is H or OH;

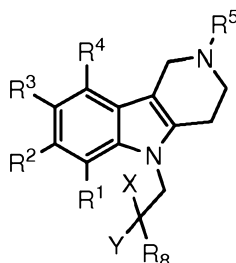
Y is H or C_1 - C_8 alkyl; and

R^8 is a substituted or unsubstituted heteroaryl,

or a salt thereof, such as a pharmaceutically acceptable salt thereof, or solvate of the foregoing.

[0022] In one variation of formula (F1), R^1 , R^2 , R^3 and R^4 are as defined for formula (A).

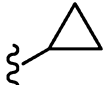
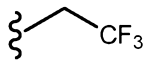
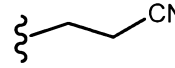
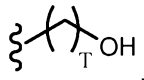
[0023] In another embodiment, compounds of the formula (F2) are provided,



(F2)

wherein:

R^1 , R^2 , R^3 and R^4 are independently H, halo, C_1 - C_8 unsubstituted alkyl or C_1 - C_8 unsubstituted alkoxy;

R^5 is , ,  or  where T is 3 or 4

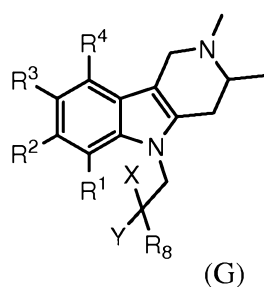
X is H or OH;

Y is H or C₁-C₈ alkyl; and

R^8 is a substituted or unsubstituted heteroaryl,

or a salt thereof, such as a pharmaceutically acceptable salt thereof, or solvate of the foregoing.

[0024] Compounds of the formula (G) are also detailed herein:



wherein:

R^1 , R^2 , R^3 and R^4 are independently H, halo, C₁-C₈ unsubstituted alkyl or C₁-C₈ unsubstituted alkoxy;

R^3 is methyl or chloro, provided that R^3 is methyl when R^8 is a substituted heteroaryl;

X is H or OH;

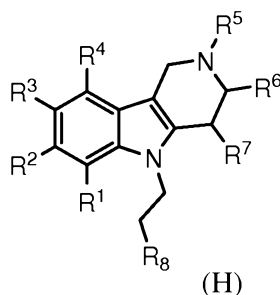
Y is H or C₁-C₈ alkyl; and

R^8 is a substituted or unsubstituted heteroaryl,

or a salt thereof, such as a pharmaceutically acceptable salt thereof, or solvate of the foregoing.

[0025] In one variation of formula (G), R^1 , R^2 , R^3 and R^4 are as defined for formula (A).

[0026] Compounds of the formula (H) are also detailed herein:



wherein:

R^1 , R^2 , R^3 and R^4 are independently H, halo, C_1 - C_8 unsubstituted alkyl or C_1 - C_8 unsubstituted alkoxy;

R^5 , R^6 and R^7 are each independently H or unsubstituted C_1 - C_8 alkyl; and

R^8 is a 6-substituted pyridin-3-yl,

or a salt thereof, such as a pharmaceutically acceptable salt thereof, or solvate of the foregoing.

[0027] In one variation of formula (H), R^1 , R^2 , R^3 and R^4 are as defined for formula A.

[0028] Various other compounds are detailed herein, including compounds of Table 1. In one variation, compounds of the invention exclude compound 1-4 of Table 1.

[0029] The invention also includes all salts of compounds referred to herein, such as pharmaceutically acceptable salts. A pharmaceutically acceptable salt intends ionic interactions and not a covalent bond. As such, an *N*-oxide is not considered a salt. Examples of pharmaceutically acceptable salts include those listed in Berge et al., *Pharmaceutical Salts*, J. Pharm. Sci. 1977 Jan; 66(1):1-19. The invention also includes any or all of the stereochemical forms, including any enantiomeric or diastereomeric forms, of the compounds described. Unless stereochemistry is explicitly indicated in a chemical structure or name, the structure or name is intended to embrace all possible stereoisomers of a compound depicted. All forms of the compounds are also embraced by the invention, such as crystalline or non-crystalline forms of the compounds. Compositions comprising a compound of the invention are also intended, such as a composition of substantially pure compound, including a specific stereochemical form thereof. Compositions comprising a mixture of compounds of the invention in any ratio are also embraced by the invention, including mixtures of two or more stereochemical forms of a compound of the invention in any ratio, such that racemic, non-racemic, enantio-enriched and scalemic mixtures of a compound are embraced, or mixtures thereof.

[0030] Compounds of the invention may be presented in the form of chemical structures or names. Chemical structures and names have been generated using graphical software, *e.g.*, ChemBioDraw Ultra 11.0 (CambridgeSoft Co.), which includes a facility to generate IUPAC-standard names from ChemDraw structures, and vice-versa, based on Beilstein's AutoNom conversion algorithms.

[0031] The invention is also directed to pharmaceutical compositions comprising a compound of the invention and a pharmaceutically acceptable carrier or excipient. Kits comprising a compound of the invention and instructions for use are also embraced by this invention.

Compounds as detailed herein or a pharmaceutically acceptable salt thereof are also provided for the manufacture of a medicament for the treatment of a cognitive disorder, psychotic disorder, neurotransmitter-mediated disorder or a neuronal disorder.

[0032] In one aspect, compounds of the invention are used to treat, prevent, delay the onset and/or delay the development of any one or more of the following: cognitive disorders, psychotic disorders, neurotransmitter-mediated disorders and/or neuronal disorders in individuals in need thereof, such as humans. In one variation, compounds of the invention are used to treat, prevent, delay the onset and/or delay the development of diseases or conditions for which the modulation of an aminergic G protein-coupled receptor is believed to be or is beneficial. In one variation, compounds of the invention are used to treat, prevent, delay the onset and/or delay the development of any one or more of diseases or conditions for which neurite outgrowth and/or neurogenesis and/or neurotrophic effects are believed to be or are beneficial. In another variation, compounds of the invention are used to treat, prevent, delay the onset and/or delay the development of diseases or conditions for which the modulation of an aminergic G protein-coupled receptor and neurite outgrowth and/or neurogenesis and/or neurotrophic effects are believed to be or are beneficial. In one variation, the disease or condition is a cognitive disorder, psychotic disorder, neurotransmitter-mediated disorder and/or a neuronal disorder.

[0033] In another aspect, compounds of the invention are used to improve cognitive function and/or reduce psychotic effects in an individual, comprising administering to an individual in need thereof an amount of a compound described herein or a pharmaceutically acceptable salt thereof effective to improve cognitive function and/or reduce psychotic effects.

[0034] In a further aspect, compounds of the invention are used to stimulate neurite outgrowth and/or promote neurogenesis and/or enhance neurotrophic effects in an individual comprising administering to an individual in need thereof an amount of a compound described herein or a pharmaceutically acceptable salt thereof effective to stimulate neurite outgrowth and/or to promote neurogenesis and/or to enhance neurotrophic effects. Synapse loss is associated with a variety of neurodegenerative diseases and conditions including Alzheimer's disease, schizophrenia, Huntington's disease, Parkinson's disease, amyotrophic lateral sclerosis, stroke, head trauma and spinal cord injury. Compounds of the invention that stimulate neurite outgrowth may have a benefit in these settings.

[0035] In another aspect, compounds described herein are used to modulate an aminergic G protein-coupled receptor comprising administering to an individual in need thereof an amount of a compound described herein or a pharmaceutically acceptable salt thereof effective to modulate an aminergic G protein-coupled receptor. In one variation, a compound of the invention modulates at least one of the following receptors: adrenergic receptor (*e.g.*, α_{1D} , α_{2A} and/or α_{2B}), serotonin receptor (*e.g.*, 5-HT_{2A}, 5-HT_{2C}, 5-HT₆ and/or 5-HT₇), dopamine receptor (*e.g.*, D_{2L}) and histamine receptor (*e.g.*, H₁, H₂ and/or H₃). In another variation, at least two of the following receptors are modulated: adrenergic receptor (*e.g.*, α_{1D} , α_{2A} and/or α_{2B}), serotonin receptor (*e.g.*, 5-HT_{2A}, 5-HT_{2C}, 5-HT₆ and/or 5-HT₇), dopamine receptor (*e.g.*, D_{2L}) and histamine receptor (*e.g.*, H₁, H₂ and/or H₃). In another variation, at least three of the following receptors are modulated: adrenergic receptor (*e.g.*, α_{1D} , α_{2A} and/or α_{2B}), serotonin receptor (*e.g.*, 5-HT_{2A}, 5-HT_{2C}, 5-HT₆ and/or 5-HT₇), dopamine receptor (*e.g.*, D_{2L}) and histamine receptor (*e.g.*, H₁, H₂ and/or H₃). In another variation, each of the following receptors is modulated: adrenergic receptor (*e.g.*, α_{1D} , α_{2A} and/or α_{2B}), serotonin receptor (*e.g.*, 5-HT_{2A}, 5-HT_{2C}, 5-HT₆ and/or 5-HT₇), dopamine receptor (*e.g.*, D_{2L}) and histamine receptor (*e.g.*, H₁, H₂ and/or H₃). In another variation, at least one of the following receptors is modulated: α_{1D} , α_{2A} , α_{2B} , 5-HT_{2A}, 5-HT_{2C}, 5-HT₆, 5-HT₇, D_{2L}, H₁, H₂ and H₃. In another variation, at least one of the following receptors is modulated: α_{1D} , α_{2A} , α_{2B} , 5-HT_{2A}, 5-HT_{2C}, 5-HT₆, 5-HT₇, D₂, H₁, H₂ and H₃. In another variation, at least two or three or four or five or six or seven or eight or nine or ten or eleven of the following receptors are modulated: α_{1D} , α_{2A} , α_{2B} , 5-HT_{2A}, 5-HT_{2C}, 5-HT₆, 5-HT₇, D_{2L}, H₁, H₂ and H₃. In another variation, at least two or three or four or five or six or seven or eight or nine or ten or eleven of the following receptors are modulated: α_{1D} , α_{2A} , α_{2B} , 5-HT_{2A}, 5-HT_{2C}, 5-HT₆, 5-HT₇, D₂, H₁, H₂ and H₃. In a particular variation, at least dopamine receptor D₂ is modulated. In still another variation, at least dopamine receptor D_{2L} is modulated. In another particular variation, at least dopamine receptor D₂ and serotonin receptor 5-HT_{2A} are modulated. In another particular variation, at least dopamine receptor D_{2L} and serotonin receptor 5-HT_{2A} are modulated. In a further particular variation, at least adrenergic receptors α_{1D} , α_{2A} , α_{2B} and serotonin receptor 5-HT₆ are modulated. In another particular variation, at least adrenergic receptors α_{1D} , α_{2A} , α_{2B} , serotonin receptor 5-HT₆ and one or more of serotonin receptor 5-HT₇, 5-HT_{2A}, 5-HT_{2C} and histamine receptor H₁ and H₂ are modulated. In a further particular variation, histamine receptor H₁ is modulated. In another variation, compounds of the invention exhibit any receptor modulation activity detailed herein and further stimulate neurite outgrowth and/or

neurogenesis and/or enhance neurotrophic effects. In one variation, compounds detailed herein inhibit binding of a ligand to histamine receptor H₁ and/or H₂ by less than about 80% as determined by a suitable assay known in the art such as the assays described herein. In another variation, binding of a ligand to histamine receptor H₁ and/or H₂ is inhibited by less than about any of 75%, 70%, 65%, 60%, 55%, or 50% as determined by a suitable assay known in the art such as the assays described herein. In a further variation, compounds detailed herein:

(a) inhibit binding of a ligand to histamine receptor H₁ and/or H₂ by less than about 80% (which can in different variations be less than about any of 75%, 70%, 65%, 60%, 55%, or 50%) as determined by a suitable assay known in the art such as the assays described herein and (b) inhibit binding of a ligand to dopamine receptor D_{2L} by greater than about any of 80%, 85%, 90%, 95%, 100% or between about 85% and about 95% or between about 90% and about 100%, as determined in a suitable assay known in the art such as the assays described herein. In a further variation, compounds detailed herein: (a) inhibit binding of a ligand to histamine receptor H₁ and/or H₂ by less than about 80% (which can in different variations be less than about any of 75%, 70%, 65%, 60%, 55%, or 50%) as determined by a suitable assay known in the art such as the assays described herein and (b) inhibit binding of a ligand to a dopamine receptor D₂ by greater than about any of 80%, 85%, 90%, 95%, 100% or between about 85% and about 95% or between about 90% and about 100%, as determined in a suitable assay known in the art such as the assays described herein.

DETAILED DESCRIPTION OF THE INVENTION

Definitions

[0036] For use herein, unless clearly indicated otherwise, use of the terms “a”, “an” and the like refers to one or more.

[0037] As used herein, reference to “about” a value or parameter herein includes (and describes) embodiments that are directed to that value or parameter per se. For example, description referring to “about X” includes description of “X”.

[0038] As used herein, the term “aminergic G protein-coupled receptors” refers to a family of transmembrane proteins involved in cellular communication. Aminergic G protein coupled receptors are activated by biogenic amines and represent a subclass of the superfamily of G protein coupled receptors, which are structurally characterized by seven transmembrane helices.

Aminergic G protein-coupled receptors include but are not limited to adrenergic receptors, serotonin receptors, dopamine receptors, histamine receptors and imidazoline receptors.

[0039] As used herein, the term “adrenergic receptor modulator” intends and encompasses a compound that binds to or inhibits binding of a ligand to an adrenergic receptor or reduces or eliminates or increases or enhances or mimics an activity of an adrenergic receptor. As such, an “adrenergic receptor modulator” encompasses both an adrenergic receptor antagonist and an adrenergic receptor agonist. In some aspects, the adrenergic receptor modulator binds to or inhibits binding to a ligand to an α_1 -adrenergic receptor (*e.g.*, α_{1A} , α_{1B} and/or α_{1D}) and/or a α_2 -adrenergic receptor (*e.g.*, α_{2A} , α_{2B} and/or α_{2C}) and/or reduces or eliminates or increases or enhances or mimics an activity of a α_1 -adrenergic receptor (*e.g.*, α_{1A} , α_{1B} and/or α_{1D}) and/or a α_2 -adrenergic receptor (*e.g.*, α_{2A} , α_{2B} and/or α_{2C}) in a reversible or irreversible manner. In some aspects, the adrenergic receptor modulator inhibits binding of a ligand by at least about or about any one of 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 95% or 100% as determined in the assays described herein. In some aspects, the adrenergic receptor modulator reduces an activity of an adrenergic receptor by at least or about any of 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 95% or 100% as compared to the corresponding activity in the same subject prior to treatment with the adrenergic receptor modulator or compared to the corresponding activity in other subjects not receiving the adrenergic receptor modulator. In some aspects, the adrenergic receptor modulator enhances an activity of an adrenergic receptor by at least about or about any of 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 95% or 100 or 200% or 300% or 400% or 500% or more as compared to the corresponding activity in the same subject prior to treatment with the adrenergic receptor modulator or compared to the corresponding activity in other subjects not receiving the adrenergic receptor modulator. In some aspects, the adrenergic receptor modulator is capable of binding to the active site of an adrenergic receptor (*e.g.*, a binding site for a ligand). In some embodiments, the adrenergic receptor modulator is capable of binding to an allosteric site of an adrenergic receptor.

[0040] As used herein, the term “dopamine receptor modulator” intends and encompasses a compound that binds to or inhibits binding of a ligand to a dopamine receptor or reduces or eliminates or increases or enhances or mimics an activity of a dopamine receptor. As such, a “dopamine receptor modulator” encompasses both a dopamine receptor antagonist and a dopamine receptor agonist. In some aspects, the dopamine receptor modulator binds to or inhibits binding of a ligand to a dopamine-1 (D_1) and/or a dopamine-2 (D_2) receptor or reduces

or eliminates or increases or enhances or mimics an activity of a dopamine-1 (D₁) and/or a dopamine-2 (D₂) receptor in a reversible or irreversible manner. Dopamine D₂ receptors are divided into two categories, D_{2L} and D_{2S}, which are formed from a single gene by differential splicing. D_{2L} receptors have a longer intracellular domain than D_{2S}. In some embodiments, the dopamine receptor modulator inhibits binding of a ligand by at least about or about any one of 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 95% or 100% as determined in the assays described herein. In some embodiments, the dopamine receptor modulator reduces an activity of a dopamine receptor by at least about or about any of 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 95% or 100% as compared to the corresponding activity in the same subject prior to treatment with the dopamine receptor modulator or compared to the corresponding activity in other subjects not receiving the dopamine receptor modulator. In some embodiments, the dopamine receptor modulator enhances an activity of a dopamine receptor by at least about or about any of 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 95% or 100 or 200% or 300% or 400% or 500% or more as compared to the corresponding activity in the same subject prior to treatment with the dopamine receptor modulator or compared to the corresponding activity in other subjects not receiving the dopamine receptor modulator. In some embodiments, the dopamine receptor modulator is capable of binding to the active site of a dopamine receptor (*e.g.*, a binding site for a ligand). In some embodiments, the dopamine receptor modulator is capable of binding to an allosteric site of a dopamine receptor.

[0041] As used herein, the term “serotonin receptor modulator” intends and encompasses a compound that binds to or inhibits binding of a ligand to a serotonin receptor or reduces or eliminates or increases or enhances or mimics an activity of a serotonin receptor. As such, a “serotonin receptor modulator” encompasses both a serotonin receptor antagonist and a serotonin receptor agonist. In some embodiments, the serotonin receptor modulator binds to or inhibits binding of a ligand to a 5-HT_{1A} and/or a 5-HT_{1B} and/or a 5-HT_{2A} and/or a 5-HT_{2B} and/or a 5-HT_{2C} and/or a 5-HT₃ and/or a 5-HT₄ and/or a 5-HT₆ and/or a 5-HT₇ receptor or reduces or eliminates or increases or enhances or mimics an activity of a 5-HT_{1A} and/or a 5-HT_{1B} and/or a 5-HT_{2A} and/or a 5-HT_{2B} and/or a 5-HT_{2C} and/or a 5-HT₃ and/or a 5-HT₄ and/or a 5-HT₆ and/or a 5-HT₇ receptor in a reversible or irreversible manner. In some embodiments, the serotonin receptor modulator inhibits binding of a ligand by at least about or about any one of 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 95% or 100% as determined in the assays described herein. In some embodiments, the serotonin receptor modulator reduces an activity of a

serotonin receptor by at least about or about any of 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 95% or 100% as compared to the corresponding activity in the same subject prior to treatment with the serotonin receptor modulator or compared to the corresponding activity in other subjects not receiving the serotonin receptor modulator. In some embodiments, the serotonin receptor modulator enhances an activity of a serotonin receptor by at least about or about any of 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 95% or 100 or 200% or 300% or 400% or 500% or more as compared to the corresponding activity in the same subject prior to treatment with the serotonin receptor modulator or compared to the corresponding activity in other subjects not receiving the serotonin receptor modulator. In some embodiments, the serotonin receptor modulator is capable of binding to the active site of a serotonin receptor (*e.g.*, a binding site for a ligand). In some embodiments, the serotonin receptor modulator is capable of binding to an allosteric site of a serotonin receptor.

[0042] As used herein, the term “histamine receptor modulator” intends and encompasses a compound that reduces or eliminates or increases or enhances an activity of a histamine receptor. As such, a “histamine receptor modulator” encompasses both a histamine receptor antagonist and a histamine receptor agonist. In some embodiments, the histamine receptor modulator reduces or eliminates or increases or enhances an activity of a histamine receptor in a reversible or irreversible manner. In some embodiments, the histamine receptor modulator reduces an activity of a histamine receptor by at least or about any of 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 95% or 100% as compared to the corresponding activity in the same individual prior to treatment with the histamine receptor modulator or compared to the corresponding activity in like individuals not receiving the histamine receptor modulator. In some embodiments, the histamine receptor modulator enhances an activity of a histamine receptor by at least or about any of 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 95% or 100 or 200% or 300% or 400% or 500% or more as compared to the corresponding activity in the same individual prior to treatment with the histamine receptor modulator or compared to the corresponding activity in like individuals not receiving the histamine receptor modulator. In some embodiments, the histamine receptor modulator is capable of binding to the active site of a histamine receptor (*e.g.*, a binding site for a ligand). In some embodiments, the histamine receptor modulator is capable of binding to an allosteric site of a histamine receptor.

[0043] Unless clearly indicated otherwise, “an individual” as used herein intends a mammal, including but not limited to a human. An individual includes but is not limited to human,

bovine, primate, equine, canine, feline, porcine, and ovine animals. Thus, the invention finds use in both human medicine and in the veterinary context, including use in agricultural animals and domestic pets. The individual may be a human who has been diagnosed with or is suspected of having a cognitive disorder, a psychotic disorder, a neurotransmitter-mediated disorder and/or a neuronal disorder. The individual may be a human who exhibits one or more symptoms associated with a cognitive disorder, a psychotic disorder, a neurotransmitter-mediated disorder and/or a neuronal disorder. The individual may be a human who has a mutated or abnormal gene associated with a cognitive disorder, a psychotic disorder, a neurotransmitter-mediated disorder and/or a neuronal disorder. The individual may be a human who is genetically or otherwise predisposed to developing a cognitive disorder, a psychotic disorder, a neurotransmitter-mediated disorder and/or a neuronal disorder.

[0044] As used herein, “treatment” or “treating” is an approach for obtaining a beneficial or desired result, such as a clinical result.

[0045] For purposes of this invention, beneficial or desired clinical results include, but are not limited to, alleviation of a symptom and/or diminishment of the extent of a symptom and/or preventing a worsening of a symptom associated with a disease or condition. In one variation, beneficial or desired clinical results include, but are not limited to, alleviation of a symptom and/or diminishment of the extent of a symptom and/or preventing a worsening of a symptom associated with a cognitive disorder, a psychotic disorder, a neurotransmitter-mediated disorder and/or a neuronal disorder. Preferably, treatment of a disease or condition with a compound of the invention or a pharmaceutically acceptable salt thereof is accompanied by no or fewer side effects than are associated with currently available therapies for the disease or condition and/or improves the quality of life of the individual.

[0046] As used herein, “delaying” development of a disease or condition means to defer, hinder, slow, retard, stabilize and/or postpone development of the disease or condition. This delay can be of varying lengths of time, depending on the history of the disease and/or individual being treated. As is evident to one skilled in the art, a sufficient or significant delay can, in effect, encompass prevention, in that the individual does not develop the disease or condition. For example, a method that “delays” development of Alzheimer’s disease is a method that reduces probability of disease development in a given time frame and/or reduces extent of the disease in a given time frame, when compared to not using the method. Such comparisons are typically based on clinical studies, using a statistically significant number of subjects. For

example, Alzheimer's disease development can be detected using standard clinical techniques, such as routine neurological examination, patient interview, neuroimaging, detecting alterations of levels of specific proteins in the serum or cerebrospinal fluid (*e.g.*, amyloid peptides and Tau), computerized tomography (CT) or magnetic resonance imaging (MRI). Similar techniques are known in the art for other diseases and conditions. Development may also refer to disease progression that may be initially undetectable and includes occurrence, recurrence and onset.

[0047] As used herein, an "at risk" individual is an individual who is at risk of developing a cognitive disorder, a psychotic disorder, a neurotransmitter-mediated disorder and/or a neuronal disorder that can be treated with a compound of the invention. An individual "at risk" may or may not have a detectable disease or condition, and may or may not have displayed detectable disease prior to the treatment methods described herein. "At risk" denotes that an individual has one or more so-called risk factors, which are measurable parameters that correlate with development of a disease or condition and are known in the art. An individual having one or more of these risk factors has a higher probability of developing the disease or condition than an individual without these risk factor(s). These risk factors include, but are not limited to, age, sex, race, diet, history of previous disease, presence of precursor disease, genetic (*i.e.*, hereditary) considerations, and environmental exposure. For example, individuals at risk for Alzheimer's disease include, *e.g.*, those having relatives who have experienced this disease and those whose risk is determined by analysis of genetic or biochemical markers. Genetic markers of risk for Alzheimer's disease include mutations in the APP gene, particularly mutations at position 717 and positions 670 and 671 referred to as the Hardy and Swedish mutations, respectively (Hardy, *Trends Neurosci.*, 20:154-9, 1997). Other markers of risk are mutations in the presenilin genes (*e.g.*, PS1 or PS2), ApoE4 alleles, family history of Alzheimer's disease, hypercholesterolemia and/or atherosclerosis. Other such factors are known in the art for other diseases and conditions.

[0048] As used herein, the term "pro-cognitive" includes but is not limited to an improvement of one or more mental processes such as memory, attention, perception and/or thinking, which may be assessed by methods known in the art.

[0049] As used herein, the term "neurotrophic" effects includes but is not limited to effects that enhance neuron function such as growth, survival and/or neurotransmitter synthesis.

[0050] As used herein, the term "cognitive disorders" refers to and intends diseases and conditions that are believed to involve or be associated with or do involve or are associated with

progressive loss of structure and/or function of neurons, including death of neurons, and where a central feature of the disorder may be the impairment of cognition (*e.g.*, memory, attention, perception and/or thinking). These disorders include pathogen-induced cognitive dysfunction, *e.g.*, HIV associated cognitive dysfunction and Lyme disease associated cognitive dysfunction. Examples of cognitive disorders include Alzheimer's Disease, Huntington's Disease, Parkinson's Disease, schizophrenia, amyotrophic lateral sclerosis (ALS), autism, mild cognitive impairment (MCI), stroke, traumatic brain injury (TBI) and age-associated memory impairment (AAMI).

[0051] As used herein, the term "psychotic disorders" refers to and intends mental diseases or conditions that are believed to cause or do cause abnormal thinking and perceptions. Psychotic disorders are characterized by a loss of reality which may be accompanied by delusions, hallucinations (perceptions in a conscious and awake state in the absence of external stimuli which have qualities of real perception, in that they are vivid, substantial, and located in external objective space), personality changes and/or disorganized thinking. Other common symptoms include unusual or bizarre behavior, as well as difficulty with social interaction and impairment in carrying out the activities of daily living. Exemplary psychotic disorders are schizophrenia, bipolar disorders, psychosis, anxiety and depression.

[0052] As used herein, the term "neurotransmitter-mediated disorders" refers to and intends diseases or conditions that are believed to involve or be associated with or do involve or are associated with abnormal levels of neurotransmitters such as histamine, serotonin, dopamine, norepinephrine or impaired function of aminergic G protein-coupled receptors. Exemplary neurotransmitter-mediated disorders include spinal cord injury, diabetic neuropathy, allergic diseases and diseases involving geroprotective activity such as age-associated hair loss (alopecia), age-associated weight loss and age-associated vision disturbances (cataracts). Abnormal neurotransmitter levels are associated with a wide variety of diseases and conditions including, but not limited, to Alzheimer's disease, Parkinson's Disease, autism, Guillain-Barré syndrome, mild cognitive impairment, schizophrenia, anxiety, multiple sclerosis, stroke, traumatic brain injury, spinal cord injury, diabetic neuropathy, fibromyalgia, bipolar disorders, psychosis, depression and a variety of allergic diseases.

[0053] As used herein, the term "neuronal disorders" refers to and intends diseases or conditions that are believed to involve, or be associated with, or do involve or are associated with neuronal cell death and/or impaired neuronal function or decreased neuronal function.

Exemplary neuronal indications include neurodegenerative diseases and disorders such as Alzheimer's disease, Huntington's disease, amyotrophic lateral sclerosis (ALS), Parkinson's disease, canine cognitive dysfunction syndrome (CCDS), Lewy body disease, Menkes disease, Wilson disease, Creutzfeldt-Jakob disease, Fahr disease, an acute or chronic disorder involving cerebral circulation, such as ischemic or hemorrhagic stroke or other cerebral hemorrhagic insult, age-associated memory impairment (AAMI), mild cognitive impairment (MCI), injury-related mild cognitive impairment (MCI), post-concussion syndrome, post-traumatic stress disorder, adjuvant chemotherapy, traumatic brain injury (TBI), neuronal death mediated ocular disorder, macular degeneration, age-related macular degeneration, autism, including autism spectrum disorder, Asperger syndrome, and Rett syndrome, an avulsion injury, a spinal cord injury, myasthenia gravis, Guillain-Barré syndrome, multiple sclerosis, diabetic neuropathy, fibromyalgia, neuropathy associated with spinal cord injury, schizophrenia, bipolar disorder, psychosis, anxiety or depression.

[0054] As used herein, the term “neuron” represents a cell of ectodermal embryonic origin derived from any part of the nervous system of an animal. Neurons express well-characterized neuron-specific markers, including neurofilament proteins, NeuN (Neuronal Nuclei marker), MAP2, and class III tubulin. Included as neurons are, for example, hippocampal, cortical, midbrain dopaminergic, spinal motor, sensory, sympathetic, septal cholinergic, and cerebellar neurons.

[0055] As used herein, the term “neurite outgrowth” or “neurite activation” refers to the extension of existing neuronal processes (*e.g.*, axons and dendrites) and the growth or sprouting of new neuronal processes (*e.g.*, axons and dendrites). Neurite outgrowth or neurite activation may alter neural connectivity, resulting in the establishment of new synapses or the remodeling of existing synapses.

[0056] As used herein, the term “neurogenesis” refers to the generation of new nerve cells from undifferentiated neuronal progenitor cells, also known as multipotential neuronal stem cells. Neurogenesis actively produces new neurons, astrocytes, glia, Schwann cells, oligodendrocytes and/or other neural lineages. Much neurogenesis occurs early in human development, though it continues later in life, particularly in certain localized regions of the adult brain.

[0057] As used herein, the term “neural connectivity” refers to the number, type, and quality of connections (“synapses”) between neurons in an organism. Synapses form between neurons,

between neurons and muscles (a “neuromuscular junction”), and between neurons and other biological structures, including internal organs, endocrine glands, and the like. Synapses are specialized structures by which neurons transmit chemical or electrical signals to each other and to non-neuronal cells, muscles, tissues, and organs. Compounds that affect neural connectivity may do so by establishing new synapses (*e.g.*, by neurite outgrowth or neurite activation) or by altering or remodeling existing synapses. Synaptic remodeling refers to changes in the quality, intensity or type of signal transmitted at particular synapses.

[0058] As used herein, the term “neuropathy” refers to a disorder characterized by altered function and/or structure of motor, sensory, and autonomic neurons of the nervous system, initiated or caused by a primary lesion or other dysfunction of the nervous system. Patterns of peripheral neuropathy include polyneuropathy, mononeuropathy, mononeuritis multiplex and autonomic neuropathy. The most common form is (symmetrical) peripheral polyneuropathy, which mainly affects the feet and legs. A radiculopathy involves spinal nerve roots, but if peripheral nerves are also involved the term radiculoneuropathy is used. The form of neuropathy may be further broken down by cause, or the size of predominant fiber involvement, *e.g.*, large fiber or small fiber peripheral neuropathy. Central neuropathic pain can occur in spinal cord injury, multiple sclerosis, and some strokes, as well as fibromyalgia. Neuropathy may be associated with varying combinations of weakness, autonomic changes and sensory changes. Loss of muscle bulk or fasciculations, a particular fine twitching of muscle may also be seen. Sensory symptoms encompass loss of sensation and “positive” phenomena including pain. Neuropathies are associated with a variety of disorders, including diabetes (*e.g.*, diabetic neuropathy), fibromyalgia, multiple sclerosis, and *herpes zoster* infection, as well as with spinal cord injury and other types of nerve damage.

[0059] As used herein, the term “Alzheimer's disease” refers to a degenerative brain disorder characterized clinically by progressive memory deficits, confusion, behavioral problems, inability to care for oneself, gradual physical deterioration and, ultimately, death. Histologically, the disease is characterized by neuritic plaques, found primarily in the association cortex, limbic system and basal ganglia. The major constituent of these plaques is amyloid beta peptide (A β), which is the cleavage product of beta amyloid precursor protein (β APP or APP). APP is a type I transmembrane glycoprotein that contains a large ectopic N-terminal domain, a transmembrane domain and a small cytoplasmic C-terminal tail. Alternative splicing of the transcript of the single APP gene on chromosome 21 results in several isoforms that differ in the number of

amino acids. A β appears to have a central role in the neuropathology of Alzheimer's disease. Familial forms of the disease have been linked to mutations in APP and the presenilin genes (Tanzi *et al.*, 1996, *Neurobiol. Dis.*, 3:159-168; Hardy, 1996, *Ann. Med.*, 28:255-258). Diseased-linked mutations in these genes result in increased production of the 42-amino acid form of A β , the predominant form found in amyloid plaques. Mitochondrial dysfunction has also been reported to be an important component of Alzheimer's disease (Bubber *et al.*, Mitochondrial abnormalities in Alzheimer brain: Mechanistic Implications, *Ann Neurol.*, 2005, 57(5), 695-703; Wang *et al.*, "Insights into amyloid- β -induced mitochondrial dysfunction in Alzheimer disease," *Free Radical Biology & Medicine*, 2007, 43, 1569-1573; Swerdlow *et al.*, "Mitochondria in Alzheimer's disease," *Int. Rev. Neurobiol.* 2002, 53, 341-385; and Reddy *et al.*, "Are mitochondria critical in the pathogenesis of Alzheimer's disease?," *Brain Res Rev.* 2005, 49(3), 618-32). It has been proposed that mitochondrial dysfunction has a causal relationship with neuronal function (including neurotransmitter synthesis and secretion) and viability. Compounds which stabilize mitochondria may therefore have a beneficial impact on Alzheimer's patients.

[0060] As used herein, the term "Huntington's disease" refers to a fatal neurological disorder characterized clinically by symptoms such as involuntary movements, cognition impairment or loss of cognitive function and a wide spectrum of behavioral disorders. Common motor symptoms associated with Huntington's disease include chorea (involuntary writhing and spasming), clumsiness, and progressive loss of the abilities to walk, speak (*e.g.*, exhibiting slurred speech) and swallow. Other symptoms of Huntington's disease can include cognitive symptoms such as loss of intellectual speed, attention and short-term memory and/or behavioral symptoms that can span the range of changes in personality, depression, irritability, emotional outbursts and apathy. Clinical symptoms typically appear in the fourth or fifth decade of life. Huntington's disease is a devastating and often protracted illness, with death usually occurring approximately 10-20 years after the onset of symptoms. Huntington's disease is inherited through a mutated or abnormal gene encoding an abnormal protein called the mutant huntingtin protein; the mutated huntingtin protein produces neuronal degeneration in many different regions of the brain. The degeneration focuses on neurons located in the basal ganglia, structures deep within the brain that control many important functions including coordinating movement, and on neurons on the outer surface of the brain or cortex, which controls thought, perception and memory.

[0061] “Amyotrophic lateral sclerosis” or “ALS” is used herein to denote a progressive neurodegenerative disease that affects upper motor neurons (motor neurons in the brain) and/or lower motor neurons (motor neurons in the spinal cord) and results in motor neuron death. As used herein, the term “ALS” includes all of the classifications of ALS known in the art, including, but not limited to classical ALS (typically affecting both lower and upper motor neurons), Primary Lateral Sclerosis (PLS, typically affecting only the upper motor neurons), Progressive Bulbar Palsy (PBP or Bulbar Onset, a version of ALS that typically begins with difficulties swallowing, chewing and speaking), Progressive Muscular Atrophy (PMA, typically affecting only the lower motor neurons) and familial ALS (a genetic version of ALS).

[0062] The term “Parkinson’s disease” as used herein refers to any medical condition wherein an individual experiences one or more symptoms associated with Parkinson’s disease, such as without limitation one or more of the following symptoms: rest tremor, cogwheel rigidity, bradykinesia, postural reflex impairment, symptoms having good response to 1-dopa treatment, the absence of prominent oculomotor palsy, cerebellar or pyramidal signs, amyotrophy, dyspraxia and/or dysphasia. In a specific embodiment, the present invention is utilized for the treatment of a dopaminergic dysfunction-related disorder. In a specific embodiment, the individual with Parkinson’s disease has a mutation or polymorphism in a synuclein, parkin or NURR1 nucleic acid that is associated with Parkinson’s disease. In one embodiment, the individual with Parkinson’s disease has defective or decreased expression of a nucleic acid or a mutation in a nucleic acid that regulates the development and/or survival of dopaminergic neurons.

[0063] As used herein, the term “canine cognitive dysfunction syndrome,” or “CCDS” refers to an age-related deterioration of mental function typified by multiple cognitive impairments that affect an afflicted canine’s ability to function normally. The decline in cognitive ability that is associated with CCDS cannot be completely attributed to a general medical condition such as neoplasia, infection, sensory impairment, or organ failure. Diagnosis of CCDS in canines, such as dogs, is generally a diagnosis of exclusion, based on thorough behavior and medical histories and the presence of clinical symptoms of CCDS that are unrelated to other disease processes. Owner observation of age-related changes in behavior is a practical means used to detect the possible onset of CCDS in aging domestic dogs. A number of laboratory cognitive tasks may be used to help diagnose CCDS, while blood counts, chemistry panels and urinalysis can be used to rule out other underlying diseases that could mimic the clinical symptoms of CCDS. Symptoms

of CCDS include memory loss, which in domestic dogs may be manifested by disorientation and/or confusion, decreased or altered interaction with family members and/or greeting behavior, changes in sleep-wake cycle, decreased activity level, and loss of house training or frequent, inappropriate elimination. A canine suffering from CCDS may exhibit one or more of the following clinical or behavioral symptoms: decreased appetite, decreased awareness of surroundings, decreased ability to recognize familiar places, people or other animals, decreased hearing, decreased ability to climb up and down stairs, decreased tolerance to being alone, development of compulsive behavior or repetitive behaviors or habits, circling, tremors or shaking, disorientation, decreased activity level, abnormal sleep wake cycles, loss of house training, decreased or altered responsiveness to family members, and decreased or altered greeting behavior. CCDS can dramatically affect the health and well-being of an afflicted canine. Moreover, the companionship offered by a pet with CCDS can become less rewarding as the severity of the disease increases and its symptoms become more severe.

[0064] As used herein, the term “age-associated memory impairment” or “AAMI” refers to a condition that may be identified as GDS stage 2 on the global deterioration scale (GDS) (Reisberg, *et al.* (1982) *Am. J. Psychiatry* 139: 1136-1139) which differentiates the aging process and progressive degenerative dementia in seven major stages. The first stage of the GDS is one in which individuals at any age have neither subjective complaints of cognitive impairment nor objective evidence of impairment. These GDS stage 1 individuals are considered normal. The second stage of the GDS applies to those generally elderly persons who complain of memory and cognitive functioning difficulties such as not recalling names as well as they could five or ten years previously or not recalling where they have placed things as well as they could five or ten years previously. These subjective complaints appear to be very common in otherwise normal elderly individuals. AAMI refers to persons in GDS stage 2, who may differ neurophysiologically from elderly persons who are normal and free of subjective complaints, *e.g.*, GDS stage 1. For example, AAMI subjects have been found to have more electrophysiologic slowing on a computer analyzed EEG than GDS stage 1 elderly persons (Pritch, John, Ferris, Reisberg, *et al.* (1994) *Neurobiol. Aging* 15:85-90).

[0065] As used herein, the term “mild cognitive impairment” or “MCI” refers to a type of cognitive disorder characterized by a more pronounced deterioration in cognitive functions than is typical for normal age-related decline. As a result, elderly or aged patients with MCI have greater than normal difficulty performing complex daily tasks and learning, but without the

inability to perform normal social, everyday, and/or professional functions typical of patients with Alzheimer's disease, or other similar neurodegenerative disorders eventually resulting in dementia. MCI is characterized by subtle, clinically manifest deficits in cognition, memory, and functioning, amongst other impairments, which are not of sufficient magnitude to fulfill criteria for diagnosis of Alzheimer's disease or other dementia. MCI also encompasses injury-related MCI, defined herein as cognitive impairment resulting from certain types of injury, such as nerve injury (*e.g.*, battlefield injuries, including post-concussion syndrome, and the like), neurotoxic treatment (*i.e.*, adjuvant chemotherapy resulting in "chemo brain" and the like), and tissue damage resulting from physical injury or other neurodegeneration, which is separate and distinct from mild cognitive impairment resulting from stroke, ischemia, hemorrhagic insult, blunt force trauma, and the like.

[0066] As used herein, the term "traumatic brain injury" or "TBI" refers to a brain injury caused by a sudden trauma, such as a blow or jolt or a penetrating head injury, which disrupts the function or damages the brain. Symptoms of TBI can range from mild, moderate to severe and can significantly affect many cognitive (deficits of language and communication, information processing, memory, and perceptual skills), physical (ambulation, balance, coordination, fine motor skills, strength, and endurance), and psychological skills.

[0067] "Neuronal death mediated ocular disease" intends an ocular disease in which death of the neuron is implicated in whole or in part. The disease may involve death of photoreceptors. The disease may involve retinal cell death. The disease may involve ocular nerve death by apoptosis. Particular neuronal death mediated ocular diseases include but are not limited to macular degeneration, glaucoma, retinitis pigmentosa, congenital stationary night blindness (Oguchi disease), childhood onset severe retinal dystrophy, Leber congenital amaurosis, Bardet-Biedle syndrome, Usher syndrome, blindness from an optic neuropathy, Leber's hereditary optic neuropathy, color blindness and Hansen-Larson-Berg syndrome.

[0068] As used herein, the term "macular degeneration" includes all forms and classifications of macular degeneration known in the art, including, but not limited to diseases that are characterized by a progressive loss of central vision associated with abnormalities of Bruch's membrane, the choroid, the neural retina and/or the retinal pigment epithelium. The term thus encompasses disorders such as age-related macular degeneration (ARMD) as well as rarer, earlier-onset dystrophies that in some cases can be detected in the first decade of life. Other

maculopathies include North Carolina macular dystrophy, Sorsby's fundus dystrophy, Stargardt's disease, pattern dystrophy, Best disease, and Malattia Leventinese.

[0069] As used herein, the term “autism” refers to a brain development disorder that impairs social interaction and communication and causes restricted and repetitive behavior, typically appearing during infancy or early childhood. The cognitive and behavioral defects are thought to result in part from altered neural connectivity. Autism encompasses related disorders sometimes referred to as “autism spectrum disorder,” as well as Asperger syndrome and Rett syndrome.

[0070] As used herein, the term “nerve injury” or “nerve damage” refers to physical damage to nerves, such as avulsion injury (*e.g.*, where a nerve or nerves have been torn or ripped) or spinal cord injury (*e.g.*, damage to white matter or myelinated fiber tracts that carry sensation and motor signals to and from the brain). Spinal cord injury can occur from many causes, including physical trauma (*e.g.*, car accidents, sports injuries, and the like), tumors impinging on the spinal column, developmental disorders, such as spina bifida, and the like.

[0071] As used herein, the term “myasthenia gravis” or “MG” refers to a non-cognitive neuromuscular disorder caused by immune-mediated loss of acetylcholine receptors at neuromuscular junctions of skeletal muscle. Clinically, MG typically appears first as occasional muscle weakness in approximately two-thirds of patients, most commonly in the extraocular muscles. These initial symptoms eventually worsen, producing drooping eyelids (ptosis) and/or double vision (diplopia), often causing the patient to seek medical attention. Eventually, many patients develop general muscular weakness that may fluctuate weekly, daily, or even more frequently. Generalized MG often affects muscles that control facial expression, chewing, talking, swallowing, and breathing; before recent advances in treatment, respiratory failure was the most common cause of death.

[0072] As used herein, the term “Guillain-Barré syndrome” refers to a non-cognitive disorder in which the body's immune system attacks part of the peripheral nervous system. The first symptoms of this disorder include varying degrees of weakness or tingling sensations in the legs. In many instances the weakness and abnormal sensations spread to the arms and upper body. These symptoms can increase in intensity until certain muscles cannot be used at all and, when severe, the patient is almost totally paralyzed. In these cases the disorder is life threatening – potentially interfering with breathing and, at times, with blood pressure or heart rate – and is

considered a medical emergency. Most patients, however, recover from even the most severe cases of Guillain-Barré syndrome, although some continue to have a certain degree of weakness.

[0073] As used herein, the term “multiple sclerosis” or “MS” refers to an autoimmune condition in which the immune system attacks the central nervous system (CNS), leading to demyelination of neurons. It may cause numerous symptoms, many of which are non-cognitive, and often progresses to physical disability. MS affects the areas of the brain and spinal cord known as the white matter. White matter cells carry signals between the grey matter areas, where the processing is done, and the rest of the body. More specifically, MS destroys oligodendrocytes which are the cells responsible for creating and maintaining a fatty layer, known as the myelin sheath, which helps the neurons carry electrical signals. MS results in a thinning or complete loss of myelin and, less frequently, the cutting (transection) of the neuron's extensions or axons. When the myelin is lost, the neurons can no longer effectively conduct their electrical signals. Almost any neurological symptom can accompany the disease. MS takes several forms, with new symptoms occurring either in discrete attacks (relapsing forms) or slowly accumulating over time (progressive forms). Most people are first diagnosed with relapsing-remitting MS but develop secondary-progressive MS (SPMS) after a number of years. Between attacks, symptoms may go away completely, but permanent neurological problems often persist, especially as the disease advances.

[0074] As used herein, the term “schizophrenia” refers to a chronic, mental disorder characterized by one or more positive symptoms (*e.g.*, delusions and hallucinations) and/or negative symptoms (*e.g.*, blunted emotions and lack of interest) and/or disorganized symptoms (*e.g.*, disorganized thinking and speech or disorganized perception and behavior). Schizophrenia as used herein includes all forms and classifications of schizophrenia known in the art, including, but not limited to catatonic type, hebephrenic type, disorganized type, paranoid type, residual type or undifferentiated type schizophrenia and deficit syndrome and/or those described in American Psychiatric Association: *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition, Washington D.C., 2000 or in International Statistical Classification of Diseases and Related Health Problems, or otherwise known to those of skill in the art.

[0075] “Cognitive impairment associated with schizophrenia” or “CIAS” includes neuropsychological deficits in attention, working memory, verbal learning, and problem solving. These deficits are believed to be linked to impairment in functional status (*e.g.*, social behavior, work performance, and activities of daily living).

[0076] As used herein “geroprotective activity” or “geroprotector” means a biological activity that slows down ageing and/or prolongs life and/or increases or improves the quality of life via a decrease in the amount and/or the level of intensity of pathologies or conditions that are not life-threatening but are associated with the aging process and which are typical for elderly people. Pathologies or conditions that are not life-threatening but are associated with the aging process include such pathologies or conditions as loss of sight (cataract), deterioration of the dermatohairy integument (alopecia), and an age-associated decrease in weight due to the death of muscular and/or fatty cells.

[0077] As used herein, attention-deficit hyperactivity disorder (ADHD) is the most common child neuropsychiatric condition present in school-aged children, affecting about 5-8% of this population. ADHD refers to a chronic disorder that initially manifests in childhood and is characterized by hyperactivity, impulsivity, and/or inattention. ADHD is characterized by persistent patterns of inattention and/or impulsivity-hyperactivity that are much more extreme than is observed in individuals at the same developmental level or stage. There is considerable evidence, from family and twin studies, that ADHD has a significant genetic component. This disorder is thought to be due to an interaction of environmental and genetic factors. ADHD includes all known types of ADHD. For example, *Diagnostic & Statistical Manual for Mental Disorders* (DSM-IV) identifies three subtypes of ADHD: (1) ADHD, Combined Type which is characterized by both inattention and hyperactivity-impulsivity symptoms; (2) ADHD, Predominantly Inattentive Type which is characterized by inattention but not hyperactivity-impulsivity symptoms; and (3) ADHD, Predominantly Hyperactive-Impulsive Type which is characterized by Hyperactivity-impulsivity but not inattention symptoms.

[0078] As used herein, attention-deficit disorder (ADD) refers to a disorder in processing neural stimuli that is characterized by distractibility and impulsivity that can result in inability to control behavior and can impair an individual’s social, academic, or occupational function and development. ADD may be diagnosed by known methods, which may include observing behavior and diagnostic interview techniques.

[0079] As used herein “allergic disease” refers to a disorder of the immune system which is characterized by excessive activation of mast cells and basophils and production of IgE immunoglobulins, resulting in an extreme inflammatory response. It represents a form of hypersensitivity to an environmental substance known as allergen and is an acquired disease. Common allergic reactions include eczema, hives, hay fever, asthma, food allergies, and

reactions to the venom of stinging insects such as wasps and bees. Allergic reactions are accompanied by an excessive release of histamines, and can thus be treated with antihistaminic agents.

[0080] As used herein, by “combination therapy” is meant a therapy that includes two or more different compounds. Thus, in one aspect, a combination therapy comprising a compound detailed herein and another compound is provided. In some variations, the combination therapy optionally includes one or more pharmaceutically acceptable carriers or excipients, non-pharmaceutically active compounds, and/or inert substances. In various embodiments, treatment with a combination therapy may result in an additive or even synergistic (*e.g.*, greater than additive) result compared to administration of a single compound of the invention alone. In some embodiments, a lower amount of each compound is used as part of a combination therapy compared to the amount generally used for individual therapy. Preferably, the same or greater therapeutic benefit is achieved using a combination therapy than by using any of the individual compounds alone. In some embodiments, the same or greater therapeutic benefit is achieved using a smaller amount (*e.g.*, a lower dose or a less frequent dosing schedule) of a compound in a combination therapy than the amount generally used for individual compound or therapy. Preferably, the use of a small amount of compound results in a reduction in the number, severity, frequency, and/or duration of one or more side-effects associated with the compound.

[0081] As used herein, the term “effective amount” intends such amount of a compound of the invention which in combination with its parameters of efficacy and toxicity, as well as based on the knowledge of the practicing specialist should be effective in a given therapeutic form. As is understood in the art, an effective amount may be in one or more doses, *e.g.*, a single dose or multiple doses may be required to achieve the desired treatment endpoint. An effective amount may be considered in the context of administering one or more therapeutic agents, and a single agent may be considered to be given in an effective amount if, in conjunction with one or more other agents, a desirable or beneficial result may be or is achieved. Suitable doses of any of the co-administered compounds may optionally be lowered due to the combined action (*e.g.*, additive or synergistic effects) of the compounds.

[0082] As used herein, “unit dosage form” refers to physically discrete units, suitable as unit dosages, each unit containing a predetermined quantity of active ingredient calculated to produce the desired therapeutic effect in association with the required pharmaceutical carrier. Unit dosage forms may contain a single or a combination therapy.

[0083] As used herein, the term “controlled release” refers to a drug-containing formulation or fraction thereof in which release of the drug is not immediate, *e.g.*, with a “controlled release” formulation, administration does not result in immediate release of the drug into an absorption pool. The term encompasses depot formulations designed to gradually release the drug compound over an extended period of time. Controlled release formulations can include a wide variety of drug delivery systems, generally involving mixing the drug compound with carriers, polymers or other compounds having the desired release characteristics (*e.g.*, pH-dependent or non-pH-dependent solubility, different degrees of water solubility, and the like) and formulating the mixture according to the desired route of delivery (*e.g.*, coated capsules, implantable reservoirs, injectable solutions containing biodegradable capsules, and the like).

[0084] As used herein, by “pharmaceutically acceptable” or “pharmacologically acceptable” is meant a material that is not biologically or otherwise undesirable, *e.g.*, the material may be incorporated into a pharmaceutical composition administered to a patient without causing any significant undesirable biological effects or interacting in a deleterious manner with any of the other components of the composition in which it is contained. Pharmaceutically acceptable carriers or excipients have preferably met the required standards of toxicological and manufacturing testing and/or are included on the Inactive Ingredient Guide prepared by the U.S. Food and Drug administration.

[0085] “Pharmaceutically acceptable salts” are those salts which retain at least some of the biological activity of the free (non-salt) compound and which can be administered as drugs or pharmaceuticals to an individual. Such salts, for example, include: (1) acid addition salts, formed with inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, and the like; or formed with organic acids such as acetic acid, oxalic acid, propionic acid, succinic acid, maleic acid, tartaric acid and the like; (2) salts formed when an acidic proton present in the parent compound either is replaced by a metal ion, *e.g.*, an alkali metal ion, an alkaline earth ion, or an aluminum ion; or coordinates with an organic base. Acceptable organic bases include ethanolamine, diethanolamine, triethanolamine and the like. Acceptable inorganic bases include aluminum hydroxide, calcium hydroxide, potassium hydroxide, sodium carbonate, sodium hydroxide, and the like. Further examples of pharmaceutically acceptable salts include those listed in Berge *et al.*, *Pharmaceutical Salts*, *J. Pharm. Sci.* 1977 Jan; 66(1):1-19. Pharmaceutically acceptable salts can be prepared *in situ* in the manufacturing process, or by separately reacting a purified compound of the invention in its

free acid or base form with a suitable organic or inorganic base or acid, respectively, and isolating the salt thus formed during subsequent purification. It should be understood that a reference to a pharmaceutically acceptable salt includes the solvent addition forms or crystal forms thereof, particularly solvates or polymorphs. Solvates contain either stoichiometric or non-stoichiometric amounts of a solvent, and are often formed during the process of crystallization. Hydrates are formed when the solvent is water, or alcoholates are formed when the solvent is alcohol. Polymorphs include the different crystal packing arrangements of the same elemental composition of a compound. Polymorphs usually have different X-ray diffraction patterns, infrared spectra, melting points, density, hardness, crystal shape, optical and electrical properties, stability, and solubility. Various factors such as the recrystallization solvent, rate of crystallization, and storage temperature may cause a single crystal form to dominate.

[0086] The term “excipient” as used herein means an inert or inactive substance that may be used in the production of a drug or pharmaceutical, such as a tablet containing a compound of the invention as an active ingredient. Various substances may be embraced by the term excipient, including without limitation any substance used as a binder, disintegrant, coating, compression/encapsulation aid, cream or lotion, lubricant, solutions for parenteral administration, materials for chewable tablets, sweetener or flavoring, suspending/gelling agent, or wet granulation agent. Binders include, *e.g.*, carbomers, povidone, xanthan gum, etc.; coatings include, *e.g.*, cellulose acetate phthalate, ethylcellulose, gellan gum, maltodextrin, enteric coatings, etc.; compression/encapsulation aids include, *e.g.*, calcium carbonate, dextrose, fructose dc (dc = “directly compressible”), honey dc, lactose (anhydrate or monohydrate; optionally in combination with aspartame, cellulose, or microcrystalline cellulose), starch dc, sucrose, etc.; disintegrants include, *e.g.*, croscarmellose sodium, gellan gum, sodium starch glycolate, etc.; creams or lotions include, *e.g.*, maltodextrin, carrageenans, etc.; lubricants include, *e.g.*, magnesium stearate, stearic acid, sodium stearyl fumarate, etc.; materials for chewable tablets include, *e.g.*, dextrose, fructose dc, lactose (monohydrate, optionally in combination with aspartame or cellulose), etc.; suspending/gelling agents include, *e.g.*, carrageenan, sodium starch glycolate, xanthan gum, etc.; sweeteners include, *e.g.*, aspartame, dextrose, fructose dc, sorbitol, sucrose dc, etc.; and wet granulation agents include, *e.g.*, calcium carbonate, maltodextrin, microcrystalline cellulose, etc.

[0087] “Alkyl” refers to and includes saturated linear, branched, or cyclic univalent hydrocarbon structures and combinations thereof. Particular alkyl groups are those having 1 to 20 carbon atoms (a “C₁-C₂₀ alkyl”). More particular alkyl groups are those having 1 to 8 carbon atoms (a “C₁-C₈ alkyl”). When an alkyl residue having a specific number of carbons is named, all geometric isomers having that number of carbons are intended to be encompassed and described; thus, for example, “butyl” is meant to include *n*-butyl, *sec*-butyl, *iso*-butyl, *tert*-butyl and cyclobutyl; “propyl” includes *n*-propyl, *iso*-propyl and cyclopropyl. This term is exemplified by groups such as methyl, *t*-butyl, *n*-heptyl, octyl, cyclohexylmethyl, cyclopropyl and the like. Cycloalkyl is a subset of alkyl and can consist of one ring, such as cyclohexyl, or multiple rings, such as adamantyl. A cycloalkyl comprising more than one ring may be fused, spiro or bridged, or combinations thereof. A preferred cycloalkyl is a saturated cyclic hydrocarbon having from 3 to 13 annular carbon atoms. A more preferred cycloalkyl is a saturated cyclic hydrocarbon having from 3 to 7 annular carbon atoms (a “C₃-C₇ cycloalkyl”). A saturated cyclic hydrocarbon having from 3 to 8 annular carbon atoms is also embraced (a “C₃-C₈ cycloalkyl”). Examples of cycloalkyl groups include adamantyl, decahydronaphthalenyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and the like.

[0088] “Alkylene” refers to the same residues as alkyl, but having bivalency. Examples of alkylene include methylene (-CH₂-), ethylene (-CH₂CH₂-), propylene (-CH₂CH₂CH₂-), butylene (-CH₂CH₂CH₂CH₂-) and the like.

[0089] “Alkenyl” refers to an unsaturated hydrocarbon group having at least one site of olefinic unsaturation (*i.e.*, having at least one moiety of the formula C=C) and preferably having from 2 to 10 carbon atoms and more preferably 2 to 8 carbon atoms. Examples of alkenyl include but are not limited to -CH₂-CH=CH-CH₃ and -CH₂-CH₂-cyclohexenyl, where the ethyl group of the latter example can be attached to the cyclohexenyl moiety at any available position on the ring.

[0090] Cycloalkenyl is a subset of alkenyl and can consist of one ring, such as cyclohexyl, or multiple rings, such as norbornenyl. A more preferred cycloalkenyl is an unsaturated cyclic hydrocarbon having from 3 to 8 annular carbon atoms (a “C₃-C₈ cycloalkenyl”). Examples of cycloalkenyl groups include cyclopropenyl, cyclobutenyl, cyclopentenyl, cyclohexenyl and the like.

[0091] “Alkynyl” refers to an unsaturated hydrocarbon group having at least one site of acetylenic unsaturation (*i.e.*, having at least one moiety of the formula C≡C) and preferably

having from 2 to 10 carbon atoms and more preferably 3 to 8 carbon atoms. Alkynyl groups having 2 to 8 carbon atoms, and the like, is embraced.

[0092] “Substituted alkyl” refers to an alkyl group having from 1 to 5 substituents including, but not limited to, substituents such as alkoxy, substituted alkoxy, acyl, acyloxy, carbonylalkoxy, acylamino, substituted or unsubstituted amino, aminoacyl, aminocarbonylamino, aminocarbonyloxy, aryl, substituted aryl, heteroaryl, substituted heteroaryl, aryloxy, substituted aryloxy, cyano, halo, hydroxyl, nitro, carboxyl, thiol, thioalkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aralkyl, aminosulfonyl, sulfonylamino, sulfonyl, oxo, carbonylalkylenealkoxy and the like.

[0093] “Substituted alkenyl” refers to alkenyl group having from 1 to 5 substituents including, but not limited to, substituents such as alkoxy, substituted alkoxy, acyl, acyloxy, carbonylalkoxy, acylamino, substituted or unsubstituted amino, aminoacyl, aminocarbonylamino, aminocarbonyloxy, aryl, substituted aryl, heteroaryl, substituted heteroaryl, aryloxy, substituted aryloxy, cyano, halo, hydroxyl, nitro, carboxyl, thiol, thioalkyl, substituted or unsubstituted alkyl, substituted or unsubstituted alkynyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aralkyl, aminosulfonyl, sulfonylamino, sulfonyl, oxo, carbonylalkylenealkoxy and the like.

[0094] “Substituted alkynyl” refers to alkynyl groups having from 1 to 5 substituents including, but not limited to, groups such as alkoxy, substituted alkoxy, acyl, acyloxy, carbonylalkoxy, acylamino, substituted or unsubstituted amino, aminoacyl, aminocarbonylamino, aminocarbonyloxy, aryl, substituted aryl, heteroaryl, substituted heteroaryl, aryloxy, substituted aryloxy, cyano, halo, hydroxyl, nitro, carboxyl, thiol, thioalkyl, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aralkyl, aminosulfonyl, sulfonylamino, sulfonyl, oxo, carbonylalkylenealkoxy and the like.

[0095] “Acyl” refers to the groups H-C(O)-, alkyl-C(O)-, substituted alkyl-C(O)-, alkenyl-C(O)-, substituted alkenyl-C(O)-, alkynyl-C(O)-, substituted alkynyl-C(O)-, aryl-C(O)-, substituted aryl-C(O)-, heteroaryl-C(O)-, substituted heteroaryl-C(O)-, heterocyclic-C(O)-, and substituted heterocyclic-C(O)-, wherein alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic and substituted heterocyclic are as defined herein.

[0096] “Acyloxy” refers to the groups H-C(O)O-, alkyl-C(O)O-, substituted alkyl-C(O)O-, alkenyl-C(O)O-, substituted alkenyl-C(O)O-, alkynyl-C(O)O-, substituted alkynyl-C(O)O-, aryl-C(O)O-, substituted aryl-C(O)O-, heteroaryl-C(O)O-, substituted heteroaryl-C(O)O-, heterocyclic-C(O)O-, and substituted heterocyclic-C(O)O-, wherein alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic and substituted heterocyclic are as defined herein.

[0097] In one variation, acyloxy is a cycloalkyl-C(O)O-, substituted cycloalkyl-C(O)O-moiety.

[0098] “Heterocycle”, “heterocyclic”, or “heterocyclyl” refers to a saturated or an unsaturated non-aromatic group having a single ring or multiple condensed rings, and having from 1 to 10 annular carbon atoms and from 1 to 4 annular heteroatoms, such as nitrogen, sulfur or oxygen. A heterocycle comprising more than one ring may be fused, spiro or bridged, or any combination thereof. In fused ring systems, one or more of the rings can be aryl or heteroaryl. A heterocycle having more than one ring where at least one ring is aromatic may be connected to the parent structure at either a non-aromatic ring position or at an aromatic ring position. In one variation, a heterocycle having more than one ring where at least one ring is aromatic is connected to the parent structure at a non-aromatic ring position.

[0099] “Substituted heterocyclic” or “substituted heterocyclyl” refers to a heterocycle group which is substituted with from 1 to 3 substituents including, but not limited to, substituents such as alkoxy, substituted alkoxy, acyl, acyloxy, carbonylalkoxy, acylamino, substituted or unsubstituted amino, aminoacyl, aminocarbonylamino, aminocarbonyloxy, aryl, substituted aryl, heteroaryl, substituted heteroaryl, aryloxy, substituted aryloxy, cyano, halo, hydroxyl, nitro, carboxyl, thiol, thioalkyl, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted aralkyl, aminosulfonyl, sulfonylamino, sulfonyl, oxo, carbonylalkylenealkoxy and the like. In one variation, a substituted heterocycle is a heterocycle substituted with an additional ring, wherein the additional ring may be aromatic or non-aromatic.

[0100] “Aryl” or “Ar” refers to an unsaturated aromatic carbocyclic group having a single ring (*e.g.*, phenyl) or multiple condensed rings (*e.g.*, naphthyl or anthryl) which condensed rings may or may not be aromatic. In one variation, the aryl group contains from 6 to 14 annular carbon atoms. An aryl group having more than one ring where at least one ring is non-aromatic may be

connected to the parent structure at either an aromatic ring position or at a non-aromatic ring position. In one variation, an aryl group having more than one ring where at least one ring is non-aromatic is connected to the parent structure at an aromatic ring position.

[0101] “Heteroaryl” or “HetAr” refers to an unsaturated aromatic carbocyclic group having from 2 to 10 annular carbon atoms and at least one annular heteroatom, including but not limited to heteroatoms such as nitrogen, oxygen and sulfur. A heteroaryl group may have a single ring (*e.g.*, pyridyl, furyl) or multiple condensed rings (*e.g.*, indolizinyl, benzothienyl) which condensed rings may or may not be aromatic. A heteroaryl group having more than one ring where at least one ring is non-aromatic may be connected to the parent structure at either an aromatic ring position or at a non-aromatic ring position. In one variation, a heteroaryl group having more than one ring where at least one ring is non-aromatic is connected to the parent structure at an aromatic ring position.

[0102] “Substituted aryl” refers to an aryl group having 1 to 5 substituents including, but not limited to, groups such as alkoxy, substituted alkoxy, acyl, acyloxy, carbonylalkoxy, acylamino, substituted or unsubstituted amino, aminoacyl, aminocarbonylamino, aminocarbonyloxy, heteroaryl, substituted heteroaryl, aryloxy, substituted aryloxy, cyano, halo, hydroxyl, nitro, carboxyl, thiol, thioalkyl, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aralkyl, aminosulfonyl, sulfonylamino, sulfonyl, oxo, carbonylalkylenealkoxy and the like.

[0103] In one variation, a substituted aryl comprises an aryl group substituted by an aryl and/or substituted aryl substituent.

[0104] “Substituted heteroaryl” refers to a heteroaryl group having 1 to 5 substituents including, but not limited to, groups such as alkoxy, substituted alkoxy, acyl, acyloxy, carbonylalkoxy, acylamino, substituted or unsubstituted amino, aminoacyl, aminocarbonylamino, aminocarbonyloxy, aryl, substituted aryl, heteroaryl, substituted heteroaryl, aryloxy, substituted aryloxy, cyano, halo, hydroxyl, nitro, carboxyl, thiol, thioalkyl, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aralkyl, aminosulfonyl, sulfonylamino, sulfonyl, oxo, carbonylalkylenealkoxy and the like.

[0105] In one variation, a substituted heteroaryl comprises a heteroaryl group substituted by a heteroaryl and/or substituted heteroaryl substituent.

[0106] “Aralkyl” refers to a residue in which an aryl moiety is attached to an alkyl residue and wherein the aralkyl group may be attached to the parent structure at either the aryl or the alkyl residue. Preferably, an aralkyl is connected to the parent structure via the alkyl moiety. A “substituted aralkyl” refers to a residue in which an aryl moiety is attached to a substituted alkyl residue and wherein the aralkyl group may be attached to the parent structure at either the aryl or the alkyl residue.

[0107] In one variation, an aralkyl is a fused ring system where at least one cycloalkyl moiety is fused with at least one aryl moiety.

[0108] When an aralkyl is connected to the parent structure via the alkyl moiety, it may also be referred to as an “alkaryl”. More particular alkaryl groups are those having 1 to 3 carbon atoms in the alkyl moiety (a “C₁-C₃ alkaryl”).

[0109] “Alkoxy” refers to the group alkyl-O-, which includes, by way of example, methoxy, ethoxy, n-propoxy, iso-propoxy, n-butoxy, tert-butoxy, sec-butoxy, n-pentoxy, n-hexoxy, 1,2-dimethylbutoxy, and the like. Similarly, alkenyloxy refers to the group “alkenyl-O-” and alkynyloxy refers to the group “alkynyl-O-”. “Substituted alkoxy” refers to the group substituted alkyl-O.

[0110] “Unsubstituted amino” refers to the group -NH₂.

[0111] “Substituted amino” refers to the group -NR_aR_b, where either (a) each R_a and R_b group is independently selected from the group consisting of H, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic, substituted heterocyclic, provided that both R_a and R_b groups are not H; or (b) R_a and R_b are joined together with the nitrogen atom to form a heterocyclic or substituted heterocyclic ring.

[0112] “Acylamino” refers to the group -C(O)NR_aR_b where R_a and R_b are independently selected from the group consisting of H, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic, substituted heterocyclic or R_a and R_b groups can be joined together with the nitrogen atom to form a heterocyclic or substituted heterocyclic ring.

[0113] “Aminocarbonylalkoxy” refers to the group -NR_aC(O)OR_b where each R_a and R_b group is independently selected from the group consisting of H, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic and substituted heterocyclic.

[0114] “Aminoacyl” refers to the group $-NR_aC(O)R_b$ where each R_a and R_b group is independently selected from the group consisting of H, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic or substituted heterocyclic. Preferably, R_a is H or alkyl.

[0115] “Aminosulfonyl” refers to the groups $-NRSO_2$ -alkyl, $-NRSO_2$ substituted alkyl, $-NRSO_2$ -alkenyl, $-NRSO_2$ -substituted alkenyl, $-NRSO_2$ -alkynyl, $-NRSO_2$ -substituted alkynyl, $-NRSO_2$ -aryl, $-NRSO_2$ -substituted aryl, $-NRSO_2$ -heteroaryl, $-NRSO_2$ -substituted heteroaryl, $-NRSO_2$ -heterocyclic, and $-NRSO_2$ -substituted heterocyclic, where R is H or alkyl and wherein alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic and substituted heterocyclic are as defined herein.

[0116] In one variation, an aminosulfonyl is $-NRSO_2$ -cycloalkyl or $-NRSO_2$ -substituted cycloalkyl.

[0117] “Sulfonylamino” refers to the groups $-SO_2NH_2$, $-SO_2NR$ -alkyl, $-SO_2NR$ -substituted alkyl, $-SO_2NR$ -alkenyl, $-SO_2NR$ -substituted alkenyl, $-SO_2NR$ -alkynyl, $-SO_2NR$ -substituted alkynyl, $-SO_2NR$ -aryl, $-SO_2NR$ -substituted aryl, $-SO_2NR$ -heteroaryl, $-SO_2NR$ -substituted heteroaryl, $-SO_2NR$ -heterocyclic, and $-SO_2NR$ -substituted heterocyclic, where R is H or alkyl, or $-SO_2NR_2$, where the two R groups are taken together and with the nitrogen atom to which they are attached to form a heterocyclic or substituted heterocyclic ring.

[0118] “Sulfonyl” refers to the groups $-SO_2$ -alkyl, $-SO_2$ -substituted alkyl, $-SO_2$ -alkenyl, $-SO_2$ -substituted alkenyl, $-SO_2$ -alkynyl, $-SO_2$ -substituted alkynyl, $-SO_2$ -aryl, $-SO_2$ -substituted aryl, $-SO_2$ -heteroaryl, $-SO_2$ -substituted heteroaryl, $-SO_2$ -heterocyclic, and $-SO_2$ -substituted heterocyclic.

[0119] “Carbonylalkylenealkoxy” refers to the group $-C(=O)-(CH_2)_n-OR$ where R is a substituted or unsubstituted alkyl and n is an integer from 1 to 100, more preferably n is an integer from 1 to 10 or 1 to 5.

[0120] “Halo” or “halogen” refers to elements of the Group 17 series having atomic number 9 to 85. Preferred halo groups include the radicals of fluorine, chlorine, bromine and iodine. Where a residue is substituted with more than one halogen, it may be referred to by using a prefix corresponding to the number of halogen moieties attached, *e.g.*, dihaloaryl, dihaloalkyl, trihaloaryl etc. refer to aryl and alkyl substituted with two (“di”) or three (“tri”) halo groups, which may be but are not necessarily the same halogen; thus 4-chloro-3-fluorophenyl is within

the scope of dihaloaryl. An alkyl group in which each H is replaced with a halo group is referred to as a “perhaloalkyl.” A preferred perhaloalkyl group is trifluoroalkyl ($-\text{CF}_3$). Similarly, “perhaloalkoxy” refers to an alkoxy group in which a halogen takes the place of each H in the hydrocarbon making up the alkyl moiety of the alkoxy group. An example of a perhaloalkoxy group is trifluoromethoxy ($-\text{OCF}_3$).

[0121] “Carbonyl” refers to the group $\text{C}=\text{O}$.

[0122] “Cyano” refers to the group $-\text{CN}$.

[0123] “Oxo” refers to the moiety $=\text{O}$.

[0124] “Nitro” refers to the group $-\text{NO}_2$.

[0125] “Thioalkyl” refers to the groups $-\text{S-alkyl}$.

[0126] “Alkylsulfonylamino” refers to the groups $-\text{R}^1\text{SO}_2\text{NR}_a\text{R}_b$ where R_a and R_b are independently selected from the group consisting of H, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic, substituted heterocyclic, or the R_a and R_b groups can be joined together with the nitrogen atom to form a heterocyclic or substituted heterocyclic ring and R^1 is an alkyl group.

[0127] “Carbonylalkoxy” refers to as used herein refers to the groups $-\text{C}(\text{O})\text{O-alkyl}$, $-\text{C}(\text{O})\text{O-substituted alkyl}$, $-\text{C}(\text{O})\text{O-aryl}$, $-\text{C}(\text{O})\text{O-substituted aryl}$, $-\text{C}(\text{O})\text{O-alkenyl}$, $-\text{C}(\text{O})\text{O-substituted alkenyl}$, $-\text{C}(\text{O})\text{O-alkynyl}$, $-\text{C}(\text{O})\text{O-substituted alkynyl}$, $-\text{C}(\text{O})\text{O-heteroaryl}$, $-\text{C}(\text{O})\text{O-substituted heteroaryl}$, $-\text{C}(\text{O})\text{O-heterocyclic}$ or $-\text{C}(\text{O})\text{O-substituted heterocyclic}$.

[0128] “Geminal” refers to the relationship between two moieties that are attached to the same atom. For example, in the residue $-\text{CH}_2-\text{CHR}^1\text{R}^2$, R^1 and R^2 are geminal and R^1 may be referred to as a geminal R group to R^2 .

[0129] “Vicinal” refers to the relationship between two moieties that are attached to adjacent atoms. For example, in the residue $-\text{CHR}^1-\text{CH}_2\text{R}^2$, R^1 and R^2 are vicinal and R^1 may be referred to as a vicinal R group to R^2 .

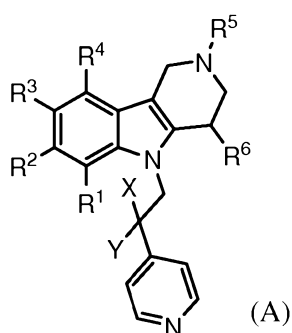
[0130] A composition of “substantially pure” compound means that the composition contains no more than 15% or preferably no more than 10% or more preferably no more than 5% or even more preferably no more than 3% and most preferably no more than 1% impurity, which impurity may be the compound in a different stereochemical form. For instance, a composition of substantially pure S compound means that the composition contains no more than 15% or no

more than 10% or no more than 5% or no more than 3% or no more than 1% of the R form of the compound.

Compounds of the Invention

[0131] Compounds according to the invention are detailed herein, including in the Brief Summary of the Invention and the appended claims. The invention includes the use of all of the compounds described herein, including any and all stereoisomers, salts and solvates of the compounds described herein, as well as methods of making such compounds.

[0132] Compounds of the formula (A) are provided:



wherein:

R¹, R², R³ and R⁴ are independently H, halo, C₁-C₈ unsubstituted alkyl or C₁-C₈ unsubstituted alkoxy, provided that R³ is other than methyl or chloro when R¹, R² and R⁴ are each H and X is OH and Y is methyl;

R⁵ is unsubstituted C₁-C₈ alkyl or a C₁-C₈ alkyl substituted with a perhaloalkyl moiety;

R⁶ is H or an unsubstituted C₁-C₈ alkyl;

X is OH, C₁-C₈ alkyl or is taken together with Y to form a cyclopropyl moiety; and

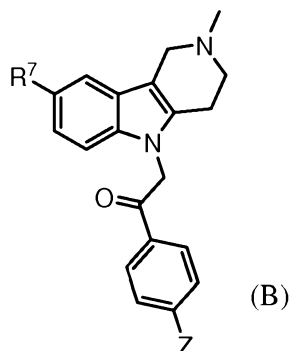
Y is H, C₁-C₈ alkyl or is taken together with X to form a cyclopropyl moiety,

or a salt thereof, such as a pharmaceutically acceptable salt thereof, or solvate of the foregoing.

[0133] In a particular variation of formula (A), R⁶ is H. In one variation of formula (A), R¹ is H, halo or C₁-C₈ unsubstituted alkoxy; R² is H; R³ is H, halo, C₁-C₈ unsubstituted alkyl or C₁-C₈ unsubstituted alkoxy, provided that R³ is other than methyl or chloro when R¹, R² and R⁴ are each H and X is OH and Y is methyl; R⁴ is H or halo; R⁵ is methyl; R⁶ is H or methyl; X is OH, C₁-C₈ alkyl or is taken together with Y to form a cyclopropyl moiety and Y is H, C₁-C₈ alkyl or is taken together with X to form a cyclopropyl moiety. In another variation of formula (A), at least two of R¹, R², R³ and R⁴ are halo (*e.g.*, when R² and R³ are chloro). In another variation of

formula (A), X is OH and Y is H, methyl, ethyl or isopropyl. In a further variation of formula (A), R^1 , R^2 and R^4 are H. In another variation of formula (A), three of R^1 , R^2 , R^3 and R^4 are H and one is methyl, methoxy, isopropyl, chloro or fluoro.

[0134] Also provided are compounds of the formula (B):



wherein:

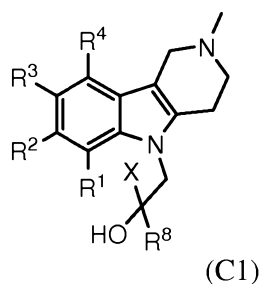
R^7 is H, hydroxyl, nitro, cyano, halo, C_1 - C_8 perhaloalkyl, substituted or unsubstituted C_1 - C_8 alkyl, substituted or unsubstituted C_2 - C_8 alkenyl, substituted or unsubstituted C_2 - C_8 alkynyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, C_1 - C_8 perhaloalkoxy, C_1 - C_8 alkoxy, aryloxy, carboxyl, carbonylalkoxy, thiol, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aralkyl, thioalkyl, substituted or unsubstituted amino, acylamino, aminoacyl, aminocarbonylamino, aminocarbonyloxy, aminosulfonyl, sulfonylamino, sulfonyl, carbonylalkylenealkoxy, alkylsulfonylamino or acyl; and

Z is H, halo or C_1 - C_8 alkyl,

or a salt thereof, such as a pharmaceutically acceptable salt thereof, or solvate of the foregoing.

[0135] In one variation of formula (B), R^7 is unsubstituted C_1 - C_8 alkyl or halo. In another variation of formula (B), Z is H or halo. In a further variation of formula (B), R^7 is an unsubstituted C_1 - C_8 alkyl or halo and Z is H or halo. In a particular variation, R^7 is methyl or chloro and Z is H, chloro or fluoro.

[0136] Compounds of the formula (C1) are provided:



wherein:

R^1 , R^2 , R^3 and R^4 are independently H, halo, C_1 - C_8 unsubstituted alkyl or C_1 - C_8 unsubstituted alkoxy;

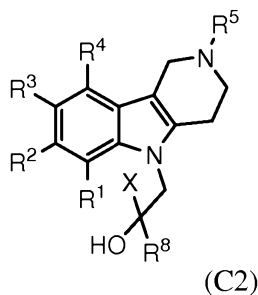
R^8 is a substituted or unsubstituted aryl or a substituted or unsubstituted heteroaryl; and

X is a C_4 - C_6 unsubstituted alkyl,

or a salt thereof, such as a pharmaceutically acceptable salt thereof, or solvate of the foregoing.

[0137] In one variation of formula (C1), R^1 , R^2 , R^3 and R^4 are as defined for formula (A).

[0138] Compounds of the formula (C2) are also provided:



wherein:

R^1 , R^2 , R^3 and R^4 are independently H, halo, C_1 - C_8 unsubstituted alkyl or C_1 - C_8 unsubstituted alkoxy;

R^5 is C_1 - C_6 unsubstituted alkyl or CF_3 ;

R^8 is a substituted or unsubstituted aryl or a substituted or unsubstituted heteroaryl; and

X is a C_4 - C_6 unsubstituted n-alkyl or cycloalkyl or a C_3 - C_6 unsubstituted branched alkyl,

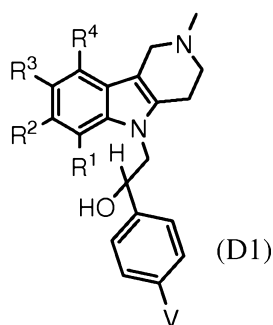
or a salt thereof, such as a pharmaceutically acceptable salt thereof, or solvate of the foregoing.

[0139] In one variation of formula (C1) or (C2), R^1 , R^2 and R^4 are each H and R^3 is an unsubstituted C_1 - C_8 alkyl (*e.g.*, methyl) or halo (*e.g.*, chloro). In another variation of formula (C1) or (C2), X is cyclohexyl, cyclobutyl, n-butyl or iso-propyl. In a particular variation of

formula (C1) or (C2), R^1 , R^2 and R^4 are each H; R^3 is an unsubstituted C_1 - C_8 alkyl or halo and X is cyclohexyl, cyclobutyl, n-butyl or iso-propyl. In a further variation of formula (C1) or (C2), R^8 is a substituted aryl or an unsubstituted heteroaryl. In one aspect, R^8 of formula (C1) or (C2) is a substituted phenyl or an unsubstituted pyridyl. In a particular aspect, R^8 of formula (C1) or (C2) is 4-halo-phenyl or 4-pyridyl. In another variation of formula (C1) or (C2), R^1 , R^2 and R^4 are each H; R^3 is an unsubstituted C_1 - C_8 alkyl or halo; X is cyclohexyl, cyclobutyl, n-butyl and R^8 is a substituted phenyl. In another variation of formula (C1) or (C2), R^1 , R^2 and R^4 are each H; R^3 is an unsubstituted C_1 - C_8 alkyl or halo; X is isopropyl and R^8 is an unsubstituted pyridyl.

[0140] In another variation of formula (C2), R^1 , R^2 , R^3 and R^4 are as defined for formula (A), R^5 is CH_3 or CF_3 ; R^8 is a substituted or unsubstituted aryl or a substituted or unsubstituted heteroaryl; and X is a C_1 - C_6 unsubstituted alkyl.

[0141] Compounds of the formula (D1) are also provided:



wherein:

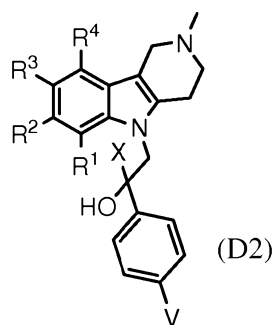
R^1 , R^2 , R^3 and R^4 are independently H, halo, C_1 - C_8 unsubstituted alkyl or C_1 - C_8 unsubstituted alkoxy; and

V is a halo,

or a salt thereof, such as a pharmaceutically acceptable salt thereof, or solvate of the foregoing.

[0142] In one variation of (D1), R^1 , R^2 , R^3 and R^4 are as defined for formula (A).

[0143] Compounds of the formula (D2) are also provided:



wherein:

R^1 , R^2 , R^3 and R^4 are independently H, halo, C_1 - C_8 unsubstituted alkyl or C_1 - C_8 unsubstituted alkoxy;

X is H or a C_1 - C_3 unsubstituted alkyl; and

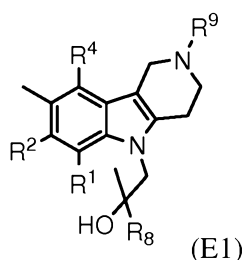
V is a halo,

or a salt thereof, such as a pharmaceutically acceptable salt thereof, or solvate of the foregoing.

[0144] In one variation of formula (D1) or (D2), R^1 , R^2 and R^4 are H and R^3 is an unsubstituted C_1 - C_8 alkyl such as methyl. In another variation of formula (D1) or (D2), V is fluoro.

[0145] In another variation of formula (D2), R^1 , R^2 , R^3 and R^4 are independently H, halo, C_1 - C_8 unsubstituted alkyl or C_1 - C_8 unsubstituted alkoxy or are as defined for formula (A); X is a C_1 - C_3 unsubstituted alkyl; and V is a halo.

[0146] Compounds of the formula (E1) are also detailed herein:



wherein:

R^1 , R^2 , R^3 and R^4 are independently H, halo, C_1 - C_8 unsubstituted alkyl or C_1 - C_8 unsubstituted alkoxy; and

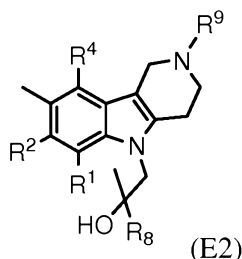
R^8 is 6-pyrimidyl, 3-methyl-4-pyridyl or a phenyl substituted either: (i) with at least one alkoxy or hydroxyl group or (ii) with at least two halo groups;

R^9 is an unsubstituted C_1 - C_3 alkyl;

or a salt thereof, such as a pharmaceutically acceptable salt thereof, or solvate of the foregoing.

[0147] In one variation of (E1), R^1 , R^2 , R^3 and R^4 are as defined for formula (A).

[0148] Compounds of the formula (E2) are also detailed herein:



wherein:

R^1 , R^2 , R^3 and R^4 are independently H, halo, C_1 - C_8 unsubstituted alkyl or C_1 - C_8 unsubstituted alkoxy;

R^8 is 6-pyrimidyl, 2-pyrazinyl, 3-methyl-4-pyridyl or a phenyl substituted either: (i) with at least one alkoxy or hydroxyl group or (ii) with at least two halo groups; and

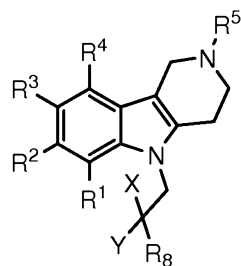
R^9 is an unsubstituted C_1 - C_3 alkyl;

or a salt thereof, such as a pharmaceutically acceptable salt thereof, or solvate of the foregoing.

[0149] In one variation of formula (E1) or (E2), R^1 , R^2 and R^4 are each H. In another variation of formula (E1) or (E2), R^9 is methyl. In a further variation of formula (E1) or (E2), R^1 , R^2 and R^4 are each H and R^9 is methyl. In another variation of formula (E1) or (E2), R^8 is a phenyl substituted with at least one unsubstituted C_1 - C_8 alkoxy group such as methoxy. In one aspect of formula (E1) or (E2), R^1 , R^2 and R^4 are each H and R^8 is a methoxy-substituted phenyl. In another aspect of formula (E1) or (E2), R^9 is methyl and R^8 is a methoxy or hydroxyl-substituted phenyl. In another variation, R^8 is a phenyl substituted with at least two halo groups and R^1 , R^2 and R^4 are each H.

[0150] In another variation of formula (E2), R^1 , R^2 and R^4 are as defined for formula (A); R^8 is 6-pyrimidyl, 2-pyrazinyl, 3-methyl-4-pyridyl or a phenyl substituted either: (i) with at least one alkoxy or hydroxyl group or (ii) with at least two halo groups; and R^9 is methyl.

[0151] Also provided are compounds of the formula (F1):



(F1)

wherein:

R^1 , R^2 , R^3 and R^4 are independently H, halo, C_1 - C_8 unsubstituted alkyl or C_1 - C_8 unsubstituted alkoxy;

R^5 is ζ -CH₂CH₂CF₃, ζ -CH₂CH₂CN or ζ -(CH₂)_TOH where T is 3 or 4;

X is H or OH;

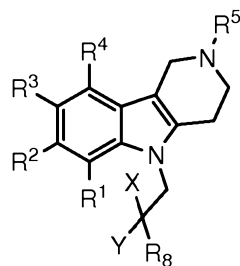
Y is H or C_1 - C_8 alkyl; and

R^8 is a substituted or unsubstituted heteroaryl,

or a salt thereof, such as a pharmaceutically acceptable salt thereof, or solvate of the foregoing.

[0152] In one variation of (F1), R^1 , R^2 , R^3 and R^4 are as defined for formula (A).

[0153] Also provided are compounds of the formula (F2):



(F2)

wherein:

R^1 , R^2 , R^3 and R^4 are independently H, halo, C_1 - C_8 unsubstituted alkyl or C_1 - C_8 unsubstituted alkoxy;

R^5 is ζ -cyclopropyl, ζ -CH₂CH₂CF₃, ζ -CH₂CH₂CN or ζ -(CH₂)_TOH where T is 3 or 4

X is H or OH;

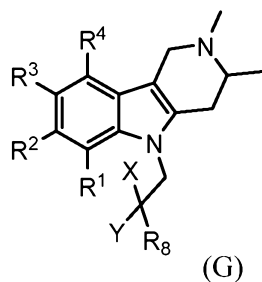
Y is H or C₁-C₈ alkyl; and

R⁸ is a substituted or unsubstituted heteroaryl,

or a salt thereof, such as a pharmaceutically acceptable salt thereof, or solvate of the foregoing.

[0154] In one variation of formula (F1) or (F2), R¹, R² and R⁴ are H. In another variation of formula (F1) or (F2), R³ is unsubstituted C₁-C₈ alkyl. In another variation of formula (F1) or (F2), R¹, R² and R⁴ are H and R³ is unsubstituted C₁-C₈ alkyl. In another variation of formula (F1) or (F2), R⁸ is a substituted or unsubstituted pyridyl. When R⁸ is an unsubstituted pyridyl, it may be bound to the parent structure at any available position, *e.g.*, 4-pyridyl. When R⁸ is a substituted pyridyl, in one aspect the pyridyl is substituted with an unsubstituted C₁-C₈ alkyl such as methyl. When R⁸ is a substituted pyridyl, it may be bound to the parent structure at any available ring position, *e.g.*, 6-methyl-3-pyridyl. In a particular variation of formula (F1) or (F2), R¹, R² and R⁴ are H; R³ is unsubstituted C₁-C₈ alkyl and R⁸ is a substituted or unsubstituted pyridyl. In a further variation of formula (F1) or (F2), X and Y are both H. For example, in one aspect a compound is of the formula (F1) or (F2) where R¹, R² and R⁴ are H; R³ is unsubstituted C₁-C₈ alkyl and R⁸ is a substituted or unsubstituted pyridyl and X and Y are both H.

[0155] Compounds of the formula (G) are also detailed herein:



wherein:

R¹, R², R³ and R⁴ are independently H, halo, C₁-C₈ unsubstituted alkyl or C₁-C₈ unsubstituted alkoxy;

R³ is methyl or chloro, provided that R³ is methyl when R⁸ is a substituted heteroaryl;

X is H or OH;

Y is H or C₁-C₈ alkyl; and

R⁸ is a substituted or unsubstituted heteroaryl,

or a salt thereof, such as a pharmaceutically acceptable salt thereof, or solvate of the foregoing.

[0156] In one variation of formula (G), R^1 , R^2 , R^3 and R^4 are as defined for formula (A).

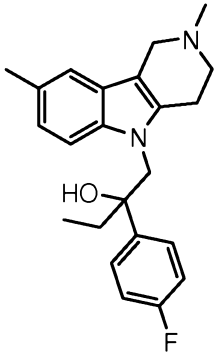
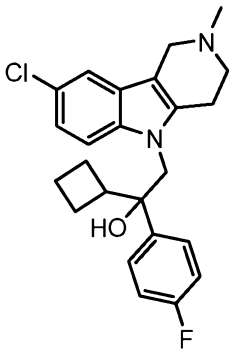
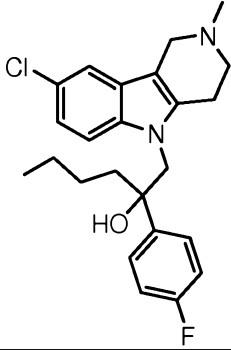
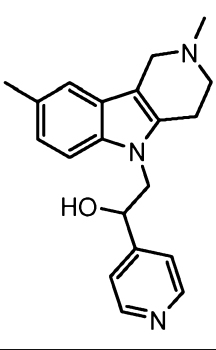
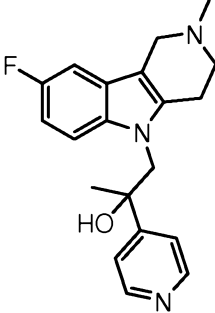
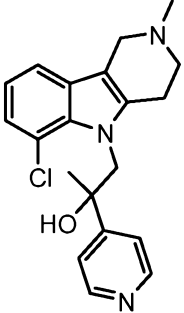
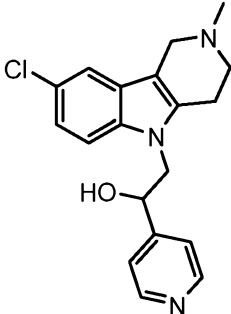
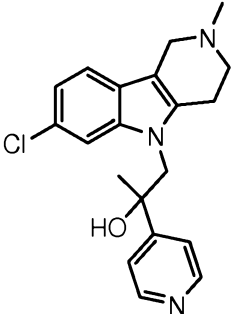
[0157] In one aspect of formula (G), R^1 , R^2 and R^4 are each H. In another aspect of formula (G), X is H and Y is an unsubstituted C_1 - C_8 alkyl. In another aspect of formula (G), X and Y are both H. In a particular variation of formula (G), R^1 , R^2 and R^4 are each H and either (i) X and Y are both H or (ii) X is H and Y is an unsubstituted C_1 - C_8 alkyl such as methyl. In a particular variation, R^8 is a substituted or unsubstituted pyridyl. In a specific variation of formula (G), R^8 is a substituted or unsubstituted pyridyl and either (i) X and Y are both H or (ii) X is H and Y is an unsubstituted C_1 - C_8 alkyl.

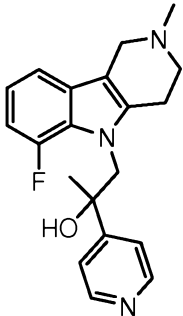
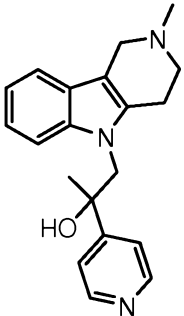
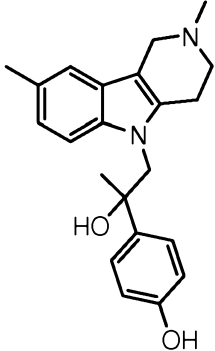
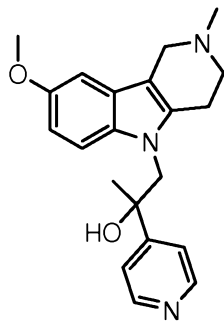
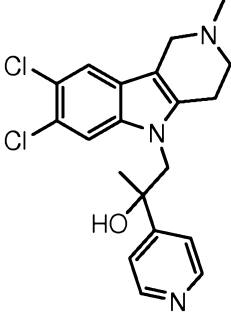
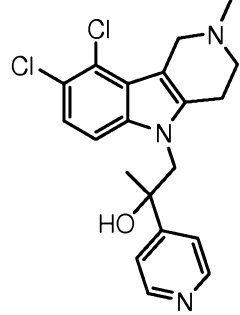
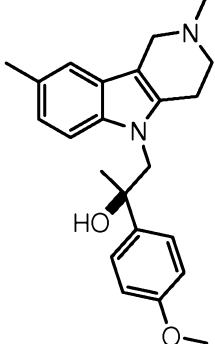
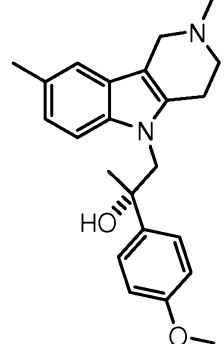
[0158] Additional compounds are detailed herein.

[0159] Examples of compounds according to the invention are depicted in Table 1. The compounds depicted may be present as salts even if salts are not depicted and it is understood that the invention embraces all salts and solvates of the compounds depicted here, as well as the non-salt and non-solvate form of the compound, as is well understood by the skilled artisan.

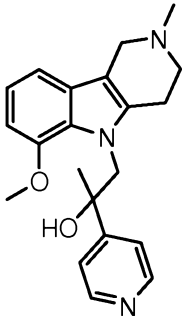
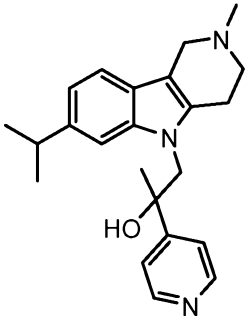
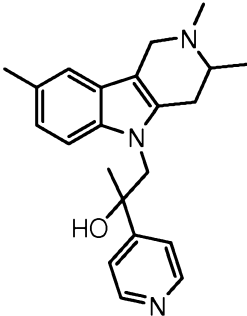
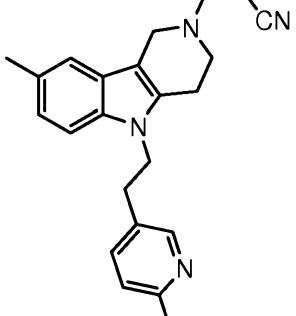
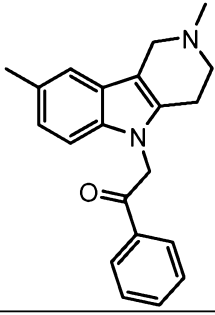
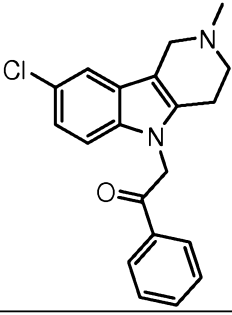
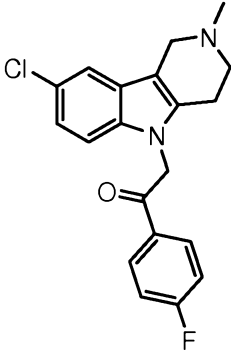
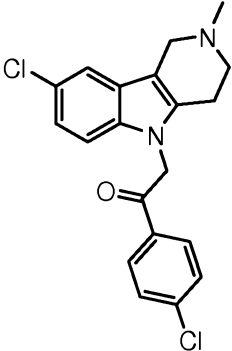
Table 1. Representative Compounds According to the Invention.

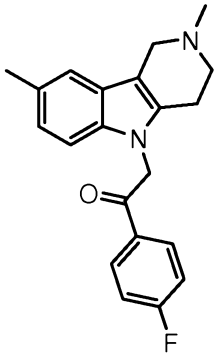
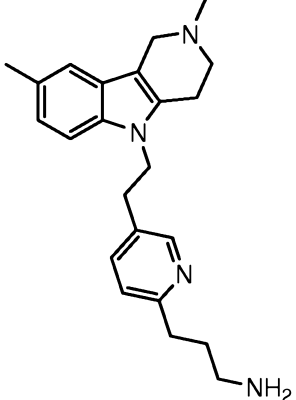
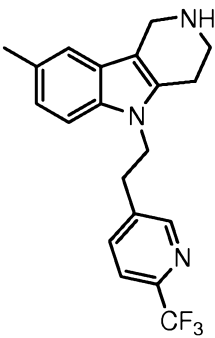
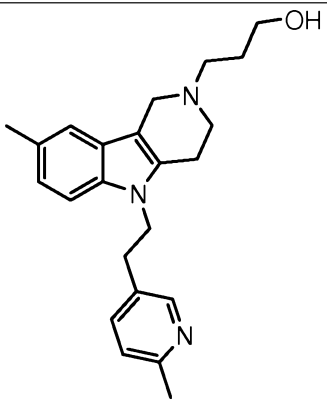
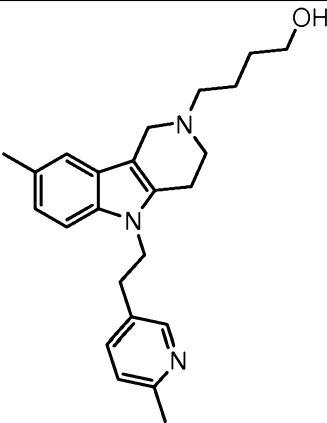
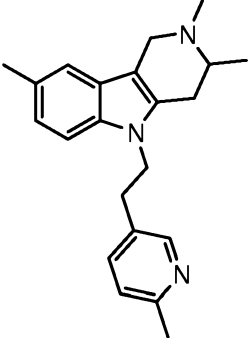
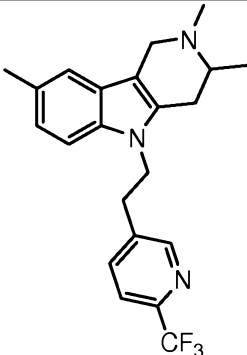
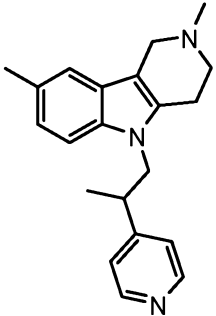
Compound #	Compound Structure	Compound #	Compound Structure
1-1		1-2	
1-3		1-4	

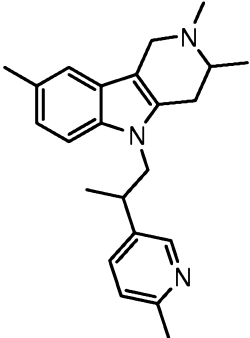
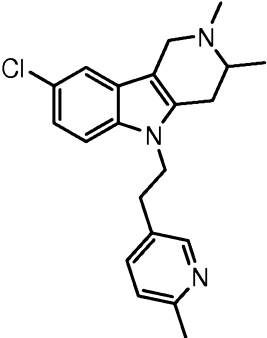
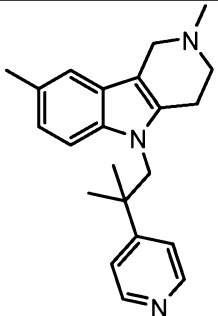
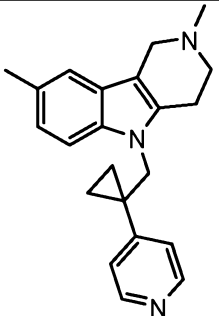
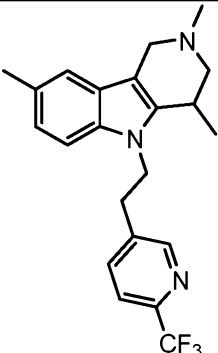
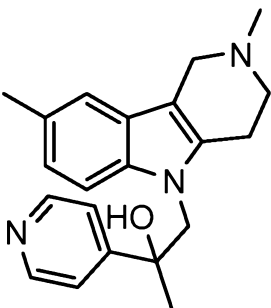
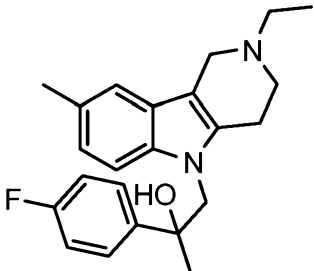
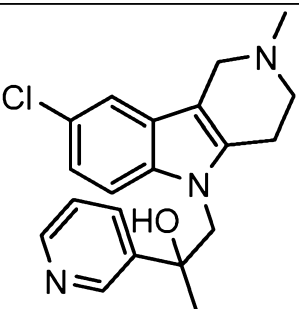
Compound #	Compound Structure	Compound #	Compound Structure
1-5		1-6	
1-7		1-8	
1-9		1-10	
1-11		1-12	

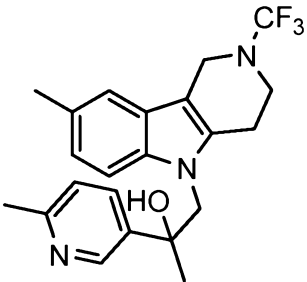
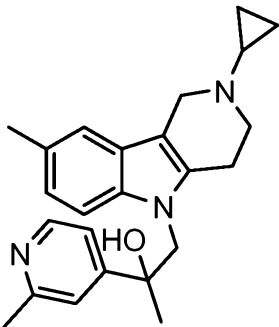
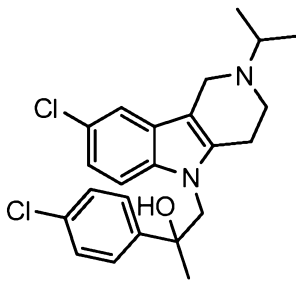
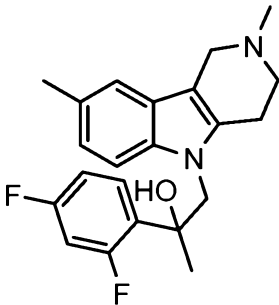
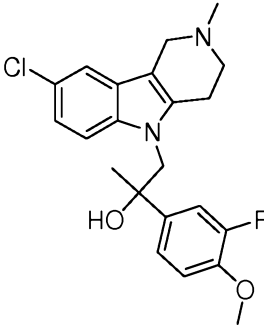
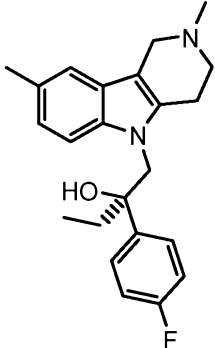
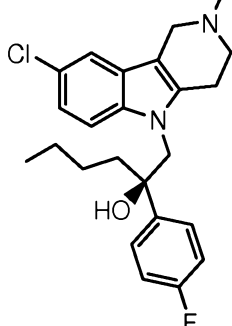
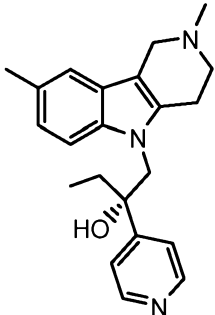
Compound #	Compound Structure	Compound #	Compound Structure
1-13		1-14	
1-15		1-16	
1-17		1-18	
1-19		1-20	

Compound #	Compound Structure	Compound #	Compound Structure
1-21		1-22	
1-23		1-24	
1-25		1-26	
1-27		1-28	
1-29		1-30	

Compound #	Compound Structure	Compound #	Compound Structure
1-31		1-32	
1-33		1-34	
1-35		1-36	
1-37		1-38	

Compound #	Compound Structure	Compound #	Compound Structure
1-39		1-40	
1-41		1-42	
1-43		1-44	
1-45		1-46	

Compound #	Compound Structure	Compound #	Compound Structure
1-47		1-48	
1-49		1-50	
1-51		1-52	
1-53		1-54	

Compound #	Compound Structure	Compound #	Compound Structure
1-55		1-56	
1-57		1-58	
1-59		1-60	
1-61		1-62	

Compound #	Compound Structure	Compound #	Compound Structure
1-63		1-64	
1-65		1-66	
1-67			

Table 1. Compound Names.

Compound #	Compound Name
1-1	1-Cyclohexyl-2-(2,8-dimethyl-3,4-dihydro-1H-pyrido[4,3-b]indol-5(2H)-yl)-1-(4-fluorophenyl)ethanol
1-2	2-(2,8-Dimethyl-3,4-dihydro-1H-pyrido[4,3-b]indol-5(2H)-yl)-1-(4-fluorophenyl)ethanol
1-3	1-(2,8-Dimethyl-3,4-dihydro-1H-pyrido[4,3-b]indol-5(2H)-yl)-2-(3-fluoro-4-methoxyphenyl)propan-2-ol

Compound #	Compound Name
1-4	1-(2,8-dimethyl-3,4-dihydro-1H-pyrido[4,3-b]indol-5(2H)-yl)-2-(4-methoxyphenyl)propan-2-ol
1-5	1-(2,8-dimethyl-3,4-dihydro-1H-pyrido[4,3-b]indol-5(2H)-yl)-2-(4-fluorophenyl)butan-2-ol
1-6	2-(8-Chloro-2-methyl-3,4-dihydro-1H-pyrido[4,3-b]indol-5(2H)-yl)-1-cyclobutyl-1-(4-fluorophenyl)ethanol
1-7	1-(8-chloro-2-methyl-3,4-dihydro-1H-pyrido[4,3-b]indol-5(2H)-yl)-2-(4-fluorophenyl)hexan-2-ol
1-8	2-(2,8-Dimethyl-3,4-dihydro-1H-pyrido[4,3-b]indol-5(2H)-yl)-1-(pyridine-4-yl)ethanol
1-9	1-(8-Fluoro-2-methyl-3,4-dihydro-1H-pyrido[4,3-b]indol-5(2H)-yl)-2-(pyridine-4-yl)propan-2-ol
1-10	1-(6-Chloro-2-methyl-3,4-dihydro-1H-pyrido[4,3-b]indol-5(2H)-yl)-2-(pyridine-4-yl)propan-2-ol
1-11	2-(8-Chloro-2-methyl-3,4-dihydro-1H-pyrido[4,3-b]indol-5(2H)-yl)-1-(pyridine-4-yl)ethanol
1-12	1-(7-Chloro-2-methyl-3,4-dihydro-1H-pyrido[4,3-b]indol-5(2H)-yl)-2-(pyridine-4-yl)propan-2-ol
1-13	1-(6-Fluoro-2-methyl-3,4-dihydro-1H-pyrido[4,3-b]indol-5(2H)-yl)-2-(pyridine-4-yl)propan-2-ol
1-14	1-(2-Methyl-3,4-dihydro-1H-pyrido[4,3-b]indol-5(2H)-yl)-2-(pyridine-4-yl)propan-2-ol
1-15	4-(1-(2,8-Dimethyl-3,4-dihydro-1H-pyrido[4,3-b]indol-5(2H)-yl)-2-hydroxypropan-2-yl)phenol
1-16	1-(8-Methoxy-2-methyl-3,4-dihydro-1H-pyrido[4,3-b]indol-5(2H)-yl)-2-(pyridine-4-yl)propan-2-ol
1-17	1-(7,8-Dichloro-2-methyl-3,4-dihydro-1H-pyrido[4,3-b]indol-5(2H)-yl)-2-(pyridine-4-yl)propan-2-ol
1-18	1-(8,9-Dichloro-2-methyl-3,4-dihydro-1H-pyrido[4,3-b]indol-5(2H)-yl)-2-(pyridine-4-yl)propan-2-ol

Compound #	Compound Name
1-19	(R)-1-(2,8-Dimethyl-3,4-dihydro-1H-pyrido[4,3-b]indol-5(2H)-yl)-2-(4-methoxyphenyl)propan-2-ol
1-20	(S)-1-(2,8-Dimethyl-3,4-dihydro-1H-pyrido[4,3-b]indol-5(2H)-yl)-2-(4-methoxyphenyl)propan-2-ol
1-21	1-(8-Chloro-2-methyl-3,4-dihydro-1H-pyrido[4,3-b]indol-5(2H)-yl)-3-methyl-2-(pyridine-4-yl)butan-2-ol
1-22	1-(2,8-Dimethyl-3,4-dihydro-1H-pyrido[4,3-b]indol-5(2H)-yl)-3-methyl-2-(pyridine-4-yl)butan-2-ol
1-23	1-(8-Chloro-2-methyl-3,4-dihydro-1H-pyrido[4,3-b]indol-5(2H)-yl)-2-(pyridine-4-yl)butan-2-ol
1-24	1-(2,8-Dimethyl-3,4-dihydro-1H-pyrido[4,3-b]indol-5(2H)-yl)-2-(pyridine-4-yl)butan-2-ol
1-25	1-(2,8-Dimethyl-3,4-dihydro-1H-pyrido[4,3-b]indol-5(2H)-yl)-2-(pyrimidin-4-yl)propan-2-ol
1-26	1-(8-Chloro-2-methyl-3,4-dihydro-1H-pyrido[4,3-b]indol-5(2H)-yl)-2-(pyrimidin-4-yl)propan-2-ol
1-27	1-(8-Chloro-2-methyl-3,4-dihydro-1H-pyrido[4,3-b]indol-5(2H)-yl)-2-(pyrazin-2-yl)propan-2-ol
1-28	1-(2,8-Dimethyl-3,4-dihydro-1H-pyrido[4,3-b]indol-5(2H)-yl)-2-(pyrazin-2-yl)propan-2-ol
1-29	1-(8-Methyl-2-(2,2,2-trifluoroethyl)-3,4-dihydro-1H-pyrido[4,3-b]indol-5(2H)-yl)-2-(pyridine-4-yl)propan-2-ol
1-30	1-(2-Cyclopropyl-8-methyl-3,4-dihydro-1H-pyrido[4,3-b]indol-5(2H)-yl)-2-(pyridine-4-yl)propan-2-ol
1-31	1-(6-Methoxy-2-methyl-3,4-dihydro-1H-pyrido[4,3-b]indol-5(2H)-yl)-2-(pyridine-4-yl)propan-2-ol
1-32	1-(7-Isopropyl-2-methyl-3,4-dihydro-1H-pyrido[4,3-b]indol-5(2H)-yl)-2-(pyridine-4-yl)propan-2-ol
1-33	2-(Pyridin-4-yl)-1-(2,3,8-trimethyl-3,4-dihydro-1H-pyrido[4,3-b]indol-5(2H)-yl)propan-2-ol

Compound #	Compound Name
1-34	3-(8-Methyl-5-(2-(6-methylpyridin-3-yl)ethyl)-3,4-dihydro-1H-pyrido[4,3-b]indol-2(5H)-yl)propanenitrile
1-35	2-(2,8-Dimethyl-3,4-dihydro-1H-pyrido[4,3-b]indol-5(2H)-yl)-1-phenylethanone
1-36	2-(8-Chloro-2-methyl-3,4-dihydro-1H-pyrido[4,3-b]indol-5(2H)-yl)-1-phenylethanone
1-37	2-(8-Chloro-2-methyl-3,4-dihydro-1H-pyrido[4,3-b]indol-5(2H)-yl)-1-(4-fluorophenyl)ethanone
1-38	2-(8-Chloro-2-methyl-3,4-dihydro-1H-pyrido[4,3-b]indol-5(2H)-yl)-1-(4-chlorophenyl)ethanone
1-39	2-(2,8-Dimethyl-3,4-dihydro-1H-pyrido[4,3-b]indol-5(2H)-yl)-1-(4-fluorophenyl)ethanone
1-40	3-(5-(2-(2,8-Dimethyl-3,4-dihydro-1H-pyrido[4,3-b]indol-5(2H)-yl)ethyl)pyridine-2-yl)propan-1-amine
1-41	8-Methyl-5-(2-(6-(trifluoromethyl)pyridine-3-yl)ethyl)-2,3,4,5-tetrahydro-1H-pyrido[4,3-b]indole
1-42	3-(8-Methyl-5-(2-(6-methylpyridin-3-yl)ethyl)-3,4-dihydro-1H-pyrido[4,3-b]indol-2(5H)-yl)propan-1-ol
1-43	4-(8-Methyl-5-(2-(6-methylpyridin-3-yl)ethyl)-3,4-dihydro-1H-pyrido[4,3-b]indol-2(5H)-yl)butan-1-ol
1-44	2,3,8-Trimethyl-5-(2-(6-methylpyridin-3-yl)ethyl)-2,3,4,5-tetrahydro-1H-pyrido[4,3-b]indole
1-45	2,3,8-Trimethyl-5-(2-(6-(trifluoromethyl)pyridine-3-yl)ethyl)-2,3,4,5-tetrahydro-1H-pyrido[4,3-b]indole
1-46	2,8-Dimethyl-5-(2-(pyridine-4-yl)propyl)-2,3,4,5-tetrahydro-1H-pyrido[4,3-b]indole
1-47	2,3,8-Trimethyl-5-(2-(6-methylpyridin-3-yl)propyl)-2,3,4,5-tetrahydro-1H-pyrido[4,3-b]indole
1-48	8-Chloro-2,3-dimethyl-5-(2-(6-methylpyridin-3-yl)ethyl)-2,3,4,5-tetrahydro-1H-pyrido[4,3-b]indole

Compound #	Compound Name
1-49	2,8-Dimethyl-5-(2-methyl-2-(pyridine-4-yl)propyl)-2,3,4,5-tetrahydro-1H-pyrido[4,3-b]indole
1-50	2,8-Dimethyl-5-((1-(pyridine-4-yl)cyclopropyl)methyl)-2,3,4,5-tetrahydro-1H-pyrido[4,3-b]indole
1-51	2,4,8-Trimethyl-5-(2-(6-(trifluoromethyl)pyridine-3-yl)ethyl)-2,3,4,5-tetrahydro-1H-pyrido[4,3-b]indole
1-52	1-(2,8-Dimethyl-3,4-dihydro-1H-pyrido[4,3-b]indol-5(2H)-yl)-2-(pyridine-4-yl)propan-2-ol
1-53	1-(2-Ethyl-8-methyl-3,4-dihydro-1H-pyrido[4,3-b]indol-5(2H)-yl)-2-(4-fluorophenyl)propan-2-ol
1-54	1-(8-Chloro-2-methyl-3,4-dihydro-1H-pyrido[4,3-b]indol-5(2H)-yl)-2-(pyridine-3-yl)propan-2-ol
1-55	1-(8-Methyl-2-(trifluoromethyl)-3,4-dihydro-1H-pyrido[4,3-b]indol-5(2H)-yl)-2-(6-methylpyridin-3-yl)propan-2-ol
1-56	1-(2-Cyclopropyl-8-methyl-3,4-dihydro-1H-pyrido[4,3-b]indol-5(2H)-yl)-2-(2-methylpyridin-4-yl)propan-2-ol
1-57	1-(8-Chloro-2-isopropyl-3,4-dihydro-1H-pyrido[4,3-b]indol-5(2H)-yl)-2-(4-chlorophenyl)propan-2-ol
1-58	2-(2,4-Difluorophenyl)-1-(2,8-dimethyl-3,4-dihydro-1H-pyrido[4,3-b]indol-5(2H)-yl)propan-2-ol
1-59	1-(8-Chloro-2-methyl-3,4-dihydro-1H-pyrido[4,3-b]indol-5(2H)-yl)-2-(3-fluoro-4-methoxyphenyl)propan-2-ol
1-60	(R)-1-(2,8-Dimethyl-3,4-dihydro-1H-pyrido[4,3-b]indol-5(2H)-yl)-2-(4-fluorophenyl)butan-2-ol
1-61	(R)-1-(8-Chloro-2-methyl-3,4-dihydro-1H-pyrido[4,3-b]indol-5(2H)-yl)-2-(4-fluorophenyl)hexan-2-ol
1-62	(S)-1-(2,8-Dimethyl-3,4-dihydro-1H-pyrido[4,3-b]indol-5(2H)-yl)-2-(pyridine-4-yl)butan-2-ol
1-63	(R)-1-(2,8-Dimethyl-3,4-dihydro-1H-pyrido[4,3-b]indol-5(2H)-yl)-2-(pyridine-4-yl)butan-2-ol

Compound #	Compound Name
1-64	1-(8-Chloro-2-methyl-3,4-dihydro-1H-pyrido[4,3-b]indol-5(2H)-yl)-2-(4-fluorophenyl)hexan-2-ol
1-65	8-Methyl-5-(2-(6-methylpyridin-3-yl)ethyl)-2-(2,2,2-trifluoroethyl)-2,3,4,5-tetrahydro-1H-pyrido[4,3-b]indole
1-66	(S)-1-(2,8-dimethyl-3,4-dihydro-1H-pyrido[4,3-b]indol-5(2H)-yl)-2-(4-fluorophenyl)butan-2-ol
1-67	(S)-1-(8-chloro-2-methyl-3,4-dihydro-1H-pyrido[4,3-b]indol-5(2H)-yl)-2-(4-fluorophenyl)hexan-2-ol

[0160] Pharmaceutical compositions of any of the compounds detailed herein are embraced by this invention. Thus, the invention includes pharmaceutical compositions comprising a compound of the invention or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier or excipient. In one aspect, the pharmaceutically acceptable salt is an acid addition salt, such as a salt formed with an inorganic or organic acid. Pharmaceutical compositions according to the invention may take a form suitable for oral, buccal, parenteral, nasal, topical or rectal administration, or a form suitable for administration by inhalation.

[0161] A compound as detailed herein may in one aspect be in a purified form and compositions comprising a compound in purified forms are detailed herein. Compositions comprising a compound as detailed herein or a salt thereof are provided, such as compositions of substantially pure compounds. In some embodiments, a composition containing a compound as detailed herein or a salt thereof is in substantially pure form. Unless otherwise stated, "substantially pure" intends a composition that contains no more than 35% impurity, wherein the impurity denotes a compound other than the compound comprising the majority of the composition or a salt thereof. Taking compound 1 as an example, a composition of substantially pure compound 1 intends a composition that contains no more than 35% impurity, wherein the impurity denotes a compound other than compound 1 or a salt thereof. In one variation, a composition of substantially pure compound or a salt thereof is provided wherein the composition contains no more than 25% impurity. In another variation, a composition of substantially pure compound or a salt thereof is provided wherein the composition contains or no more than 20% impurity. In still another variation, a composition of substantially pure compound or a salt thereof is provided wherein the composition contains or no more than 10%

impurity. In a further variation, a composition of substantially pure compound or a salt thereof is provided wherein the composition contains or no more than 5% impurity. In another variation, a composition of substantially pure compound or a salt thereof is provided wherein the composition contains or no more than 3% impurity. In still another variation, a composition of substantially pure compound or a salt thereof is provided wherein the composition contains or no more than 1% impurity. In a further variation, a composition of substantially pure compound or a salt thereof is provided wherein the composition contains or no more than 0.5% impurity.

[0162] In one variation, the compounds herein are synthetic compounds prepared for administration to an individual. In another variation, compositions are provided containing a compound in substantially pure form. In another variation, the invention embraces pharmaceutical compositions comprising a compound detailed herein and a pharmaceutically acceptable carrier. In another variation, methods of administering a compound are provided. The purified forms, pharmaceutical compositions and methods of administering the compounds are suitable for any compound or form thereof detailed herein.

General Description of Biological Assays

[0163] The binding properties of compounds disclosed herein to a panel of aminergic G protein-coupled receptors including adrenergic receptors, dopamine receptors, serotonin receptors, histamine receptors and an imidazoline receptor may be determined. Binding properties may be assessed by methods known in the art, such as competitive binding assays. In one variation, compounds are assessed by the binding assays detailed herein. Compounds disclosed herein may also be tested in cell-based assays or in *in vivo* models for further characterization. In one aspect, compounds disclosed herein are of any formula detailed herein and further display one or more of the following characteristics: inhibition of binding of a ligand to an adrenergic receptor (*e.g.*, α_{1D} , α_{2A} and α_{2B}), inhibition of binding of a ligand to a serotonin receptor (*e.g.*, 5-HT_{2A}, 5-HT_{2C}, 5-HT₆ and 5-HT₇), inhibition of binding of a ligand to a dopamine receptor (*e.g.*, D_{2L}), and inhibition of binding of a ligand to a histamine receptor (*e.g.*, H₁, H₂ and H₃); agonist/antagonist activity to a serotonin receptor (*e.g.*, 5-HT_{2A}, 5-HT₆); agonist/antagonist activity to a dopamine receptor (*e.g.*, D_{2L}, D_{2S}); agonist/antagonist activity to a histamine receptor (*e.g.*, H₁); activity in a neurite outgrowth assay; efficacy in a preclinical model of memory dysfunction associated with cholinergic dysfunction/hypofunction; efficacy in

a preclinical model of attention impulsivity and executive function, and efficacy in a preclinical model of schizophrenia.

[0164] In one variation, inhibition of binding of a ligand to a receptor is measured in the assays described herein. In another variation, inhibition of binding of a ligand is measured in an assay known in the art. In one variation, binding of a ligand to a receptor is inhibited by at least about 80% as determined in a suitable assay known in the art such as the assays described herein. In one variation, binding of a ligand to a receptor is inhibited by greater than about any one of 80%, 85%, 90%, 95%, 100%, or between about 85% and about 95% or between about 90 and about 100% as determined in a suitable assay known in the art such as the assays described herein. In one variation, binding of a ligand to a receptor is inhibited by at least about 80% \pm 20% as determined in an assay known in the art.

[0165] In one variation, a compound of the invention inhibits binding of a ligand to at least one receptor and as many as eleven as detailed herein (*e.g.*, a_{1D} , a_{2A} , a_{2B} , 5-HT_{2A}, 5-HT_{2C}, 5-HT₆, 5-HT₇, D_{2L}, H₁, H₂, H₃). In one variation, a compound of the invention inhibits binding of a ligand to at least one receptor and as many as eleven as detailed herein (*e.g.*, a_{1D} , a_{2A} , a_{2B} , 5-HT_{2A}, 5-HT_{2C}, 5-HT₆, 5-HT₇, D₂, H₁, H₂, H₃). In one variation, a compound of the invention inhibits binding of a ligand to at least one and as many as eleven receptors detailed herein and further displays agonist or antagonist activity to one or more receptors detailed herein (*e.g.*, serotonin receptor 5-HT_{2A}, serotonin receptor 5-HT₆, dopamine receptor D_{2L}, dopamine receptor D_{2S} and histamine receptor H₁) as measured in the assays described herein. In one variation, agonist response of serotonin receptor 5-HT_{2A} is inhibited by compounds of the invention by at least about any one of 50%, 50%, 70%, 80%, 90%, 100%, 110%, 120%, 130%, 140%, 150% as determined in a suitable assay such as the assay described herein.

[0166] In one variation, a compound of the invention displays the above described neurotransmitter receptor binding profile, *e.g.*, inhibits binding of a ligand to at least one receptor and as many as eleven as detailed herein and further stimulates neurite outgrowth, *e.g.*, as measured by the assays described herein. Certain compounds of the invention showed activity in neurite outgrowth assays using primary neurons in culture. Data is presented indicating that a compound of the invention has activity comparable in magnitude to that of naturally occurring prototypical neurotrophic proteins such as brain derived neurotrophic factor (BDNF) and nerve growth factor (NGF). Notably, neurite outgrowth plays a critical part of new synaptogenesis, which is beneficial for the treatment of neuronal disorders. In one variation,

neuronal disorders include ADHD. In one variation, neurite outgrowth is observed with a potency of about 1 μ M as measured in a suitable assay known in the art such as the assays described herein. In another variation, neurite outgrowth is observed with a potency of about 500 nM. In a further variation, neurite outgrowth is observed with a potency of about 50 nM. In another variation, neurite outgrowth is observed with a potency of about 5 nM.

[0167] In another variation, a compound of the invention inhibits binding of a ligand to at least one receptor and as many as eleven as detailed herein, further displays agonist or antagonist activity to one or more receptors detailed herein and further stimulates neurite outgrowth.

[0168] In a further variation, a compound of the invention inhibits binding of a ligand to at least one and as many as eleven receptors as detailed herein and/or display the above described neurotransmitter receptor binding profile and further shows efficacy in a preclinical model of memory dysfunction associated with cholinergic dysfunction/hypofunction, and in preclinical models of attention/impulsivity and executive function, *e.g.*, shows pro-cognitive effects in a preclinical model of memory dysfunction. Compounds of the invention have been shown to be effective in a preclinical model of memory dysfunction associated with cholinergic hypofunction. As H_1 antagonism may contribute to sedation, weight gain and reduced cognition, low affinity (less than about 80% inhibition of binding of Pyrillamine at 1 μ M in the assay described herein) for this receptor may be associated with pro-cognitive effects and a more desirable side effect profile. Furthermore, compounds of the invention with increased potency as a 5-HT₆ antagonist may have cognition-enhancing effects as serotonin acting through this receptor may impair memory.

[0169] In another variation, a compound of the invention inhibits binding of a ligand to at least one and as many as eleven receptors as detailed herein, further shows efficacy in a preclinical model of memory dysfunction associated with cholinergic dysfunction/hypofunction, *e.g.*, shows pro-cognitive effects in a preclinical model of memory dysfunction, in preclinical models of attention/impulsivity and executive function, and further displays agonist or antagonist activity to one or more receptors detailed herein.

[0170] In a further variation, a compound of the invention inhibits binding of a ligand to at least one and as many as eleven receptors as detailed herein, further shows efficacy in a preclinical model of memory dysfunction associated with cholinergic dysfunction/hypofunction, *e.g.*, shows pro-cognitive effects in a preclinical model of memory dysfunction, and in

preclinical models of attention/impulsivity and executive function, and further stimulates neurite outgrowth.

[0171] In another variation, a compound of the invention inhibits at least one and as many as eleven receptors as detailed herein, further shows efficacy in a preclinical model of memory dysfunction associated with cholinergic dysfunction/hypofunction, *e.g.*, shows pro-cognitive effects in a preclinical model of memory dysfunction, in preclinical models of attention/impulsivity and executive function, further displays agonist or antagonist activity to one or more receptor detailed herein and further stimulates neurite outgrowth.

[0172] In a further variation, a compound of the invention inhibits binding of a ligand to at least one and as many as eleven receptors and further possesses anti-psychotic effects as measured in a preclinical model of schizophrenia, *e.g.*, shows efficacy in a preclinical model of schizophrenia.

[0173] In another variation, a compound of the invention inhibits binding of a ligand to at least one and as many as eleven receptors, further shows efficacy in a preclinical model of schizophrenia and further displays agonist or antagonist activity to one or more receptors detailed herein.

[0174] In a further variation, a compound of the invention inhibits binding of a ligand to at least one and as many as eleven receptors, further shows efficacy in a preclinical model of schizophrenia and further stimulates neurite outgrowth.

[0175] In a further variation, a compound of the invention inhibits binding of a ligand to at least one and as many as eleven receptors, further shows efficacy in a preclinical model of memory dysfunction associated with cholinergic dysfunction/hypofunction such as enhancement of memory retention and reduction of memory impairment, and in preclinical models of attention/impulsivity and executive function, and further shows efficacy in a preclinical model of schizophrenia.

[0176] In another variation, a compound of the invention inhibits binding of a ligand to at least one and as many as eleven receptors, further shows efficacy in a preclinical model of schizophrenia, further displays agonist or antagonist activity to one or more receptors detailed herein and further shows efficacy in a preclinical model of memory dysfunction associated with cholinergic dysfunction/hypofunction such as enhancement of memory retention and reduction of memory impairment, and in preclinical models of attention/impulsivity and executive function.

[0177] In another variation, a compound of the invention inhibits binding of a ligand to at least one and as many as eleven receptors, further shows efficacy in a preclinical model of schizophrenia, further stimulates neurite outgrowth and further shows efficacy in a preclinical model of memory dysfunction associated with cholinergic dysfunction/hypofunction such as enhancement of memory retention and reduction of memory impairment, and in preclinical models of attention/impulsivity and executive function.

[0178] In a further variation, a compound of the invention inhibits binding of a ligand to at least one and as many as eleven receptors detailed herein, further displays agonist or antagonist activity to one or more receptors detailed herein, further stimulates neurite outgrowth and further shows efficacy in a preclinical model of schizophrenia.

[0179] In another variation, a compound of the invention inhibits binding of a ligand to at least one and as many as eleven receptors, further shows efficacy in a preclinical model of schizophrenia, further displays agonist or antagonist activity to one or more receptors detailed herein, further stimulates neurite outgrowth and further shows efficacy in a preclinical model of memory dysfunction associated with cholinergic dysfunction/hypofunction such as enhancement of memory retention and reduction of memory impairment, and in preclinical models of attention/impulsivity and executive function.

[0180] In another variation, a compound of the invention stimulates neurite outgrowth. In another variation, a compound of the invention shows efficacy in a preclinical model of schizophrenia and further stimulates neurite outgrowth. In another variation, a compound of the invention stimulates neurite outgrowth and further shows efficacy in a preclinical model of memory dysfunction associated with cholinergic dysfunction/hypofunction such as enhancement of memory retention and reduction of memory impairment, and in preclinical models of attention/impulsivity and executive function. In another variation, a compound of the invention shows efficacy in a preclinical model of schizophrenia, further stimulates neurite outgrowth and further shows efficacy in a preclinical model of memory dysfunction associated with cholinergic dysfunction/hypofunction such as enhancement of memory retention and reduction of memory impairment, and in preclinical models of attention/impulsivity and executive function.

[0181] In one aspect, compounds of the invention inhibit binding of a ligand to adrenergic receptors α_{1D} , α_{2A} , α_{2B} and inhibit binding of a ligand to serotonin receptor 5-HT₆. In another variation, compounds of the invention inhibit binding of a ligand to adrenergic receptors α_{1D} , α_{2A} , α_{2B} , to serotonin receptor 5-HT₆ and to any one or more of the following receptors:

serotonin receptor 5-HT₇, 5-HT_{2A} and 5-HT_{2C}. In another variation, compounds of the invention inhibit binding of a ligand to adrenergic receptors α_{1D} , α_{2A} , α_{2B} , to serotonin receptor 5-HT₆ and to any one or more of the following receptors: serotonin receptor 5-HT₇, 5-HT_{2A} and 5-HT_{2C} and further show weak inhibition of binding of a ligand to histamine receptor H₁ and/or H₂. In one variation, compounds of the invention that also display strong inhibition of binding of a ligand to the serotonin receptor 5-HT₇ are particularly desired. In another variation, compounds of the invention inhibit binding of a ligand to adrenergic receptors α_{1D} , α_{2A} , α_{2B} , to serotonin receptor 5-HT₆ and further show weak inhibition of binding of a ligand to histamine receptor H₁ and/or H₂. Weak inhibition of binding of a ligand to the histamine H₁ receptor is permitted as agonists of this receptor have been implicated in stimulating memory as well as weight gain. In one variation, binding to histamine receptor H₁ is inhibited by less than about 80%. In another variation, binding of a ligand to histamine receptor H₁ is inhibited by less than about any of 75%, 70%, 65%, 60%, 55%, or 50% as determined by a suitable assay known in the art such as the assays described herein.

[0182] In another variation, compounds of the invention inhibit binding of a ligand to a dopamine receptor D₂. In another variation, compounds of the invention inhibit binding of a ligand to dopamine receptor D_{2L}. In another variation, compounds of the invention inhibit binding of a ligand to dopamine receptor D₂ and to serotonin receptor 5-HT_{2A}. In another variation, compounds of the invention inhibit binding of a ligand to dopamine receptor D_{2L} and to serotonin receptor 5-HT_{2A}. In another variation, compounds of the invention inhibit binding of a ligand to histamine receptor H₁. In certain aspects, compounds of the invention further show one or more of the following properties: strong inhibition of binding of a ligand to the serotonin 5-HT₇ receptor, strong inhibition of binding of a ligand to the serotonin 5-HT_{2A} receptor, strong inhibition of binding of a ligand to the serotonin 5-HT_{2C} receptor, weak inhibition of binding of a ligand to the histamine H₁ receptor, weak inhibition of binding of ligands to the histamine H₂ receptor, and antagonist activity to serotonin receptor 5-HT_{2A}.

[0183] In one variation, compounds of the invention show any of the receptor binding aspects detailed herein and further display agonist/antagonist activity to one or more of the following receptors: serotonin receptor 5-HT_{2A}, serotonin receptor 5-HT₆, dopamine receptor D_{2L}, dopamine receptor D_{2S} and histamine receptor H₁. In one variation, compounds of the invention show any of the receptor binding aspects detailed herein and further stimulate neurite outgrowth. In one variation, compounds of the invention show any of the receptor binding aspects detailed

herein and further show efficacy in a preclinical model of memory dysfunction associated with cholinergic dysfunction/hypofunction, such as enhancement of memory retention and reduction of memory impairment and in preclinical models of attention/impulsivity and executive function. In one variation, compounds of the invention show any of the receptor binding aspects detailed herein and further show efficacy in a preclinical model of schizophrenia. In one variation, compounds of the invention show any of the receptor binding aspects detailed herein and further show efficacy in any one or more of agonist/antagonist assays (*e.g.*, to serotonin receptor 5-HT_{2A}, 5-HT₆, dopamine receptor D_{2L}, dopamine receptor D_{2S} and histamine receptor H₁), neurite outgrowth, a preclinical model of memory dysfunction associated with cholinergic dysfunction/hypofunction and a preclinical model of schizophrenia.

[0184] In some aspects, compounds of the invention inhibit binding of a ligand to adrenergic receptors α_{1D} , α_{2A} , α_{2B} , serotonin receptor 5-HT₆ and a dopamine receptor D₂ by at least about 80% as determined in a suitable assay known in the art such as the assays described herein. In one variation binding is inhibited by at least about 80% as measured in a suitable assay such as the assays described herein. In some aspects, compounds of the invention inhibit binding of a ligand to adrenergic receptors α_{1D} , α_{2A} , α_{2B} , serotonin receptor 5-HT₆ and dopamine receptor D_{2L} by at least about 80% as determined in a suitable assay known in the art such as the assays described herein. In one variation binding is inhibited by at least about 80% as measured in a suitable assay such as the assays described herein. In one variation, binding of a ligand to a receptor is inhibited by greater than about any one of 80%, 85%, 90%, 95%, 100%, or between about 85% and about 95% or between about 90% and about 100% as determined in a suitable assay known in the art such as the assays described herein.

[0185] In some aspects, compounds of the invention display the above described neurotransmitter receptor binding profile and further show antipsychotic effects. It is recognized that compounds of the invention have binding profiles similar to compounds with antipsychotic activity and several compounds of the invention have been shown to be effective in a preclinical model of schizophrenia. In addition, compounds of the invention might possess the cognitive enhancing properties of dimebon and thus add to the beneficial pharmacology profile of these antipsychotic molecules. In one variation, compounds of the invention display the above described neurotransmitter receptor binding profile and further show pro-cognitive effects in a preclinical model of memory dysfunction such as enhancement of memory retention and reduction of memory impairment. In another variation, compounds of the invention display the

above described neurotransmitter receptor binding profile and do not show pro-cognitive effects in a preclinical model of memory dysfunction, learning and memory.

[0186] In one variation, compounds of the invention demonstrate pro-cognitive effects in a preclinical model of memory dysfunction, learning and memory. In a further variation, compounds of the invention possess anti-psychotic effects in a preclinical model of schizophrenia. In a further variation, compounds of the invention demonstrate pro-cognitive effects in a preclinical model of memory dysfunction, learning and memory and further possess anti-psychotic effects in a preclinical model of schizophrenia.

Overview of the Methods

[0187] A method of administering a compound of the invention to an individual, such as a human, are detailed herein, wherein the method comprises administering to an individual in thereof an effective amount of compound or a salt thereof. The compounds described herein may be used to treat, prevent, delay the onset and/or delay the development of cognitive disorders, psychotic disorders, neurotransmitter-mediated disorders and/or neuronal disorders in individuals, such as humans. In one aspect, the compounds described herein may be used to treat, prevent, delay the onset and/or delay the development of a cognitive disorder. In one variation, cognitive disorder as used herein includes and intends disorders that contain a cognitive component, such as psychotic disorders (*e.g.*, schizophrenia) containing a cognitive component (*e.g.*, CIAS). In one variation, cognitive disorder includes ADHD. In another aspect, the compounds described herein may be used to treat, prevent, delay the onset and/or delay the development of a psychotic disorder. In one variation, psychotic disorder as used herein includes and intends disorders that contain a psychotic component, for example cognitive disorders (*e.g.*, Alzheimer's disease) that contain a psychotic component (*e.g.*, psychosis of Alzheimer's Disease or dementia). In one variation, methods of improving at least one cognitive and/or psychotic symptom associated with schizophrenia are provided. In one aspect, methods of improving cognition in an individual who has or is suspected of having CIAS are provided. In a particular aspect, methods of treating schizophrenia are provided wherein the treatment provides for an improvement in one or more negative symptom and/or one or more positive symptom and/or one or more disorganized symptom of schizophrenia. In yet another aspect, the compounds described herein may be used to treat, prevent, delay the onset and/or delay the development of a neurotransmitter-mediated disorders disorder. In one aspect, a neurotransmitter-mediated disorder includes ADHD. In one embodiment, the neurotransmitter-

mediated disorder includes spinal cord injury, diabetic neuropathy, allergic diseases (including food allergies) and diseases involving geroprotective activity such as age-associated hair loss (alopecia), age-associated weight loss and age-associated vision disturbances (cataracts). In another variation, the neurotransmitter-mediated disorder includes spinal cord injury, diabetic neuropathy, fibromyalgia and allergic diseases (including food allergies). In still another embodiment, the neurotransmitter-mediated disorder includes Alzheimer's disease, Parkinson's Disease, autism, Guillain-Barré syndrome, mild cognitive impairment, multiple sclerosis, stroke and traumatic brain injury. In yet another embodiment, the neurotransmitter-mediated disorder includes schizophrenia, anxiety, bipolar disorders, psychosis, depression and ADHD. In one variation, depression as used herein includes and intends treatment-resistant depression, depression related to a psychotic disorder, or depression related to a bipolar disorder. In another aspect, the compounds described herein may be used to treat, prevent, delay the onset and/or delay the development of a neuronal disorder. In one aspect, the compounds described herein may also be used to treat, prevent, delay the onset and/or delay the development of cognitive disorders, psychotic disorders, neurotransmitter-mediated disorders and/or neuronal disorders for which the modulation of an aminergic G protein-coupled receptor is believed to be or is beneficial.

[0188] The invention also provides methods of improving cognitive functions and/or reducing psychotic effects comprising administering to an individual in need thereof an amount of a compound of the invention or a pharmaceutically acceptable salt thereof effective to improve cognitive functions and/or reduce psychotic effects. In a particular variation, a method of treating schizophrenia is provided, wherein the treatment provides an improvement in at least one cognitive function, such as an improvement in a cognitive function in an individual who has or is suspected of having CIAS. In a further variation, a method of treating schizophrenia is provided wherein the method reduces psychotic effects associated with schizophrenia. In one embodiment, a method of treating schizophrenia is provided wherein the method improves the negative symptoms of schizophrenia in an individual in need thereof. In one embodiment, a method of treating schizophrenia is provided wherein the method improves the positive symptoms of schizophrenia in an individual in need thereof. In a further variation, a method of treating schizophrenia is provided wherein the method both improves cognitive function and reduces psychotic effects in an individual in need thereof. A method of improving one or more negative, positive and disorganized symptoms of schizophrenia is also provided, where the

method entails administering a compound as detailed herein, or a pharmaceutically acceptable salt thereof, to an individual in need of such improvement. In one variation, a method of improving at least one negative symptom of schizophrenia is provided, where the method entails administering a compound as detailed herein, or a pharmaceutically acceptable salt thereof, to an individual in need of such improvement. In another variation, a method of improving at least one negative and at least one positive symptom of schizophrenia is provided, where the method entails administering a compound as detailed herein, or a pharmaceutically acceptable salt thereof, to an individual in need of such improvement. In yet another variation, a method of improving at least one negative and at least one disorganized symptom of schizophrenia is also provided, where the method entails administering a compound as detailed herein, or a pharmaceutically acceptable salt thereof, to an individual in need of such improvement. In still another variation, a method of improving at least one positive and at least one disorganized symptom of schizophrenia is also provided, where the method entails administering a compound as detailed herein, or a pharmaceutically acceptable salt thereof, to an individual in need of such improvement. In still a further variation, a method of improving at least one negative, at least one positive and at least one disorganized symptom of schizophrenia is provided, where the method entails administering a compound as detailed herein, or a pharmaceutically acceptable salt thereof, to an individual in need of such improvement.

[0189] The invention also provides methods of stimulating neurite outgrowth and/or promoting neurogenesis and/or enhancing neurotrophic effects in an individual comprising administering to an individual in need thereof an amount of a compound of the invention or a pharmaceutically acceptable salt thereof effective to stimulate neurite outgrowth and/or to promote neurogenesis and/or to enhance neurotrophic effects.

[0190] The invention further encompasses methods of modulating an aminergic G protein-coupled receptor comprising administering to an individual in need thereof an amount of a compound of the invention or a pharmaceutically acceptable salt thereof effective to modulate an aminergic G protein-coupled receptor.

[0191] It is to be understood that methods described herein also encompass methods of administering compositions comprising the compounds of the invention.

Methods for Treating, Preventing, Delaying the Onset, and/or Delaying the Development of Cognitive Disorders, Psychotic Disorders, Neurotransmitter-mediated Disorders and/or Neuronal Disorders

[0192] In one aspect, the invention provides methods for treating, preventing, delaying the onset, and/or delaying the development of cognitive disorders, psychotic disorders, neurotransmitter-mediated disorders and/or neuronal disorders for which the modulation of an aminergic G protein-coupled receptor is believed to be or is beneficial, the method comprising administering to an individual in need thereof a compound of the invention. In some variations, modulation of adrenergic receptor α_{1D} , α_{2A} , α_{2B} , serotonin receptor 5-HT_{2A}, 5-HT₆, 5-HT₇, histamine receptor H₁ and/or H₂ is expected to be or is beneficial for the cognitive disorders, psychotic disorders, neurotransmitter-mediated disorders and/or neuronal disorders. In some variations, modulation of adrenergic receptor α_{1D} , α_{2A} , α_{2B} and a serotonin receptor 5-HT₆ receptor is expected to be or is beneficial for the cognitive disorders, psychotic disorders, neurotransmitter-mediated disorders and/or neuronal disorders. In some variations, modulation of adrenergic receptor α_{1D} , α_{2A} , α_{2B} , and a serotonin receptor 5-HT₆ receptor and modulation of one or more of the following receptors serotonin 5-HT₇, 5-HT_{2A}, 5-HT_{2C} and histamine H₁ and H₂ is expected to be or is beneficial for the cognitive disorders, psychotic disorders, neurotransmitter-mediated disorders and/or neuronal disorders. In some variations, modulation of a dopamine receptor D₂ is expected to be or is beneficial for the cognitive disorders, psychotic disorders, neurotransmitter-mediated disorders and/or neuronal disorders. In some variations, modulation of dopamine receptor D_{2L} is expected to be or is beneficial for the cognitive disorders, psychotic disorders, neurotransmitter-mediated disorders and/or neuronal disorders. In certain variations, modulation of a dopamine D_{2L} receptor and serotonin receptor 5-HT_{2A} is expected to be or is beneficial for the cognitive disorders, psychotic disorders, neurotransmitter-mediated disorders and/or neuronal disorders. In some variations, the cognitive disorders, psychotic disorders, neurotransmitter-mediated disorders and/or neuronal disorders are treated, prevented and/or their onset or development is delayed by administering a compound of the invention.

Methods to improve cognitive functions and/or reduce psychotic effects

[0193] The invention provides methods for improving cognitive functions by administering a compound of the invention to an individual in need thereof. In some variations, modulation of

one or more of adrenergic receptor α_{1D} , α_{2A} , α_{2B} , serotonin receptor 5-HT_{2A}, 5-HT₆, 5-HT₇, histamine receptor H₁ and/or H₂ is desirable or expected to be desirable to improve cognitive functions. In some variations modulation of α_{1D} , α_{2A} , α_{2B} adrenergic receptors and a serotonin 5-HT₆ receptor is desirable or expected to be desirable to improve cognitive functions. In some variations, modulation of α_{1D} , α_{2A} , α_{2B} adrenergic receptors and serotonin receptor 5-HT₆ and modulation of one or more of the following receptors: serotonin receptor 5-HT₇, 5-HT_{2A}, 5-HT_{2C} and histamine receptor H₁ and H₂, is desirable or expected to be desirable to improve cognitive functions. In another aspect, the invention encompasses methods to reduce psychotic effects by administering a compound of the invention to an individual in need thereof. In some embodiments, modulation of a dopamine D₂ receptor is expected to be or is desirable to reduce psychotic effects. In some embodiments, modulation of a dopamine D_{2L} receptor is expected to be or is desirable to reduce psychotic effects. In some embodiments, modulation of a dopamine D₂ receptor and a serotonin 5-HT_{2A} receptor is expected to be or is desirable to reduce psychotic effects. In some embodiments, modulation of a dopamine D_{2L} receptor and a serotonin 5-HT_{2A} receptor is expected to be or is desirable to reduce psychotic effects. In some variations, a compound of the invention is administered to an individual in need thereof.

Methods to stimulate neurite outgrowth, promote neurogenesis and/or enhance neurotrophic effects

[0194] In a further aspect, the invention provides methods of stimulating neurite outgrowth and/or enhancing neurogenesis and/or enhancing neurotrophic effects comprising administering a compound of the invention or pharmaceutically acceptable salt thereof under conditions sufficient to stimulate neurite outgrowth and/or to enhance neurogenesis and/or enhance neurotrophic effects to an individual in need thereof. In some variations, a compound of the invention stimulates neurite outgrowth at a potency of about 1 μ M as measured in a suitable assay such as the assays described herein. In some variations, a compound of the invention stimulates neurite outgrowth at a potency of about 500 nM as measured in a suitable assay such as the assays described herein. In some variations, a compound of the invention stimulates neurite outgrowth at a potency of about 50 nM as measured in a suitable assay such as the assays described herein. In some variations, a compound of the invention stimulates neurite outgrowth at a potency of about 5 nM as measured in a suitable assay such as the assays described herein.

Methods to modulate an aminergic G protein-coupled receptor

[0195] The invention further contemplates methods for modulating the activity of an aminergic G-protein-coupled receptor comprising administering a compound of the invention or pharmaceutically acceptable salt thereof under conditions sufficient to modulate the activity of an aminergic G protein-coupled receptor. In some variations, the aminergic G protein-coupled receptor is a α_{1D} , α_{2A} , α_{2B} adrenergic receptor and a serotonin 5-HT₆ receptor. In some variations, the aminergic G protein-coupled receptor is a α_{1D} , α_{2A} , α_{2B} adrenergic receptor and a serotonin 5-HT₆ and 5-HT₇ receptor. In some variations, the aminergic G protein-coupled receptor is a α_{1D} , α_{2A} , α_{2B} adrenergic receptor, a serotonin 5-HT₆ and one or more of the following receptors: serotonin 5-HT₇, 5-HT_{2A} and 5-HT_{2C} and histamine H₁ and H₂ receptor. In some variations, the aminergic G protein-coupled receptor is a dopamine D₂ receptor. In some variations, the aminergic G protein-coupled receptor is a dopamine D_{2L} receptor. In some variations, the aminergic G protein-coupled receptor is a dopamine D₂ receptor and a serotonin 5-HT_{2A} receptor. In some variations, the aminergic G protein-coupled receptor is a dopamine D_{2L} receptor and a serotonin 5-HT_{2A} receptor. In some variations, the aminergic G protein-coupled receptor is a histamine H₁ receptor.

General Synthetic Methods

[0196] The compounds of the invention may be prepared by methods as described in U.S. Patent Application No. 12/259,234 filed October 27, 2008 and which is incorporated herein by reference in its entirety and specifically with respect to the synthetic methods for pyrido[4,3-b]indoles.

[0197] The compounds of the invention may be prepared by a number of processes as generally described below and more specifically in the Examples hereinafter. In the following process descriptions, the symbols when used in the formulae depicted are to be understood to represent those groups described above in relation to the formulae hereinabove unless otherwise indicated.

[0198] Where it is desired to obtain a particular enantiomer of a compound, this may be accomplished from a corresponding mixture of enantiomers using any suitable conventional procedure for separating or resolving enantiomers. Thus, for example, diastereomeric derivatives may be produced by reaction of a mixture of enantiomers, *e.g.*, a racemate, and an appropriate chiral compound. The diastereomers may then be separated by any convenient

means, for example by crystallization and the desired enantiomer recovered. In another resolution process, a racemate may be separated using chiral High Performance Liquid Chromatography. Alternatively, if desired a particular enantiomer may be obtained by using an appropriate chiral intermediate in one of the processes described.

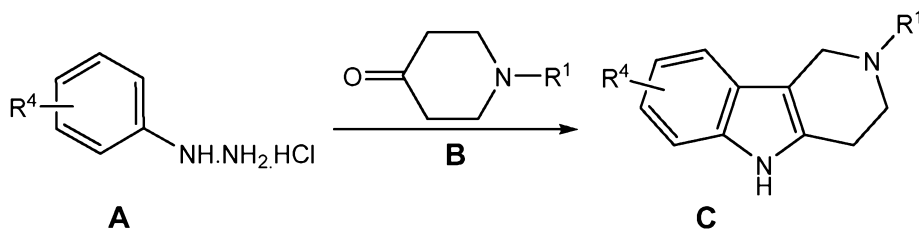
[0199] Chromatography, recrystallization and other conventional separation procedures may also be used with intermediates or final products where it is desired to obtain a particular isomer of a compound or to otherwise purify a product of a reaction.

[0200] The following abbreviations are used herein: thin layer chromatography (TLC); Hour (h); Minute (min); Second (sec); ethanol (EtOH); dimethylsulfoxide (DMSO); *N,N*-dimethylformamide (DMF); trifluoroacetic acid (TFA); tetrahydrofuran (THF); ethyl acetate (EtOAc); Normal (N); aqueous (aq.); methanol (MeOH); dichloromethane (DCM); retention factor (R_f); room temperature (RT).

[0201] General methods of preparing compounds according to the invention are depicted in exemplified methods below.

[0202] A method of synthesizing carboline intermediates used in the synthesis of compounds of the invention is shown as General Method 1. Although identifiers such as R⁴ and R¹ are shown in the method below, it is understood that these moieties apply to the compounds detailed herein even if different identifiers are used elsewhere (*e.g.*, Formula A uses R⁵ at the position indicated by identifier R¹ below and it is understood that in one variation, R¹ of General Method 1 may be the moieties detailed herein for R⁵. Likewise, formula A uses identifiers R¹-R⁴ for substituents on the ring in which R⁴ is used below and it is understood that in one variation, R⁴ of General Method 1 may be the moieties detailed herein for R¹, R², R³ and R⁴ and that as such, more than one R⁴ may be utilized in the General Method detailed below.).

General Method 1.

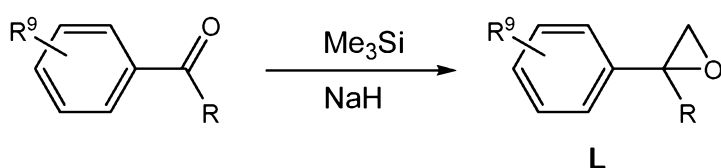


[0203] Compound A (1 equiv.) and compound B (0.76–1.4 equiv.) are mixed in a suitable solvent such as EtOH and heated at 80 °C for 16 h (overnight) after which the solvent is removed in vacuo. The remaining residue is basified, *e.g.*, with saturated aq. NaHCO₃. The aqueous

layer is extracted with DCM and the combined organic layers are dried over sodium sulfate, concentrated in vacuo, and purified, *e.g.*, by silica gel chromatography (230-400 mesh) using a suitable solvent gradient such as either a MeOH-DCM gradient or an EtOAc-hexane gradient to give pure compound C.

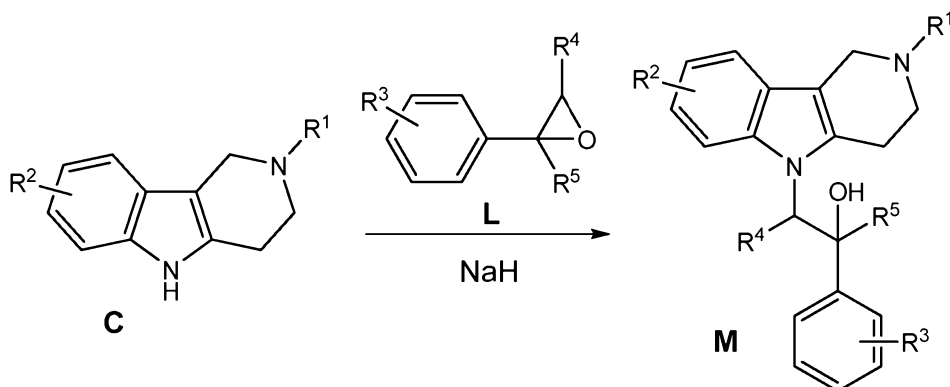
[0204] A method of synthesizing epoxide intermediates used in the synthesis of certain compounds of the invention is shown as General Method 2. Although identifier R⁹ is shown in the method below, it is understood that the moiety applies to the compounds detailed herein even if different identifiers are used elsewhere.

General Method 2.



[0205] DMSO is added to NaH 60% dispersion in oil (1-1.8 equiv.) and heated it to 65 °C for one hour. THF (10 mL) is added to the solution at 65 °C and heating is continued for another 10 min. The reaction mixture is then cooled to 0 °C and trimethylsulfonium iodide (1-1.2 equiv.) is added. The reaction mixture is stirred for another 10 min after which appropriate aldehyde/ketone (1 equiv.) is added as a solution in THF. The reaction mixture is further stirred at RT until the reaction is complete (monitored by TLC and LCMS). The reaction mixture is then poured in ice water and the product is extracted in organic solvent (ether or EtOAc), dried over sodium sulfate and concentrated at 25 °C to obtain the product L.

[0206] A general method of synthesizing certain compounds detailed herein by epoxide ring opening using a carboline is shown as General Method 3. Although identifiers R¹- R⁵ are shown in the method below, it is understood that these moieties apply to the compounds detailed herein even if different identifiers are used elsewhere.

General Method 3.

[0207] Compound C (1 equiv.), compound L (2-7.5 equiv.) and NaH (1-3 equiv.) are heated in DMF at 120 °C for 16 h. The contents are quenched by MeOH and evaporated to dryness. The resulting crude product M is purified by silica gel chromatography (230-400 mesh) using MeOH-DCM gradient followed by reverse-phase chromatography (C-18, 500 mm × 50 mm, Mobile Phase A= 0.05% TFA in water, B= 0.05% TFA in acetonitrile, Gradient:10% B to 80% B in 30 min, injection vol. 5 mL).

[0208] The indo-5-yl alcohol compounds of Table 1 may be prepared according to General Method 3.

[0209] Additional synthetic methods which may be adapted to arrive at the compounds detailed herein are found in U.S. Application No. 12/259,234 and PCT Application No. PCT/US2008/081390, both filed October 27, 2008.

[0210] The methods detailed above may be adapted as known by those of skill in the art. Particular examples of each General Method are provided in the Examples below.

[0211] The following Examples are provided to illustrate but not limit the invention.

[0212] All references disclosed herein are incorporated by reference in their entireties.

EXAMPLES

Example 1. Preparation of 3-(8-methyl-5-(2-(6-methylpyridin-3-yl)ethyl)-3,4-dihydro-1H-pyrido[4,3-b]indol-2(5H)-yl)propanenitrile (Compound No. 1-34)

[0213] 8-Methyl-5-(2-(6-methylpyridin-3-yl)ethyl)-2,3,4,5-tetrahydro-1H-pyrido[4,3-b] indole (250 mg, 8.19 mmol) was taken into water (3 mL) along with acrylonitrile (0.065 mL, 0.982 mmol) and stirred for 10 min. Ceric ammonium nitrate (133 mg, 0.245 mmol) was added to it at once and the reaction mixture was stirred for 2 h. Product was detected by LCMS and TLC.

The reaction mixture was basified with sat. NaHCO_3 solution and extracted into EtOAc. The organic layer was dried over anhydrous sodium sulfate, concentrated and the crude product purified by column chromatography (Silica gel, 2-4% MeOH in DCM) to get product 180 mg (61.43%). This was converted into the oxalate salt (143 mg). ^1H NMR (CD_3OD , Oxalate salt) δ (ppm): 7.88 (s, 1H), 7.68-7.64 (d, 1H), 7.38-7.34 (d, 1H), 7.22 (s, 1H), 7.18-7.15 (d, 1H), 7.02-6.97 (d, 1H), 4.42 (s, 2H), 4.40-4.36 (t, 2H), 3.58-3.38 (m, 4H), 3.19-3.08 (m, 4H), 2.88-2.80 (t, 2H), 2.53 (s, 3H), 2.40 (s, 3H).

Example 2. Preparation of 2-(2,8-dimethyl-3,4-dihydro-1H-pyrido[4,3-b]indol-5(2H)-yl)-1-phenylethanone (Compound No. 1-35)

[0214] 2,8-Dimethyl-2,3,4,5-tetrahydro-1H-pyrido[4,3-b]indole (100 mg, 5 mmol) was dissolved in NMP (1 mL). KOH (280 mg, 5 mmol) was then added to it, followed by addition of 2-bromoacetophenone (208 mg, 1 mmol). The reaction was kept overnight at RT and was monitored by TLC and LC/MS. The reaction was quenched by adding water, and the compound extracted using EtOAc, which was washed with water (2-3x). The organic layer was dried over sodium sulfate and then concentrated to yield 10 mg of dark brown crude oil, which was then purified by column chromatography using 100-200 mesh silica in 5% MeOH:DCM. ^1H NMR (CD_3OD , TFA salt) δ (ppm): 8.15 (m, 1H), 7.70 (m, 1H), 7.60 (m, 2H), 7.28 (d, 1H), 7.20 (m, 1H), 7.0 (m, 1H), 5.80 (m, 2H), 4.70 (m, 1H), 4.40 (m, 1H), 4.20 (m, 1H), 3.80 (m, 1H), 3.60 (m, 2H), 3.10 (s, 1H), 2.40 (s, 3H), 2.30 (m, 1H), 2.0 (m, 1H), 1.80 (m, 1H).

Example 3. Preparation of 2-(8-chloro-2-methyl-3,4-dihydro-1H-pyrido[4,3-b]indol-5(2H)-yl)-1-phenylethanone (Compound No. 1-36)

[0215] 8-Chloro-2-methyl-2,3,4,5-tetrahydro-1H-pyrido[4,3-b]indole (220 mg, 10 mmol) was dissolved in NMP (2 mL). KOH (560 mg, 0.010 mol) was then added, followed by addition of 2-bromoacetophenone (199 mg, 0.001 mol). The reaction was kept overnight at RT and was monitored by TLC & LC/MS. The reaction was quenched by adding water, and extracted using EtOAc, which was then washed with water (2-3x). The organic layer was dried over sodium sulfate and then concentrated to yield 60 mg of dark brown crude oil that was purified by column chromatography using 100-200 mesh silica gel with 4% MeOH:DCM as eluent. ^1H NMR (CDCl_3 , TFA salt) δ (ppm): 8.0 (m, 2H), 7.70 (m, 1H), 7.60 (m, 2H), 7.40 (d, 1H), 7.20 (m, 1H), 7.05 (m, 1H), 5.60 (m, 1H), 5.38 (m, 1H), 4.80 (m, 1H), 4.20 (m, 1H), 3.90 (m, 1H), 3.40 (m, 2H), 3.05 (s, 3H), 1.90 (m, 1H).

Example 4. Preparation of 2-(8-chloro-2-methyl-3,4-dihydro-1H-pyrido[4,3-b]indol-5(2H)-yl)-1-(4-fluorophenyl)ethanone (Compound No. 1-37)

[0216] 8-Chloro-2-methyl-2,3,4,5-tetrahydro-1H-pyrido[4,3-b]indole (220 mg, 1 mmol) was dissolved in 2 mL NMP and to this was added KOH (560 mg, 10 mmol) followed by 4-fluoro-2-bromoacetophenone (217 mg, 1 mmol). The reaction was kept overnight at RT. Water was added and the compound extracted with EtOAc. The organic layer was washed with water, concentrated and purified by column chromatography using silica gel (#100-200 mesh) using 0-3% MeOH:DCM as eluent. ¹HNMR (CD₃OD, TFA salt) δ (ppm): 8.22 (m, 2H), 7.50 (s, 1H), 7.30 (m, 3H), 7.18 (m, 1H), 5.80 (m, 2H), 4.75 (m, 1H), 4.40 (m, 1H), 3.85 (m, 1H), 3.55 (m, 1H), 3.10 (m, 5H).

Example 5. Preparation of 2-(8-chloro-2-methyl-3,4-dihydro-1H-pyrido[4,3-b]indol-5(2H)-yl)-1-(4-chlorophenyl)ethanone (Compound No. 1-38)

[0217] 8-Chloro-2-methyl-2,3,4,5-tetrahydro-1H-pyrido[4,3-b]indole (220 mg, 1 mmol) was dissolved in 2 mL NMP and to this was added KOH (560 mg, 10 mmol) followed by 2-bromo-1-(4-chloro-phenyl)-ethanone (233 mg, 1 mmol). The reaction was kept overnight at RT. Water was added and the compound extracted with EtOAc. The organic layer was washed with water, concentrated and purified by column chromatography using silica gel (#100-200 mesh) using 0-3% MeOH:DCM as eluent. The compound was further purified by reverse phase chromatography. ¹HNMR (CD₃OD, TFA salt) δ (ppm): 8.10 (m, 2H), 7.60 (d, 2H), 7.50 (s, 1H), 7.30 (d, 1H), 7.10 (m, 1H), 5.80 (m, 2H), 4.70 (m, 1H), 4.40 (m, 1H), 3.80 (m, 1H), 3.60 (m, 1H), 3.05 (s, 5H).

Example 6. Preparation of 2-(2,8-dimethyl-3,4-dihydro-1H-pyrido[4,3-b]indol-5(2H)-yl)-1-(4-fluorophenyl)ethanone (Compound No. 1-39)

[0218] To a solution of 2,8-dimethyl-2,3,4,5-tetrahydro-1H-pyrido[4,3-b]indole (7 g, 0.032 mol) in 3 mL of NMP, KOH (12.7 g, 0.226 mol) was added at RT. The reaction mixture was stirred well at RT for 20 min. Then a solution of 2-bromo-1-(4-fluorophenyl) ethanone (6.5 g, 0.032 mol) in 2 mL NMP was added dropwise into the reaction mixture at RT over 2-4 h. The reaction was monitored by LCMS and TLC. The reaction mixture was diluted with water and extracted with EtOAc. The organic layer was dried over sodium sulfate and concentrated under reduced pressure. The residue obtained was purified by column chromatography, providing the desired product (1.2 g, 11.02%). ¹HNMR (CDCl₃, TFA salt) δ (ppm): 8.18-8.01 (m, 2H), 7.71

(s, 1H), 7.30 (s, 1H), 7.22-7.10 (m, 2H), 7.00 (d, 1H), 3.60-3.31 (m, 4H), 3.20-3.06 (m, 2H), 2.85-2.70 (m, 2H), 2.45 (s, 6H).

Example 7. Preparation of 3-(5-(2-(2,8-dimethyl-3,4-dihydro-1H-pyrido[4,3-b]indol-5(2H)-yl)ethyl)pyridin-2-yl)propan-1-amine (Compound No. 1-40)

[0219] 2,8-Dimethyl-2,3,4,5-tetrahydro-1H-pyrido[4,3-b]indole (100 mg, 0.005 mol) was taken into NMP (3 mL), and to it was added finely crushed KOH (280 mg, 0.005 mol) and 2-(3-(5-vinylpyridin-2-yl)propyl)isoindoline-1,3-dione (146 mg, 0.005 mol). The reaction was heated at 120 °C for 12 h. The reaction was monitored by LCMS. After 12 h, 2 mL of water was added to the reaction mixture and heated at 120 °C for 12 h. The reaction was monitored by LCMS. After completion of reaction the mixture was cooled and water was added, followed by extraction with EtOAc. The organic extract was dried over sodium sulfate and concentrated under vacuum to yield 800 mg of crude product. ¹HNMR (CDCl₃, Oxalate salt) δ (ppm): 8.17 (s, 1H), 7.22 (s, 1H), 1.18 (d, 1H), 7.15 (d, 1H), 6.95 (m, 2H), 4.20 (t, 2H), 3.70 (s, 2H), 3.0 (t, 2H), 2.90 (t, 2H), 2.80 (t, 2H), 2.70 (t, 2H), 2.58 (s, 3H), 2.40 (s, 3H), 2.37 (m, 2H), 1.80 (t, 2H).

Example 8. Preparation of 8-methyl-5-(2-(6-(trifluoromethyl)pyridin-3-yl)ethyl)-2,3,4,5-tetrahydro-1H-pyrido[4,3-b]indole (Compound No. 1-41)

[0220] 5-(2-(1-p-Tolylhydrazinyl)ethyl)-2-(trifluoromethyl)pyridine (88 mg, 0.29 mmol) was dissolved in 1,4-dioxane (2 mL) and 4-piperidone hydrate hydrochloride was added with one drop of TFA. The reaction mixture became acidic. The mixture was heated at 100 °C for 2 h. The reaction was monitored by TLC and LCMS. After completion of reaction, the mixture was diluted with sat. NaHCO₃ solution and extracted with EtOAc. The organic extracts were dried over anhydrous sodium sulfate and concentrated. The compound was purified by reverse phase chromatography. ¹HNMR (CD₃OD, TFA salt) δ (ppm): 8.20 (s, 1H), 7.60 (m, 2H), 7.25 (d, 1H), 7.18 (d, 1H), 6.98 (d, 1H), 4.40 (m, 4H), 3.50 (t, 2H), 3.20 (m, 2H), 2.82 (t, 2H), 2.40 (s, 3H).

Example 9. Preparation of 3-(8-methyl-5-(2-(6-methylpyridin-3-yl)ethyl)-3,4-dihydro-1H-pyrido[4,3-b]indol-2(5H)-yl)propan-1-ol (Compound No. 1-42)

[0221] A mixture of 2-methyl-5-(2-(1-p-tolylhydrazinyl)ethyl)pyridine hydrochloride (0.6 g, 0.00216 mol), 1-(3-hydroxypropyl) piperidin-4-one (0.2 g, 0.00127 mol), and isopropanol (10 mL) was heated at 95 °C for 1 h. The reaction was monitored by TLC. After completion, the reaction mixture was cooled to RT, basified with aq. NaOH solution (10 mL) and extracted with

EtOAc (3x100 mL). The organic extract was dried over anhydrous sodium sulfate, concentrated and purified by column chromatography (silica 100-200 mesh, desired product was eluted in 7% MeOH/DCM.). Further purification by preparative TLC gave the product as a yellow oil (0.22 g, 54% yield). The product (0.1 g, 0.311 mmol) was dissolved in THF (1.0 mL). A solution of oxalic acid dihydrate (0.039 g, 0.311 mmol) in THF (2 mL) was added and stirred for 30 min at RT. The precipitate obtained was filtered and dried to give the oxalate salt as a yellow colored solid (0.040 g, 31% yield). ¹HNMR (CD₃OD, Oxalate salt) δ (ppm): 7.90 (m, 1H), 7.60 (d, 1H), 7.38 (d, 1H), 7.22 (s, 1H), 7.18 (d, 1H), 7.0 (d, 1H), 4.50 (m, 2H), 4.38 (m, 2H), 3.75 (m, 2H), 3.42 (m, 3H), 3.15 (m, 2H), 2.80 (m, 2H), 2.50 (s, 3H), 2.40 (s, 3H), 2.0 (m, 2H), 1.30 (m, 2H).

Example 10. Preparation of 4-(8-methyl-5-(2-(6-methylpyridin-3-yl)ethyl)-3,4-dihydro-1H-pyrido[4,3-b]indol-2(5H)-yl)butan-1-ol (Compound No. 1-43)

[0222] A mixture of 2-methyl-5-(2-(1-p-tolylhydrazinyl)ethyl)pyridine hydrochloride (0.6 g, 0.00216 mol), and 1-(4-hydroxybutyl)piperidin-4-one (0.24 g, 0.00108 mol), in isopropanol (10 mL), was heated at 95 °C for 5 h. After completion of reaction (monitored by TLC), the reaction mixture was basified by addition of 2N aq. NaOH (30 mL) and extracted with EtOAc (3x70 mL). The combined organic layers were dried over sodium sulfate and concentrated. The crude product was purified by column chromatography using silica gel (100-200 mesh). The desired product was eluted in 10% MeOH/DCM. Further purification by HPLC provided the title compound as the TFA salt (0.08 g). ¹HNMR (CD₃OD, TFA salt) δ (ppm): 8.22 (s, 1H), 8.10 (d, 1H), 7.70 (d, 1H), 7.25 (s, 1H), 7.10 (d, 1H), 6.90 (d, 1H), 4.70 (m, 1H), 4.45 (m, 2H), 4.38 (m, 1H), 3.90 (m, 1H), 3.70 (t, 2H), 3.55 (m, 2H), 3.40 (t, 2H), 3.20 (m, 3H), 2.70 (s, 3H), 2.40 (s, 3H), 2.0 (m, 2H), 1.70 (m, 2H).

Example 11. Preparation of 2,3,8-trimethyl-5-(2-(6-methylpyridin-3-yl)ethyl)-2,3,4,5-tetrahydro-1H-pyrido[4,3-b]indole (Compound No. 1-44)

[0223] To a solution of N-[2-(6-methyl-pyridin-3-yl)-ethyl]-N-p-tolyl-hydrazine (200 mg, 0.829 mmol) in dioxane (7 mL) was added 1,2-dimethyl-piperidin-4-one (137 mg, 1.078 mmol) in dioxane (3 mL) at RT. To this mixture was added sulfuric acid (0.1 mL) at RT. After complete addition the mixture was stirred at 85 °C for 1 h. The reaction was monitored by TLC. After completion of reaction, the mixture was basified with NaHCO₃ solution and extracted with EtOAc (300 mL). The organic layer was dried over sodium sulfate, concentrated under vacuum and purified by HPLC to obtain 28.5 mg of desired compound as the TFA salt. ¹HNMR

(CD₃OD, TFA salt) d (ppm): 8.20 (s, 1H), 8.05 (d, 1H), 7.63 (d, 1H), 7.25 (s, 1H), 7.10 (d, 1H), 6.95 (d, 1H), 4.70 (m, 1H), 4.45 (t, 2H), 4.36 (m, 1H), 4.05 (m, 1H), 3.75 (m, 1H), 3.20 (m, 2H), 3.0 (m, 3H), 2.90 (m, 1H), 2.62 (s, 3H), 2.40 (s, 3H), 1.50 (d, 3H).

Example 12. Preparation of 2,3,8-trimethyl-5-(2-(6-(trifluoromethyl)pyridin-3-yl)ethyl)-2,3,4,5-tetrahydro-1H-pyrido[4,3-b]indole (Compound No. 1-45)

[0224] To a solution of 2,3,8-trimethyl-2,3,4,5-tetrahydro-1H-pyrido[4,3-b]indole (200 mg, 0.935 mmol) in N-methyl-2-pyrrolidone (2.5 mL) was added powdered KOH (463 mg, 8.27 mmol) and stirred for 10 min at RT. 2-Trifluoromethyl-5-vinyl pyridine (300 mg, 1.73 mmol) was added and stirred further for 4 h at RT. The reaction was monitored by TLC. After completion of reaction, water (10 mL) was added to the mixture, which was then filtered. Water was added to the filtrate, which was then extracted with EtOAc (50 mL). The organic layer was dried over sodium sulfate, concentrated in vacuum and the residue purified by column chromatography (100-200 mesh silica gel) to obtain 20 mg of desired compound. The free base compound was converted into the oxalate salt. ¹HNMR (CDCl₃, Freebase) d (ppm): 8.40 (s, 1H), 7.45 (d, 1H), 7.25 (m, 2H), 7.10 (d, 1H), 6.98 (d, 1H), 4.22 (t, 2H), 3.82 (d, 1H), 3.62 (d, 1H), 3.50 (m, 1H), 3.10 (t, 2H), 2.80 (m, 1H), 2.45 (s, 3H), 2.38 (s, 3H), 2.10 (dd, 1H), 1.10 (d, 3H).

Example 13. Preparation of 2,8-dimethyl-5-(2-(pyridin-4-yl)propyl)-2,3,4,5-tetrahydro-1H-pyrido[4,3-b]indole (Compound No. 1-46)

[0225] 2,8-Dimethyl-2,3,4,5-tetrahydro-1H-pyrido[4,3-b]indole (100mg, 0.5 mmol) was dissolved in NMP (3 mL) and KOH (280 mg, 5 mmol) was added with vinyl 4-(prop-1-en-2-yl)pyridine (178 mg, 1.5 mmol). The reaction was stirred at RT for 14 h. After completion, the mixture was diluted with water and extracted with EtOAc. The organic layer was washed with water, concentrated and the residue purified by HPLC. ¹HNMR (CD₃OD, Oxalate salt) d (ppm): 8.4 (d, 2H), 7.25-7.15 (m, 4H), 7.05 (d, 1H), 4.4-4.2 (m, 3H), 3.80-3.79 (m, 2H), 3.50-3.40 (m, 2H), 3.15(m, 1H), 3.05 (s, 3H) 2.70 (m, 1H), 2.40 (s, 3H), 1.40 (d, 3H).

Example 14. Preparation of 2,3,8-trimethyl-5-(2-(6-methylpyridin-3-yl)propyl)-2,3,4,5-tetrahydro-1H-pyrido[4,3-b]indole (Compound No. 1-47)

[0226] A flask was charged with 2,3,8-trimethyl-2,3,4,5-tetrahydro-1H-pyrido[4,3-b]indole (117 mg, 0.5 mmol) and KOH (392 mg, 7 mmol) in NMP (2 mL) and heated at 140 °C for 10

min. The mixture was cooled to 0 °C and to it was added 2-methyl-5-(prop-1-en-2-yl)pyridine (199 mg, 1.5 mmol) dropwise. The mixture was heated at 140 °C for 2 h. The progress of the reaction was monitored by LCMS (5% conversion). The mixture was cooled to RT, water was added and the mixture filtered and evaporated. The solid obtained was purified by HPLC.

¹HNMR (CD₃OD, TFA salt) δ (ppm): 8.10 (m, 2H), 7.60 (m, 1H), 7.22 (s, 1H), 7.10 (d, 1H), 6.96 (d, 1H), 4.62 (m, 1H), 4.38 (m, 2H), 4.22 (m, 2H), 3.50 (m, 2H), 3.0 (s, 3H), 2.80 (s, 3H), 2.40 (s, 3H), 1.60-1.30 (m, 7H).

Example 15. Preparation of 8-chloro-2,3-dimethyl-5-(2-(6-methylpyridin-3-yl)ethyl)-2,3,4,5-tetrahydro-1H-pyrido[4,3-b]indole (Compound No. 1-48)

[0227] To a stirred solution of 1-(4-chlorophenyl)-1-(2-(6-methylpyridin-3-yl)ethyl)hydrazine (1 g, 3.83 mmol) in dioxane (10 mL) was added 1,2-dimethylpiperidin-4-one (0.538 g, 4.59 mmol) and 0.5 mL of conc. sulfuric acid at RT. The reaction was heated at 90 °C for 2 h. After completion of reaction, the mixture was basified by addition of a saturated solution of NaHCO₃. The product was extracted with EtOAc, and the organic layer washed with water, dried over sodium sulfate and concentrated. The solid obtained was purified by HPLC. ¹HNMR (CD₃OD, TFA salt) δ (ppm): 8.30 (s, 1H), 8.05 (d, 1H), 7.64 (d, 1H), 7.50 (s, 1H), 7.24 (d, 1H), 7.10 (d, 1H), 4.50 (t, 2H), 4.40 (m, 1H), 4.0 (m, 1H), 3.80 (m, 1H), 3.30 (m, 3H), 3.0 (m, 4H), 2.62 (s, 3H), 1.50 (d, 3H).

Example 16. Preparation of 2,8-dimethyl-5-(2-methyl-2-(pyridin-4-yl)propyl)-2,3,4,5-tetrahydro-1H-pyrido[4,3-b]indole (Compound No. 1-49)

[0228] 2,8-Dimethyl-2,3,4,5-tetrahydro-1H-pyrido[4,3-b]indole (145 mg, 0.727 mmol), tetra n-butyl ammonium bromide (11 mg, 0.036 mmol), and 2-methyl-2-(pyridin-4-yl)propyl methanesulfonate (200 mg, 1.20 mmol) were taken into 50% NaOH (6 mL). The reaction mixture was heated overnight at 100 °C. Reaction was monitored by TLC and LCMS. After completion of the reaction, the reaction mixture was extracted with EtOAc and water. The organic layer was separated, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The crude compound was purified by column chromatography to yield 30 mg of product. ¹H NMR (CDCl₃, Freebase) δ (ppm): 8.50 (d, 2H), 7.2-7.13 (m, 3H), 6.88 (d, 2H), 4.03 (s, 2H), 3.62 (s, 2H), 2.63 (t, 2H), 2.50 (s, 3H), 2.42 (s, 3H), 2.25 (t, 2H), 1.43 (s, 6H).

Example 17. Preparation of 2,8-dimethyl-5-((1-(pyridin-4-yl)cyclopropyl)methyl)-2,3,4,5-tetrahydro-1H-pyrido[4,3-b]indole (Compound No. 1-50)

[0229] 2,8-Dimethyl-2,3,4,5-tetrahydro-1H-pyrido[4,3-b]indole (183 mg, 0.917 mmol), tetra n-butyl ammonium bromide (14 mg, 0.045 mmol), and (1-(pyridin-4-yl)cyclopropyl)methyl methanesulfonate (250 mg, 1.10 mmol) were taken into 50% NaOH (6 mL). The reaction mixture was stirred overnight at 100 °C. Reaction was monitored by TLC and LCMS. After completion of the reaction, reaction mixture was extracted with EtOAc and water. The organic layer was separated, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The crude compound was purified by column chromatography to yield 37 mg of product. ¹H NMR (CDCl₃, Freebase) δ (ppm): 8.45 (d, 2H), 7.1-7.0 (m, 3H), 6.9 (d, 2H), 4.28 (s, 2H), 3.63 (s, 2H), 2.7 (t, 2H), 2.5-2.6 (m, 5H), 2.42 (s, 3H), 1.0 -0.85 (m, 4H).

Example 18. Preparation of 2,4,8-trimethyl-5-(2-(6-(trifluoromethyl)pyridin-3-yl)ethyl)-2,3,4,5-tetrahydro-1H-pyrido[4,3-b]indole (Compound No. 1-51)

[0230] To a solution of 2,3,4,5-tetrahydro-2,4,8-trimethyl-1H-pyrido[4,3-b]indole (200 mg, 0.934 mmol) in N-methyl-2-pyrrolidone (2.5 mL) was added powdered KOH (463 mg, 8.27 mmol) and allow to stir for 10 min at RT. 2-Trifluoromethyl-5-vinyl pyridine (323 mg, 1.87 mmol) was added and stirred further for 12 h at RT. The reaction was monitored by TLC. After completion of reaction, water (10 mL) was added and the mixture filtered. Water was added to the filtrate and the product extracted with EtOAc (50 mL). The organic layer was dried over sodium sulfate, evaporated in vacuum and purified by HPLC to obtain the product.

Example 19. Preparation of 1-(1,2,3,4-tetrahydro-2,8-dimethylpyrido[4,3-b]indol-5-yl)-2-phenylpropan-2-ol

[0231] Sodium hydride (38 mg, 1.6 mmol, 1.1 equiv.) was added to a solution of 2,3,4,5-tetrahydro-2,8-dimethyl-1H-pyrido[4,3-b]indole (290 mg, 1.4 mmol, 1.0 equiv.) in DMF (6 mL), and heated to 120 °C for 1 h with stirring. The reaction mixture was cooled to 0 °C and 2-methyl-2-phenyloxirane (400 mg, 2.98 mmol, 2.1 equiv.) was added dropwise over 5 min. The temperature was raised to 120 °C and stirred for 2 h. The reaction mixture was cooled to RT and partitioned between ethyl acetate (60 mL) and water (15 mL). The organic layer was separated and the aqueous layer was extracted with ethyl acetate (1x20 mL). The combined organic layers were washed with water and followed by brine, dried over sodium sulfate and concentrated under vacuum to provide the crude product. The product was purified by flash column chromatography over silica gel (230-400 mesh, deactivated with 1% triethylamine/ hexane) using a gradient of 5 to 15% methanol/ ethyl acetate to yield the free base. The pure compound

was converted to its oxalate salt. An analytical sample was prepared by dissolving free base in 10 mL THF and treatment with 1 equiv. of oxalic acid dihydrate.

Example 20. Preparation of 1-(8-chloro-1,2,3,4-tetrahydro-2-methylpyrido[4,3-b]indol-5-yl)-2-(3-fluoro-4-methoxyphenyl)propan-2-ol (Compound No. 1-59)

[0232] Sodium hydride (38 mg, 1.6 mmol, 1.2 equiv.) was added to a solution of 8-chloro-2,3,4,5-tetrahydro-2-methyl-1H-pyrido[4,3-b]indole (290 mg, 1.31 mmol, 1.0 equiv.) in DMF (6 mL), and heated to 120 °C for 1 h with stirring. The reaction mixture was cooled to 0 °C and 2-(3-fluoro-4-methoxyphenyl)-2-methyloxirane (400 mg, 2.2 mmol, 1.7 equiv.) was added dropwise over 5 min. The temperature was raised to 120 °C and stirred for 2 h. The reaction mixture was cooled to RT and partitioned between EtOAc (60 mL) and water (15 mL). The organic layer was separated and the aqueous layer was extracted with EtOAc (1x20 mL). The combined organic layer was washed with water and followed by brine, dried over sodium sulfate and concentrated under vacuum to provide the crude product. The product was purified by flash column chromatography over silica gel (230-400 mesh, deactivated with 1% triethylamine/hexane) using a gradient of 5 to 15% MeOH/ EtOAc to yield the free base. The pure compound was converted to its oxalate salt. An analytical sample was prepared by dissolving free base in 10 mL THF and treatment with 1 equiv. of oxalic acid dihydrate. ¹HNMR (DMSO, Oxalate salt) δ (ppm): 7.45 (m, 2H), 7.24 (m, 2H), 7.07 (m, 2H), 4.24 (m, 2H), 4.11 (m, 2H), 3.88 (s, 3H), 2.97 (m, 4H), 2.84 (s, 3H), 1.45 (s, 3H).

Example 21. Preparation of 1-(8-chloro-1,2,3,4-tetrahydro-2-methylpyrido[4,3-b]indol-5-yl)-2-(pyridin-3-yl)propan-2-ol (Compound No. 1-54)

[0233] Sodium hydride (38 mg, 1.6 mmol, 1.2 equiv.) was added to a solution of 8-chloro-2,3,4,5-tetrahydro-2-methyl-1H-pyrido[4,3-b]indole (290 mg, 1.3 mmol, 1.0 equiv.) in DMF (6 mL), and heated to 120 °C for 1 h with stirring. The reaction mixture was cooled to 0 °C and 3-(2-methyloxiran-2-yl)pyridine (400 mg, 2.96 mmol, 2.3 equiv.) was added dropwise over 5 min. The temperature was raised to 120 °C and stirred for 2 h. The reaction mixture was cooled to RT and partitioned between EtOAc (60 mL) and water (15 mL). The organic layer was separated and the aqueous layer was extracted with EtOAc (1x20 mL). The combined organic layer was washed with water and followed by brine, dried over sodium sulfate and concentrated under vacuum to provide the crude product. The product was purified by flash column chromatography over silica gel (230-400 mesh, deactivated with 1% triethylamine/hexane)

using a gradient of 5 to 15% MeOH/EtOAc to yield the free base. The pure compound was converted to its oxalate salt. An analytical sample was prepared by dissolving free base in 10 mL THF and treatment with 1 equiv. of oxalic acid dihydrate. ¹HNMR (CD₃OD, Oxalate salt) δ (ppm): 8.43 (s, 1H), 8.34 (d, 1H), 7.87 (d, 1H), 7.37 (s, 1H), 7.30 (m, 1H), 6.97 (m, 1H), 6.93 (d, 1H), 4.48 (m, 2H), 4.32 (m, 2H), 3.71 (m, 2H), 3.12 (s, 3H), 2.81 (m, 2H), 1.70 (s, 3H).

Example 22. Preparation of 1-(1,2,3,4-tetrahydro-2,8-dimethylpyrido[4,3-b]indol-5-yl)-2-(pyridin-4-yl)propan-2-ol (Compound Nos. 1-52)

[0234] Sodium hydride (38 mg, 1.6 mmol, 1.14 equiv.) was added to a solution of 2,3,4,5-tetrahydro-2,8-dimethyl-1H-pyrido[4,3-b]indole (290 mg, 1.4 mmol, 1.0 equiv.) in DMF (6 mL), and heated to 120 °C for 1 h with stirring. The reaction mixture was cooled to 0 °C and 4-(2-methyloxiran-2-yl)pyridine (400 mg, 2.96 mmol, 2.1 equiv.) was added dropwise over 5 min. The temperature was raised to 120 °C and stirred for 2 h. The reaction mixture was cooled to RT and partitioned between EtOAc (60 mL) and water (15 mL). The organic layer was separated and the aqueous layer was extracted with EtOAc (1x20 mL). The combined organic layer was washed with water and followed by brine, dried over sodium sulfate and concentrated under vacuum to provide the crude product. The product was purified by flash column chromatography over silica gel (230-400 mesh, deactivated with 1% triethylamine/ hexane) using a gradient of 5 to 15% MeOH/ EtOAc to yield the free base. The pure compound was converted to its oxalate salt. An analytical sample was prepared by dissolving free base in 10 mL THF and treatment with 1 equiv. of oxalic acid dihydrate. ¹HNMR (CD₃OD, Oxalate salt) δ (ppm): 8.38 (d, 2H), 7.50 (d, 2H), 7.15 (s, 1H), 7.06 (d, 1H), 6.86 (d, 1H), 4.45 (m, 2H), 4.31 (m, 1H), 4.22 (m, 1H), 3.61 (m, 2H), 3.19 (m, 1H), 3.06 (s, 3H), 2.78 (m, 2H), 2.35 (s, 3H), 1.60 (s, 3H).

Example 23. Preparation of 1-cyclohexyl-2-(2,8-dimethyl-3,4-dihydro-1H-pyrido[4,3-b]indol-5(2H)-yl)-1-(4-fluorophenyl)ethanol (Compound No. 1-1)

[0235] Activated magnesium turnings (480 mg, 20 g/atom) and 2-3 crystals of iodine were stirred under anhydrous conditions. The excess of iodine was removed by heating with a heat gun. The magnesium turnings were now yellow in color. To this was added diethyl ether (15 mL) at 0 °C and stirred for 15 min (until the color of the magnesium becomes white). To this was added cyclohexyl bromide (2.5 mL, 20 mmol) dropwise with constant stirring. The reaction mixture was stirred until a dark grey-colored solution was obtained. Into a separate flask was

placed 2-(2,8-dimethyl-3,4-dihydro-1H-pyrido[4,3-b]indol-5(2H)-yl)-1-(4-fluorophenyl)ethanone (168 mg, 5 mmol) in THF under anhydrous conditions. The solution of the prepared cyclohexylmagnesium bromide (5 mL) was added dropwise. After addition, the mixture was allowed to come to RT and stirred at RT for 2 h. The reaction was monitored by TLC and NMR. The reaction was quenched with ice water and the product extracted into EtOAc. The organic extracts were concentrated and the residue purified by silica gel column chromatography (#100-200 mesh) using 0-3% MeOH:DCM as eluent. The compound was further purified by HPLC. ¹HNMR (CD₃OD, TFA salt) δ (ppm): 7.25 (m, 2H), 7.10 (d, 1H), 6.92 (m, 1H), 6.80 (m, 3H), 4.60 (m, 1H), 4.65 (m, 1H), 4.22 (m, 2H), 3.70 (m, 1H), 3.40 (m, 1H), 3.20 (m, 2H), 3.0 (s, 3H), 2.70 (m, 1H), 2.38 (s, 3H), 2.20 (m, 2H), 1.80 (m, 2H), 1.70 (m, 3H), 1.50-1.20 (m, 4H).

Example 24. Preparation of 2-(2,8-dimethyl-3,4-dihydro-1H-pyrido[4,3-b]indol-5(2H)-yl)-1-(4-fluorophenyl)ethanol (Compound No. 1-2)

[0236] Activated magnesium turnings (480 mg, 20 g/atom) and 2-3 crystals of iodine were stirred under anhydrous conditions. The excess of iodine was removed by heating with a heat gun. The magnesium turnings were now yellow in color. To this was added diethyl ether (15 mL) at 0 °C and stirred for 15 min (until the color of the magnesium becomes white). To this was added cyclopentyl bromide (480 mg, 20 g/atom) dropwise with constant stirring. The reaction mixture was stirred until a dark grey-colored solution was obtained. Into a separate flask was placed the starting material (168 mg, 5 mmol) in THF under anhydrous conditions. The solution of the prepared cyclopentylmagnesium bromide (5 mL) was added dropwise. After addition, the mixture was allowed to come to RT and stirred at RT for 2 h. The reaction was monitored by TLC and NMR. The reaction was quenched with ice water and the product extracted into EtOAc. The organic extracts were concentrated and the residue purified by silica gel column chromatography (#100-200 mesh) using 0-3% MeOH:DCM as eluent. (Note: Desired compound not formed but reduction of keto group occurs). ¹HNMR (DMSO, Oxalate salt) δ (ppm): 7.55 (m, 3H), 7.18 (m, 3H), 6.95 (d, 1H), 4.85 (s, 1H), 4.30 (m, 2H), 4.15 (m, 2H), 3.60 (m, 2H), 3.10 (m, 3H), 2.90 (s, 3H), 2.40 (s, 3H).

Example 25. Preparation of 1-(2,8-dimethyl-3,4-dihydro-1H-pyrido[4,3-b]indol-5(2H)-yl)-2-(3-fluoro-4-methoxyphenyl)propan-2-ol (Compound No. 1-3)

[0237] A flask was charged with sodium hydride 60% (461 mg, 1.15 mmol) in DMF and stirred at RT for 10 min. 2,8-Dimethyl-2,3,4,5-tetrahydro-1H-pyrido[4,3-b]indole (0.76 g, 3.8 mmol) was added and the mixture stirred at RT for 1 h. 2-(3-Fluoro-4-methoxyphenyl)-2-methyloxirane (1 g, 5.4 mmol) was added and the mixture stirred at RT overnight. Ice water was added and the mixture extracted with EtOAc (3x). The combined organic layers were washed with water (4x) and concentrated, followed by purification of the product on silica gel (#100-200 mesh) using 0-5% MeOH:DCM as eluent. ¹HNMR (DMSO, Oxalate salt) δ (ppm): 7.30 (m, 3H), 7.18 (s, 1H), 7.10 (d, 1H), 6.90 (d, 1H), 4.30 (m, 2H), 4.18 (d, 1H), 4.05 (d, 1H), 3.80 (s, 3H), 3.60 (m, 2H), 3.0 (m, 2H), 2.80 (s, 3H), 2.35 (s, 3H), 1.70 (m, 1H), 1.40 (s, 3H).

Example 26. Preparation of 1-(2,8-dimethyl-3,4-dihydro-1H-pyrido[4,3-b]indol-5(2H)-yl)-2-(4-methoxyphenyl)propan-2-ol (Compound No. 1-4)

[0238] A flask was charged with sodium hydride 60% (0.803mg, 20.12 mmol) in DMF and stirred at RT for 10 min. 2,8-Dimethyl-2,3,4,5-tetrahydro-1H-pyrido[4,3-b]indole (1.28 g, 6.4 mmol) was added and the mixture stirred at RT for 1 h. 2-(4-Methoxyphenyl)-2-methyloxirane (1.5 g, 9.14 mmol) was added and the mixture stirred at RT overnight. Ice water was added and the mixture extracted with ethyl acetate (3x). The combined organic layers were washed with water (4x) and concentrated, followed by purification of the product on silica gel (#100-200 mesh) using 0-5% MeOH:DCM as eluent

Example 27a. Preparation of 1-(2,8-dimethyl-3,4-dihydro-1H-pyrido[4,3-b]indol-5(2H)-yl)-2-(4-fluorophenyl)butan-2-ol (Compound No. 1-5)

[0239] 2-(2,8-Dimethyl-3,4-dihydro-1H-pyrido[4,3-b]indol-5(2H)-yl)-1-(4-fluorophenyl)ethanone (168 mg, 5 mmol) was dissolved in 10 mL anhydrous THF. Ethyl magnesium bromide (1.5 mL, 0.0015 mol) was then added dropwise at RT under nitrogen. The reaction mixture was stirred at RT for 2 h. The reaction was monitored by LCMS. On completion of the reaction, water (3 mL) was added to the reaction mixture and the product extracted with ethyl acetate (3x). The combined organic layers were washed with water, dried over sodium sulfate, and the solvent evaporated under reduced pressure to obtain the crude product, which was purified by HPLC. The pure compound was isolated as the TFA salt.

Example 27b. Preparation of (R) and (S) 1-(2,8-dimethyl-3,4-dihydro-1H-pyrido[4,3-b]indol-5(2H)-yl)-2-(4-fluorophenyl)butan-2-ol (Compound Nos. 1-66 and 1-60)

[0240] 2-(2,8-Dimethyl-3,4-dihydro-1H-pyrido[4,3-b]indol-5(2H)-yl)-1-(4-fluorophenyl)ethanone (168 mg, 5 mmol) was dissolved in 10 mL anhydrous THF. Ethyl magnesium bromide (1.5 mL, 0.0015 mol) was then added dropwise at RT under nitrogen. The reaction mixture was stirred at RT for 2 h. The reaction was monitored by LCMS. On completion of the reaction, water (3 mL) was added to the reaction mixture and the product extracted with EtOAc (3x). The combined organic layers were washed with water, dried over sodium sulfate, and the solvent evaporated under reduced pressure to obtain the crude product, which was purified by HPLC. The pure compound was isolated as the TFA salt. Separation of the (R) and (S) enantiomers was performed by chiral HPLC. ¹HNMR (CD₃OD, TFA salt) δ (ppm): 7.38 (m, 2H), 7.18 (d, 1H), 7.10 (m, 1H), 7.0 (m, 2H), 6.85 (d, 1H), 4.60 (m, 1H), 4.30 (m, 2H), 3.75 (m, 1H), 3.42 (m, 1H), 3.10 (s, 3H), 2.90 (m, 2H), 2.42 (d, 1H), 2.38 (s, 3H), 2.20 (m, 1H), 1.80 (m, 2H), 0.8 (t, 3H).

Example 28. Preparation of 2-(8-chloro-2-methyl-3,4-dihydro-1H-pyrido[4,3-b]indol-5(2H)-yl)-1-cyclobutyl-1-(4-fluorophenyl)ethanol (Compound No. 1-6)

[0241] 8-Chloro-2,3,4,5-tetrahydro-2-methyl-1H-pyrido[4,3-b]indole (1.5 g, 6 mmol) was dissolved in DMF (15 mL) and stirred for 5 min. Sodium hydride (720 mg, 10 mmol) was then added to it portionwise under nitrogen. This was followed by addition of 2-cyclobutyl-2-(4-fluorophenyl)oxirane (1.906 g, 18 mmol) at RT, and the reaction mixture was stirred for 18 h. After completion of reaction, the reaction mixture was poured into ice water and the product extracted with EtOAc. The organic layer was washed with water, dried over sodium sulfate and concentrated under reduced pressure to give the crude product which was purified by silica gel (#100-200 mesh) column chromatography using 1% MeOH in DCM as eluent. The pure compound was converted into the oxalate salt. ¹HNMR (CDCl₃, Oxalate salt) δ (ppm): 7.30 (d, 1H), 7.20 (m, 2H), 6.95 (m, 4H), 4.20 (m, 1H), 4.0 (m, 1H), 3.80 (m, 2H), 3.10 (m, 1H), 2.70 (m, 4H), 2.50 (s, 3H), 2.20 (m, 2H), 2.0 (d, 1H), 1.80 (t, 2H), 1.70 (m, 1H).

Example 29a. Preparation of 1-(8-chloro-2-methyl-3,4-dihydro-1H-pyrido[4,3-b]indol-5(2H)-yl)-2-(4-fluorophenyl)hexan-2-ol (Compound No. 1-7)

[0242] 8-Chloro-2,3,4,5-tetrahydro-2-methyl-1H-pyrido[4,3-b]indole (1.3 g, 5 mmol) was dissolved in DMF (10 mL) and stirred for 5 min. Sodium hydride (709 mg, 17.7 mmol) was then added to it portionwise under nitrogen. This was followed by addition of 2-butyl-2-(4-fluorophenyl)oxirane (3.4 g, 17.7 mmol) at RT and the reaction mixture was stirred for 18 h.

After completion of reaction, the reaction mixture was poured into ice water and the product extracted with ethyl acetate. The organic layer was washed with water, dried over sodium sulfate and concentrated under reduced pressure to give the crude product which was purified by silica gel (#100-200 mesh) column chromatography using 1% methanol in DCM as eluent. The pure compound was converted into the oxalate salt.

Example 29b. Preparation of (R) and (S) 1-(8-chloro-2-methyl-3,4-dihydro-1H-pyrido[4,3-b]indol-5(2H)-yl)-2-(4-fluorophenyl)hexan-2-ol (Compound Nos. 1-67 and 1-61)

[0243] 8-Chloro-2,3,4,5-tetrahydro-2-methyl-1H-pyrido[4,3-b]indole (1.3 g, 5 mmol) was dissolved in DMF (10 mL) and stirred for 5 min. Sodium hydride (709 mg, 17.7 mmol) was then added to it portionwise under nitrogen. This was followed by addition of 2-butyl-2-(4-fluorophenyl)oxirane (3.4 g, 17.7 mmol) at RT and the reaction mixture was stirred for 18 h. After completion of reaction, the reaction mixture was poured into ice water and the product extracted with EtOAc. The organic layer was washed with water, dried over sodium sulfate and concentrated under reduced pressure to give the crude product which was purified by silica gel (#100-200 mesh) column chromatography using 1% MeOH in DCM as eluent. The pure compound was converted into the oxalate salt. Separation of the (R) and (S) enantiomers was performed by chiral HPLC. ¹HNMR (CDCl₃, Oxalate salt) δ (ppm): 7.30 (m, 3H), 7.10 (d, 1H), 6.95 (m, 3H), 4.20 (m, 1H), 4.0 (m, 1H), 3.62 (m, 2H), 2.70 (m, 3H), 2.50 (s, 3H), 2.20 (m, 1H), 2.0 (m, 1H), 1.80 (m, 1H), 1.22 (m, 3H), 1.0 (m, 1H), 0.80 (t, 3H).

Example 30. Preparation of 2-(2,8-dimethyl-3,4-dihydro-1H-pyrido[4,3-b]indol-5(2H)-yl)-1-(pyridin-4-yl)ethanol (Compound No. 1-8)

[0244] Sodium hydride (2.4 g, 100 mmol) was washed with hexane and dried under vacuum. To this was added DMF (15 mL) and cooled to 0 °C. Then to this was added 2,8-dimethyl-2,3,4,5-tetrahydro-1H-pyrido[4,3-b]indole (4 g, 20 mmol) and the mixture stirred at 0 °C for 30 min. Then 4-oxiranyl-pyridine (2.90 g, 23.96 mmol) was dissolved in 5 mL DMF and added dropwise to the mixture, which was then left stirred at RT overnight. The reaction was monitored by TLC. The reaction mixture was poured into ice water and extracted with EtOAc (3x). The combined organic layer was washed with water, dried over anhydrous sodium sulfate and concentrated. The resultant solid material was washed with hexane and crystallized from ethanol and ether. ¹HNMR (DMSO, HCl salt) δ (ppm): 8.70 (d, 2H), 7.70 (d, 2H), 7.38 (m, 1H),

7.20 (s, 1H), 6.90 (d, 1H), 5.05 (m, 1H), 4.58 (m, 1H), 4.30 (m, 1H), 4.20 (m, 2H), 3.70 (m, 2H), 3.20 (m, 4H), 2.90 (s, 1H), 2.38 (s, 3H).

Example 31. Preparation of 1-(8-fluoro-2-methyl-3,4-dihydro-1H-pyrido[4,3-b]indol-5(2H)-yl)-2-(pyridin-4-yl)propan-2-ol (Compound No. 1-9)

[0245] A flask was charged with 6-fluoro-2-methyl-2,3,4,5-tetrahydro-1H-pyrido[4,3-b]indole (1.9 g, 4.5 mmol) in DMF (20 mL) and stirred for 5 min. To this was added NaH (60% in hexane) (1.16 g, 27.9 mmol) and stirred at RT for 10 min, followed by 4-(2-methyloxiran-2-yl)pyridine (2.5 g, 18.6 mmol) and stirred at RT for 16 h. The progress of reaction was monitored by TLC. The mixture was poured into ice water and filtered. The filtrate was washed with water and concentrated. The residue was recrystallized from ether to get pure product. ¹HNMR (DMSO, HCl salt) δ (ppm): 8.78 (d, 2H), 8.0 (d, 2H), 7.40 (s, 1H), 7.20 (d, 1H), 6.80 (m, 1H), 6.10 (m, 1H), 4.50 (m, 1H), 4.30 (m, 2H), 4.20 (m, 1H), 3.70 (m, 2H), 3.20 (m, 2H), 2.90 (s, 3H), 1.60 (s, 3H).

Example 32. Preparation of 1-(6-chloro-2-methyl-3,4-dihydro-1H-pyrido[4,3-b]indol-5(2H)-yl)-2-(pyridin-4-yl)propan-2-ol (Compound No. 1-10)

[0246] A flask was charged with 6-chloro-2-methyl-2,3,4,5-tetrahydro-1H-pyrido[4,3-b]indole (1.0 g, 4.5 mmol) in DMF (10 mL) and stirred for 5 min. To this was added NaH (60% in hexane) (220 mg, 6.8 mmol) and stirred at RT for 10 min, followed by 4-(2-methyloxiran-2-yl)pyridine (1.08 g, 9 mmol) and stirred at RT for 16 h. The progress of reaction was monitored by TLC. The mixture was poured into ice water and filtered. The filtrate was washed with water and concentrated. The residue was recrystallized from ether to get pure product. ¹HNMR (DMSO, HCl salt) δ (ppm): 8.70 (d, 2H), 7.90 (d, 2H), 7.40 (m, 1H), 7.0 (m, 2H), 6.0 (m, 1H), 4.80 (m, 1H), 4.60 (m, 2H), 4.25 (m, 2H), 3.80 (m, 2H), 2.90 (s, 3H), 1.60 (s, 3H).

Example 33. Preparation of 2-(8-chloro-2-methyl-3,4-dihydro-1H-pyrido[4,3-b]indol-5(2H)-yl)-1-(pyridin-4-yl)ethanol (Compound No. 1-11)

[0247] Sodium hydride (2.72 g, 113.33 mmol) was washed with hexane and dried under vacuum. To this was added DMF (15 mL) and the mixture cooled to 0 °C. 8-Chloro-2-methyl-2,3,4,5-tetrahydro-1H-pyrido[4,3-b]indole (5 g, 22.72 mmol) was added and the mixture stirred at 0 °C for 30 min, followed by 4-oxiranylpiperidine (3.3 g, 27.27 mmol) dissolved in 5 mL DMF added dropwise. The reaction mixture was stirred at RT overnight. The reaction was

monitored by TLC. The reaction mixture was poured into ice water and the product extracted into EtOAc (3x). The combined organic layers were washed with water, dried over anhydrous sodium sulfate and concentrated. The resultant solid material was washed with hexane and crystallized from ethanol and ether. ¹HNMR (CD₃OD, HCl salt) δ (ppm): 8.80 (d, 2H), 8.18 (d, 2H), 7.50 (s, 1H), 7.30 (m, 1H), 7.10 (d, 1H), 5.30 (m, 1H), 4.70 (m, 1H), 4.50 (m, 1H), 4.40 (m, 2H), 3.90 (m, 1H), 3.60 (m, 2H), 3.40 (m, 2H), 3.10 (s, 3H).

Example 34. Preparation of 1-(7-chloro-2-methyl-3,4-dihydro-1H-pyrido[4,3-b]indol-5(2H)-yl)-2-(pyridin-4-yl)propan-2-ol (Compound No. 1-12)

[0248] A flask was charged with 7-chloro-2-methyl-2,3,4,5-tetrahydro-1H-pyrido[4,3-b]indole (1.2 g, 5.0 mmol) in DMF (10 mL) and stirred for 5 min. NaH (60% in hexane) (654 mg, 16 mmol) was added and the mixture stirred at RT for 10 min. Then 4-(2-methyloxiran-2-yl)pyridine (1.35 g, 10 mmol) was added and the mixture stirred at RT for 16 h. The progress of reaction was monitored by TLC. The reaction mixture was poured into ice water and filtered. The filtrate was washed with water and concentrated. The residue was recrystallized from ether to get pure product. ¹HNMR (DMSO, HCl salt) δ (ppm): 8.70 (d, 2H), 7.95 (d, 2H), 7.50 (m, 1H), 7.40 (m, 1H), 7.0 (t, 1H), 6.10 (m, 1H), 4.60 (m, 1H), 4.42-4.20 (m, 3H), 3.30 (m, 3H), 2.90 (s, 3H), 1.60 (d, 3H).

Example 35. Preparation of 1-(6-fluoro-2-methyl-3,4-dihydro-1H-pyrido[4,3-b]indol-5(2H)-yl)-2-(pyridin-4-yl)propan-2-ol (Compound No. 1-13)

[0249] A flask was charged with 6-fluoro-2-methyl-2,3,4,5-tetrahydro-1H-pyrido[4,3-b]indole (1.2 g, 5.8 mmol) in DMF (10 mL) and stirred for 5 min. NaH (60% in hexane) (705 mg, 17.6 mmol) was added and the mixture stirred at RT for 10 min. Then 4-(2-methyloxiran-2-yl)pyridine (1.56 g, 11.6 mmol) was added and the mixture stirred at RT for 16 h. The progress of reaction was monitored by TLC. The reaction mixture was poured into ice water and filtered. The filtrate was washed with water and concentrated. The residue was recrystallized from ether to get pure product. ¹HNMR (DMSO, HCl salt) δ (ppm): 8.70 (d, 2H), 8.0 (d, 2H), 7.40 (m, 1H), 7.20 (d, 1H), 6.85 (m, 1H), 6.10 (m, 1H), 4.58 (d, 1H), 4.38 (m, 2H), 4.22 (m, 1H), 3.20 (m, 3H), 2.90 (s, 3H), 1.60 (d, 3H).

Example 36. Preparation of 1-(2-methyl-3,4-dihydro-1H-pyrido[4,3-b]indol-5(2H)-yl)-2-(pyridin-4-yl)propan-2-ol (Compound No. 1-14)

[0250] 2-Methyl-2,3,4,5-tetrahydro-1H-pyrido[4,3-b]indole (740 mg, 3.9 mmol) was dissolved in DMF and the mixture stirred for 5 min. NaH (60% in oil, 468 mg, 11.7 mmol) was added and the mixture stirred for 10 min, followed by 4-(oxiran-2-yl)pyridine (1.0 g, 7.9 mmol) and the mixture stirred at RT for 3 h. The progress of reaction was monitored by TLC. The reaction mixture was poured into ice water and filtered. The filtrate was washed with water and concentrated. The residue was recrystallized from ether to get pure product. ¹HNMR (CD₃OD, HCl salt) δ (ppm): 8.70 (d, 2H), 8.20 (d, 2H), 7.40 (m, 1H), 7.10 (m, 1H), 7.0 (m, 2H), 4.70 (d, 1H), 4.45 (m, 2H), 4.38 (m, 1H), 3.90 (m, 1H), 3.45 (m, 2H), 3.40 (m, 1H), 3.10 (s, 3H), 1.70 (d, 3H).

Example 37. Preparation of 4-(1-(2,8-dimethyl-3,4-dihydro-1H-pyrido[4,3-b]indol-5(2H)-yl)-2-hydroxypropan-2-yl)phenol (Compound No. 1-15)

[0251] To a stirred solution of 1-(1,2,3,4-tetrahydro-2,8-dimethylpyrido[4,3-b]indol-5-yl)-2-(4-methoxyphenyl)propan-2-ol (0.145 g, 0.39 mmol) in DCM (10 mL) at -78 °C was added borontribromide (0.293 g in 5 mL DCM). The reaction mixture was stirred at -78 °C for 30 min and then at 25 °C for 1 h. The solution was poured into ice water, saturated NaHCO₃ was added, and the mixture extracted with EtOAc. The organic layer was dried over anhydrous sodium sulfate, and the solvent was removed under reduced pressure. The crude product was purified by column chromatography (silica gel, 0-75% MeOH:DCM) to give the product as an off-white solid, 20 mg. ¹HNMR (CDCl₃, Freebase) δ (ppm): 7.25 (d, 1H), 7.10 (m, 3H), 6.98 (d, 1H), 6.70 (d, 2H), 4.10 (m, 2H), 3.82 (m, 2H), 2.80 (m, 2H), 2.60 (s, 3H), 2.42 (s, 3H), 2.38 (m, 2H), 1.60 (s, 3H).

Example 38. Preparation of 1-(8-methoxy-2-methyl-3,4-dihydro-1H-pyrido[4,3-b]indol-5(2H)-yl)-2-(pyridin-4-yl)propan-2-ol (Compound No. 1-16)

[0252] A flask was charged with 8-methoxy-2-methyl-2,3,4,5-tetrahydro-1H-pyrido[4,3-b]indole (1.5 g, 6.9 mmol) in DMF (15 mL) and stirred for 5 min. To this was added NaH (60% in hexane) (828 mg, 20 mmol) and the mixture stirred at RT for 10 min. 4-(2-Methyloxiran-2-yl)pyridine (1.89 g, 13.8 mmol) was added and the mixture stirred at RT for 16 h. The progress of reaction was monitored by TLC. The reaction mixture was poured into ice water and filtered. The filtrate was washed with water and concentrated. The residue was recrystallized from ether to get pure product. ¹HNMR (DMSO, Di-HCl salt) δ (ppm): 8.75 (m, 2H), 8.0 (dd, 2H), 7.30 (d,

1H), 6.90 (s, 1H), 6.60 (t, 1H), 6.10 (bs, 1H), 4.50 (m, 1H), 4.30 (m, 2H), 4.18 (m, 1H), 3.80 (s, 3H), 3.60 (m, 2H), 3.25 (m, 1H), 2.10 (m, 1H), 2.95 (s, 3H), 1.60 (s, 3H).

Example 39. Preparation of 1-(7,8-dichloro-2-methyl-3,4-dihydro-1H-pyrido[4,3-b]indol-5(2H)-yl)-2-(pyridin-4-yl)propan-2-ol (Compound No. 1-17)

[0253] A flask was charged with 7,8-dichloro-2-methyl-2,3,4,4a,5,9b-hexahydro-1H-pyrido[4,3-b]indole (1 g, 3.9 mmol) in DMF (10 mL) and stirred for 5 min. To this was added NaH (60% in hexane) (470 mg, 11.7 mmol) and the mixture stirred at RT for 10 min. 4-(2-Methyloxiran-2-yl)pyridine (795 mg, 5.8 mmol) was added and the mixture stirred at RT for 16 h. The progress of reaction was monitored by TLC. The reaction mixture was poured into ice water and filtered. The filtrate was washed with water and concentrated. The residue was recrystallized from ether to get pure product. ¹HNMR (CD₃OD, Formate salt) δ (ppm): 8.38 (d, 2H), 7.56 (s, 1H), 7.48 (d, 2H), 7.30 (s, 1H), 4.60 (m, 2H), 4.30 (m, 2H), 3.58 (m, 1H), 3.50 (m, 1H), 3.35 (m, 1H), 3.10 (m, 1H), 3.0 (s, 3H), 1.70 (s, 3H).

Example 40. Preparation of 1-(8,9-dichloro-2-methyl-3,4-dihydro-1H-pyrido[4,3-b]indol-5(2H)-yl)-2-(pyridin-4-yl)propan-2-ol (Compound No. 1-18)

[0254] A flask was charged with 7,8-dichloro-2-methyl-2,3,4,4a,5,9b-hexahydro-1H-pyrido[4,3-b]indole (1 g, 3.9 mmol) in DMF (10 mL) and stirred for 5 min. To this was added NaH (60% in hexane) (470 mg, 11.7 mmol) and the mixture stirred at RT for 10 min. 4-(2-Methyloxiran-2-yl)pyridine (795 mg, 5.8 mmol) was added and the mixture stirred at RT for 16 h. The progress of reaction was monitored by TLC. The reaction mixture was poured into ice water and filtered. The filtrate was washed with water and concentrated. The residue was recrystallized from ether to get pure product. ¹HNMR (CD₃OD, Formate salt) δ (ppm): 8.40 (m, 2H), 7.50 (d, 2H), 7.10 (m, 2H), 4.60 (m, 2H), 4.35 (m, 2H), 3.60 (m, 2H), 3.16 (m, 2H), 3.10 (s, 3H), 1.62 (s, 3H).

Example 41. Preparation of 1-(2,8-dimethyl-3,4-dihydro-1H-pyrido[4,3-b]indol-5(2H)-yl)-2-(4-methoxyphenyl)propan-2-ol (Compound No. 1-19)

[0255] A flask was charged with sodium hydride 60% (0.803 mg, 20.12 mmol) in DMF and stirred at RT for 10 min. To this was added 2,8-dimethyl-2,3,4,5-tetrahydro-1H-pyrido[4,3-b]indole (1.28 g, 6.4 mmol) and again stirred at RT for 1 h. 2-(4-Methoxyphenyl)-2-methyloxirane (1.5 g, 9.14 mmol) was added and the mixture stirred at RT overnight. Ice water

was added and the mixture extracted with EtOAc (3x). The combined organic layers were washed with water (4x) and concentrated. The product was purified on silica gel (#100-200 mesh) using 0-5% MeOH:DCM as eluent. ¹HNMR (DMSO, Oxalate salt) δ (ppm): 7.40 (d, 2H), 7.35 (d, 1H), 7.15 (s, 1H), 6.86 (m, 3H), 4.30 (m, 2H), 4.18 (d, 1H), 4.0 (d, 1H), 3.80 (s, 3H), 3.40 (m, 3H), 2.90 (m, 1H), 2.82 (s, 3H), 2.38 (s, 3H), 1.40 (s, 3H).

Example 42. Preparation of 1-(2,8-dimethyl-3,4-dihydro-1H-pyrido[4,3-b]indol-5(2H)-yl)-2-(4-methoxyphenyl)propan-2-ol (Compound No. 1-20)

[0256] A flask was charged with sodium hydride 60% (0.803 mg, 20.12 mmol) in DMF and stirred at RT for 10 min. To this was added 2,8-dimethyl-2,3,4,5-tetrahydro-1H-pyrido[4,3-b]indole (1.28 g, 6.4 mmol) and again stirred at RT for 1 h. 2-(4-Methoxyphenyl)-2-methyloxirane (1.5 g, 9.14 mmol) was added and the mixture stirred at RT overnight. Ice water was added and the mixture extracted with EtOAc (3x). The combined organic layers were washed with water (4x) and concentrated. The product was purified on silica gel (#100-200 mesh) using 0-5% MeOH:DCM as eluent. ¹HNMR (DMSO, Oxalate salt) δ (ppm): 7.40 (d, 2H), 7.35 (d, 1H), 7.15 (s, 1H), 6.86 (m, 3H), 4.30 (m, 2H), 4.18 (d, 1H), 4.0 (d, 1H), 3.80 (s, 3H), 3.40 (m, 3H), 2.90 (m, 1H), 2.82 (s, 3H), 2.38 (s, 3H), 1.40 (s, 3H).

Example 43. Preparation of 1-(8-chloro-2-methyl-3,4-dihydro-1H-pyrido[4,3-b]indol-5(2H)-yl)-3-methyl-2-(pyridin-4-yl)butan-2-ol (Compound No. 1-21)

[0257] To a stirred solution of sodium hydride (0.261 g, 50-60%) in dry DMF (5 mL) at 0 °C was added 8-chloro-2,3,4,5-tetrahydro-2-methyl-1H-pyrido[4,3-b]indole (0.3 g). The reaction mixture was stirred at RT for 30 min. To the reaction mixture was added 4-(2-isopropoxyloxiran-2-yl)pyridine (0.288 g in 2 mL DMF) at RT. After 12 h stirring, the reaction mixture was diluted with ice-water and extracted with EtOAc (3x10 mL). The combined organic layers were washed with brine, dried over anhydrous sodium sulfate and evaporated. The crude product was triturated with diethyl ether to obtain pure product (90 mg). ¹HNMR (DMSO, Oxalate salt) δ (ppm): 8.30 (d, 2H), 7.30 (m, 3H), 7.10 (d, 1H), 6.82 (d, 1H), 4.50 (m, 2H), 4.22 (m, 2H), 3.42 (m, 1H), 3.30 (m, 2H), 2.80 (s, 3H), 2.62 (m, 1H), 1.78 (m, 1H), 1.15 (d, 3H), 0.6 (d, 3H).

Example 44. Preparation of 1-(2,8-dimethyl-3,4-dihydro-1H-pyrido[4,3-b]indol-5(2H)-yl)-3-methyl-2-(pyridin-4-yl)butan-2-ol (Compound No. 1-22)

[0258] To a stirred solution of sodium hydride (0.192 g, 50-60%) in dry DMF (5 mL) at 0 °C was added 2,3,4,5-tetrahydro-2,8-dimethyl-1H-pyrido[4,3-b]indole (0.3 g). The reaction mixture was stirred at RT for 30 min. To the reaction mixture was added 4-(2-isopropoxyloxiran-2-yl)pyridine (0.317 g in 2 mL DMF) at RT. After 12 h stirring, the reaction mixture was diluted with ice-water and extracted with EtOAc (3x10 mL). The combined organic layers were washed with brine, dried over anhydrous sodium sulfate and evaporated. The crude product was purified by column chromatography (silica gel 100-200 mesh, 5% MeOH:DCM) to obtain pure product (50 mg). ¹HNMR (DMSO, Oxalate salt) δ (ppm): 8.30 (d, 2H), 7.30 (d, 2H), 7.15 (s, 1H), 7.10 (d, 1H), 6.82 (d, 1H), 4.40 (m, 2H), 4.22 (m, 2H), 3.4 (m, 2H), 3.20 (m, 1H), 2.80 (s, 3H), 2.62 (m, 1H), 2.5 (m, 1H), 2.25 (s, 3H), 1.15 (d, 3H), 0.6 (d, 3H).

Example 45. Preparation of 1-(8-chloro-2-methyl-3,4-dihydro-1H-pyrido[4,3-b]indol-5(2H)-yl)-2-(pyridin-4-yl)butan-2-ol (Compound Nos. 1-23)

[0259] A flask was charged with sodium hydride (0.581 g, 50-60%) in dry DMF (10 mL) at 0 °C and to it was added 8-chloro-2,3,4,5-tetrahydro-2-methyl-1H-pyrido[4,3-b]indole (0.8 g). The reaction mixture was stirred at RT for 30 min, and then to this was added 4-(2-ethyloxiran-2-yl)pyridine (0.758 g) dissolved in DMF (2 mL), and stirred at RT for 12 h. The reaction mixture was diluted with ice-water and extracted with EtOAc (3x30 mL). The combined organic layers were washed with brine, dried over anhydrous sodium sulfate and evaporated. The crude product was triturated with diethyl ether to obtain the desired compound. ¹HNMR (DMSO, Oxalate salt) δ (ppm): 8.45 (d, 2H), 7.40 (m, 4H), 7.0 (d, 1H), 4.38 (m, 1H), 4.22 (m, 1H), 3.60 (m, 2H), 3.35 (m, 2H), 3.10 (m, 2H), 2.90 (s, 3H), 2.10 (m, 2H), 0.6 (t, 3H).

Example 46. Preparation of ±, (R) and (S) 1-(2,8-dimethyl-3,4-dihydro-1H-pyrido[4,3-b]indol-5(2H)-yl)-2-(pyridin-4-yl)butan-2-ol (Compound Nos. 1-24, 1-62 and 1-63)

[0260] A flask was charged with sodium hydride (0.640 g, 50-60%) in dry DMF (10 mL) at 0 °C and to this was added 2,8-dimethyl-2,3,4,4a,5,9b-hexahydro-1H-pyrido[4,3-b]indole (0.8 g). The mixture was stirred at RT for 30 min and then 4-(2-ethyloxiran-2-yl)pyridine (0.834g) dissolved in DMF (2 mL) was added, stirred at RT for 12 h. The reaction mixture was diluted with ice-water and extracted with EtOAc (3x30 mL). The combined organic layers were washed with brine, dried over anhydrous sodium sulfate and evaporated. The crude product was triturated with diethyl ether to obtain the desired compound. The racemic compound was further separated into the (R) and (S) enantiomers by use of chiral HPLC. ¹HNMR (DMSO, Oxalate

salt) d (ppm): 8.45 (d, 2H), 7.42 (d, 2H), 7.30 (d, 1H), 7.10 (s, 1H), 6.82 (d, 1H), 4.30 (d, 1H), 4.18 (d, 1H), 3.60 (s, 2H), 3.50 (m, 2H), 3.38 (m, 1H), 3.0 (m, 2H), 2.90 (s, 3H), 3.32 (s, 3H), 2.10 (m, 1H), 0.6 (t, 3H).

Example 47. Preparation of 1-(2,8-dimethyl-3,4-dihydro-1H-pyrido[4,3-b]indol-5(2H)-yl)-2-(pyrimidin-4-yl)propan-2-ol (Compound No. 1-25)

[0261] Sodium hydride (200 mg, 8.33 mmol) was washed with hexane and dried under vacuum. DMF (4 mL) was added, resulting in a suspension. 2,8-Dimethyl-2,3,4,5-tetrahydro-1H-pyrido[4,3-b]indole (400 mg, 2 mmol) in 2 mL DMF was added dropwise and stirred for 30 min at RT. 4-(2-Methyl-oxiranyl)-pyrimidine (490 mg, 3.60 mmol) in 2mL DMF was added dropwise and the reaction mixture was stirred overnight at RT. After the completion of reaction, the reaction mixture was quenched with ice-cold water and extracted three times with EtOAc. The combined organic layers were washed with water several times followed by brine, and then dried over sodium sulfate. The solvent was evaporated and the residue washed with hexane and crystallized from ether-DCM and hexane to obtain 350 mg of desired product. ¹HNMR (CD₃OD, Oxalate salt) d (ppm): 9.10 (s, 1H), 8.50 (d, 1H), 7.50 (d, 1H), 7.10 (s, 1H), 6.95 (d, 1H), 6.80 (d, 1H), 4.40 (m, 4H), 3.60 (m, 2H), 3.40 (m, 1H), 3.20 (m, 1H), 3.0 (s, 3H), 2.50 (s, 3H), 1.60 (s, 3H).

Example 48. Preparation of 1-(8-chloro-2-methyl-3,4-dihydro-1H-pyrido[4,3-b]indol-5(2H)-yl)-2-(pyrimidin-4-yl)propan-2-ol (Compound No. 1-26)

[0262] Sodium hydride (275 mg, 11.45 mmol) was washed with hexane and dried under vacuum. DMF (4 mL) was added, resulting in a suspension. 2,3,4,5-Tetrahydro-2-methyl-8-chloro-1H-pyrido[4,3-b]indole (500 mg, 2.27 mmol) dissolved in DMF(2 mL) was added dropwise and the reaction mixture stirred for 30 min at RT. 4-(2-Methyl-oxiranyl)-pyrimidine (620 mg, 4.55 mmol) dissolved in DMF(2 mL) was added dropwise and the reaction mixture was stirred overnight at RT. The progress of reaction was monitored by TLC. The mixture was quenched with ice-cold water and the mixture extracted with EtOAc (3x30 mL). The combined organic layer was washed with water (4x20 mL) followed by brine (1x20 mL), dried over sodium sulfate and the solvent evaporated under vacuum. The residue was washed with hexane and crystallized from ether: DCM and hexane. ¹HNMR (CD₃OD, Oxalate salt) d (ppm): 9.10 (s, 1H), 8.50 (d, 1H), 7.50 (d, 1H), 7.36 (s, 1H), 7.10 (d, 1H), 6.95 (d, 1H), 4.40 (m, 4H), 3.60 (m, 2H), 3.40 (m, 1H), 3.20 (m, 1H), 3.05 (s, 3H), 1.60 (s, 3H).

Example 49. Preparation of 1-(8-chloro-2-methyl-3,4-dihydro-1H-pyrido[4,3-b]indol-5(2H)-yl)-2-(pyrazin-2-yl)propan-2-ol (Compound No. 1-27)

[0263] To a solution of 8-chloro 2-methyl-2,3,4,5-tetrahydro-1H-pyrido (4,3-b) indole (1.0 g, 4.54 mmol) in DMF (10 mL) was added sodium hydride (600 mg, 13.63 mmol). After stirring for 10 min at RT, 2-(2-methyl oxiranyl)pyrazine (804 mg, 5.9 mmol) was added dropwise at 0-10 °C and the reaction mixture was stirred at RT for 16 h. The reaction mixture was poured into ice water and extracted with EtOAc (3x150 mL). The organic layer was washed with water, dried over anhydrous sodium sulfate and concentrated to afford crude product, which was crystallized in ether-hexane to yield a yellow solid product as the free base (1.2 g). ¹H NMR (DMSO, Oxalate salt) d (ppm): 8.65 (s, 1H), 8.55 (s, 1H), 8.50 (d, 1H), 7.42 (s, 1H), 7.05 (d, 1H), 6.95 (d, 1H), 4.40 (m, 4H), 3.20 (m, 2H), 3.0 (m, 2H), 2.90 (s, 3H), 1.58 (s, 3H).

Example 50. Preparation of 1-(2,8-dimethyl-3,4-dihydro-1H-pyrido[4,3-b]indol-5(2H)-yl)-2-(pyrazin-2-yl)propan-2-ol (Compound No. 1-28)

[0264] To a stirred solution of 2,8-dimethyl-2,3,4,5-tetrahydro-1H-pyrido(4,3-b)indole (350 mg, 1.75 mmol) in DMF (4 mL) was added sodium hydride (210 mg, 5.25 mmol) followed by dropwise addition of 2-(2-methyl oxiranyl)pyrazine (310 mg, 2.275 mmol) at 10 °C and the reaction mixture was further stirred at RT for 16 h. After completion, the reaction mixture was poured into ice cooled water, extracted with EtOAc (3x75 mL). The organic layer was washed with water, dried over anhydrous sodium sulfate and concentrated yielding crude product, which was re-crystallized in ether and hexane to yield a yellow solid product (350 mg). ¹H NMR (DMSO, Oxalate salt) d (ppm): 8.65 (s, 1H), 8.55 (s, 1H), 8.50 (d, 1H), 7.10 (s, 1H), 6.90 (d, 1H), 6.78 (d, 1H), 4.30 (m, 4H), 3.20 (m, 2H), 3.0 (m, 2H), 2.90 (s, 3H), 2.30 (s, 3H), 1.50 (s, 3H).

Example 51. Preparation of 1-(8-methyl-2-(2,2,2-trifluoroethyl)-3,4-dihydro-1H-pyrido[4,3-b]indol-5(2H)-yl)-2-(pyridin-4-yl)propan-2-ol (Compound No. 1-29)

[0265] Step 1: To a stirred solution of 8-methyl-2-(2,2,2-trifluoroethyl)-2,3,4,5-tetrahydro-1H-pyrido[4,3-b]indole (0.9 g, 0.00319 mol) in dry THF (45 mL) was added borane-dimethylsulfide solution (0.63 mL, 0.00638 mol) at 0 °C. The reaction mass was heated at 80 °C for 2 h. After completion, the reaction mixture was cooled to RT and quenched with MeOH (20 mL). The solvent was removed under reduced pressure to yield 8-methyl-2-(2,2,2-

trifluoroethyl)-2,3,4,5-tetrahydro-1H-pyrido[4,3-b]indole as a yellow colored oil (0.7 g, 82% yield).

[0266] Step 2: To a solution of 8-methyl-2-(2,2,2-trifluoroethyl)-2,3,4,5-tetrahydro-1H-pyrido[4,3b] indole (500 mg, 1.8 mmol) in DMF (10 mL) was added sodium hydride (216 mg, 5.4 mmol) and stirred for 10 min at RT followed by addition of 4-(2-methyl-oxiranyl)-pyridine (377 mg, 2.7 mmol) and stirring continued for 16 h. The reaction mixture was poured into ice water and extracted with EtOAc. The organic layer was washed with water, dried over anhydrous sodium sulfate and concentrated to afford crude material, which was re-crystallized in ether and hexane to yield 1-(8-methyl-2-(2,2,2-trifluoroethyl)-3,4-dihydro-1H-pyrido[4,3-b]indol-5(2H)-yl)-2-(pyridin-4-yl)propan-2-ol (320 mg). ¹H NMR (DMSO, HCl salt) δ (ppm): 8.65 (d, 2H), 8.05 (d, 2H), 7.10 (m, 2H), 6.78 (d, 1H), 4.25 (m, 2H), 4.0 (s, 2H), 3.60 (m, 2H), 3.16 (m, 2H), 2.85 (m, 2H), 2.30 (s, 3H), 1.58 (s, 3H).

Example 52. Preparation of 1-(2-cyclopropyl-8-methyl-3,4-dihydro-1H-pyrido[4,3-b]indol-5(2H)-yl)-2-(pyridin-4-yl)propan-2-ol (Compound No. 1-30)

[0267] Step 1: A solution of (4-methylphenyl)hydrazine hydrochloride (1.5 g, 0.00948 mol) and 1-cyclopropylpiperidin-4-one (1.3 g, 0.00948 mol) in 7% sulfuric acid in dioxane (20 mL) was heated at 80 °C for 2 h. The progress of reaction was monitored by TLC. After completion, the reaction mixture was cooled to RT and the dioxane layer was decanted. The residue was basified with 10% sodium hydroxide solution and extracted with EtOAc (3x100 mL). The organic layer was dried over anhydrous sodium sulfate and concentrated affording crude material, which was purified by silica gel column chromatography (2% MeOH:DCM) to yield 2-cyclopropyl-8-methyl-2,3,4,5-tetrahydro-1H-pyrido[4,3-b]indole (1.4 g, 66% yield).

[0268] Step 2: To a stirred solution of 2-cyclopropyl-8-methyl-2,3,4,5-tetrahydro-1H-pyrido[4,3-b]indole (500 mg, 2.2 mmol) in DMF (10 mL) was added sodium hydride (264 mg, 6.6 mmol). After stirring for 10 min at RT, 4-(2-methyl-oxiranyl)-pyridine (448 mg, 3.3 mmol) was added and stirring continued for another 16 h. The reaction mixture was poured into ice water and extracted with EtOAc. The organic layer was washed with water, dried over anhydrous sodium sulfate and concentrated to afford crude material, which was re-crystallized in ether and hexane to yield 1-(2-cyclopropyl-8-methyl-3,4-dihydro-1H-pyrido[4,3-b]indol-5(2H)-yl)-2-(pyridin-4-yl)propan-2-ol (600 mg). ¹H NMR (CD₃OD, TFA salt) δ (ppm): 8.62 (d, 2H), 8.18 (d, 2H), 7.20 (s, 1H), 6.95 (d, 1H), 6.80 (d, 1H), 4.50 (m, 1H), 4.40 (s, 2H), 4.0 (m, 1H), 3.70 (m, 1H), 3.30 (m, 3H), 3.10 (m, 1H), 2.36 (s, 3H), 1.78 (s, 3H), 1.20 (m, 4H).

Example 53. Preparation of 1-(6-methoxy-2-methyl-3,4-dihydro-1H-pyrido[4,3-b]indol-5(2H)-yl)-2-(pyridin-4-yl)propan-2-ol (Compound No. 1-31)

[0269] Step 1: To a stirred solution of (2-methoxyphenyl)hydrazine hydrochloride (5 g, 0.0286 mol) and 1-methyl-4-piperidone (2.83 mL, 0.0229 mol) in ethanol (50 mL) was added ethanolic hydrochloric acid (5 mL). The reaction mixture was heated at 80 °C for 2 h. After completion, the reaction mixture was cooled to RT and solvent removed under reduced pressure. The residue was basified with 10% sodium hydroxide solution and extracted with EtOAc (3x100 mL). The organic layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure to afford crude material, which was purified by silica gel column chromatography (6% MeOH:DCM) to yield 6-methoxy-2-methyl-2,3,4,5-tetrahydro-1H-pyrido[4,3-b]indole (1.5 g, 24 % yield).

[0270] Step 2: To a stirred solution of 6-methoxy-2-methyl-2,3,4,5-tetrahydro-1H-pyrido[4,3-b]indole (500 mg, 2.3 mmol) in DMF (10 mL) was added sodium hydride (276 mg, 6.9 mmol) and stirred for 10 min at RT, followed by addition of 4-(2-methyl-oxiranyl)-pyridine (468 mg, 3.4 mmol) and stirring continued for another 16 h. The reaction mixture was poured into ice water and extracted with EtOAc. The organic layer was washed with water, dried over sodium sulfate and concentrated to afford crude material, which was re-crystallized in ether and hexane to yield 1-(6-methoxy-2-methyl-3,4-dihydro-1H-pyrido[4,3-b]indol-5(2H)-yl)-2-(pyridin-4-yl)propan-2-ol. ¹H NMR (CD₃OD, TFA salt) δ (ppm): 8.60 (m, 2H), 7.95 (m, 2H), 6.95 (m, 2H), 6.50 (m, 1H), 4.65 (m, 2H), 4.30 (m, 2H), 3.90 (m, 2H), 3.80 (s, 3H), 3.60 (m, 2H), 3.10 (s, 3H), 1.70 (s, 3H).

Example 54. Preparation of 1-(7-isopropyl-2-methyl-3,4-dihydro-1H-pyrido[4,3-b]indol-5(2H)-yl)-2-(pyridin-4-yl)propan-2-ol (Compound No. 1-32)

[0271] Step 1: A solution of (3-isopropylphenyl)hydrazine hydrochloride (5 g, 0.0267 mol) and 1-methyl-4-piperidone (3.3 mL, 0.0267 mol) in 7% sulfuric acid in dioxane (100 mL) was heated at 80 °C for 1 h. After completion, the reaction mixture was cooled to RT and the organic layer decanted. The residue was basified with 10% sodium hydroxide solution and extracted with EtOAc (3x100 mL). The organic layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure affording crude material, which was purified by silica gel column chromatography (6% MeOH:DCM) to yield 7-isopropyl-2-methyl-2,3,4,5-tetrahydro-1H-pyrido[4,3-b]indole (1.1g, 18% yield).

[0272] Step 2: To a solution of 7-isopropyl-2-methyl-2,3,4,5-tetrahydro-1H-pyrido[4,3-b]indole (500 mg, 2.1 mmol) in DMF (10 mL) was added sodium hydride (252 mg, 6.3 mmol). After stirring for 10 min at RT, 4-(2-methyl-oxiranyl)-pyridine (444 mg, 3.2 mmol) was added and stirring continued for another 16 h. The reaction mixture was poured into ice water and extracted with EtOAc. The organic layer was washed with water, dried over sodium sulfate and concentrated to afford crude product which was re-crystallized in ether and hexane to yield 1-(7-isopropyl-2-methyl-3,4-dihydro-1H-pyrido[4,3-b]indol-5(2H)-yl)-2-(pyridin-4-yl)propan-2-ol. ¹H NMR (CD₃OD, TFA salt) δ (ppm): 8.60 (d, 2H), 8.05 (d, 2H), 7.25 (d, 1H), 6.90 (d, 1H), 6.78 (s, 1H), 4.65 (m, 1H), 4.42 (s, 2H), 4.30 (m, 1H), 3.90 (m, 1H), 3.60 (m, 2H), 3.30 (m, 1H), 3.10 (s, 3H), 2.85 (m, 1H), 1.80 (s, 3H), 1.18 (m, 6H).

Example 55. Preparation of 2-(pyridin-4-yl)-1-(2,3,8-trimethyl-3,4-dihydro-1H-pyrido[4,3-b]indol-5(2H)-yl)propan-2-ol (Compound No. 1-33)

[0273] Step 1: To a solution of 4-tolyl hydrazine hydrochloride salt (1.39 g, 8.814 mmol) in dioxane (15 mL) was added a solution of 1,2-dimethyl-piperidin-4-one (1.350 g, 10.62 mmol) in dioxane (5 mL) at RT followed by addition of sulfuric acid (0.69 mL). The reaction mixture was stirred at 85 °C for 1 h. After completion of reaction, the reaction mixture was basified with NaHCO₃ solution and extracted with EtOAc (300 mL). The organic layer was dried over sodium sulfate and concentrated yielding crude material, which was re-crystallized with ether/hexane to yield 2,3,8-trimethyl-2,3,4,5-tetrahydro-1H-pyrido[4,3-b]indole (852 mg).

[0274] Step 2: To a solution of 2,3,8-trimethyl-2,3,4,5-tetrahydro-1H-pyrido[4,3-b]indole (500 mg, 2.3 mmol) in DMF (10 mL) was added sodium hydride (276 mg, 6.9 mmol). After stirring for 10 min at RT, 4-(2-methyl-oxiranyl)-pyridine (473 mg, 3.5 mmol) was added and stirring continued for another 16 h. The reaction mixture was poured into ice water and extracted with EtOAc. The organic layer was washed with water, dried over sodium sulfate and concentrated to afford crude material, which was re-crystallized in ether-hexane to yield 2-(pyridin-4-yl)-1-(2,3,8-trimethyl-3,4-dihydro-1H-pyrido[4,3-b]indol-5(2H)-yl)propan-2-ol. ¹H NMR (DMSO, HCl salt) δ (ppm): 8.62 (d, 2H), 8.10 (d, 2H), 7.18 (s, 1H), 6.90 (m, 1H), 6.80 (m, 1H), 4.62 (m, 2H), 4.40 (m, 3H), 4.05 (m, 1H), 3.80 (m, 1H), 3.05 (s, 3H), 2.38 (s, 3H), 1.75 (d, 3H), 1.70-1.50 (m, 3H).

Example 56. Preparation of 1-(8-chloro-2-methyl-3,4-dihydro-1H-pyrido[4,3-b]indol-5(2H)-yl)-2-(4-fluorophenyl)hexan-2-ol (Compound No. 1-64)

[0275] To a solution of 8-chloro-2,3,4,5-tetrahydro-2-methyl-1H-pyrido[4,3-b]indole (1.3 g, 5 mmol) in dimethylformamide (10 mL) was added sodium hydride (709 mg, 17.7 mmol) in portions followed by addition of 2-butyl-2-(4-fluorophenyl)oxirane (3.4 g, 17.7 mmol), and the reaction mixture was stirred for 18 h at RT. After completion, reaction mixture was poured into ice water and extracted with EtOAc. The organic layer was washed with water, dried over anhydrous sodium sulfate and concentrated under reduced pressure to afford crude material, which was purified by silica gel (100-200 mesh) column chromatography using 1% MeOH-DCM as eluent. The pure compound was converted into oxalate salt by treatment with oxalic acid in ethanol. ¹H NMR (CDCl₃, Oxalate salt) δ (ppm): 7.30 (m, 3H), 7.10 (d, 1H), 6.95 (m, 3H), 4.20 (m, 1H), 4.0 (m, 1H), 3.62 (m, 2H), 2.70 (m, 3H), 2.50 (s, 3H), 2.20 (m, 1H), 2.0 (m, 1H), 1.80 (m, 1H), 1.22 (m, 3H), 1.0 (m, 1H), 0.80 (t, 3H).

Example 57. Preparation of 8-methyl-5-(2-(6-methylpyridin-3-yl)ethyl)-2-(2,2,2-trifluoroethyl)-2,3,4,5-tetrahydro-1H-pyrido[4,3-b]indole (Compound No. 1-65)

[0276] To a solution of 8-methyl-2-(2,2,2-trifluoroethyl)-2,3,4,5-tetrahydro-1H-pyrido[4,3-b]indole (100 mg, 0.372 mmol) in DMF (2 mL) were added sodium hydride (50 mg, 1.11 mmol) and 2-(6-methylpyridin-3-yl)ethyl 4-methylbenzenesulfonate (271.3 mg, 0.932 mmol). The reaction mixture was irradiated in a microwave reactor at 90 °C for 1 h. The reaction mixture was cooled to RT, quenched with water and extracted with EtOAc (3x10 mL). The organic layer was washed with water (2x10 mL), dried over anhydrous sodium sulfate and concentrated under reduced pressure to afford crude material, which was purified by reverse phase HPLC. ¹H NMR (CD₃OD, TFA salt) δ (ppm): 8.16 (s, 1H), 8.1 (d, 1H), 7.65 (d, 1H), 7.2 (s, 1H), 7.0 (d, 1H), 6.9 (d, 1H), 4.48 (s, 2H), 4.4 (t, 2H), 4.17 (q, 2H), 3.62 (t, 2H), 3.2 (t, 2H), 3.08 (t, 2H), 2.64 (s, 3H), 2.4 (s, 3H).

Example 58. Preparation of Compound Nos. 1-53; 1-55; 1-56; 1-57; and 1-58

[0277] The following compounds are prepared according to General Method 3.

1-(2-Ethyl-8-methyl-3,4-dihydro-1H-pyrido[4,3-b]indol-5(2H)-yl)-2-(4-fluorophenyl)propan-2-ol (Compound No. 1-53);

1-(8-Methyl-2-(trifluoromethyl)-3,4-dihydro-1H-pyrido[4,3-b]indol-5(2H)-yl)-2-(6-methylpyridin-3-yl)propan-2-ol (Compound No. 1-55);

1-(2-Cyclopropyl-8-methyl-3,4-dihydro-1H-pyrido[4,3-b]indol-5(2H)-yl)-2-(2-methylpyridin-4-yl)propan-2-ol (Compound No. 1-56);

1-(8-Chloro-2-isopropyl-3,4-dihydro-1H-pyrido[4,3-b]indol-5(2H)-yl)-2-(4-chlorophenyl)propan-2-ol (Compound No. 1-57); and

2-(2,4-Difluorophenyl)-1-(2,8-dimethyl-3,4-dihydro-1H-pyrido[4,3-b]indol-5(2H)-yl)propan-2-ol (Compound No. 1-58).

Example B1: Determination of the ability of compounds of the invention to bind a histamine receptor.

Histamine H₁

[0278] To evaluate in radioligand binding assays the activity of compounds of the invention, human recombinant histamine H₁ receptor expressed in Chinese hamster ovary (CHO) cells (De Backer, M.D. et al., Biochem. Biophys. Res. Comm. 197(3):1601, 1993) in a modified Tris-HCl buffer (50 mM Tris-HCl, pH 7.4, 2 mM MgCl₂, 100 mM NaCl, 250 mM Sucrose) was used. Compounds of the invention were incubated with 1.2 nM [³H]Pyrilamine for 180 min at 25 °C. Non-specific binding was estimated in the presence of 1 μM pyrilamine. Receptor proteins were filtered and washed, the filters were then counted to determine [³H]Pyrilamine specifically bound. Compounds were screened at 1 μM or lower, using 1% DMSO as vehicle. Biochemical assay results are presented as the percent inhibition of specific binding in Table 2.

Histamine H₂

[0279] To evaluate in radioligand binding assays the activity of compounds of the invention, human recombinant histamine H₂ receptor expressed in Chinese hamster ovary (CHO) K1 cells (Ruat, M., Proc. Natl. Acad. Sci. USA. 87(5):1658, 1990) in a 50 mM Phosphate buffer, pH 7.4 was used. Compounds of the invention were incubated with 0.1 nM [¹²⁵I]Aminopotentidine for 120 min at 25 °C. Non-specific binding was estimated in the presence of 3 μM Tiotidine. Receptor proteins were filtered and washed, the filters were then counted to determine [¹²⁵I]Aminopotentidine specifically bound. Compounds were screened at 1 μM or lower, using 1% DMSO as vehicle. Biochemical assay results are presented as the percent inhibition of specific binding in Table 2.

Histamine H₃

[0280] To evaluate in radioligand binding assays the activity of compounds of the invention, human recombinant histamine H₃ receptor expressed in Chinese hamster ovary (CHO-K1) cells (Yanai K et al. Jpn. J. Pharmacol. 65(2):107, 1994 ; Zhu Y et al. Mol. Pharmacol. 59(3):434,

2001) in a modified Tris-HCl buffer (50 mM Tris-HCl, pH 7.4, 5 mM MgCl₂, 0.04% BSA) is used. Compounds of invention are incubated with 3 nM [³H]R(-)- α -Methylhistamine for 90 min at 25 °C. Non-specific binding is estimated in the presence of 1 μ M R(-)- α -Methylhistamine. Receptor proteins are filtered and washed, the filters are counted to determine [³H] R(-)- α -Methylhistamine specifically bound. Compounds are screened at 1 μ M or lower, using 1% DMSO as vehicle. Compounds of the invention are tested in this biochemical assay and percent inhibition of specific binding is determined.

Example B2: Determination of the ability of compounds of the invention to bind a imidazoline I₂ receptor.

Central Imidazoline I₂

[0281] To evaluate in radioligand binding assays the activity of compounds of the invention, rat central imidazoline I₂ receptor obtained from Wistar Rat cerebral cortex (Brown, C.M. et al., *Br. J. Pharmacol.* 99:803, 1990) in a modified Tris-HCl buffer (50 mM Tris-HCl buffer, pH 7.4, 0.5 mM EDTA) is used. Compounds of the invention are incubated with 2 nM [³H]Idazoxan for 30 min at 25 °C. Non-specific binding is estimated in the presence of 1 μ M Idazoxan. Receptor proteins are filtered and washed, the filters are then counted to determine [³H]Idazoxan specifically bound. Compounds are screened at 1 μ M or lower, using 1% DMSO as vehicle. Compounds of the invention are tested in this biochemical assay and percent inhibition of specific binding is determined.

Table 2. Binding Data (% Inhibition)

Compound No.	Histamine Binding (1 μ M)		Histamine Binding (0.1 μ M)
	H ₁	H ₂	H ₁
1-1	22	85	
1-2	95	65	
1-3	91	78	
1-4	34/43	80	
1-5	71	91	
1-6	83	101	
1-7	30	89	
1-8	84	24	
1-9	0	25	
1-10	26	53	
1-11	91	47	
1-12	23	57	
1-13	8	29	
1-14	1	22	
1-15	36	57	
1-16	8	13	
1-17	77	85	
1-18	-11	9	
1-19	23		
1-20	61		
1-21	-7		
1-22	9		
1-23	20		
1-24	19		
1-25	61		
1-26	64		
1-27	61		
1-28	45		
1-29	11		
1-30	48		
1-31	22		
1-32	7		
1-33	56		
1-34	65	0	
1-35	52	11	
1-36	84	48	
1-37	83	80	
1-38	91	56	
1-39	86	66	
1-40	81	18	

Compound No.	Histamine Binding (1 μ M)		Histamine Binding (0.1 μ M)
	H ₁	H ₂	H ₁
1-41	72	6	
1-42	93	16	
1-43	97	21	
1-44	100		
1-45	96		
1-46	90		
1-47	91		
1-48	101		
1-49	94		
1-50	97		
1-51	65		
1-52	38	43	
1-54	52	41	
1-59	63	58	
1-60			10
1-61			-7
1-62			3
1-63			18
1-64	30	89	
1-65			11
1-66			-12
1-67			-2

Example B3: Determination of the ability of compounds of the invention to bind an adrenergic receptor.

Adrenergic α_{1A}

[0282] To evaluate in radioligand binding assays the activity of compounds of the invention, rat adrenergic α_{1A} receptor obtained from Wistar Rat submaxillary glands (Michel, A.D. et al., *Br. J. Pharmacol.* 98:883, 1989) in a modified Tris-HCl buffer (50 mM Tris-HCl buffer, pH 7.4, 0.5 mM EDTA) is used. Compounds of the invention are incubated with 0.25 nM [³H]Prozosin for 60 min at 25 °C. Non-specific binding is estimated in the presence of 10 μ M phentolamine. Receptor proteins are filtered and washed, the filters are then counted to determine [³H]Prozosin specifically bound. Compounds of the invention are screened at 1 μ M or lower, using 1% DMSO as vehicle. Compounds of the invention are tested in this biochemical assay and percent inhibition of specific binding is determined.

Adrenergic α_{1B}

[0283] To evaluate in radioligand binding assays the activity of compounds of the invention, rat adrenergic α_{1B} receptor obtained from Wistar Rat liver (Garcia-S'ainz, J.A. et al., *Biochem. Biophys. Res. Commun.* 186:760, 1992; Michel A.D. et al., *Br. J. Pharmacol.* 98:883, 1989) in a modified Tris-HCl buffer (50 mM Tris-HCl buffer, pH 7.4, 0.5 mM EDTA) is used.

Compounds of the invention are incubated with 0.25 nM [3 H]Prozosin for 60 min at 25 °C.

Non-specific binding is estimated in the presence of 10 μ M phentolamine. Receptor proteins are filtered and washed, the filters are then counted to determine [3 H]Prozosin specifically bound.

Compounds are screened at 1 μ M or lower, using 1% DMSO as vehicle. Compounds of the invention are tested in this biochemical assay and percent inhibition of specific binding is determined.

Adrenergic α_{1D}

[0284] To evaluate in radioligand binding assays the activity of compounds of the invention, human recombinant adrenergic α_{1D} receptor expressed in human embryonic kidney (HEK-293) cells (Kenny, B.A. et al. *Br. J. Pharmacol.* 115(6):981, 1995) in a 50 mM Tris-HCl buffer, pH 7.4, was used. Compounds of invention were incubated with 0.6 nM [3 H]Prozosin for 60 min at 25 °C. Non-specific binding was estimated in the presence of 10 μ M phentolamine. Receptor proteins were filtered and washed, the filters were then counted to determine [3 H]Prozosin specifically bound. Compounds were screened at 1 μ M or lower, using 1% DMSO as vehicle. Biochemical assay results are presented as the percent inhibition of specific binding in Table 3.

Adrenergic α_{2A}

[0285] To evaluate in radioligand binding assays the activity of compounds of the invention, human recombinant adrenergic α_{2A} receptor expressed in insect Sf9 cells (Uhlen S et al. *J. Pharmacol. Exp. Ther.* 271:1558, 1994) in a modified Tris-HCl buffer (50 mM Tris-HCl, pH 7.4, 12.5 mM $MgCl_2$, 2mM EDTA) was used. Compounds of invention were incubated with 1 nM [3 H]MK-912 for 60 min at 25 °C. MK912 is (2S-trans)-1,3,4,5',6,6',7,12b-octahydro-1',3'-dimethyl-spiro[2H-benzofuro[2,3-a]quinolizine-2,4'(1'H)-pyrimidin]-2'(3'H)-one hydrochloride. Non-specific binding was estimated in the presence of 10 μ M WB-4101 (2-(2,6-dimethoxyphenoxyethyl) aminomethyl-1,4-benzodioxane hydrochloride). Receptor proteins were filtered and washed, the filters were then counted to determine [3 H]MK-912 specifically

bound. Compounds were screened at 1 μ M or lower, using 1% DMSO as vehicle. Biochemical assay results are presented as the percent inhibition of specific binding in Table 3.

Adrenergic α_{2B}

[0286] To evaluate in radioligand binding assays the activity of compounds of the invention, human recombinant adrenergic α_{2B} receptor expressed in Chinese hamster ovary (CHO-K1) cells (Uhlen S et al., *Eur. J. Pharmacol.* 343(1):93, 1998) in a modified Tris-HCl buffer (50 mM Tris-HCl, pH 7.4, 12.5 mM $MgCl_2$, 1 mM EDTA, 0.2% BSA) was used. Compounds of the invention were incubated with 2.5 nM [3H]Rauwolscine for 60 min at 25 °C. Non-specific binding was estimated in the presence of 10 μ M Prozolin. Receptor proteins were filtered and washed, the filters were then counted to determine [3H]Rauwolscine specifically bound. Compounds were screened at 1 μ M or lower, using 1% DMSO as vehicle. Biochemical assay results are presented as the percent inhibition of specific binding in Table 3.

Adrenergic α_{2C}

[0287] To evaluate in radioligand binding assays the activity of compounds of the invention, human recombinant adrenergic α_{2C} receptor expressed in insect Sf9 cells (Uhlen S et al. *J. Pharmacol. Exp. Ther.* 271:1558, 1994) in a modified Tris-HCl buffer (50 mM Tris-HCl, pH 7.4, 12.5 mM $MgCl_2$, 2 mM EDTA) is used. Compounds of the invention are incubated with 1 nM [3H]MK-912 for 60 min at 25 °C. Non-specific binding is estimated in the presence of 10 μ M WB-4101. Receptor proteins are filtered and washed, the filters are then counted to determine [3H]MK-912 specifically bound. Compounds are screened at 1 μ M or lower, using 1% DMSO as vehicle. Compounds of the invention are tested in this biochemical assay and percent inhibition of specific binding is determined.

Example B4: Determination of the ability of compounds of the invention to bind a dopamine receptor.

Dopamine D_{2L}

[0288] To evaluate in radioligand binding assays the activity of compounds of the invention, human recombinant dopamine D_{2L} receptor expressed in Chinese hamster ovary (CHO) cells (Grandy, D.K. et al. *Proc. Natl. Acad. Sci. USA.* 86:9762, 1989; Hayes, G. et al., *Mol. Endocrinol.* 6:920, 1992) in a modified Tris-HCl buffer (50 mM Tris-HCl, pH 7.4, 1.4 mM Ascorbic Acid, 0.001% BSA, 150 mM NaCl) was used. Compounds of the invention were

incubated with 0.16 nM [^3H]Spiperone for 120 min at 25 °C. Non-specific binding was estimated in the presence of 10 μM Haloperidol. Receptor proteins were filtered and washed, the filters were then counted to determine [^3H]Spiperone specifically bound. Compounds were screened at 1 μM or lower, using 1% DMSO as vehicle. Biochemical assay results are presented as the percent inhibition of specific binding in Table 3.

Table 3: Percent Inhibition of ligand binding to aminergic G protein-coupled receptors by compounds of the invention:

Compound No.	Adrenergic (1 μM)			Adrenergic (0.1 μM)						Dopamine (1 μM)
	α_{1D}	α_{2A}	α_{2B}	α_{1A}	α_{1B}	α_{1D}	α_{2A}	α_{2B}	α_{2C}	
1-1	49	83	86							13
1-2	88	98	104							36
1-3	58	94	98							32
1-4	57	93	88							
1-5	75	94	96							
1-66				-1	11	19	29	20	18	6
1-6	70	96	94							33
1-7	46	88	79							
1-67				2	-2	23	26	-3	13	20
1-8	60	84	105	9	54	12	37	100	5	10
1-9										8
1-10				-8	12	7	28	86	19	8
1-11				12	60	12	41	101	26	15
1-12										1
1-13										-1
1-14										3
1-15				36	81	31	32	103	5	35
1-16										-5
1-17				0	55	18	64	64	39	2
1-18										-15
1-19				20	75	36	58	85	16	15
1-20				13	63	22	57	79	28	34
1-21										14
1-22										12
1-23										17
1-24										9
1-25										14
1-26										5
1-27										16
1-28										6
1-29										2
1-30										11

Compound No.	Adrenergic (1 μ M)			Adrenergic (0.1 μ M)						Dopamine (1 μ M)
	a _{1D}	a _{2A}	a _{2B}	a _{1A}	a _{1B}	a _{1D}	a _{2A}	a _{2B}	a _{2C}	
1-31										9
1-32										10
1-33										15
1-34	6	3	23							-4
1-35	18	19	59							4
1-36	52	43	92							73
1-37	56	87	87							85
1-38	56	90	92							44
1-39	57	88	92							57
1-40	53	31	63							3
1-41	74	58	89							-8
1-42	55	35	39							11
1-43										10
1-44										8
1-45										0
1-46				12	55	43	63	96	22	37
1-47										12
1-48										12
1-49				13	45	26	54	92	43	54
1-50										47
1-51										14
1-52	82	57	103							7
1-54	87	76	107							19
1-59	81	83	95							17
1-60				-8	-2	13	3	1	9	-14
1-61				1	0	14	-7	2	11	14
1-62				10	9	6	10	62	-5	9
1-63				8	5	-13	12	47	4	14
1-64	46	88	79							30
1-65				-10	-4	4	6	-9	-1	12

Example B5: Determination of the ability of compounds of the invention to bind a serotonin receptor.

Serotonin (5-Hydroxytryptamine) 5-HT_{1A}

[0289] To evaluate in radioligand binding assays the activity of compounds of the invention, human recombinant serotonin (5-Hydroxytryptamine) 5-HT_{1A} receptor expressed in Chinese hamster ovary (CHO-K1) cells (Martin GR and Humphrey PPA. *Neuropharmacol.* 33:261, 1994; May JA, et al. *J. Pharmacol. Exp. Ther.* 306(1):301, 2003) in a modified Tris-HCl buffer (50 mM Tris-HCl, pH 7.4, 0.1% Ascorbic Acid, 0.5 mM EDTA, 10 mM MgSO₄) is used.

Compounds of invention are incubated with 1.5 nM [³H]8-OH-DPAT for 60 min at 25 °C. Non-specific binding is estimated in the presence of 10 µM Metergoline. Receptor proteins are filtered and washed, the filters are then counted to determine [³H] 8-OH-DPAT specifically bound. Compounds are screened at 1 µM or lower, using 1% DMSO as vehicle. Compounds of the invention are tested in this biochemical assay and percent inhibition of specific binding is determined.

Serotonin (5-Hydroxytryptamine) 5-HT_{1B}

[0290] To evaluate in radioligand binding assays the activity of compounds of the invention, serotonin (5-Hydroxytryptamine) 5-HT_{1B} receptor from Wistar Rat cerebral cortex (Hoyer et al. *Eur. J. Pharmacol.* 118:1, 1985; Pazos et al., *Eur. J. Pharmacol.* 106:531, 1985) in a modified Tris-HCl buffer (50 mM Tris-HCl, pH 7.4, 154 mM NaCl, 10 µM Pargyline, 30 µM Isoprenaline) is used. Compounds of invention are incubated with 10 pM [¹²⁵I]Cyanopindolol for 90 min at 37 °C. Non-specific binding is estimated in the presence of 10 µM Serotonin (5-HT). Receptor proteins are filtered and washed, the filters are then counted to determine [¹²⁵I]Cyanopindolol specifically bound. Compounds are screened at 1 µM or lower, using 1% DMSO as vehicle. Compounds of the invention are tested in this biochemical assay and percent inhibition of specific binding is determined.

Serotonin (5-Hydroxytryptamine) 5-HT_{2A}

[0291] To evaluate in radioligand binding assays the activity of compounds of the invention, human recombinant serotonin (5-Hydroxytryptamine) 5-HT_{2A} receptor expressed in Chinese hamster ovary (CHO-K1) cells (Bonhaus, D.W. et al. *Br. J. Pharmacol.* 115:622, 1995; Saucier, C. and Albert, P.R., *J. Neurochem.* 68:1998, 1997) in a 50 mM Tris-HCl buffer, pH 7.4, was used. Compounds of the invention were incubated with 0.5 nM [³H]Ketanserin for 60 min at 25 °C. Non-specific binding was estimated in the presence of 1 µM Mianserin. Receptor proteins were filtered and washed, the filters were then counted to determine [³H]Ketanserin specifically bound. Compounds were screened at 1 µM or lower, using 1% DMSO as vehicle. Biochemical assay results are presented as the percent inhibition of specific binding in Table 4.

Serotonin (5-Hydroxytryptamine) 5-HT_{2B}

[0292] To evaluate in radioligand binding assays the activity of compounds of the invention, human recombinant serotonin (5-Hydroxytryptamine) 5-HT_{2B} receptor expressed in Chinese hamster ovary (CHO-K1) cells (Bonhaus, D.W. et al., *Br. J. Pharmacol.* 115:622, 1995) in a

modified Tris-HCl buffer (50 mM Tris-HCl, pH 7.4, 4 mM CaCl₂, 0.1% Ascorbic Acid) is used. Compounds of invention are incubated with 1.2 nM [³H]Lysergic acid diethylamide (LSD) for 60 min at 37 °C. Non-specific binding is estimated in the presence of 10 μM Serotonin (5-HT). Receptor proteins are filtered and washed, the filters are then counted to determine [³H]LSD specifically bound. Compounds are screened at 1 μM or lower, using 1% DMSO as vehicle. Compounds of the invention are tested in this biochemical assay and percent inhibition of specific binding is determined.

Serotonin (5-Hydroxytryptamine) 5-HT_{2C}

[0293] To evaluate in radioligand binding assays the activity of compounds of the invention, human recombinant serotonin (5-Hydroxytryptamine) 5-HT_{2C} receptor expressed in Chinese hamster ovary (CHO-K1) cells (Wolf, W.A. and Schutz, J.S., *J. Neurochem.* 69:1449, 1997) in a modified Tris-HCl buffer (50 mM Tris-HCl, pH 7.4, 0.1% Ascorbic Acid, 10 μM Pargyline) was used. Compounds of the invention were incubated with 1 nM [³H]Mesulergine for 60 min at 25 °C. Non-specific binding was estimated in the presence of 1 μM Mianserin. Receptor proteins were filtered and washed, the filters were then counted to determine [³H]Mesulergine specifically bound. Compounds were screened at 1 μM or lower, using 1% DMSO as vehicle. Biochemical assay results are presented as the percent inhibition of specific binding in Table 4.

Serotonin (5-Hydroxytryptamine) 5-HT₃

[0294] To evaluate in radioligand binding assays the activity of compounds of the invention, human recombinant serotonin (5-Hydroxytryptamine) 5-HT₃ receptor expressed in human embryonic kidney (HEK-293) cells (Miller K et al. *Synapse.* 11:58, 1992; Boess FG et al. *Neuropharmacology.* 36:637, 1997) in a modified Tris-HCl buffer (50 mM Tris-HCl, pH 7.4, 1 mM EDTA, 5 mM MgCl₂) is used. Compounds of invention are incubated with 0.69 nM [³H]GR-65630 for 60 min at 25 °C. Non-specific binding is estimated in the presence of 10 μM MDL-72222. Receptor proteins are filtered and washed, the filters are then counted to determine [³H]GR-65630 specifically bound. Compounds are screened at 1 μM or lower, using 1% DMSO as vehicle. Compounds of the invention are tested in this biochemical assay and percent inhibition of specific binding is determined.

Serotonin (5-Hydroxytryptamine) 5-HT₄

[0295] To evaluate in radioligand binding assays the activity of compounds of the invention, serotonin (5-Hydroxytryptamine) 5-HT₄ receptor from Duncan Hartley derived Guinea pig

striatum (Grossman CJ et al., *Br. J. Pharmacol.* 109:618, 1993) in a 50 mM Tris-HCl, pH 7.4, is used. Compounds of invention are incubated with 0.7 nM [³H]GR-113808 for 30 min at 25 °C. Non-specific binding is estimated in the presence of 30 µM Serotonin (5-HT). Receptor proteins are filtered and washed, the filters are then counted to determine [³H]GR-113808 specifically bound. Compounds are screened at 1 µM or lower, using 1% DMSO as vehicle. Compounds of the invention are tested in this biochemical assay and percent inhibition of specific binding is determined.

Serotonin (5-Hydroxytryptamine) 5-HT_{5A}

[0296] To evaluate in radioligand binding assays the activity of compounds of the invention, human recombinant serotonin (5-Hydroxytryptamine) 5-HT_{5A} receptor expressed in Chinese hamster ovary (CHO-K1) cells (Rees, S. et al., *FEBS Lett.* 355:242, 1994) in a modified Tris-HCl buffer (50 mM Tris-HCl, pH 7.4, 10 mM MgCl₂, 0.5 mM EDTA) was used. Compounds of the invention were incubated with 1.7 nM [³H]Lysergic acid diethylamide (LSD) for 60 min at 37 °C. Non-specific binding was estimated in the presence of 100 µM Serotonin (5-HT). Receptor proteins were filtered and washed, the filters were then counted to determine [³H]LSD specifically bound. Compounds were screened at 1 µM or lower, using 1% DMSO as vehicle. Compounds of the invention were tested in this biochemical assay and percent inhibition of specific binding was determined. Biochemical assay results are presented as the percent inhibition of specific binding in Table 4.

Serotonin (5-Hydroxytryptamine) 5-HT₆

[0297] To evaluate in radioligand binding assays the activity of compounds of the invention, human recombinant serotonin (5-Hydroxytryptamine) 5-HT₆ receptor expressed in human HeLa cells (Monsma, F.J. Jr. et al., *Mol. Pharmacol.* 43:320, 1993) in a modified Tris-HCl buffer (50 mM Tris-HCl, pH 7.4, 150 mM NaCl, 2 mM Ascorbic Acid, 0.001% BSA) was used. Compounds of the invention were incubated with 1.5 nM [³H]Lysergic acid diethylamide (LSD) for 120 min at 37 °C. Non-specific binding was estimated in the presence of 5 µM Serotonin (5-HT). Receptor proteins were filtered and washed, the filters were then counted to determine [³H]LSD specifically bound. Compounds were screened at 1 µM or lower, using 1% DMSO as vehicle. Biochemical assay results are presented as the percent inhibition of specific binding in Table 4.

Serotonin (5-Hydroxytryptamine) 5-HT₇

[0298] To evaluate in radioligand binding assays the activity of compounds of the invention, human recombinant serotonin (5-Hydroxytryptamine) 5-HT₇ receptor expressed in Chinese hamster ovary (CHO) cells (Roth, B.L. et al., *J. Pharmacol. Exp. Ther.* 268:1403, 1994; Shen, Y. et al., *J. Biol. Chem.* 268:18200, 1993) in a modified Tris-HCl buffer (50 mM Tris-HCl, pH 7.4, 10 mM MgCl₂, 0.5 mM EDTA) was used. Compounds of invention were incubated with 5.5 nM [³H] Lysergic acid diethylamide (LSD) for 2 h at 25 °C. Non-specific binding was estimated in the presence of 10 μM Serotonin (5-HT). Receptor proteins were filtered and washed, the filters were then counted to determine [³H]LSD specifically bound. Compounds were screened at 1 μM or lower, using 1% DMSO as vehicle. Biochemical assay results are presented as the percent inhibition of specific binding in Table 4.

Table 4: Percent Inhibition of ligand binding to aminergic G protein-coupled receptors by compounds of the invention:

Compound No.	Serotonin (1 μM)				Serotonin (0.1 μM)				
	5-HT _{2A}	5-HT _{2C}	5-HT ₆	5-HT ₇	5-HT _{2A}	5-HT _{2C}	5-HT _{5A}	5-HT ₆	5-HT ₇
1-1	97	98	93	42	60	51		35	
1-2	91	97	93	100					
1-3	99	98	85	103					
1-4	97/100	95/98	82/87	95/98					
1-5	102	95	100	79					
1-66					77	84	31	72	19
1-6	97	95	100	42					
1-7	98	95	95	48					
1-67					39	51	-11	25	-8
1-8	86	74	72	77					
1-9	77	80	32	30					
1-10	91	93	47	54					
1-11	82	78	72	74					
1-12	82	65	31	48					
1-13	82	83	26	41					
1-14	74	72	12	37					
1-15	102	99	98	94					
1-16	50	66	9	45					
1-17	96	91	87	82					
1-18	71	52	31	47					
1-19					98	94		45	69
1-20					91	81		38	78
1-21					68	44		3	40

Compound No.	Serotonin (1 μ M)				Serotonin (0.1 μ M)				
	5-HT _{2A}	5-HT _{2C}	5-HT ₆	5-HT ₇	5-HT _{2A}	5-HT _{2C}	5-HT _{5A}	5-HT ₆	5-HT ₇
1-22					71	47		7	16
1-23					62	43		32	18
1-24					36	8		10	12
1-25					17	16		4	10
1-26					23	-1		11	4
1-27					40	33		25	30
1-28					30	17		20	31
1-29					11	3		2	2
1-30					14	4		1	6
1-31					8	5		-7	-1
1-32					-6	-6		-1	31
1-33					43	56		-1	40
1-34	0	16	6						
1-35	90	75	14						
1-36	98	94	71						
1-37	98	97	71	73					
1-38	100	101	57	81					
1-39	98	104	62	95					
1-40	78	91	24						
1-41	66	41	14	59					
1-42	87	90	43	63					
1-43	47	49	22	66					
1-44					16	45		46	74
1-45					51	50		18	78
1-46					71	83		45	93
1-47					46	70		19	85
1-48					30	40		50	86
1-49					78	96		38	95
1-50					77	-1		30	95
1-51					77	92		4	15
1-52	88	89	43						
1-54	77	90	65						
1-59	96	99	54						
1-60					67	67	26	48	16
1-61					81	88	5	68	-12
1-62					43	33	6	28	30
1-63					21	25	15	25	25
1-64	98	95	95	48					
1-65					-10	6	-12	-6	-15

Example B6: Determination of Serotonin (5-Hydroxytryptamine) 5-HT_{2A} agonist/antagonist activity of compounds of the invention

[0299] To determine for agonist or antagonist activity of compounds of the invention in functional assays, human recombinant serotonin 5-HT_{2A} receptor expressed in human embryonic kidney (HEK-293) cells (Jerman JC, Brough SJ, Gager T, Wood M, Coldwell MC, Smart D and Middlemiss DN. *Eur. J. Pharmacol.* 414:23-30, 2001) is used. Cells are suspended in DMEM buffer, and distributed in microplates. A cytoplasmic calcium fluorescent indicator which varies proportionally to the free cytosolic Ca²⁺ ion concentration is mixed with probenecid in HBSS buffer complemented with 20 mM HEPES (pH 7.4), added into each well and equilibrated with the cells for 30 min at 37 °C followed by 30 min at 22 °C.

[0300] To measure agonist effects, compounds of the invention, reference agonist or HBSS buffer (basal control) is added to the cells and changes in fluorescence intensity are measured using a microplate reader. For stimulated control measurements, 5-HT at 100 nM is added in separate assay wells.

[0301] The results are expressed as a percent of the control response to 100 nM 5-HT. The standard reference agonist is 5-HT, which is tested in each experiment at several concentrations to generate a concentration-response curve from which its EC₅₀ value is calculated.

[0302] To measure antagonist effects, the addition of the compounds of the invention, reference antagonist or HBSS buffer is followed by the addition of 3 nM 5-HT or HBSS buffer (basal control) prior the fluorescence measurements. The results are expressed as a percent inhibition of the control response to 3 nM 5-HT. The standard reference antagonist is ketanserin, which is tested in each experiment at several concentrations to generate a concentration-response curve from which its IC₅₀ value is calculated. Compounds are screened at 3 µM or lower, using DMSO as vehicle.

Example B7: Determination of Serotonin (5-Hydroxytryptamine) 5-HT₆ agonist/antagonist activity of compounds of the invention

[0303] To determine for agonist or antagonist activity of compounds of the invention in functional assays, human recombinant 5-HT₆ receptor is transfected in CHO cells (Kohen, R., Metcalf, M.A., Khan, N., Druck, T., Huebner, K., Lachowicz, J.E., Meltzer, H.Y., Sibley, D.R., Roth, B.L., and Hamblin, M.W. "Cloning, characterization and chromosomal localization of a human 5-HT₆ serotonin receptor," *J. Neurochem.* 66:47, 1996) and the activity of compounds of

the invention is determined by measuring their effects on cAMP production using the Homogeneous Time Resolved Fluorescence (HTRF) detection method. Cells are suspended in HBSS buffer complemented with HEPES 20 mM (pH 7.4) and 500 μ M IBMX, and then distributed in microplates and incubated for 45 min at 37 °C in the absence (control) or presence of compounds of the invention or the reference agonist or antagonist.

[0304] For agonist determinations, stimulated control measurement, separate assay wells contain 10 μ M 5-HT. Following incubation, the cells are lysed and the fluorescence acceptor (D2-labeled cAMP) and fluorescence donor (anti-cAMP antibody labeled with europium cryptate) are added. After 60 min at RT, the fluorescence transfer is measured at λ_{ex} =337 nm and λ_{em} =620 and 665 nm using a microplate reader. The cAMP concentration is determined by dividing the signal measured at 665 nm by that measured at 620 nm (ratio).

[0305] The results are expressed as a percent of the control response to 10 μ M 5-HT. The standard reference agonist is 5-HT, which is tested in each experiment at several concentrations to generate a concentration-response curve from which its EC₅₀ value is calculated.

[0306] For antagonist determinations, the reference agonist 5-HT is added at a final concentration of 100 nM. For basal control measurements, separate assay wells do not contain 5-HT. Following 45 min incubation at 37 °C, the cells are lysed and the fluorescence acceptor (D2-labeled cAMP) and fluorescence donor (anti-cAMP antibody labeled with europium cryptate) are added.

[0307] After 60 min at RT, the fluorescence transfer is measured as mentioned above. The results are expressed as a percent inhibition of the control response to 100 nM 5-HT. The standard reference antagonist is methiothepin

Example B8: Determination of Dopamine D_{2L} antagonist activity of compounds

[0308] To determine for agonist or antagonist activity of compounds of the invention in functional assays, human recombinant dopamine D_{2L} receptor stably expressed in Chinese hamster ovary (CHO) cells (Senogles, SE et al. *J. Biol. Chem.* 265(8):4507, 1990) is used. Compounds of invention are pre-incubated with the membranes (0.1 mg/mL) and 10 mM GDP in modified HEPES buffer (20 mM HEPES, pH 7.4, 100 mM NaCl, 10 mM MgCl₂, 1 mM DTT, 1mM EDTA) for 20 min and Scintillation Proximity Assay (SPA) beads are added for another 60 min at 30 °C. The reaction is initiated by 0.3 nM [³⁵S]GTP γ S for an additional 15 min incubation period. Increase of [³⁵S]GTP γ S binding by 50% or more (350%) relative to the 1 mM dopamine response by compounds of the invention indicates possible dopamine D_{2L}

receptor agonist activity. Inhibition of a 10 μ M dopamine-induced increase of [35 S]GTP γ S binding response by 50% or more (350%) by compounds of the invention indicates receptor antagonist activity. Compounds are screened at 3 μ M or lower, using 0.4% DMSO as vehicle. Assay results are presented as the percent response of specific binding.

Example B9: Determination of Dopamine D_{2S} antagonist activity of compounds of the invention

[0309] To determine for agonist or antagonist activity of compounds of the invention in functional assays, human recombinant dopamine D_{2S} receptor stably expressed in Chinese hamster ovary (CHO) cells (Gilliland SL and Alper RH. *Naunyn-Schmiedeberg's Archives of Pharmacology* 361:498, 2000) is used. Compounds of invention are pre-incubated with the membranes (0.05 mg/mL) and 3 μ M GDP in modified HEPES buffer (20 mM HEPES, pH 7.4, 100 mM NaCl, 10 mM MgCl₂, 1 mM DTT, 1mM EDTA) for 20 min and Scintillation Proximity Assay (SPA) beads are then added for another 60 min at 30°C. The reaction is initiated by 0.3 nM [35 S]GTP γ S for an additional 30 min incubation period. Increase of [35 S]GTP γ S binding by 50% or more (350%) relative to the 100 μ M dopamine response by compounds of the invention indicates possible dopamine D_{2S} receptor agonist activity. Inhibition of a 3 μ M dopamine-induced increase of [35 S]GTP γ S binding response by 50% or more (350%) by compounds of the invention indicates receptor antagonist activity. Compounds are screened at 3 μ M or lower, using 0.4% DMSO as vehicle. Assay results are presented as the percent response of specific binding.

Example B10: Determination for agonist or antagonist activity of compounds of the invention in a histamine H₁ functional assay

[0310] To determine for agonist or antagonist activity of compounds of the invention in functional assays, human recombinant Histamine H₁ receptor expressed in human embryonic kidney (HEK-293) cells (Miller, T.R., Witte, D.G., Ireland, L.M., Kang, C.H., Roch, J.M., Masters, J.N., Esbenshade, T.A And Hancock, A.A. *J. Biomol. Screen.* 4:249-258, 1999) is used. Cells are suspended in DMEM buffer, and then distributed in microplates. A cytoplasmic calcium fluorescent indicator—which varies proportionally to the free cytosolic Ca²⁺ ion concentration—is mixed with probenecid in HBSS buffer complemented with 20 mM HEPES (pH 7.4) and is then added into each well and equilibrated with the cells for 30 min at 37 °C and then for another 30 min at 22 °C. To measure agonist effects, compounds of the invention, reference agonist or HBSS buffer (basal control) are added to the cells and changes in

fluorescence intensity are measured using a microplate reader. For stimulated control measurements, histamine at 10 μ M is added in separate assay wells.

[0311] The results are expressed as a percent of the control response to 10 μ M histamine. The standard reference agonist is histamine, which is tested in each experiment at several concentrations to generate a concentration-response curve from which its EC₅₀ value is calculated.

[0312] To measure antagonist effects, the addition of the compounds of the invention, reference antagonist or HBSS buffer is followed by the addition of 300 nM histamine or HBSS buffer (basal control) prior the fluorescence measurements. The results are expressed as percent inhibition of the control response to 300 nM histamine. The standard reference antagonist is ketanserin, which is tested in each experiment at several concentrations to generate a concentration-response curve from which its IC₅₀ value is calculated. Compounds are screened at 3 μ M or lower, using DMSO as vehicle.

Example B11: Increase of neurite outgrowth.

Neurite Outgrowth in Cortical Neurons

[0313] Compounds are tested to determine their ability to stimulate neurite outgrowth of cortical neurons. Standard methods are used to isolate cortical neurons. For the isolation of primary rat cortical neurons, the fetal brain from a pregnant rat at 17 days of gestation is prepared in Leibovitz's medium (L15; Gibco). The cortex is dissected out, and the meninges are removed. Trypsin (Gibco) is used to dissociate cortical C with DNase I. The cells are triturated for 30 min with a pipette in Dulbecco's Modified Eagle Media ("DMEM"; Gibco) with 10% Fetal Bovine Serum ("FBS") (Gibco) and centrifuged at 350 x g for 10 min at RT. The cells are suspended in Neurobasal medium supplemented with 2% B27 (Gibco) and 0.5 mM L-glutamine (Gibco). The cells are maintained at 30,000 cells per well of poly-L-lysine coated plates at 37 °C in 5% CO₂-95% air atmosphere. After adhesion, a vehicle control or compounds of the invention are added at different concentrations to the medium. BDNF (50 ng/mL) is used as a positive control for neurite growth. After treatment, cultures are washed in phosphate-buffered saline ("PBS"; Gibco) and fixed in glutaraldehyde 2.5% in PBS. Cells are fixed after 3 days growth. Several pictures (~80) of cells with neurites are taken per condition with a camera. The length measurements are made by analysis of the pictures using software from Image-Pro Plus

(France). The results are expressed as mean (s.e.m.). Statistical analysis of the data is performed using one way analysis of variance (ANOVA).

Neurite Outgrowth in Rat Mixed Cortical Cultures

[0314] Cortical mixed cultures are prepared from E18 Wistar rat embryos. The cortices are dissected out and the tissue is cut to small pieces. The cells are separated by 15-min incubation with DNase and papain. The cells are collected by centrifugation (1500 rpm, 5 min). The tissue is triturated with a pipette and the cells are plated using the micro-islet protocol (20,000 cells in 25 μ L medium) on poly-L-lysine coated 48 wells, in MEM supplemented with 2 mM glutamine, 0,1 μ g/mL gentamicin, 10% heat-inactivated fetal bovine serum (FBS-HI) and 10% heat-inactivated horse serum (HS-HI). After the cells attach to the well, 250 μ L medium is added to the wells. Four hours after plating the medium is changed to fresh medium (MEM with supplements and 5% HS-HI) containing test compound at 0.5, 5 and 50 nM concentrations. As positive controls BDNF (50, 100 and/or 150 ng/mL), and/or NGF (50 ng/mL and/or 100 ng/mL) are used. After 2 days *in vitro*, the cell's conditioned media are collected from plates before fixing the cells. The media samples are centrifuged 13,000 rpm 3 min to get rid of cell debris. The samples are stored at -20 °C for later analysis. Cells are formaldehyde-fixed and processed for immunocytochemistry. BDNF levels in the conditioned media are determined with a BDNF ELISA using the manufacturers (Promega, BDNF Emax® ImmunoAssay System, catalog number: G7610) instructions.

[0315] The cultures are fixed with 4% formaldehyde in 0.01M PBS for 30 min and washed once with PBS. The fixed cells are first permeabilized and non-specific binding is blocked by a 30-min incubation with blocking buffer containing 1% bovine serum albumin and 0.3% Triton X-100 in PBS. Rabbit anti-MAP-2 (dilution 1:1000, AB5622, Chemicon, in blocking buffer) is used as a primary antibody. The cells are incubated with the primary antibody for 48 h at +4 °C, washed with PBS and incubated with secondary antibody goat anti-rabbit IgG conjugated to Alexa Fluor568 (1:200, A11036, Molecular Probes) for 2 h at RT. The immunopositive cells are visualized by a fluorescence microscope equipped with appropriate filter set, and documented by a high resolution image capturing. The number of cells per field (4 field per well) are counted, and the neurite outgrowth is quantified using Image Pro Plus software.

[0316] The number of wells per compound concentration used is 6 (n=6). All data are presented as mean \pm standard deviation (SD) or standard error of mean (SEM), and differences are considered to be statistically significant at the $p < 0.05$ level. Statistical analysis is performed

using StatsDirect statistical software. Differences between group means are analyzed by using 1-way-ANOVA followed by Dunnet's test (comparison to the vehicle treated group).

Example B12: Use of an *in vivo* model to evaluate the ability of compounds to enhance cognition, learning and memory in scopolamine treated rats

[0317] The two-trial object recognition paradigm developed by Ennaceur and Delacour in the rat is used as a model of episodic/ short-term memory. Ennaceur, A., and Delacour, J. (1988), *Behav. Brain Res.* 31:47-59. The paradigm is based on spontaneous exploratory activity of rodents and does not involve rule learning or reinforcement. The novel object recognition paradigm is sensitive to the effects of ageing and cholinergic dysfunction. See, *e.g.*, Scali, C., et al., (1994), *Neurosci. Letts.* 170:117-120; and Bartolini, L., et al., (1996), *Biochem. Behav.* 53:277-283.

[0318] Male Sprague-Dawley rats between six and seven weeks old, weighing between 220-300 grams are obtained, *e.g.*, from Centre d'Elevage (Rue Janvier, B.P. 55, Le Genest-Saint-Isle 53940, France). The animals are housed in groups of 2 to 4 in polypropylene cages (with a floor area of 1032 cm²) under standard conditions: at RT (22 ± 2 °C), under a 12 h light/12 h dark cycle, with food and water provided *ad libitum*. Animals are permitted to acclimate to environmental conditions for at least 5 days before the experiment begins, and are numbered on their tails with indelible marker.

[0319] The experimental arena is a square wooden box (60 cm × 60 cm × 40 cm) painted dark blue, with 15 cm × 15 cm black squares under a clear plexiglass floor. The arena and objects placed inside the arena are cleaned with water between each trial to eliminate any odor trails left by rats. The arena is placed in a dark room illuminated only by halogen lamps directed towards the ceiling in order to produce a uniformly dim light in the box of approximately 60 lux. The day before testing, animals are allowed to freely explore the experimental arena for 3 min in the presence of two objects (habituation). Animals to be tested are placed in the experimental room at least 30 min before testing.

[0320] Novel object recognition test is comprised of two trials separated by an interval of 120 min or 24 h. When agents that disrupt memory such as the cholinergic antagonist scopolamine are used an inter-trial interval of 120 min is preferred. Alternatively a 24 h inter-trial interval is used when studying effect of natural forgetting on novel object recognition task. During the first, or acquisition, trial (T₁), rats are placed in the arena, where two identical objects have been previously placed. The time required for each animal to complete 15 sec of object exploration is

determined, with a cut-off time of 4 min. Exploration is considered to be directing the nose at a distance less than 2 centimeters ("cm") from the object and/or touching the object. During the second, or testing, trial (T_2), one of the objects presented in the first trial is replaced with an unknown or novel object, while the second, familiar object is left in place. Rats are placed back in the arena for 3 min, and exploration of both objects is determined. Locomotor activity of rats (number of times rats cross grid lines visible under the clear plexiglass floor) is scored for during T_1 and T_2 . At the conclusion of the experiments, the rats are sacrificed by an overdose of pentobarbital given intraperitoneally.

[0321] The following parameters are measured as part of the novel object recognition task: (1) time required to achieve 15 sec of object exploration during T_1 ; (2) locomotor activity during T_1 (number of crossed lines); (3) time spent in active exploration of the familiar object during T_2 (T_{Familiar}); (4) time spent in active exploration of the novel object during T_2 (T_{Novel}); and (5) locomotor activity during T_2 (number of crossed lines). The difference between time spent in active exploration of the novel object during T_2 and time spent in active exploration of the familiar object during T_2 ($\Delta T_{\text{Novel}} - T_{\text{Familiar}}$) is evaluated. The percent of animals in each group with $T_{\text{Novel}} - T_{\text{Familiar}}$ greater than or equal to 5 sec is also derived; described as percent of good learners.

[0322] Animals not meeting a minimal level of object exploration are excluded from the study as having naturally low levels of spontaneous exploration. Thus, only rats exploring the objects for at least five sec ($T_{\text{Novel}} + T_{\text{Familiar}} > 5 \text{ sec}$) are included in the study.

[0323] Animals are randomly assigned to groups of 14. Compounds of the invention and controls are administered to animals the groups as follows: Solutions of compounds are prepared freshly each day at a concentration of 0.25 mg/mL using purified water or saline as vehicle. Donepezil, used as a positive control, and scopolamine are administered simultaneously in a single solution of saline (5 mL/kg) prepared freshly each day. Scopolamine is purchased from Sigma Chemical Co. (Catalog No.S-1875; St. Quentin Fallavier, France) is dissolved in saline to a concentration of 0.06 mg/mL.

[0324] Donepezil or its vehicle and scopolamine are administered intraperitoneally 40 min before the acquisition trial (T_1). Compounds or their vehicle are administered by gavage 25 min before the acquisition trial (T_1), *e.g.*, 5 min after administration of scopolamine. The volume of administration is 5 mL/kg body weight for compounds administered intraperitoneally, and 10

mL/kg for compounds administered orally. Recognition scores and percent of good learners for compounds of the invention are determined.

Example B13: Use of an *in vivo* model to determine the ability of compounds to treat, prevent and/or delay the onset and/or the development of schizophrenia in PCP treated animals

[0325] *In vivo* models of schizophrenia can be used to determine the ability of the compounds described herein to treat and/or prevent and/or delay the onset and/or the development of schizophrenia.

[0326] One exemplary model for testing the activity of one or more compounds described herein to treat and/or prevent and/or delay the onset and/or development of schizophrenia employs phencyclidine (PCP), which is administered to the animal (*e.g.*, non-primate (rat) or primate (monkey)), resulting in dysfunctions similar to those seen in schizophrenic humans. See Jentsch et al., 1997, *Science* 277:953–955 and Piercey et al., 1988, *Life Sci.* 43(4):375–385). Standard experimental protocols may be employed in this or in other animal models. One protocol involves PCP-induced hyperactivity.

[0327] Male mice (various strains, *e.g.*, C57Bl/6J) from appropriate vendor (for example, Jackson Laboratories (Bar Harbor, Maine)) are used. Mice are received at 6-weeks of age. Upon receipt, mice are assigned unique identification numbers (tail marked) and are group housed with 4 mice/cage in OPTI mouse ventilated cages. All animals remain housed in groups of four during the remainder of the study. All mice are acclimated to the colony room for at least two weeks prior to testing and are subsequently tested at an average age of 8 weeks. During the period of acclimation, mice are examined on a regular basis, handled, and weighed to assure adequate health and suitability. Animals are maintained on a 12/12 light/dark cycle. The room temperature is maintained between 20 and 23 °C with a relative humidity maintained between 30% and 70%. Food and water are provided *ad libitum* for the duration of the study. In each test, animals are randomly assigned across treatment groups.

[0328] The open field (OF) test assesses locomotor behavior, *e.g.*, to measure mouse locomotor activity at baseline and in response to pharmacological agents. The open field chambers are Plexiglas square chambers (27.3 x 27.3 x 20.3 cm; Med Associates Inc., St Albans, VT) surrounded by infrared photobeams (16 x 16 x 16) to measure horizontal and vertical activity. The analysis is configured to divide the open field into a center and periphery zone such that the infrared photobeams allow measurement of activity in the center and periphery of

the field. Distance traveled is measured from horizontal beam breaks as the mouse moved whereas rearing activity is measured from vertical beam breaks.

[0329] Mice (10 to 12 animals per treatment group) are brought to the activity experimental room for at least 1 h acclimation to the experimental room conditions prior to testing. Eight animals are tested in each run. Mice are administered vehicle (*e.g.*, 10% DMSO or 5% PEG200 and 1% Tween 80), compound of the invention, clozapine (positive control, 1 mg/kg ip) and placed in the OF chambers for 30 min following which they are injected with either water or PCP and placed back in the OF chambers for a 60-min session. At the end of each OF test session the OF chambers are thoroughly cleaned.

PCP Hyperactivity Mouse Model of Schizophrenia

[0330] The test compound at the desired dose is dissolved in appropriate vehicle, *e.g.*, 5%PEG200, 1%Tween80 and administered orally 30 min prior to PCP injection. Clozapine (1 mg/kg) is dissolved in 10% DMSO and administered i.p. 30 min prior to PCP injection. PCP (5 mg/kg) is dissolved in sterile injectable saline solution and administered i.p.

[0331] Data are analyzed by analysis of variance (ANOVA) followed by post-hoc comparisons with Fisher Tests when appropriate. Baseline activity is measured during the first 30 min of the test prior to PCP injection. PCP-induced activity is measured during the 60 min following PCP injection. Statistical outliers that fell above or below 2 standard deviations from the mean are removed from the final analyses. An effect is considered significant if $p < 0.05$. Total distances traveled and total rearing following PCP administration are compared between groups treated with compounds and groups treated with vehicle and positive control clozapine.

[0332] Protocol is as described above with the exception of the treatment groups which are as follows: All injections are at a dose volume of 10mL/kg. The test compound at the desired dose is dissolved in Phosphate Buffered Saline (PBS) and administered orally 30 min.prior to PCP injection. Clozapine (0.5 and 1.0 mg/kg) is dissolved in 10% DMSO and administered i.p. 30 min.prior to Phencyclidine (PCP) injection. PCP (5.0 mg/kg) is dissolved in sterile injectable saline and administered i.p. Total distances traveled for is determined.

Example B14: Use of an *in vivo* model to determine the ability of compounds to treat, prevent and/or delay the onset and/or the development of schizophrenia in amphetamine treated animals

[0333] Male mice (various strains *e.g.*, C57Bl/6J) from appropriate supplier (for example Jackson Laboratories, Bar Harbor, Maine) are used. Mice typically are received at 6-weeks of

age. Mice are acclimated to the colony room for at least two weeks prior to testing. During the period of acclimation, mice are examined on a regular basis, handled, and weighed to assure adequate health and suitability and maintained on a 12 /12 light/dark cycle. The room temperature is maintained between 20 and 23 °C with a relative humidity maintained between 30% and 70%. Food and water are provided *ad libitum* for the duration of the study. In each test, animals are randomly assigned between treatment groups.

[0334] The open field test (OF) is used to assess motor activity. The open field chambers are plexiglass square chambers (*e.g.*, 27.3 x 27.3 x 20.3 cm; Med Associates Inc., St Albans, VT) surrounded by infrared photobeam sources (16 x 16 x 16). The enclosure is configured to split the open field into a center and periphery zone and the photocell beams are set to measure activity in the center and in the periphery of the OF chambers. Horizontal activity (distance traveled) and vertical activity (rearing) are measured from consecutive beam breaks.

[0335] On the day of testing, animals are brought to the experimental room for at least 1 h acclimation prior to start of treatment. Animals are administered with vehicle, haloperidol (positive control, 0.1 mg/kg ip) or test compound and placed in the OF. The time of administration of client compound to each animal is recorded. Baseline activity is recorded for 30 min following which mice receive amphetamine (4 mg/kg) or water and are placed back in the OF chambers for a 60-min session. At the end of each open field test session the OF chambers are thoroughly cleaned. Typically ten to twelve mice are tested in each group. Test compound doses typically range from 0.01 mg/kg to 60 mg/kg.

[0336] Data are analyzed by analysis of variance (ANOVA) followed by post-hoc comparisons with Fisher Tests when appropriate. Baseline activity is measured during the first 30 min of the test prior to amphetamine injection. Amphetamine-induced activity is measured during the 60 min following amphetamine injection. Statistical outliers that fall above or below 2 standard deviations from the mean are removed from the final analyses. An effect is considered significant if $p < 0.05$. Total distance traveled and total rearing following amphetamine administration are compared between groups treated with compound and groups treated with vehicle and positive control haloperidol.

Example B15: Use of the *in vivo* conditioned avoidance response (CAR) model to determine the ability of compounds to treat, prevent and/or delay the onset and/or the development of schizophrenia

[0337] All currently approved antipsychotic agents (typical and atypical) are known to have the ability to selectively suppress conditioned avoidance response (CAR) behavior in the rat. This evidence makes CAR one of the primary tests to assess antipsychotic activity of novel compounds.

[0338] Rats (various strains, 2 months of age) are trained and tested in a computer-assisted, two-way active avoidance apparatus (shuttle box). This box consists of two compartments of equal size divided by a stainless steel partition containing an opening of 7x7 cm. Each compartment is equipped with an electrified grid floor made of stainless steel rods spaced 1 cm apart. Rats trained to avoid the foot shock are placed each day in the shuttle box for a 4 min habituation period followed by 30 trials spaced by inter-trial interval varying at random between 20 and 30 sec. Each trial consists of a 10-sec stimulus light (conditioned stimulus, CS) followed by a 10-sec foot shock (unconditioned stimulus, US) in presence of the light presented in the compartment where the rat is located. If the animal leaves the compartment prior to the delivery of the foot shock, the response is considered an avoidance response. If the rat does not change compartment during the 10-sec light period and during the 10-sec shock + light period, an escape failure is recorded. This test requires animals to be trained 5 days/week. On each training day, rats are submitted to one training session of 30-trials. Treatment with test compound is initiated only when rats reach an avoidance performance of at least 80% on at least two consecutive training sessions. The test compound is administered orally at various doses and various pre-treatment times (depending upon specific pharmacokinetic properties).

[0339] Compounds with antipsychotic profile inhibit conditioned avoidance responses with or without increases in escape failures. Statistical analysis is performed using a Friedman two-way ANOVA by ranks followed by the Wilcoxon matched-pairs signed-ranks test to test each dose of the test compound administered versus vehicle control treated rats.

Example B16: An animal model of the negative symptoms of schizophrenia: subchronic PCP-induced social interaction deficits

[0340] Phencyclidine (PCP) administered to humans as well to experimental animals induces full-spectrum of schizophrenia symptoms, including negative symptoms and cognitive deficits. A major symptom of schizophrenia is considered to be social isolation/withdrawal as part of the cluster of negative symptoms. Subchronic treatment with PCP in rats leads to the development of clear signs of social withdrawal as measured by deficits in the interaction time with a cage intruder rat. Male Sprague Dawley rats (about 150 g, obtained from different vendors, for

example Harlan, Indiana) are used in this study. Upon receipt, rats are group housed in OPTI rat ventilated cages. Rats are housed in groups of 2-3 per cage for the remainder of the study.

During the period of acclimation, rats are examined on a regular basis, handled, and weighed to assure adequate health and suitability. Rats are maintained on a 12 /12 light/dark cycle with the light on at 7:00 a.m. The room temperature is maintained between 20-23 °C with a relative humidity maintained between 30-70%. Food and water are provided ad libitum for the duration of the study. Animals are randomly assigned across treatment groups and balanced by age.

[0341] For five days prior to test, rats are injected twice daily with either PCP (2 mg/kg; s.c) or saline (s.c). On day 6 and following a 30 min pretreatment with vehicle, clozapine (2.5 mg/kg ip dissolved in 5% PEG:5% Tween 80) as positive control and test compound at desired dose dissolved in appropriate vehicle, a pair of rats, unfamiliar to each other, receiving the same treatment are placed in a white plexiglas open field arena (24" x 17" x 8") and allowed to interact with each other for 6 min. Social interactions ('SI') include: sniffing the other rat; grooming the other rat; climbing over or under or around the other rat; following the other rat; or exploring the ano-genital area of the other rat. Passive contact and aggressive contact are not considered a measure of social interaction. The time the rats spent interacting with each other during the 6 min test is recorded by a trained observer. The social interaction chambers are thoroughly cleaned between the different rats. Data are analyzed by analysis of variance (ANOVA) followed by post-hoc analysis (*e.g.*, Fischer, Dunnett) when appropriate. An effect is considered significant if $p < 0.05$.

Example B17: An animal model of extrapyramidal syndrome (EPS): measurement of catalepsy in the mouse bar test

[0342] Antipsychotic drugs are known to induce extrapyramidal syndrome (EPS) in animals and in humans. An animal model considered to be predictive of EPS is the mouse bar test, which measures cataleptic responses to pharmacological agents. Male mice (various strains) from appropriate vendor (for example, Jackson Laboratories (Bar Harbor, Maine) are used. Mice are received at 6-weeks of age. Upon receipt, mice are assigned unique identification numbers (tail marked) and are group housed with 4 mice per cage in OPTI mouse ventilated cages. All animals remain housed in groups of four during the remainder of the study. All mice are acclimated to the colony room for at least two weeks prior to testing and are subsequently tested at an average age of 8 weeks. During the period of acclimation, mice are examined on a

regular basis, handled, and weighed to assure adequate health and suitability. Animals are maintained on a 12/12 light/dark cycle. The room temperature is maintained between 20-23 °C with a relative humidity maintained between 30-70%. Food and water are provided *ad libitum* for the duration of the study. In each test, animals are randomly assigned across treatment groups.

[0343] In the mouse bar test, the front paws of a mouse are placed on a horizontal bar raised 2" above a Plexiglas platform and time is recorded for up to 30 sec per trial. The test ends when the animal's front paws return to the platform or after 30 sec. The test is repeated 3 times and the average of 3 trials is recorded as index of catalepsy. In these studies the typical antipsychotic agent haloperidol (2 mg/kg ip dissolved in 10% DMSO) is used as positive control and induces rigidity and catalepsy as measured by time spent holding on the bar. 30 min prior to the trial, test compound at desired dose and dissolved in appropriate vehicle is administered PO, vehicle and positive control haloperidol (2 mg/kg ip) are administered to separate groups of mice. Catalepsy responses are measure 30 min, 1 h and 3 h following treatments. A trained observer is measuring time spent holding onto the bar during the 30 sec trial. Data are analyzed by analysis of variance (ANOVA) followed by post-hoc analysis (*e.g.*, Fischer, Dunnett) when appropriate. An effect is considered significant if $p < 0.05$.

Example B18: An animal model to test the anxiolytic effects of compounds using the elevated plus maze (EPM) test

[0344] This study may be used to test the anxiolytic properties of compounds detailed herein using the elevated plus maze (EPM) test in C57Bl/6J mice.

[0345] Male C57Bl/6J mice from Jackson Laboratories (Bar Harbor, Maine) are used for the open field study. Mice are received at 6-weeks of age. Upon receipt, mice are assigned unique identification numbers (tail marked) and are group housed with 4 mice/cage in OPTI mouse ventilated cages. All animals remain housed in groups of four during the remainder of the study. All mice are acclimated to the colony room for approximately 2 week prior to testing and are subsequently tested at an average age of 8 weeks of age. During the period of acclimation, mice and rats are examined on a regular basis, handled, and weighed to assure adequate health and suitability. Animals are maintained on a 12 h/12 h light/dark cycle. The room temperature is maintained between 20 and 23 °C with a relative humidity maintained between 30% and 70%. Chow and water are provided *ad libitum* for the duration of the study. In each test, animals are

randomly assigned across treatment groups. All animals are euthanized after the completion of the study.

[0346] Compounds may be dissolved in 5% PEG200 / H₂O and administered orally at a dose volume of 10 mL/kg 30 min prior to test; 2) Diazepam (2.5 mg/kg) is dissolved in 45% hydroxypropyl- β -cyclodextrin and administered orally at a dose volume of 10 mL/kg 30 min prior to test.

[0347] The elevated plus maze test assesses anxiety. The maze (Hamilton Kinder) consists of two closed arms (14.5 h x 5 w x 35 cm length) and two open arms (6 w x 35 l cm) forming a cross, with a square center platform (6 x 6 cm). All visible surfaces are made of black acrylic. Each arm of the maze is placed on a support column 56 cm above the floor. Antistatic black vinyl curtains (7' tall) surround the EPM to make a 5' x 5" enclosure. Animals are brought to acclimate to the experimental room at least 1 h before the test. Mice are placed in the center of the elevated plus maze facing the closed arm for a 5-min run. All animals are tested once. The time spent, distance traveled and entries in each arm are automatically recorded by a computer. The EPM is thoroughly cleaned after each mouse.

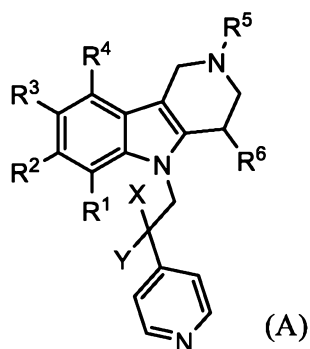
[0348] Data are analyzed using analysis of variance (ANOVA) followed by Fisher's LSD post hoc analysis when appropriate. An effect is considered significant if $p < 0.05$.

[0349] All references throughout, such as publications, patents, patent applications and published patent applications, are incorporated herein by reference in their entireties.

[0350] Although the foregoing invention has been described in some detail by way of illustration and example for purposes of clarity of understanding, it is apparent to those skilled in the art that certain minor changes and modifications will be practiced. Therefore, the description and examples should not be construed as limiting the scope of the invention.

CLAIMS

1. A compound of the formula (A):



wherein:

R^1 , R^2 , R^3 and R^4 are independently H, halo, C_1 - C_8 unsubstituted alkyl or C_1 - C_8 unsubstituted alkoxy, provided that R^3 is other than methyl or chloro when R^1 , R^2 and R^4 are each H and X is OH and Y is methyl;

R^5 is unsubstituted C_1 - C_8 alkyl or a C_1 - C_8 alkyl substituted with a perhaloalkyl moiety;

R^6 is H or an unsubstituted C_1 - C_8 alkyl;

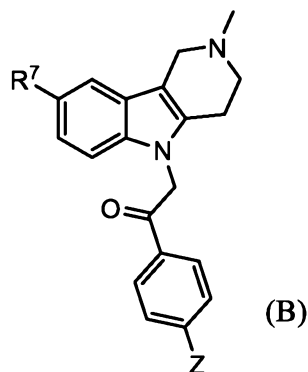
X is OH, C_1 - C_8 alkyl or is taken together with Y to form a cyclopropyl moiety; and

Y is H, C_1 - C_8 alkyl or is taken together with X to form a cyclopropyl moiety,

or a salt or solvate thereof.

2. The compound of claim 1 or a salt or solvate thereof, wherein R^5 is methyl, ethyl, cyclopropyl, trifluoroethyl, isopropyl, tert-butyl, sec-butyl, 2-methylbutyl, cyclobutyl, cyclopentyl, or cyclohexyl.
3. The compound of claim 2 or a salt or solvate thereof, wherein R^5 is methyl.
4. The compound of claim 1 or a salt or solvate thereof, wherein R^3 is halo or C_1 - C_8 unsubstituted alkyl.
5. The compound of claim 4 or a salt or solvate thereof, wherein R^3 is chloro or methyl.
6. The compound of claim 1 or a salt or solvate thereof, wherein X is OH and Y is C_1 - C_8 alkyl.

7. The compound of claim 6 or a salt or solvate thereof, wherein Y is methyl.
8. A compound of the formula (B):



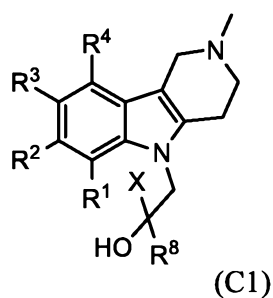
wherein:

R^7 is H, hydroxyl, nitro, cyano, halo, C_1 - C_8 perhaloalkyl, substituted or unsubstituted C_1 - C_8 alkyl, substituted or unsubstituted C_2 - C_8 alkenyl, substituted or unsubstituted C_2 - C_8 alkynyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, C_1 - C_8 perhaloalkoxy, C_1 - C_8 alkoxy, aryloxy, carboxyl, carbonylalkoxy, thiol, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aralkyl, thioalkyl, substituted or unsubstituted amino, acylamino, aminoacyl, aminocarbonylamino, aminocarbonyloxy, aminosulfonyl, sulfonylamino, sulfonyl, carbonylalkylenealkoxy, alkylsulfonylamino or acyl; and

Z is H, halo or C_1 - C_8 alkyl,

or a salt or solvate thereof.

9. The compound of claim 8 or a salt or solvate thereof, wherein R^7 is halo or C_1 - C_8 unsubstituted alkyl.
10. The compound of claim 9 or a salt or solvate thereof, wherein R^7 is chloro or methyl.
11. The compound of claim 8 or a salt or solvate thereof, wherein Z is H or halo.
12. A compound of the formula (C1):



wherein:

R^1 , R^2 , R^3 and R^4 are independently H, halo, C_1 - C_8 unsubstituted alkyl or C_1 - C_8 unsubstituted alkoxy;

R^8 is a substituted or unsubstituted aryl or a substituted or unsubstituted heteroaryl; and

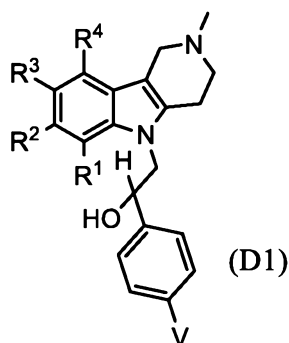
X is a C_4 - C_6 unsubstituted alkyl,
or a salt or solvate thereof.

13. The compound of claim 12 or a salt or solvate thereof, wherein R^3 is halo or C_1 - C_8 unsubstituted alkyl.

14. The compound of claim 12 or a salt or solvate thereof, wherein R^3 is chloro or methyl.

15. The compound of claim 14 or a salt or solvate thereof, wherein R^8 is a substituted or unsubstituted pyridyl, phenyl, pyrimidinyl, pyrazinyl, imidazolyl, oxazolyl, oxadiazolyl, furanyl, pyrrolyl or thiophenyl group.

16. A compound of the formula (D1):



wherein:

R^1 , R^2 , R^3 and R^4 are independently H, halo, C_1 - C_8 unsubstituted alkyl or C_1 - C_8 unsubstituted alkoxy; and

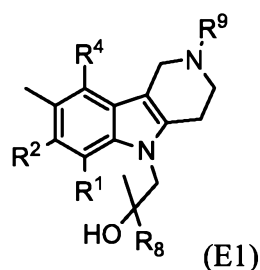
V is a halo,

or a salt or solvate thereof.

17. The compound of claim 16 or a salt or solvate thereof, wherein R^3 is halo or C_1 - C_8 unsubstituted alkyl.

18. The compound of claim 17 or a salt or solvate thereof, wherein R^3 is chloro or methyl.

19. A compound of the formula (E1):



wherein:

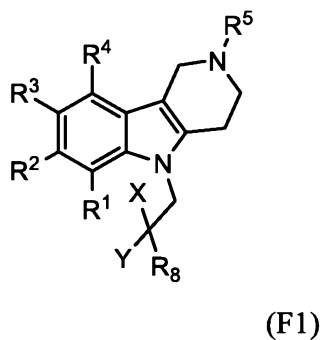
R^1 , R^2 , and R^4 are independently H, halo, C_1 - C_8 unsubstituted alkyl or C_1 - C_8 unsubstituted alkoxy;

R^8 is 6-pyrimidyl, 3-methyl-4-pyridyl or a phenyl substituted either: (i) with at least one alkoxy or hydroxyl group or (ii) with at least two halo groups; and

R^9 is an unsubstituted C_1 - C_3 alkyl,
or a salt or solvate thereof.

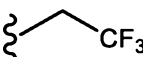
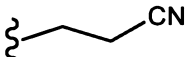
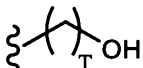
20. The compound of claim 19 or a salt or solvate thereof, wherein R^9 is methyl.

21. A compound of the formula (F1):



wherein:

R^1 , R^2 , R^3 and R^4 are independently H, halo, C_1 - C_8 unsubstituted alkyl or C_1 - C_8 unsubstituted alkoxy;

R^5 is ,  or  where T is 3 or 4

X is OH;

Y is H or C_1 - C_8 alkyl; and

R^8 is a substituted or unsubstituted heteroaryl,
or a salt or solvate thereof.

22. The compound of claim 21 or a salt or solvate thereof, wherein R^3 is halo or C_1 - C_8 unsubstituted alkyl.

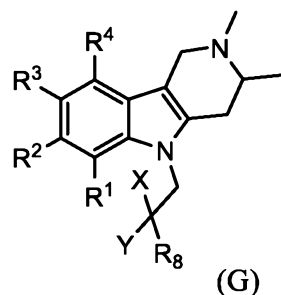
23. The compound of claim 22 or a salt or solvate thereof, wherein R^3 is chloro or methyl.

24. The compound of claim 21 or a salt or solvate thereof, wherein X is OH and Y is C_1 - C_8 alkyl.

25. The compound of claim 24 or a salt or solvate thereof, wherein Y is methyl.

26. The compound of claim 21 or a salt or solvate thereof, wherein R^8 is a substituted or unsubstituted pyridyl, phenyl, pyrimidinyl, pyrazinyl, imidazolyl, oxazolyl, oxadiazolyl, furanyl, pyrrolyl or thiophenyl group.

27. A compound of the formula (G):



wherein:

R^1 , R^2 and R^4 are independently H, halo, C_1 - C_8 unsubstituted alkyl or C_1 - C_8 unsubstituted alkoxy;

R^3 is methyl or chloro, provided that R^3 is methyl when R^8 is a substituted heteroaryl;

X is OH;

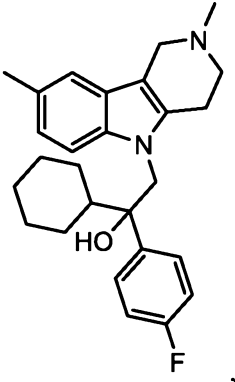
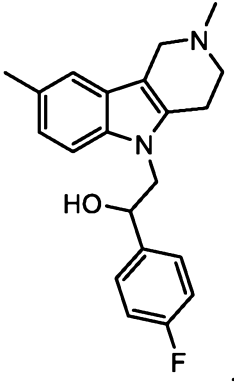
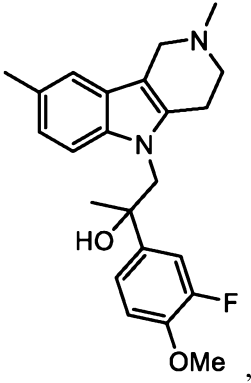
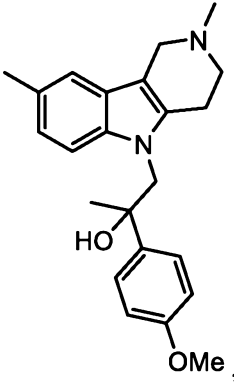
Y is H or C₁-C₈ alkyl; and

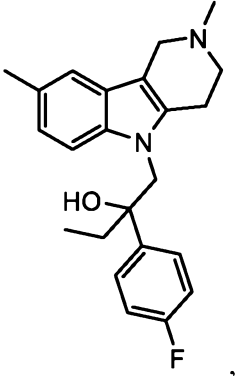
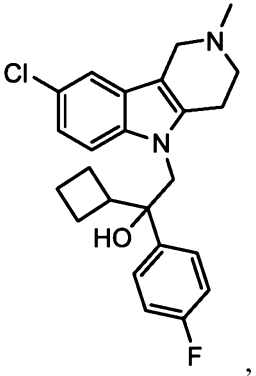
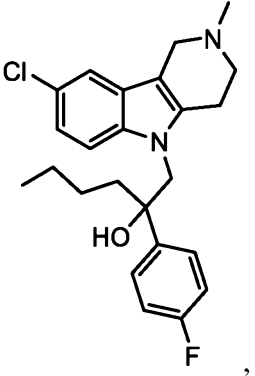
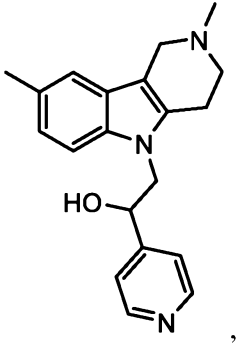
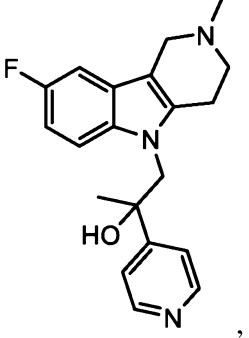
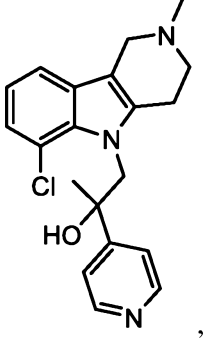
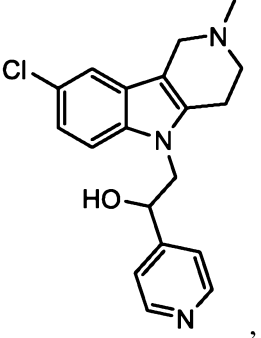
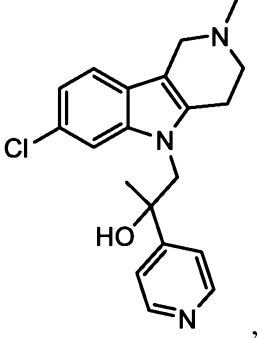
R⁸ is a substituted or unsubstituted heteroaryl,
or a salt or solvate thereof.

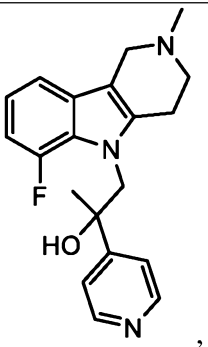
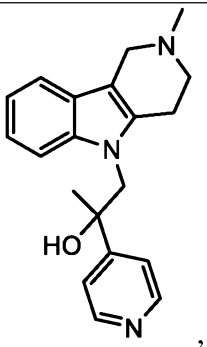
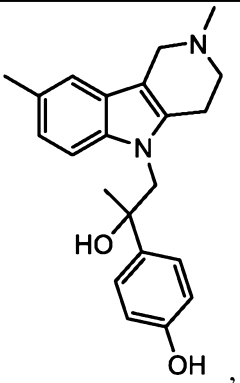
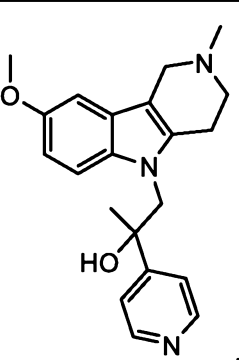
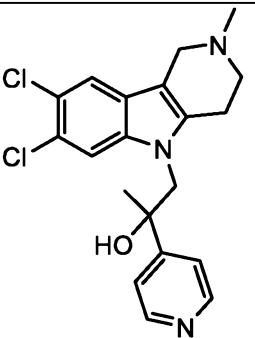
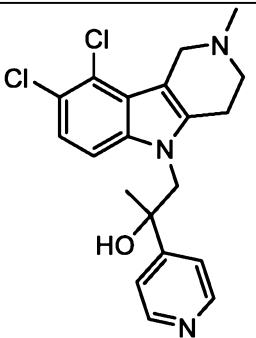
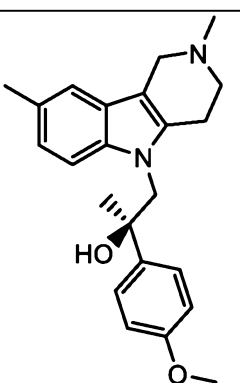
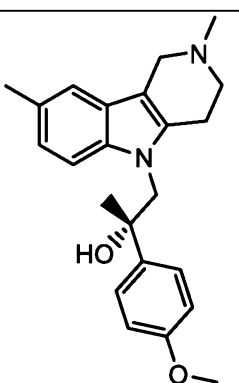
28. The compound of claim 27 or a salt or solvate thereof, wherein Y is C₁-C₈ alkyl.

29. The compound of claim 28 or a salt or solvate thereof, wherein Y is methyl.

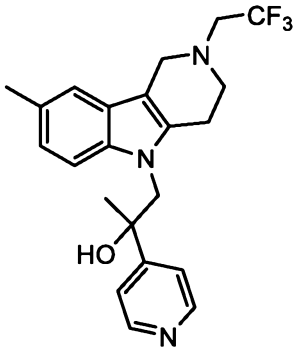
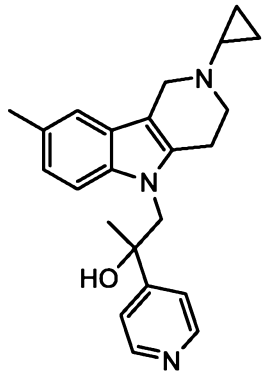
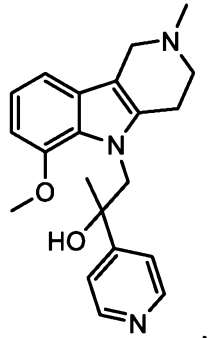
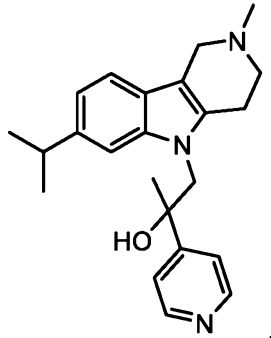
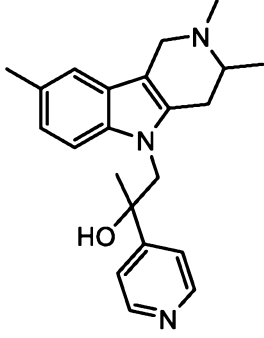
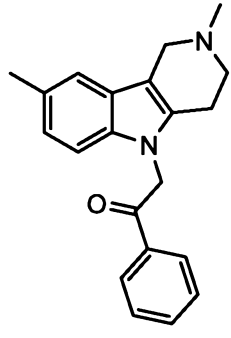
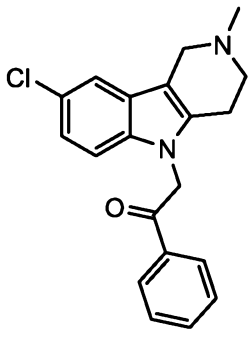
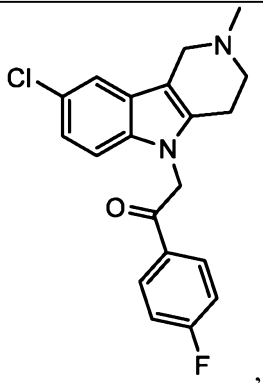
30. A compound selected from the group consisting of:

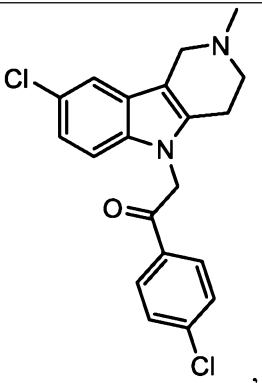
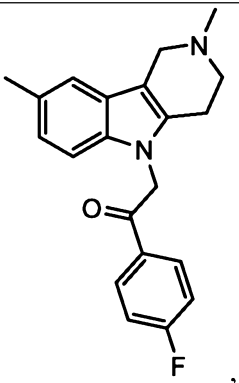
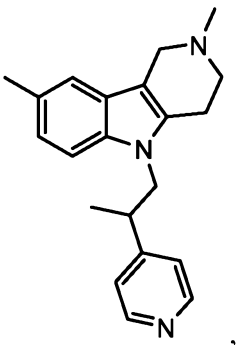
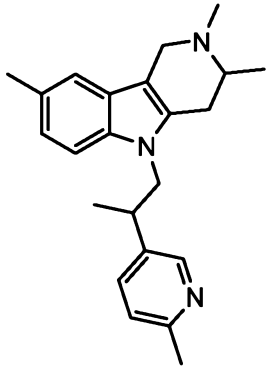
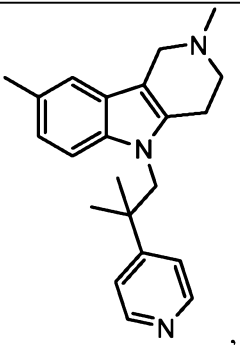
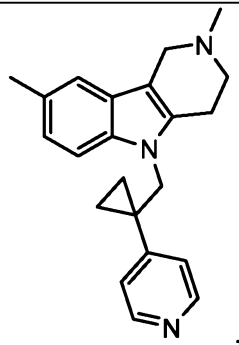
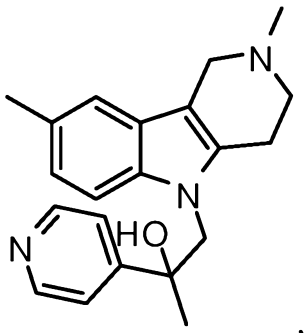
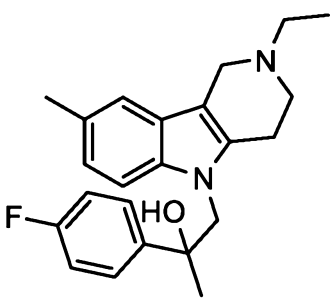
Comp.#	Compound Structure	Comp.#	Compound Structure
1-1		1-2	
1-3		1-4	

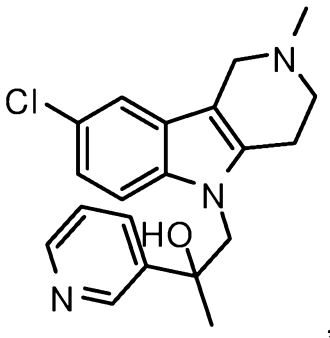
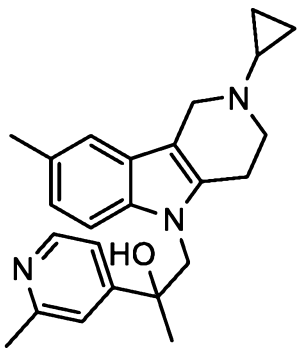
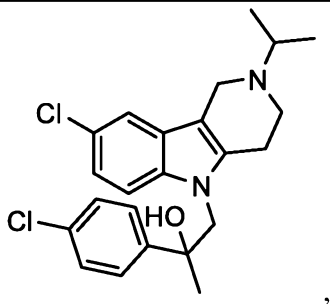
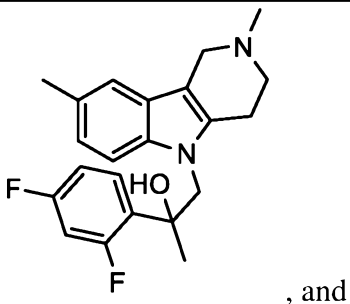
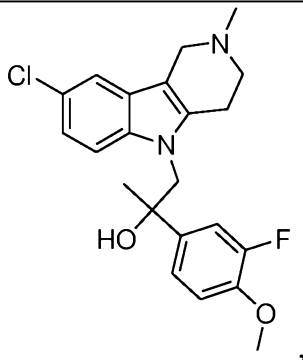
Comp.#	Compound Structure	Comp.#	Compound Structure
1-5		1-6	
1-7		1-8	
1-9		1-10	
1-11		1-12	

Comp.#	Compound Structure	Comp.#	Compound Structure
1-13		1-14	
1-15		1-16	
1-17		1-18	
1-19		1-20	

Comp.#	Compound Structure	Comp.#	Compound Structure
1-21		1-22	
1-23		1-24	
1-25		1-26	
1-27		1-28	

Comp.#	Compound Structure	Comp.#	Compound Structure
1-29		1-30	
1-31		1-32	
1-33		1-35	
1-36		1-37	

Comp.#	Compound Structure	Comp.#	Compound Structure
1-38		1-39	
1-46		1-47	
1-49		1-50	
1-52		1-53	

Comp.#	Compound Structure	Comp.#	Compound Structure
1-54		1-56	
1-57		1-58	
1-59			

or a pharmaceutically acceptable salt or solvate thereof.

31. A method of modulating a histamine receptor in an individual comprising administering to an individual in need thereof a compound according to any of claims 1-30, or a pharmaceutically acceptable salt or solvate thereof.

32. A pharmaceutical composition comprising (a) a compound of any of claims 1-30, or a pharmaceutically acceptable salt or solvate thereof, and (b) a pharmaceutically acceptable carrier.

33. A kit comprising a compound according to any of claims 1-30, or a pharmaceutically acceptable salt or solvate thereof, and instructions for use.
34. A method of treating a cognitive disorder or a disorder characterized by causing at least one symptom associated with impaired cognition comprising administering to an individual in need thereof an effective amount of a compound of any of claims 1-30, or a pharmaceutically acceptable salt or solvate thereof.
35. Use of a compound of any of claims 1-30, or a pharmaceutically acceptable salt or solvate thereof, in the manufacture of a medicament for modulating a histamine receptor.
36. Use of a compound of any of claims 1-30, or a pharmaceutically acceptable salt or solvate thereof, in the manufacture of a medicament for the treatment of a cognitive disorder or a disorder characterized by causing at least one symptom associated with impaired cognition.