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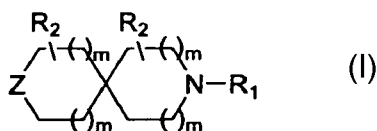
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(54) Title: SUBSTITUTED AZASPIRO DERIVATIVES



(57) Abstract: Substituted azaspiro derivatives of the Formula (I) are provided, in which variables are as described herein. Such compounds may be used to modulate ligand binding to histamine H3 receptors in vivo or in vitro, and are particularly useful in the treatment of a variety of central nervous system (CNS) and other disorders

in humans, domesticated companion animals and livestock animals. Compounds provided herein may be administered alone or in combination with one or more other CNS agents to potentiate the effects of the other CNS agent(s). Pharmaceutical compositions and methods for treating such disorders are provided, as are methods for using such ligands for detecting histamine H3 receptors (*e.g.*, receptor localization studies).

5 SUBSTITUTED AZASPIRO DERIVATIVES

RELATED APPLICATIONS

This application claims the benefit of U.S. Patent Application No. 11/745,448, filed May 7, 2007, and U.S. Provisional Patent Application No. 60/746,680, filed May 8, 2006.

10 The contents of these applications are incorporated herein by reference in their entirety.

FIELD OF THE INVENTION

This invention relates generally to substituted azaspiro derivatives, and to the use of such compounds for treating conditions responsive to histamine H3 receptor modulation. The invention further relates to the use of such compounds as probes for the detection and
15 localization of histamine H3 receptors.

BACKGROUND OF THE INVENTION

Hormones and neurotransmitters regulate a wide variety of biological functions, often
20 via specific receptor proteins located on the surface of living cells. Many of these receptors carry out intracellular signaling via the activation of coupled guanosine triphosphate-binding proteins (G proteins); such receptors are collectively called G protein-coupled receptors or GPCRs. The important role of GPCRs in the regulation of cell and organ function has attracted attention to these receptors as targets for new pharmaceutical agents.

25 Histamine is a multifunctional chemical transmitter that signals through specific cell surface GPCRs. To date, four histamine receptor subtypes have been identified: H1, H2, H3 and H4. Histamine H3 receptor is a presynaptic GPCR that is found primarily in the central nervous system, although lower levels are also found in the peripheral nervous system. Genes encoding the H3 receptor have been reported in various organisms, including humans (*see*
30 Lovenberg et al. (1999) *Molecular Pharmacology* 55:1101-07), and alternative splicing of this gene appears to result in multiple isoforms. The histamine H3 receptor is an auto- and hetero-receptor whose activation leads to a decreased release of neurotransmitters (including histamine, acetylcholine, norepinephrine and glutamate) from neurons in the brain. Histamine H3 receptor is involved in the regulation of processes such as sleep and wakefulness, feeding
35 and memory.

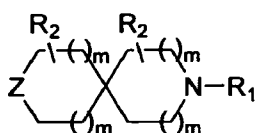
Antagonists of histamine H3 receptor increase synthesis and release of cerebral histamine and other neurotransmitters, inducing an extended wakefulness, an improvement in cognitive processes, a reduction in food intake and a normalization of vestibular reflexes.

Such antagonists are useful, for example, as therapeutics for central nervous system disorders such as Alzheimer's disease, Parkinson's disease, schizophrenia, mood and attention alterations including attention deficit hyperactivity disorder and attention deficit disorder, memory and learning disorders, cognitive disorders (such as mild cognitive impairment and cognitive deficits in psychiatric pathologies), epilepsy, migraine, and disorders associated with the regulation of sleep and wakefulness, as well as in the treatment and prevention of conditions such as obesity, eating disorders, diabetes, vertigo, motion sickness and allergic rhinitis.

Accordingly, there is a need for new H3 receptor modulators. The present invention fulfills this need, and provides further related advantages.

SUMMARY OF THE INVENTION

In certain aspects, the present invention provides substituted azaspiro derivatives of Formula I:



Formula I

and pharmaceutically acceptable salts, solvates and esters of such compounds. Within Formula I:

Z is CHR_3 or NR_4 ;

Each m is independently 0, 1, 2 or 3;

R_1 is C_1 - C_6 alkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, $(\text{C}_3$ - C_8 cycloalkyl) C_0 - C_2 alkyl or (3- to 8-membered heterocycloalkyl) C_0 - C_2 alkyl, each of which is optionally substituted, and each of which is preferably substituted with from 0 to 4 substituents independently chosen from oxo, nitro, halogen, amino, cyano, hydroxy, aminocarbonyl, C_1 - C_6 alkyl, C_2 - C_6 alkenyl, C_1 - C_6 haloalkyl, C_1 - C_6 haloalkoxy, C_1 - C_6 alkylthio, C_2 - C_6 alkyl ether, C_1 - C_6 alkanoyl, mono- or di- $(\text{C}_1$ - C_6 alkyl)amino, mono- or di- $(\text{C}_1$ - C_6 alkyl)aminocarbonyl, C_3 - C_7 cycloalkyl and 3- to 7-membered heterocycloalkyl; such that R_1 does not comprise a $-\text{COOH}$ group;

Each R_2 independently represents from 0 to 4 substituents; preferably such substituent(s), if present, are independently chosen from C_1 - C_3 alkyl and C_1 - C_3 haloalkyl;

R_3 is:

- (i) C_1 - C_6 alkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, C_1 - C_6 alkoxy, C_1 - C_6 alkylthio, C_1 - C_6 alkylsulfonyl, C_1 - C_6 alkanoyl, C_1 - C_6 alkoxycarbonyl, mono- or di- $(\text{C}_1$ - C_8 alkyl)amino, mono- or di- $(\text{C}_1$ - C_8 alkyl)aminocarbonyl or mono- or di- $(\text{C}_1$ - C_8 alkyl)aminosulfonyl, each of which is optionally substituted, and each of which is preferably substituted with from 0 to 4 substituents independently chosen from R_4 ; or

(ii) a group of the Formula W-Y-X-;

R₄ is:

(i) C₁-C₆alkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, C₁-C₆alkylsulfonyl, C₁-C₆alkanoyl, C₁-C₆alkoxycarbonyl, mono- or di-(C₁-C₆alkyl)amino, mono- or di-(C₁-C₆alkyl)aminocarbonyl or mono- or di-(C₁-C₆alkyl)aminosulfonyl, each of which is optionally substituted, and each of which is preferably substituted with from 0 to 4 substituents independently chosen from R_a; or

(ii) a group of the Formula W-Y-;

W is C₃-C₁₀cycloalkyl, 3- to 10-membered heterocycloalkyl, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl, each of which is optionally substituted, and each of which is preferably substituted with from 0 to 4 or from 1 to 4 substituents independently chosen from R_a;

Y is absent or C₁-C₆alkylene;

X is absent, NH, S, SO₂, or O; and

Each R_a is independently:

(i) halogen, cyano, hydroxy, amino, nitro, aminocarbonyl or oxo;

(ii) C₁-C₈alkyl, C₁-C₈haloalkyl, (C₃-C₈cycloalkyl)C₀-C₄alkyl, C₁-C₈alkoxy, C₁-C₈alkoxycarbonyl, C₁-C₈alkanoyl, C₁-C₈alkylsulfonyl, mono- or di-(C₁-C₈alkyl)amino, mono- or di-(C₁-C₈alkyl)aminocarbonyl or mono- or di-(C₁-C₈alkyl)aminosulfonyl; each of which is optionally substituted and each of which is preferably substituted with from 0 to 4 substituents independently chosen from halogen, oxo, amino, C₁-C₄alkyl, C₂-C₆alkenyl, C₁-C₈alkoxy; or

(iii) (6- to 10-membered aryl)-L-, or (5- to 10-membered heterocycle)-L-, wherein L is a single covalent bond, O, SO₂, C(=O), (CH₂)_n-NH-C(=O) or (CH₂)_n-O-C(=O) and n is 0, 1 or 2; each of which aryl or heterocycle is optionally substituted, and each of which aryl or heterocycle is preferably substituted with from 0 to 3 substituents independently chosen from:

(a) halogen, cyano, hydroxy, amino, nitro, aminocarbonyl, oxo, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆aminoalkyl, C₂-C₆alkyl ether, C₁-C₆alkoxy, C₁-C₆alkoxycarbonyl, C₁-C₆alkanoyl, C₁-C₆alkylsulfonyl, mono- or di-(C₁-C₆alkyl)amino, mono- or di-(C₁-C₆alkyl)aminocarbonyl or mono- or di-(C₁-C₆alkyl)aminosulfonyl;

(b) (5- to 10-membered, N-linked heterocycloalkyl)-(CO)_p-, wherein p is 0 or 1, which heterocycloalkyl is substituted with from 0 to 3 substituents independently chosen from halogen, C₁-C₄alkyl, C₂-C₄alkenyl, C₁-C₄alkoxy and C₂-C₄alkyl ether; and

(c) groups that are taken together with the atoms to which they are attached to form a fused, partially or fully saturated 5- or 6-membered ring that is optionally

substituted (*e.g.*, with from 0 to 2 substituents independently chosen from oxo and C₁-C₄alkyl).

Within certain aspects, substituted azaspiro derivatives provided herein are histamine H3 receptor modulators that exhibit a K_i at a histamine H3 receptor, preferably a human H3 receptor, that is no greater than 4 micromolar, 1 micromolar, 500 nanomolar, 100 nanomolar, 50 nanomolar or 10 nanomolar, as determined using a histamine-induced H3 receptor GTP binding assay.

Within certain aspects, compounds provided herein are labeled with a detectable marker (*e.g.*, radiolabeled or fluorescein conjugated).

The present invention further provides, within other aspects, pharmaceutical compositions comprising at least one substituted azaspiro derivative as provided herein in combination with a physiologically acceptable carrier or excipient.

Within further aspects, methods are provided for modulating H3 receptor activity, comprising contacting a cell (*e.g.*, neuronal) expressing H3 receptor with at least one H3 receptor modulator as described herein. Such contact may occur *in vivo* or *in vitro* and is generally performed using a concentration of compound that is sufficient to alter H3 receptor GTP binding *in vitro* (*e.g.*, using an assay provided in Example 7 or Example 8, herein).

The present invention further provides methods for treating a condition responsive to H3 receptor modulation in a patient, comprising administering to the patient a therapeutically effective amount of at least one H3 receptor modulator. Such conditions include, for example, attention deficit disorder, attention deficit hyperactivity disorder, dementia, schizophrenia, cognitive disorders (including mild cognitive impairment), epilepsy, migraine, excessive daytime sleepiness (EDS) and related disorders such as shift work sleep disorder, jet lag, narcolepsy, sleep apnea, allergic rhinitis, vertigo, motion sickness, memory disorders such as Alzheimer's disease, Parkinson's disease, obesity, eating disorders, diabetes, fatigue, and fatigue-related disorders such as sleep/fatigue disorders, sleep impairment due to perimenopausal hormonal shifts, Parkinson's-related fatigue, multiple sclerosis-related fatigue, and chemotherapy-induced fatigue.

Within further aspects, the present invention provides methods for determining the presence or absence of H3 receptor in a sample, comprising: (a) contacting a sample with a H3 receptor modulator as described herein under conditions that permit binding of the H3 receptor modulator to H3 receptor; and (b) detecting a level of the H3 modulator bound to H3 receptor.

The present invention also provides packaged pharmaceutical preparations, comprising: (a) a pharmaceutical composition as described herein in a container; and (b) instructions for using the composition to treat one or more conditions responsive to H3 receptor modulation, such as the conditions recited herein.

In yet another aspect, the present invention provides methods of preparing the compounds disclosed herein, including the intermediates.

These and other aspects of the present invention will become apparent upon reference to the following detailed description.

5 DETAILED DESCRIPTION

As noted above, the present invention provides substituted azaspiro derivatives. Such compounds may be used *in vitro* or *in vivo*, to modulate H3 receptor activity in a variety of contexts.

TERMINOLOGY

- 10 Compounds are generally described herein using standard nomenclature. For compounds having asymmetric centers, it should be understood that (unless otherwise specified) all of the optical isomers and mixtures thereof are encompassed. In addition, compounds with carbon-carbon double bonds may occur in *Z*- and *E*- forms, with all isomeric forms of the compounds being included in the present invention unless otherwise specified.
- 15 Where a compound exists in various tautomeric forms, a recited compound is not limited to any one specific tautomer, but rather is intended to encompass all tautomeric forms. Certain compounds are described herein using a general formula that includes variables (*e.g.*, R_1 , X , n). Unless otherwise specified, each variable within such a formula is defined independently of any other variable, and any variable that occurs more than one time in a formula is defined
- 20 independently at each occurrence.

The phrase "substituted azaspiro derivative," as used herein, encompasses all compounds of Formula I, including any enantiomers, racemates and stereoisomers, as well as pharmaceutically acceptable salts, solvates (*e.g.*, hydrates) and esters of such compounds.

- 25 A "pharmaceutically acceptable salt" of a compound recited herein is an acid or base salt that is suitable for use in contact with the tissues of human beings or animals without excessive toxicity or carcinogenicity, and preferably without irritation, allergic response, or other problem or complication. Such salts include mineral and organic acid salts of basic residues such as amines, as well as alkali or organic salts of acidic residues such as carboxylic acids. Specific pharmaceutically acceptable anions for use in salt formation include, but are
- 30 not limited to, acetate, 2-acetoxybenzoate, ascorbate, benzoate, bicarbonate, bromide, calcium edetate, carbonate, chloride, citrate, dihydrochloride, diphosphate, ditartrate, edetate, estolate (ethylsuccinate), formate, fumarate, gluceptate, gluconate, glutamate, glycolate, glycolylarsanilate, hexylresorcinate, hydrabamine, hydrobromide, hydrochloride, hydroiodide, hydroxymaleate, hydroxynaphthoate, iodide, isethionate, lactate, lactobionate,
- 35 malate, maleate, mandelate, methylbromide, methylnitrate, methylsulfate, mucate, napsylate,

nitrate, pamoate, pantothenate, phenylacetate, phosphate, polygalacturonate, propionate, salicylate, stearate, subacetate, succinate, sulfamate, sulfanilate, sulfate, sulfonates including besylate (benzenesulfonate), camsylate (camphorsulfonate), edisylate (ethane-1,2-disulfonate), esylate (ethanesulfonate) 2-hydroxyethylsulfonate, mesylate (methanesulfonate),
5 triflate (trifluoromethanesulfonate) and tosylate (*p*-toluenesulfonate), tannate, tartrate, teoclate and triethiodide. Similarly, pharmaceutically acceptable cations for use in salt formation include, but are not limited to ammonium, benzathine, chlorprocaine, choline, diethanolamine, ethylenediamine, meglumine, procaine, and metals such as aluminum, calcium, lithium, magnesium, potassium, sodium and zinc. Those of ordinary skill in the art
10 will recognize further pharmaceutically acceptable salts for the compounds provided herein. In general, a pharmaceutically acceptable acid or base salt can be synthesized from a parent compound that contains a basic or acidic moiety by any conventional chemical method. Briefly, such salts can be prepared by reacting the free acid or base forms of these compounds with a stoichiometric amount of the appropriate base or acid in water or in an organic solvent,
15 or in a mixture of the two; generally, the use of nonaqueous media, such as ether, ethyl acetate, ethanol, methanol, isopropanol or acetonitrile, is preferred.

It will be apparent that each compound provided herein may, but need not, be formulated as a solvate (*e.g.*, hydrate) or non-covalent complex. In addition, the various crystal forms and polymorphs are within the scope of the present invention. Also provided
20 herein are prodrugs of the compounds of the recited Formulas. A "prodrug" is a compound that may not fully satisfy the structural requirements of the compounds provided herein, but is modified *in vivo*, following administration to a patient, to produce a compound a formula provided herein. For example, a prodrug may be an acylated derivative of a compound as provided herein. Prodrugs include compounds wherein hydroxy, amine or sulfhydryl groups
25 are bonded to any group that, when administered to a mammalian subject, cleaves to form a free hydroxy, amino, or sulfhydryl group, respectively. Examples of prodrugs include, but are not limited to, acetate, formate and benzoate derivatives of alcohol and amine functional groups within the compounds provided herein. Prodrugs of the compounds provided herein may be prepared by modifying functional groups present in the compounds in such a way that
30 the modifications are cleaved *in vivo* to yield the parent compounds.

As used herein, the term "alkyl" refers to a straight or branched chain saturated aliphatic hydrocarbon. Alkyl groups include groups having from 1 to 8 carbon atoms (C₁-C₈alkyl), from 1 to 6 carbon atoms (C₁-C₆alkyl) and from 1 to 4 carbon atoms (C₁-C₄alkyl), such as methyl, ethyl, propyl, isopropyl, n-butyl, *sec*-butyl, *tert*-butyl, pentyl, 2-pentyl,
35 isopentyl, neopentyl, hexyl, 2-hexyl, 3-hexyl and 3-methylpentyl. "C₀-C₄alkyl" refers to a single covalent bond (C₀) or an alkylene group having from 1 to 4 carbon atoms.

"Alkylene" refers to a divalent alkyl group. C₁-C₄alkylene is an alkylene group having from 1 to 4 carbon atoms. C₀-C₄alkylene is a single covalent bond or an alkylene group having from 1 to 4 carbon atoms.

"Alkenyl" refers to straight or branched chain alkene groups, which comprise at least one unsaturated carbon-carbon double bond. Alkenyl groups include C₂-C₈alkenyl, C₂-C₆alkenyl and C₂-C₄alkenyl groups, which have from 2 to 8, 2 to 6 or 2 to 4 carbon atoms, respectively, such as ethenyl, allyl or isopropenyl. "Alkynyl" refers to straight or branched chain alkyne groups, which have one or more unsaturated carbon-carbon bonds, at least one of which is a triple bond. Alkynyl groups include C₂-C₈alkynyl, C₂-C₆alkynyl and C₂-C₄alkynyl groups, which have from 2 to 8, 2 to 6 or 2 to 4 carbon atoms, respectively.

A "cycloalkyl" is a group that comprises one or more saturated and/or partially saturated rings in which all ring members are carbon, such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, adamantyl, decahydro-naphthalenyl, octahydro-indenyl, and partially saturated variants of the foregoing, such as cyclohexenyl. Cycloalkyl groups do not comprise an aromatic ring or a heterocyclic ring. A "(C₃-C₈cycloalkyl)C₀-C₄alkyl" is a C₃-C₈cycloalkyl group linked via a single covalent bond or a C₁-C₄alkylene group.

By "alkoxy," as used herein, is meant an alkyl group attached via an oxygen bridge. Alkoxy groups include C₁-C₈alkoxy, C₁-C₆alkoxy and C₁-C₄alkoxy groups, which have from 1 to 8, from 1 to 6, or from 1 to 4 carbon atoms, respectively. Methoxy, ethoxy, propoxy, isopropoxy, n-butoxy, *sec*-butoxy, *tert*-butoxy, n-pentoxy, 2-pentoxy, 3-pentoxy, isopentoxy, neopentoxy, hexoxy, 2-hexoxy, 3-hexoxy, and 3-methylpentoxy are specific alkoxy groups. Similarly, "alkylthio" refers to an alkyl group attached via a sulfur bridge.

The term "oxo" is used herein to refer to an oxygen substituent of a carbon atom that results in the formation of a carbonyl group (C=O). An oxo group that is a substituent of a nonaromatic carbon atom results in a conversion of -CH₂- to -C(=O)-. An oxo group that is a substituent of an aromatic carbon atom results in a conversion of -CH- to -C(=O)- and may result in a loss of aromaticity.

The term "alkanoyl" refers to an acyl group (*e.g.*, -(C=O)-alkyl), in which carbon atoms are in a linear or branched alkyl arrangement and where attachment is through the carbon of the carbonyl group. Alkanoyl groups have the indicated number of carbon atoms, with the carbonyl carbon being included in the numbered carbon atoms. For example a C₂alkanoyl group is an acetyl group having the formula -(C=O)CH₃; "C₁alkanoyl" refers to -(C=O)H. Alkanoyl groups include, for example, C₁-C₈alkanoyl, C₁-C₆alkanoyl and C₁-C₄alkanoyl groups, which have from 1 to 8, from 1 to 6 or from 1 to 4 carbon atoms, respectively.

An "alkanone" is a ketone group in which carbon atoms are in a linear or branched alkyl arrangement. "C₃-C₈alkanone," "C₃-C₆alkanone" and "C₃-C₄alkanone" refer to an alkanone having from 3 to 8, 6 or 4 carbon atoms, respectively. By way of example, a C₃alkanone group has the structure $-\text{CH}_2-(\text{C}=\text{O})-\text{CH}_3$.

5 Similarly, "alkyl ether" refers to a linear or branched ether substituent (*i.e.*, an alkyl group that is substituted with an alkoxy group). Alkyl ether groups include C₂-C₈alkyl ether, C₂-C₆alkyl ether and C₂-C₄alkyl ether groups, which have 2 to 8, 6 or 4 carbon atoms, respectively. A C₂alkyl ether has the structure $-\text{CH}_2-\text{O}-\text{CH}_3$.

10 The term "alkoxycarbonyl" refers to an alkoxy group attached through a carbonyl ($-\text{C}(\text{O})-$) bridge (*i.e.*, a group having the general structure $-\text{C}(\text{O})-\text{O}-\text{alkyl}$). Alkoxycarbonyl groups include C₁-C₈, C₁-C₆ and C₁-C₄alkoxycarbonyl groups, which have from 1 to 8, 6 or 4 carbon atoms, respectively, in the alkyl portion of the group (*i.e.*, the carbon of the keto bridge is not included in the indicated number of carbon atoms). "C₁alkoxycarbonyl" refers to $-\text{C}(\text{O})-\text{O}-\text{CH}_3$; C₃alkoxycarbonyl indicates $-\text{C}(\text{O})-\text{O}-(\text{CH}_2)_2\text{CH}_3$ or $-\text{C}(\text{O})-\text{O}-$
15 $(\text{CH})(\text{CH}_3)_2$.

"Alkylsulfonyl" refers to groups of the formula $-(\text{SO}_2)-\text{alkyl}$, in which the sulfur atom is the point of attachment. Alkylsulfonyl groups include C₁-C₈alkylsulfonyl, C₁-C₆alkylsulfonyl and C₁-C₄alkylsulfonyl groups, each of which has the indicated number of carbon atoms in the alkyl group.

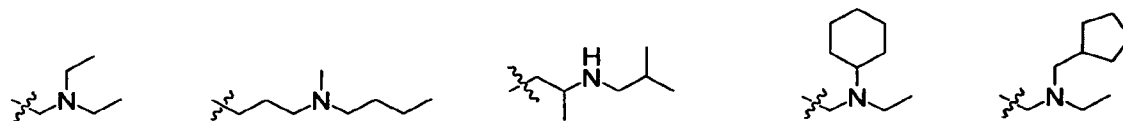
20 "Aminosulfonyl" refers to groups of the formula $-(\text{SO}_2)-\text{NH}_2$, in which the sulfur atom is the point of attachment. The term "mono- or di-(C₁-C₆alkyl)aminosulfonyl" refers to groups that satisfy the formula $-(\text{SO}_2)-\text{NR}_2$, in which the sulfur atom is the point of attachment, and in which one R is C₁-C₆alkyl and the other R is hydrogen or an independently chosen C₁-C₆alkyl.

25 The term "aminocarbonyl" refers to an amide group (*i.e.*, $-(\text{C}=\text{O})\text{NH}_2$). The term "mono- or di-(C₁-C₈alkyl)aminocarbonyl" refers to groups of the formula $-(\text{C}=\text{O})-\text{N}(\text{R})_2$, in which the carbonyl is the point of attachment, one R is C₁-C₈alkyl and the other R is hydrogen or an independently chosen C₁-C₈alkyl.

30 "Alkylamino" refers to a secondary or tertiary amine that has the general structure $-\text{NH}-\text{alkyl}$ or $-\text{N}(\text{alkyl})(\text{alkyl})$, wherein each alkyl is selected independently from alkyl, cycloalkyl and (cycloalkyl)alkyl groups. Such groups include, for example, mono- and di-(C₁-C₈alkyl)amino groups, in which each C₁-C₈alkyl may be the same or different, as well as mono- and di-(C₁-C₆alkyl)amino groups and mono- and di-(C₁-C₄alkyl)amino groups.

35 "Alkylaminoalkyl" refers to an alkylamino group linked via an alkylene group (*i.e.*, a group having the general structure $-\text{alkylene}-\text{NH}-\text{alkyl}$ or $-\text{alkylene}-\text{N}(\text{alkyl})(\text{alkyl})$) in which each alkyl is selected independently from alkyl, cycloalkyl and (cycloalkyl)alkyl groups. Alkylaminoalkyl groups include, for example, mono- and di-(C₁-C₈alkyl)aminoC₁-C₄alkyl.

"Mono- or di-(C₁-C₈alkyl)aminoC₀-C₄alkyl" refers to a mono- or di-(C₁-C₈alkyl)amino group linked via a single covalent bond or a C₁-C₄alkylene group. The following are representative alkylaminoalkyl groups:



5 It will be apparent that the definition of "alkyl" as used in the terms "alkylamino" and "alkylaminoalkyl" differs from the definition of "alkyl" used for all other alkyl-containing groups, in the inclusion of cycloalkyl and (cycloalkyl)alkyl groups (*e.g.*, (C₃-C₇cycloalkyl)C₀-C₆alkyl).

The term "halogen" refers to fluorine, chlorine, bromine or iodine.

10 A "haloalkyl" is an alkyl group that is substituted with 1 or more halogen atoms (*e.g.*, "C₁-C₄haloalkyl" groups have from 1 to 4 carbon atoms). Examples of haloalkyl groups include, but are not limited to, mono-, di- or tri-fluoromethyl; mono-, di- or tri-chloromethyl; mono-, di-, tri-, tetra- or penta-fluoroethyl; mono-, di-, tri-, tetra- or penta-chloroethyl; and 1,2,2,2-tetrafluoro-1-trifluoromethyl-ethyl. Typical haloalkyl groups are trifluoromethyl and
15 difluoromethyl. The term "haloalkoxy" refers to a haloalkyl group as defined above attached via an oxygen bridge. "C₁-C₄haloalkoxy" groups have 1 to 4 carbon atoms.

A dash ("-") that is not between two letters or symbols is used to indicate a point of attachment for a substituent. For example, -COOH is attached through the carbon atom.

A "heteroatom," as used herein, is oxygen, sulfur or nitrogen.

20 A "carbocycle" or "carbocyclic group" comprises at least one ring formed entirely by carbon-carbon bonds (referred to herein as a carbocyclic ring), and does not contain a heterocycle. Certain representative carbocycles are cycloalkyl as described above. Other carbocycles are aryl (*i.e.*, contain at least one aromatic ring).

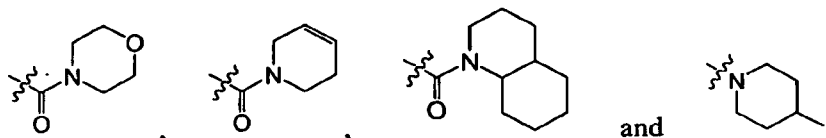
A "heterocycle" or "heterocyclic group" has from 1 to 3 fused, pendant or spiro rings, at least
25 one of which is a heterocyclic ring (*i.e.*, one or more ring atoms is a heteroatom independently chosen from O, S and N, with the remaining ring atoms being carbon). Additional rings, if present, may be heterocyclic or carbocyclic. Typically, a heterocyclic ring comprises 1, 2, 3 or 4 heteroatoms; within certain embodiments each heterocyclic ring has 1 or 2 heteroatoms per ring. Each heterocyclic ring generally contains from 4 to 8 ring members (rings having
30 from 4 or 5 to 7 ring members are recited in certain embodiments) and heterocycles comprising fused, pendant or spiro rings typically contain from 9 to 14 ring members. Certain heterocycles comprise a sulfur atom as a ring member; in certain embodiments, the sulfur atom is oxidized to SO or SO₂. Heterocycles may be optionally substituted with a variety of substituents, as indicated. Unless otherwise specified, a heterocycle may be a
35 heterocycloalkyl group (*i.e.*, each ring is saturated or partially saturated) or a heteroaryl group

(i.e., at least one ring within the group is aromatic), and may be linked via any ring atom, provided that a stable compound results. A nitrogen-linked (N-linked) heterocycle is linked by a single covalent bond at a ring nitrogen atom. Additional heteroatoms may, but need not, be present.

5 Certain heterocyclic groups include, for example, acridinyl, azepanyl, azocinyl, benzimidazolyl, benzimidazoliny, benzisothiazolyl, benzisoxazolyl, benzofuranyl, benzothiofuranyl, benzothiophenyl, benzoxazolyl, benzothiazolyl, benzotriazolylcarbazolyl, benzotetrazolyl, NH-carbazolyl, carbolinyl, chromanyl, chromenyl, cinnolinyl, decahydroquinolinyl, dihydrofuro[2,3-b]tetrahydrofuran, dihydroisoquinolinyl, 10 dihydrotetrahydrofuranyl, 1,4-dioxo-8-aza-spiro[4.5]dec-8-yl, dithiazinyl, furanyl, furazanyl, imidazoliny, imidazolidinyl, imidazolyl, indazolyl, indolenyl, indoliny, indoliziny, indolyl, isobenzofuranyl, isochromanyl, isoindazolyl, isoindoliny, isoindolyl, isothiazolyl, isoxazolyl, isoquinolinyl, morpholinyl, naphthyridinyl, octahydroisoquinolinyl, oxadiazolyl, oxazolidinyl, oxazolyl, phenanthridinyl, phenanthroliny, phenazinyl, phenothiazinyl, 15 phenoxathiinyl, phenoxazinyl, phthalazinyl, piperazinyl, piperidinyl, piperidonyl, pteridinyl, purinyl, pyranyl, pyrazinyl, pyrazolidinyl, pyrazoliny, pyrazolyl, pyridazinyl, pyridoimidazolyl, pyridooxazolyl, pyridothiazolyl, pyridyl, pyrimidyl, pyrrolidinyl, pyrrolidonyl, pyrroliny, pyrrolyl, quinazolinyl, quinolinyl, quinoxaliny, quinuclidiny, tetrahydroisoquinolinyl, tetrahydroquinolinyl, tetrazolyl, thiadiazinyl, thiadiazolyl, 20 thianthrenyl, thiazolyl, thienothiazolyl, thienooxazolyl, thienoimidazolyl, thienyl, thiophenyl, thiomorpholinyl and variants thereof in which the sulfur atom is oxidized, triazinyl, xanthenyl and any of the foregoing that are substituted with from 1 to 4 substituents as described above.

Certain heterocycles are 5- to 10-membered heteroaryl groups, 5- or 6-membered heteroaryl (e.g., pyridyl, pyrimidyl and pyridazinyl), or 9- to 10-membered heteroaryl groups, 25 each of which may be substituted as indicated. 9- to 10-membered heteroaryl groups comprise two fused rings, at least one of which comprises a heteroatom and at least one of which is aromatic; preferably both rings are aromatic. Representative such groups include, for example, quinolinyl, quinazolinyl, isoquinolinyl, pyridoimidazolyl and pyridopyrazinyl. Other heterocycles are 3- to 10-membered heterocycloalkyl groups, which are saturated or 30 partially saturated heterocycles as described above, containing 3, 4, 5, 6, 7, 8, 9 or 10 ring members.

Other heterocycles recited herein are 5- to 10-membered, N-linked heterocycloalkyl groups. Such groups comprise a ring nitrogen atom at the point of attachment. It will be apparent that other ring members may, but need not, be heteroatoms. Certain such groups are 35 attached via a single covalent bond or a carbonyl linker; such moieties are referred to as "(5- to 10-membered, N-linked heterocycloalkyl)-(CO)_p," wherein p is 0 or 1. Such groups may be substituted, as indicated. Representative such groups include, for example:



Other such groups are designated "(N-linked, 5- to 10-membered heterocycloalkyl) C_0 - C_2 alkyl." Within such groups, the N-linked heterocycle is attached via a single covalent bond or a methylene or ethylene linker. When substituted, such groups may be substituted on the heterocycle or on the methylene or ethylene linker. It will be apparent that substitution of a methylene linker with an oxo group will result in the N-linked heterocycle being linked via a carbonyl linker – such groups are within the scope of "(N-linked, 5- to 10-membered heterocycloalkyl) C_0 - C_2 alkyl" when optionally substituted with oxo.

A "substituent," as used herein, refers to a molecular moiety that is covalently bonded to an atom within a molecule of interest. For example, a "ring substituent" may be a moiety such as a halogen, alkyl group, haloalkyl group or other group discussed herein that is covalently bonded to an atom (preferably a carbon or nitrogen atom) that is a ring member. The term "substitution" refers to replacing a hydrogen atom in a molecular structure with a substituent as described above, such that the valence on the designated atom is not exceeded, and such that a chemically stable compound (*i.e.*, a compound that can be isolated, characterized, and tested for biological activity) results from the substitution.

Groups that are "optionally substituted" are unsubstituted or substituted by other than hydrogen at one or more available positions, typically 1, 2, 3, 4, 5 or 6 positions, by one or more suitable groups (which may be the same or different). Optional substitution is also indicated by the phrase "substituted with from 0 to X substituents," where X is the maximum number of permissible substituents. Certain optionally substituted groups are substituted with from 0 to 2, 3 or 4 independently selected substituents (*i.e.*, are unsubstituted or substituted with up to the recited maximum number of substituents). Other optionally substituted groups are substituted with at least one substituent (*e.g.*, substituted with from 1 to 2, 3 or 4 independently selected substituents).

Unless otherwise specified, the term "H3 receptor" is used herein to refer to any histamine H3 subtype receptor, including human H3 receptor (*see, e.g.*, U.S. Patent No. 6,136,559), H3 receptor found in other mammals and chimeric receptors retaining H3 function, including the chimeric H3 receptor provided as SEQ ID NO:8 in US Patent Application Serial Number 11/355,711, which published as US 2006/0188960.

A "H3 receptor modulator" is a compound that modulates H3 receptor GTP binding. A H3 receptor modulator may be a H3 receptor agonist or antagonist. A H3 receptor modulator binds with "high affinity" if the K_i at H3 receptor is less than 4 micromolar, preferably less than 1 micromolar, 500 nanomolar, 100 nanomolar, 50 nanomolar or 10

nanomolar. Representative assays for evaluating an effect on H3 receptor GTP binding are provided in Examples 7 and 8, herein.

Unless otherwise specified, the terms "IC₅₀" and "EC₅₀," as used herein, refer to values obtained using the assay as described in Example 7.

5 A H3 receptor modulator is considered an "antagonist" if it detectably inhibits H3 receptor agonist-stimulated GTP binding (using, for example, the representative assay provided in Example 7); in general, such an antagonist inhibits such GTP binding with a IC₅₀ value of less than 4 micromolar, preferably less than 1 micromolar, 500 nanomolar, 100 nanomolar, 50 nanomolar or 10 nanomolar. H3 receptor antagonists include neutral
10 antagonists and inverse agonists.

An "inverse agonist" of H3 receptor is a compound that reduces the GTP binding activity of H3 receptor below its basal activity level in the absence of added agonist. Inverse agonists of H3 receptor may also inhibit the activity in the presence of agonist. The basal activity of H3 receptor, as well as the reduction in H3 receptor GTP binding activity due to
15 the presence of H3 receptor antagonist, may be determined using an assay provided in Example 7 or Example 8.

A "neutral antagonist" of H3 receptor is a compound that inhibits the activity of H3 receptor agonist, but does not significantly change the basal activity of the receptor (*i.e.*, within the assay of Example 7 or Example 8 performed in the absence of agonist, H3 receptor
20 activity is reduced by no more than 10%, preferably by no more than 5%, and more preferably by no more than 2%; most preferably, there is no detectable reduction in activity). The basal activity is the level of GTP binding observed in the assay in the absence of added histamine or any other agonist, and in the further absence of any test compound. Neutral antagonists of H3 receptor may, but need not, inhibit the binding of agonist to H3 receptor.

25 As used herein a "H3 receptor agonist" is a compound that elevates the activity of the receptor above the basal activity level of the receptor. H3 receptor agonist activity may be identified using the representative assays provided in Example 7 and Example 8. In general, such an agonist has an EC₅₀ value of less than 4 micromolar, preferably less than 1 micromolar, 500 nanomolar, 100 nanomolar, 50 nanomolar or 10 nanomolar within the assay
30 provided in Example 7. If the GTP binding activity brought about by a test compound attains the same level to that of histamine, it is defined as a full agonist. If the level of GTP binding activity brought about by a test compound is above baseline but below the level attained by histamine, it is defined as a partial agonist. Preferred antagonist compounds provided herein do not elevate GTP binding activity under such conditions more than 10% above baseline,
35 preferably not more than 5% above baseline, and most preferably not more than 2% above baseline.

A "therapeutically effective amount" (or dose) is an amount that, upon administration to a patient, results in a discernible patient benefit (e.g., provides detectable relief from a condition being treated). Such relief may be detected using any appropriate criteria, including alleviation of one or more symptoms characteristic of the condition. A therapeutically effective amount or dose generally results in a concentration of compound in a body fluid (such as blood, plasma, serum, CSF, synovial fluid, lymph, cellular interstitial fluid, tears or urine) that is sufficient to alter H3 receptor GTP binding *in vitro*.

A "patient" is any individual treated with a compound or pharmaceutically acceptable salt thereof provided herein. Patients include humans, as well as other animals such as companion animals (e.g., dogs and cats) and livestock. Patients may be experiencing one or more symptoms of a condition responsive to H3 receptor modulation, or may be free of such symptom(s) (e.g., treatment may be prophylactic).

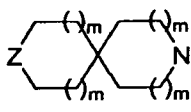
SUBSTITUTED AZASPIRO DERIVATIVES

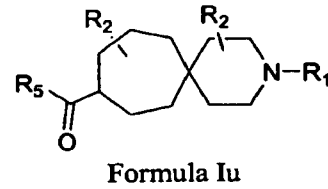
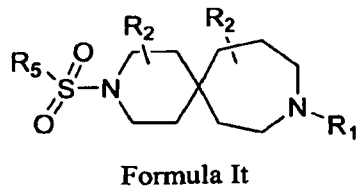
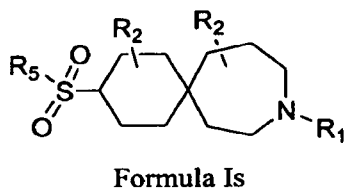
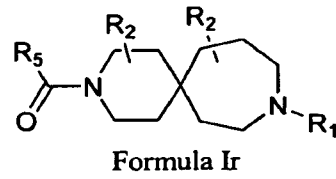
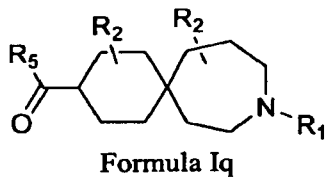
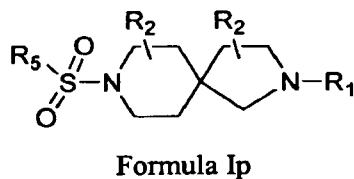
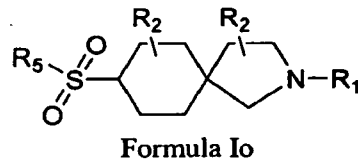
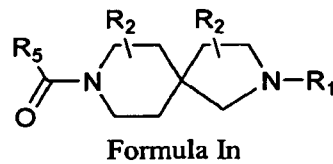
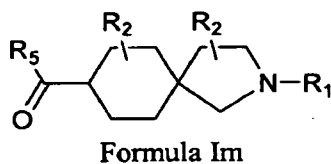
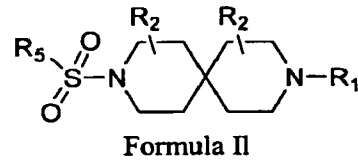
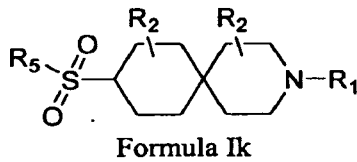
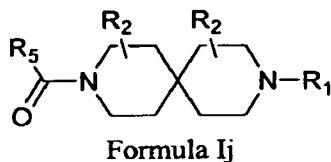
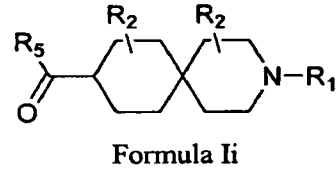
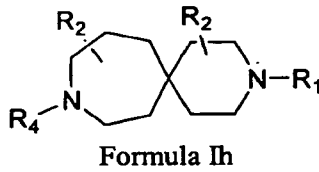
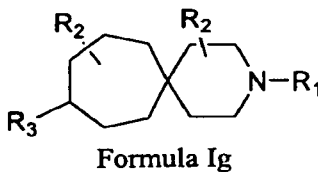
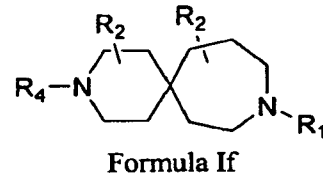
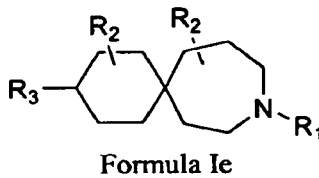
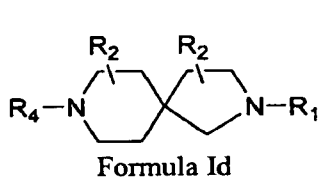
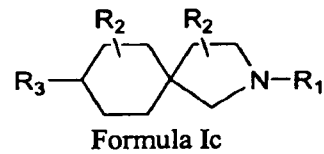
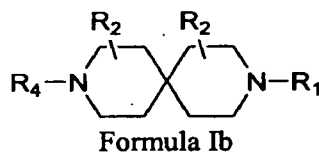
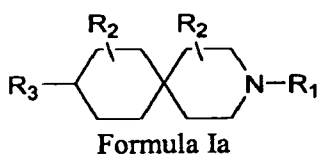
As noted above, the present invention provides substituted azaspiro derivatives of Formula I. Within certain aspects, such compounds are H3 receptor modulators that may be used in a variety of contexts, including in the therapeutic treatment of human and animal patients as discussed below. H3 receptor modulators may also be used within *in vitro* assays (e.g., assays for receptor activity), and as probes for detection and localization of H3 receptor.

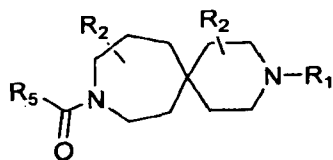
Within certain substituted azaspiro derivatives of Formula I, Z is CHR_3 . Within other substituted azaspiro derivatives of Formula I, Z is NR_4 . R_3 and R_4 groups include, for example, C_1 - C_6 alkanoyl, C_1 - C_6 alkylsulfonyl, mono- or di- $(\text{C}_1$ - C_8 alkyl)aminosulfonyl and mono- or di- $(\text{C}_1$ - C_8 alkyl)aminocarbonyl. Other representative R_3 and R_4 include phenyl and 5- or 6-membered heteroaryl groups, each of which is substituted with from 0 to 3 (or from 1 to 3) substituents independently chosen from halogen, cyano, C_1 - C_6 alkyl, C_1 - C_6 haloalkyl, C_1 - C_6 alkoxy, C_2 - C_6 alkyl ether, C_1 - C_6 alkanoyl, C_1 - C_6 haloalkyl, C_1 - C_8 alkylsulfonyl, mono- or di- $(\text{C}_1$ - C_8 alkyl)aminocarbonyl, mono- or di- $(\text{C}_1$ - C_8 alkyl)aminosulfonyl, (N-linked, 5- to 7-membered heterocycloalkyl) $\text{C}(=\text{O})$ -, phenyl and 5- or 6-membered heteroaryl, each of which heterocycloalkyl, phenyl or heteroaryl is substituted with from 0 to 3 substituents independently chosen from halogen, cyano, hydroxy, amino, nitro, aminocarbonyl, C_1 - C_6 alkyl, C_1 - C_6 haloalkyl, C_1 - C_6 aminoalkyl, C_2 - C_6 alkyl ether, C_1 - C_6 alkoxy, C_1 - C_6 alkoxycarbonyl, C_1 - C_6 alkanoyl, C_1 - C_6 alkylsulfonyl, mono- or di- $(\text{C}_1$ - C_6 alkyl)amino, mono- or di- $(\text{C}_1$ - C_6 alkyl)aminocarbonyl or mono- or di- $(\text{C}_1$ - C_6 alkyl)aminosulfonyl. Certain R_3 and R_4 groups are designated herein as groups of the formula W-Y-X- or W-Y- . It will be apparent that in groups of the formula W-Y-X- , attachment is via the X moiety if X is present, attachment is via the Y moiety if X is absent and Y is present, and W is attached via a single covalent bond if X

and Y are both absent. Similarly, in groups of the formula W-Y-, attachment is via the Y moiety if Y is present, and W is attached via a single covalent bond if Y is absent.

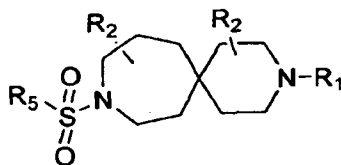
As noted above, each variable "m" is independently chosen from 0, 1, 2 and 3. In certain embodiments, each "m" is chosen such that each ring with the spiro core:

5  contains 5, 6 or 7 ring members. Certain such substituted azaspiro derivatives further satisfy one or more of Formulas Ia-Iee:

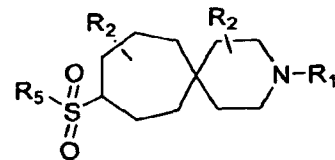




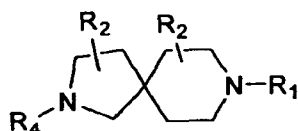
Formula Iv



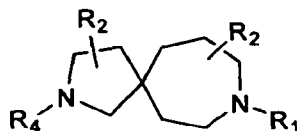
Formula Iw



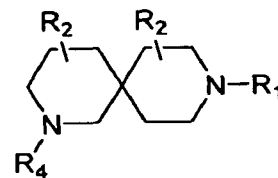
Formula Ix



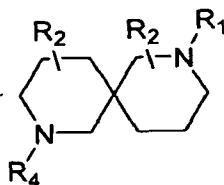
Formula Iy



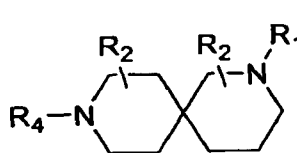
Formula Iz



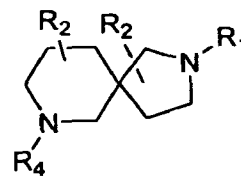
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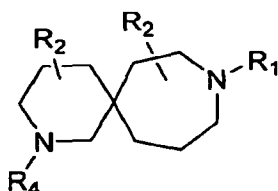
Formula Ibb



Formula Icc



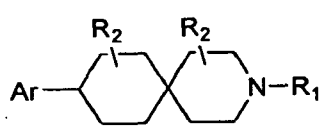
Formula Idd



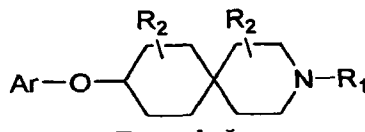
Formula Iee

wherein R_5 is C_1 - C_6 alkyl, mono- or di- $(C_1$ - C_6 alkyl)amino or phenyl that is substituted with C_1 - C_6 alkyl, C_1 - C_6 alkanoyl, C_1 - C_6 haloalkyl, C_1 - C_6 alkylsulfonyl or mono- or di- $(C_1$ - C_6 alkyl)aminocarbonyl.

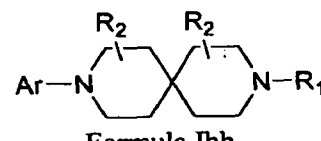
- 5 Within other embodiments, substituted azaspiro derivatives of Formula I further satisfy any one of Formulas Iff-Ifff:



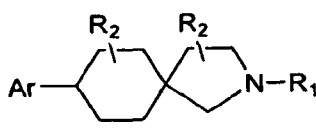
Formula Iff



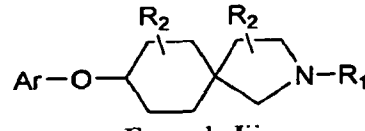
Formula Igg



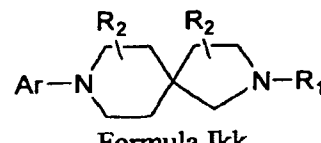
Formula Ihh



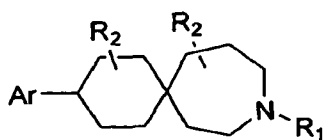
Formula Iii



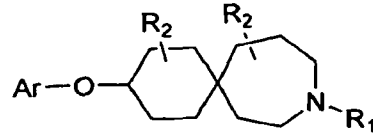
Formula Ijj



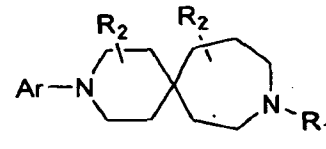
Formula Ikk



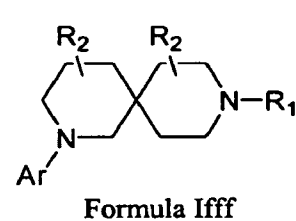
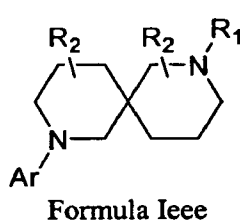
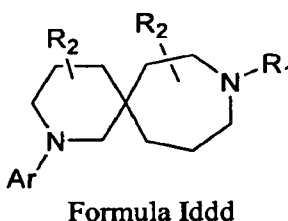
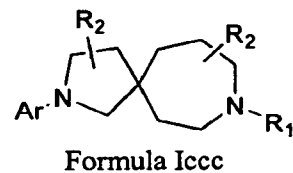
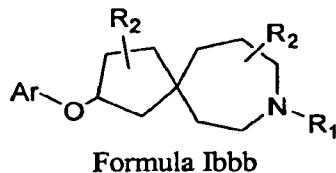
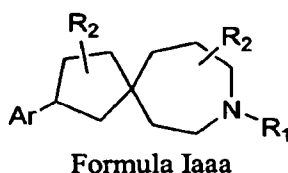
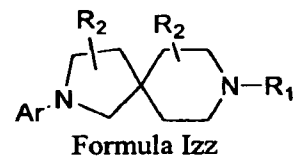
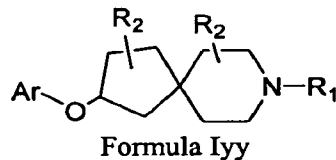
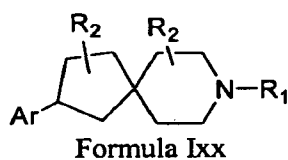
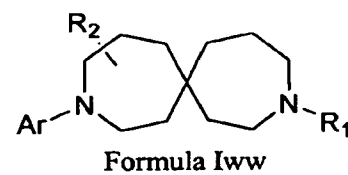
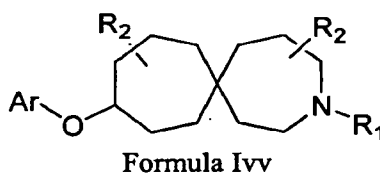
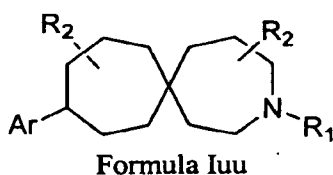
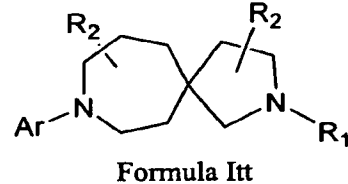
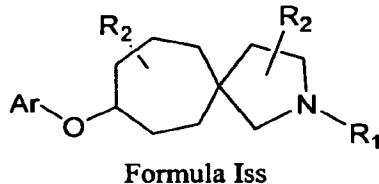
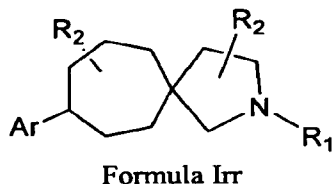
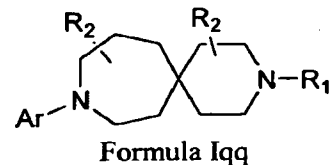
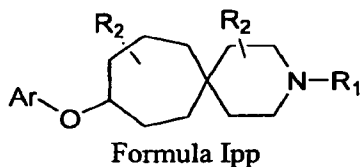
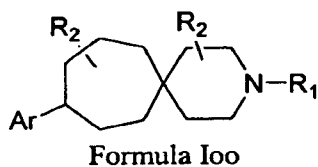
Formula Ill



Formula Imm



Formula Inn



wherein Ar is phenylC₀-C₂alkyl or (5- or 6-membered heteroaryl)C₀-C₂alkyl, each of which is substituted with from 0 to 3 substituents (or from 1 to 3 substituents, *e.g.*, 1 or 2 substituents) independently chosen from:

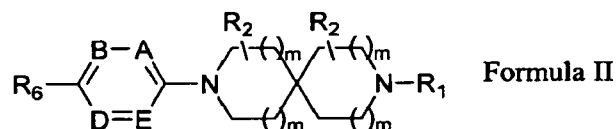
- (i) halogen, cyano, C₁-C₈alkyl, C₁-C₈alkoxy, C₁-C₈alkanoyl, C₂-C₈alkyl ether or C₁-C₈haloalkyl;
- (ii) C₁-C₈alkylsulfonyl, C₁-C₈alkoxycarbonyl, mono- or di-(C₁-C₈alkyl)aminocarbonyl or (N-linked, 5- to 10-membered heterocycloalkyl)C₀-C₂alkyl, each of which is substituted with from 0 to 4 substituents independently chosen from hydroxy, halogen, oxo, C₁-C₆alkyl, C₂-C₆alkenyl, C₁-C₆alkoxy and C₂-C₆alkyl ether;
- (iii) phenyl or 5- or 6-membered heteroaryl, each of which is optionally substituted with R_a; in certain embodiments, each R_a is independently chosen from C₁-C₆alkyl, C₁-C₆alkanoyl, C₁-

C₆haloalkyl, C₁-C₄alkoxycarbonyl, C₁-C₆alkylsulfonyl, mono- or di-(C₁-C₆alkyl)aminocarbonyl; and (5- to 10-membered, N-linked heterocycloalkyl)-(CO)_p-, wherein p is 0 or 1, which heterocycloalkyl is substituted with from 0 to 3 substituents independently chosen from hydroxy, oxo, C₁-C₄alkyl, C₁-C₄alkoxy and C₂-C₄alkyl ether; and

(iv) groups that are taken together with the atoms to which they are attached to form a fused, partially saturated 5- or 6-membered ring that is optionally substituted with oxo or C₁-C₄alkyl.

Within certain such compounds, Ar is phenyl or a 5- or 6-membered heteroaryl, each of which is substituted with mono- or di-(C₁-C₈alkyl)aminocarbonyl or (N-linked, 5- to 10-membered heterocycloalkyl)C(=O)- that is substituted with from 0 to 2 substituents independently chosen from C₁-C₄alkyl. Representative such N-linked heterocycloalkyl groups include, for example, piperidiny, morpholinyl, thiomorpholinyl, azapanyl, dihydropyridinyl, pyrrolidinyl and octahydroisoquinolinyl, each of which is optionally substituted.

Certain substituted azaspiro derivatives of Formula I further satisfy Formula II:



wherein:

A, B, D and E are independently selected from N and CR₇;

R₆ is:

(i) hydrogen, halogen, cyano, amino, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆aminoalkyl, C₁-C₆alkoxy, C₂-C₆alkyl ether, C₁-C₆alkanoyl, C₁-C₆alkoxycarbonyl, C₁-C₆alkylsulfonyl and mono- or di-(C₁-C₆alkyl)aminocarbonyl;

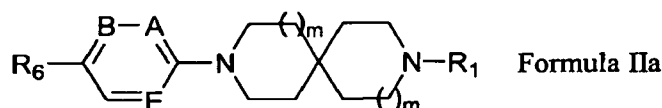
(ii) (5- to 10-membered, N-linked heterocycloalkyl)-(CO)_p-, wherein p is 0 or 1, which is substituted with from 1 to 3 substituents independently chosen from halogen, C₁-C₄alkyl, C₂-C₄alkenyl, C₁-C₄alkoxy and C₂-C₄alkyl ether; or

(iii) (5- to 10-membered heterocycloalkyl)C₀-C₂alkyl, phenylC₀-C₂alkyl or (5- or 6-membered heteroaryl)C₀-C₂alkyl, each of which is substituted with from 1 to 3 substituents independently chosen from halogen, cyano, C₁-C₆alkyl, C₁-C₆alkanoyl, C₁-C₆haloalkyl, C₁-C₄alkoxycarbonyl, C₁-C₆alkylsulfonyl, mono- or di-(C₁-C₈alkyl)aminocarbonyl and (5- to 10-membered, N-linked heterocycloalkyl)-(CO)_p-, wherein p is 0 or 1, which heterocycloalkyl is substituted with from 0 to 3 substituents independently chosen from halogen, C₁-C₄alkyl, C₂-C₄alkenyl, C₁-C₄alkoxy and C₂-C₄alkyl ether; and

Each R₇ is independently hydrogen, C₁-C₆alkyl, C₁-C₆alkanoyl, C₁-C₆haloalkyl, C₁-

C₆alkylsulfonyl or mono- or di-(C₁-C₆alkyl)aminocarbonyl.

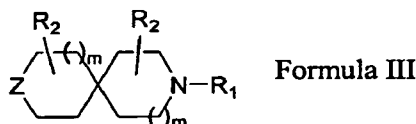
Certain substituted azaspiro derivatives of Formula II further satisfy Formula IIa:



wherein A, B and E are independently is CH or N, and the remaining variables are as described for Formula II.

- 5 R₁, within certain substituted azaspiro derivatives as described above, is C₃-C₆alkyl, cyclobutyl, cyclopentyl or cyclohexyl.

Certain substituted azaspiro derivatives of Formula I further satisfy Formula III:



wherein:

Z is CHR₃ or NR₄;

- 10 Each m is independently 0, 1 or 2;

R₁ is C₃-C₆alkyl, cyclobutyl, cyclopentyl or cyclohexyl;

Each R₂ independently represents from 0 to 2 substituents independently chosen from C₁-C₄alkyl and C₁-C₄haloalkyl;

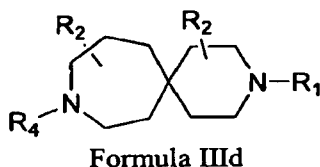
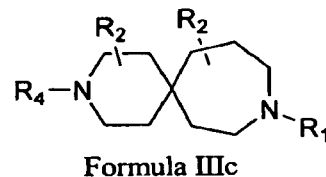
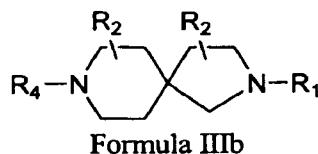
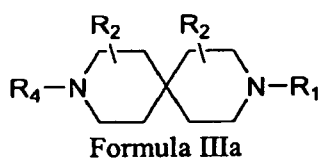
- 15 R₃ is: (i) C₁-C₆alkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, C₁-C₆alkoxy, C₁-C₆alkylthio, C₁-C₆alkylsulfonyl, C₁-C₆alkanoyl, C₁-C₆alkoxycarbonyl, mono- or di-(C₁-C₈alkyl)amino, mono- or di-(C₁-C₈alkyl)aminocarbonyl or mono- or di-(C₁-C₈alkyl)aminosulfonyl, each of which is substituted with from 0 to 4 substituents independently chosen from R_a; or (ii) a group of the Formula W-Y-X-;

- 20 R₄ is: (i) C₁-C₆alkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, C₁-C₆alkylsulfonyl, C₁-C₆alkanoyl, C₁-C₆alkoxycarbonyl, mono- or di-(C₁-C₆alkyl)amino, mono- or di-(C₁-C₆alkyl)aminocarbonyl or mono- or di-(C₁-C₆alkyl)aminosulfonyl, each of which is substituted with from 0 to 4 substituents independently chosen from R_a; or (ii) a group of the Formula W-Y-;

W is C₃-C₁₀cycloalkyl, 3- to 10-membered heterocycloalkyl, 6- to 10-membered aryl or 5- to 10-membered heteroaryl, each of which is substituted with from 0 to 4 substituents independently chosen from R_a;

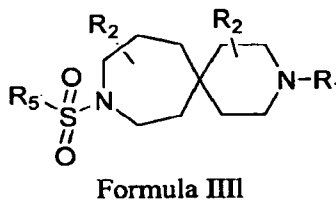
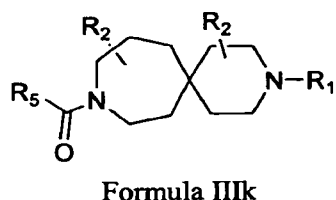
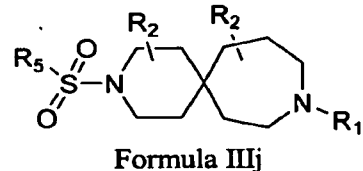
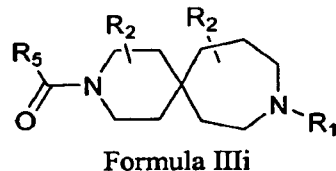
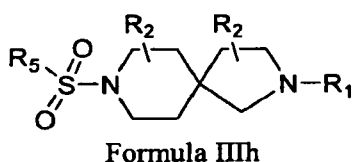
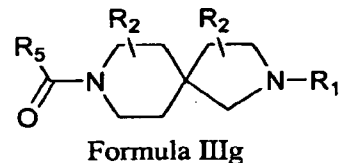
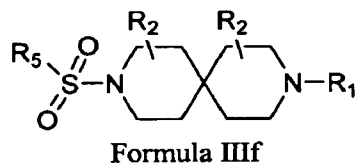
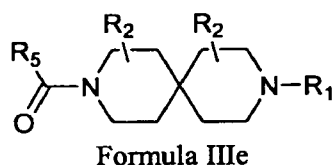
Y, X and each R_a are as described for Formula I.

Within certain embodiments, substituted azaspiro derivatives of Formula III further satisfy one or more of Formulas IIIa-IIIId:



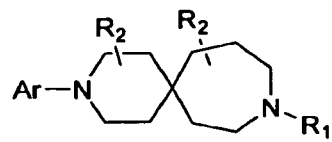
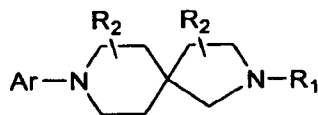
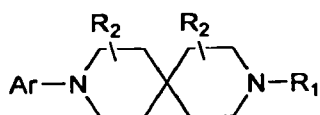
- 5 R_4 , within certain substituted azaspiro derivatives of Formulas III, IIIa, IIIb, IIIc and IIIId, is C_1 - C_6 alkanoyl, C_1 - C_6 alkylsulfonyl, mono- or di- $(C_1$ - C_6 alkyl)aminosulfonyl or mono- or di- $(C_1$ - C_6 alkyl)aminocarbonyl.

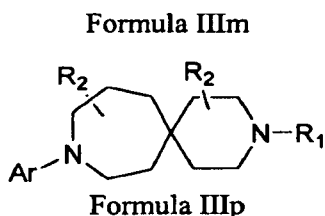
Within certain embodiments, substituted azaspiro derivatives of Formula III further satisfy one or more of Formulas IIIe-IIIl:



- 10 wherein R_5 is C_1 - C_6 alkyl, mono- or di- $(C_1$ - C_6 alkyl)amino or phenyl that is optionally substituted with C_1 - C_6 alkyl, C_1 - C_6 alkanoyl, C_1 - C_6 haloalkyl, C_1 - C_6 alkylsulfonyl or mono- or di- $(C_1$ - C_6 alkyl)aminocarbonyl.

Within further embodiments, substituted azaspiro derivatives of Formula III further satisfy one or more of Formulas IIIm-IIIp:





Formula IIIn

Formula IIIo

wherein Ar is phenylC₀-C₂alkyl or (5- or 6-membered heteroaryl)C₀-C₂alkyl, each of which is substituted with from 0 to 2 substituents independently chosen from:

(i) halogen, cyano, C₁-C₈alkyl, C₁-C₈alkoxy, C₁-C₈alkanoyl, C₂-C₈alkyl ether or C₁-C₈haloalkyl;

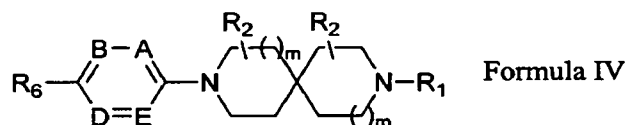
5 (ii) C₁-C₈alkylsulfonyl, C₁-C₈alkoxycarbonyl, mono- or di-(C₁-C₈alkyl)aminocarbonyl or (N-linked, 5- to 10-membered heterocycloalkyl)C₀-C₂alkyl, each of which is substituted with from 0 to 4 substituents independently chosen from hydroxy, halogen, oxo, C₁-C₆alkyl, C₂-C₆alkenyl, C₁-C₆alkoxy and C₂-C₆alkyl ether;

10 (iii) phenyl or 5- or 6-membered heteroaryl, each of which is optionally substituted with R_a; in certain embodiments, each R_a is independently chosen from C₁-C₆alkyl, C₁-C₆alkanoyl, C₁-C₆haloalkyl, C₁-C₄alkoxycarbonyl, C₁-C₆alkylsulfonyl, mono- or di-(C₁-C₆alkyl)aminocarbonyl; and (5- to 10-membered, N-linked heterocycloalkyl)-(CO)_p, wherein p is 0 or 1, which heterocycloalkyl is substituted with from 0 to 3 substituents independently chosen from hydroxy, oxo, C₁-C₄alkyl, C₁-C₄alkoxy and C₂-C₄alkyl ether;

15 and

(iv) groups that are taken together with the atoms to which they are attached to form a fused, partially saturated 5- or 6-membered ring that is optionally substituted with oxo or C₁-C₄alkyl.

Certain substituted azaspiro derivatives of Formula III further satisfy Formula IV:



20 wherein:

A, B, D and E are independently selected from N and CR₇;

R₆ is:

(i) hydrogen, halogen, cyano, amino, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆aminoalkyl, C₁-C₆alkoxy, C₂-C₆alkyl ether, C₁-C₆alkanoyl, C₁-C₆alkoxycarbonyl, C₁-C₆alkylsulfonyl and mono- or di-(C₁-C₆alkyl)aminocarbonyl; or

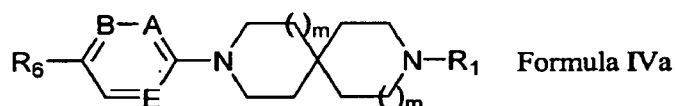
25

(ii) (5- to 7-membered heterocycloalkyl)C₀-C₂alkyl, phenylC₀-C₂alkyl or (5- or 6-membered heteroaryl)C₀-C₂alkyl, each of which is substituted with from 1 to 3 substituents independently chosen from halogen, cyano, C₁-C₆alkyl, C₁-C₆alkanoyl, C₁-

C₆haloalkyl, C₁-C₄alkoxycarbonyl, C₁-C₆alkylsulfonyl, mono- or di-(C₁-C₈alkyl)aminocarbonyl and (5- to 10-membered, N-linked heterocycloalkyl)-(CO)_p-, wherein p is 0 or 1, which heterocycloalkyl is substituted with from 0 to 3 substituents independently chosen from halogen, C₁-C₄alkyl, C₂-C₄alkenyl, C₁-C₄alkoxy and C₂-C₄alkyl ether; and

Each R₇ is independently hydrogen, C₁-C₆alkyl, C₁-C₆alkanoyl, C₁-C₆haloalkyl, C₁-C₆alkylsulfonyl or mono- or di-(C₁-C₆alkyl)aminocarbonyl.

Certain substituted azaspiro derivatives of Formula IV further satisfy Formula IVa:



wherein A, B and E are independently CH or N.

Each R₂, within certain substituted azaspiro derivatives as described above, independently represents 0 substituents or 1 or 2 methyl substituents.

R₆, within certain substituted azaspiro derivatives of Formula II, IIa, IV or IVa, is: (i) C₁-C₆alkanoyl, mono- or di-(C₁-C₈alkyl)aminocarbonyl, C₁-C₆haloalkyl or C₁-C₈alkylsulfonyl; or (ii) (5- to 10-membered, N-linked heterocycloalkyl)-(CO)_p-, wherein p is 0 or 1, which is substituted with from 1 to 3 substituents independently chosen from halogen, C₁-C₄alkyl, C₂-C₄alkenyl, C₁-C₄alkoxy and C₂-C₄alkyl ether. Within further substituted azaspiro derivatives of Formula II, IIa, IV or IVa, R₆ is (5- to 7-membered heterocycloalkyl)C₀-C₂alkyl, phenyl or a 5- or 6-membered heteroaryl, each of which is substituted with from 1 to 3 substituents independently chosen from halogen, cyano, C₁-C₆alkyl, C₁-C₆alkanoyl, C₁-C₆haloalkyl, C₁-C₄alkoxycarbonyl, C₁-C₆alkylsulfonyl, mono- or di-(C₁-C₈alkyl)aminocarbonyl and (5- to 10-membered, N-linked heterocycloalkyl)-(CO)_p-, wherein p is 0 or 1, which heterocycloalkyl is substituted with from 0 to 3 substituents independently chosen from halogen, C₁-C₄alkyl, C₂-C₄alkenyl, C₁-C₄alkoxy and C₂-C₄alkyl ether.

Representative substituted azaspiro derivatives provided herein include, but are not limited to, those specifically described in Examples 1-3. It will be apparent that the specific compounds recited herein are representative only, and are not intended to limit the scope of the present invention. Further, as noted above, all compounds of the present invention may be present as a free acid or base or as a pharmaceutically acceptable salt, solvate (e.g., hydrate) or ester.

In certain aspects, compounds provided are H3 receptor modulators, as determined using an assay for H3 receptor GTP binding. References herein to a "histamine-induced H3 receptor GTP binding assay" are intended to refer to either of the *in vitro* GTP binding assays provided in Examples 7 and 8, which may be performed in the presence or absence of added agonist. Briefly, to assess H3 receptor agonist-stimulated GTP binding, a H3 receptor

preparation is incubated with a H3 receptor agonist (*e.g.*, histamine or an analogue thereof such as R-alpha-methylhistamine), labeled (*e.g.*, ³⁵S) GTP and unlabeled test compound. Within the assays provided herein, the H3 receptor used is preferably mammalian H3 receptor (*e.g.*, human or rat H3 receptor, and preferably human H3 receptor), and more preferably a
5 chimeric human H3 receptor such as a receptor having the sequence provided in SEQ ID NO:8 in US Patent Application Serial Number 11/355,711, which published as US 2006/0188960. The H3 receptor may be recombinantly expressed or naturally expressed. The H3 receptor preparation may be, for example, a membrane preparation from cells that recombinantly express H3 receptor. Incubation with a H3 receptor modulator results in a
10 decrease or increase in the amount of label bound to the H3 receptor preparation, relative to the amount of label bound in the absence of the compound.

As noted above, compounds that are H3 receptor antagonists are preferred within certain embodiments. When agonist-contacted cells are contacted with a compound that is a H3 receptor antagonist, the response is preferably reduced by at least 20%, more preferably at
15 least 50% and still more preferably at least 80%, as compared to cells that are contacted with the agonist in the absence of test compound. The IC₅₀ for H3 receptor antagonists provided herein is preferably less than 4 micromolar, less than 1 micromolar, less than 500nM, less than 100 nM, less than 50 nM or less than 10 nM. In certain embodiments, H3 receptor antagonists provided herein exhibit no detectable agonist activity in the assay of Example 7 at
20 a concentration of compound equal to the IC₅₀. Certain preferred antagonists exhibit no detectable agonist activity in the assay at a concentration of compound that is 100-fold higher than the IC₅₀.

In certain embodiments, preferred H3 receptor modulators provided herein are non-sedating. In other words, a dose of H3 receptor modulator that is twice the minimum
25 therapeutically effective dose causes only transient (*i.e.*, lasting for no more than ½ the time that the therapeutic effect lasts) or preferably no statistically significant sedation in an animal model assay of sedation (using the method described by Fitzgerald et al. (1988) *Toxicology* 49(2-3):433-9). Preferably, a dose that is any of 5, 10, 20, 30, 40, 50, 60, 70, 80, 90 or 100 times the minimum therapeutically effective dose does not produce statistically significant
30 sedation.

If desired, H3 receptor modulators provided herein may be evaluated for certain pharmacological properties including, but not limited to, oral bioavailability (preferred compounds are orally bioavailable to an extent allowing for therapeutically effective concentrations of the compound to be achieved at oral doses of less than 140 mg/kg,
35 preferably less than 50 mg/kg, more preferably less than 30 mg/kg, even more preferably less than 10 mg/kg, and still more preferably less than 1 mg/kg), toxicity (a preferred H3 receptor modulator is nontoxic when a therapeutically effective amount is administered to a subject),

side effects (a preferred H3 receptor modulator produces side effects comparable to placebo when a therapeutically effective amount of the compound is administered to a subject), serum protein binding and *in vitro* and *in vivo* half-life (a preferred H3 receptor modulator exhibits an *in vivo* half-life allowing for Q.I.D. dosing, preferably T.I.D. dosing, more preferably B.I.D. dosing, and most preferably once-a-day dosing). In addition, differential penetration of the blood brain barrier may be desirable for certain H3 receptor modulators. Routine assays that are well known in the art may be used to assess these properties, and identify superior compounds for a particular use. For example, assays used to predict bioavailability include transport across human intestinal cell monolayers, including Caco-2 cell monolayers. Penetration of the blood brain barrier of a compound in humans may be predicted from the brain levels of the compound in laboratory animals given the compound (*e.g.*, intravenously). Serum protein binding may be predicted from albumin binding assays or whole serum binding assays. *In vitro* half-lives of compounds may be predicted from assays of microsomal half-life as described within Example 8 of PCT Publication Number WO 06/089076.

As noted above, preferred compounds provided herein are nontoxic. In general, the term "nontoxic" as used herein shall be understood in a relative sense and is intended to refer to any substance that has been approved by the United States Food and Drug Administration ("FDA") for administration to mammals (preferably humans) or, in keeping with established criteria, is susceptible to approval by the FDA for administration to mammals (preferably humans). In addition, a highly preferred nontoxic compound generally satisfies one or more of the following criteria: (1) does not substantially inhibit cellular ATP production; (2) does not significantly prolong heart QT intervals; (3) does not cause substantial liver enlargement, or (4) does not cause substantial release of liver enzymes.

As used herein, a compound that does not substantially inhibit cellular ATP production is a compound that satisfies the criteria set forth in Example 9 of PCT Publication Number WO 06/089076. In other words, cells treated as described in Example 9 therein with 100 μ M of such a compound exhibit ATP levels that are at least 50% of the ATP levels detected in untreated cells. In more highly preferred embodiments, such cells exhibit ATP levels that are at least 80% of the ATP levels detected in untreated cells.

A compound that does not significantly prolong heart QT intervals is a compound that does not result in a statistically significant prolongation of heart QT intervals (as determined by electrocardiography) in guinea pigs, minipigs or dogs upon administration of a dose that yields a serum concentration equal to the EC_{50} or IC_{50} for the compound. In certain preferred embodiments, a dose of 0.01, 0.05, 0.1, 0.5, 1, 5, 10, 40 or 50 mg/kg administered parenterally or orally does not result in a statistically significant prolongation of heart QT intervals. By "statistically significant" is meant results varying from control at the $p < 0.1$ level

or more preferably at the $p < 0.05$ level of significance as measured using a standard parametric assay of statistical significance such as a student's T test.

A compound does not cause substantial liver enlargement if daily treatment of laboratory rodents (*e.g.*, mice or rats) for 5-10 days with a dose that yields a serum concentration equal to the EC_{50} or IC_{50} for the compound results in an increase in liver to body weight ratio that is no more than 100% over matched controls. In more highly preferred embodiments, such doses do not cause liver enlargement of more than 75% or 50% over matched controls. If non-rodent mammals (*e.g.*, dogs) are used, such doses should not result in an increase of liver to body weight ratio of more than 50%, preferably not more than 25%, and more preferably not more than 10% over matched untreated controls. Preferred doses within such assays include 0.01, 0.05, 0.1, 0.5, 1, 5, 10, 40 or 50 mg/kg administered parenterally or orally.

Similarly, a compound does not promote substantial release of liver enzymes if administration of twice the minimum dose that yields a serum concentration equal to the EC_{50} or IC_{50} for the compound does not elevate serum levels of ALT, LDH or AST in laboratory rodents by more than 100% over matched mock-treated controls. In more highly preferred embodiments, such doses do not elevate such serum levels of ALT, LDH or AST by more than 75% or 50% over matched controls. Alternatively, a H3 receptor modulator does not promote substantial release of liver enzymes if, in an *in vitro* hepatocyte assay, concentrations (in culture media or other such solutions that are contacted and incubated with hepatocytes *in vitro*) that are equal to the EC_{50} or IC_{50} for the compound do not cause detectable release of any such liver enzymes into culture medium above baseline levels seen in media from matched mock-treated control cells. In more highly preferred embodiments, there is no detectable release of any of such liver enzymes into culture medium above baseline levels when such compound concentrations are five-fold, and preferably ten-fold the EC_{50} or IC_{50} for the compound.

In other embodiments, certain preferred compounds do not substantially inhibit or induce microsomal cytochrome P450 enzyme activities, such as CYP1A2 activity, CYP2A6 activity, CYP2C9 activity, CYP2C19 activity, CYP2D6 activity, CYP2E1 activity or CYP3A4 activity at a concentration equal to the EC_{50} or IC_{50} for the compound.

Certain preferred compounds are not clastogenic (*e.g.*, as determined using a mouse erythrocyte precursor cell micronucleus assay, an Ames micronucleus assay, a spiral micronucleus assay or the like) at a concentration equal the EC_{50} or IC_{50} for the compound. In other embodiments, certain preferred H3 receptor modulators do not induce sister chromatid exchange (*e.g.*, in Chinese hamster ovary cells) at such concentrations.

For detection purposes, as discussed in more detail below, H3 receptor modulators provided herein may be isotopically-labeled or radiolabeled. For example, compounds may

have one or more atoms replaced by an atom of the same element having an atomic mass or mass number different from the atomic mass or mass number usually found in nature. Examples of isotopes that can be present in the compounds provided herein include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorous, fluorine and chlorine, such as ^2H , ^3H , ^{11}C , ^{13}C , ^{14}C , ^{15}N , ^{18}O , ^{17}O , ^{31}P , ^{32}P , ^{35}S , ^{18}F and ^{36}Cl . In addition, substitution with heavy isotopes such as deuterium (*i.e.*, ^2H) can afford certain therapeutic advantages resulting from greater metabolic stability, for example increased in vivo half-life or reduced dosage requirements and, hence, may be preferred in some circumstances.

PREPARATION OF SUBSTITUTED AZASPIRO DERIVATIVES

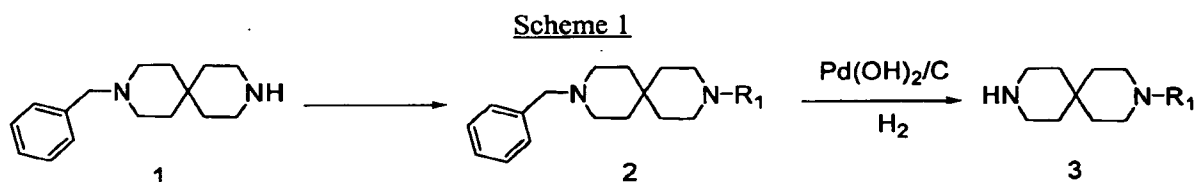
Substituted azaspiro derivatives provided herein may generally be prepared using standard synthetic methods. Starting materials illustrated in the schemes and in the examples are commercially available from suppliers such as Sigma-Aldrich Corp. (St. Louis, MO), or may be synthesized from commercially available precursors using established protocols. By way of example, a synthetic route similar to that shown in any of the following Schemes may be used, together with synthetic methods known in the art of synthetic organic chemistry, or variations thereon as appreciated by those skilled in the art. Each variable in the following schemes refers to any group consistent with the description of the substituted azaspiro derivatives provided herein.

Certain abbreviations used in the following Schemes and elsewhere herein are:

20	BOP	benzotriazol-1-yl-oxy-tris(dimethylamino)phosphonium hexafluorophosphate
	Bu	butyl
	CDI	N,N'-carbonyldiimidazole
	δ	chemical shift
	DCC	dicyclohexylcarbodiimide
25	DCM	dichloromethane
	DMC	2-chloro-1,3-dimethylimidazolinium chloride
	DME	1,2-dimethoxyethane
	DMSO	dimethylsulfoxide
	DPPF	1,1'-Bis(diphenylphosphino)ferrocene
30	EA	ethyl acetate
	EtOH	ethanol
	Eq.	equivalent(s)
	HPLC	high pressure liquid chromatography
	hr	hour(s)
35	Hz	hertz
	LAH	lithium aluminum hydride
	LCMS	liquid chromatography/mass spectrometry

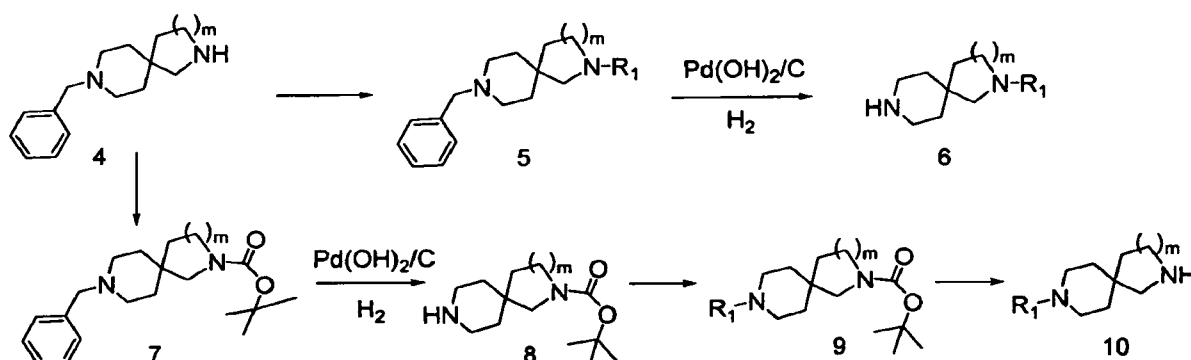
	MS	mass spectrometry
	(M+1)	mass + 1
	mCPBA	3-chloroperbenzoic acid
	Me	methyl
5	MeOH	methanol
	min	minute(s)
	NBS	<i>N</i> -bromosuccinimide
	<i>n</i> -BuLi	<i>n</i> -butyl lithium
	Pd ₂ (dba) ₃	tris(dibenzylideneacetone)dipalladium(0)
10	Pd(PPh ₃) ₄	tetrakis(triphenylphosphine)palladium(0)
	PTLC	preparative thin layer chromatography
	rt	room temperature
	<i>t</i> -bu-XPhos	2-di- <i>tert</i> -butylphosphino-2',4',6'-triisopropylbiphenyl
	TEA	triethylamine
15	TfO	trifluoromethane sulfonate
	THF	tetrahydrofuran
	TLC	thin layer chromatography

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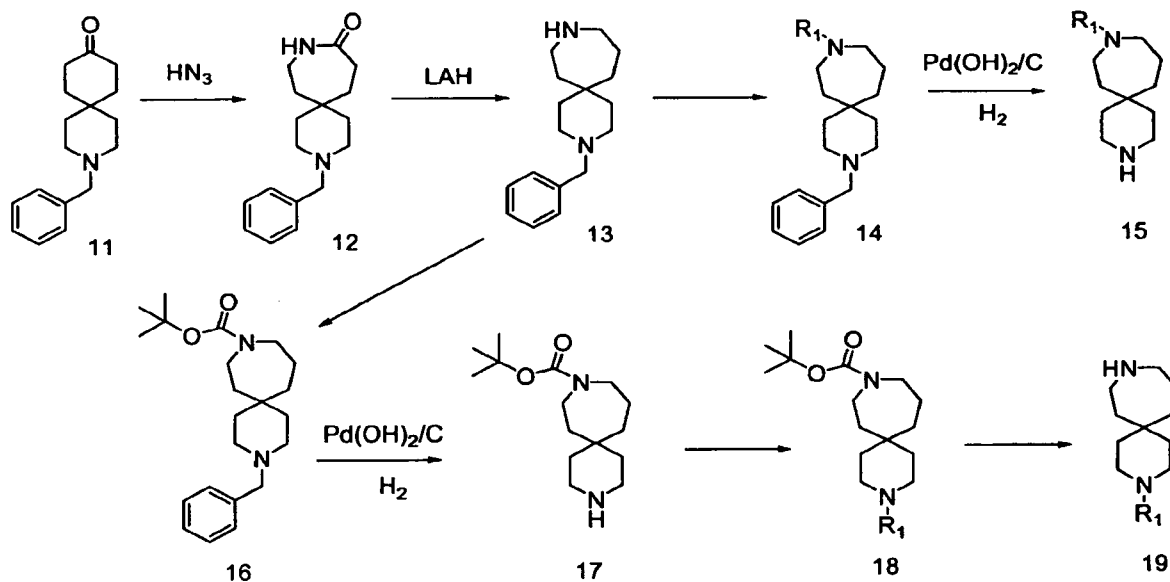
Scheme 1 illustrates the synthesis of compounds of formula 3. 1 (prepared essentially as described in PCT International Application Publication Number WO 97/11940) is alkylated with an alkyl halide or reacted with a ketone or an aldehyde under reductive amination conditions to give 2. Hydrogenolysis of 2 in the presence of palladium hydroxide on charcoal provides 3.

Scheme 2



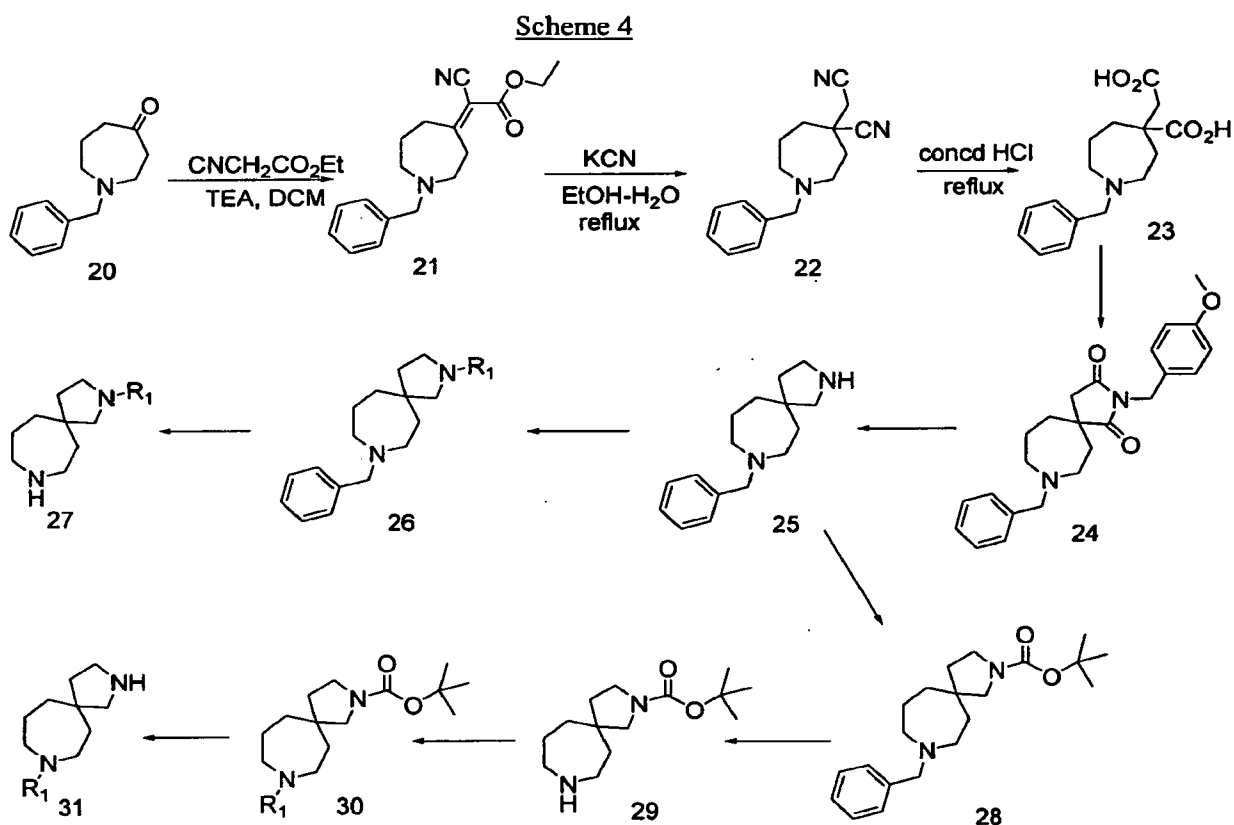
Scheme 2 illustrates the synthesis of compounds of formulas 6 and 10. 4 (prepared essentially as described in *Bioorg. Med. Chem. Lett.* (1998) 8:1851-56 if $m = 1$, and prepared essentially as described in EP 00417631A2 if $m = 0$) is alkylated with an alkyl halide or reacted with a ketone or an aldehyde using reductive amination conditions to give 5. Hydrogenolysis of 5 in the presence of palladium hydroxide on charcoal gives 6. Alternatively, 4 is Boc-protected, followed by removal of the benzyl group using standard hydrogenolysis over palladium hydroxide on charcoal to give 8. 8 is alkylated with an alkyl halide or reacted with a ketone or an aldehyde using reductive amination conditions to give 9, which is treated with trifluoroacetic acid to form 10.

Scheme 3



Scheme 3 illustrates the synthesis of compounds of formulas 15 and 19. 11 (prepared essentially as described in PCT International Application Publication Number WO 97/11940) is reacted with hydrazoic acid in chloroform to form the spiro amide 12, which is reduced to

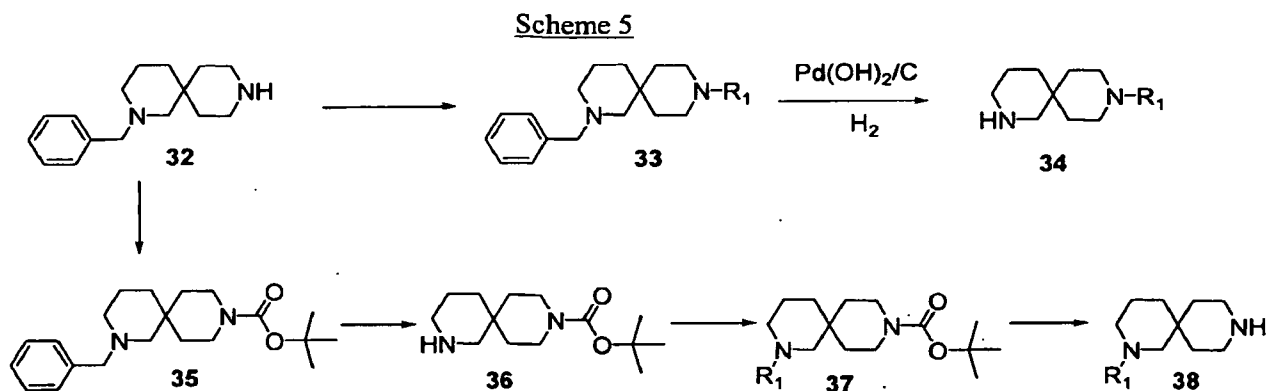
spiro amine 13 with LAH. 15 and 19 are prepared from 13 essentially as described in Scheme 2 for the preparation of 6 and 10, respectively.



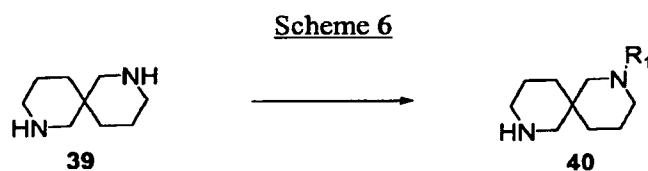
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Scheme 4 illustrates the synthesis of compounds of formulas 27 and 31. Condensation of 20 (prepared essentially as described in *J. Med. Chem.* (2004) 47:497-508) with ethyl cyanoacetate provides 21, which is heated with potassium cyanide in ethanol/water followed by hydrolysis with hydrochloric acid to give diacid 23. The diacid 23 is treated with DCC followed by reaction of the resulting cyclic anhydride with 4-methoxybenzyl amine to produce imide 24 upon treatment with sodium acetate in acetic anhydride. Imide 24 is reduced using BH_3 -THF complex, followed by removal of the 4-methoxy benzyl group using ceric ammonium nitrate to form 25. The preparation of 27 and 31 from 25 is performed essentially as described in Scheme 2.

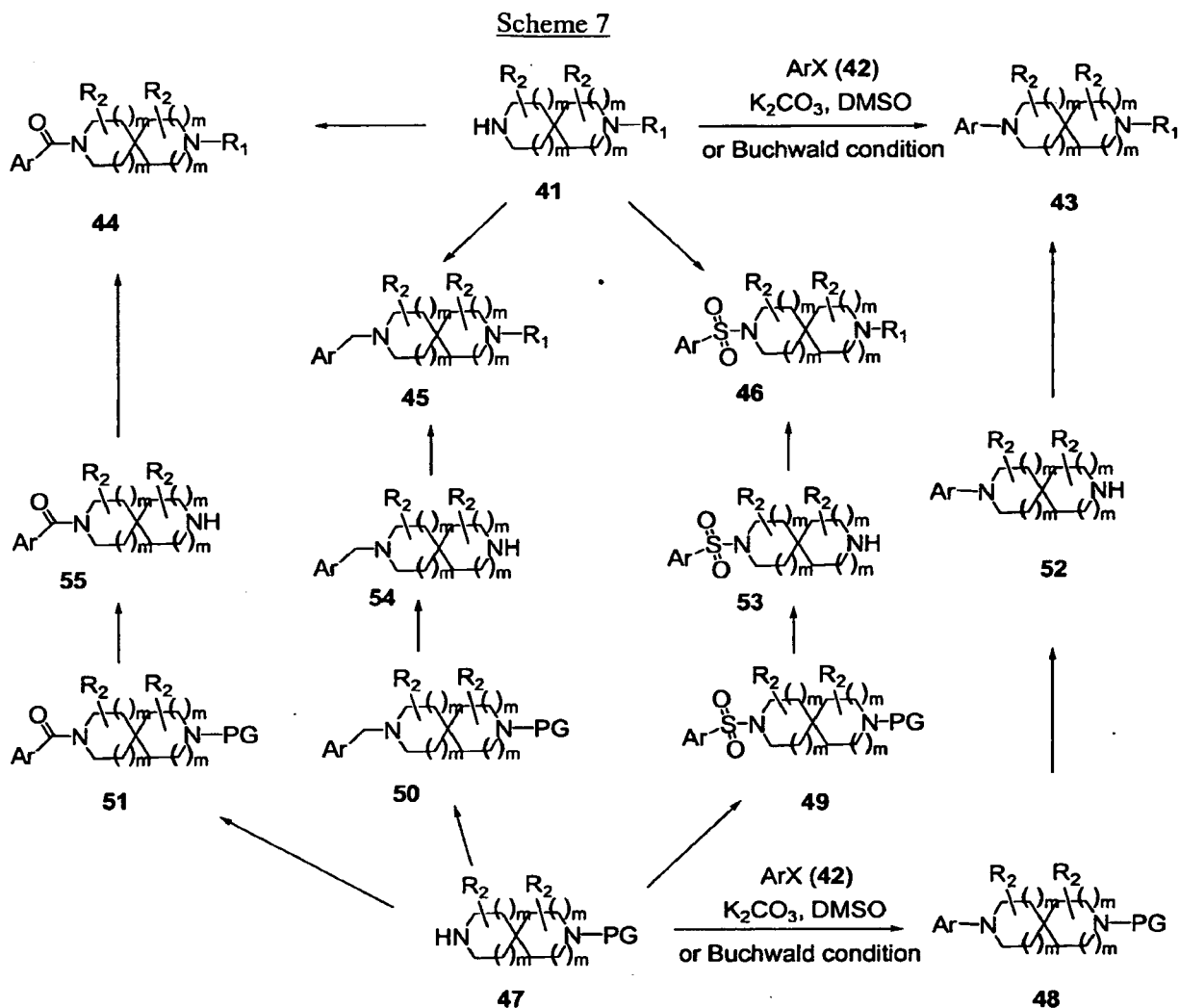
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Scheme 5 illustrates the synthesis of compounds of formulas 34 and 38. 32 is prepared essentially as described in PCT International Application Number WO 2005/097795. 34 and 38 are prepared from 32 using a procedure analogous to that described in Scheme 2.

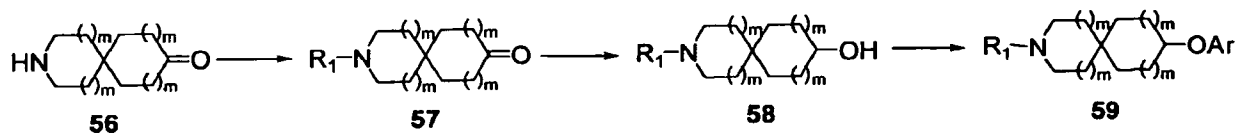


Scheme 6 illustrated the synthesis of compounds of formula 40. 39 (prepared essentially as described in *J. Med. Chem.* (1990) 33: 2270-2275) is alkylated with an alkyl halide or reacted with a ketone or an aldehyde under reductive amination conditions to give 40.



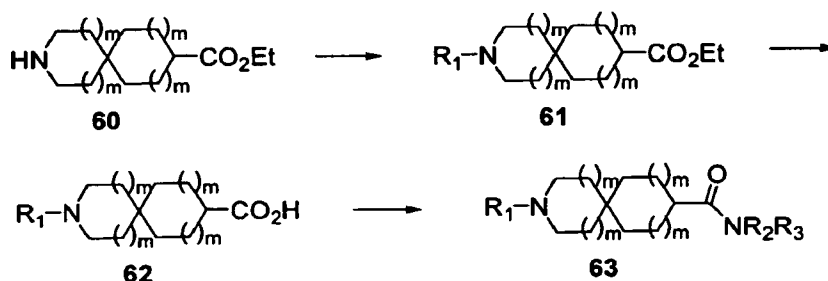
Scheme 7 illustrates the synthesis of compounds of formulas 43-46. 41 is prepared as
 5 described in Schemes 1 to 6 (designated as 3, 6, 10, 15, 19, 27, 31, 34, 38 and 40). 41
 undergoes nucleophilic substitution or Pd-catalyzed coupling reaction with aryl halide 42
 (Buckward, et al. (1996) *J. Org. Chem.* 61:7240) to afford 43. Reaction of 41 with an
 appropriate acid using a standard coupling agent such as BOP or DMC affords 44.
 10 Sulfonylation of 41 with an arylsulfonyl chloride gives 46. 41 is alkylated with a benzyl
 bromide or reacted with an aryl aldehyde under reductive amination conditions to give 45.
 Alternatively, 47, which is prepared as described in Schemes 1 to 6, undergoes reactions
 similar to those described above to give 48-51 respectively. Deprotection of 48-51 under
 appropriate conditions affords 52-55 respectively, which are alkylated with an alkyl halide or
 15 reacted with a ketone or an aldehyde under reductive amination conditions to give 43-46,
 respectively.

Scheme 8



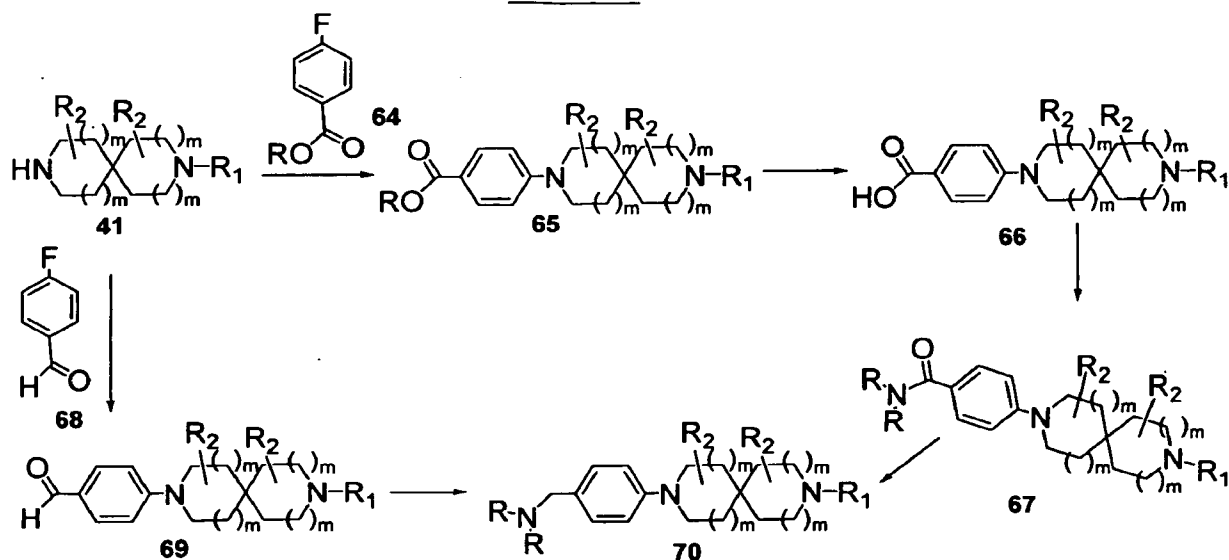
Scheme 8 illustrates the synthesis of compounds of formula 59. 56 (prepared essentially as described in PCT International Application Publication Number WO 97/11940) is alkylated with an alkyl halide or reacted with a ketone or an aldehyde under reductive amination conditions to give ketone 57, which is reduced with NaBH₄ to form alcohol 58. Treatment of 58 with NaH in DMSO, followed by reaction with aryl halide at elevated temperature affords 59.

Scheme 9



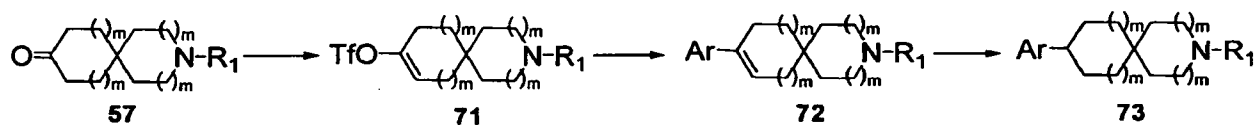
Scheme 9 illustrates the synthesis of compounds of formula 63. 60 (prepared essentially as described in PCT International Application Publication Number WO 97/11940) is alkylated with an alkyl halide or reacted with a ketone or an aldehyde under reductive amination conditions to give 61. Hydrolysis of 61 forms 62, which is reacted with an amine using a standard coupling reagent such as BOP or DMC to afford 63.

Scheme 10



Scheme 10 illustrates the synthesis of compounds of formulas **67** and **70**. **41** is
 5 reacted with benzyl 4-fluorobenzoate **64** in the presence of a base to give **65**. Hydrolysis or
 de-benzylation under hydrogenolysis conditions (when R = benzyl) provides **66**, which is
 reacted with an amine using a standard coupling agent such as BOP or DMC to afford **67**.
 Reduction of **67** with LAH gives **70**. Alternatively, **41** is reacted with 4-fluorobenzaldehyde
 68 in the presence of a base to give **69**, which is reacted with amine under reductive amination
 10 conditions to provide **70**.

Scheme 11



Scheme 11 illustrates the synthesis of compounds of formula **73**. **57** is reacted with
 trifluoromethanesulfonic acid anhydride after treatment with a base to form **71**, which is
 15 coupled with an aryl boronic acid or an aryl tributyltin to give **72**. Reduction of **72** with
 hydrogen in the presence of catalytic palladium on carbon forms **73**.

The scheme shows the reaction of compound **41**, a macrocyclic diamine with two nitrogen atoms substituted with R_2 and R_1 groups, and a central cross-linked core. Compound **41** reacts with a dihalide **74**, where $B=A$ and $D=E$ are heteroatoms, and the halogens are hal . This reaction yields intermediate **75**, where the halogens have been replaced by the $B-A$ and $D-E$ groups. Intermediate **75** can then follow two pathways:

- Pathway 1: Reaction with a group R_6 to form compound **76**, where R_6 is attached to the B atom.
- Pathway 2: Reaction with a cyclic acetal-protected boronate to form compound **77**, where the boron atom is part of a five-membered cyclic acetal structure.

 The definition for R_6 is provided as: alkoxy, thioalkoxy, CN, aryl, heteroaryl, etc.

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appropriate. Preparation of radiolabeled compounds may be conveniently performed by a radioisotope supplier specializing in custom synthesis of radiolabeled probe compounds.

PHARMACEUTICAL COMPOSITIONS

The present invention also provides pharmaceutical compositions comprising one or
5 more compounds provided herein, together with at least one physiologically acceptable carrier or excipient. Pharmaceutical compositions may comprise, for example, water, buffers (*e.g.*, neutral buffered saline or phosphate buffered saline), ethanol, mineral oil, vegetable oil, dimethylsulfoxide, carbohydrates (*e.g.*, glucose, mannose, sucrose or dextrans), mannitol, proteins, adjuvants, polypeptides or amino acids such as glycine, antioxidants, chelating
10 agents such as EDTA or glutathione and/or preservatives. Preferred pharmaceutical compositions are formulated for oral delivery to humans or other animals (*e.g.*, companion animals such as dogs or cats). In addition, other active ingredients may (but need not) be included in the pharmaceutical compositions provided herein.

Pharmaceutical compositions may be formulated for any appropriate manner of
15 administration, including, for example, inhalation (*e.g.*, nasal or oral), topical, oral, nasal, rectal or parenteral administration. The term parenteral as used herein includes subcutaneous, intradermal, intravascular (*e.g.*, intravenous), intramuscular, spinal, intracranial, intrathecal and intraperitoneal injection, as well as any similar injection or infusion technique. In certain embodiments, compositions in a form suitable for oral use are preferred. Such forms include,
20 for example, tablets, troches, lozenges, aqueous or oily suspensions, dispersible powders or granules, emulsion, hard or soft capsules, or syrups or elixirs. Within yet other embodiments, compositions of the present invention may be formulated as a lyophilizate.

Compositions intended for oral use may further comprise one or more components such as sweetening agents, flavoring agents, coloring agents and/or preserving agents in order
25 to provide appealing and palatable preparations. Tablets contain the active ingredient in admixture with physiologically acceptable excipients that are suitable for the manufacture of tablets. Such excipients include, for example, inert diluents to increase the bulk weight of the material to be tableted (*e.g.*, calcium carbonate, sodium carbonate, lactose, calcium phosphate or sodium phosphate), granulating and disintegrating agents that modify the disintegration
30 rate in the environment of use (*e.g.*, corn starch, starch derivatives, alginic acid and salts of carboxymethylcellulose), binding agents that impart cohesive qualities to the powdered material(s) (*e.g.*, starch, gelatin, acacia and sugars such as sucrose, glucose, dextrose and lactose) and lubricating agents (*e.g.*, magnesium stearate, calcium stearate, stearic acid or talc). Tablets may be formed using standard techniques, including dry granulation, direct
35 compression and wet granulation. The tablets may be uncoated or they may be coated by known techniques.

Formulations for oral use may also be presented as hard gelatin capsules wherein the active ingredient is mixed with an inert solid diluent (*e.g.*, calcium carbonate, calcium phosphate or kaolin), or as soft gelatin capsules wherein the active ingredient is mixed with water or an oil medium (*e.g.*, peanut oil, liquid paraffin or olive oil).

5 Aqueous suspensions comprise the active material(s) in admixture with one or more suitable excipients, such as suspending agents (*e.g.*, sodium carboxymethylcellulose, methylcellulose, hydroxypropylmethylcellulose, sodium alginate, polyvinylpyrrolidone, gum tragacanth and gum acacia); and dispersing or wetting agents (*e.g.*, naturally-occurring phosphatides such as lecithin, condensation products of an alkylene oxide with fatty acids
10 such as polyoxyethylene stearate, condensation products of ethylene oxide with long chain aliphatic alcohols such as heptadecaethyleneoxycetanol, condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol such as polyoxyethylene sorbitol monooleate, or condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol anhydrides such as polyethylene sorbitan monooleate). Aqueous
15 suspensions may also comprise one or more preservatives, such as ethyl or n-propyl p-hydroxybenzoate, one or more coloring agents, one or more flavoring agents, and one or more sweetening agents, such as sucrose or saccharin.

Oily suspensions may be formulated by suspending the active ingredients in a vegetable oil (*e.g.*, arachis oil, olive oil, sesame oil or coconut oil) or in a mineral oil such as
20 liquid paraffin. The oily suspensions may contain a thickening agent such as beeswax, hard paraffin or cetyl alcohol. Sweetening agents and/or flavoring agents may be added to provide palatable oral preparations. Such suspensions may be preserved by the addition of an anti-oxidant such as ascorbic acid.

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

Pharmaceutical compositions may also be formulated as oil-in-water emulsions. The
30 oily phase may be a vegetable oil (*e.g.*, olive oil or arachis oil), a mineral oil (*e.g.*, liquid paraffin) or a mixture thereof. Suitable emulsifying agents include naturally-occurring gums (*e.g.*, gum acacia or gum tragacanth), naturally-occurring phosphatides (*e.g.*, soy bean lecithin, and esters or partial esters derived from fatty acids and hexitol), anhydrides (*e.g.*, sorbitan monooleate) and condensation products of partial esters derived from fatty acids and
35 hexitol with ethylene oxide (*e.g.*, polyoxyethylene sorbitan monooleate). An emulsion may also comprise one or more sweetening and/or flavoring agents.

Syrups and elixirs may be formulated with sweetening agents, such as glycerol, propylene glycol, sorbitol or sucrose. Such formulations may also comprise one or more demulcents, preservatives, flavoring agents and/or coloring agents.

A pharmaceutical composition may be prepared as a sterile injectable aqueous or oleaginous suspension. The active ingredient(s), depending on the vehicle and concentration used, can either be suspended or dissolved in the vehicle. Such a composition may be formulated according to the known art using suitable dispersing, wetting agents and/or suspending agents such as those mentioned above. Among the acceptable vehicles and solvents that may be employed are water, 1,3-butanediol, Ringer's solution and isotonic sodium chloride solution. In addition, sterile, fixed oils may be employed as a solvent or suspending medium. For this purpose any bland fixed oil may be employed, including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid find use in the preparation of injectable compositions, and adjuvants such as local anesthetics, preservatives and/or buffering agents can be dissolved in the vehicle.

Pharmaceutical compositions may also be prepared in the form of suppositories (*e.g.*, for rectal administration). Such compositions can be prepared by mixing the drug with a suitable non-irritating excipient that is solid at ordinary temperatures but liquid at the body temperature and will therefore melt in the body to release the drug. Suitable excipients include, for example, cocoa butter and polyethylene glycols.

Compositions for inhalation typically can be provided in the form of a solution, suspension or emulsion that can be administered as a dry powder or in the form of an aerosol using a conventional propellant (*e.g.*, dichlorodifluoromethane or trichlorofluoromethane).

Pharmaceutical compositions may be formulated for release at a pre-determined rate. Instantaneous release may be achieved, for example, via sublingual administration (*i.e.*, administration by mouth in such a way that the active ingredient(s) are rapidly absorbed via the blood vessels under the tongue rather than via the digestive tract). Controlled release formulations (*i.e.*, formulations such as a capsule, tablet or coated tablet that slows and/or delays release of active ingredient(s) following administration) may be administered by, for example, oral, rectal or subcutaneous implantation, or by implantation at a target site. In general, a controlled release formulation comprises a matrix and/or coating that delays disintegration and absorption in the gastrointestinal tract (or implantation site) and thereby provides a delayed action or a sustained action over a longer period. One type of controlled-release formulation is a sustained-release formulation, in which at least one active ingredient is continuously released over a period of time at a constant rate. Preferably, the therapeutic agent is released at such a rate that blood (*e.g.*, plasma) concentrations are maintained within the therapeutic range, but below toxic levels, over a period of time that is at least 4 hours, preferably at least 8 hours, and more preferably at least 12 hours. Such formulations may

generally be prepared using well known technology and administered by, for example, oral, rectal or subcutaneous implantation, or by implantation at the desired target site. Carriers for use within such formulations are biocompatible, and may also be biodegradable; preferably the formulation provides a relatively constant level of H3 receptor modulator release. The amount of H3 receptor modulator contained within a sustained release formulation depends upon, for example, the site of implantation, the rate and expected duration of release and the nature of the condition to be treated or prevented.

Controlled release may be achieved by combining the active ingredient(s) with a matrix material that itself alters release rate and/or through the use of a controlled-release coating. The release rate can be varied using methods well known in the art, including (a) varying the thickness or composition of coating, (b) altering the amount or manner of addition of plasticizer in a coating, (c) including additional ingredients, such as release-modifying agents, (d) altering the composition, particle size or particle shape of the matrix, and (e) providing one or more passageways through the coating. The amount of H3 receptor modulator contained within a sustained release formulation depends upon, for example, the method of administration (*e.g.*, the site of implantation), the rate and expected duration of release and the nature of the condition to be treated or prevented.

The matrix material, which itself may or may not serve a controlled-release function, is generally any material that supports the active ingredient(s). For example, a time delay material such as glyceryl monostearate or glyceryl distearate may be employed. Active ingredient(s) may be combined with matrix material prior to formation of the dosage form (*e.g.*, a tablet). Alternatively, or in addition, active ingredient(s) may be coated on the surface of a particle, granule, sphere, microsphere, bead or pellet that comprises the matrix material. Such coating may be achieved by conventional means, such as by dissolving the active ingredient(s) in water or other suitable solvent and spraying. Optionally, additional ingredients are added prior to coating (*e.g.*, to assist binding of the active ingredient(s) to the matrix material or to color the solution). The matrix may then be coated with a barrier agent prior to application of controlled-release coating. Multiple coated matrix units may, if desired, be encapsulated to generate the final dosage form.

In certain embodiments, a controlled release is achieved through the use of a controlled release coating (*i.e.*, a coating that permits release of active ingredient(s) at a controlled rate in aqueous medium). The controlled release coating should be a strong, continuous film that is smooth, capable of supporting pigments and other additives, non-toxic, inert and tack-free. Coatings that regulate release of the H3 receptor modulator include pH-independent coatings, pH-dependent coatings (which may be used to release H3 receptor modulator in the stomach) and enteric coatings (which allow the formulation to pass intact through the stomach and into the small intestine, where the coating dissolves and the contents

are absorbed by the body). It will be apparent that multiple coatings may be employed (*e.g.*, to allow release of a portion of the dose in the stomach and a portion further along the gastrointestinal tract). For example, a portion of active ingredient(s) may be coated over an enteric coating, and thereby released in the stomach, while the remainder of active ingredient(s) in the matrix core is protected by the enteric coating and released further down the GI tract. pH dependent coatings include, for example, shellac, cellulose acetate phthalate, polyvinyl acetate phthalate, hydroxypropylmethylcellulose phthalate, methacrylic acid ester copolymers and zein.

In certain embodiments, the coating is a hydrophobic material, preferably used in an amount effective to slow the hydration of the gelling agent following administration. Suitable hydrophobic materials include alkyl celluloses (*e.g.*, ethylcellulose or carboxymethylcellulose), cellulose ethers, cellulose esters, acrylic polymers (*e.g.*, poly(acrylic acid), poly(methacrylic acid), acrylic acid and methacrylic acid copolymers, methyl methacrylate copolymers, ethoxy ethyl methacrylates, cyanoethyl methacrylate, methacrylic acid alkamide copolymer, poly(methyl methacrylate), polyacrylamide, ammonio methacrylate copolymers, aminoalkyl methacrylate copolymer, poly(methacrylic acid anhydride) and glycidyl methacrylate copolymers) and mixtures of the foregoing. Representative aqueous dispersions of ethylcellulose include, for example, AQUACOAT® (FMC Corp., Philadelphia, PA) and SURELEASE® (Colorcon, Inc., West Point, PA), both of which can be applied to the substrate according to the manufacturer's instructions. Representative acrylic polymers include, for example, the various EUDRAGIT® (Rohm America, Piscataway, NJ) polymers, which may be used singly or in combination depending on the desired release profile, according to the manufacturer's instructions.

The physical properties of coatings that comprise an aqueous dispersion of a hydrophobic material may be improved by the addition of one or more plasticizers. Suitable plasticizers for alkyl celluloses include, for example, dibutyl sebacate, diethyl phthalate, triethyl citrate, tributyl citrate and triacetin. Suitable plasticizers for acrylic polymers include, for example, citric acid esters such as triethyl citrate and tributyl citrate, dibutyl phthalate, polyethylene glycols, propylene glycol, diethyl phthalate, castor oil and triacetin.

Controlled-release coatings are generally applied using conventional techniques, such as by spraying in the form of an aqueous dispersion. If desired, the coating may comprise pores or channels or to facilitate release of active ingredient. Pores and channels may be generated by well known methods, including the addition of organic or inorganic material that is dissolved, extracted or leached from the coating in the environment of use. Certain such pore-forming materials include hydrophilic polymers, such as hydroxyalkylcelluloses (*e.g.*, hydroxypropylmethylcellulose), cellulose ethers, synthetic water-soluble polymers (*e.g.*, polyvinylpyrrolidone, cross-linked polyvinylpyrrolidone and polyethylene oxide), water-

soluble polydextrose, saccharides and polysaccharides and alkali metal salts. Alternatively, or in addition, a controlled release coating may include one or more orifices, which may be formed by methods such as those described in US Patent Nos. 3,845,770; 4,034,758; 4,077,407; 4,088,864; 4,783,337 and 5,071,607. Controlled-release may also be achieved through the use of transdermal patches, using conventional technology (*see, e.g.*, US Patent No. 4,668,232).

Further examples of controlled release formulations, and components thereof, may be found, for example, in US Patent Nos. 4,572,833; 4,587,117; 4,606,909; 4,610,870; 4,684,516; 4,777,049; 4,994,276; 4,996,058; 5,128,143; 5,202,128; 5,376,384; 5,384,133; 5,445,829; 5,510,119; 5,618,560; 5,643,604; 5,891,474; 5,958,456; 6,039,980; 6,143,353; 6,126,969; 6,156,342; 6,197,347; 6,387,394; 6,399,096; 6,437,000; 6,447,796; 6,475,493; 6,491,950; 6,524,615; 6,838,094; 6,905,709; 6,923,984; 6,923,988; and 6,911,217; each of which is hereby incorporated by reference for its teaching of the preparation of controlled release dosage forms.

In addition to or together with the above modes of administration, a compound provided herein may be conveniently added to food or drinking water (*e.g.*, for administration to non-human animals including companion animals (such as dogs and cats) and livestock). Animal feed and drinking water compositions may be formulated so that the animal takes in an appropriate quantity of the composition along with its diet. It may also be convenient to present the composition as a premix for addition to feed or drinking water.

Compounds provided herein are generally present within a pharmaceutical composition at levels providing a therapeutically effective amount upon administration, as described above. Dosage forms providing dosage levels ranging from about 0.1 mg to about 140 mg per kilogram of body weight per day are preferred (about 0.5 mg to about 7 g per human patient per day). The amount of active ingredient that may be combined with the carrier materials to produce a single dosage form will vary depending upon the host treated and the particular mode of administration. Dosage unit forms generally contain between from about 0.1 mg to about 2 g, preferably 0.5 mg to 1 g, and more preferably 1 mg to 500 mg, of an active ingredient. It will be understood, however, that the optimal dose for any particular patient will depend upon a variety of factors, including the activity of the specific compound employed; the age, body weight, general health, sex and diet of the patient; the time and route of administration; the rate of excretion; any simultaneous treatment, such as a drug combination; and the type and severity of the particular disease undergoing treatment. Optimal dosages may be established using routine testing and procedures that are well known in the art.

Pharmaceutical compositions may be packaged for treating conditions responsive to H3 receptor modulation, including those specifically recited herein (*e.g.*, attention deficit

disorder, attention deficit hyperactivity disorder, schizophrenia, a cognitive disorder (such as mild cognitive impairment), epilepsy, migraine, narcolepsy, allergic rhinitis, vertigo, motion sickness, a memory disorder such as Alzheimer's disease, Parkinson's disease, obesity, an eating disorder or diabetes). Packaged pharmaceutical preparations comprise a container
5 holding one or more dosage units comprising a therapeutically effective amount of at least one H3 receptor modulator as described herein and instructions (*e.g.*, labeling) indicating that the contained composition is to be used for treating a condition responsive to H3 receptor modulation in the patient.

METHODS OF USE

10 H3 receptor modulators provided herein may be used to alter activity and/or activation of H3 receptors in a variety of contexts, both *in vitro* and *in vivo*. Within certain aspects, H3 receptor modulators may be used to inhibit or enhance (preferably to inhibit) H3 receptor activity *in vitro* or *in vivo*. In general, such methods comprise the step of contacting a H3 receptor with one or more H3 receptor modulators provided herein, in aqueous solution
15 and under conditions otherwise suitable for binding of the H3 receptor modulator(s) to H3 receptor. The H3 receptor modulator(s) are generally present at a concentration that is sufficient to alter H3 receptor GTP binding activity *in vitro* (using the assay provided in Example 7). The H3 receptor may be present in solution or suspension (*e.g.*, in an isolated membrane or cell preparation), or in a cultured or isolated cell. Within certain embodiments,
20 the H3 receptor is present in a patient (*e.g.*, expressed by a neuronal cell), and the aqueous solution is a body fluid. Preferably, one or more H3 receptor modulators are administered to a patient in an amount such that each H3 receptor modulator is present in at least one body fluid of the patient at a therapeutically effective concentration that is 1 micromolar or less; preferably 500 nanomolar or less; more preferably 100 nanomolar or less, 50 nanomolar or
25 less, 20 nanomolar or less, or 10 nanomolar or less. For example, such compounds may be administered at a dose that is less than 20 mg/kg body weight, preferably less than 5 mg/kg and, in some instances, less than 1 mg/kg. *In vivo*, modulation of H3 receptor activity may be assessed by detecting an alteration of a symptom (*e.g.*, memory or attention) in a patient being treated with one or more H3 receptor modulators provided herein.

30 The present invention further provides methods for treating conditions responsive to H3 receptor modulation. Within the context of the present invention, the term "treatment" encompasses both disease-modifying treatment and symptomatic treatment, either of which may be prophylactic (*i.e.*, before the onset of symptoms, in order to prevent, delay or reduce the severity of symptoms) or therapeutic (*i.e.*, after the onset of symptoms, in order to reduce
35 the severity and/or duration of symptoms). A condition is "responsive to H3 receptor modulation" if it is characterized by inappropriate activity of H3 receptor, regardless of the

amount of H3 receptor ligand present locally, and/or if modulation of H3 receptor activity results in alleviation of the condition or a symptom thereof. Such conditions may be diagnosed and monitored using criteria that have been established in the art. Patients may include humans, domesticated companion animals and livestock, with dosages as described
5 above.

Conditions that are responsive to H3 receptor modulation include, for example:

Cardiovascular disorders, including atherosclerosis, hypertension, myocardial infarction, coronary heart disease and stroke;

10 Cancer (*e.g.*, endometrial, breast, prostate and colon cancer, cutaneous carcinoma, medullary thyroid carcinoma and melanoma);

Metabolic disorders including impaired glucose tolerance, dyslipidaemia, and diabetes (*e.g.*, non-insulin dependent diabetes mellitus);

Immune conditions and disorders including osteoarthritis, allergy (*e.g.*, allergic rhinitis), and inflammation;

15 Respiratory conditions including nasal congestion, upper airway allergic response, asthma and chronic obstructive pulmonary disease;

Disorders associated with the regulation of sleep and wakefulness, or arousal and vigilance, including narcolepsy, jet lag, sleep apnea, and sleep disorders, such as excessive daytime sleepiness (EDS) (*e.g.*, shift work sleep disorder), insomnia (*e.g.*, primary insomnia),
20 idiopathic hypersomnia, circadian rhythm sleep disorder, dyssomnia NOS, parasomnias including nightmare disorder, sleep terror disorder, sleep disorders secondary to depression, anxiety and/or other mental disorders and substance-induced sleep disorder;

Eating disorders (*e.g.*, bulimia, binge eating and anorexia) and obesity;

25 Digestive system and gastrointestinal disorders including gallbladder disease, ulcer, hyper- and hypo-motility of the gastrointestinal tract and irritable bowel syndrome;

CNS disorders including hyper- and hypo-activity of the central nervous system, migraine, epilepsy, seizures, convulsions, mood disorders, attention deficit disorder, attention deficit hyperactivity disorder, bipolar disorder, depression, manic disorders, obsessive compulsive disorder, schizophrenia, migraine, vertigo, motion sickness, dementia,
30 cognitive deficit (*e.g.*, in psychiatric disorder, such as mild cognitive impairment), learning deficit, memory deficit (*e.g.*, age-related memory dysfunction), multiple sclerosis, Parkinson's disease, Alzheimer's disease and other neurodegenerative disorders, addiction (*e.g.*, resulting from drug abuse), neurogenic inflammation and Tourette's syndrome;

35 Fatigue, and fatigue-related disorders such as sleep/fatigue disorders, sleep impairment due to perimenopausal hormonal shifts, Parkinson's-related fatigue, multiple sclerosis-related fatigue, and chemotherapy-induced fatigue;

Vestibular dysfunction (*e.g.*, Meniere's disease, dizziness and motion sickness);

Pain (*e.g.*, inflammatory pain or neuropathic pain) and itch;

Septic shock; and

Glaucoma.

5 H3 receptor modulators may further be used to enhance a patient's cognitive ability.

In certain embodiments, compounds provided herein are used to treat attention deficit disorder, attention deficit hyperactivity disorder, schizophrenia, a cognitive disorder (such as mild cognitive impairment), epilepsy, migraine, narcolepsy, allergic rhinitis, vertigo, motion sickness, a memory disorder such as Alzheimer's disease, Parkinson's disease, obesity, an eating disorder, diabetes, fatigue, and fatigue-related disorders such as sleep/fatigue disorders, sleep impairment due to perimenopausal hormonal shifts, Parkinson's-related fatigue, multiple sclerosis-related fatigue, and chemotherapy-induced fatigue. Treatment regimens may vary depending on the compound used and the particular condition to be treated. However, for treatment of most disorders, a frequency of administration of 4 times daily or less is preferred.

10

15 In general, a dosage regimen of 2 times daily is more preferred, with once a day dosing particularly preferred. It will be understood, however, that the specific dose level and treatment regimen for any particular patient will depend upon a variety of factors including the activity of the specific compound employed, the age, body weight, general health, sex, diet, time of administration, route of administration, and rate of excretion, drug combination

20 and the severity of the particular disease undergoing therapy. In general, the use of the minimum dose sufficient to provide effective therapy is preferred. Patients may generally be monitored for therapeutic effectiveness using medical or veterinary criteria suitable for the condition being treated or prevented.

Within other aspects, H3 receptor modulators provided herein may be used within combination therapy for the treatment of conditions that are responsive to H3 receptor modulation, as described above. Within such combination therapy, a H3 receptor modulator is administered to a patient along with a second therapeutic agent that is not a H3 receptor modulator. The H3 receptor modulator and second therapeutic agent may be present in the same pharmaceutical composition, or may be administered separately in either order. It will

25

30 be apparent that additional therapeutic agents may, but need not, also be administered.

Second therapeutic agents suitable for use in such combination therapy include, for example, antiobesity agents, antidiabetics, antihypertensive agents, antidepressants, antipsychotic agents and anti-inflammatory agents. In certain combinations, the second therapeutic agent is a compound for the treatment of attention deficit disorder or attention deficit hyperactivity disorder, an antipsychotic agent or an anti-obesity agent.

35

Histamine H1 receptor modulators represent one class of second therapeutic agents. Combination with H1 receptor modulators may be used, for example, in the treatment of

Alzheimer's disease, inflammatory diseases and allergic conditions. Representative H1 receptor antagonists include, for example, loratadine (CLARITIN™), desloratadine (CLARINEX™), fexofenadine (ALLEGRA™) and cetirizine (Zyrtec™). Other H1 receptor antagonists include ebastine, mizolastine, acrivastine, astemizole, azatadine, azelastine, brompheniramine, chlorpheniramine, clemastine, cyproheptadine, dexchlorpheniramine, diphenhydramine, hydroxyzine, levocabastine, promethazine and tripelenamine.

Antiobesity therapeutic agents for use in combination therapy include, for example, leptin, leptin receptor agonists, melanin concentrating hormone (MCH) receptor antagonists, melanocortin receptor 3 (MC3) agonists, melanocortin receptor 4 (MC4) agonists, melanocyte stimulating hormone (MSH) agonists, cocaine and amphetamine regulated transcript (CART) agonists, dipeptidyl aminopeptidase inhibitors, a growth hormone secretagogue, beta-3 adrenergic agonists, 5HT-2 agonists, orexin antagonists, neuropeptide Y₁ or Y₅ antagonists, tumor necrosis factor (TNF) agonists, galanin antagonists, urocortin agonists, cholecystikinin (CCK) agonists, GLP-1 agonists, serotonin (5HT) agonists, bombesin agonists, CB1 antagonists such as rimonabant, growth hormone, growth factors such as prolactin or placental lactogen, growth hormone releasing compounds, thyrotropin (TRH) agonists, uncoupling protein 2 or 3 (UCP 2 or 3) modulators, dopamine agonists, agents that modify lipid metabolism such as antilipidemic agents (e.g., cholestyramine, colestipol, clofibrate, gemfibrozil, lovastatin, pravastatin, simvastatin, probucol or dextrothyroxine), lipase/amylase inhibitors, peroxisome proliferator-activated receptor (PPAR) modulators, retinoid X receptor (RXR) modulators, TR-beta agonists, agouti-related protein (AGRP) inhibitors, opioid antagonists such as naltrexone, exendin-4, GLP-1, ciliary neurotrophic factor, corticotropin-releasing factor binding protein (CRF BP) antagonists and/or corticotropin-releasing factor (CRF) agonists. Representative such agents include, for example, sibutramine, dexfenfluramine, dextroamphetamine, amphetamine, orlistat, mazindol, phentermine, phendimetrazine, diethylpropion, fluoxetine, bupropion, topiramate and ecopipam.

Antihypertensive therapeutic agents for use in combination therapy include, for example, beta-blockers such as alprenolol, atenolol, timolol, pindolol, propranolol and metoprolol, angiotensin converting enzyme (ACE) inhibitors such as benazepril, captopril, enalapril, fosinopril, lisinopril, quinapril and ramipril, calcium channel blockers such as nifedipine, felodipine, nicardipine, isradipine, nimodipine, diltiazem and verapamil, alpha-blockers such as doxazosin, urapidil, prazosin and terazosin, and angiotensin receptor blockers such as losartan.

CNS-active agents for use in combination therapy include, but are not limited to the following: for anxiety, depression, mood disorders or schizophrenia - serotonin receptor (e.g.,

5-HT_{1A}) agonists and antagonists, neurokinin receptor antagonists, GABAergic agents, and corticotropin releasing factor receptor (CRF₁) antagonists; for sleep disorders - melatonin receptor agonists; and for neurodegenerative disorders - such as Alzheimer's dementia, nicotinic agonists, muscarinic agents, acetylcholinesterase inhibitors and dopamine receptor agonists. For example, such combination therapy may include a selective serotonin reuptake inhibitor (SSRI) or a non-selective serotonin, dopamine and/or norepinephrine reuptake inhibitor. Such agents include, for example, fluoxetine, sertraline, paroxetine, amitriptyline, seroxat and citalopram. For cognitive disorders, representative agents for use in combination therapy include GABAergic agents.

Other therapeutic agents suitable for combination therapy include, for example, agents that modify cholinergic transmission (e.g., 5-HT₆ antagonists), M1 muscarinic agonists, M2 muscarinic antagonists and acetylcholinesterase inhibitors.

Suitable doses for H3 receptor modulator within such combination therapy are generally as described above. Doses and methods of administration of other therapeutic agents can be found, for example, in the manufacturer's instructions in the *Physician's Desk Reference*. In certain embodiments, the combination administration of a H3 receptor modulator with the second therapeutic agent results in a reduction of the dosage of the second therapeutic agent required to produce a therapeutic effect (i.e., a decrease in the minimum therapeutically effective amount). Thus, preferably, the dosage of second therapeutic agent in a combination or combination treatment method is less than the maximum dose advised by the manufacturer for administration of the second therapeutic agent without combination administration of a H3 receptor modulator. More preferably this dosage is less than $\frac{3}{4}$, even more preferably less than $\frac{1}{2}$, and highly preferably, less than $\frac{1}{4}$ of the maximum dose, while most preferably the dose is less than 10% of the maximum dose advised by the manufacturer for the second therapeutic agent when administered without combination administration of a H3 receptor modulator. It will be apparent that the dosage amount of H3 receptor modulator component(s) of the combination needed to achieve the desired effect may similarly be affected by the dosage amount and potency of the other therapeutic component(s) of the combination.

In certain preferred embodiments, the combination administration of a H3 receptor modulator with other therapeutic agent(s) is accomplished by packaging one or more H3 receptor modulators and one or more other therapeutic agents in the same package, either in separate containers within the package or in the same contained as a mixture of one or more H3 receptor modulators and one or more other therapeutic agents. Preferred mixtures are formulated for oral administration (e.g., as pills, capsules, tablets or the like). In certain embodiments, the package comprises a label bearing indicia indicating that the one or more H3 receptor modulators and one or more other therapeutic agents are to be taken together for

the treatment of attention deficit disorder, attention deficit hyperactivity disorder, schizophrenia, a cognitive disorder (such as mild cognitive impairment), epilepsy, migraine, narcolepsy, allergic rhinitis, vertigo, motion sickness, a memory disorder such as Alzheimer's disease, Parkinson's disease, obesity, an eating disorder, diabetes, fatigue, and fatigue-related disorders such as sleep/fatigue disorders, sleep impairment due to perimenopausal hormonal shifts, Parkinson's-related fatigue, multiple sclerosis-related fatigue, and chemotherapy-induced fatigue.

Within separate aspects, the present invention provides a variety of non-pharmaceutical *in vitro* and *in vivo* uses for the compounds provided herein. For example, such compounds may be labeled and used as probes for the detection and localization of H3 receptor (in samples such as cell preparations or tissue sections, preparations or fractions thereof). In addition, compounds provided herein that comprise a suitable reactive group (such as an aryl carbonyl, nitro or azide group) may be used in photoaffinity labeling studies of receptor binding sites. In addition, compounds provided herein may be used as positive controls in assays for receptor activity, as standards for determining the ability of a candidate agent to bind to H3 receptor, or as radiotracers for positron emission tomography (PET) imaging or for single photon emission computerized tomography (SPECT). Such methods can be used to characterize H3 receptors in living subjects. For example, a H3 receptor modulator may be labeled using any of a variety of well known techniques (*e.g.*, radiolabeled with a radionuclide such as tritium, as described herein), and incubated with a sample for a suitable incubation time (*e.g.*, determined by first assaying a time course of binding). Following incubation, unbound compound is removed (*e.g.*, by washing), and bound compound detected using any method suitable for the label employed (*e.g.*, autoradiography or scintillation counting for radiolabeled compounds; spectroscopic methods may be used to detect luminescent groups and fluorescent groups). As a control, a matched sample containing labeled compound and a greater (*e.g.*, 10-fold greater) amount of unlabeled compound may be processed in the same manner. A greater amount of detectable label remaining in the test sample than in the control indicates the presence of H3 receptor in the sample. Detection assays, including receptor autoradiography (receptor mapping) of H3 receptor in cultured cells or tissue samples may be performed as described by Kuhar in sections 8.1.1 to 8.1.9 of Current Protocols in Pharmacology (1998) John Wiley & Sons, New York.

Compounds provided herein may also be used within a variety of well known cell separation methods. For example, H3 receptor modulators may be linked to the interior surface of a tissue culture plate or other support, for use as affinity ligands for immobilizing and thereby isolating, H3 receptors (*e.g.*, isolating receptor-expressing cells) *in vitro*. Within one preferred embodiment, a H3 receptor modulator linked to a fluorescent marker, such as

fluorescein, is contacted with the cells, which are then analyzed (or isolated) by fluorescence activated cell sorting (FACS).

H3 receptor modulators provided herein may further be used within assays for the identification of other agents that bind to H3 receptor. In general, such assays are standard competition binding assays, in which bound, labeled H3 receptor modulator is displaced by a test compound. Briefly, such assays are performed by: (a) contacting H3 receptor with a radiolabeled H3 receptor modulator as described herein, under conditions that permit binding of the H3 receptor modulator to H3 receptor, thereby generating bound, labeled H3 receptor modulator; (b) detecting a signal that corresponds to the amount of bound, labeled H3 receptor modulator in the absence of test agent; (c) contacting the bound, labeled H3 receptor modulator with a test agent; (d) detecting a signal that corresponds to the amount of bound labeled H3 receptor modulator in the presence of test agent; and (e) detecting a decrease in signal detected in step (d), as compared to the signal detected in step (b).

The following Examples are offered by way of illustration and not by way of limitation. Unless otherwise specified all reagents and solvent are of standard commercial grade and are used without further purification. Using routine modifications, the starting materials may be varied and additional steps employed to produce other compounds provided herein.

EXAMPLES

Mass spectroscopy data in the following Examples is Electrospray MS, obtained in positive ion mode using a Micromass Time-of-Flight LCT (Waters Corp.; Milford, MA), equipped with a Waters 600 pump (Waters Corp.; Milford, MA), Waters 996 photodiode array detector (Waters Corp.; Milford, MA), and a Gilson 215 autosampler (Gilson, Inc.; Middleton, WI). MassLynx™ (Waters Corp.; Milford, MA) version 4.0 software with OpenLynx Global Server™, OpenLynx™ and AutoLynx™ processing is used for data collection and analysis.

For Methods 1, 2 and 3, MS conditions are as follows: capillary voltage = 3.5 kV; cone voltage = 30 V, desolvation and source temperature = 350°C and 120°C, respectively; mass range = 181-750 with a scan time of 0.22 seconds and an interscan delay of 0.05 seconds.

For Method 4, MS conditions are as follows: capillary voltage = 3.2 kV; cone voltage = 25 V, desolvation and source temperature = 300°C and 100°C, respectively; mass range = 100-700 with a scan time of 0.22 seconds and an interscan delay of 0.05 seconds.

Analyses are performed using one of the following procedures:

Method 1: Sample volume of 1 microliter is injected onto a 30x4.6mm XBridge™ C18, 5μ, column (Waters Corp.; Milford, MA), and eluted using a 2-phase linear gradient at a

flow rate of 6 ml/min. Sample is detected using total absorbance count over the 220-340nm UV range. The elution conditions are: Mobile Phase A - 95% water, 5% MeOH with 0.025% ammonium hydroxide; Mobile Phase B - 5% water, 95% MeOH with 0.025% ammonium hydroxide. The following gradient is used: 0-0.5 min 5-100% B, hold at 100% B to 1.2 min, return to 5% B at 1.21 min. Inject to inject cycle is 2.15 min.

Method 2: Sample volume of 1 microliter is injected onto a 50x4.6mm Chromolith SpeedROD RP-18e column (Merck KGaA, Darmstadt, Germany), and eluted using a 2-phase linear gradient at a flow rate of 6 ml/min. Sample is detected using total absorbance count over the 220-340nm UV range. The elution conditions are: Mobile Phase A - 95% water, 5% MeOH with 0.05% TFA; Mobile Phase B - 5% water, 95% MeOH with 0.025% TFA. The following gradient is used: 0-0.5 min 5-100% B, hold at 100% B to 1.2 min, return to 5% B at 1.21 min. Inject to inject cycle is 2.15 min.

Method 3: Sample volume of 1 microliter is injected onto a 50x4.6mm Chromolith SpeedROD RP-18e column (Merck KGaA, Darmstadt, Germany), and eluted using a 2-phase linear gradient at a flow rate of 6 ml/min. Sample is detected using total absorbance count over the 220-340nm UV range. The elution conditions are: Mobile Phase A - 95% water, 5% MeOH with 0.05% TFA; Mobile Phase B - 5% water, 95% MeOH with 0.025% TFA. The following gradient is used: 0-0.5 min 10-100%B, hold at 100% B to 1.2 min, return to 10% B at 1.21 min. Inject to inject cycle is 2.15 min.

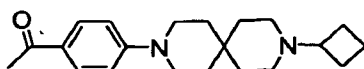
Method 4: Sample volume of 1 microliter is injected onto a 30x4.6mm XBridge™ C18, 5μ, column (Waters Corp.; Milford, MA), and eluted using a 2-phase linear gradient at a flow rate of 6 ml/min. Sample is detected using total absorbance count over the 220-340nm UV range. The elution conditions are: Mobile Phase A - 95% water, 5% MeOH with 0.025% Ammonium Hydroxide; Mobile Phase B - 5% water, 95% MeOH with 0.025% Ammonium Hydroxide. The following gradient is used: 0-0.5 min 10-100%B, hold at 100%B to 1.2 min, return to 10%B at 1.21 min. Inject to inject cycle is 2.15 min.

Unless otherwise specified, MS data is presented as M+1. Compounds 1-35 exhibit a K_i in the assay of Example 7 that is less than 1 micromolar.

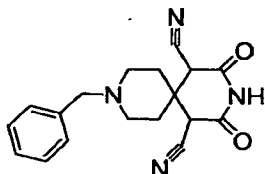
EXAMPLE 1

Preparation of Representative Substituted Azaspiro Derivatives

A. 1-[4-(9-CYCLOBUTYL-3,9-DIAZASPIRO[5.5]UNDEC-3-YL)PHENYL]ETHANONE
(COMPOUND 1)

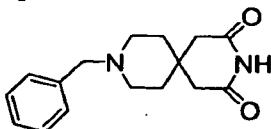


Step 1. 9-Benzyl-2,4-dioxo-3,9-diazaspiro[5.5]undecane;-1,5-dicarbonitrile



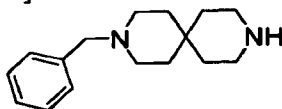
A solution of ethyl cyanoacetate (0.2 mol) and 1-benzyl-4-piperidone (0.1 mol) is added to 80 ml of 7 N NH_3 in MeOH with stirring at 0 °C. The solution is stored in the refrigerator for 2 days, and the precipitate is filtered, washed with cold MeOH, and dried. The salt is treated with 200 ml of hot water, and the boiling suspension is acidified with 2N HCl (150 ml). The resulting solution is cooled to rt to give a yellow precipitate, which is filtered to afford the title compound. LC-MS (Method 1) 323.05.

Step 2. 9-Benzyl-3,9-diazaspiro[5.5]undecane;-2,4-dione



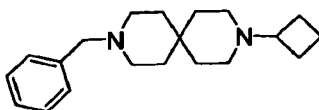
A mixture of 9-benzyl-2,4-dioxo-3,9-diazaspiro[5.5]undecane-1,5-dicarbonitrile (60 mmol) in 65% H_2SO_4 (39 mL) is refluxed for 2 hours. The solution is cooled to 0 °C, and neutralized with 10 N NaOH to pH about 8. The solution is extracted with DCM (3 x 25 mL). The combined organic layers are dried (MgSO_4) and solvent removed *in vacuo* to give the title compound. ^1H NMR (CDCl_3) δ 8.01 (1H, s), 7.22-7.34 (5H, m), 3.52 (2H, s), 2.52 (4H, s), 2.41-2.51 (4H, m), 1.59 (4H, t).

Step 3. 3-Benzyl-3,9-diazaspiro[5.5]undecane



To a solution of 9-benzyl-3,9-diazaspiro[5.5]undecane-2,4-dione (24.6 mmol) in ether (30 ml), 1M LAH (74 mL) is added. The resulting mixture is heated under reflux for 8 hours. The mixture is cooled to rt, and water (20 ml) is added slowly. After stirring for 1 hr, the mixture is filtered. The filtrate is dried over Na_2SO_4 , filtered and the solvent is removed to give the title compound. ^1H NMR (CDCl_3) δ 7.23-7.31 (5H, m), 3.49 (2H, s), 2.77 (4H, t), 2.38 (4H, t), 1.69 (1H, s), 1.52 (4H, t), 1.41 (4H, t).

Step 4. 3-Benzyl-9-cyclobutyl-3,9-diazaspiro[5.5]undecane



3-Benzyl-3,9-diazaspiro[5.5]undecane (6.14 mmol) is dissolved in 2.5% acetic acid in DCM (24 mL) at 0 °C and treated dropwise with cyclobutanone (9.21 mmol). The mixture is

stirred for 30 min and then sodium triacetoxyborohydride (9.21 mmol) is added in portions. The reaction mixture is stirred at rt overnight, basified with saturated sodium carbonate solution and extracted with DCM. The combined extracts are washed with water, and then brine, dried over anhydrous Na_2SO_4 and concentrated *in vacuo* to afford the title compound.

5. LC-MS (Method 1) = 299.19; R_T = 1.26 min.

Step 5. 3-Cyclobutyl-3,9-diazaspiro[5.5]undecane

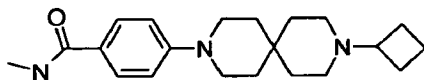


3-Benzyl-9-cyclobutyl-3,9-diazaspiro[5.5]undecane (6 mmol) is dissolved in EtOH (20 ml). Palladium hydroxide (0.5 g, 20% on carbon powder, moisture ca. 60%) is added and the mixture is stirred at rt under hydrogen (50 psi) overnight. The reaction mixture is filtered through celite and the filtrate is concentrated *in vacuo* to afford the title compound.

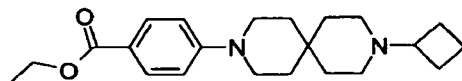
Step 6. 1-[4-(9-cyclobutyl-3,9-diazaspiro[5.5]undec-3-yl)phenyl]ethanone (Compound 1)

To a solution of 3-cyclobutyl-3,9-diazaspiro[5.5]undecane (0.25 mmol) in anhydrous DMSO (5 mL) is added 1-(4-fluoro-phenyl)-ethanone (0.25 mmol) and potassium carbonate (0.25 mmol). The resulting mixture is heated at 120 °C overnight. The reaction mixture is allowed to cool to rt, poured into cold water (10 mL), and extracted with EA (10 mL x 3). The combined organic layers are washed with water and brine, dried over sodium sulfate, and concentrated. The crude product is purified through PTLC (4% TEA in EA) to give the title compound as a white solid. ^1H NMR (300 MHz, CDCl_3) δ 7.84 (2H, d), 6.83 (2H, d), 3.32 (4H, t), 2.70-2.74 (1H, m), 2.50 (3H, s), 2.31 (4H, m), 1.84-2.10 (4H, m), 1.50-1.80 (10H, m). LC-MS (Method 3) = 327.12; R_T = 1.1 min.

B. 4-(9-CYCLOBUTYL-3,9-DIAZASPIRO[5.5]UNDEC-3-YL)-N-METHYLBENZAMIDE (COMPOUND 4)



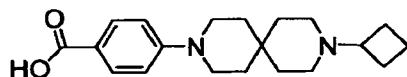
25 Step 1. Ethyl 4-(9-cyclobutyl-3,9-diazaspiro[5.5]undec-3-yl)benzoate (Compound 2)



To a solution of 3-cyclobutyl-3,9-diazaspiro[5.5]undecane (1.73 mmol) in anhydrous DMSO (5 mL) is added ethyl 4-fluorobenzoate (1.73 mmol) and potassium carbonate (1.73 mmol). The resulting mixture is heated at 120 °C overnight. The reaction mixture is allowed to cool to rt, poured into cold water (10 mL), and extracted with EA (10 mL x 3). The combined organic layers are washed with water and brine, dried over sodium sulfate, and concentrated. The crude product is purified through PTLC (4% TEA in EA) to give the title

compound as a white solid. ^1H NMR (300 MHz, CDCl_3) δ 7.88 (2H, d), 6.83 (2H, d), 4.31 (2H, q), 3.28 (4H, t), 2.63-2.74 (1H, m), 2.28 (4H, m), 1.84-2.10 (4H, m), 1.50-1.80 (10H, m), 1.35 (3H, t). LC-MS (Method 3) = 357.13; R_T = 1.18 min.

Step 2. 4-(9-Cyclobutyl-3,9-diazaspiro[5.5]undec-3-yl)benzoic acid (Compound 3)

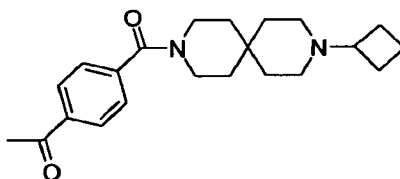


To a solution of ethyl 4-(9-cyclobutyl-3,9-diazaspiro[5.5]undec-3-yl)benzoate (0.6 mmol) in THF (5 mL) is added LiOH (1 mmol). The resulting mixture is stirred at rt overnight. The organic solvent is evaporated, and the residue is acidified to pH = 4-5. The solid is collected and dried *in vacuo* to give the title compound. LC-MS (Method 3) = 329.16; R_T = 0.96.

Step 3. 4-(9-Cyclobutyl-3,9-diazaspiro[5.5]undec-3-yl)-N-methylbenzamide (Compound 4)

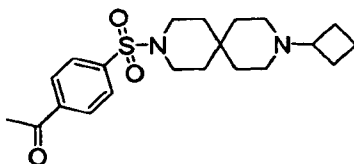
To a solution of 4-(9-cyclobutyl-3,9-diazaspiro[5.5]undec-3-yl)benzoic acid (0.15 mmol) in anhydrous DCM (2 mL) is added a solution of methylamine in THF (2M, 0.5 mL) and BOP (0.18 mmol). The resulting mixture is stirred at rt overnight. DCM is evaporated. The residue is dissolved in EA (20 ml), washed with water (5 mL x 3) and brine, dried over sodium sulfate, and concentrated. The crude product is purified through PTLC to give the title compound. ^1H NMR (300 MHz, CDCl_3) δ 7.65 (2H, d), 6.85 (2H, d), 5.99 (1H, m), 3.25 (4H, t), 2.97 (3H, d), 2.63-2.74 (1H, m), 2.28 (4H, m), 1.84-2.10 (4H, m), 1.50-1.80 (10H, m). LC-MS (Method 3) = 342.18; R_T = 0.61 min.

C. 1-{4-[(9-CYCLOBUTYL-3,9-DIAZASPIRO[5.5]UNDEC-3-YL)CARBONYL]PHENYL} ETHANONE (COMPOUND 5)



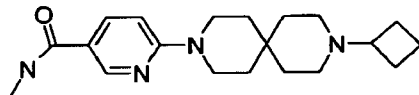
To a solution of 4-acetylbenzoic acid (0.4 mmol) in anhydrous DCM (2 mL) is added 3-cyclobutyl-3,9-diazaspiro[5.5]undecane (0.4 mmol) and BOP (0.47 mmol). The resulting mixture is stirred at rt overnight. DCM is evaporated. The residue is dissolved in EA (20 ml), washed with water (5 mL x 3) and brine, dried over sodium sulfate, and concentrated. The crude product is purified through PTLC to give the title compound. ^1H NMR (300 MHz, CDCl_3) δ 7.95 (2H, d), 7.44 (2H, d), 3.69 (2H, m), 3.27 (2H, m), 2.59-2.70 (4H, m), 2.25 (4H, m), 1.84-2.10 (4H, m), 1.37-1.80 (10H, m). LC-MS (Method 3) = 355.12; R_T = 1.02.

D. 1-{4-[(9-CYCLOBUTYL-3,9-DIAZASPIRO[5.5]UNDEC-3-YL) SULFONYL]PHENYL}
ETHANONE (COMPOUND 6)

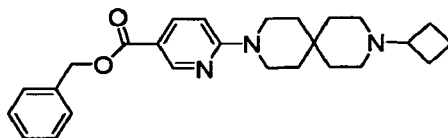


To a solution of 4-acetylbenzenesulfonyl chloride (0.2 mmol) in anhydrous DCM (2 mL) is added 3-cyclobutyl-3,9-diazaspiro[5.5]undecane (0.2 mmol), and TEA (0.25 mmol). The resulting mixture is stirred at rt overnight. The mixture is diluted with DCM (20 mL), washed with water (5 mL x 2) and brine, dried over sodium sulfate, and concentrated. The crude product is purified through PTLC to give the title compound. ¹H NMR (300 MHz, CDCl₃) δ 8.06 (2H, d), 7.83 (2H, d), 2.98 (4H, m), 2.59-2.70 (4H, m), 2.17 (4H, m), 1.95 (2H, m), 1.82 (2H, m), 1.52-1.64 (6H, m), 1.37 (4H, m). LC-MS (Method 3) 391.11; R_T = 0.98 min.

E. 6-(9-CYCLOBUTYL-3,9-DIAZASPIRO[5.5]UNDEC-3-YL)-N-METHYLNICOTINAMIDE
(COMPOUND 8)

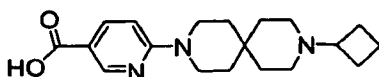


15 Step 1. Benzyl 6-(9-cyclobutyl-3,9-diazaspiro[5.5]undec-3-yl)nicotinate



To a solution of 3-cyclobutyl-3,9-diazaspiro[5.5]undecane (4.8 mmol) in anhydrous DMSO (5 mL) is added benzyl 6-chloronicotinate (4.8 mmol) and potassium carbonate (4.8 mmol). The resulting mixture is heated at 120 °C overnight. The reaction mixture is allowed to cool to rt, poured into cold water (10 mL), and extracted with EA (10 mL x 3). The combined organic layers are washed with water and brine, dried over sodium sulfate, and concentrated. The crude product is purified through PTLC (4% TEA in EA) to give the product as a white solid.

Step 2. 6-(9-Cyclobutyl-3,9-diazaspiro[5.5]undec-3-yl)nicotinic acid (Compound 7)



25

To a solution of benzyl 6-(9-cyclobutyl-3,9-diazaspiro[5.5]undec-3-yl)nicotinate (4 mmol) in EtOH, a catalytic amount of 10% Pd(OH)₂/C is added. The mixture is

hydrogenated at 50 psi overnight. The mixture is filtered over celite, washed with MeOH. The solvent is removed to give the title product. LC-MS (Method 1) = 330.12; R_T = 0.97 min.

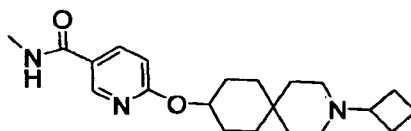
Step 3. 6-(9-Cyclobutyl-3,9-diazaspiro[5.5]undec-3-yl)-N-methylnicotinamide (compound 8)

- 5 To a solution of 6-(9-cyclobutyl-3,9-diazaspiro[5.5]undec-3-yl)nicotinic acid (0.15 mmol) in anhydrous DCM (2 mL) is added a solution of methylamine in THF (2M, 0.5 mL), and BOP (0.18 mmol). The resulting mixture is stirred at rt overnight. DCM is evaporated. The residue is dissolved in EA (20 mL), washed with water (5 mL x 3) and brine, dried over sodium sulfate, and concentrated. The crude product is purified through PTLC to give the
- 10 title compound. ^1H NMR (300 MHz, CDCl_3) δ 8.84 (1H, d), 8.07 (1H, dd), 6.58 (1H, d), 3.61 (4H, m), 3.05 (1H, m), 2.66 (4H, m), 2.61 (3H, d), 2.39 (2H, m), 2.10 (2H, m), 1.74 (4H, m), 1.57 (4H, m). LC-MS (Method 3) = 343.12; R_T = 0.33 min.

EXAMPLE 2

Preparation of Additional Representative Substituted Azaspiro Derivatives

- 15 A. 6-[(3-CYCLOBUTYL-3-AZASPIRO[5.5]UNDEC-9-YL)OXY]-N-METHYLNICOTINAMIDE (COMPOUND 9)



Step 1. 3-Azaspiro[5.5]undecan-9-one



- 20 This spirocyclic enone is synthesized essentially as described in PCT International Application Publication Number WO 97/11940 from benzyl 4-formylpiperidine-1-carboxylate.

Step 2. 3-Cyclobutyl-3-azaspiro[5.5]undecan-9-one



- 25 3-Azaspiro[5.5]undecan-9-one (7.6 mmol) is dissolved in 2.5% acetic acid in DCM (24 mL) at 0 °C and treated dropwise with cyclobutanone (22.8 mmol). The mixture is stirred for 30 min, and then sodium triacetoxyborohydride (22.8 mmol) is added in portions. The reaction mixture is stirred at rt overnight, basified with saturated sodium carbonate solution

and extracted with DCM. The combined extracts are washed with water, brine, dried over anhydrous Na_2SO_4 and concentrated *in vacuo* to afford the title compound.

Step 3. 3-Cyclobutyl-3-azaspiro[5.5]undecan-9-ol

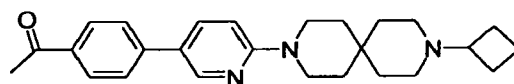


To a solution of 3-cyclobutyl-3-azaspiro[5.5]undecan-9-one (0.45 mmol) in EtOH (5 mL), NaBH_4 (0.1 g) is added portionwise. The mixture is stirred at rt for 2 hr. The solvent is removed. The residue is dissolved in DCM (20 mL). The mixture is washed with water, dried over Na_2SO_4 , and evaporated to give the title compound.

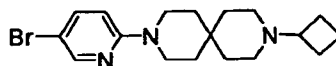
Step 4. 6-[(3-Cyclobutyl-3-azaspiro[5.5]undec-9-yl)oxy]-N-methylnicotinamide (Compound 9)

To a solution of 3-cyclobutyl-3-azaspiro[5.5]undecan-9-ol (0.44 mmol) in DMSO (4 ml), sodium hydride (65% disp. in mineral oil, 0.8 mmol) is added. After 30 min, 6-chloro-N-methyl-nicotinamide (0.26 mmol) is added and the reaction mixture is heated to 120 °C overnight. The reaction is allowed to cool to rt and then partitioned between EA and water. The EA layer is separated and the water layer is extracted with EA. The combined organic layer is washed with water, and then with brine, dried (Na_2SO_4) and filtered. The mixture is concentrated *in vacuo* and the residue is purified with PTLC to afford the title compound. MS (Method 1): 358.2.

B. 1-{4-[6-(9-CYCLOBUTYL-3,9-DIAZASPIRO[5.5]UNDEC-3-YL)PYRIDIN-3-YL]PHENYL}ETHANONE (COMPOUND 10)



Step 1. 3-(5-Bromopyridin-2-yl)-9-cyclobutyl-3,9-diazaspiro[5.5]undecane

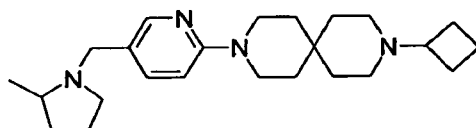


To a solution of 3-cyclobutyl-3,9-diazaspiro[5.5]undecane (0.62 mmol) in anhydrous DMSO (5 mL) is added 2-chloro-5-bromopyridine (0.94 mmol) and potassium carbonate (0.7 mmol). The resulting mixture is heated at 120 °C overnight. The reaction mixture is allowed to cool to rt, poured into cold water (10 mL), and extracted with EA (10 mL x 3). The combined organic layers are washed with water and brine, dried over sodium sulfate, and concentrated. The crude product is purified through PTLC (4% TEA in EA) to give the title compound as a white solid.

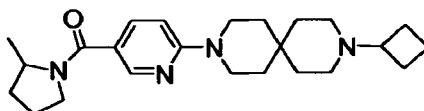
Step 2. 1-{4-[6-(9-Cyclobutyl-3,9-diazaspiro[5.5]undec-3-yl)pyridin-3-yl]phenyl}ethanone (Compound 10)

A mixture of 3-(5-bromopyridin-2-yl)-9-cyclobutyl-3,9-diazaspiro[5.5]undecane (25 mg, 0.07 mmol), acetylphenylboronic acid (14 mg, 0.08 mmol), Pd(PPh)₄ (5.5 mg) and Na₂CO₃ (20 mg) in DME (3 mL) and water (1 mL) is heated overnight at 80 °C. Water is added and the mixture is extracted with DCM. The combined organic layers are dried (MgSO₄) and solvent removed *in vacuo* to give the crude product, which is purified by PTLC (4% TEA in EA) to give the title compound. ¹H NMR (CDCl₃) δ 8.48 (d, 1H), 7.99 (d, 2H), 7.72 (dd, 1H), 7.60 (d, 2H), 6.70 (d, 1H), 3.62-3.55 (m, 4H), 2.82 (m, 1H), 2.62 (s, 3H), 2.37 (m, 4H), 2.04 (m, 4H), 1.80-1.56 (m, 10H). LC-MS (Method 3) = 404.24; R_T = 1.08 min.

C. 3-CYCLOBUTYL-9-{5-[(2-METHYLPYRROLIDIN-1-YL)METHYL]PYRIDIN-2-YL}-3,9-DIAZASPIRO[5.5]UNDECANE (COMPOUND 12)



Step 1. 3-Cyclobutyl-9-{5-[(2-methylpyrrolidin-1-yl)carbonyl]pyridin-2-yl}-3,9-diazaspiro[5.5]undecane (Compound 11)



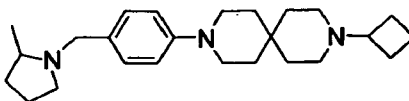
To a solution of 6-(9-cyclobutyl-3,9-diazaspiro[5.5]undec-3-yl)nicotinic acid (0.61 mmol) in anhydrous DCM (2 mL) is added 2-methylpyrrolidine (0.72 mmol), TEA (1.6 mmol) and DMC (1.2 mmol). The resulting mixture is stirred at 50°C for three hours. DCM is evaporated. The residue is dissolved in EA (20 mL), washed with water (5 mL x 3) and brine, dried over sodium sulfate, and concentrated. The crude product is purified through PTLC to give the title compound. ¹H NMR (300 MHz, CDCl₃) δ 8.36 (1H, d), 7.67 (1H, dd), 6.58 (1H, d), 4.25 (1H, m), 3.55 (4H, m), 2.68-2.80 (1H, m), 2.31 (4H, m), 2.20-1.80 (8H, d), 1.78-1.50 (12H, m), 1.27 (3H, m). LC-MS (Method 3) = 397.32; R_T = 1.01 min.

Step 2. 3-Cyclobutyl-9-{5-[(2-methylpyrrolidin-1-yl)methyl]pyridin-2-yl}-3,9-diazaspiro[5.5]undecane (Compound 12)

To a solution of 3-cyclobutyl-9-{5-[(2-methylpyrrolidin-1-yl)carbonyl]pyridin-2-yl}-3,9-diazaspiro[5.5]undecane (0.1 mmol) in ether is added a solution of LAH (1 M in THF, 1 mL). The resulting mixture is heated at reflux for three hours. The mixture is cooled to RT, and is quenched with water. The mixture is filtered through celite, and washed with ether.

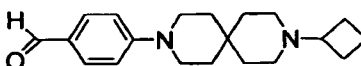
The filtrates are dried over MgSO_4 , the solvent is removed. The residue is purified through PTLC to give the title compound. LC-MS (Method 1) = 383.18; R_T = 1.26 min.

D. 3-CYCLOBUTYL-9-{4-[(2-METHYLPYRROLIDIN-1-YL)METHYL]PHENYL}-3,9-DIAZASPIRO[5.5]UNDECANE (COMPOUND 13)



5

Step 1. 4-(9-Cyclobutyl-3,9-diaza-spiro[5.5]undec-3-yl-benzaldehyde

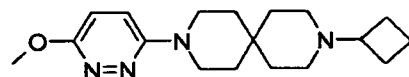


To a solution of 3-cyclobutyl-3,9-diazaspiro[5.5]undecane (2.95 mmol) in anhydrous DMSO (5 mL) is added ethyl 4-fluorobenzaldehyde (2 mmol) and potassium carbonate (3 mmol). The resulting mixture is heated at 120 °C overnight. The reaction mixture is allowed to cool to rt, poured into cold water (10 mL), and extracted with EA (10 mL x 3). The combined organic layers are washed with water and brine, dried over sodium sulfate, and concentrated. The crude product is purified through PTLC (4% TEA in EA) to give the title compound as a white solid.

Step 2. 3-Cyclobutyl-9-{4-[(2-methylpyrrolidin-1-yl)methyl]phenyl}-3,9-diazaspiro[5.5]undecane (Compound 13)

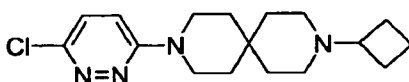
A mixture of 4-(9-cyclobutyl-3,9-diaza-spiro[5.5]undec-3-yl-benzaldehyde (0.17 mmol), 2-methylpyrrolidine (0.25 mmol) and $\text{NaBH}(\text{OAc})_3$ (0.25 mmol) in DCM (5 mL) is stirred at rt overnight. The mixture is washed with saturated NaHCO_3 , and dried over MgSO_4 , and the solvent is removed under reduced pressure. The residue is purified through PTLC (4% TEA in EA) to give the title compound. LC-MS (Method 4) = 382.22; R_T = 1.32 min.

E. 3-CYCLOBUTYL-9-(6-METHOXPYRIDAZIN-3-YL)-3,9-DIAZASPIRO[5.5]UNDECANE (COMPOUND 15)



25

Step 1. 3-(6-Chloropyridazin-3-yl)-9-cyclobutyl-3,9-diazaspiro[5.5]undecane (Compound 14)

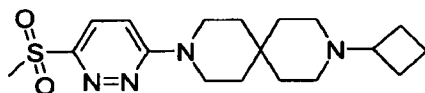


To a solution of 3-cyclobutyl-3,9-diazaspiro[5.5]undecane (3.55 mmol) in anhydrous DMSO (5 mL) is added 3,6-dichloropyridazine (3.55 mmol) and potassium carbonate (3.6 mmol). The resulting mixture is heated at 120 °C overnight. The reaction mixture is allowed to cool to rt, poured into cold water (10 mL), and extracted with EA (10 mL x 3). The combined organic layers are washed with water and brine, dried over sodium sulfate, and concentrated. The crude product is purified through PTLC (4% TEA in EA) to give the title compound as a white solid. LC-MS (Method 3) = 321.26; R_T = 0.79 min.

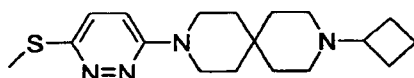
Step 2. 3-Cyclobutyl-9-(6-methoxypyridazin-3-yl)-3,9-diazaspiro[5.5]undecane (Compound 15)

A mixture of 3-(6-chloropyridazin-3-yl)-9-cyclobutyl-3,9-diazaspiro[5.5]undecane (0.12 mmol) and sodium methoxide (0.5 ml, 25% wt in methanol) in methanol (3 ml) is heated at 100°C in a sealed tube overnight. After cooling the crude mixture is evaporated under reduced pressure. Water (5 ml) is added, the inorganic phase is extracted with DCM (3 X 10 ml). The combined organic layers are washed with water and brine, dried over sodium sulfate, and concentrated. The crude product is purified through PTLC (4% TEA in EA) to give the title compound as a white solid. LC-MS (Method 1) = 317.12; R_T = 1.15 min.

F. 3-CYCLOBUTYL-9-[6-(METHYLSULFONYL)PYRIDAZIN-3-YL]-3,9-DIAZASPIRO[5.5]UNDECANE (COMPOUND 17)



Step 1. 3-Cyclobutyl-9-[6-(methylthio)pyridazin-3-yl]-3,9-diazaspiro[5.5]undecane (Compound 16)

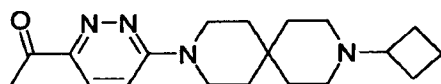


A mixture of 3-(6-chloropyridazin-3-yl)-9-cyclobutyl-3,9-diazaspiro[5.5]undecane (0.31 mmol) and sodium thiomethoxide (1.4 mmol) in EtOH (5 ml) is heated at 100 °C in a sealed tube overnight. After cooling, the crude mixture is evaporated under reduced pressure. Water (5 ml) is added, the inorganic phase is extracted with DCM (3 x 10 ml). The combined organic layers are washed with water and brine, dried over sodium sulfate, and concentrated. The crude product is purified through PTLC (4% TEA in EA) to give the title compound as a white solid. LC-MS (Method 3) = 333.29; R_T = 0.44 min.

Step 2. 3-Cyclobutyl-9-[6-(methylsulfonyl)pyridazin-3-yl]-3,9-diazaspiro[5.5]undecane (Compound 17)

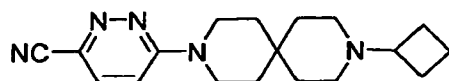
To a mixture of 3-cyclobutyl-9-[6-(methylthio)pyridazin-3-yl]-3,9-diazaspiro[5.5]undecane (0.13 mmol) in DCM (5 ml) is added mCPBA (0.34 mmol). The mixture is stirred at rt for two hours. The mixture is washed with saturated NaHCO₃, brine, and dried over NaSO₄. The solvent is removed, and the residue is purified through PTLC (DCM:MeOH:TEA = 100:5:5) to give the title compound as a white solid. LC-MS (Method 3) = 365.17; R_T = 0.94 min.

G. 1-[6-(9-CYCLOBUTYL-3,9-DIAZASPIRO[5.5]UNDEC-3-YL)PYRIDAZIN-3-YL]ETHANONE (COMPOUND 18)



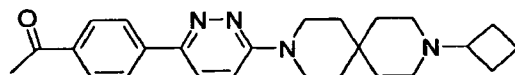
A mixture of 3-(6-chloropyridazin-3-yl)-9-cyclobutyl-3,9-diazaspiro[5.5]undecane (0.31 mmol), tributyl(1-ethoxy-vinyl)tin and Pd(PPh₃)₄ (20 mg) in toluene (5 ml) is heated at 130 °C in a sealed tube overnight. After cooling, the crude mixture is evaporated under reduced pressure. 1 M HCl solution (5 ml) is added, and the mixture is heated at 60 °C for three hours. The mixture is neutralized with saturated NaHCO₃, and the inorganic phase is extracted with DCM (3 x 10 ml). The combined organic layers are washed with water and brine, dried over sodium sulfate, and concentrated. The crude product is purified through PTLC (4% TEA in EA) to give the title compound. LC-MS (Method 3) = 329.31; R_T = 0.79 min.

H. 6-(9-CYCLOBUTYL-3,9-DIAZASPIRO[5.5]UNDEC-3-YL)PYRIDAZINE-3-CARBONITRILE (COMPOUND 19)



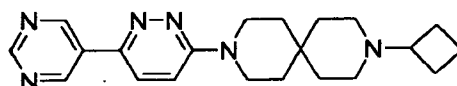
A mixture of 3-(6-chloropyridazin-3-yl)-9-cyclobutyl-3,9-diazaspiro[5.5]undecane (0.12 mmol), zinc cyanide (0.19 mmol), Pd₂(dba)₃ (3 mg) and DPPF (3 mg) in DMF (10 ml) is heated at 115 °C in a sealed tube overnight. After cooling, the crude mixture is evaporated under reduced pressure. Water (10 ml) is added, and the inorganic phase is extracted with DCM (3 x 10 ml). The combined organic layers are washed with water and brine, dried over sodium sulfate, and concentrated. The crude product is purified through PTLC (4% TEA in EA) to give the title compound. LC-MS (Method 3) = 312.22; R_T = 0.94 min.

I. 1-{4-[6-(9-CYCLOBUTYL-3,9-DIAZASPIRO[5.5]UNDEC-3-YL)PYRIDAZIN-3-YL]PHENYL}ETHANONE (COMPOUND 20)



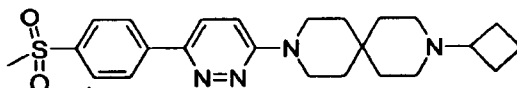
A mixture of 3-(6-chloropyridazin-3-yl)-9-cyclobutyl-3,9-diazaspiro[5.5]undecane (42 mg, 0.13 mmol), acetylphenylboronic acid (32 mg, 0.19 mmol), Pd(PPh)₄ (15 mg) and Na₂CO₃ (62 mg) in DME (3mL) and water (1 mL) is heated overnight at 80 °C. Water is added and the mixture is extracted with DCM. The combined organic layers are dried (MgSO₄) and solvent removed *in vacuo* to give the crude product, which is purified by PTLC (4% TEA in EA) to give the title compound. LC-MS (Method 3) = 405.23; R_T = 0.99 min.

10 J. 3-CYCLOBUTYL-9-(6-PYRIMIDIN-5-YLPYRIDAZIN-3-YL)-3,9-DIAZASPIRO[5.5]UNDECANE (COMPOUND 21)



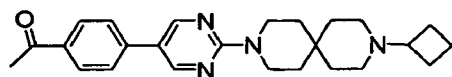
A mixture of 3-(6-chloropyridazin-3-yl)-9-cyclobutyl-3,9-diazaspiro[5.5]undecane (30 mg, 0.09 mmol), pyrimidine-5-boronic acid (20 mg, 0.16 mmol), Pd(PPh)₄ (10 mg) and Na₂CO₃ (35 mg) in DME (3mL) and water (1 mL) is heated overnight at 80 °C. Water is added and the mixture is extracted with DCM. The combined organic layers are dried (MgSO₄) and solvent removed *in vacuo* to give the crude product, which is purified by PTLC (4% TEA in EA) to give the title compound. LC-MS (Method 3) = 365.22; R_T = 0.56 min.

20 K. 3-CYCLOBUTYL-9-{6-[4-(METHYLSULFONYL)PHENYL]PYRIDAZIN-3-YL}-3,9-DIAZASPIRO[5.5]UNDECANE (COMPOUND 22)

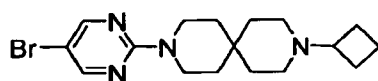


A mixture of 3-(6-chloropyridazin-3-yl)-9-cyclobutyl-3,9-diazaspiro[5.5]undecane (19 mg, 0.06 mmol), 4-(methanesulfonyl)phenylboronic acid (12 mg, 0.06 mmol), Pd(PPh)₄ (10 mg) and Na₂CO₃ (13 mg) in DME (3mL) and water (1 mL) is heated overnight at 80 °C. Water is added and the mixture is extracted with DCM. The combined organic layers are dried (MgSO₄) and solvent removed *in vacuo* to give the crude product, which is purified by PTLC (4% TEA in EA) to give the title compound. LC-MS (Method 3) = 441.19; R_T = 0.94 min.

30 L. 1-{4-[2-(9-CYCLOBUTYL-3,9-DIAZASPIRO[5.5]UNDEC-3-YL)-PYRIMIDINE-5-YL]PHENYL}ETHANONE (COMPOUND 24)



Step 1. 3-(5-Bromo-pyrimidin-2-yl)-9-cyclobutyl-3,3-diazaspiro[5.5]undecane (Compound 23)

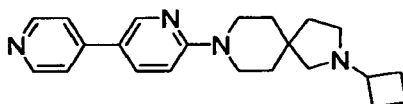


5 To a solution of 3-cyclobutyl-3,9-diazaspiro[5.5]undecane (2.4 mmol) in anhydrous DMSO (5 mL) is added 5-bromo-2-chloropyrimidine (3.63 mmol) and potassium carbonate (3.6 mmol). The resulting mixture is heated at 120 °C overnight. The reaction mixture is allowed to cool to rt, poured into cold water (10 mL), and extracted with EA (10 mL x 3). The combined organic layers are washed with water and brine, dried over sodium sulfate, and
10 concentrated. The crude product is purified through PTLC (4% TEA in EA) to give the title compound. LC-MS (Method 3) = 365.13; R_T = 1.12 min.

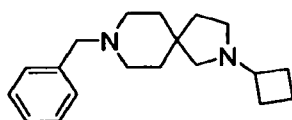
Step 2. 1-{4-[2-(9-Cyclobutyl-3,9-diaza-spiro[5.5]undec-3-yl)-pyrimidine-5-yl]phenyl}ethanone (Compound 24)

A mixture of 3-(5-bromo-pyrimidin-2-yl)-9-cyclobutyl-3,3-diazaspiro[5.5]undecane
15 (42 mg, 0.12 mmol), acetylphenylboronic acid (32 mg, 0.19 mmol), Pd(PPh)₄ (20 mg) and Na₂CO₃ (40 mg) in DME (3mL) and water (1 mL) is heated overnight at 80 °C. Water is added and the mixture is extracted with DCM. The combined organic layers are dried (MgSO₄) and solvent removed *in vacuo* to give the crude product, which is purified by PTLC (4% TEA in EA) to give the title compound. LC-MS (Method 3) = 405.24; R_T = 1.13 min.

20 M. 6-(2-CYCLOBUTYL-2,8-DIAZASPIRO[4.5]DEC-8-YL)-3,4'-BIPYRIDINE (COMPOUND 26)



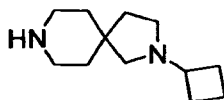
Step 1. 8-benzyl-2-cyclobutyl-2,8-diazaspiro[4.5]decane



8-Benzyl-2,8-diazaspiro[4.5]decane (6.14 g, 26.7 mmol) is dissolved in TEA (6.84
25 mL) in DCM (200 mL) at 0 °C and treated dropwise with cyclobutanone (2.60 mL, 34.7 mmol). The mixture is stirred for 30 min and then sodium triacetoxyborohydride (8.48 g, 40.06 mmol) is added in portions. The reaction mixture is stirred at rt overnight, basified with 1N NaOH solution and extracted with DCM (2 x 100 mL). The combined extracts are

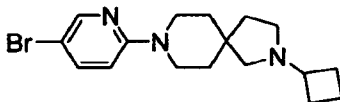
washed with water and brine, dried over anhydrous Na_2SO_4 and concentrated *in vacuo* to afford the title compound. LC-MS (Method 1): 285.3.

Step 2. 2-Cyclobutyl-2,8-diazaspiro[4.5]decane



8-Benzyl-2-cyclobutyl-2,8-diazaspiro[4.5]decane (7.00 g, 24.6 mmol) is dissolved in EtOH (100 ml). Palladium hydroxide (1.0 g, 20% on carbon powder, moisture ca. 60%) is added and the mixture is stirred at rt under hydrogen (50 psi) overnight. The reaction mixture is filtered through Celite and the filtrate is concentrated *in vacuo* to afford the title compound. LC-MS (Method 1): 195.3.

Step 3. 8-(5-Bromopyridin-2-yl)-2-cyclobutyl-2,8-diazaspiro[4.5]decane (Compound 25)



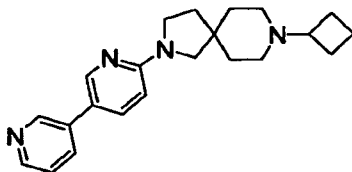
To a solution of 2-cyclobutyl-2,8-diazaspiro[4.5]decane (1.00 g, 5.15 mmol) in anhydrous DMSO (10 mL) is added 5-bromo-2-chloropyridine (1.09 g, 5.66 mmol) and potassium carbonate (1.42 g, 10.3 mmol). The resulting mixture is heated at 120 °C overnight. The reaction mixture is allowed to cool to rt, poured into cold water (10 mL), and extracted with EA (10 mL x 3). The combined organic layers are washed with water and brine, dried over Na_2SO_4 , and concentrated. The crude product is purified by silica gel chromatography (5% TEA in EA) to give the desired product. LC-MS (Method 3): 350.11. $R_T = 0.97$ min.

Step 4. 6-(2-Cyclobutyl-2,8-diazaspiro[4.5]dec-8-yl)-3,4'-bipyridine (Compound 26)

A mixture of 8-(5-bromopyridin-2-yl)-2-cyclobutyl-2,8-diazaspiro[4.5]decane (50 mg, 0.17 mmol), 4-pyridylboronic acid (53 mg, 0.43 mmol), $\text{Pd}(\text{PPh})_4$ (20 mg, 0.017) and K_2CO_3 (138 mg) in dioxane (4 mL) and water (0.5 mL) is heated overnight at 100 °C. Water is added and the mixture is extracted with DCM (2 x 20 mL). The combined organic layers are dried (Na_2SO_4) and solvent removed *in vacuo* to give the crude product. The residue is dissolved in DCM and passed through an SCX (ion-exchange) column. The column is first washed with EA/MeOH (95:5) (discarded to waste) and second with EA/MeOH/TEA (90:10:10) which is collected. The solvent is removed and the crude product is purified by PTLC (4% TEA in hexane/acetone [2:1]) to give the title compound. ^1H NMR (300 MHz, CDCl_3) δ 8.61(2H, d), 8.51 (1H, d), 7.75 (1H, dd), 7.43 (2H, d), 6.74 (1H, d), 3.67-3.58 (4H,

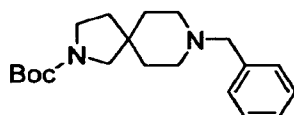
m), 3.17 (1H, m), 2.89 (2H, m), 2.70 (2H, m), 2.28 (2H, m), 2.12 (2H, m), 1.89 (2H, m), 1.76 (6H, m); LC-MS (Method 1): 349.20. $R_T = 1.19$ min.

N. 6-(8-CYCLOBUTYL-2,8-DIAZASPIRO[4.5]DEC-2-YL)-3,3'-BIPYRIDINE (COMPOUND 28)



5

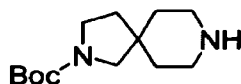
Step 1. *tert*-Butyl 8-benzyl-2,8-diazaspiro[4.5]decane-2-carboxylate



10

To a solution of 8-benzyl-2,8-diazaspiro[4.5]decane (16.7 g, 72.5 mmol) in anhydrous DCM (250 mL) is added di-*t*-butyl dicarbonate (15.8 g, 72.45 mmol). The reaction mixture is stirred at rt overnight. The organic layer is washed with 1 N NaOH (2 x 100 mL). The organic extract is dried over Na_2SO_4 , and concentrated to give the title compound. LC-MS (Method 1): 331.2.

Step 2. *tert*-Butyl 2,8-diazaspiro[4.5]decane-2-carboxylate

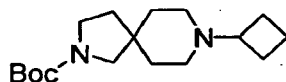


15

tert-Butyl-8-benzyl-2,8-diazaspiro[4.5]decane-2-carboxylate (10.0 g, 30.3 mmol) is dissolved in EtOH (100 mL). Palladium hydroxide (1.0 g, 20% on carbon powder, moisture ca. 60%) is added and the mixture is stirred at rt under hydrogen (50 psi) overnight. The reaction mixture is filtered through Celite and the filtrate is concentrated *in vacuo* to afford the title compound. LC-MS (Method 1): 241.3.

20

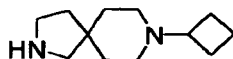
Step 3. *tert*-Butyl 8-cyclobutyl-2,8-diazaspiro[4.5]decane-2-carboxylate



25

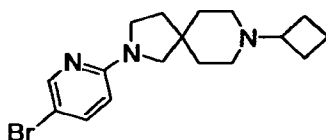
tert-Butyl 2,8-diazaspiro[4.5]decane-2-carboxylate (7.21 g, 30.0 mmol) is dissolved in TEA (7.69 mL) in DCM (200 mL) at 0 °C and treated dropwise with cyclobutanone (2.92 mL, 38.9 mmol). The mixture is stirred for 30 min and sodium triacetoxyborohydride (9.53 g, 4.56 mmol) is added in portions. The reaction mixture is stirred at rt overnight, basified with 1N NaOH solution and extracted with DCM (2 x 100 mL). The combined extracts are washed with water, brine, dried over anhydrous Na_2SO_4 and concentrated *in vacuo* to afford the title compound. LC-MS (Method 1): 295.4.

Step 4. 8-Cyclobutyl-2,8-diazaspiro[4.5]decane



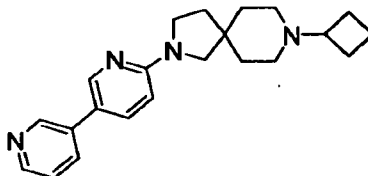
tert-Butyl 8-cyclobutyl-2,8-diazaspiro[4.5]decane-2-carboxylate (8.23 g, 27.9 mmol) is dissolved in 4N HCl in dioxane (100 ml). The mixture is stirred at rt for 3 h. The solvent is removed *in vacuo* to afford the dihydrochloride salt of the title compound. The crude salt is dissolved in a mixture of acetonitrile (200 mL) and K₂CO₃ (19.3 g, 140 mmol). The mixture is stirred 2 h at rt. The mixture is filtered through Celite to remove the inorganic salts and the solution concentrated *in vacuo* to yield the title compound. LC-MS (Method 1): 195.3.

Step 5. 2-(5-Bromopyridin-2-yl)-8-cyclobutyl-2,8-diazaspiro[4.5]decane (Compound 27)



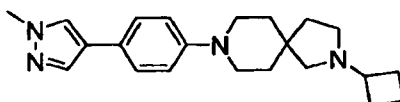
2-(5-Bromopyridin-2-yl)-8-cyclobutyl-2,8-diazaspiro[4.5]decane is synthesized essentially as described above for the preparation of 8-(5-bromopyridin-2-yl)-2-cyclobutyl-2,8-diazaspiro[4.5]decane, using 8-cyclobutyl-2,8-diazaspiro[4.5]decane as the starting material. LC-MS (Method 3): 350.18; R_T = 0.46 min.

Step 6. 6-(8-Cyclobutyl-2,8-diazaspiro[4.5]dec-2-yl)-3,3'-bipyridine (Compound 28)

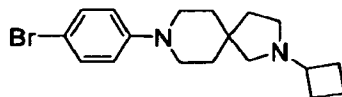


6-(8-Cyclobutyl-2,8-diazaspiro[4.5]dec-2-yl)-3,3'-bipyridine is synthesized essentially as described above for the preparation of 6-(2-cyclobutyl-2,8-diazaspiro[4.5]dec-8-yl)-3,4'-bipyridine, using 2-(5-bromopyridin-2-yl)-8-cyclobutyl-2,8-diazaspiro[4.5]decane and 3-pyridyl boronic acid as the starting materials. ¹H NMR (300 MHz, CDCl₃) δ 8.77 (1H, dd), 8.52 (1H, dd), 8.40 (1H, d), 7.79 (1H, dd), 7.68 (1H, dd), 7.34 (1H, dd), 6.45 (1H, d), 3.56-3.41 (4H, m), 2.85 (2H, m), 2.76 (1H, m), 2.49 (2H, m), 2.26 (2H, m), 2.07-1.89 (6H, m), 1.76 (4H, m); LC-MS (Method 1): 349.17; R_T = 1.16 min.

O. 2-CYCLOBUTYL-8-[4-(1-METHYL-1H-PYRAZOL-4-YL)PHENYL]-2,8-DIAZASPIRO-[4.5]DECANE (COMPOUND 29)



Step 1. 8-(4-Bromophenyl)-2-cyclobutyl-2,8-diazaspiro[4.5]decane

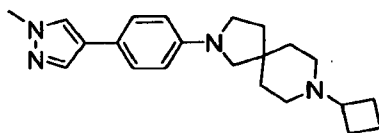


In a sealed tube, dissolve 2-cyclobutyl-2,8-diazaspiro[4.5]decane (307 mg, 1.58 mmol), 1-bromo-4-iodobenzene (893 mg, 3.16 mmol), Cs_2CO_3 (772 mg, 2.37 mmol), Pd_2dba_3 (36 mg, 0.0395 mmol) and BINAP (49 mg, 0.079 mmol) in dry toluene (8 mL). Degas the mixture with nitrogen and heat at 120 °C overnight. Cool and filter through Celite washing with EA. Evaporate the filtrate and dissolve the crude residue in 6N HCl. Wash the aqueous solution with EA (2 x 25 mL). Basify the aqueous portion with 10N NaOH and extract with DCM (2 x 50 mL). Combine, dry and evaporate the organic extracts to yield the title compound. LC-MS (Method 1): 349.2.

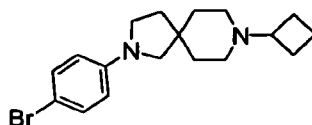
10 Step 2. 2-Cyclobutyl-8-[4-(1-methyl-1H-pyrazol-4-yl)phenyl]-2,8-diazaspiro[4.5]decane (Compound 29)

A mixture of 8-(4-bromophenyl)-2-cyclobutyl-2,8-diazaspiro[4.5]decane (56 mg, 0.16 mmol), 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-doxaborolan-2-yl)-1H-pyrazole (66 mg, 0.32 mmol), $\text{Pd}(\text{PPh})_4$ (18 mg, 0.016) and K_2CO_3 (138 mg) in dioxane (4 mL) and water (0.5 mL) is heated overnight at 100 °C. Water is added and the mixture is extracted with DCM (2 x 20 mL). The combined organic layers are dried (Na_2SO_4) and the solvent removed *in vacuo* to give the crude product. The residue is dissolved in DCM and passed through an SCX (ion-exchange) column. The column is first washed with EA/MeOH (95:5) (discarded to waste) and second with EA/MeOH/TEA (90:10:10) which is collected. The solvent is removed and the crude product is purified by PTLC (4% TEA in hexane/acetone [2:1]) to give the title compound. ^1H NMR (300 MHz, CDCl_3) δ 7.68 (1H, s), 7.52 (1H, s), 7.35 (2H, d), 6.93 (2H, d), 3.92 (3H, s), 3.15 (4H, t), 3.05 (1H, m), 2.66 (2H, t), 2.50 (2H, m), 2.04-2.01 (4H, m), 1.78-1.72 (8H, m). LC-MS (Method 3): 351.27; R_T = 0.91 min.

25 P. 8-CYCLOBUTYL-2-[4-(1-METHYL-1H-PYRAZOL-4-YL)PHENYL]-2,8-DIAZASPIRO[4.5]DECANE (COMPOUND 30)



Step 1. 2-(4-Bromophenyl)-8-cyclobutyl-2,8-diazaspiro[4.5]decane

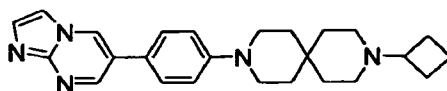


2-(4-Bromophenyl)-8-cyclobutyl-2,8-diazaspiro[4.5]decane is made essentially as described above for the preparation of 8-(4-bromophenyl)-2-cyclobutyl-2,8-diazaspiro[4.5]decane using 8-cyclobutyl-2,8-diazaspiro[4.5]decane as the starting material. LC-MS (Method 1): 349.2.

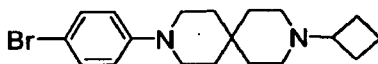
5 Step 2. 8-Cyclobutyl-2-[4-(1-methyl-1H-pyrazol-4-yl)phenyl]-2,8-diazaspiro[4.5]decane (Compound 30)

8-Cyclobutyl-2-[4-(1-methyl-1H-pyrazol-4-yl)phenyl]-2,8-diazaspiro[4.5]decane is synthesized essentially as described above for the preparation of 2-cyclobutyl-8-[4-(1-methyl-1H-pyrazol-4-yl)phenyl]-2,8-diazaspiro[4.5]decane, using 2-(4-bromophenyl)-8-cyclobutyl-2,8-diazaspiro[4.5]decane as the starting material. ¹H NMR (300 MHz, CDCl₃) δ 7.66 (1H, s), 7.48 (1H, s), 7.33 (2H, d), 6.54 (2H, d), 3.92-3.90 (7H, m), 3.36 (2H, t), 3.16 (2H, s), 2.86 (1H, m), 2.56 (2H, m), 2.40 (2H, m), 2.05-2.01 (2H, m), 1.88 (2H, t), 1.78-1.72 (4H, m). LC-MS (Method 3): 351.27; R_T = 1.11 min.

15 Q. 3-CYCLOBUTYL-9-(4-IMIDAZO[1,2-A]PYRIMIDIN-6-YLPHENYL)-3,9-DIAZASPIRO[5.5]UNDECANE (COMPOUND 31)

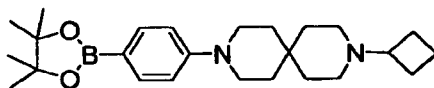


Step 1. 3-(4-Bromophenyl)-9-cyclobutyl-3,9-diazaspiro[5.5]undecane



20 3-(4-Bromophenyl)-9-cyclobutyl-3,9-diazaspiro[5.5]undecane is synthesized essentially as described above for the preparation of 8-(4-bromophenyl)-2-cyclobutyl-2,8-diazaspiro[4.5]decane, using 3-cyclobutyl-3,9-diazaspiro[5.5]undecane as the starting material. LC-MS (Method 1): 363.3.

Step 2. 3-Cyclobutyl-9-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]-3,9-diazaspiro[5.5]undecane



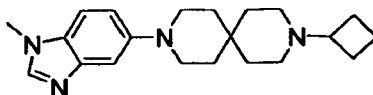
25 In a sealed tube dissolve 3-(4-bromophenyl)-9-cyclobutyl-3,9-diazaspiro[5.5]undecane (745 mg, 2.05 mmol), bis(pinacolato)diboron (573 g, 2.25 mmol), PdCl₂dppf•CHCl₃ (51 mg, 0.0615 mmol), and KOAc (604 mg, 6.15 mmol) in anhydrous dioxane (15 ml). The mixture is degassed with nitrogen for 5 minutes. Seal the tube and heat
30 at 85 °C overnight. Cool and filter through Celite. Wash the Celite bed with EA.

Concentrate and chromatograph the crude product on silica gel eluting with EA / TEA (95:5) to yield the title compound. LC-MS (Method 1): 411.4.

Step 3. 3-Cyclobutyl-9-(4-imidazo[1,2-a]pyrimidin-6-ylphenyl)-3,9-diazaspiro[5.5]undecane (Compound 31)

- 5 A mixture of 3-cyclobutyl-9-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]-3,9-diazaspiro[5.5]undecane (60 mg, 0.15 mmol), 6-bromoimidazo[1,2-a]pyrimidine (35 mg, 0.18 mmol), Pd(PPh)₄ (18 mg, 0.015) and K₂CO₃ (138 mg) in dioxane (4 mL) and water (0.5 mL) is heated overnight at 100 °C. Water is added and the mixture is extracted with EA (2 x 10 mL). The combined organic layers are placed directly on an SCX (ion-exchange) column.
- 10 The column is first washed with EA (discarded to waste) and second with EA/MeOH/TEA (90:10:10) which is collected. The solvent is removed and the crude product is purified by PTLC (5% TEA in EA/MeOH [95:5]) to give the title compound. ¹H NMR (300 MHz, CDCl₃) δ 8.79 (1H, d), 8.50 (1H, d), 7.82 (1H, d), 7.56 (1H, d), 7.46 (2H, d), 7.03 (2H, d), 3.74-3.24 (4H, m), 2.93 (1H, m), 2.56-2.45 (4H, m), 2.12-2.09 (2H, m), 1.8-1.67 (12H, m).
- 15 LC-MS (Method 1): 402.13; R_T = 1.2 min.

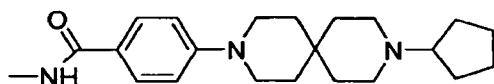
R. 3-CYCLOBUTYL-9-(1-METHYL-1H-BENZIMIDAZOL-5-YL)-3,9-DIAZASPIRO[5.5]-UNDECANE (COMPOUND 32)



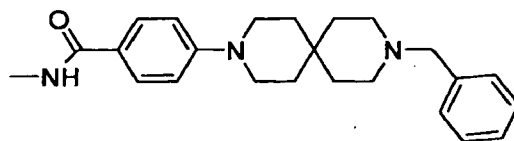
- In a sealed tube, dissolve 3-cyclobutyl-3,9-diazaspiro[5.5]undecane (100 mg, 0.48 mmol), 5-bromo-1-methyl-1H-benzimidazole (122 mg, 0.58 mmol), KOt-Bu (108 mg, 0.96 mmol), Pd₂dba₃ (11 mg, 0.012 mmol) and t-Bu-XPhos (11 mg, 0.024 mmol) in dry toluene (5 mL). Degas the mixture with nitrogen and heat at 120 °C overnight. Cool and partition between EA and water. The organic extract is placed directly on an SCX (ion-exchange) column. The column is first washed with EA/MeOH (95:5) (discarded to waste) and second
- 25 with EA/MeOH/TEA (90:10:10) which is collected. The solvent is removed and the crude product is purified by PTLC (10% TEA in EA/MeOH [90:10]) to give the title compound. ¹H NMR (300 MHz, CDCl₃) δ 7.80 (1H, s), 7.32 (1H, d), 7.27 (1H, d), 7.08 (1H, dd), 3.80 (3H, s), 3.15-3.11 (4H, m), 2.93 (1H, m), 2.56-2.45 (4H, m), 2.32-2.09 (2H, m), 1.8-1.67 (12H, m); LC-MS (Method 3): 339.36; R_T = 0.36 min.

30

S. 4-(9-CYCLOPENTYL-3,9-DIAZASPIRO[5.5]UNDEC-3-YL)-N-METHYLBENZAMIDE (COMPOUND 33)

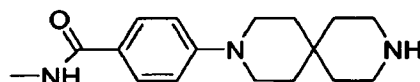


Step 1. 4-(9-Benzyl-3,9-diazaspiro[5.5]undec-3-yl)-N-methylbenzamide



To a solution of 3-benzyl-3,9-diazaspiro[5.5]undecane (3.3 mmol) in anhydrous
 5 DMSO (5 mL) is added 4-fluoro-N-methylbenzamide (3.9 mmol) and potassium carbonate (3.9 mmol). The resulting mixture is heated at 140 °C for 2 days. The reaction mixture is allowed to cool to rt, poured into cold water (10 mL), and extracted with EA (10 mL x 3). The combined organic layers are washed with water and brine, dried over sodium sulfate, and concentrated. The crude product is purified through PTLC (4% TEA in EA) to give the title
 10 compound as a white solid.

Step 2. 4-(3,9-Diazaspiro[5.5]undec-3-yl)-N-methylbenzamide

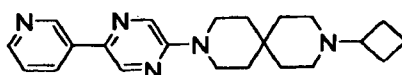


4-(9-Benzyl-3,9-diazaspiro[5.5]undec-3-yl)-N-methylbenzamide (2.6 mmol) is dissolved in EtOH (20 ml). Palladium hydroxide (0.5 g, 20% on carbon powder, moisture ca.
 15 60%) is added and the mixture is stirred at rt under hydrogen (50 psi) overnight. The reaction mixture is filtered through celite and the filtrate is concentrated *in vacuo* to afford the title compound.

Step 3. 4-(9-Cyclopentyl-3,9-diazaspiro[5.5]undec-3-yl)-N-methylbenzamide (Compound 33)

4-(3,9-Diazaspiro[5.5]undec-3-yl)-N-methylbenzamide (0.17 mmol) is dissolved in 2.5% acetic acid in DCM (10 mL) at 0 °C and treated dropwise with cyclobutanone (0.26 mmol). The mixture is stirred for 30 min and then sodium triacetoxyborohydride (0.26 mmol) is added in portions. The reaction mixture is stirred at rt overnight, basified with saturated sodium carbonate solution and extracted with DCM. The combined extracts are
 25 washed with water, and then brine, dried over anhydrous Na₂SO₄ and concentrated *in vacuo* to afford the title compound. LC-MS (Method 3): 356.37; R_T = 0.97 min.

T. 3-CYCLOBUTYL-9-(5-PYRIDIN-3-YPYRAZIN-2-YL)-3,9-DIAZASPIRO[5.5]UNDECANE (COMPOUND 35)

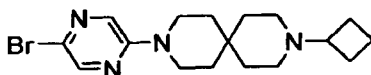


Step 1. 3-Cyclobutyl-9-pyrazin-2-yl-3,9-diazaspiro[5.5]undecane (Compound 34)



To a solution of 3-cyclobutyl-3,9-diazaspiro[5.5]undecane (2.49 mmol) in anhydrous DMSO (5 mL) is added 5-bromo-2-chloropyrimidine (2.96 mmol) and potassium carbonate (3.0 mmol). The resulting mixture is heated at 120 °C overnight. The reaction mixture is allowed to cool to rt, poured into cold water (10 mL), and extracted with EA (10 mL x 3). The combined organic layers are washed with water and brine, dried over sodium sulfate, and concentrated. The crude product is purified through PTLC (4% TEA in EA) to give the title compound. LC-MS (Method 3): 287.28; R_T = 0.85 min.

Step 2. 3-(5-Bromopyrazin-2-yl)-9-cyclobutyl-3,9-diazaspiro[5.5]undecane



To a solution of 3-cyclobutyl-9-pyrazin-2-yl-3,9-diazaspiro[5.5]undecane (0.51 mmol) in DCM (10 ml) is added NaHCO_3 (0.1g) and NBS (0.56 mmol). The mixture is stirred at rt overnight. The reaction mixture is poured into water, and extracted with DCM (10 ml x 2). The combined organic layers are washed with water and brine, dried over sodium sulfate, and concentrated. The crude product is purified through PTLC (4% TEA in EA) to give the title compound.

Step 3. 3-Cyclobutyl-9-(5-pyridin-3-yl pyrazin-2-yl)-3,9-diazaspiro[5.5]undecane (Compound 35)

A mixture of 3-(5-bromopyrazin-2-yl)-9-cyclobutyl-3,9-diazaspiro[5.5]undecane (40 mg, 0.12 mmol), 3-pyridylboronic acid (40 mg, 0.32 mmol), Pd(PPh)_4 (20 mg) and Na_2CO_3 (40 mg) in DME (3mL) and water (1 mL) is heated overnight at 80 °C. Water is added and the mixture is extracted with DCM. The combined organic layers are dried (MgSO_4) and solvent removed *in vacuo* to give the crude product, which is purified by PTLC (4% TEA in EA) to give the title compound. LC-MS (Method 3): 364.29; R_T = 0.95 min.

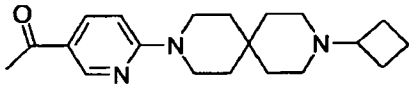
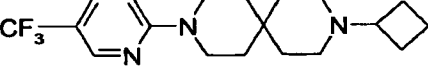
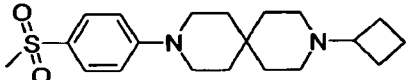
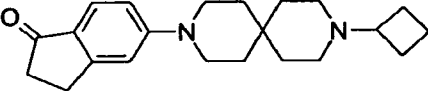
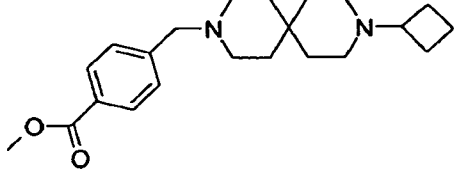
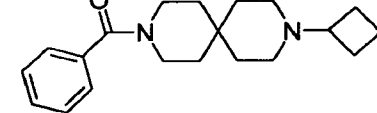
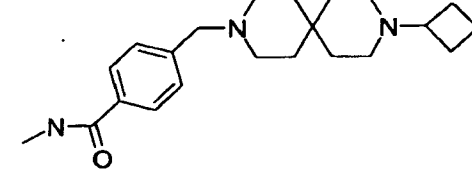
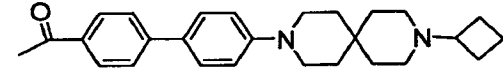
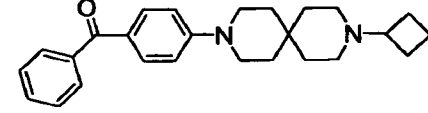
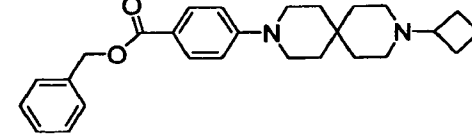
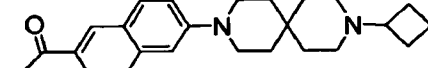
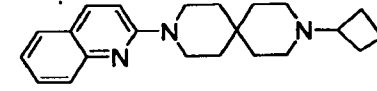
EXAMPLE 3

Preparation of Additional Representative Substituted Azaspiro Derivatives

Compounds in Tables I-IV are prepared using the methods described above. In some cases, synthetic modifications and/or additional steps that will be readily apparent are employed. All compounds listed in Tables I-III have a K_i in the assay of Example 7 that is less than 1 micromolar. The determined molecular weight (presented as M+1) obtained using

the method indicated in parentheses is shown in the column headed "MS" in Tables I-III, with retention time (R_T) given in minutes.

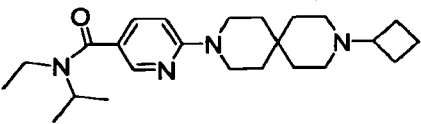
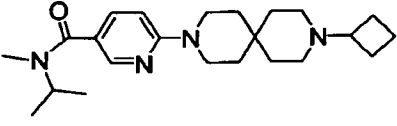
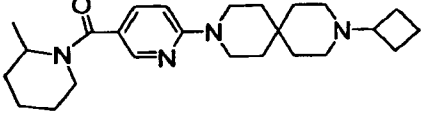
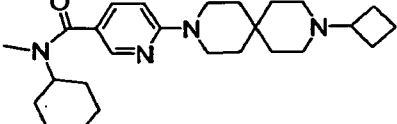
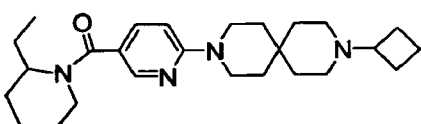
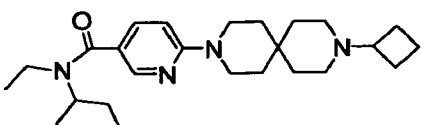
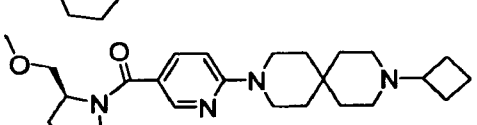
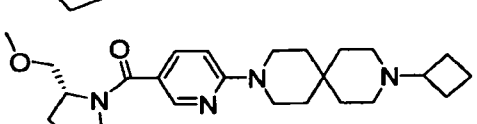
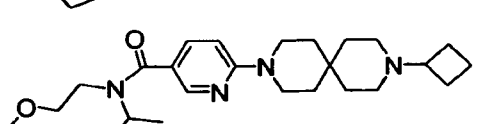
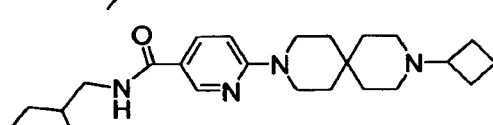
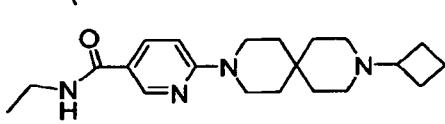
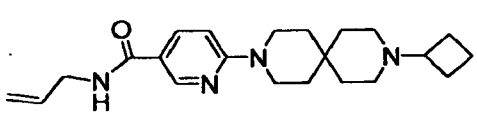
Table I
Representative Substituted Azaspiro Derivatives

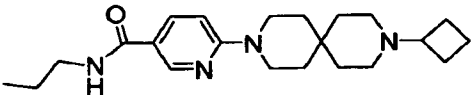
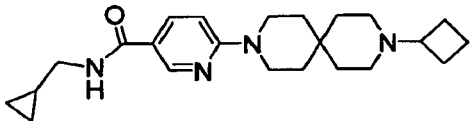
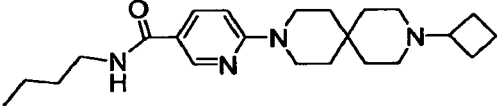
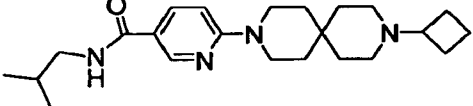
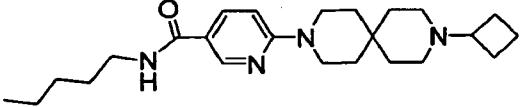
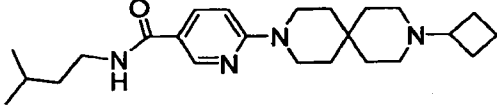
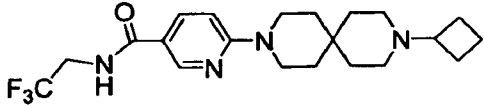
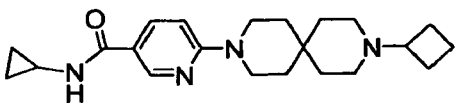
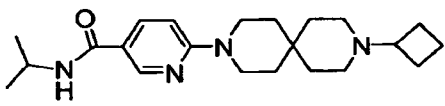
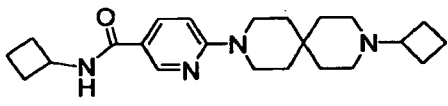
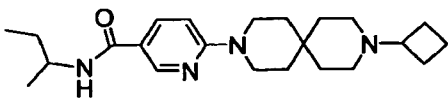
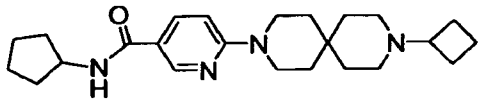
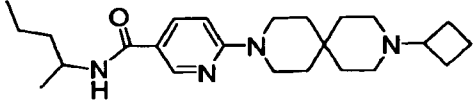
	Compound	Name	MS	R_T
36		1-[6-(9-cyclobutyl-3,9-diazaspiro[5.5]undec-3-yl)pyridin-3-yl]ethanone	328.12 (3)	0.39
37		3-cyclobutyl-9-[5-(trifluoromethyl)pyridin-2-yl]-3,9-diazaspiro[5.5]undecane	354.07 (3)	1.14
38		3-cyclobutyl-9-[4-(methylsulfonyl)phenyl]-3,9-diazaspiro[5.5]undecane	363.06 (3)	1.06
39		5-(9-cyclobutyl-3,9-diazaspiro[5.5]undec-3-yl)indan-1-one	339.11 (3)	1.11
40		methyl 4-[(9-cyclobutyl-3,9-diazaspiro[5.5]undec-3-yl)methyl]benzoate	357.15 (3)	0.52
41		3-benzoyl-9-cyclobutyl-3,9-diazaspiro[5.5]undecane	313.13 (3)	1.04
42		4-[(9-cyclobutyl-3,9-diazaspiro[5.5]undec-3-yl)methyl]-N-methylbenzamide	356.15 (1)	1.13
43		1-[4'-(9-cyclobutyl-3,9-diazaspiro[5.5]undec-3-yl)biphenyl-4-yl]ethanone	403.18 (3)	1.04
44		[4-(9-cyclobutyl-3,9-diazaspiro[5.5]undec-3-yl)phenyl](phenyl)methanone	389.17 (3)	1.1
45		benzyl 4-(9-cyclobutyl-3,9-diazaspiro[5.5]undec-3-yl)benzoate	419.18 (3)	1.15
46		1-[6-(9-cyclobutyl-3,9-diazaspiro[5.5]undec-3-yl)-2-naphthyl]ethanone	377.19 (3)	0.98
47		3-cyclobutyl-9-quinolin-2-yl-3,9-diazaspiro[5.5]undecane	336.24 (3)	0.99

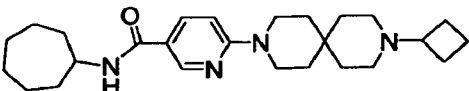
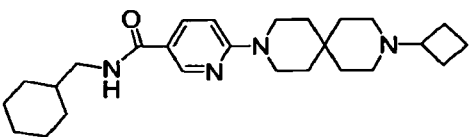
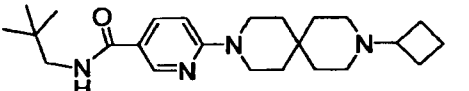
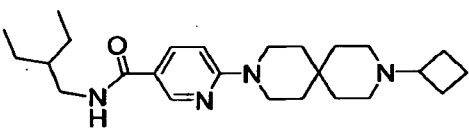
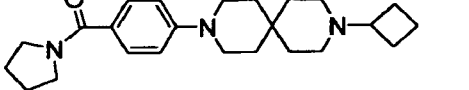
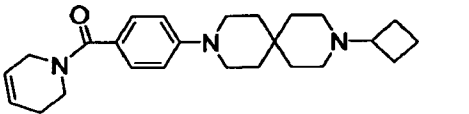
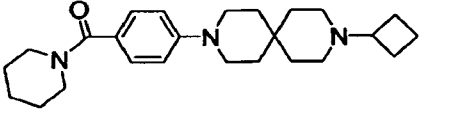
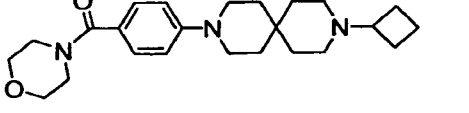
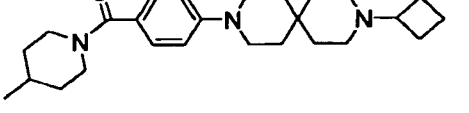
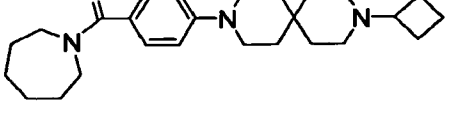
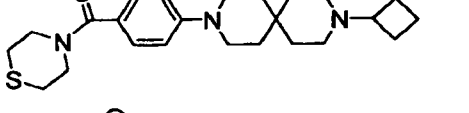
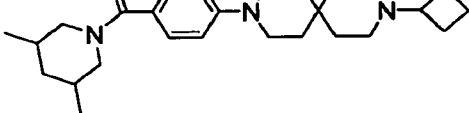
	<u>Compound</u>	<u>Name</u>	<u>MS</u>	<u>R_T</u>
48		1-{4-[4-(9-cyclobutyl-3,9-diazaspiro[5.5]undec-3-yl)piperidin-1-yl]phenyl}ethanone	410.30 (3)	0.98
49		methyl 4-[6-(9-cyclobutyl-3,9-diazaspiro[5.5]undec-3-yl)pyridin-3-yl]benzoate	420.23 (3)	1.03
50		4-[6-(9-cyclobutyl-3,9-diazaspiro[5.5]undec-3-yl)pyridin-3-yl]-N-methylbenzamide	419.33 (3)	0.94
51		3-cyclobutyl-9-{5-[4-(methylsulfonyl)phenyl]pyridin-2-yl}-3,9-diazaspiro[5.5]undecane	440.30 (3)	0.92
52		methyl 4-[6-(9-cyclobutyl-3,9-diazaspiro[5.5]undec-3-yl)pyridazin-3-yl]benzoate	421.23 (3)	1.03
53		3-cyclobutyl-9-{6-[3-(methylsulfonyl)phenyl]pyridazin-3-yl}-3,9-diazaspiro[5.5]undecane	441.20 (3)	0.93
54		{4-[6-(9-cyclobutyl-3,9-diazaspiro[5.5]undec-3-yl)pyridazin-3-yl]-phenyl}-(2-methyl-pyrrolidin-1-yl)-methanone	474.33 (3)	1.03
55		4-[6-(9-cyclobutyl-3,9-diazaspiro[5.5]undec-3-yl)pyridazin-3-yl]-N-methylbenzamide	420.25 (3)	0.94
56		3-cyclobutyl-9-(4-piperidin-1-ylmethyl-phenyl)-3,9-diazaspiro[5.5]undecane	382.3 (4)	1.38
57		3-cyclobutyl-9-{5-[4-[(2-methylpyrrolidin-1-yl)carbonyl]phenyl]pyridin-2-yl}-3,9-diazaspiro[5.5]undecane	474.33 (3)	1.04
58		4-[6-(9-cyclobutyl-3,9-diazaspiro[5.5]undec-3-yl)pyridin-3-yl]-N-ethylbenzamide	433.27 (3)	1.00

Table II
Additional Representative Substituted Azaspiro Derivatives

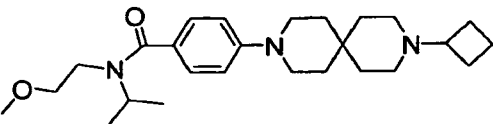
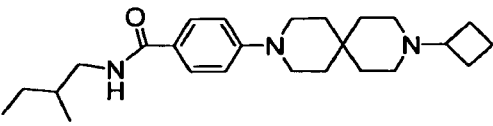
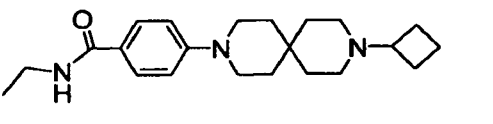
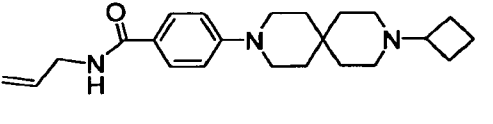
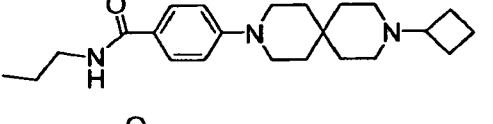
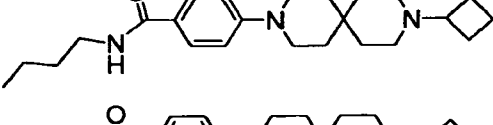
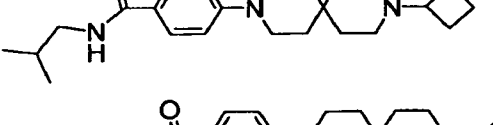
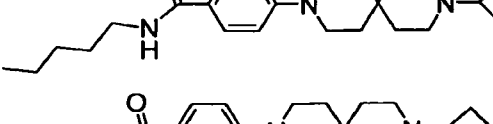
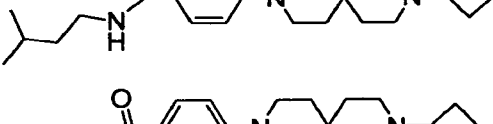
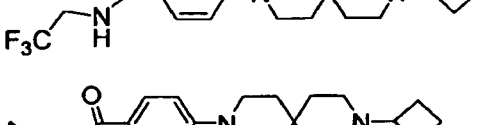
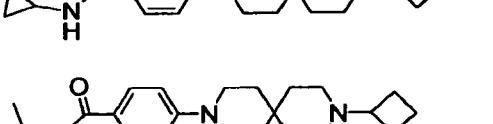
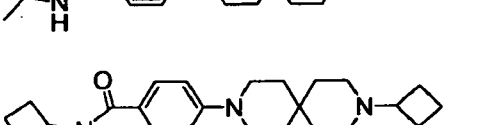
	<u>Compound</u>	<u>Name</u>	<u>MS</u>	<u>R_T</u>
59		3-cyclobutyl-9-[5-(pyrrolidin-1-ylcarbonyl)pyridin-2-yl]-3,9-diazaspiro[5.5]undecane	383.32 (3)	0.89
60		3-cyclobutyl-9-[5-(3,6-dihydropyridin-1(2H)-ylcarbonyl)pyridin-2-yl]-3,9-diazaspiro[5.5]undecane	395.31 (3)	1
61		3-cyclobutyl-9-[5-(piperidin-1-ylcarbonyl)pyridin-2-yl]-3,9-diazaspiro[5.5]undecane	397.32 (3)	1.01
62		3-cyclobutyl-9-[5-(morpholin-4-ylcarbonyl)pyridin-2-yl]-3,9-diazaspiro[5.5]undecane	399.32 (3)	0.28
63		3-cyclobutyl-9-[5-[(4-methylpiperidin-1-yl)carbonyl]pyridin-2-yl]-3,9-diazaspiro[5.5]undecane	411.34 (3)	1.08
64		3-[5-(azepan-1-ylcarbonyl)pyridin-2-yl]-9-cyclobutyl-3,9-diazaspiro[5.5]undecane	411.34 (3)	1.06
65		3-cyclobutyl-9-[5-(thiomorpholin-4-ylcarbonyl)pyridin-2-yl]-3,9-diazaspiro[5.5]undecane	415.29 (3)	0.92
66		3-cyclobutyl-9-[5-[(3,5-dimethylpiperidin-1-yl)carbonyl]pyridin-2-yl]-3,9-diazaspiro[5.5]undecane	425.34 (3)	1.13
67		3-cyclobutyl-9-[5-[(4aR,8aS)-octahydroisoquinolin-2(1H)-ylcarbonyl]pyridin-2-yl]-3,9-diazaspiro[5.5]undecane	451.35 (3)	1.19
68		3-cyclobutyl-9-[5-[(4aS,8aS)-octahydroisoquinolin-2(1H)-ylcarbonyl]pyridin-2-yl]-3,9-diazaspiro[5.5]undecane	451.36 (3)	1.17
69		3-cyclobutyl-9-[5-[(2,6-dimethylmorpholin-4-yl)carbonyl]pyridin-2-yl]-3,9-diazaspiro[5.5]undecane	427.33 (3)	1.01

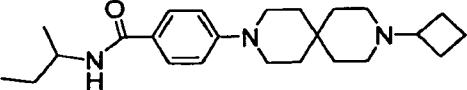
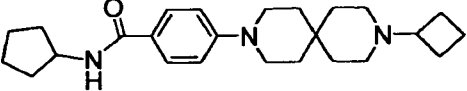
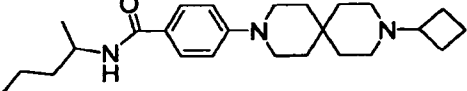
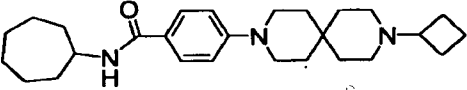
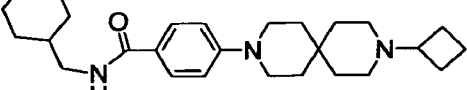
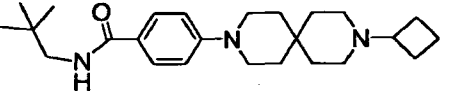
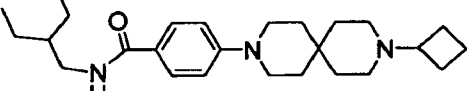
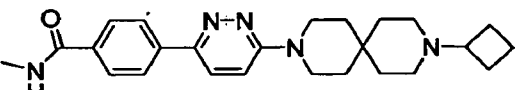
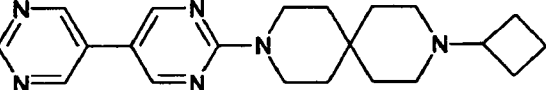
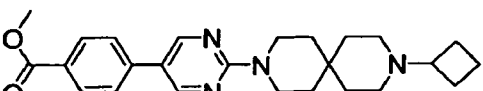
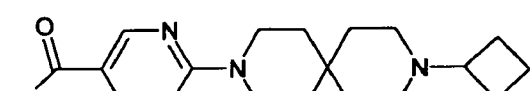
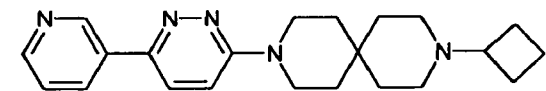
	Compound	Name	MS	R _T
70		6-(9-cyclobutyl-3,9-diazaspiro[5.5]undec-3-yl)-N-ethyl-N-isopropylnicotinamide	399.34 (3)	1.04
71		6-(9-cyclobutyl-3,9-diazaspiro[5.5]undec-3-yl)-N-isopropyl-N-methylnicotinamide	385.33 (3)	0.99
72		3-cyclobutyl-9-{5-[(2-methylpiperidin-1-yl)carbonyl]pyridin-2-yl}-3,9-diazaspiro[5.5]undecane	411.33 (3)	1.07
73		6-(9-cyclobutyl-3,9-diazaspiro[5.5]undec-3-yl)-N-cyclohexyl-N-methylnicotinamide	425.34 (3)	1.12
74		3-cyclobutyl-9-{5-[(2-ethylpiperidin-1-yl)carbonyl]pyridin-2-yl}-3,9-diazaspiro[5.5]undecane	425.34 (3)	1.11
75		6-(9-cyclobutyl-3,9-diazaspiro[5.5]undec-3-yl)-N-cyclohexyl-N-ethylnicotinamide	439.36 (3)	1.15
76		3-cyclobutyl-9-{5-[(2S)-2-(methoxymethyl)pyrrolidin-1-yl]carbonyl}pyridin-2-yl}-3,9-diazaspiro[5.5]undecane	397.32 (3)	1.01
77		3-cyclobutyl-9-{5-[(2R)-2-(methoxymethyl)pyrrolidin-1-yl]carbonyl}pyridin-2-yl}-3,9-diazaspiro[5.5]undecane	427.32 (3)	1
78		6-(9-cyclobutyl-3,9-diazaspiro[5.5]undec-3-yl)-N-isopropyl-N-(2-methoxyethyl)nicotinamide	427.33 (3)	0.99
79		6-(9-cyclobutyl-3,9-diazaspiro[5.5]undec-3-yl)-N-(2-methylbutyl)nicotinamide	429.34 (3)	1.03
80		6-(9-cyclobutyl-3,9-diazaspiro[5.5]undec-3-yl)-N-ethylnicotinamide	399.35 (3)	1.1
81		N-allyl-6-(9-cyclobutyl-3,9-diazaspiro[5.5]undec-3-yl)nicotinamide	357.32 (3)	0.46

	Compound	Name	MS	R _T
82		6-(9-cyclobutyl-3,9-diazaspiro[5.5]undec-3-yl)-N-propylnicotinamide	369.32 (3)	0.83
83		6-(9-cyclobutyl-3,9-diazaspiro[5.5]undec-3-yl)-N-(cyclopropylmethyl)nicotinamide	371.34 (3)	0.98
84		N-butyl-6-(9-cyclobutyl-3,9-diazaspiro[5.5]undec-3-yl)nicotinamide	383.31 (3)	1
85		6-(9-cyclobutyl-3,9-diazaspiro[5.5]undec-3-yl)-N-isobutylnicotinamide	385.33 (3)	1.06
86		6-(9-cyclobutyl-3,9-diazaspiro[5.5]undec-3-yl)-N-pentylnicotinamide	385.34 (3)	1.06
87		6-(9-cyclobutyl-3,9-diazaspiro[5.5]undec-3-yl)-N-(3-methylbutyl)nicotinamide	399.34 (3)	1.12
88		6-(9-cyclobutyl-3,9-diazaspiro[5.5]undec-3-yl)-N-(2,2,2-trifluoroethyl)nicotinamide	399.34 (3)	1.11
89		6-(9-cyclobutyl-3,9-diazaspiro[5.5]undec-3-yl)-N-cyclopropylnicotinamide	411.28 (3)	0.99
90		6-(9-cyclobutyl-3,9-diazaspiro[5.5]undec-3-yl)-N-isopropylnicotinamide	411.33 (3)	1.11
91		N-cyclobutyl-6-(9-cyclobutyl-3,9-diazaspiro[5.5]undec-3-yl)nicotinamide	371.33 (3)	0.94
92		N-(sec-butyl)-6-(9-cyclobutyl-3,9-diazaspiro[5.5]undec-3-yl)nicotinamide	383.31 (3)	0.95
93		6-(9-cyclobutyl-3,9-diazaspiro[5.5]undec-3-yl)-N-cyclopentylnicotinamide	385.34 (3)	1.03
94		6-(9-cyclobutyl-3,9-diazaspiro[5.5]undec-3-yl)-N-(1-methylbutyl)nicotinamide	397.33 (3)	1.07

	Compound	Name	MS	R _T
95		6-(9-cyclobutyl-3,9-diazaspiro[5.5]undec-3-yl)-N-cycloheptylnicotinamide	399.34 (3)	1.1
96		6-(9-cyclobutyl-3,9-diazaspiro[5.5]undec-3-yl)-N-(cyclohexylmethyl)nicotinamide	425.34 (3)	1.15
97		6-(9-cyclobutyl-3,9-diazaspiro[5.5]undec-3-yl)-N-(2,2-dimethylpropyl)nicotinamide	425.35 (3)	1.16
98		6-(9-cyclobutyl-3,9-diazaspiro[5.5]undec-3-yl)-N-(2-ethylbutyl)nicotinamide	399.34 (3)	1.1
99		3-cyclobutyl-9-[4-(pyrrolidin-1-ylcarbonyl)phenyl]-3,9-diazaspiro[5.5]undecane	413.35 (3)	1.15
100		3-cyclobutyl-9-[4-(3,6-dihydropyridin-1(2H)-ylcarbonyl)phenyl]-3,9-diazaspiro[5.5]undecane	382.32 (3)	1.06
101		3-cyclobutyl-9-[4-(piperidin-1-ylcarbonyl)phenyl]-3,9-diazaspiro[5.5]undecane	394.31 (3)	1.1
102		3-cyclobutyl-9-[4-(morpholin-4-ylcarbonyl)phenyl]-3,9-diazaspiro[5.5]undecane	396.33 (3)	1.1
103		3-cyclobutyl-9-[4-[(4-methylpiperidin-1-yl)carbonyl]phenyl]-3,9-diazaspiro[5.5]undecane	398.32 (3)	0.96
104		3-[4-(azepan-1-ylcarbonyl)phenyl]-9-cyclobutyl-3,9-diazaspiro[5.5]undecane	410.34 (3)	1.16
105		3-cyclobutyl-9-[4-(thiomorpholin-4-ylcarbonyl)phenyl]-3,9-diazaspiro[5.5]undecane	410.35 (3)	1.13
106		3-cyclobutyl-9-[4-[(3,5-dimethylpiperidin-1-yl)carbonyl]phenyl]-3,9-diazaspiro[5.5]undecane	414.28 (3)	1.08

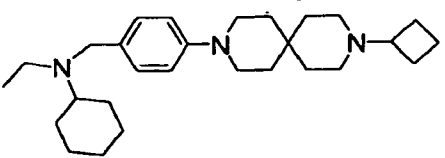
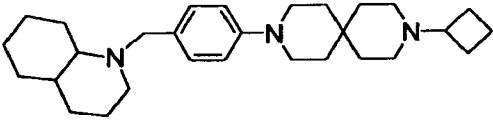
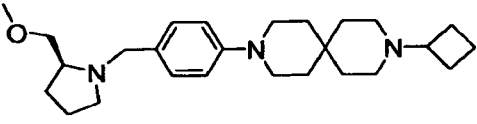
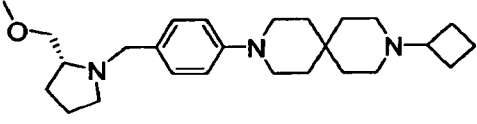
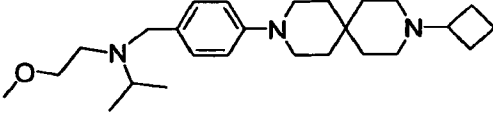
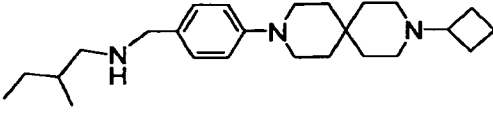
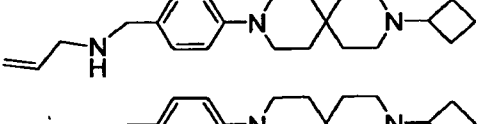
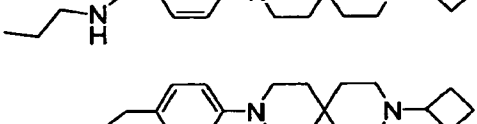
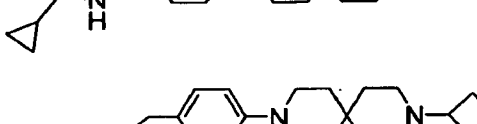
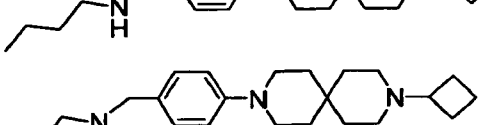
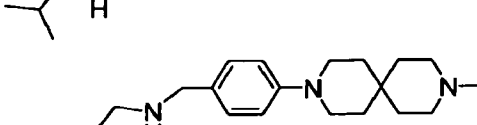
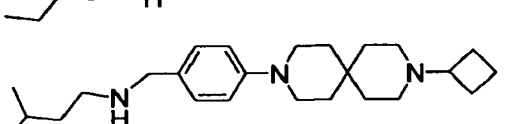
	Compound	Name	MS	R _T
107		3-cyclobutyl-9-{4-[(4aR,8aS)-octahydroisoquinolin-2(1H)-ylcarbonyl]phenyl}-3,9-diazaspiro[5.5]undecane	424.36 (3)	1.2
108		3-cyclobutyl-9-{4-[(4aS,8aS)-octahydroisoquinolin-2(1H)-ylcarbonyl]phenyl}-3,9-diazaspiro[5.5]undecane	450.37 (3)	1.25
109		3-cyclobutyl-9-{4-[(2,6-dimethylmorpholin-4-yl)carbonyl]phenyl}-3,9-diazaspiro[5.5]undecane	450.37 (3)	1.23
110		4-(9-cyclobutyl-3,9-diazaspiro[5.5]undec-3-yl)-N-ethyl-N-isopropylbenzamide	426.34 (3)	1.1
111		4-(9-cyclobutyl-3,9-diazaspiro[5.5]undec-3-yl)-N-isopropyl-N-methylbenzamide	398.35 (3)	1.11
112		3-cyclobutyl-9-{4-[(2-methylpiperidin-1-yl)carbonyl]phenyl}-3,9-diazaspiro[5.5]undecane	384.33 (3)	1.07
113		4-(9-cyclobutyl-3,9-diazaspiro[5.5]undec-3-yl)-N-cyclohexyl-N-methylbenzamide	410.34 (3)	1.14
114		3-cyclobutyl-9-{4-[(2-ethylpiperidin-1-yl)carbonyl]phenyl}-3,9-diazaspiro[5.5]undecane	424.36 (3)	1.18
115		4-(9-cyclobutyl-3,9-diazaspiro[5.5]undec-3-yl)-N-cyclohexyl-N-ethylbenzamide	424.36 (3)	1.17
116		3-cyclobutyl-9-[4-(octahydroquinolin-1(2H)-ylcarbonyl)phenyl]-3,9-diazaspiro[5.5]undecane	438.37 (3)	1.22
117		3-cyclobutyl-9-(4-{[(2S)-2-(methoxymethyl)pyrrolidin-1-yl]carbonyl}phenyl)-3,9-diazaspiro[5.5]undecane	396.33 (3)	1.1
118		3-cyclobutyl-9-(4-{[(2R)-2-(methoxymethyl)pyrrolidin-1-yl]carbonyl}phenyl)-3,9-diazaspiro[5.5]undecane	426.34 (3)	1.09

	Compound	Name	MS	R _T
119		4-(9-cyclobutyl-3,9-diazaspiro[5.5]undec-3-yl)-N-isopropyl-N-(2-methoxyethyl)benzamide	426.33 (3)	1.09
120		4-(9-cyclobutyl-3,9-diazaspiro[5.5]undec-3-yl)-N-(2-methylbutyl)benzamide	428.36 (3)	1.11
121		4-(9-cyclobutyl-3,9-diazaspiro[5.5]undec-3-yl)-N-ethylbenzamide	398.36 (3)	1.17
122		N-allyl-4-(9-cyclobutyl-3,9-diazaspiro[5.5]undec-3-yl)benzamide	356.34 (3)	0.89
123		4-(9-cyclobutyl-3,9-diazaspiro[5.5]undec-3-yl)-N-propylbenzamide	368.33 (3)	1.04
124		N-butyl-4-(9-cyclobutyl-3,9-diazaspiro[5.5]undec-3-yl)benzamide	382.35 (3)	1.09
125		4-(9-cyclobutyl-3,9-diazaspiro[5.5]undec-3-yl)-N-isobutylbenzamide	384.35 (3)	1.13
126		4-(9-cyclobutyl-3,9-diazaspiro[5.5]undec-3-yl)-N-pentylbenzamide	384.37 (3)	1.12
127		4-(9-cyclobutyl-3,9-diazaspiro[5.5]undec-3-yl)-N-(3-methylbutyl)benzamide	398.35 (3)	1.18
128		4-(9-cyclobutyl-3,9-diazaspiro[5.5]undec-3-yl)-N-(2,2,2-trifluoroethyl)benzamide	398.35 (3)	1.17
129		4-(9-cyclobutyl-3,9-diazaspiro[5.5]undec-3-yl)-N-cyclopropylbenzamide	410.28 (3)	1.11
130		4-(9-cyclobutyl-3,9-diazaspiro[5.5]undec-3-yl)-N-isopropylbenzamide	410.34 (3)	1.17
131		N-cyclobutyl-4-(9-cyclobutyl-3,9-diazaspiro[5.5]undec-3-yl)benzamide	370.35 (3)	1.06

	Compound	Name	MS	R _T
132		N-(sec-butyl)-4-(9-cyclobutyl-3,9-diazaspiro[5.5]undec-3-yl)benzamide	382.34 (3)	1
133		4-(9-cyclobutyl-3,9-diazaspiro[5.5]undec-3-yl)-N-cyclopentylbenzamide	384.34 (3)	1.1
134		4-(9-cyclobutyl-3,9-diazaspiro[5.5]undec-3-yl)-N-(1-methylbutyl)benzamide	396.33 (3)	1.13
135		4-(9-cyclobutyl-3,9-diazaspiro[5.5]undec-3-yl)-N-cycloheptylbenzamide	398.34 (3)	1.16
136		4-(9-cyclobutyl-3,9-diazaspiro[5.5]undec-3-yl)-N-(cyclohexylmethyl)benzamide	424.35 (3)	1.2
137		4-(9-cyclobutyl-3,9-diazaspiro[5.5]undec-3-yl)-N-(2,2-dimethylpropyl)benzamide	424.35 (3)	1.21
138		4-(9-cyclobutyl-3,9-diazaspiro[5.5]undec-3-yl)-N-(2-ethylbutyl)benzamide	398.35 (3)	1.17
139		4-[6-(9-cyclobutyl-3,9-diazaspiro[5.5]undec-3-yl)pyridazin-3-yl]-N-methylbenzamide	419.6 (3)	1.08
140		2-(9-cyclobutyl-3,9-diazaspiro[5.5]undec-3-yl)-5,5'-bipyrimidine	365.23 (3)	1.02
141		methyl 4-[2-(9-cyclobutyl-3,9-diazaspiro[5.5]undec-3-yl)pyrimidin-5-yl]benzoate	421.23 (3)	1.17
142		1-[2-(9-cyclobutyl-3,9-diazaspiro[5.5]undec-3-yl)pyrimidin-5-yl]ethanone	329.23 (3)	1.02
143		3-cyclobutyl-9-(6-pyridin-3-ylpyridazin-3-yl)-3,9-diazaspiro[5.5]undecane	364.23 (3)	0.41

	Compound	Name	MS	R _T
144		3-cyclobutyl-9-(6-pyridin-4-ylpyridazin-3-yl)-3,9-diazaspiro[5.5]undecane	364.16 (1)	1.16
145		4-[2-(9-cyclobutyl-3,9-diazaspiro[5.5]undec-3-yl)pyrimidin-5-yl]-N-methylbenzamide	420.21 (3)	1.07
146		3-cyclobutyl-9-(5-{4-[(2-methylpyrrolidin-1-yl)carbonyl]phenyl}pyrimidin-2-yl)-3,9-diazaspiro[5.5]undecane	474.25 (3)	1.14
147		3-cyclobutyl-9-[6-(4-ethoxyphenyl)pyridazin-3-yl]-3,9-diazaspiro[5.5]undecane	407.26 (1)	1.23
148		3-cyclobutyl-9-(4-pyridin-4-ylphenyl)-3,9-diazaspiro[5.5]undecane	362.24 (3)	0.97
149		3-cyclobutyl-9-(4-pyrimidin-5-ylphenyl)-3,9-diazaspiro[5.5]undecane	363.23 (3)	0.96
150		3-cyclobutyl-9-[6-(6-methoxypyridin-3-yl)pyridazin-3-yl]-3,9-diazaspiro[5.5]undecane	394.23 (3)	0.98
151		3-cyclobutyl-9-(6-pyridin-2-ylpyridazin-3-yl)-3,9-diazaspiro[5.5]undecane	363.5 (3)	0.96
152		3-cyclobutyl-9-(6-pyrazin-2-ylpyridazin-3-yl)-3,9-diazaspiro[5.5]undecane	365.23 (3)	0.89
153		3-cyclobutyl-9-[6-(1,3-thiazol-2-yl)pyridazin-3-yl]-3,9-diazaspiro[5.5]undecane	370.18 (3)	0.99
154		3-cyclobutyl-9-[4-(pyrrolidin-1-ylmethyl)phenyl]-3,9-diazaspiro[5.5]undecane	368.20 (4)	1.28
155		3-cyclobutyl-9-[4-(3,6-dihydropyridin-1(2H)-ylmethyl)phenyl]-3,9-diazaspiro[5.5]undecane	380.21 (4)	1.29
156		3-cyclobutyl-9-[4-(piperidin-1-ylmethyl)phenyl]-3,9-diazaspiro[5.5]undecane	382.22 (4)	1.32

	Compound	Name	MS	R _T
157		3-cyclobutyl-9-[4-(morpholin-4-ylmethyl)phenyl]-3,9-diazaspiro[5.5]undecane	384.28 (1)	1.23
158		3-cyclobutyl-9-{4-[(4-methylpiperidin-1-yl)methyl]phenyl}-3,9-diazaspiro[5.5]undecane	396.22 (4)	1.36
159		3-[4-(azepan-1-ylmethyl)phenyl]-9-cyclobutyl-3,9-diazaspiro[5.5]undecane	396.23 (4)	1.38
160		3-cyclobutyl-9-[4-(thiomorpholin-4-ylmethyl)phenyl]-3,9-diazaspiro[5.5]undecane	400.18 (4)	1.29
161		3-cyclobutyl-9-{4-[(3,5-dimethylpiperidin-1-yl)methyl]phenyl}-3,9-diazaspiro[5.5]undecane	410.25 (4)	1.46
162		3-cyclobutyl-9-{4-[(4aR,8aS)-octahydroisoquinolin-2(1H)-ylmethyl]phenyl}-3,9-diazaspiro[5.5]undecane	436.25 (4)	1.46
163		3-cyclobutyl-9-{4-[(4aS,8aS)-octahydroisoquinolin-2(1H)-ylmethyl]phenyl}-3,9-diazaspiro[5.5]undecane	436.24 (4)	1.49
164		3-cyclobutyl-9-{4-[(2,6-dimethylmorpholin-4-yl)methyl]phenyl}-3,9-diazaspiro[5.5]undecane	412.21 (4)	1.27
165		N-[4-(9-cyclobutyl-3,9-diazaspiro[5.5]undec-3-yl)benzyl]-N-ethylpropan-2-amine	384.24 (4)	1.37
166		3-cyclobutyl-9-{4-[(2-methylpiperidin-1-yl)methyl]phenyl}-3,9-diazaspiro[5.5]undecane	396.23 (4)	1.35
167		N-[4-(9-cyclobutyl-3,9-diazaspiro[5.5]undec-3-yl)benzyl]-N-methylcyclohexanamine	410.24 (4)	1.4
168		3-cyclobutyl-9-{4-[(2-ethylpiperidin-1-yl)methyl]phenyl}-3,9-diazaspiro[5.5]undecane	410.24 (4)	1.41

	Compound	Name	MS	R _T
169		N-[4-(9-cyclobutyl-3,9-diazaspiro[5.5]undec-3-yl)benzyl]-N-ethylcyclohexanamine	424.37 (4)	0.97
170		3-cyclobutyl-9-[4-(octahydroquinolin-1(2H)-ylmethyl)phenyl]-3,9-diazaspiro[5.5]undecane	436.35 (4)	1.01
171		3-cyclobutyl-9-(4-([(2S)-2-(methoxymethyl)pyrrolidin-1-yl]methyl)phenyl)-3,9-diazaspiro[5.5]undecane	412.22 (4)	1.28
172		3-cyclobutyl-9-(4-([(2R)-2-(methoxymethyl)pyrrolidin-1-yl]methyl)phenyl)-3,9-diazaspiro[5.5]undecane	412.22 (4)	1.28
173		N-[4-(9-cyclobutyl-3,9-diazaspiro[5.5]undec-3-yl)benzyl]-N-(2-methoxyethyl)propan-2-amine	414.24 (4)	1.34
174		N-[4-(9-cyclobutyl-3,9-diazaspiro[5.5]undec-3-yl)benzyl]-2-methylbutan-1-amine	384.35 (3)	1.02
175		N-[4-(9-cyclobutyl-3,9-diazaspiro[5.5]undec-3-yl)benzyl]prop-2-en-1-amine	354.30 (3)	0.97
176		N-[4-(9-cyclobutyl-3,9-diazaspiro[5.5]undec-3-yl)benzyl]propan-1-amine	356.33 (3)	0.98
177		1-[4-(9-cyclobutyl-3,9-diazaspiro[5.5]undec-3-yl)phenyl]-N-(cyclopropylmethyl)methanamine	368.31 (3)	0.98
178		N-[4-(9-cyclobutyl-3,9-diazaspiro[5.5]undec-3-yl)benzyl]butan-1-amine	370.33 (3)	1
179		N-[4-(9-cyclobutyl-3,9-diazaspiro[5.5]undec-3-yl)benzyl]-2-methylpropan-1-amine	370.34 (3)	1
180		N-[4-(9-cyclobutyl-3,9-diazaspiro[5.5]undec-3-yl)benzyl]pentan-1-amine	384.34 (3)	1.02
181		N-[4-(9-cyclobutyl-3,9-diazaspiro[5.5]undec-3-yl)benzyl]-3-methylbutan-1-amine	384.36 (3)	1.02

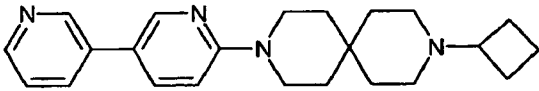
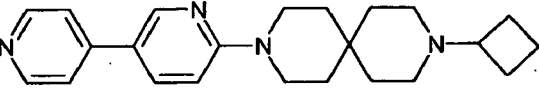
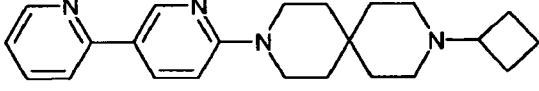
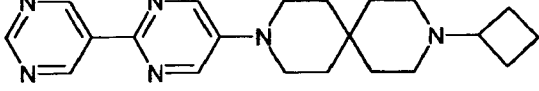
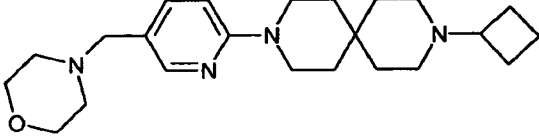
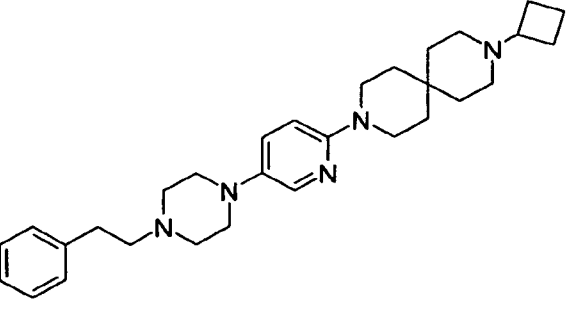
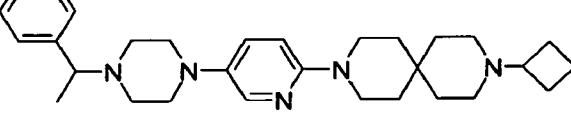
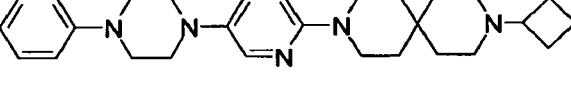
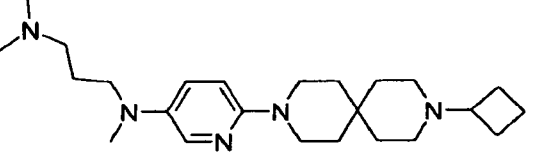
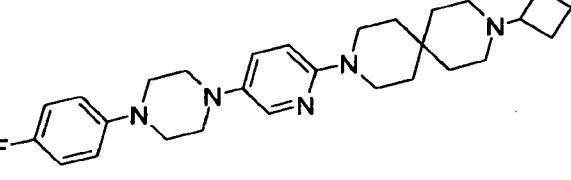
	<u>Compound</u>	<u>Name</u>	<u>MS</u>	<u>R_T</u>
182		N-[4-(9-cyclobutyl-3,9-diazaspiro[5.5]undec-3-yl)benzyl]cyclopropanamine	376.66 (4)	1.4
183		N-[4-(9-cyclobutyl-3,9-diazaspiro[5.5]undec-3-yl)benzyl]cyclohexanamine	396.24 (4)	1.32
184		N-[4-(9-cyclobutyl-3,9-diazaspiro[5.5]undec-3-yl)benzyl]propan-2-amine	356.32 (4)	0.96
185		N-[4-(9-cyclobutyl-3,9-diazaspiro[5.5]undec-3-yl)benzyl]cyclobutanamine	368.32 (4)	0.98
186		N-[4-(9-cyclobutyl-3,9-diazaspiro[5.5]undec-3-yl)benzyl]butan-2-amine	370.34 (3)	0.99
187		N-[4-(9-cyclobutyl-3,9-diazaspiro[5.5]undec-3-yl)benzyl]cyclopentanamine	382.23 (3)	1
188		N-[4-(9-cyclobutyl-3,9-diazaspiro[5.5]undec-3-yl)benzyl]pentan-2-amine	384.34 (3)	1.01
189		N-[4-(9-cyclobutyl-3,9-diazaspiro[5.5]undec-3-yl)benzyl]cycloheptanamine	410.36 (3)	1.03
190		1-[4-(9-cyclobutyl-3,9-diazaspiro[5.5]undec-3-yl)phenyl]-N-(cyclohexylmethyl)methanamine	410.38 (3)	1.04
191		N-[4-(9-cyclobutyl-3,9-diazaspiro[5.5]undec-3-yl)benzyl]-2,2-dimethylpropan-1-amine	384.36 (3)	1.02
192		N-[4-(9-cyclobutyl-3,9-diazaspiro[5.5]undec-3-yl)benzyl]-2-ethylbutan-1-amine	398.36 (3)	1.03

Table III
Representative Substituted Azaspiro Derivatives

	<u>Compound</u>	<u>Name</u>	<u>MS</u>	<u>R_T</u>
193		3-cyclobutyl-9-[6-(2-methoxy-1,3-thiazol-4-yl)pyridazin-3-yl]-3,9-diazaspiro[5.5]undecane	400.18 (3)	0.99
194		3-cyclobutyl-9-[5-(piperidin-1-ylmethyl)pyridin-2-yl]-3,9-diazaspiro[5.5]undecane	383.28 (1)	1.27
195		3-cyclobutyl-9-(5-pyridin-3-ylpyrimidin-2-yl)-3,9-diazaspiro[5.5]undecane	364.28 (3)	0.92
196		ethyl 4-[6-(9-cyclobutyl-3,9-diazaspiro[5.5]undec-3-yl)pyridin-3-yl]piperazine-1-carboxylate	442.15 (1)	1.21
197		3-[5-(4-acetylpiperazin-1-yl)pyridin-2-yl]-9-cyclobutyl-3,9-diazaspiro[5.5]undecane	412.39 (2)	0.94
198		1-[6-(9-cyclobutyl-3,9-diazaspiro[5.5]undec-3-yl)pyridin-3-yl]-N,N-diethylpiperidine-3-carboxamide	468.20 (1)	1.21
199		3-{4-[6-(9-cyclobutyl-3,9-diazaspiro[5.5]undec-3-yl)pyridin-3-yl]piperazin-1-yl}-N,N-dimethylpropan-1-amine	455.24 (1)	1.2
200		3-cyclobutyl-9-[5-(4-methylpiperazin-1-yl)pyridin-2-yl]-3,9-diazaspiro[5.5]undecane	384.29 (1)	1.17

	Compound	Name	MS	R _T
201		3-cyclobutyl-9-[5-[4-(2-methoxyethyl)piperazin-1-yl]pyridin-2-yl]-3,9-diazaspiro[5.5]undecane	428.25 (1)	1.18
202		3-cyclobutyl-9-[5-(4-isopropylpiperazin-1-yl)pyridin-2-yl]-3,9-diazaspiro[5.5]undecane	412.27 (1)	1.23
203		3-cyclobutyl-9-[5-(4-cyclopentylpiperazin-1-yl)pyridin-2-yl]-3,9-diazaspiro[5.5]undecane	438.28 (1)	1.27
204		2-[4-[6-(9-cyclobutyl-3,9-diazaspiro[5.5]undec-3-yl)pyridin-3-yl]piperazin-1-yl]-N,N-dimethylethanamine	441.22 (1)	1.18
205		3-cyclobutyl-9-[5-(4-ethylpiperazin-1-yl)pyridin-2-yl]-3,9-diazaspiro[5.5]undecane	398.27 (1)	1.2
206		1-[6-(9-cyclobutyl-3,9-diazaspiro[5.5]undec-3-yl)pyridin-3-yl]-N,N-diethylpiperidin-4-amine	440.30 (1)	1.26
207		3-cyclobutyl-9-[5-(4-morpholin-4-ylpiperidin-1-yl)pyridin-2-yl]-3,9-diazaspiro[5.5]undecane	454.27 (1)	1.19
208		3-cyclobutyl-9-[5-(4-pyrrolidin-1-ylpiperidin-1-yl)pyridin-2-yl]-3,9-diazaspiro[5.5]undecane	438.31 (1)	1.25
209		1'-[6-(9-cyclobutyl-3,9-diazaspiro[5.5]undec-3-yl)pyridin-3-yl]-1,4'-bipiperidine	452.31 (1)	1.27
210		1-[6-(9-cyclobutyl-3,9-diazaspiro[5.5]undec-3-yl)pyridin-3-yl]-N,N-dimethylpiperidin-4-amine	412.22 (1)	1.2
211		1-[6-(9-cyclobutyl-3,9-diazaspiro[5.5]undec-3-yl)pyridin-3-yl]-N,N-dimethylpyrrolidin-3-amine	398.30 (1)	1.2
212		1-[6-(9-cyclobutyl-3,9-diazaspiro[5.5]undec-3-yl)pyridin-3-yl]-N,N-diethylpyrrolidin-3-amine	426.30 (1)	1.25

Compound	Name	MS	R _T
213	6-(9-cyclobutyl-3,9-diazaspiro[5.5]undec-3-yl)-N-methyl-N-(1-methylpiperidin-4-yl)pyridin-3-amine	412.31 (1)	1.21
214	1'-[6-(9-cyclobutyl-3,9-diazaspiro[5.5]undec-3-yl)pyridin-3-yl]-2-methyl-1,4'-bipiperidine	466.34 (1)	1.3
215	1'-[6-(9-cyclobutyl-3,9-diazaspiro[5.5]undec-3-yl)pyridin-3-yl]-4-methyl-1,4'-bipiperidine	466.34 (1)	1.31
216	2-{4-[6-(9-cyclobutyl-3,9-diazaspiro[5.5]undec-3-yl)pyridin-3-yl]piperazin-1-yl}-N,N-diethylethanamine	469.38 (1)	1.23
217	3-cyclobutyl-9-(5-pyrrolidin-1-ylpyridin-2-yl)-3,9-diazaspiro[5.5]undecane	355.26 (1)	1.26
218	3-cyclobutyl-9-(5-piperidin-1-ylpyridin-2-yl)-3,9-diazaspiro[5.5]undecane	369.26 (1)	1.28
219	3-cyclobutyl-9-(5-morpholin-4-ylpyridin-2-yl)-3,9-diazaspiro[5.5]undecane	371.25 (1)	1.17
220	3-cyclobutyl-9-[5-(4-methylpiperidin-1-yl)pyridin-2-yl]-3,9-diazaspiro[5.5]undecane	383.27 (1)	1.31
221	3-cyclobutyl-9-{5-[(2S)-2-(methoxymethyl)pyrrolidin-1-yl]pyridin-2-yl}-3,9-diazaspiro[5.5]undecane	399.26 (1)	1.26
222	3-cyclobutyl-9-{5-[(2R)-2-(methoxymethyl)pyrrolidin-1-yl]pyridin-2-yl}-3,9-diazaspiro[5.5]undecane	399.27 (1)	1.25
223	3-cyclobutyl-9-(5-pyrimidin-5-ylpyridin-2-yl)-3,9-diazaspiro[5.5]undecane	364.28 (3)	0.55

	Compound	Name	MS	R _T
224		6-(9-cyclobutyl-3,9-diazaspiro[5.5]undec-3-yl)-3,3'-bipyridine	363.29 (3)	0.37
225		6-(9-cyclobutyl-3,9-diazaspiro[5.5]undec-3-yl)-3,4'-bipyridine	363.32 (3)	0.48
226		6'-(9-cyclobutyl-3,9-diazaspiro[5.5]undec-3-yl)-2,3'-bipyridine	363.29 (3)	0.93
227		5-(9-cyclobutyl-3,9-diazaspiro[5.5]undec-3-yl)-2,5'-bipyrimidine	365.26 (3)	1.05
228		3-cyclobutyl-9-[5-(morpholin-4-ylmethyl)pyridin-2-yl]-3,9-diazaspiro[5.5]undecane	385.26 (1)	1.17
229		3-cyclobutyl-9-{5-[4-(2-phenylethyl)piperazin-1-yl]pyridin-2-yl}-3,9-diazaspiro[5.5]undecane	474.23 (1)	1.28
230		3-cyclobutyl-9-{5-[4-(1-phenylethyl)piperazin-1-yl]pyridin-2-yl}-3,9-diazaspiro[5.5]undecane	474.22 (1)	1.31
231		3-cyclobutyl-9-[5-(4-phenylpiperazin-1-yl)pyridin-2-yl]-3,9-diazaspiro[5.5]undecane	446.27 (1)	1.29
232		N-[6-(9-cyclobutyl-3,9-diazaspiro[5.5]undec-3-yl)pyridin-3-yl]-N,N',N'-trimethylpropane-1,3-diamine	400.32 (1)	1.21
233		3-cyclobutyl-9-{5-[4-(4-fluorophenyl)piperazin-1-yl]pyridin-2-yl}-3,9-diazaspiro[5.5]undecane	464.27 (1)	1.28

	Compound	Name	MS	R _T
234		3-cyclobutyl-9-{5-[4-(4-methoxyphenyl)piperazin-1-yl]pyridin-2-yl}-3,9-diazaspiro[5.5]undecane	476.30 (1)	1.27
235		3-cyclobutyl-9-[5-(3,5-dimethylpiperidin-1-yl)pyridin-2-yl]-3,9-diazaspiro[5.5]undecane	397.30 (1)	1.35
236		3-[5-(4-benzylpiperazin-1-yl)pyridin-2-yl]-9-cyclobutyl-3,9-diazaspiro[5.5]undecane	460.29 (1)	1.28
237		1-[6-(9-cyclobutyl-3,9-diazaspiro[5.5]undec-3-yl)pyridin-3-yl]-N,N-dipropylpiperidin-4-amine	468.37 (1)	1.36
238		3-cyclobutyl-9-[4-(1-methyl-1H-pyrazol-4-yl)phenyl]-3,9-diazaspiro[5.5]undecane	365.29 (3)	0.86
239		3-cyclobutyl-9-(4-pyridin-3-ylphenyl)-3,9-diazaspiro[5.5]undecane	362.29 (3)	0.81
240		3-cyclobutyl-9-(6-phenylpyridazin-3-yl)-3,9-diazaspiro[5.5]undecane	363.23 (1)	1.2
241		3-[6-(3-chlorophenyl)pyridazin-3-yl]-9-cyclobutyl-3,9-diazaspiro[5.5]undecane	397.20 (1)	1.25
242		3-[6-(4-chlorophenyl)pyridazin-3-yl]-9-cyclobutyl-3,9-diazaspiro[5.5]undecane	397.20 (1)	1.25
243		3-cyclobutyl-9-[6-(4-fluorophenyl)pyridazin-3-yl]-3,9-diazaspiro[5.5]undecane	381.22 (1)	1.2
244		3-cyclobutyl-9-[6-(3-fluorophenyl)pyridazin-3-yl]-3,9-diazaspiro[5.5]undecane	381.22 (1)	1.22
245		3-cyclobutyl-9-[6-(2-fluorophenyl)pyridazin-3-yl]-3,9-diazaspiro[5.5]undecane	381.22 (1)	1.21

	Compound	Name	MS	R _T
246		3-cyclobutyl-9-[6-(2-naphthyl)pyridazin-3-yl]-3,9-diazaspiro[5.5]undecane	413.25 (1)	1.26
247		3-cyclobutyl-9-[6-(2-fluoro-4-methylphenyl)pyridazin-3-yl]-3,9-diazaspiro[5.5]undecane	395.23 (1)	1.25
248		3-cyclobutyl-9-[6-(2-fluoro-5-methylphenyl)pyridazin-3-yl]-3,9-diazaspiro[5.5]undecane	395.24 (1)	1.25
249		3-cyclobutyl-9-[6-(3-fluoro-4-methylphenyl)pyridazin-3-yl]-3,9-diazaspiro[5.5]undecane	395.24 (1)	1.24
250		3-cyclobutyl-9-[6-(4-fluoro-3-methylphenyl)pyridazin-3-yl]-3,9-diazaspiro[5.5]undecane	395.24 (1)	1.25
251		3-cyclobutyl-9-[6-(3-methylphenyl)pyridazin-3-yl]-3,9-diazaspiro[5.5]undecane	377.26 (1)	1.23
252		3-cyclobutyl-9-[6-(4-methylphenyl)pyridazin-3-yl]-3,9-diazaspiro[5.5]undecane	377.26 (1)	1.23
253		3-cyclobutyl-9-[6-(3-isopropylphenyl)pyridazin-3-yl]-3,9-diazaspiro[5.5]undecane	405.30 (1)	1.29
254		3-cyclobutyl-9-[6-(4-isopropylphenyl)pyridazin-3-yl]-3,9-diazaspiro[5.5]undecane	405.30 (1)	1.29
255		3-cyclobutyl-9-[6-(3,4-dimethylphenyl)pyridazin-3-yl]-3,9-diazaspiro[5.5]undecane	391.28 (1)	1.26
256		3-[6-(4-butylphenyl)pyridazin-3-yl]-9-cyclobutyl-3,9-diazaspiro[5.5]undecane	419.31 (1)	1.33

	<u>Compound</u>	<u>Name</u>	<u>MS</u>	<u>R_T</u>
257		3-cyclobutyl-9-[6-(3,5-dimethylphenyl)pyridazin-3-yl]-3,9-diazaspiro[5.5]undecane	391.27 (1)	1.27
258		3-cyclobutyl-9-[6-(4-ethylphenyl)pyridazin-3-yl]-3,9-diazaspiro[5.5]undecane	391.27 (1)	1.26
259		3-cyclobutyl-9-[6-(4-propylphenyl)pyridazin-3-yl]-3,9-diazaspiro[5.5]undecane	405.28 (1)	1.29
260		3-cyclobutyl-9-[6-(3-ethylphenyl)pyridazin-3-yl]-3,9-diazaspiro[5.5]undecane	391.27 (1)	1.26
261		3-[6-(4-tert-butylphenyl)pyridazin-3-yl]-9-cyclobutyl-3,9-diazaspiro[5.5]undecane	419.30 (1)	1.3
262		3-cyclobutyl-9-[6-(3-methoxyphenyl)pyridazin-3-yl]-3,9-diazaspiro[5.5]undecane	393.25 (1)	1.21
263		3-cyclobutyl-9-[6-(4-(trifluoromethoxy)phenyl)pyridazin-3-yl]-3,9-diazaspiro[5.5]undecane	447.19 (1)	1.26
264		3-cyclobutyl-9-[6-(3-ethoxyphenyl)pyridazin-3-yl]-3,9-diazaspiro[5.5]undecane	407.26 (1)	1.23
265		3-cyclobutyl-9-[6-(4-phenoxyphenyl)pyridazin-3-yl]-3,9-diazaspiro[5.5]undecane	455.25 (1)	1.28
266		3-cyclobutyl-9-[6-(3-(trifluoromethoxy)phenyl)pyridazin-3-yl]-3,9-diazaspiro[5.5]undecane	447.19 (1)	1.26
267		3-cyclobutyl-9-[6-(3-(methylthio)phenyl)pyridazin-3-yl]-3,9-diazaspiro[5.5]undecane	409.21 (1)	1.24

	<u>Compound</u>	<u>Name</u>	<u>MS</u>	<u>R_T</u>
268		3-cyclobutyl-9-[6-(4'-methoxybiphenyl-4-yl)pyridazin-3-yl]-3,9-diazaspiro[5.5]undecane	469.28 (1)	1.27
269		3-cyclobutyl-9-[6-(3-fluoro-4-methoxyphenyl)pyridazin-3-yl]-3,9-diazaspiro[5.5]undecane	411.24 (1)	1.2
270		3-cyclobutyl-9-[6-(2,5-difluoro-4-methoxyphenyl)pyridazin-3-yl]-3,9-diazaspiro[5.5]undecane	429.23 (1)	1.22
271		3-cyclobutyl-9-[6-(6-methoxy-2-naphthyl)pyridazin-3-yl]-3,9-diazaspiro[5.5]undecane	444.28 (1)	1.26
272		3-cyclobutyl-9-[6-(3-isopropoxyphenyl)pyridazin-3-yl]-3,9-diazaspiro[5.5]undecane	421.29 (1)	1.25
273		3-cyclobutyl-9-[6-(3,4,5-trimethoxyphenyl)pyridazin-3-yl]-3,9-diazaspiro[5.5]undecane	453.26 (1)	1.18
274		3-cyclobutyl-9-[6-(4-methoxyphenyl)pyridazin-3-yl]-3,9-diazaspiro[5.5]undecane	393.24 (1)	1.21

	<u>Compound</u>	<u>Name</u>	<u>MS</u>	<u>R_T</u>
275		3-[6-(1,3-benzodioxol-5-yl)pyridazin-3-yl]-9-cyclobutyl-3,9-diazaspiro[5.5]undecane	407.21 (1)	1.2
276		3-cyclobutyl-9-[6-(3,4-dimethoxyphenyl)pyridazin-3-yl]-3,9-diazaspiro[5.5]undecane	423.24 (1)	1.18
277		4-[6-(9-cyclobutyl-3,9-diazaspiro[5.5]undec-3-yl)pyridazin-3-yl]-N,N-dimethylaniline	406.28 (1)	1.23
278		3-cyclobutyl-9-[6-(2,3-dihydro-1,4-benzodioxin-6-yl)pyridazin-3-yl]-3,9-diazaspiro[5.5]undecane	421.25 (1)	1.2
279		3-[6-(9-cyclobutyl-3,9-diazaspiro[5.5]undec-3-yl)pyridazin-3-yl]-N,N-dimethylaniline	406.29 (1)	1.23
280		3-cyclobutyl-9-[6-(4-methoxy-3-methylphenyl)pyridazin-3-yl]-3,9-diazaspiro[5.5]undecane	407.27 (1)	1.24
281		3-cyclobutyl-9-[6-(4-propoxyphenyl)pyridazin-3-yl]-3,9-diazaspiro[5.5]undecane	421.28 (1)	1.26
282		3-cyclobutyl-9-[6-(4-methoxy-2-methylphenyl)pyridazin-3-yl]-3,9-diazaspiro[5.5]undecane	407.26 (1)	1.21
283		3-cyclobutyl-9-[6-(2-methoxyphenyl)pyridazin-3-yl]-3,9-diazaspiro[5.5]undecane	393.25 (1)	1.2

	Compound	Name	MS	R _T
284		3-cyclobutyl-9-[6-(5-isopropyl-2-methoxyphenyl)pyridazin-3-yl]-3,9-diazaspiro[5.5]undecane	435.30 (1)	1.29
285		3-[6-(5-chloro-2-methoxyphenyl)pyridazin-3-yl]-9-cyclobutyl-3,9-diazaspiro[5.5]undecane	427.23 (1)	1.24
286		3-cyclobutyl-9-[6-(2,5-dimethoxyphenyl)pyridazin-3-yl]-3,9-diazaspiro[5.5]undecane	423.27 (1)	1.21
287		3-cyclobutyl-9-[6-(2,4-dimethoxyphenyl)pyridazin-3-yl]-3,9-diazaspiro[5.5]undecane	423.25 (1)	1.21
288		3-cyclobutyl-9-[6-(2-ethoxyphenyl)pyridazin-3-yl]-3,9-diazaspiro[5.5]undecane	407.25 (1)	1.23
289		3-cyclobutyl-9-(6-dibenzo[b,d]furan-4-ylpyridazin-3-yl)-3,9-diazaspiro[5.5]undecane	453.25 (1)	1.32
290		3-cyclobutyl-9-[6-(5-fluoro-2-methoxyphenyl)pyridazin-3-yl]-3,9-diazaspiro[5.5]undecane	411.23 (1)	1.21
291		3-cyclobutyl-9-[6-(2-methoxy-5-methylphenyl)pyridazin-3-yl]-3,9-diazaspiro[5.5]undecane	407.25 (1)	1.23
292		3-cyclobutyl-9-[6-(2-phenoxyphenyl)pyridazin-3-yl]-3,9-diazaspiro[5.5]undecane	455.26 (1)	1.27
293		3-[6-(3-chloro-4-fluorophenyl)pyridazin-3-yl]-9-cyclobutyl-3,9-diazaspiro[5.5]undecane	415.19 (1)	1.25

	<u>Compound</u>	<u>Name</u>	<u>MS</u>	<u>R_T</u>
294		3-cyclobutyl-9-[6-(2,5-difluorophenyl)pyridazin-3-yl]-3,9-diazaspiro[5.5]undecane	399.22 (1)	1.22
295		3-cyclobutyl-9-[6-(2,4-difluorophenyl)pyridazin-3-yl]-3,9-diazaspiro[5.5]undecane	399.21 (1)	1.23
296		3-cyclobutyl-9-[6-(3,4-difluorophenyl)pyridazin-3-yl]-3,9-diazaspiro[5.5]undecane	399.20 (1)	1.23
297		3-cyclobutyl-9-[6-(3,5-dichlorophenyl)pyridazin-3-yl]-3,9-diazaspiro[5.5]undecane	431.16 (1)	1.31
298		3-[6-(4-chloro-2-fluorophenyl)pyridazin-3-yl]-9-cyclobutyl-3,9-diazaspiro[5.5]undecane	415.17 (1)	1.27
299		3-[6-(4-chloro-3-fluorophenyl)pyridazin-3-yl]-9-cyclobutyl-3,9-diazaspiro[5.5]undecane	415.17 (1)	1.26
300		3-cyclobutyl-9-[6-(2,6-difluorophenyl)pyridazin-3-yl]-3,9-diazaspiro[5.5]undecane	399.21 (1)	1.18
301		3-cyclobutyl-9-[6-(3,4-dichlorophenyl)pyridazin-3-yl]-3,9-diazaspiro[5.5]undecane	431.17 (1)	1.29
302		3-cyclobutyl-9-[6-(3,5-difluorophenyl)pyridazin-3-yl]-3,9-diazaspiro[5.5]undecane	399.21 (1)	1.23
303		3-cyclobutyl-9-[6-(2,3-difluorophenyl)pyridazin-3-yl]-3,9-diazaspiro[5.5]undecane	399.22 (1)	1.22
304		3-[6-(2-chlorophenyl)pyridazin-3-yl]-9-cyclobutyl-3,9-diazaspiro[5.5]undecane	397.21 (1)	1.22
305		3-cyclobutyl-9-[6-(2,4-dichlorophenyl)pyridazin-3-yl]-3,9-diazaspiro[5.5]undecane	431.16 (1)	1.26

	<u>Compound</u>	<u>Name</u>	<u>MS</u>	<u>R_T</u>
306		3-cyclobutyl-9-{6-[2-(trifluoromethyl)phenyl]pyridazin-3-yl}-3,9-diazaspiro[5.5]undecane	431.21 (1)	1.21
307		3-cyclobutyl-9-[6-(2,6-dimethoxyphenyl)pyridazin-3-yl]-3,9-diazaspiro[5.5]undecane	423.24 (1)	1.18
308		3-cyclobutyl-9-[6-(2-isopropylphenyl)pyridazin-3-yl]-3,9-diazaspiro[5.5]undecane	405.28 (1)	1.26
309		3-cyclobutyl-9-[6-(2,6-dimethylphenyl)pyridazin-3-yl]-3,9-diazaspiro[5.5]undecane	391.28 (1)	1.22
310		3-cyclobutyl-9-[6-(2,5-dichlorophenyl)pyridazin-3-yl]-3,9-diazaspiro[5.5]undecane	431.18 (1)	1.25
311		3-[6-(2-chloro-6-fluoro-3-methylphenyl)pyridazin-3-yl]-9-cyclobutyl-3,9-diazaspiro[5.5]undecane	429.22 (1)	1.22
312		3-cyclobutyl-9-(6-mesitylpyridazin-3-yl)-3,9-diazaspiro[5.5]undecane	405.28 (1)	1.25
313		3-[6-(9-cyclobutyl-3,9-diazaspiro[5.5]undec-3-yl)pyridazin-3-yl]benzonitrile	388.22 (1)	1.17
314		4-[6-(9-cyclobutyl-3,9-diazaspiro[5.5]undec-3-yl)pyridazin-3-yl]benzonitrile	388.22 (1)	1.18
315		3-cyclobutyl-9-{6-[4-(trifluoromethyl)phenyl]pyridazin-3-yl}-3,9-diazaspiro[5.5]undecane	431.19 (1)	1.25
316		1-{3-[6-(9-cyclobutyl-3,9-diazaspiro[5.5]undec-3-yl)pyridazin-3-yl]phenyl}ethanone	405.24 (1)	1.18
317		3-{6-[3,5-bis(trifluoromethyl)phenyl]pyridazin-3-yl}-9-cyclobutyl-3,9-diazaspiro[5.5]undecane	499.19 (1)	1.3

	Compound	Name	MS	R _T
318		3-cyclobutyl-9-{6-[3-(trifluoromethyl)phenyl]pyridazin-3-yl}-3,9-diazaspiro[5.5]undecane	431.22 (1)	1.25
319		3-{6-[4-chloro-3-(trifluoromethyl)phenyl]pyridazin-3-yl}-9-cyclobutyl-3,9-diazaspiro[5.5]undecane	465.18 (1)	1.29
320		3-{6-[2-chloro-5-(trifluoromethyl)phenyl]pyridazin-3-yl}-9-cyclobutyl-3,9-diazaspiro[5.5]undecane	465.20 (1)	1.25
321		ethyl 4-[6-(9-cyclobutyl-3,9-diazaspiro[5.5]undec-3-yl)pyridazin-3-yl]benzoate	435.25 (1)	1.23
322		ethyl 3-[6-(9-cyclobutyl-3,9-diazaspiro[5.5]undec-3-yl)pyridazin-3-yl]benzoate	435.25 (1)	1.23
323		3-cyclobutyl-9-(2-pyridin-3-ylpyrimidin-5-yl)-3,9-diazaspiro[5.5]undecane	364.33 (3)	0.97
324		3-cyclobutyl-9-[6-(1-methyl-1H-pyrazol-4-yl)pyridazin-3-yl]-3,9-diazaspiro[5.5]undecane	367.24 (1)	1.13
325		3-cyclobutyl-9-[6-(5-methoxypyridin-3-yl)pyridazin-3-yl]-3,9-diazaspiro[5.5]undecane	394.35 (3)	0.94
326		3-cyclobutyl-9-[6-(1-methyl-1H-benzimidazol-5-yl)pyridazin-3-yl]-3,9-diazaspiro[5.5]undecane	417.26 (1)	1.15
327		3-cyclobutyl-9-[6-(6-isopropyl-2-methoxypyridin-3-yl)pyridazin-3-yl]-3,9-diazaspiro[5.5]undecane	436.40 (3)	1.16
328		3-(3-bromophenyl)-9-cyclobutyl-3,9-diazaspiro[5.5]undecane	363.24 (3)	1.16
329		1-[4-(9-cyclobutyl-3,9-diazaspiro[5.5]undec-3-yl)-3-fluorophenyl]ethanone	345.33 (3)	1.13

	Compound	Name	MS	R _T
330		3-cyclobutyl-9-(6-pyrimidin-5-ylpyridin-3-yl)-3,9-diazaspiro[5.5]undecane	364.34 (3)	1.03
331		3-cyclobutyl-9-[5-(pyrrolidin-1-ylmethyl)pyridin-2-yl]-3,9-diazaspiro[5.5]undecane	369.28 (1)	1.23
332		3-cyclobutyl-9-{5-[(4,4-difluoropiperidin-1-yl)methyl]pyridin-2-yl}-3,9-diazaspiro[5.5]undecane	419.25 (1)	1.24
333		4-(9-isopropyl-3,9-diazaspiro[5.5]undec-3-yl)-N-methylbenzamide	330.35 (3)	0.51
334		3-cyclobutyl-9-{5-[(4-fluoropiperidin-1-yl)methyl]pyridin-2-yl}-3,9-diazaspiro[5.5]undecane	401.33 (1)	1.23
335		1-[6-(9-cyclobutyl-3,9-diazaspiro[5.5]undec-3-yl)pyridin-3-yl]-N,N-dimethylmethanamine	343.31 (1)	1.22
336		1-[4-(9-cyclobutyl-3,9-diazaspiro[5.5]undec-3-yl)-3,5-difluorophenyl]ethanone	363.25 (3)	1.15
337		3-cyclobutyl-9-[3-(1-methyl-1H-pyrazol-4-yl)phenyl]-3,9-diazaspiro[5.5]undecane	365.30 (3)	0.97
338		3-cyclobutyl-9-(3-pyrimidin-5-ylphenyl)-3,9-diazaspiro[5.5]undecane	363.28 (3)	0.96

	Compound	Name	MS	R _T
339		3-(9-cyclobutyl-3,9-diazaspiro[5.5]undec-3-yl)benzonitrile	310.19 (3)	1.08
340		1-[4-(9-cyclobutyl-3,9-diazaspiro[5.5]undec-3-yl)-2-methoxyphenyl]ethanone	357.28 (3)	1.1
341		1-[4-(9-cyclobutyl-3,9-diazaspiro[5.5]undec-3-yl)-3-methoxyphenyl]ethanone	357.19 (3)	0.98
342		N-methyl-4-[9-(tetrahydro-2H-pyran-4-yl)-3,9-diazaspiro[5.5]undec-3-yl]benzamide	372.18 (3)	0.48
343		4-(9-ethyl-3,9-diazaspiro[5.5]undec-3-yl)-N-methylbenzamide	316.18 (3)	0.34
344		[6-(9-cyclobutyl-3,9-diazaspiro[5.5]undec-3-yl)pyridin-3-yl]methanol	316.26 (1)	1.14
345		3-[6-(9-cyclobutyl-3,9-diazaspiro[5.5]undec-3-yl)pyridazin-3-yl]-1-methylpyridin-2(1H)-one	394.30 (3)	0.95
346		5-[6-(9-cyclobutyl-3,9-diazaspiro[5.5]undec-3-yl)pyridazin-3-yl]-1-methylpyridin-2(1H)-one	394.27 (1)	1.12
347		3-[4-(9-cyclobutyl-3,9-diazaspiro[5.5]undec-3-yl)phenyl]-1-methylpyridin-2(1H)-one	392.32 (3)	0.92
348		5-[4-(9-cyclobutyl-3,9-diazaspiro[5.5]undec-3-yl)phenyl]-1-methylpyridin-2(1H)-one	392.33 (3)	0.89
349		3-(2-methylcyclopentyl)-9-(6-pyrazin-2-ylpyridazin-3-yl)-3,9-diazaspiro[5.5]undecane	393.46 (3)	1

	Compound	Name	MS	R _T
350		3-ethyl-9-(6-pyrazin-2-ylpyridazin-3-yl)-3,9-diazaspiro[5.5]undecane	339.45 (3)	0.56
351		6-(9-cyclobutyl-3,9-diazaspiro[5.5]undec-3-yl)-3,3'-bipyridazine	365.49 (3)	0.86
352		N-methyl-4-[9-(2-methylcyclopentyl)-3,9-diazaspiro[5.5]undec-3-yl]benzamide	370.51 (3)	0.98
353		3-cyclobutyl-9-(6-imidazo[1,2-a]pyridin-6-ylpyridazin-3-yl)-3,9-diazaspiro[5.5]undecane	403.49 (3)	0.57
354		3-cyclobutyl-9-[6-(1H-indazol-5-yl)pyridazin-3-yl]-3,9-diazaspiro[5.5]undecane	403.32 (3)	1.03
355		5-[4-(9-cyclobutyl-3,9-diazaspiro[5.5]undec-3-yl)phenyl]-1-methylpyrimidin-2(1H)-one	393.27 (3)	0.38
356		4-(9-cyclobutyl-3,9-diazaspiro[5.5]undec-3-yl)-N-(tetrahydro-2H-pyran-4-yl)benzamide	412.28 (3)	1.01
357		4-(9-cyclobutyl-3,9-diazaspiro[5.5]undec-3-yl)-N-(tetrahydro-2H-pyran-4-ylmethyl)benzamide	426.29 (3)	1.03
358		6-[4-(9-cyclobutyl-3,9-diazaspiro[5.5]undec-3-yl)phenyl]-1-methylpyridin-2(1H)-one	392.26 (3)	1.04

	Compound	Name	MS	R _T
359		4-(9-cyclobutyl-3,9-diazaspiro[5.5]undec-3-yl)-N-(pyridin-4-ylmethyl)benzamide	419.26 (3)	0.66
360		4-(9-cyclobutyl-3,9-diazaspiro[5.5]undec-3-yl)-3-fluoro-N-methylbenzamide	360.26 (3)	1.04
361		4-[4-(9-cyclobutyl-3,9-diazaspiro[5.5]undec-3-yl)phenyl]-1-methylpyridin-2(1H)-one	392.26 (3)	1.03
362		3-cyclobutyl-9-[4-(1H-pyrazol-1-ylmethyl)phenyl]-3,9-diazaspiro[5.5]undecane	365.24 (3)	0.61
363		4-(9-cyclobutyl-3,9-diazaspiro[5.5]undec-3-yl)-N-pyridin-2-ylbenzamide	405.21 (3)	1.05
364		4-(9-cyclobutyl-3,9-diazaspiro[5.5]undec-3-yl)-N,N-dimethylbenzamide	356.24 (3)	0.72
365		5-[4-(9-cyclobutyl-3,9-diazaspiro[5.5]undec-3-yl)phenyl]-1-ethylpyridin-2(1H)-one	406.25 (3)	0.98
366		5-[4-(9-cyclobutyl-3,9-diazaspiro[5.5]undec-3-yl)phenyl]-1-propylpyridin-2(1H)-one	420.27 (3)	1.03
367		5-[4-(9-cyclobutyl-3,9-diazaspiro[5.5]undec-3-yl)phenyl]-1-isopropylpyridin-2(1H)-one	420.27 (3)	1.02

	Compound	Name	MS	R _T
368		5-[4-(9-cyclobutyl-3,9-diazaspiro[5.5]undec-3-yl)phenyl]-1-(2,2,2-trifluoroethyl)pyridin-2(1H)-one	460.22 (3)	1.05
369		3-cyclobutyl-9-(5-[1,2,4]triazolo[4,3-a]pyridin-6-ylpyridin-2-yl)-3,9-diazaspiro[5.5]undecane	403.24 (3)	0.83
370		6'-(9-cyclobutyl-3,9-diazaspiro[5.5]undec-3-yl)-N-methyl-2,3'-bipyridine-5-carboxamide	420.25 (3)	0.98
371		3-cyclobutyl-9-(4-[1,2,4]triazolo[4,3-a]pyridin-6-ylphenyl)-3,9-diazaspiro[5.5]undecane	402.09 (1)	1.2
372		7-[4-(9-cyclobutyl-3,9-diazaspiro[5.5]undec-3-yl)phenyl]-N-methylimidazo[1,2-a]pyridine-2-carboxamide	458.25 (3)	1.03
373		7-[6-(9-cyclobutyl-3,9-diazaspiro[5.5]undec-3-yl)pyridin-3-yl]-N-methylimidazo[1,2-a]pyridine-2-carboxamide	459.24 (3)	0.94
374		4-(9-cyclobutyl-3,9-diazaspiro[5.5]undec-3-yl)benzamide	328.26 (3)	0.42
375		4-(9-cyclobutyl-3,9-diazaspiro[5.5]undec-3-yl)-N,2-dimethylbenzamide	356.13 (1)	1.17
376		2-chloro-4-(9-cyclobutyl-3,9-diazaspiro[5.5]undec-3-yl)-N-methylbenzamide	376.20 (3)	0.95
377		4-(9-cyclobutyl-3,9-diazaspiro[5.5]undec-3-yl)-N-methyl-1-naphthamide	392.26 (3)	1.03
378		4-(9-cyclobutyl-3,9-diazaspiro[5.5]undec-3-yl)-N-methyl-2-(trifluoromethyl)benzamide	410.25 (3)	0.98

	Compound	Name	MS	R _T
379		3-cyclobutyl-9-(4-[1,2,4]triazolo[4,3-b]pyridazin-6-ylphenyl)-3,9-diazaspiro[5.5]undecane	403.25 (3)	1.02
380		3-cyclobutyl-9-(5-[1,2,4]triazolo[4,3-b]pyridazin-6-ylpyridin-2-yl)-3,9-diazaspiro[5.5]undecane	404.26 (3)	0.91
381		3-cyclobutyl-9-(5-imidazo[1,2-a]pyrimidin-6-ylpyridin-2-yl)-3,9-diazaspiro[5.5]undecane	403.13 (1)	1.16
382		3-cyclobutyl-9-(4-{[2-(3-fluoropyridin-2-yl)-1H-imidazol-1-yl]methyl}phenyl)-3,9-diazaspiro[5.5]undecane	460.15 (3)	0.62
383		4-(9-cyclobutyl-3,9-diazaspiro[5.5]undec-3-yl)-2-fluoro-N-methylbenzamide	360.32 (3)	1.02
384		1-[4-(9-cyclobutyl-3,9-diazaspiro[5.5]undec-3-yl)benzyl]pyrrolidin-2-one	382.27 (1)	1.19
385		6-[9-(3,3-difluorocyclobutyl)-3,9-diazaspiro[5.5]undec-3-yl]-N-methylnicotinamide	379.24 (1)	1.1
386		8-(6-chloropyridazin-3-yl)-2-cyclobutyl-2,8-diazaspiro[4.5]decane	307.18 (3)	0.77
387		1-[6-(2-cyclobutyl-2,8-diazaspiro[4.5]dec-8-yl)pyridin-3-yl]ethanone	314.22 (3)	0.48
388		6-(2-cyclobutyl-2,8-diazaspiro[4.5]dec-8-yl)-6'-methoxy-3,3'-bipyridine	379.28 (3)	0.99
389		2-cyclobutyl-8-(6-pyridin-4-ylpyridazin-3-yl)-2,8-diazaspiro[4.5]decane	350.20 (1)	1.12

	<u>Compound</u>	<u>Name</u>	<u>MS</u>	<u>R_T</u>
390		2-cyclobutyl-8-[6-(6-methoxypyridin-3-yl)pyridazin-3-yl]-2,8-diazaspiro[4.5]decane	380.28 (3)	0.97
391		2-(6-chloropyridazin-3-yl)-8-cyclobutyl-2,8-diazaspiro[4.5]decane	307.22 (3)	0.32
392		1-[6-(8-cyclobutyl-2,8-diazaspiro[4.5]dec-2-yl)pyridin-3-yl]ethanone	314.20 (1)	1.12
393		8-cyclobutyl-2-(6-pyridin-3-ylpyridazin-3-yl)-2,8-diazaspiro[4.5]decane	350.21 (1)	1.11
394		8-cyclobutyl-2-(6-pyridin-4-ylpyridazin-3-yl)-2,8-diazaspiro[4.5]decane	350.21 (1)	1.11
395		8-cyclobutyl-2-(4-pyridin-3-ylphenyl)-2,8-diazaspiro[4.5]decane	348.26 (3)	1.01
396		2-cyclobutyl-8-(4-pyridin-3-ylphenyl)-2,8-diazaspiro[4.5]decane	348.27 (3)	0.89

Table IV

5

Additional Representative Substituted Azaspiro Derivatives

	<u>Compound</u>	<u>Name</u>
397		3-cyclobutyl-9-(5-methanesulfonylpyrazin-2-yl)-3,9-diazaspiro[5.5]undecane

	Compound	Name
398		1-[5-(9-cyclobutyl-3,9-diazaspiro[5.5]undec-3-yl)pyrazin-2-yl]ethanone
399		1-[4-(3-cyclobutyl-3-azaspiro[5.5]undec-9-yl)-phenyl]-ethanone
400		2-[4-(9-cyclobutyl-3,9-diazaspiro[5.5]undec-3-yl)-phenyl]-2H-pyridazin-3-one
401		1-[4'-(3-cyclobutyl-3-azaspiro[5.5]undec-9-yl)-biphenyl-4-yl]-ethanone
402		4-(3-cyclobutyl-3,9-diazaspiro[5.6]dodec-9-yl)-N-methylbenzamide
403		4-(9-cyclobutyl-3,9-diazaspiro[5.6]dodec-3-yl)-N-methylbenzamide
404		3-cyclobutyl-9-imidazo[1,2-a]pyrazin-6-yl-3,9-diazaspiro[5.5]undecane
405		3-cyclobutyl-9-imidazo[1,2-b]pyridazin-6-yl-3,9-diazaspiro[5.5]undecane
406		6-(2-cyclobutyl-2,7-diazaspiro[3.5]non-7-yl)-3,3'-bipyridine
407		6-(7-Cyclobutyl-2,7-diazaspiro[3.5]non-2-yl)-3,3'-bipyridine

EXAMPLE 4

Preparation of Chimeric Human H3 Receptor

Chimeric H3 receptor cDNA from human H3 receptor is generated from three cDNA fragments: (1) a human H3 receptor cDNA 5' fragment; (2) a human H3 receptor cDNA 3' fragment; and (3) a rat $G\alpha_{i2}$ cDNA fragment, each containing appropriate, overlapping linker sequences, as described in Example 1 of US Patent Application Serial Number 11/355,711, which published as US 2006/0188960, and is hereby incorporated by reference for its teaching of the preparation of a chimeric human H3 receptor-rat $G\alpha_{i2}$ baculoviral expression

construct that has the sequence provided in SEQ ID NO:7 of US 2006/0188960, and encodes a polypeptide that has the sequence provided in SEQ ID NO:8 of US 2006/0188960.

EXAMPLE 5

Chimeric Human H3 Receptor Baculovirus Preparation and Infection

5 The chimeric human H3 receptor-rat $G\alpha_{12}$ baculoviral expression vector is co-transfected along with BACULOGOLD DNA (BD PHARMINGEN, San Diego, CA) into Sf9 cells. The Sf9 cell culture supernatant is harvested three days post-transfection. The recombinant virus-containing supernatant is serially diluted in Hink's TNM-FH insect medium (JRH Biosciences, Kansas City, KS) supplemented Grace's salts and with 4.1 mM L-
10 Gln, 3.3 g/L LAH, 3.3 g/L ultrafiltered yeastolate and 10% heat-inactivated fetal bovine serum (hereinafter "insect medium") and plaque assayed for recombinant plaques. After four days, recombinant plaques are selected and harvested into 1 ml of insect medium for amplification. Each 1 ml volume of recombinant baculovirus (at passage 0) is used to infect a separate T25 flask containing 2×10^6 Sf9 cells in 5 ml of insect medium. After five days of
15 incubation at 27°C, supernatant medium is harvested from each of the T25 infections for use as passage 1 inoculum.

Two of seven recombinant baculoviral clones are chosen for a second round of amplification, using 1 ml of passage 1 stock to infect 1×10^8 cells in 100 ml of insect medium divided into two T175 flasks. Forty-eight hours post infection, passage 2 medium from each
20 100 ml prep is harvested and plaque assayed to determine virus titer. The cell pellets from the second round of amplification are assayed by affinity binding as described below to verify recombinant receptor expression. A third round of amplification is then initiated using a multiplicity of infection of 0.1 to infect a liter of Sf9 cells. Forty hours post-infection, the supernatant medium is harvested to yield passage 3 baculoviral stock.

25 The remaining cell pellet is assayed for affinity binding using the protocol of DeMartino et al. (1994) *J. Biol. Chem.* 269(20):14446-50 (which is incorporated herein by reference for its teaching of binding assays at page 14447), adapted as follows. Radioligand ranges from 0.40 – 40 nM [^{3} H]-N-(α)methylhistamine (Perkin Elmer, Boston, MA) and assay buffer contains 50 mM Tris, 1 mM $CaCl_2$, 5 mM $MgCl_2$, 0.1% BSA, 0.1 mM bacitracin, and
30 100 KIU/ml aprotinin, pH 7.4. Filtration is carried out using GF/C WHATMAN filters (presoaked in 1.0% polyethyleneimine for 2 hr prior to use). Filters are washed three times with 5 ml cold assay buffer without BSA, bacitracin, or aprotinin and air dried for 12-16 hr. Radioactivity retained on filters is measured on a beta scintillation counter.

Titer of the passage 3 baculoviral stock is determined by plaque assay and a
35 multiplicity of infection, incubation time course, binding assay experiment is carried out to determine conditions for optimal receptor expression. A multiplicity of infection of 0.5 and a

72-hr incubation period are preferred infection parameters for chimeric human H3 receptor-rat $G\alpha_{i2}$ expression in up to 1-liter Sf9 cell infection cultures.

Log-phase Sf9 cells (INVITROGEN), are infected with one or more stocks of recombinant baculovirus followed by culturing in insect medium at 27°C. Infections are carried out with virus directing the expression of human H3 receptor-rat $G\alpha_{i2}$ in combination with three G-protein subunit-expression virus stocks: 1) rat $G\alpha_{i2}$ G-protein-encoding virus stock (BIOSIGNAL #V5J008), 2) bovine $\beta 1$ G-protein-encoding virus stock (BIOSIGNAL #V5H012), and 3) human $\gamma 2$ G-protein-encoding virus stock (BIOSIGNAL #V6B003), which may be obtained from BIOSIGNAL Inc., Montreal.

The infections are conveniently carried out at a multiplicity of infection of 0.5:1.0:0.5:0.5. At 72 hr post-infection, an aliquot of cell suspension is analyzed for viability by trypan blue dye exclusion. If no blue is detected by visual inspection, the Sf9 cells are harvested via centrifugation (3000 rpm / 10 min / 4°C).

EXAMPLE 6

Chimeric Human H3 Receptor Cell Membrane Preparations

Sf9 cell pellets obtained as described in Example 5 are resuspended in homogenization buffer (10 mM HEPES, 250 mM sucrose, 0.5 μ g/ml leupeptin, 2 μ g/ml Aprotinin, 200 μ M PMSF, and 2.5 mM EDTA, pH 7.4) and homogenized using a POLYTRON PT10-35 homogenizer (KINEMATICA AG, Lucerne, Switzerland; setting 5 for 30 seconds). The homogenate is centrifuged (536 x g/ 10 min at 4°C) to pellet the nuclei and unbroken cells. The supernatant containing the membranes is decanted to a clean centrifuge tube, centrifuged (48,000 x g/ 30 min, 4°C) and the resulting pellet resuspended in 30 ml homogenization buffer. This centrifugation and resuspension step is repeated twice. The final pellet is resuspended in ice cold Dulbecco's PBS containing 5 mM EDTA and stored in frozen aliquots at -80°C until used for radioligand binding or functional response assays. The protein concentration of the resulting membrane preparation (hereinafter termed "P2 membranes") is conveniently measured using a Bradford protein assay (BIO-RAD LABORATORIES, Hercules, CA). By this measure, a 1-liter culture of cells typically yields 100-150 mg of total membrane protein.

EXAMPLE 7

Chimeric Human H3 Receptor GTP Binding Assays

This Example illustrates a representative assay for evaluating agonist-stimulated GTP- γ - ^{35} S binding ("GTP binding") activity. Such GTP binding activity can be used to identify H3 antagonists and to differentiate neutral antagonist compounds from those that

possess inverse agonist activity. This agonist-stimulated GTP binding activity can also be used to detect partial agonism mediated by antagonist compounds. A compound analyzed in this assay is referred to herein as a "test compound."

Four independent baculoviral stocks (one directing the expression of the chimeric human H3 receptor and three directing the expression of each of the three subunits of a heterotrimeric G-protein) are used to infect a culture of *Sf9* cells as described above. P2 membranes are prepared as described above, and agonist-stimulated GTP binding on the P2 membranes is assessed using histamine (Sigma Chemical Co., St. Louis, MO) as agonist in order to ascertain that the receptor/G-protein-alpha-beta-gamma combination(s) yield a functional response as measured by GTP binding. P2 membranes are resuspended by Dounce homogenization (tight pestle) in GTP binding assay buffer (50 mM Tris pH 7.4, 120 mM NaCl, 5 mM MgCl₂, 2 mM EGTA, 1 mg/ml BSA, 0.2 mg/ml bacitracin, 0.02 mg/ml aprotinin, 0.01 mg/ml saponin, 10 μM GDP) and added to assay tubes at a concentration of 35 μg protein/reaction tube. After adding increasing doses of histamine at concentrations ranging from 10⁻¹² M to 10⁻⁵ M, reactions are initiated by the addition of 125 pM GTP-gamma³⁵S (PERKIN ELMER; Boston, MA) with a final assay volume of 0.20 ml. In competition experiments, non-radiolabeled test compounds are added to separate reactions at concentrations ranging from 10⁻¹⁰ M to 10⁻⁶ M along with 1 μM histamine to yield a final volume of 0.20 ml.

Neutral antagonists are antagonists that are substantially free of inherent agonist activity, and include those test compounds that reduce the histamine-stimulated GTP binding activity towards, but not below, baseline levels. In contrast, in the absence of added histamine, inverse agonists reduce the GTP binding activity of the receptor-containing membranes below baseline. The elevation of GTP binding activity above baseline by a compound in the absence of added histamine in this assay demonstrates agonist activity.

After a 60-min incubation at room temperature, reactions are terminated by vacuum filtration over WHATMAN GF/C filters (pre-soaked in wash buffer, 0.1% BSA) followed by washing with ice-cold wash buffer (50 mM Tris pH 7.4, 120mM NaCl). The amount of receptor-bound (and thereby membrane-bound) GTP-gamma³⁵S is determined by measuring the filter-bound radioactivity, preferably by liquid scintillation spectrometry of the washed filters. Non-specific binding is determined in parallel assays including 10 μM unlabeled GTP-gammaS and typically represents less than 5 percent of total binding. Data is expressed as percent above basal (baseline). The results of GTP binding experiments are analyzed using SIGMAPLOT software (SPSS Inc., Chicago, IL). IC₅₀ values are calculated by non-linear regression analysis of dose-response curves using Kaleidograph (Synergy Software, Reading, PA).

Alternatively the data is analyzed as follows. First, the average bound radioactivity from negative control wells (no agonist) is subtracted from the bound radioactivity detected for each of the other experimental wells. Second, average bound radioactivity is calculated for the positive control wells (agonist wells). Then, percent inhibition for each compound tested is calculated using the equation:

$$\text{Percent Inhibition} = 100 - 100 \times \left[\frac{\text{Bound radioactivity in Test Wells}}{\text{Bound radioactivity in Agonist Wells}} \right]$$

The % inhibition data is plotted as a function of test compound concentration and test compound IC_{50} is determined using a linear regression in which x is $\ln(\text{concentration of test compound})$ and y is $\ln(\text{percent inhibition}/(100 - \text{percent inhibition}))$. Data with a percent inhibition that is greater than 90% or less than 15% are rejected and are not used in the regression. The IC_{50} is $e^{(-\text{intercept}/\text{slope})}$.

Calculated IC_{50} values are converted to K_i values by the Cheng-Prusoff correction (Cheng and Prusoff (1973) *Biochem. Pharmacol.* 22(23):3099-3108). Accordingly, the following equation: $K_i = IC_{50}/(1 + [L]/EC_{50})$ is used, where $[L]$ is the histamine concentration in the GTP binding assay, and EC_{50} is the concentration of histamine producing a 50% response, as determined by a dose-response analysis using concentrations of histamine ranging from 10^{-10} M to 10^{-6} M.

To assess agonist or inverse agonist activity of a test compound, this assay is performed in the absence of added histamine, and EC_{50} values are determined by analogous calculations, where the EC_{50} is the concentration of test compound producing a 50% response.

EXAMPLE 8

Chimeric Human H3 Receptor Screening: GTP Binding Assays

This Example illustrates a representative screening assay for evaluating inhibition of histamine-stimulated GTP- γ - ^{35}S binding. Such GTP binding activity can be used to identify H3 antagonists and inverse agonists. A compound analyzed in this assay is referred to herein as a "test compound," and the initial identification of antagonists and inverse agonists is performed using a test compound concentration of 4 μM .

Four independent baculoviral stocks (one directing the expression of the chimeric human H3 receptor and three directing the expression of each of the three subunits of a heterotrimeric G-protein) are used to infect a culture of Sf9 cells as described above. P2 membranes are prepared as described above, and are resuspended by Dounce homogenization (tight pestle) in GTP binding assay buffer (50 mM Tris pH 7.4, 120 mM NaCl, 5 mM MgCl_2 , 2 mM EGTA, 1 mg/ml BSA, 0.2 mg/ml bacitracin, 0.02 mg/ml aprotinin, 0.01 mg/ml

saponin, 10 μ M GDP) and added to assay tubes at a concentration of 35 μ g protein/reaction tube. Non-radiolabeled test compounds are added to separate reactions at a concentration of 4 μ M along with 1 μ M histamine (agonist). Reactions are initiated by the addition of 125 pM GTP-gamma³⁵S with a final assay volume of 0.20 ml.

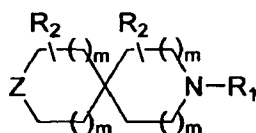
- 5 After a 60-min incubation at room temperature, reactions are terminated by vacuum filtration over GF/C filters (pre-soaked in 50 mM Tris pH 7.4, 120mM NaCl plus 0.1% BSA) followed by washing with ice-cold buffer (50 mM Tris pH 7.4, 120mM NaCl). The amount of receptor-bound (and thereby membrane-bound) GTP-gamma³⁵S is determined by measuring the bound radioactivity, preferably by liquid scintillation spectrometry of the
- 10 washed filters. Non-specific binding is determined using 10 μ M GTP-gammaS and typically represents less than 5 percent of total binding. After subtraction of non-specific binding, data is expressed as percent inhibition of 1 μ M histamine signal.

- Neutral antagonists are those test compounds that reduce the histamine-stimulated GTP binding activity towards, but not below, baseline levels. In contrast, in the absence of
- 15 added histamine, inverse agonists reduce the GTP binding activity of the receptor-containing membranes below baseline. Any test compound that elevates GTP binding activity above baseline in the absence of added histamine in this assay is defined as having agonist activity.

CLAIMS

What is claimed is:

1. A compound of the formula:



or a pharmaceutically acceptable salt or hydrate thereof, wherein:

Z is CHR_3 or NR_4 ;

Each m is independently 0, 1, 2 or 3;

R_1 is C_1 - C_6 alkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, $(\text{C}_3$ - C_8 cycloalkyl) C_0 - C_2 alkyl or (3- to 8-membered heterocycloalkyl) C_0 - C_2 alkyl, each of which is substituted with from 0 to 4 substituents independently chosen from oxo, nitro, halogen, amino, cyano, hydroxy, aminocarbonyl, C_1 - C_6 alkyl, C_2 - C_6 alkenyl, C_1 - C_6 haloalkyl, C_1 - C_6 haloalkoxy, C_1 - C_6 alkylthio, C_2 - C_6 alkyl ether, C_1 - C_6 alkanoyl, mono- or di- $(\text{C}_1$ - C_6 alkyl)amino, mono- or di- $(\text{C}_1$ - C_6 alkyl)aminocarbonyl, C_3 - C_7 cycloalkyl and 3- to 7-membered heterocycloalkyl; such that R_1 does not comprise a $-\text{COOH}$ group;

Each R_2 independently represents from 0 to 4 substituents independently chosen from C_1 - C_3 alkyl and C_1 - C_3 haloalkyl;

R_3 is:

(i) C_1 - C_6 alkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, C_1 - C_6 alkoxy, C_1 - C_6 alkylthio, C_1 - C_6 alkylsulfonyl, C_1 - C_6 alkanoyl, C_1 - C_6 alkoxycarbonyl, mono- or di- $(\text{C}_1$ - C_8 alkyl)amino, mono- or di- $(\text{C}_1$ - C_8 alkyl)aminocarbonyl or mono- or di- $(\text{C}_1$ - C_8 alkyl)aminosulfonyl, each of which is substituted with from 0 to 4 substituents independently chosen from R_a ; or

(ii) a group of the Formula W-Y-X- ;

R_4 is:

(i) C_1 - C_6 alkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, C_1 - C_6 alkylsulfonyl, C_1 - C_6 alkanoyl, C_1 - C_6 alkoxycarbonyl, mono- or di- $(\text{C}_1$ - C_6 alkyl)amino, mono- or di- $(\text{C}_1$ - C_6 alkyl)aminocarbonyl or mono- or di- $(\text{C}_1$ - C_6 alkyl)aminosulfonyl, each of which is substituted with from 0 to 4 substituents independently chosen from R_a ; or

(ii) a group of the Formula W-Y- ;

W is C_3 - C_{10} cycloalkyl, 3- to 10-membered heterocycloalkyl, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl, each of which is substituted with from 1 to 4 substituents independently chosen from R_a ;

Y is absent or C_1 - C_6 alkylene;

X is absent, NH , S , SO_2 , or O ; and

Each R_a is independently:

- (i) halogen, cyano, hydroxy, amino, nitro, aminocarbonyl or oxo;
- (ii) C₁-C₈alkyl, C₁-C₈haloalkyl, (C₃-C₈cycloalkyl)C₀-C₄alkyl, C₁-C₈alkoxy, C₁-C₈alkoxycarbonyl, C₁-C₈alkanoyl, C₁-C₈alkylsulfonyl, mono- or di-(C₁-C₈alkyl)amino, mono- or di-(C₁-C₈alkyl)aminocarbonyl or mono- or di-(C₁-C₈alkyl)aminosulfonyl; each of which is substituted with from 0 to 4 substituents independently chosen from halogen, oxo, amino, C₁-C₄alkyl, C₂-C₆alkenyl, C₁-C₈alkoxy; or
- (iii) (6- to 10-membered aryl)-L-, or (5- to 10-membered heterocycle)-L-, wherein L is a single covalent bond, O, SO₂, C(=O), (CH₂)_n-NH-C(=O) or (CH₂)_n-O-C(=O) and n is 0, 1 or 2; each of which is substituted with from 0 to 3 substituents independently chosen from:
 - (a) halogen, cyano, hydroxy, amino, nitro, aminocarbonyl, oxo, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆aminoalkyl, C₂-C₆alkyl ether, C₁-C₆alkoxy, C₁-C₆alkoxycarbonyl, C₁-C₆alkanoyl, C₁-C₆alkylsulfonyl, mono- or di-(C₁-C₆alkyl)amino, mono- or di-(C₁-C₆alkyl)aminocarbonyl or mono- or di-(C₁-C₆alkyl)aminosulfonyl;
 - (b) (5- to 10-membered, N-linked heterocycloalkyl)-(CO)_p-, wherein p is 0 or 1, which heterocycloalkyl is substituted with from 0 to 3 substituents independently chosen from halogen, C₁-C₄alkyl, C₂-C₄alkenyl, C₁-C₄alkoxy and C₂-C₄alkyl ether; and
 - (c) groups that are taken together with the atoms to which they are attached to form a fused, partially or fully saturated 5- or 6-membered ring that is substituted with from 0 to 2 substituents independently chosen from oxo and C₁-C₄alkyl.

2. A compound or salt or hydrate thereof according to claim 1, wherein Z is CHR₃.

3. A compound or salt or hydrate thereof according to claim 2, wherein R₃ is C₁-C₆alkanoyl, C₁-C₆alkylsulfonyl, mono- or di-(C₁-C₈alkyl)aminosulfonyl or mono- or di-(C₁-C₈alkyl)aminocarbonyl.

4. A compound or salt or hydrate thereof according to claim 2, wherein R₃ is phenyl or a 6-membered heteroaryl, each of which is substituted with from 1 to 3 substituents independently chosen from halogen, cyano, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆alkoxy, C₂-C₆alkyl ether, C₁-C₆alkanoyl, C₁-C₆haloalkyl, C₁-C₈alkylsulfonyl, mono- or di-(C₁-C₈alkyl)aminocarbonyl, mono- or di-(C₁-C₈alkyl)aminosulfonyl, (N-linked, 5- to 10-membered heterocycloalkyl)C(=O)-, phenyl and 5- or 6-membered heteroaryl, each of which heterocycloalkyl, phenyl or heteroaryl is substituted with from 0 to 3 substituents independently chosen from halogen, cyano, hydroxy, amino, nitro, aminocarbonyl, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆aminoalkyl, C₂-C₆alkyl ether, C₁-C₆alkoxy, C₁-C₆alkoxycarbonyl, C₁-

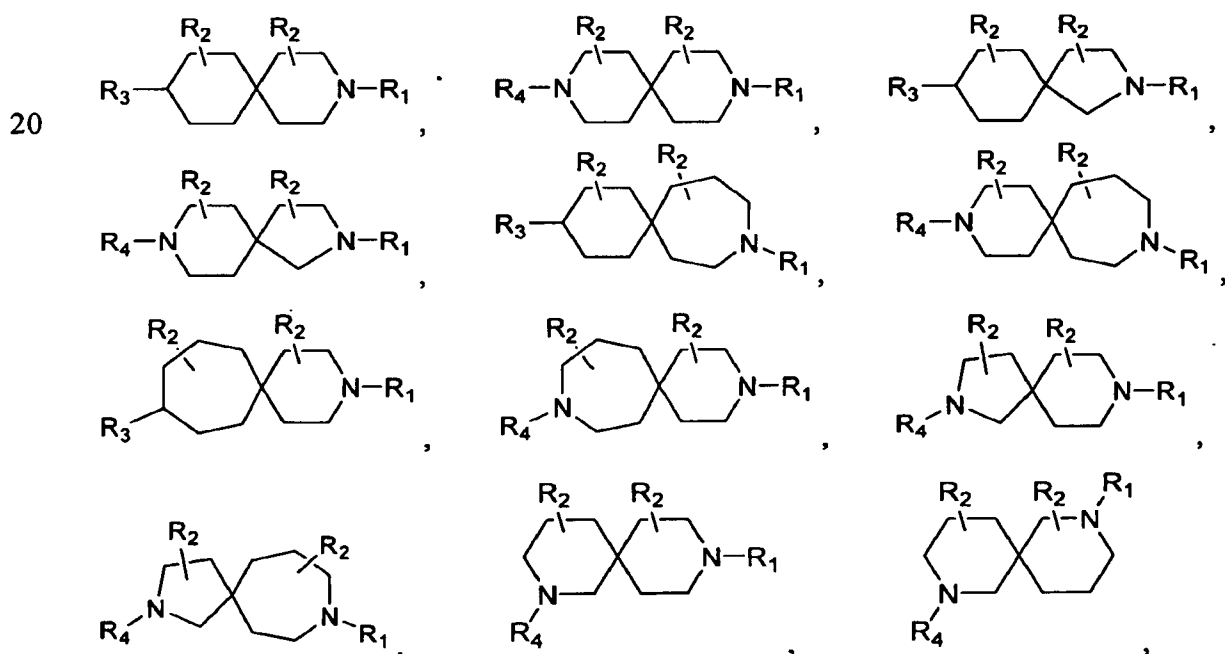
C₆alkanoyl, C₁-C₈alkylsulfonyl, mono- or di-(C₁-C₈alkyl)amino, mono- or di-(C₁-C₈alkyl)aminocarbonyl or mono- or di-(C₁-C₈alkyl)aminosulfonyl.

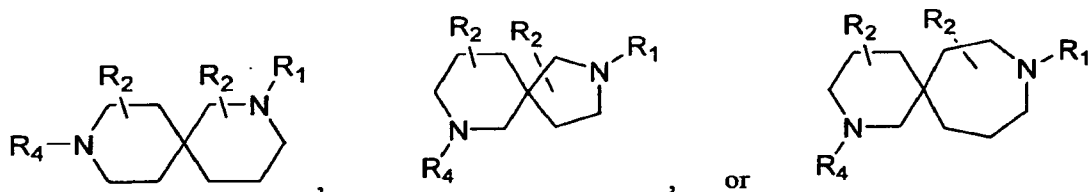
5. A compound or salt or hydrate thereof according to claim 1, wherein Z is NR₄.

6. A compound or salt or hydrate thereof according to claim 5, wherein R₄ is C₁-C₆alkanoyl, C₁-C₆alkylsulfonyl, mono- or di-(C₁-C₈alkyl)aminosulfonyl or mono- or di-(C₁-C₈alkyl)aminocarbonyl.

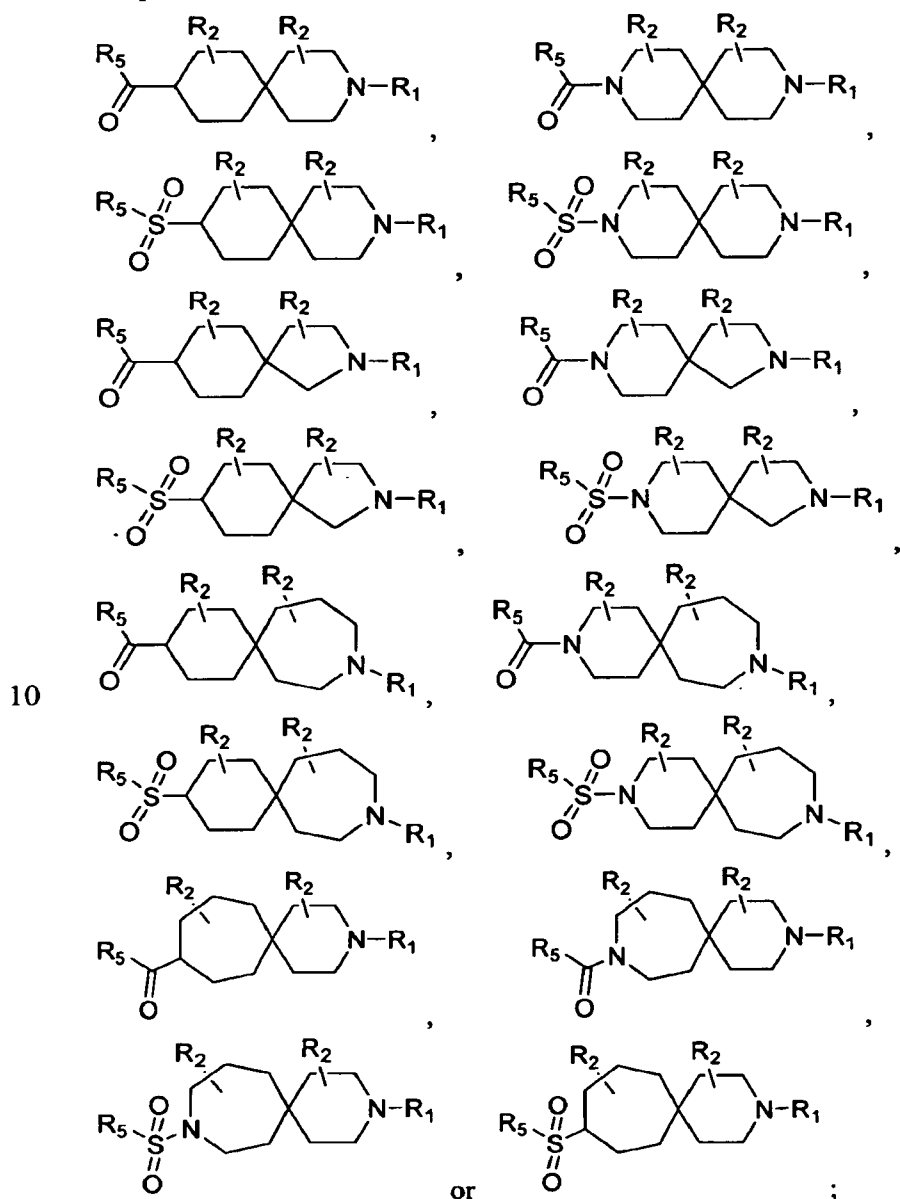
7. A compound or salt or hydrate thereof according to claim 2, wherein R₄ is phenyl or a 6-membered heteroaryl, each of which is substituted with from 1 to 3 substituents independently chosen from halogen, cyano, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆alkoxy, C₂-C₆alkyl ether, C₁-C₆alkanoyl, C₁-C₆haloalkyl, C₁-C₆alkylsulfonyl, mono- or di-(C₁-C₈alkyl)aminocarbonyl, mono- or di-(C₁-C₈alkyl)aminosulfonyl, (N-linked 5- to 7-membered heterocycloalkyl)C(=O)-, phenyl and 5- or 6-membered heteroaryl, each of which heterocycloalkyl, phenyl or heteroaryl is substituted with from 0 to 3 substituents independently chosen from halogen, cyano, hydroxy, amino, nitro, aminocarbonyl, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆aminoalkyl, C₂-C₆alkyl ether, C₁-C₆alkoxy, C₁-C₆alkoxycarbonyl, C₁-C₆alkanoyl, C₁-C₆alkylsulfonyl, mono- or di-(C₁-C₈alkyl)amino, mono- or di-(C₁-C₈alkyl)aminocarbonyl or mono- or di-(C₁-C₈alkyl)aminosulfonyl.

8. A compound or salt or hydrate thereof according to claim 1, wherein the compound satisfies one of the following formulas:





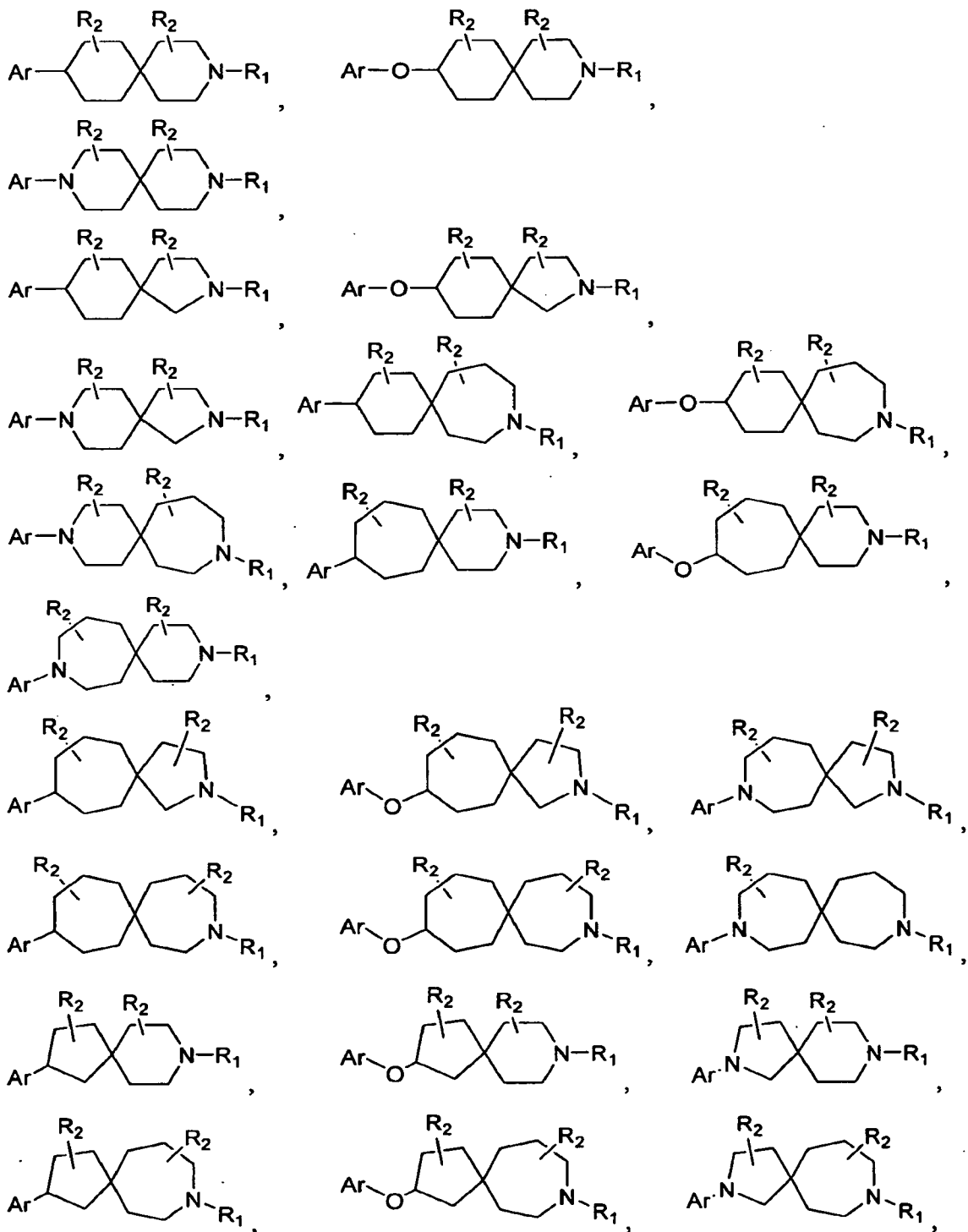
9. A compound or salt or hydrate thereof according to claim 1, wherein the
 5 compound satisfies one of the following formulas:

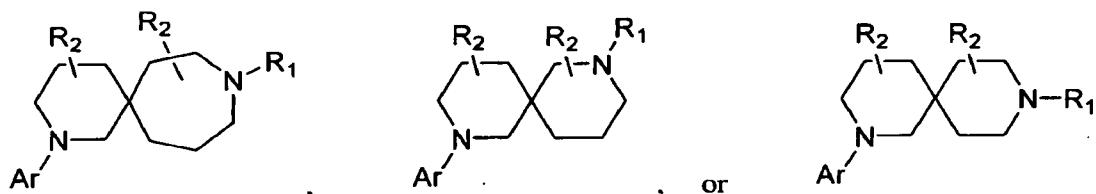


wherein R_5 is C_1 - C_6 alkyl, mono- or di- $(C_1$ - C_8 alkyl)amino or phenyl that is substituted with C_1 -
 15 C_6 alkyl, C_1 - C_6 alkanoyl, C_1 - C_6 haloalkyl, C_1 - C_6 alkylsulfonyl or mono- or di- $(C_1$ -

C₈alkyl)aminocarbonyl.

10. A compound or salt or hydrate thereof according to claim 1, wherein the compound satisfies one of the following formulas:

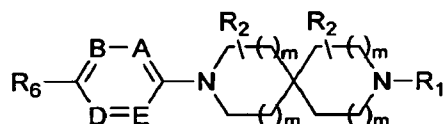




wherein Ar is phenylC₀-C₂alkyl or (5- or 6-membered heteroaryl)C₀-C₂alkyl, each of which is substituted with from 1 to 3 substituents independently chosen from:

- (i) halogen, cyano, C₁-C₈alkyl, C₁-C₈alkoxy, C₁-C₈alkanoyl, C₂-C₈alkyl ether or C₁-C₈haloalkyl;
- (ii) C₁-C₈alkylsulfonyl, C₁-C₈alkoxycarbonyl, mono- or di-(C₁-C₉alkyl)aminocarbonyl or (N-linked, 5- to 10-membered heterocycloalkyl)C₀-C₂alkyl, each of which is substituted with from 0 to 4 substituents independently chosen from hydroxy, halogen, oxo, C₁-C₆alkyl, C₂-C₆alkenyl, C₁-C₆alkoxy and C₂-C₆alkyl ether;
- (iii) phenyl or 5- or 6-membered heteroaryl, each of which is substituted with from 0 to 4 substituents independently chosen from C₁-C₆alkyl, C₁-C₆alkanoyl, C₁-C₆haloalkyl, C₁-C₄alkoxycarbonyl, C₁-C₆alkylsulfonyl, mono- or di-(C₁-C₆alkyl)aminocarbonyl; and (5- to 10-membered, N-linked heterocycloalkyl)-(CO)_p-, wherein p is 0 or 1, which heterocycloalkyl is substituted with from 0 to 3 substituents independently chosen from hydroxy, oxo, C₁-C₄alkyl, C₁-C₄alkoxy and C₂-C₄alkyl ether; and
- (iv) groups that are taken together with the atoms to which they are attached to form a fused, partially saturated 5- or 6-membered ring that is optionally substituted with oxo or C₁-C₄alkyl.

11. A compound or salt or hydrate thereof according to claim 1, wherein the compound satisfies the formula:



wherein:

A, B, D and E are independently selected from N and CR₇;

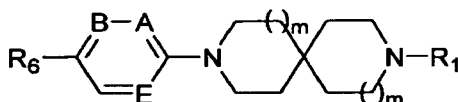
R₆ is:

- (i) hydrogen, halogen, cyano, amino, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆aminoalkyl, C₁-C₆alkoxy, C₂-C₆alkyl ether, C₁-C₆alkanoyl, C₁-C₆alkoxycarbonyl, C₁-C₆alkylsulfonyl or mono- or di-(C₁-C₆alkyl)aminocarbonyl;
- (ii) (5- to 10-membered, N-linked heterocycloalkyl)-(CO)_p-, wherein p is 0 or 1, which is substituted with from 1 to 3 substituents independently chosen from halogen, C₁-C₄alkyl, C₂-C₄alkenyl, C₁-C₄alkoxy and C₂-C₄alkyl ether; or

(iii) (5- to 7-membered heterocycloalkyl) C_0 - C_2 alkyl, phenyl C_0 - C_2 alkyl or (5- or 6-membered heteroaryl) C_0 - C_2 alkyl, each of which is substituted with from 1 to 3 substituents independently chosen from halogen, cyano, C_1 - C_6 alkyl, C_1 - C_6 alkanoyl, C_1 - C_6 haloalkyl, C_1 - C_4 alkoxycarbonyl, C_1 - C_6 alkylsulfonyl, mono- or di- $(C_1$ - C_8 alkyl)aminocarbonyl and (5- to 10-membered, N-linked heterocycloalkyl)-(CO) $_p$ -, wherein p is 0 or 1, which heterocycloalkyl is substituted with from 0 to 3 substituents independently chosen from halogen, C_1 - C_4 alkyl, C_2 - C_4 alkenyl, C_1 - C_4 alkoxy and C_2 - C_4 alkyl ether; and

Each R_7 is independently hydrogen, C_1 - C_6 alkyl, C_1 - C_6 alkanoyl, C_1 - C_6 haloalkyl, C_1 - C_6 alkylsulfonyl or mono- or di- $(C_1$ - C_6 alkyl)aminocarbonyl.

12. A compound or salt or hydrate thereof according to claim 11, wherein the compound satisfies the formula:



wherein A, B and E are independently CH or N.

13. A compound or salt or hydrate thereof according to claim 11 or claim 12, wherein R_6 is:

(i) C_1 - C_6 alkanoyl, mono- or di- $(C_1$ - C_8 alkyl)aminocarbonyl, C_1 - C_6 haloalkyl or C_1 - C_6 alkylsulfonyl; or

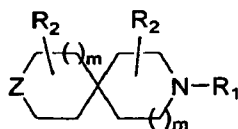
(ii) (5- to 10-membered, N-linked heterocycloalkyl)-(CO) $_p$ -, wherein p is 0 or 1, which is substituted with from 1 to 3 substituents independently chosen from halogen, C_1 - C_4 alkyl, C_2 - C_4 alkenyl, C_1 - C_4 alkoxy and C_2 - C_4 alkyl ether.

14. A compound or salt or hydrate thereof according to claim 11 or claim 12, wherein R_6 is (5- to 7-membered heterocycloalkyl) C_0 - C_2 alkyl, phenyl or a 5- or 6-membered heteroaryl, each of which is substituted with from 1 to 3 substituents independently chosen from halogen, cyano, C_1 - C_6 alkyl, C_1 - C_6 alkanoyl, C_1 - C_6 haloalkyl, C_1 - C_4 alkoxycarbonyl, C_1 - C_6 alkylsulfonyl, mono- or di- $(C_1$ - C_8 alkyl)aminocarbonyl and (5- to 10-membered, N-linked heterocycloalkyl)-(CO) $_p$ -, wherein p is 0 or 1, which heterocycloalkyl is substituted with from 0 to 3 substituents independently chosen from halogen, C_1 - C_4 alkyl, C_2 - C_4 alkenyl, C_1 - C_4 alkoxy and C_2 - C_4 alkyl ether.

15. A compound or salt or hydrate thereof according to any one of claims 1-14, wherein R_1 is C_3 - C_6 alkyl, cyclobutyl, cyclopentyl or cyclohexyl.

16. A compound or salt or hydrate thereof according to any one of claims 1-15, wherein each R_2 independently represents 0 substituents or 1 or 2 methyl substituents.

17. A compound of the formula:



or a pharmaceutically acceptable salt or hydrate thereof, wherein:

Z is CHR₃ or NR₄;

5 Each m is independently 0, 1 or 2;

R₁ is C₃-C₆alkyl, cyclobutyl, cyclopentyl or cyclohexyl;

Each R₂ independently represents from 0 to 2 substituents independently chosen from C₁-C₄alkyl and C₁-C₄haloalkyl;

R₃ is:

10 (i) C₁-C₆alkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, C₁-C₆alkoxy, C₁-C₆alkylthio, C₁-C₆alkylsulfonyl, C₁-C₆alkanoyl, C₁-C₆alkoxycarbonyl, mono- or di-(C₁-C₆alkyl)amino, mono- or di-(C₁-C₈alkyl)aminocarbonyl or mono- or di-(C₁-C₈alkyl)aminosulfonyl, each of which is substituted with from 0 to 4 substituents independently chosen from R_a; or

15 (ii) a group of the Formula W-Y-X-;

R₄ is:

(i) C₁-C₆alkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, C₁-C₆alkylsulfonyl, C₁-C₆alkanoyl, C₁-C₆alkoxycarbonyl, mono- or di-(C₁-C₆alkyl)amino, mono- or di-(C₁-C₆alkyl)aminocarbonyl or mono- or di-(C₁-C₆alkyl)aminosulfonyl, each of which is substituted with from 0 to 4 substituents independently chosen from R_a; or

(ii) a group of the Formula W-Y-;

W is C₃-C₁₀cycloalkyl, 3- to 10-membered heterocycloalkyl, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl, each of which is substituted with from 0 to 4 substituents independently chosen from R_a;

25 Y is absent or C₁-C₆alkylene;

X is absent, NH, S, SO₂, or O; and

Each R_a is independently:

(i) halogen, cyano, hydroxy, amino, nitro, aminocarbonyl or oxo;

30 (ii) C₁-C₈alkyl, C₁-C₈haloalkyl, (C₃-C₈cycloalkyl)C₀-C₄alkyl, C₁-C₈alkoxy, C₁-C₈alkoxycarbonyl, C₁-C₈alkanoyl, C₁-C₈alkylsulfonyl, mono- or di-(C₁-C₈alkyl)amino, mono- or di-(C₁-C₈alkyl)aminocarbonyl or mono- or di-(C₁-C₈alkyl)aminosulfonyl; each of which is substituted with from 0 to 4 substituents independently chosen from halogen, oxo, amino, C₁-C₄alkyl, C₂-C₆alkenyl, C₁-C₈alkoxy; or

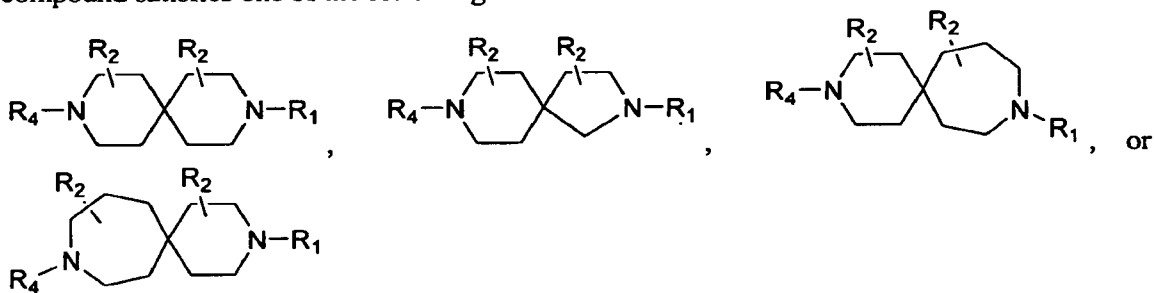
35 (iii) (6- to 10-membered aryl)-L-, or (5- to 10-membered heterocycle)-L-, wherein L is a single covalent bond, O, SO₂, C(=O), (CH₂)_n-NH-C(=O) or (CH₂)_n-O-C(=O) and n is 0,

1 or 2; each of which is substituted with from 0 to 3 substituents independently chosen from:

(a) halogen, cyano, hydroxy, amino, nitro, aminocarbonyl, oxo, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆aminoalkyl, C₂-C₆alkyl ether, C₁-C₆alkoxy, C₁-C₆alkoxycarbonyl, C₁-C₆alkanoyl, C₁-C₆alkylsulfonyl, mono- or di-(C₁-C₆alkyl)amino, mono- or di-(C₁-C₆alkyl)aminocarbonyl or mono- or di-(C₁-C₆alkyl)aminosulfonyl; and

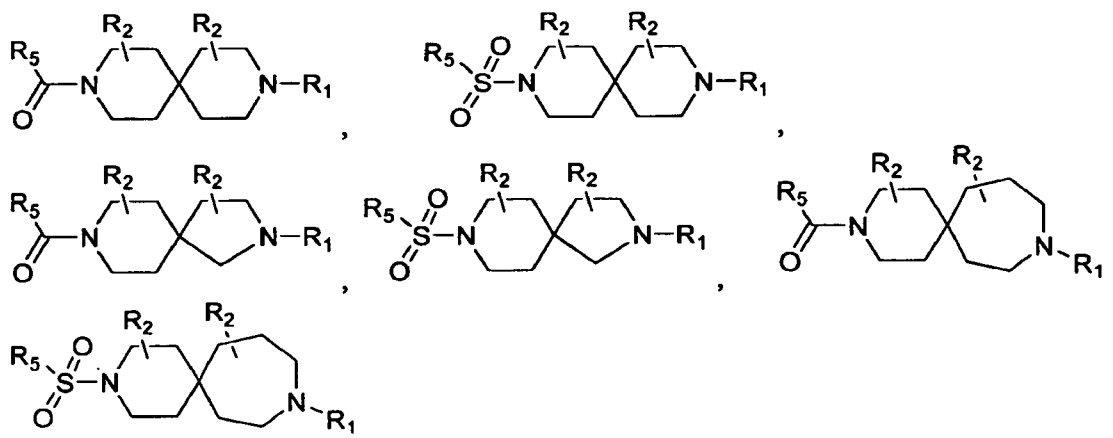
(b) groups that are taken together with the atoms to which they are attached to form a fused, partially saturated 5- or 6-membered ring that is optionally substituted with oxo or C₁-C₄alkyl.

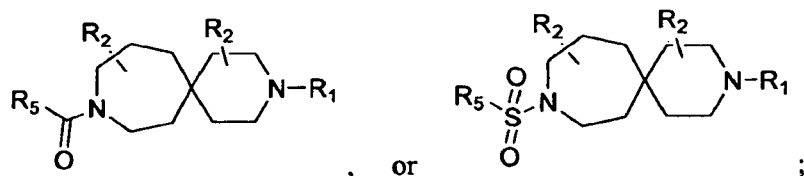
18. A compound or salt or hydrate thereof according to claim 17, wherein the compound satisfies one of the following formulas:



19. A compound or salt or hydrate thereof according to claim 17 or claim 18, wherein R₄ is C₁-C₄alkanoyl, C₁-C₄alkylsulfonyl, mono- or di-(C₁-C₆alkyl)aminosulfonyl or mono- or di-(C₁-C₆alkyl)aminocarbonyl.

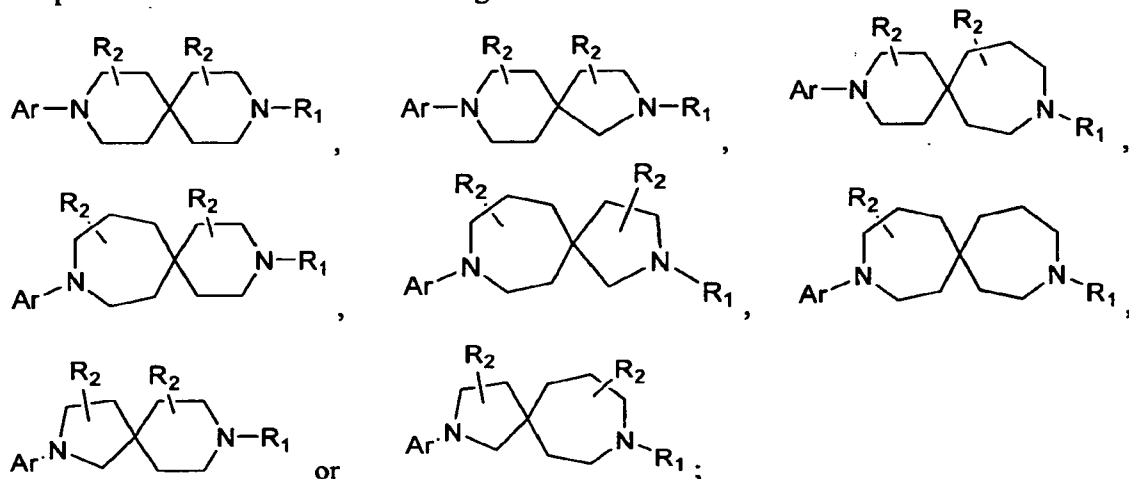
20. A compound or salt or hydrate thereof according to claim 17, wherein the compound satisfies one of the following formulas:





wherein R_5 is C_1 - C_6 alkyl, mono- or di- $(C_1$ - C_6 alkyl)amino or phenyl that is optionally substituted with C_1 - C_6 alkyl, C_1 - C_6 alkanoyl, C_1 - C_6 haloalkyl, C_1 - C_6 alkylsulfonyl or mono- or di- $(C_1$ - C_6 alkyl)aminocarbonyl.

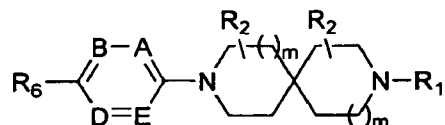
- 5 21. A compound or salt or hydrate thereof according to claim 17, wherein the compound satisfies one of the following formulas:



- 10 wherein Ar is phenyl C_0 - C_2 alkyl or (5- or 6-membered heteroaryl) C_0 - C_2 alkyl, each of which is substituted with from 0 to 3 substituents independently chosen from:

- (i) halogen, cyano, C_1 - C_8 alkyl, C_1 - C_8 alkoxy, C_1 - C_8 alkanoyl, C_2 - C_8 alkyl ether or C_1 - C_8 haloalkyl;
- (ii) C_1 - C_8 alkylsulfonyl, C_1 - C_8 alkoxycarbonyl, mono- or di- $(C_1$ - C_8 alkyl)aminocarbonyl or (N-linked, 5- to 10-membered heterocycloalkyl) C_0 - C_2 alkyl, each of which is substituted with from 0 to 4 substituents independently chosen from hydroxy, halogen, oxo, C_1 - C_6 alkyl, C_2 - C_6 alkenyl, C_1 - C_6 alkoxy and C_2 - C_6 alkyl ether;
- (iii) phenyl or 5- or 6-membered heteroaryl, each of which is substituted with from 0 to 4 substituents independently chosen from C_1 - C_6 alkyl, C_1 - C_6 alkanoyl, C_1 - C_6 haloalkyl, C_1 - C_4 alkoxycarbonyl, C_1 - C_6 alkylsulfonyl, mono- or di- $(C_1$ - C_6 alkyl)aminocarbonyl; and (5- to 10-membered, N-linked heterocycloalkyl)-(CO) $_p$ -, wherein p is 0 or 1, which heterocycloalkyl is substituted with from 0 to 3 substituents independently chosen from hydroxy, oxo, C_1 - C_4 alkyl, C_1 - C_4 alkoxy and C_2 - C_4 alkyl ether; and
- (iv) groups that are taken together with the atoms to which they are attached to form a fused, partially saturated 5- or 6-membered ring that is optionally substituted with oxo or C_1 - C_4 alkyl.

22. A compound or salt or hydrate thereof according to claim 17, wherein the compound satisfies the formula:



wherein:

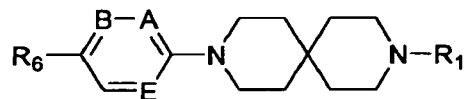
5 A, B, D and E are independently selected from N and CR₇;

R₆ is:

- (i) hydrogen, halogen, cyano, amino, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆aminoalkyl, C₁-C₆alkoxy, C₂-C₆alkyl ether, C₁-C₆alkanoyl, C₁-C₆alkoxycarbonyl, C₁-C₆alkylsulfonyl and mono- or di-(C₁-C₆alkyl)aminocarbonyl; or
- 10 (ii) (5- to 7-membered heterocycloalkyl)C₀-C₂alkyl, phenyl or a 5- or 6-membered heteroaryl, each of which is substituted with from 1 to 3 substituents independently chosen from halogen, cyano, C₁-C₆alkyl, C₁-C₆alkanoyl, C₁-C₆haloalkyl, C₁-C₄alkoxycarbonyl, C₁-C₆alkylsulfonyl, mono- or di-(C₁-C₈alkyl)aminocarbonyl and (5- to 10-membered, N-linked heterocycloalkyl)-(CO)_p-, wherein p is 0 or 1, which
- 15 heterocycloalkyl is substituted with from 0 to 3 substituents independently chosen from halogen, C₁-C₄alkyl, C₂-C₄alkenyl, C₁-C₄alkoxy and C₂-C₄alkyl ether; and

Each R₇ is independently hydrogen, C₁-C₆alkyl, C₁-C₆alkanoyl, C₁-C₆haloalkyl, C₁-C₆alkylsulfonyl or mono- or di-(C₁-C₆alkyl)aminocarbonyl.

23. A compound or salt or hydrate thereof according to claim 22, wherein the compound satisfies the formula:



wherein A, B and E are independently CH or N.

24. A compound or salt or hydrate thereof according to claim 22 or claim 23, wherein R₆ is C₁-C₄alkanoyl, mono- or di-(C₁-C₈alkyl)aminocarbonyl, C₁-C₄haloalkyl, C₁-C₄alkylsulfonyl or (5- to 10-membered, N-linked heterocycloalkyl)-C(O)_n-, wherein n is 0 or 1; each of which is substituted with from 0 to 3 substituents independently chosen from halogen, C₁-C₄alkyl, C₂-C₄alkenyl, C₁-C₄alkoxy, and C₂-C₄alkyl ether.

25. A compound or salt or hydrate thereof according to claim 22 or claim 23, wherein R₆ is (5- to 7-membered heterocycloalkyl)C₀-C₂alkyl, phenyl or a 5- or 6-membered heteroaryl, each of which is substituted with from 0 to 3 substituents independently chosen from halogen, cyano, C₁-C₆alkyl, C₁-C₆alkanoyl, C₁-C₆haloalkyl, C₁-C₄alkoxycarbonyl, C₁-C₆alkylsulfonyl, mono- or di-(C₁-C₈alkyl)aminocarbonyl and (5- to 10-membered, N-linked heterocycloalkyl)-(CO)_p-, wherein p is 0 or 1, which heterocycloalkyl is substituted with from 0

to 3 substituents independently chosen from halogen, C₁-C₄alkyl, C₂-C₄alkenyl, C₁-C₄alkoxy and C₂-C₄alkyl ether.

26. A compound or salt or hydrate thereof according to any one of claims 1-25, wherein the compound is capable of exhibiting has a K_i value that is 1 micromolar or less, as determined using an assay for H3 receptor GTP binding.

27. A compound or salt or hydrate thereof according to claim 26, wherein the compound is capable of exhibiting has a K_i value that is 100 nanomolar or less, as determined using an assay for H3 receptor GTP binding.

28. A pharmaceutical composition, comprising at least one compound or salt according to any one of claims 1-25 in combination with a physiologically acceptable carrier or excipient.

29. A pharmaceutical composition according to claim 28 wherein the composition is formulated as an injectible fluid, an aerosol, a cream, a gel, a pill, a capsule, a syrup or a transdermal patch.

30. A method for treating a condition responsive to H3 receptor modulation in a patient, comprising administering to the patient a therapeutically effective amount of a compound or salt or hydrate thereof according to any one of claims 1-25, and thereby alleviating the condition in the patient.

31. A method according to claim 30, wherein the compound exhibits H3 receptor antagonist activity.

32. A method according to claim 30, wherein the condition is attention deficit disorder, attention deficit hyperactivity disorder, dementia, schizophrenia, a cognitive disorder, epilepsy, migraine, excessive daytime sleepiness, shift work sleep disorder, jet lag, narcolepsy, sleep apnea, allergic rhinitis, vertigo, motion sickness, a memory disorder, Parkinson's disease, fatigue, or a fatigue-related disorder.

33. A method according to claim 30, wherein the condition is obesity, an eating disorder or diabetes.

34. A method according to claim 30, wherein the patient is a human.

35. A compound or salt or hydrate thereof according to any one of claims 1-25, wherein the compound or salt is radiolabeled.

36. A method for determining the presence or absence of H3 receptor in a sample, comprising the steps of:

- (a) contacting a sample with a compound or salt or hydrate thereof according to any one of claims 1-25, under conditions that permit binding of the compound to H3 receptor; and
- (b) detecting a level of the compound bound to H3 receptor, and therefrom determining the presence or absence of H3 receptor in the sample.

37. A method according to claim 36, wherein the compound is radiolabeled, and wherein the step of detection comprises the steps of:

- (i) separating unbound compound from bound compound; and
- (ii) detecting the presence or absence of bound compound in the sample.

38. A packaged pharmaceutical preparation, comprising:

- (a) a pharmaceutical composition according to claim 28 in a container; and
- (b) instructions for using the composition to treat a condition responsive to H3 receptor modulation in a patient.

39. A packaged pharmaceutical preparation according to claim 28, wherein the condition is attention deficit disorder, attention deficit hyperactivity disorder, dementia, schizophrenia, a cognitive disorder, epilepsy, migraine, excessive daytime sleepiness, shift work sleep disorder, jet lag, narcolepsy, sleep apnea, allergic rhinitis, vertigo, motion sickness, a memory disorder, Parkinson's disease, fatigue, or a fatigue-related disorder.

40. A packaged pharmaceutical preparation according to claim 28, wherein the condition is obesity, an eating disorder or diabetes.

41. The use of a compound or salt according to any one of claims 1-25 for the manufacture of a medicament for the treatment of a condition responsive to H3 receptor modulation.

42. A use according to claim 41, wherein the condition is attention deficit disorder, attention deficit hyperactivity disorder, dementia, schizophrenia, a cognitive disorder, epilepsy, migraine, excessive daytime sleepiness, shift work sleep disorder, jet lag, narcolepsy, sleep apnea, allergic rhinitis, vertigo, motion sickness, a memory disorder, Parkinson's disease, fatigue, or a fatigue-related disorder.

43. A use according to claim 41, wherein the condition is obesity, an eating disorder or diabetes.

44. A compound or salt or hydrate thereof according to claim 1, wherein the compound is:

- 1-[4-(9-cyclobutyl-3,9-diazaspiro[5.5]undec-3-yl)phenyl]ethanone;
 Ethyl 4-(9-cyclobutyl-3,9-diazaspiro[5.5]undec-3-yl)benzoate;
 4-(9-Cyclobutyl-3,9-diazaspiro[5.5]undec-3-yl)benzoic acid;
 4-(9-Cyclobutyl-3,9-diazaspiro[5.5]undec-3-yl)-N-methylbenzamide;
- 5 1-{4-[(9-cyclobutyl-3,9-diazaspiro[5.5]undec-3-yl)carbonyl]phenyl} ethanone;
 1-{4-[(9-cyclobutyl-3,9-diazaspiro[5.5]undec-3-yl) sulfonyl]phenyl} ethanone;
 6-(9-Cyclobutyl-3,9-diazaspiro[5.5]undec-3-yl)nicotinic acid;
 6-(9-Cyclobutyl-3,9-diazaspiro[5.5]undec-3-yl)-N-methylnicotinamide;
 6-[(3-Cyclobutyl-3-azaspiro[5.5]undec-9-yl)oxy]-N-methylnicotinamide;
- 10 1-{4-[6-(9-Cyclobutyl-3,9-diazaspiro[5.5]undec-3-yl)pyridin-3-yl]phenyl} ethanone;
 3-Cyclobutyl-9-{5-[(2-methylpyrrolidin-1-yl)carbonyl]pyridin-2-yl}-3,9-diazaspiro[5.5]undecane;
 3-Cyclobutyl-9-{5-[(2-methylpyrrolidin-1-yl)methyl]pyridin-2-yl}-3,9-diazaspiro[5.5]undecane;
- 15 3-Cyclobutyl-9-{4-[(2-methylpyrrolidin-1-yl)methyl]phenyl}-3,9-diazaspiro[5.5]undecane;
 3-(6-Chloropyridazin-3-yl)-9-cyclobutyl-3,9-diazaspiro[5.5]undecane;
 3-Cyclobutyl-9-(6-methoxypyridazin-3-yl)-3,9-diazaspiro[5.5]undecane;
 3-Cyclobutyl-9-[6-(methylsulfonyl)pyridazin-3-yl]-3,9-diazaspiro[5.5]undecane;
 1-[6-(9-Cyclobutyl-3,9-diazaspiro[5.5]undec-3-yl)pyridazin-3-yl]ethanone;
- 20 6-(9-cyclobutyl-3,9-diazaspiro[5.5]undec-3-yl)pyridazine-3-carbonitrile;
 1-{4-[6-(9-cyclobutyl-3,9-diazaspiro[5.5]undec-3-yl)pyridazin-3-yl]phenyl} ethanone;
 3-cyclobutyl-9-(6-pyrimidin-5-ylpyridazin-3-yl)-3,9-diazaspiro[5.5]undecane;
 3-cyclobutyl-9-{6-[4-(methylsulfonyl)phenyl]pyridazin-3-yl}-3,9-diazaspiro[5.5]undecane;
 3-(5-Bromo-pyrimidin-2-yl)-9-cyclobutyl-3,3-diazaspiro[5.5]undecane;
- 25 1-{4-[2-(9-Cyclobutyl-3,9-diaza-spiro[5.5]undec-3-yl)-pyrimidine-5-yl]phenyl} ethanone;
 8-(5-Bromopyridin-2-yl)-2-cyclobutyl-2,8-diazaspiro[4.5]decane;
 6-(2-Cyclobutyl-2,8-diazaspiro[4.5]dec-8-yl)-3,4'-bipyridine;
 2-(5-Bromopyridin-2-yl)-8-cyclobutyl-2,8-diazaspiro[4.5]decane;
 6-(8-Cyclobutyl-2,8-diazaspiro[4.5]dec-2-yl)-3,3'-bipyridine;
- 30 2-Cyclobutyl-8-[4-(1-methyl-1H-pyrazol-4-yl)phenyl]-2,8-diazaspiro[4.5]decane;
 8-Cyclobutyl-2-[4-(1-methyl-1H-pyrazol-4-yl)phenyl]-2,8-diazaspiro[4.5]decane;
 3-Cyclobutyl-9-(4-imidazo[1,2-a]pyrimidin-6-ylphenyl)-3,9-diazaspiro[5.5]undecane;
 3-cyclobutyl-9-(1-methyl-1H-benzimidazol-5-yl)-3,9-diazaspiro[5.5]-undecane;
 4-(9-Cyclopentyl-3,9-diazaspiro[5.5]undec-3-yl)-N-methylbenzamide;
- 35 3-Cyclobutyl-9-pyrazin-2-yl-3,9-diazaspiro[5.5]undecane;
 3-Cyclobutyl-9-(5-pyridin-3-yl pyrazin-2-yl)-3,9-diazaspiro[5.5]undecane;
 1-[6-(9-cyclobutyl-3,9-diazaspiro[5.5]undec-3-yl)pyridin-3-yl]ethanone;

3-cyclobutyl-9-[5-(trifluoromethyl)pyridin-2-yl]-3,9-diazaspiro[5.5]undecane;
3-cyclobutyl-9-[4-(methylsulfonyl)phenyl]-3,9-diazaspiro[5.5]undecane;
5-(9-cyclobutyl-3,9-diazaspiro[5.5]undec-3-yl)indan-1-one;
methyl 4-[(9-cyclobutyl-3,9-diazaspiro[5.5]undec-3-yl)methyl]benzoate;
3-benzoyl-9-cyclobutyl-3,9-diazaspiro[5.5]undecane;
4-[(9-cyclobutyl-3,9-diazaspiro[5.5]undec-3-yl)methyl]-N-methylbenzamide;
1-[4'-(9-cyclobutyl-3,9-diazaspiro[5.5]undec-3-yl)biphenyl-4-yl]ethanone;
[4-(9-cyclobutyl-3,9-diazaspiro[5.5]undec-3-yl)phenyl](phenyl)methanone;
benzyl 4-(9-cyclobutyl-3,9-diazaspiro[5.5]undec-3-yl)benzoate;
1-[6-(9-cyclobutyl-3,9-diazaspiro[5.5]undec-3-yl)-2-naphthyl]ethanone;
3-cyclobutyl-9-quinolin-2-yl-3,9-diazaspiro[5.5]undecane;
1-{4-[4-(9-cyclobutyl-3,9-diazaspiro[5.5]undec-3-yl)piperidin-1-yl]phenyl} ethanone;
methyl 4-[6-(9-cyclobutyl-3,9-diazaspiro[5.5]undec-3-yl)pyridin-3-yl]benzoate;
4-[6-(9-cyclobutyl-3,9-diazaspiro[5.5]undec-3-yl)pyridin-3-yl]-N-methylbenzamide;
3-cyclobutyl-9-{5-[4-(methylsulfonyl)phenyl]pyridin-2-yl}-3,9-diazaspiro[5.5]undecane;
methyl 4-[6-(9-cyclobutyl-3,9-diazaspiro[5.5]undec-3-yl)pyridazin-3-yl]benzoate;
3-cyclobutyl-9-{6-[3-(methylsulfonyl)phenyl]pyridazin-3-yl}-3,9-diazaspiro[5.5]undecane
{4-[6-(9-cyclobutyl-3,9-diazaspiro[5.5]undec-3-yl)-pyridazin-3-yl]-phenyl}-(2-methyl-pyrrolidin-1-yl)-methanone;
4-[6-(9-cyclobutyl-3,9-diazaspiro[5.5]undec-3-yl)-pyridazin-3-yl]-N-methyl-benzamide;
3-cyclobutyl-9-(4-piperidin-1-ylmethyl-phenyl)-3,9-diazaspiro[5.5]undecane;
3-cyclobutyl-9-{5-[4-[(2-methylpyrrolidin-1-yl)carbonyl]phenyl]pyridin-2-yl}-3,9-diazaspiro[5.5]undecane;
4-[6-(9-cyclobutyl-3,9-diazaspiro[5.5]undec-3-yl)pyridin-3-yl]-N-ethylbenzamide;
3-cyclobutyl-9-[5-(pyrrolidin-1-ylcarbonyl)pyridin-2-yl]-3,9-diazaspiro[5.5]undecane;
3-cyclobutyl-9-[5-(3,6-dihydropyridin-1(2H)-ylcarbonyl)pyridin-2-yl]-3,9-diazaspiro[5.5]undecane;
3-cyclobutyl-9-[5-(piperidin-1-ylcarbonyl)pyridin-2-yl]-3,9-diazaspiro[5.5]undecane;
3-cyclobutyl-9-[5-(morpholin-4-ylcarbonyl)pyridin-2-yl]-3,9-diazaspiro[5.5]undecane;
3-cyclobutyl-9-{5-[(4-methylpiperidin-1-yl)carbonyl]pyridin-2-yl}-3,9-diazaspiro[5.5]undecane;
3-[5-(azepan-1-ylcarbonyl)pyridin-2-yl]-9-cyclobutyl-3,9-diazaspiro[5.5]undecane;
3-cyclobutyl-9-[5-(thiomorpholin-4-ylcarbonyl)pyridin-2-yl]-3,9-diazaspiro[5.5]undecane;
3-cyclobutyl-9-{5-[(3,5-dimethylpiperidin-1-yl)carbonyl]pyridin-2-yl}-3,9-diazaspiro[5.5]undecane;
3-cyclobutyl-9-{5-[(4aR,8aS)-octahydroisoquinolin-2(1H)-ylcarbonyl]pyridin-2-yl}-3,9-diazaspiro[5.5]undecane;
3-cyclobutyl-9-{5-[(4aS,8aS)-octahydroisoquinolin-2(1H)-ylcarbonyl]pyridin-2-yl}-3,9-diazaspiro[5.5]undecane;
3-cyclobutyl-9-{5-[(2,6-dimethylmorpholin-4-yl)carbonyl]pyridin-2-yl}-3,9-diazaspiro[5.5]undecane;
6-(9-cyclobutyl-3,9-diazaspiro[5.5]undec-3-yl)-N-ethyl-N-isopropylnicotinamide;

6-(9-cyclobutyl-3,9-diazaspiro[5.5]undec-3-yl)-N-isopropyl-N-methylnicotinamide;
3-cyclobutyl-9-{5-[(2-methylpiperidin-1-yl)carbonyl]pyridin-2-yl}-3,9-diazaspiro[5.5]undecane;
6-(9-cyclobutyl-3,9-diazaspiro[5.5]undec-3-yl)-N-cyclohexyl-N-methylnicotinamide;
3-cyclobutyl-9-{5-[(2-ethylpiperidin-1-yl)carbonyl]pyridin-2-yl}-3,9-diazaspiro[5.5]undecane;
6-(9-cyclobutyl-3,9-diazaspiro[5.5]undec-3-yl)-N-cyclohexyl-N-ethylnicotinamide;
3-cyclobutyl-9-(5-{[(2S)-2-(methoxymethyl)pyrrolidin-1-yl]carbonyl}pyridin-2-yl)-3,9-diazaspiro[5.5]undecane;
3-cyclobutyl-9-(5-{[(2R)-2-(methoxymethyl)pyrrolidin-1-yl]carbonyl}pyridin-2-yl)-3,9-diazaspiro[5.5]undecane;
6-(9-cyclobutyl-3,9-diazaspiro[5.5]undec-3-yl)-N-isopropyl-N-(2-methoxyethyl)nicotinamide;
6-(9-cyclobutyl-3,9-diazaspiro[5.5]undec-3-yl)-N-(2-methylbutyl)nicotinamide;
6-(9-cyclobutyl-3,9-diazaspiro[5.5]undec-3-yl)-N-ethylnicotinamide;
N-allyl-6-(9-cyclobutyl-3,9-diazaspiro[5.5]undec-3-yl)nicotinamide;
6-(9-cyclobutyl-3,9-diazaspiro[5.5]undec-3-yl)-N-propylnicotinamide;
6-(9-cyclobutyl-3,9-diazaspiro[5.5]undec-3-yl)-N-(cyclopropylmethyl)nicotinamide;
N-butyl-6-(9-cyclobutyl-3,9-diazaspiro[5.5]undec-3-yl)nicotinamide;
6-(9-cyclobutyl-3,9-diazaspiro[5.5]undec-3-yl)-N-isobutylnicotinamide;
6-(9-cyclobutyl-3,9-diazaspiro[5.5]undec-3-yl)-N-pentylnicotinamide;
6-(9-cyclobutyl-3,9-diazaspiro[5.5]undec-3-yl)-N-(3-methylbutyl)nicotinamide;
6-(9-cyclobutyl-3,9-diazaspiro[5.5]undec-3-yl)-N-(2,2,2-trifluoroethyl)nicotinamide;
6-(9-cyclobutyl-3,9-diazaspiro[5.5]undec-3-yl)-N-cyclopropylnicotinamide;
6-(9-cyclobutyl-3,9-diazaspiro[5.5]undec-3-yl)-N-isopropylnicotinamide;
N-cyclobutyl-6-(9-cyclobutyl-3,9-diazaspiro[5.5]undec-3-yl)nicotinamide;
N-(sec-butyl)-6-(9-cyclobutyl-3,9-diazaspiro[5.5]undec-3-yl)nicotinamide;
6-(9-cyclobutyl-3,9-diazaspiro[5.5]undec-3-yl)-N-cyclopentylnicotinamide;
6-(9-cyclobutyl-3,9-diazaspiro[5.5]undec-3-yl)-N-(1-methylbutyl)nicotinamide;
6-(9-cyclobutyl-3,9-diazaspiro[5.5]undec-3-yl)-N-cycloheptylnicotinamide;
6-(9-cyclobutyl-3,9-diazaspiro[5.5]undec-3-yl)-N-(cyclohexylmethyl)nicotinamide;
6-(9-cyclobutyl-3,9-diazaspiro[5.5]undec-3-yl)-N-(2,2-dimethylpropyl)nicotinamide;
6-(9-cyclobutyl-3,9-diazaspiro[5.5]undec-3-yl)-N-(2-ethylbutyl)nicotinamide;
3-cyclobutyl-9-[4-(pyrrolidin-1-ylcarbonyl)phenyl]-3,9-diazaspiro[5.5]undecane;
3-cyclobutyl-9-[4-(3,6-dihydropyridin-1(2H)-ylcarbonyl)phenyl]-3,9-diazaspiro[5.5]undecane;
3-cyclobutyl-9-[4-(piperidin-1-ylcarbonyl)phenyl]-3,9-diazaspiro[5.5]undecane;
3-cyclobutyl-9-[4-(morpholin-4-ylcarbonyl)phenyl]-3,9-diazaspiro[5.5]undecane;
3-cyclobutyl-9-[4-[(4-methylpiperidin-1-yl)carbonyl]phenyl]-3,9-diazaspiro[5.5]undecane;
3-[4-(azepan-1-ylcarbonyl)phenyl]-9-cyclobutyl-3,9-diazaspiro[5.5]undecane;
3-cyclobutyl-9-[4-(thiomorpholin-4-ylcarbonyl)phenyl]-3,9-diazaspiro[5.5]undecane;
3-cyclobutyl-9-[4-[(3,5-dimethylpiperidin-1-yl)carbonyl]phenyl]-3,9-diazaspiro[5.5]undecane;

3-cyclobutyl-9-{4-[(4aR,8aS)-octahydroisoquinolin-2(1H)-ylcarbonyl]phenyl}-3,9-diazaspiro[5.5]undecane;

3-cyclobutyl-9-{4-[(4aS,8aS)-octahydroisoquinolin-2(1H)-ylcarbonyl]phenyl}-3,9-diazaspiro[5.5]undecane;

3-cyclobutyl-9-{4-[(2,6-dimethylmorpholin-4-yl)carbonyl]phenyl}-3,9-diazaspiro[5.5]undecane;

4-(9-cyclobutyl-3,9-diazaspiro[5.5]undec-3-yl)-N-ethyl-N-isopropylbenzamide;

4-(9-cyclobutyl-3,9-diazaspiro[5.5]undec-3-yl)-N-isopropyl-N-methylbenzamide;

3-cyclobutyl-9-{4-[(2-methylpiperidin-1-yl)carbonyl]phenyl}-3,9-diazaspiro[5.5]undecane;

4-(9-cyclobutyl-3,9-diazaspiro[5.5]undec-3-yl)-N-cyclohexyl-N-methylbenzamide;

3-cyclobutyl-9-{4-[(2-ethylpiperidin-1-yl)carbonyl]phenyl}-3,9-diazaspiro[5.5]undecane;

4-(9-cyclobutyl-3,9-diazaspiro[5.5]undec-3-yl)-N-cyclohexyl-N-ethylbenzamide;

3-cyclobutyl-9-[4-(octahydroquinolin-1(2H)-ylcarbonyl)phenyl]-3,9-diazaspiro[5.5]undecane;

3-cyclobutyl-9-(4-{[(2S)-2-(methoxymethyl)pyrrolidin-1-yl]carbonyl}phenyl)-3,9-diazaspiro[5.5]undecane;

3-cyclobutyl-9-(4-{[(2R)-2-(methoxymethyl)pyrrolidin-1-yl]carbonyl}phenyl)-3,9-diazaspiro[5.5]undecane;

4-(9-cyclobutyl-3,9-diazaspiro[5.5]undec-3-yl)-N-isopropyl-N-(2-methoxyethyl)benzamide;

4-(9-cyclobutyl-3,9-diazaspiro[5.5]undec-3-yl)-N-(2-methylbutyl)benzamide;

4-(9-cyclobutyl-3,9-diazaspiro[5.5]undec-3-yl)-N-ethylbenzamide;

N-allyl-4-(9-cyclobutyl-3,9-diazaspiro[5.5]undec-3-yl)benzamide;

4-(9-cyclobutyl-3,9-diazaspiro[5.5]undec-3-yl)-N-propylbenzamide;

N-butyl-4-(9-cyclobutyl-3,9-diazaspiro[5.5]undec-3-yl)benzamide;

4-(9-cyclobutyl-3,9-diazaspiro[5.5]undec-3-yl)-N-isobutylbenzamide;

4-(9-cyclobutyl-3,9-diazaspiro[5.5]undec-3-yl)-N-pentylbenzamide;

4-(9-cyclobutyl-3,9-diazaspiro[5.5]undec-3-yl)-N-(3-methylbutyl)benzamide;

4-(9-cyclobutyl-3,9-diazaspiro[5.5]undec-3-yl)-N-(2,2,2-trifluoroethyl)benzamide;

4-(9-cyclobutyl-3,9-diazaspiro[5.5]undec-3-yl)-N-cyclopropylbenzamide;

4-(9-cyclobutyl-3,9-diazaspiro[5.5]undec-3-yl)-N-isopropylbenzamide;

N-cyclobutyl-4-(9-cyclobutyl-3,9-diazaspiro[5.5]undec-3-yl)benzamide;

N-(sec-butyl)-4-(9-cyclobutyl-3,9-diazaspiro[5.5]undec-3-yl)benzamide;

4-(9-cyclobutyl-3,9-diazaspiro[5.5]undec-3-yl)-N-cyclopentylbenzamide;

4-(9-cyclobutyl-3,9-diazaspiro[5.5]undec-3-yl)-N-(1-methylbutyl)benzamide;

4-(9-cyclobutyl-3,9-diazaspiro[5.5]undec-3-yl)-N-cycloheptylbenzamide;

4-(9-cyclobutyl-3,9-diazaspiro[5.5]undec-3-yl)-N-(cyclohexylmethyl)benzamide;

4-(9-cyclobutyl-3,9-diazaspiro[5.5]undec-3-yl)-N-(2,2-dimethylpropyl)benzamide;

4-(9-cyclobutyl-3,9-diazaspiro[5.5]undec-3-yl)-N-(2-ethylbutyl)benzamide;

4-[6-(9-cyclobutyl-3,9-diazaspiro[5.5]undec-3-yl)pyridazin-3-yl]-N-methylbenzamide;

2-(9-cyclobutyl-3,9-diazaspiro[5.5]undec-3-yl)-5,5'-bipyrimidine;

methyl 4-[2-(9-cyclobutyl-3,9-diazaspiro[5.5]undec-3-yl)pyrimidin-5-yl]benzoate;
 1-[2-(9-cyclobutyl-3,9-diazaspiro[5.5]undec-3-yl)pyrimidin-5-yl]ethanone;
 3-cyclobutyl-9-(6-pyridin-3-ylpyridazin-3-yl)-3,9-diazaspiro[5.5]undecane;
 3-cyclobutyl-9-(6-pyridin-4-ylpyridazin-3-yl)-3,9-diazaspiro[5.5]undecane;
 4-[2-(9-cyclobutyl-3,9-diazaspiro[5.5]undec-3-yl)pyrimidin-5-yl]-N-methylbenzamide;
 3-cyclobutyl-9-(5-{4-[(2-methylpyrrolidin-1-yl)carbonyl]phenyl}pyrimidin-2-yl)-3,9-diazaspiro[5.5]undecane;
 3-cyclobutyl-9-[6-(4-ethoxyphenyl)pyridazin-3-yl]-3,9-diazaspiro[5.5]undecane;
 3-cyclobutyl-9-(4-pyridin-4-ylphenyl)-3,9-diazaspiro[5.5]undecane;
 3-cyclobutyl-9-(4-pyrimidin-5-ylphenyl)-3,9-diazaspiro[5.5]undecane;
 3-cyclobutyl-9-[6-(6-methoxypyridin-3-yl)pyridazin-3-yl]-3,9-diazaspiro[5.5]undecane;
 3-cyclobutyl-9-(6-pyridin-2-ylpyridazin-3-yl)-3,9-diazaspiro[5.5]undecane;
 3-cyclobutyl-9-(6-pyrazin-2-ylpyridazin-3-yl)-3,9-diazaspiro[5.5]undecane;
 3-cyclobutyl-9-[6-(1,3-thiazol-2-yl)pyridazin-3-yl]-3,9-diazaspiro[5.5]undecane;
 3-cyclobutyl-9-[4-(pyrrolidin-1-ylmethyl)phenyl]-3,9-diazaspiro[5.5]undecane;
 3-cyclobutyl-9-[4-(3,6-dihydropyridin-1(2H)-ylmethyl)phenyl]-3,9-diazaspiro[5.5]undecane;
 3-cyclobutyl-9-[4-(piperidin-1-ylmethyl)phenyl]-3,9-diazaspiro[5.5]undecane;
 3-cyclobutyl-9-[4-(morpholin-4-ylmethyl)phenyl]-3,9-diazaspiro[5.5]undecane;
 3-cyclobutyl-9-{4-[(4-methylpiperidin-1-yl)methyl]phenyl}-3,9-diazaspiro[5.5]undecane;
 3-[4-(azepan-1-ylmethyl)phenyl]-9-cyclobutyl-3,9-diazaspiro[5.5]undecane;
 3-cyclobutyl-9-[4-(thiomorpholin-4-ylmethyl)phenyl]-3,9-diazaspiro[5.5]undecane;
 3-cyclobutyl-9-{4-[(3,5-dimethylpiperidin-1-yl)methyl]phenyl}-3,9-diazaspiro[5.5]undecane;
 3-cyclobutyl-9-{4-[(4aR,8aS)-octahydroisoquinolin-2(1H)-ylmethyl]phenyl}-3,9-diazaspiro[5.5]undecane;
 3-cyclobutyl-9-{4-[(4aS,8aS)-octahydroisoquinolin-2(1H)-ylmethyl]phenyl}-3,9-diazaspiro[5.5]undecane;
 3-cyclobutyl-9-{4-[(2,6-dimethylmorpholin-4-yl)methyl]phenyl}-3,9-diazaspiro[5.5]undecane;
 N-[4-(9-cyclobutyl-3,9-diazaspiro[5.5]undec-3-yl)benzyl]-N-ethylpropan-2-amine;
 3-cyclobutyl-9-{4-[(2-methylpiperidin-1-yl)methyl]phenyl}-3,9-diazaspiro[5.5]undecane;
 N-[4-(9-cyclobutyl-3,9-diazaspiro[5.5]undec-3-yl)benzyl]-N-methylcyclohexanamine;
 3-cyclobutyl-9-{4-[(2-ethylpiperidin-1-yl)methyl]phenyl}-3,9-diazaspiro[5.5]undecane;
 N-[4-(9-cyclobutyl-3,9-diazaspiro[5.5]undec-3-yl)benzyl]-N-ethylcyclohexanamine;
 3-cyclobutyl-9-[4-(octahydroquinolin-1(2H)-ylmethyl)phenyl]-3,9-diazaspiro[5.5]undecane;
 3-cyclobutyl-9-(4-{[(2S)-2-(methoxymethyl)pyrrolidin-1-yl]methyl}phenyl)-3,9-diazaspiro[5.5]undecane;
 3-cyclobutyl-9-(4-{[(2R)-2-(methoxymethyl)pyrrolidin-1-yl]methyl}phenyl)-3,9-diazaspiro[5.5]undecane;
 N-[4-(9-cyclobutyl-3,9-diazaspiro[5.5]undec-3-yl)benzyl]-N-(2-methoxyethyl)propan-2-amine;
 N-[4-(9-cyclobutyl-3,9-diazaspiro[5.5]undec-3-yl)benzyl]-2-methylbutan-1-amine;

N-[4-(9-cyclobutyl-3,9-diazaspiro[5.5]undec-3-yl)benzyl]prop-2-en-1-amine;
N-[4-(9-cyclobutyl-3,9-diazaspiro[5.5]undec-3-yl)benzyl]propan-1-amine;
1-[4-(9-cyclobutyl-3,9-diazaspiro[5.5]undec-3-yl)phenyl]-N-(cyclopropylmethyl)methanamine;
N-[4-(9-cyclobutyl-3,9-diazaspiro[5.5]undec-3-yl)benzyl]butan-1-amine;
N-[4-(9-cyclobutyl-3,9-diazaspiro[5.5]undec-3-yl)benzyl]-2-methylpropan-1-amine;
N-[4-(9-cyclobutyl-3,9-diazaspiro[5.5]undec-3-yl)benzyl]pentan-1-amine;
N-[4-(9-cyclobutyl-3,9-diazaspiro[5.5]undec-3-yl)benzyl]-3-methylbutan-1-amine;
N-[4-(9-cyclobutyl-3,9-diazaspiro[5.5]undec-3-yl)benzyl]cyclopropanamine;
N-[4-(9-cyclobutyl-3,9-diazaspiro[5.5]undec-3-yl)benzyl]cyclohexanamine;
N-[4-(9-cyclobutyl-3,9-diazaspiro[5.5]undec-3-yl)benzyl]propan-2-amine;
N-[4-(9-cyclobutyl-3,9-diazaspiro[5.5]undec-3-yl)benzyl]cyclobutanamine;
N-[4-(9-cyclobutyl-3,9-diazaspiro[5.5]undec-3-yl)benzyl]butan-2-amine;
N-[4-(9-cyclobutyl-3,9-diazaspiro[5.5]undec-3-yl)benzyl]cyclopentanamine;
N-[4-(9-cyclobutyl-3,9-diazaspiro[5.5]undec-3-yl)benzyl]pentan-2-amine;
N-[4-(9-cyclobutyl-3,9-diazaspiro[5.5]undec-3-yl)benzyl]cycloheptanamine;
1-[4-(9-cyclobutyl-3,9-diazaspiro[5.5]undec-3-yl)phenyl]-N-(cyclohexylmethyl)methanamine;
N-[4-(9-cyclobutyl-3,9-diazaspiro[5.5]undec-3-yl)benzyl]-2,2-dimethylpropan-1-amine;
N-[4-(9-cyclobutyl-3,9-diazaspiro[5.5]undec-3-yl)benzyl]-2-ethylbutan-1-amine;
3-cyclobutyl-9-[6-(2-methoxy-1,3-thiazol-4-yl)pyridazin-3-yl]-3,9-diazaspiro[5.5]undecane;
3-cyclobutyl-9-[5-(piperidin-1-ylmethyl)pyridin-2-yl]-3,9-diazaspiro[5.5]undecane;
3-cyclobutyl-9-[5-(pyridin-3-ylpyrimidin-2-yl)-3,9-diazaspiro[5.5]undecane;
ethyl 4-[6-(9-cyclobutyl-3,9-diazaspiro[5.5]undec-3-yl)pyridin-3-yl]piperazine-1-carboxylate;
3-[5-(4-acetyl)piperazin-1-yl]pyridin-2-yl]-9-cyclobutyl-3,9-diazaspiro[5.5]undecane;
1-[6-(9-cyclobutyl-3,9-diazaspiro[5.5]undec-3-yl)pyridin-3-yl]-N,N-diethylpiperidine-3-carboxamide;
3-{4-[6-(9-cyclobutyl-3,9-diazaspiro[5.5]undec-3-yl)pyridin-3-yl]piperazin-1-yl}-N,N-dimethylpropan-1-amine;
3-cyclobutyl-9-[5-(4-methylpiperazin-1-yl)pyridin-2-yl]-3,9-diazaspiro[5.5]undecane;
3-cyclobutyl-9-[5-[4-(2-methoxyethyl)piperazin-1-yl]pyridin-2-yl]-3,9-diazaspiro[5.5]undecane;
3-cyclobutyl-9-[5-(4-isopropylpiperazin-1-yl)pyridin-2-yl]-3,9-diazaspiro[5.5]undecane;
3-cyclobutyl-9-[5-(4-cyclopentylpiperazin-1-yl)pyridin-2-yl]-3,9-diazaspiro[5.5]undecane;
2-{4-[6-(9-cyclobutyl-3,9-diazaspiro[5.5]undec-3-yl)pyridin-3-yl]piperazin-1-yl}-N,N-dimethylethanamine;
3-cyclobutyl-9-[5-(4-ethylpiperazin-1-yl)pyridin-2-yl]-3,9-diazaspiro[5.5]undecane;
1-[6-(9-cyclobutyl-3,9-diazaspiro[5.5]undec-3-yl)pyridin-3-yl]-N,N-diethylpiperidin-4-amine;
3-cyclobutyl-9-[5-(4-morpholin-4-ylpiperidin-1-yl)pyridin-2-yl]-3,9-diazaspiro[5.5]undecane;
3-cyclobutyl-9-[5-(4-pyrrolidin-1-ylpiperidin-1-yl)pyridin-2-yl]-3,9-diazaspiro[5.5]undecane;
1'-[6-(9-cyclobutyl-3,9-diazaspiro[5.5]undec-3-yl)pyridin-3-yl]-1,4'-bipiperidine;

1-[6-(9-cyclobutyl-3,9-diazaspiro[5.5]undec-3-yl)pyridin-3-yl]-N,N-dimethylpiperidin-4-amine;
1-[6-(9-cyclobutyl-3,9-diazaspiro[5.5]undec-3-yl)pyridin-3-yl]-N,N-dimethylpyrrolidin-3-amine;
1-[6-(9-cyclobutyl-3,9-diazaspiro[5.5]undec-3-yl)pyridin-3-yl]-N,N-diethylpyrrolidin-3-amine;
6-(9-cyclobutyl-3,9-diazaspiro[5.5]undec-3-yl)-N-methyl-N-(1-methylpiperidin-4-yl)pyridin-3-amine;
1'-[6-(9-cyclobutyl-3,9-diazaspiro[5.5]undec-3-yl)pyridin-3-yl]-2-methyl-1,4'-bipiperidine;
1'-[6-(9-cyclobutyl-3,9-diazaspiro[5.5]undec-3-yl)pyridin-3-yl]-4-methyl-1,4'-bipiperidine;
2-{4-[6-(9-cyclobutyl-3,9-diazaspiro[5.5]undec-3-yl)pyridin-3-yl]piperazin-1-yl}-N,N-diethylethanamine;
3-cyclobutyl-9-(5-pyrrolidin-1-ylpyridin-2-yl)-3,9-diazaspiro[5.5]undecane;
3-cyclobutyl-9-(5-piperidin-1-ylpyridin-2-yl)-3,9-diazaspiro[5.5]undecane;
3-cyclobutyl-9-(5-morpholin-4-ylpyridin-2-yl)-3,9-diazaspiro[5.5]undecane;
3-cyclobutyl-9-[5-(4-methylpiperidin-1-yl)pyridin-2-yl]-3,9-diazaspiro[5.5]undecane;
3-cyclobutyl-9-{5-[(2S)-2-(methoxymethyl)pyrrolidin-1-yl]pyridin-2-yl}-3,9-diazaspiro[5.5]undecane;
3-cyclobutyl-9-{5-[(2R)-2-(methoxymethyl)pyrrolidin-1-yl]pyridin-2-yl}-3,9-diazaspiro[5.5]undecane;
3-cyclobutyl-9-(5-pyrimidin-5-ylpyridin-2-yl)-3,9-diazaspiro[5.5]undecane;
6-(9-cyclobutyl-3,9-diazaspiro[5.5]undec-3-yl)-3,3'-bipyridine;
6-(9-cyclobutyl-3,9-diazaspiro[5.5]undec-3-yl)-3,4'-bipyridine;
6'-(9-cyclobutyl-3,9-diazaspiro[5.5]undec-3-yl)-2,3'-bipyridine;
5-(9-cyclobutyl-3,9-diazaspiro[5.5]undec-3-yl)-2,5'-bipyrimidine;
3-cyclobutyl-9-[5-(morpholin-4-ylmethyl)pyridin-2-yl]-3,9-diazaspiro[5.5]undecane;
3-cyclobutyl-9-{5-[4-(2-phenylethyl)piperazin-1-yl]pyridin-2-yl}-3,9-diazaspiro[5.5]undecane;
3-cyclobutyl-9-{5-[4-(1-phenylethyl)piperazin-1-yl]pyridin-2-yl}-3,9-diazaspiro[5.5]undecane;
3-cyclobutyl-9-[5-(4-phenylpiperazin-1-yl)pyridin-2-yl]-3,9-diazaspiro[5.5]undecane;
N-[6-(9-cyclobutyl-3,9-diazaspiro[5.5]undec-3-yl)pyridin-3-yl]-N,N',N'-trimethylpropane-1,3-diamine;
3-cyclobutyl-9-{5-[4-(4-fluorophenyl)piperazin-1-yl]pyridin-2-yl}-3,9-diazaspiro[5.5]undecane;
3-cyclobutyl-9-{5-[4-(4-methoxyphenyl)piperazin-1-yl]pyridin-2-yl}-3,9-diazaspiro[5.5]undecane;
3-cyclobutyl-9-[5-(3,5-dimethylpiperidin-1-yl)pyridin-2-yl]-3,9-diazaspiro[5.5]undecane;
3-[5-(4-benzylpiperazin-1-yl)pyridin-2-yl]-9-cyclobutyl-3,9-diazaspiro[5.5]undecane;
1-[6-(9-cyclobutyl-3,9-diazaspiro[5.5]undec-3-yl)pyridin-3-yl]-N,N-dipropylpiperidin-4-amine;
3-cyclobutyl-9-[4-(1-methyl-1H-pyrazol-4-yl)phenyl]-3,9-diazaspiro[5.5]undecane;
3-cyclobutyl-9-(4-pyridin-3-ylphenyl)-3,9-diazaspiro[5.5]undecane;
3-cyclobutyl-9-(6-phenylpyridazin-3-yl)-3,9-diazaspiro[5.5]undecane;
3-[6-(3-chlorophenyl)pyridazin-3-yl]-9-cyclobutyl-3,9-diazaspiro[5.5]undecane;
3-[6-(4-chlorophenyl)pyridazin-3-yl]-9-cyclobutyl-3,9-diazaspiro[5.5]undecane;
3-cyclobutyl-9-[6-(4-fluorophenyl)pyridazin-3-yl]-3,9-diazaspiro[5.5]undecane;

3-cyclobutyl-9-[6-(3-fluorophenyl)pyridazin-3-yl]-3,9-diazaspiro[5.5]undecane;
3-cyclobutyl-9-[6-(2-fluorophenyl)pyridazin-3-yl]-3,9-diazaspiro[5.5]undecane;
3-cyclobutyl-9-[6-(2-naphthyl)pyridazin-3-yl]-3,9-diazaspiro[5.5]undecane;
3-cyclobutyl-9-[6-(2-fluoro-4-methylphenyl)pyridazin-3-yl]-3,9-diazaspiro[5.5]undecane;
3-cyclobutyl-9-[6-(2-fluoro-5-methylphenyl)pyridazin-3-yl]-3,9-diazaspiro[5.5]undecane;
3-cyclobutyl-9-[6-(3-fluoro-4-methylphenyl)pyridazin-3-yl]-3,9-diazaspiro[5.5]undecane;
3-cyclobutyl-9-[6-(4-fluoro-3-methylphenyl)pyridazin-3-yl]-3,9-diazaspiro[5.5]undecane;
3-cyclobutyl-9-[6-(3-methylphenyl)pyridazin-3-yl]-3,9-diazaspiro[5.5]undecane;
3-cyclobutyl-9-[6-(4-methylphenyl)pyridazin-3-yl]-3,9-diazaspiro[5.5]undecane;
3-cyclobutyl-9-[6-(3-isopropylphenyl)pyridazin-3-yl]-3,9-diazaspiro[5.5]undecane;
3-cyclobutyl-9-[6-(4-isopropylphenyl)pyridazin-3-yl]-3,9-diazaspiro[5.5]undecane;
3-cyclobutyl-9-[6-(3,4-dimethylphenyl)pyridazin-3-yl]-3,9-diazaspiro[5.5]undecane;
3-[6-(4-butylphenyl)pyridazin-3-yl]-9-cyclobutyl-3,9-diazaspiro[5.5]undecane;
3-cyclobutyl-9-[6-(3,5-dimethylphenyl)pyridazin-3-yl]-3,9-diazaspiro[5.5]undecane;
3-cyclobutyl-9-[6-(4-ethylphenyl)pyridazin-3-yl]-3,9-diazaspiro[5.5]undecane;
3-cyclobutyl-9-[6-(4-propylphenyl)pyridazin-3-yl]-3,9-diazaspiro[5.5]undecane;
3-cyclobutyl-9-[6-(3-ethylphenyl)pyridazin-3-yl]-3,9-diazaspiro[5.5]undecane;
3-[6-(4-tert-butylphenyl)pyridazin-3-yl]-9-cyclobutyl-3,9-diazaspiro[5.5]undecane;
3-cyclobutyl-9-[6-(3-methoxyphenyl)pyridazin-3-yl]-3,9-diazaspiro[5.5]undecane;
3-cyclobutyl-9-[6-[4-(trifluoromethoxy)phenyl]pyridazin-3-yl]-3,9-diazaspiro[5.5]undecane;
3-cyclobutyl-9-[6-(3-ethoxyphenyl)pyridazin-3-yl]-3,9-diazaspiro[5.5]undecane;
3-cyclobutyl-9-[6-(4-phenoxyphenyl)pyridazin-3-yl]-3,9-diazaspiro[5.5]undecane;
3-cyclobutyl-9-[6-[3-(trifluoromethoxy)phenyl]pyridazin-3-yl]-3,9-diazaspiro[5.5]undecane;
3-cyclobutyl-9-[6-[3-(methylthio)phenyl]pyridazin-3-yl]-3,9-diazaspiro[5.5]undecane;
3-cyclobutyl-9-[6-(4'-methoxybiphenyl-4-yl)pyridazin-3-yl]-3,9-diazaspiro[5.5]undecane;
3-cyclobutyl-9-[6-(3-fluoro-4-methoxyphenyl)pyridazin-3-yl]-3,9-diazaspiro[5.5]undecane;
3-cyclobutyl-9-[6-(2,5-difluoro-4-methoxyphenyl)pyridazin-3-yl]-3,9-diazaspiro[5.5]undecane;
3-cyclobutyl-9-[6-(6-methoxy-2-naphthyl)pyridazin-3-yl]-3,9-diazaspiro[5.5]undecane;
3-cyclobutyl-9-[6-(3-isopropoxyphenyl)pyridazin-3-yl]-3,9-diazaspiro[5.5]undecane;
3-cyclobutyl-9-[6-(3,4,5-trimethoxyphenyl)pyridazin-3-yl]-3,9-diazaspiro[5.5]undecane;
3-cyclobutyl-9-[6-(4-methoxyphenyl)pyridazin-3-yl]-3,9-diazaspiro[5.5]undecane;
3-[6-(1,3-benzodioxol-5-yl)pyridazin-3-yl]-9-cyclobutyl-3,9-diazaspiro[5.5]undecane;
3-cyclobutyl-9-[6-(3,4-dimethoxyphenyl)pyridazin-3-yl]-3,9-diazaspiro[5.5]undecane;
4-[6-(9-cyclobutyl-3,9-diazaspiro[5.5]undec-3-yl)pyridazin-3-yl]-N,N-dimethylaniline;
3-cyclobutyl-9-[6-(2,3-dihydro-1,4-benzodioxin-6-yl)pyridazin-3-yl]-3,9-diazaspiro[5.5]undecane;
3-[6-(9-cyclobutyl-3,9-diazaspiro[5.5]undec-3-yl)pyridazin-3-yl]-N,N-dimethylaniline;
3-cyclobutyl-9-[6-(4-methoxy-3-methylphenyl)pyridazin-3-yl]-3,9-diazaspiro[5.5]undecane;

3-cyclobutyl-9-[6-(4-propoxyphenyl)pyridazin-3-yl]-3,9-diazaspiro[5.5]undecane;
3-cyclobutyl-9-[6-(4-methoxy-2-methylphenyl)pyridazin-3-yl]-3,9-diazaspiro[5.5]undecane;
3-cyclobutyl-9-[6-(2-methoxyphenyl)pyridazin-3-yl]-3,9-diazaspiro[5.5]undecane;
3-cyclobutyl-9-[6-(5-isopropyl-2-methoxyphenyl)pyridazin-3-yl]-3,9-diazaspiro[5.5]undecane;
3-[6-(5-chloro-2-methoxyphenyl)pyridazin-3-yl]-9-cyclobutyl-3,9-diazaspiro[5.5]undecane;
3-cyclobutyl-9-[6-(2,5-dimethoxyphenyl)pyridazin-3-yl]-3,9-diazaspiro[5.5]undecane;
3-cyclobutyl-9-[6-(2,4-dimethoxyphenyl)pyridazin-3-yl]-3,9-diazaspiro[5.5]undecane;
3-cyclobutyl-9-[6-(2-ethoxyphenyl)pyridazin-3-yl]-3,9-diazaspiro[5.5]undecane;
3-cyclobutyl-9-[6-(6-dibenzo[b,d]furan-4-yl)pyridazin-3-yl]-3,9-diazaspiro[5.5]undecane;
3-cyclobutyl-9-[6-(5-fluoro-2-methoxyphenyl)pyridazin-3-yl]-3,9-diazaspiro[5.5]undecane;
3-cyclobutyl-9-[6-(2-methoxy-5-methylphenyl)pyridazin-3-yl]-3,9-diazaspiro[5.5]undecane;
3-cyclobutyl-9-[6-(2-phenoxyphenyl)pyridazin-3-yl]-3,9-diazaspiro[5.5]undecane;
3-[6-(3-chloro-4-fluorophenyl)pyridazin-3-yl]-9-cyclobutyl-3,9-diazaspiro[5.5]undecane;
3-cyclobutyl-9-[6-(2,5-difluorophenyl)pyridazin-3-yl]-3,9-diazaspiro[5.5]undecane;
3-cyclobutyl-9-[6-(2,4-difluorophenyl)pyridazin-3-yl]-3,9-diazaspiro[5.5]undecane;
3-cyclobutyl-9-[6-(3,4-difluorophenyl)pyridazin-3-yl]-3,9-diazaspiro[5.5]undecane;
3-cyclobutyl-9-[6-(3,5-dichlorophenyl)pyridazin-3-yl]-3,9-diazaspiro[5.5]undecane;
3-[6-(4-chloro-2-fluorophenyl)pyridazin-3-yl]-9-cyclobutyl-3,9-diazaspiro[5.5]undecane;
3-[6-(4-chloro-3-fluorophenyl)pyridazin-3-yl]-9-cyclobutyl-3,9-diazaspiro[5.5]undecane;
3-cyclobutyl-9-[6-(2,6-difluorophenyl)pyridazin-3-yl]-3,9-diazaspiro[5.5]undecane;
3-cyclobutyl-9-[6-(3,4-dichlorophenyl)pyridazin-3-yl]-3,9-diazaspiro[5.5]undecane;
3-cyclobutyl-9-[6-(3,5-difluorophenyl)pyridazin-3-yl]-3,9-diazaspiro[5.5]undecane;
3-cyclobutyl-9-[6-(2,3-difluorophenyl)pyridazin-3-yl]-3,9-diazaspiro[5.5]undecane;
3-[6-(2-chlorophenyl)pyridazin-3-yl]-9-cyclobutyl-3,9-diazaspiro[5.5]undecane;
3-cyclobutyl-9-[6-(2,4-dichlorophenyl)pyridazin-3-yl]-3,9-diazaspiro[5.5]undecane;
3-cyclobutyl-9-[6-[2-(trifluoromethyl)phenyl]pyridazin-3-yl]-3,9-diazaspiro[5.5]undecane;
3-cyclobutyl-9-[6-(2,6-dimethoxyphenyl)pyridazin-3-yl]-3,9-diazaspiro[5.5]undecane;
3-cyclobutyl-9-[6-(2-isopropylphenyl)pyridazin-3-yl]-3,9-diazaspiro[5.5]undecane;
3-cyclobutyl-9-[6-(2,6-dimethylphenyl)pyridazin-3-yl]-3,9-diazaspiro[5.5]undecane;
3-cyclobutyl-9-[6-(2,5-dichlorophenyl)pyridazin-3-yl]-3,9-diazaspiro[5.5]undecane;
3-[6-(2-chloro-6-fluoro-3-methylphenyl)pyridazin-3-yl]-9-cyclobutyl-3,9-diazaspiro[5.5]undecane;
3-cyclobutyl-9-(6-mesitylpyridazin-3-yl)-3,9-diazaspiro[5.5]undecane;
3-[6-(9-cyclobutyl-3,9-diazaspiro[5.5]undec-3-yl)pyridazin-3-yl]benzonitrile;
4-[6-(9-cyclobutyl-3,9-diazaspiro[5.5]undec-3-yl)pyridazin-3-yl]benzonitrile;
3-cyclobutyl-9-[6-[4-(trifluoromethyl)phenyl]pyridazin-3-yl]-3,9-diazaspiro[5.5]undecane;
1-{3-[6-(9-cyclobutyl-3,9-diazaspiro[5.5]undec-3-yl)pyridazin-3-yl]phenyl}ethanone;
3-{6-[3,5-bis(trifluoromethyl)phenyl]pyridazin-3-yl}-9-cyclobutyl-3,9-diazaspiro[5.5]undecane;

3-cyclobutyl-9-{6-[3-(trifluoromethyl)phenyl]pyridazin-3-yl}-3,9-diazaspiro[5.5]undecane;
3-{6-[4-chloro-3-(trifluoromethyl)phenyl]pyridazin-3-yl}-9-cyclobutyl-3,9-diazaspiro[5.5]undecane;
3-{6-[2-chloro-5-(trifluoromethyl)phenyl]pyridazin-3-yl}-9-cyclobutyl-3,9-diazaspiro[5.5]undecane;
ethyl 4-[6-(9-cyclobutyl-3,9-diazaspiro[5.5]undec-3-yl)pyridazin-3-yl]benzoate;
ethyl 3-[6-(9-cyclobutyl-3,9-diazaspiro[5.5]undec-3-yl)pyridazin-3-yl]benzoate;
3-cyclobutyl-9-(2-pyridin-3-ylpyrimidin-5-yl)-3,9-diazaspiro[5.5]undecane;
3-cyclobutyl-9-[6-(1-methyl-1H-pyrazol-4-yl)pyridazin-3-yl]-3,9-diazaspiro[5.5]undecane;
3-cyclobutyl-9-[6-(5-methoxypyridin-3-yl)pyridazin-3-yl]-3,9-diazaspiro[5.5]undecane;
3-cyclobutyl-9-[6-(1-methyl-1H-benzimidazol-5-yl)pyridazin-3-yl]-3,9-diazaspiro[5.5]undecane;
3-cyclobutyl-9-[6-(6-isopropyl-2-methoxypyridin-3-yl)pyridazin-3-yl]-3,9-diazaspiro[5.5]undecane;
3-(3-bromophenyl)-9-cyclobutyl-3,9-diazaspiro[5.5]undecane;
1-[4-(9-cyclobutyl-3,9-diazaspiro[5.5]undec-3-yl)-3-fluorophenyl]ethanone;
3-cyclobutyl-9-(6-pyrimidin-5-ylpyridin-3-yl)-3,9-diazaspiro[5.5]undecane;
3-cyclobutyl-9-[5-(pyrrolidin-1-ylmethyl)pyridin-2-yl]-3,9-diazaspiro[5.5]undecane;
3-cyclobutyl-9-{5-[(4,4-difluoropiperidin-1-yl)methyl]pyridin-2-yl}-3,9-diazaspiro[5.5]undecane;
4-(9-isopropyl-3,9-diazaspiro[5.5]undec-3-yl)-N-methylbenzamide;
3-cyclobutyl-9-{5-[(4-fluoropiperidin-1-yl)methyl]pyridin-2-yl}-3,9-diazaspiro[5.5]undecane;
1-[6-(9-cyclobutyl-3,9-diazaspiro[5.5]undec-3-yl)pyridin-3-yl]-N,N-dimethylmethanamine;
1-[4-(9-cyclobutyl-3,9-diazaspiro[5.5]undec-3-yl)-3,5-difluorophenyl]ethanone;
3-cyclobutyl-9-[3-(1-methyl-1H-pyrazol-4-yl)phenyl]-3,9-diazaspiro[5.5]undecane;
3-cyclobutyl-9-(3-pyrimidin-5-ylphenyl)-3,9-diazaspiro[5.5]undecane;
3-(9-cyclobutyl-3,9-diazaspiro[5.5]undec-3-yl)benzonitrile;
1-[4-(9-cyclobutyl-3,9-diazaspiro[5.5]undec-3-yl)-2-methoxyphenyl]ethanone;
1-[4-(9-cyclobutyl-3,9-diazaspiro[5.5]undec-3-yl)-3-methoxyphenyl]ethanone;
N-methyl-4-[9-(tetrahydro-2H-pyran-4-yl)-3,9-diazaspiro[5.5]undec-3-yl]benzamide;
4-(9-ethyl-3,9-diazaspiro[5.5]undec-3-yl)-N-methylbenzamide;
[6-(9-cyclobutyl-3,9-diazaspiro[5.5]undec-3-yl)pyridin-3-yl]methanol;
3-[6-(9-cyclobutyl-3,9-diazaspiro[5.5]undec-3-yl)pyridazin-3-yl]-1-methylpyridin-2(1H)-one;
5-[6-(9-cyclobutyl-3,9-diazaspiro[5.5]undec-3-yl)pyridazin-3-yl]-1-methylpyridin-2(1H)-one;
3-[4-(9-cyclobutyl-3,9-diazaspiro[5.5]undec-3-yl)phenyl]-1-methylpyridin-2(1H)-one;
5-[4-(9-cyclobutyl-3,9-diazaspiro[5.5]undec-3-yl)phenyl]-1-methylpyridin-2(1H)-one;
3-(2-methylcyclopentyl)-9-(6-pyrazin-2-ylpyridazin-3-yl)-3,9-diazaspiro[5.5]undecane;
3-ethyl-9-(6-pyrazin-2-ylpyridazin-3-yl)-3,9-diazaspiro[5.5]undecane;
6-(9-cyclobutyl-3,9-diazaspiro[5.5]undec-3-yl)-3,3'-bipyridazine;
N-methyl-4-[9-(2-methylcyclopentyl)-3,9-diazaspiro[5.5]undec-3-yl]benzamide;
3-cyclobutyl-9-(6-imidazo[1,2-a]pyridin-6-ylpyridazin-3-yl)-3,9-diazaspiro[5.5]undecane;
3-cyclobutyl-9-[6-(1H-indazol-5-yl)pyridazin-3-yl]-3,9-diazaspiro[5.5]undecane;

5-[4-(9-cyclobutyl-3,9-diazaspiro[5.5]undec-3-yl)phenyl]-1-methylpyrimidin-2(1H)-one;
4-(9-cyclobutyl-3,9-diazaspiro[5.5]undec-3-yl)-N-(tetrahydro-2H-pyran-4-yl)benzamide;
4-(9-cyclobutyl-3,9-diazaspiro[5.5]undec-3-yl)-N-(tetrahydro-2H-pyran-4-ylmethyl)benzamide;
6-[4-(9-cyclobutyl-3,9-diazaspiro[5.5]undec-3-yl)phenyl]-1-methylpyridin-2(1H)-one;
4-(9-cyclobutyl-3,9-diazaspiro[5.5]undec-3-yl)-N-(pyridin-4-ylmethyl)benzamide;
4-(9-cyclobutyl-3,9-diazaspiro[5.5]undec-3-yl)-3-fluoro-N-methylbenzamide;
4-[4-(9-cyclobutyl-3,9-diazaspiro[5.5]undec-3-yl)phenyl]-1-methylpyridin-2(1H)-one;
3-cyclobutyl-9-[4-(1H-pyrazol-1-ylmethyl)phenyl]-3,9-diazaspiro[5.5]undecane;
4-(9-cyclobutyl-3,9-diazaspiro[5.5]undec-3-yl)-N-pyridin-2-ylbenzamide;
4-(9-cyclobutyl-3,9-diazaspiro[5.5]undec-3-yl)-N,N-dimethylbenzamide;
5-[4-(9-cyclobutyl-3,9-diazaspiro[5.5]undec-3-yl)phenyl]-1-ethylpyridin-2(1H)-one;
5-[4-(9-cyclobutyl-3,9-diazaspiro[5.5]undec-3-yl)phenyl]-1-propylpyridin-2(1H)-one;
5-[4-(9-cyclobutyl-3,9-diazaspiro[5.5]undec-3-yl)phenyl]-1-isopropylpyridin-2(1H)-one;
5-[4-(9-cyclobutyl-3,9-diazaspiro[5.5]undec-3-yl)phenyl]-1-(2,2,2-trifluoroethyl)pyridin-2(1H)-one;
3-cyclobutyl-9-(5-[1,2,4]triazolo[4,3-a]pyridin-6-ylpyridin-2-yl)-3,9-diazaspiro[5.5]undecane;
6'-(9-cyclobutyl-3,9-diazaspiro[5.5]undec-3-yl)-N-methyl-2,3'-bipyridine-5-carboxamide;
3-cyclobutyl-9-(4-[1,2,4]triazolo[4,3-a]pyridin-6-ylphenyl)-3,9-diazaspiro[5.5]undecane;
7-[4-(9-cyclobutyl-3,9-diazaspiro[5.5]undec-3-yl)phenyl]-N-methylimidazo[1,2-a]pyridine-2-carboxamide;
7-[6-(9-cyclobutyl-3,9-diazaspiro[5.5]undec-3-yl)pyridin-3-yl]-N-methylimidazo[1,2-a]pyridine-2-carboxamide;
4-(9-cyclobutyl-3,9-diazaspiro[5.5]undec-3-yl)benzamide;
4-(9-cyclobutyl-3,9-diazaspiro[5.5]undec-3-yl)-N,2-dimethylbenzamide;
2-chloro-4-(9-cyclobutyl-3,9-diazaspiro[5.5]undec-3-yl)-N-methylbenzamide;
4-(9-cyclobutyl-3,9-diazaspiro[5.5]undec-3-yl)-N-methyl-1-naphthamide;
4-(9-cyclobutyl-3,9-diazaspiro[5.5]undec-3-yl)-N-methyl-2-(trifluoromethyl)benzamide;
3-cyclobutyl-9-(4-[1,2,4]triazolo[4,3-b]pyridazin-6-ylphenyl)-3,9-diazaspiro[5.5]undecane;
3-cyclobutyl-9-(5-[1,2,4]triazolo[4,3-b]pyridazin-6-ylpyridin-2-yl)-3,9-diazaspiro[5.5]undecane;
3-cyclobutyl-9-(5-imidazo[1,2-a]pyrimidin-6-ylpyridin-2-yl)-3,9-diazaspiro[5.5]undecane;
3-cyclobutyl-9-(4-{[2-(3-fluoropyridin-2-yl)-1H-imidazol-1-yl]methyl}phenyl)-3,9-diazaspiro[5.5]undecane;
4-(9-cyclobutyl-3,9-diazaspiro[5.5]undec-3-yl)-2-fluoro-N-methylbenzamide;
1-[4-(9-cyclobutyl-3,9-diazaspiro[5.5]undec-3-yl)benzyl]pyrrolidin-2-one;
6-[9-(3,3-difluorocyclobutyl)-3,9-diazaspiro[5.5]undec-3-yl]-N-methylnicotinamide;
8-(6-chloropyridazin-3-yl)-2-cyclobutyl-2,8-diazaspiro[4.5]decane;
1-[6-(2-cyclobutyl-2,8-diazaspiro[4.5]dec-8-yl)pyridin-3-yl]ethanone;
6-(2-cyclobutyl-2,8-diazaspiro[4.5]dec-8-yl)-6'-methoxy-3,3'-bipyridine;
2-cyclobutyl-8-(6-pyridin-4-ylpyridazin-3-yl)-2,8-diazaspiro[4.5]decane;

2-cyclobutyl-8-[6-(6-methoxypyridin-3-yl)pyridazin-3-yl]-2,8-diazaspiro[4.5]decane;
2-(6-chloropyridazin-3-yl)-8-cyclobutyl-2,8-diazaspiro[4.5]decane;
1-[6-(8-cyclobutyl-2,8-diazaspiro[4.5]dec-2-yl)pyridin-3-yl]ethanone;
8-cyclobutyl-2-(6-pyridin-3-ylpyridazin-3-yl)-2,8-diazaspiro[4.5]decane;
8-cyclobutyl-2-(6-pyridin-4-ylpyridazin-3-yl)-2,8-diazaspiro[4.5]decane;
8-cyclobutyl-2-(4-pyridin-3-ylphenyl)-2,8-diazaspiro[4.5]decane; or
2-cyclobutyl-8-(4-pyridin-3-ylphenyl)-2,8-diazaspiro[4.5]decane.