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(54) **N-ARYL DIAZASPIROCYCLIC COMPOUNDS AND METHODS OF PREPARATION AND USE THEREOF**

N-ARYL DIAZASPIROZYKLISCHE VERBINDUNGEN, DEREN VERWENDUNG UND DAS VERFAHREN ZU IHREN HERSTELLUNG

COMPOSES DIAZASPIROCYCLIQUES N-ARYLE ET PROCEDES DE PREPARATION ET D'UTILISATION DE CES DERNIERS

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**WO-A-03/032997 GB-A- 2 142 332**
- **MEHROTRA, MUKUND M. ET AL: "Spirocyclic nonpeptide glycoprotein IIb-IIIa antagonists. Part 3: synthesis and SAR of potent and specific 2,8-diazaspiro[4.5]decanes" BIOORGANIC & MEDICINAL CHEMISTRY LETTERS (2002), 12(7), 1103-1107 , XP002257526**

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- SMYTH, M. S. ET AL: "Spirocyclic non-peptide glycoprotein IIb-IIIa antagonists. Part 1: design of potent and specific 3,9-diazaspiro[5.5]undecanes" BIOORGANIC & MEDICINAL CHEMISTRY LETTERS (2001), 11(10), 1289-1292 , XP002257527
- DATABASE WPI Derwent Publications Ltd., London, GB; AN 2001-607404 XP002257528 & WO 01 66546 A
- MULLEN G ET AL:  
"(-)-SPIROL1AZABICYCLO2.2.2OCTANE-3,5'-OXA ZOLIDIN-2'-ONE, A CONFORMATIONALLY RESTRICTED ANALOGUE OF ACETYLCHOLINE, IS A HIGHLY SELECTIVE FULL AGONIST AT THE ALPHA7 NICOTINIC ACETYLCHOLINE RECEPTOR" JOURNAL OF MEDICINAL CHEMISTRY, AMERICAN CHEMICAL SOCIETY. WASHINGTON, US, vol. 43, no. 22, 2000, pages 4045-4050, XP002940689 ISSN: 0022-2623

**Description****Field of the Invention**

5 **[0001]** The present invention relates to pharmaceutical compositions incorporating compounds capable of affecting nicotinic cholinergic receptors, for example, as modulators of specific nicotinic receptor subtypes. The present invention also relates to methods for treating a wide variety of conditions and disorders, particularly those associated with dysfunction of the central and autonomic nervous systems.

**Background of the Invention**

10 **[0002]** Nicotine exhibits a variety of pharmacological effects (Pullan et al., N. Engl. J. Med. 330:811-815 (1994)), some of which are due to neurotransmitter release (See, for example, Sjak-shie et al., Brain Res. 624:295 (1993), where neuroprotective effects of nicotine are proposed). For example, acetylcholine, dopamine, norepinephrine, serotonin and glutamate are released by neurons upon administration of nicotine (Rowell et al., J. Neurochem. 43:1593 (1984); Rapier et al., J. Neurochem. 50:1123 (1988); Sandor et al., Brain Res. 567:313 (1991) and Vizi, Br. J. Pharmacol. 47:765 (1973), (Hall et al., Biochem. Pharmacol. 21:1829 (1972), (Hery et al., Arch. Int. Pharmacodyn. Ther. 296:91 (1977)), and Toth et al., Neurochem Res. 17:265 (1992)). Confirmatory reports and additional recent studies show that nicotine administration modulates glutamate, nitric oxide, GABA, tatykinins, cytokines and peptides in the central nervous system (CNS) (reviewed in Brioni et al., Adv. Pharmacol. 37:153 (1997)). Nicotine also reportedly potentiates the pharmacological behavior of certain pharmaceutical compositions used to treat certain disorders. See, for example, Sanberg et al., Pharmacol. Biochem. & Behavior 46:303 (1993); Harsing et al., J. Neurochem. 59:48 (1993) and Hughes, Proceedings from Intl. Symp. Nic. S40 (1994). Various additional beneficial pharmacological effects of nicotine have been proposed. See, for example, Decina et al., Biol. Psychiatry 28:502 (1990); Wagner et al., Pharmacopsychiatry 21:301 (1988); Pomerleau et al., Addictive Behaviors 9:265 (1984); Onaivi et al., Life Sci. 54(3):193 (1994); Tripathi et al., J. Pharmacol. Exp. Ther. 221:91 (1982) and Hamon, Trends in Pharmacol. Res. 15:36 (1994).

25 **[0003]** In addition to nicotine itself, a variety of nicotinic compounds are purportedly useful for treating a wide variety of conditions and disorders. See, for example, Williams et al., Drug News Perspec. 7(4):205 (1994); Arneric et al., CNS Drug Rev. 1(1):1 (1995); Arneric et al., Exp. Opin. Invest. Drugs 5(1):79 (1996); Bencherif et al., J. Pharmacol. Exp. Ther. 279:1413 (1996); Lippiello et al., J. Pharmacol. Exp. Ther. 279:1422 (1996); Damaj et al., Neuroscience (1997) J. Pharmacol. Exp. Ther. 291:390 (1999); Chiari et al., Anesthesiology 91:1447 (1999); Lavand'homme and Eisenbach, Anesthesiology 91:1455 (1999); Holladay et al., J. Med. ChemChem. 40(28): 4169 (1997); Bannon et al., Science 279: 77 (1998); PCT WO 94/08992, PCT WO 96/31475, PCT WO 96/40682, and U.S. Patent Nos. 5,583,140 to Bencherif et al., 5,597,919 to Dull et al., 5,604,231 to Smith et al. and 5,852,041 to Cosford et al.

35 **[0004]** Nicotine and various nicotinic compounds are reportedly useful for treating a wide variety of CNS disorders. See, for example, U.S. Patent Nos. 5,1871,166 to Kikuchi et al., 5,672,601 to Cignarella, PCT WO 99/21834 and PCT WO 97/40049, UK Patent Application GB 2295387 and European Patent Application 297,858. CNS disorders are a type of neurological disorder. They can be drug induced; attributed to genetic predisposition, infection or trauma; or of unknown etiology. CNS disorders include neuropsychiatric disorders, neurological diseases and mental illnesses, and include neurodegenerative diseases, behavioral disorders, cognitive disorders and cognitive affective disorders. There are several CNS disorders whose clinical manifestations have been attributed to CNS dysfunction (i.e., disorders resulting from inappropriate levels of neurotransmitter release, inappropriate properties of neurotransmitter receptors, and/or inappropriate interaction between neurotransmitters and neurotransmitter receptors). Several CNS disorders can be attributed to a deficiency of choline, dopamine, norepinephrine and/or serotonin.

40 **[0005]** Relatively common CNS disorders include pre-senile dementia (early-onset Alzheimer's disease), senile dementia (dementia of the Alzheimer's type), micro-infarct dementia, AIDS-related dementia, Creutzfeld-Jakob disease, Pick's disease, Parkinsonism including Parkinson's disease, progressive supranuclear palsy, Huntington's chorea, tardive dyskinesia, hyperkinesia, mania, attention deficit disorder, anxiety, dyslexia, schizophrenia, depression, obsessive-compulsive disorders and Tourette's syndrome.

45 **[0006]** A limitation of some nicotinic compounds is that they are associated with various undesirable side effects, for example, by stimulating muscle and ganglionic receptors. It would be desirable to have compounds, compositions and methods for preventing and/or treating various conditions or disorders (e.g., CNS disorders), including alleviating the symptoms of these disorders, where the compounds exhibit nicotinic pharmacology with a beneficial effect (e.g., upon the functioning of the CNS), but without significant associated side effects. It would further be highly desirable to provide compounds, compositions and methods that effect CNS function without significantly effecting those receptor subtypes which have the potential to induce undesirable side effects (e.g., appreciable activity at cardiovascular and skeletal muscle sites). The present invention provides such compounds, compositions and methods.

## Summary of the Invention

**[0007]** The invention provides a compound according to claim 1, a composition according to claim 2 and a use according to claims 12, 16, 17, 18, 20, 22 and 24.

**[0008]** Compounds, pharmaceutical compositions including the compounds, and methods of preparation and use thereof are disclosed. The compounds are N-aryl diazaspirocyclic compounds, or prodrugs or metabolites of these compounds. The aryl group can be a five- or six-membered heterocyclic ring (heteroaryl). Examples of the N-aryl diazaspirocyclic compounds include 7-(3-pyridyl)-1,7-diazaspiro[4.4]nonane and 1-(3-pyridyl)-1,7-diazaspiro[4.4]nonane.

**[0009]** The compounds and compositions of the invention can be used to treat and/or prevent a wide variety of conditions or disorders, particularly those disorders characterized by dysfunction of nicotinic cholinergic neurotransmission, including disorders involving neuromodulation of neurotransmitter release, such as dopamine release. CNS disorders, which are characterized by an alteration in normal neurotransmitter release, are another example of disorders that can be treated and/or prevented. The compounds and compositions can also be used to alleviate pain. The methods involve administering to a subject an effective amount of a compound of the invention or prodrug or metabolite thereof to alleviate the particular disorder.

**[0010]** The pharmaceutical compositions include an effective amount of the compounds described herein. When employed in effective amounts, the compounds can interact with relevant nicotinic receptor sites of a subject and act as a therapeutic agent to prevent and/or treat a wide variety of conditions and disorders, particularly those disorders characterized by an alteration in normal neurotransmitter release. The pharmaceutical compositions provide therapeutic benefit to individuals suffering from such disorders and exhibiting clinical manifestations of such disorders. When employed in effective amounts, the compounds have the potential to: (i) exhibit nicotinic pharmacology and affect relevant nicotinic receptors sites (e.g., bind to nicotinic acetylcholine receptors and modulate their function, and/or (ii) modulate neurotransmitter secretion and thus prevent and suppress the symptoms associated with those diseases. In addition, the compounds can: (i) alter the number of nicotinic cholinergic receptors of the brain of the patient, (ii) exhibit neuroprotective effects and (iii) when employed in effective amounts, not result in appreciable adverse side effects (e.g., side effects such as significant increases in blood pressure and heart rate, significant negative effects upon the gastrointestinal tract, and significant effects upon skeletal muscle). The pharmaceutical compositions are believed to be safe and effective with regards to prevention and treatment of a wide variety of conditions and disorders.

**[0011]** The foregoing and other aspects of the present invention are explained in detail in the detailed description and examples set forth below.

## Detailed Description of the Invention

**[0012]** Compounds, pharmaceutical compositions including the compounds, and methods of preparation and use thereof are disclosed.

**[0013]** The following definitions will be useful in understanding the metes and bounds of the invention as described herein.

**[0014]** As used herein, "alkyl" refers to straight chain or branched alkyl radicals including C<sub>1</sub>-C<sub>8</sub>, preferably C<sub>1</sub>-C<sub>5</sub>, such as methyl, ethyl, or isopropyl; "substituted alkyl" refers to alkyl radicals further bearing one or more substituent groups such as hydroxy, alkoxy, aryloxy, mercapto, aryl, heterocyclo, halo, amino, carboxyl, carbamyl, cyano, and the like; "alkenyl" refers to straight chain or branched hydrocarbon radicals including C<sub>1</sub>-C<sub>8</sub>, preferably C<sub>1</sub>-C<sub>5</sub> and having at least one carbon-carbon double bond; "substituted alkenyl" refers to alkenyl radicals further bearing one or more substituent groups as defined above; "cycloalkyl" refers to saturated or unsaturated, non-aromatic, cyclic ring-containing radicals containing three to eight carbon atoms, preferably three to six carbon atoms; "substituted cycloalkyl" refers to cycloalkyl radicals further bearing one or more substituent groups as defined above; "aryl" refers to aromatic radicals having six to ten carbon atoms; "substituted aryl" refers to aryl radicals further bearing one or more substituent groups as defined above; "alkylaryl" refers to alkyl-substituted aryl radicals; "substituted alkylaryl" refers to alkylaryl radicals further bearing one or more substituent groups as defined above; "arylalkyl" refers to aryl-substituted alkyl radicals; "substituted arylalkyl" refers to arylalkyl radicals further bearing one or more substituent groups as defined above; "heterocyclyl" refers to saturated or unsaturated cyclic radicals containing one or more heteroatoms (e.g., O, N, S) as part of the ring structure and having two to seven carbon atoms in the ring; "substituted heterocyclyl" refers to heterocyclyl radicals further bearing one or more substituent groups as defined above.

## I. Compounds

**[0015]** The compounds of the invention are N-aryl diazaspirocyclic compounds, prodrugs or metabolites of these compounds, and pharmaceutically acceptable salts thereof.

**[0016]** The compounds can bind to, and modulate nicotinic acetylcholine receptors in the patient's brain in the cortex,

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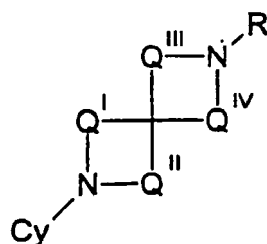
hippocampus, thalamus, basal ganglia, and spinal cord. When so bound, the compounds express nicotinic pharmacology and, in particular, modulate the release of various neurotransmitters including dopamine, other catecholamines such as norepinephrine, such as serotonin, acetylcholine, GABA, glutamate, neuropeptides, nitric oxide, cytokines and other neurotransmitters and neuromediators.

[0017] Receptor binding constants provide a measure of the ability of the compound to bind to half of the relevant receptor sites of certain brain cells of the patient. See, for example, Cheng et al., *Biochem. Pharmacol.* 22:3099 (1973). The receptor binding constants of the compounds described herein generally exceed about 0.1 nM, often exceed about 1 nM, and frequently exceed about 10 nM, and are often less than about 100  $\mu$ M, often less than about 10  $\mu$ M and frequently less than about 5  $\mu$ M. Preferred compounds generally have receptor binding constants less than about 2.5  $\mu$ M, sometimes are less than about 1  $\mu$ M, and can be less than about 100 nM.

[0018] The compounds described herein can demonstrate a nicotinic function by effectively activating neurotransmitter secretion from nerve ending preparations (i.e., synaptosomes). As such, these compounds can activate relevant neurons to release or secrete acetylcholine, dopamine, and other neurotransmitters. Generally, typical compounds activate dopamine secretion in amounts of at least one third, typically at least about 10 times less, frequently at least about 100 times less, and sometimes at least about 1,000 times less than those required for activation of muscle-type nicotinic receptors. Certain compounds elicit dopamine secretion in an amount which is comparable to that elicited by an equal molar amount of (S)-(-)-nicotine.

[0019] Preferably, the compounds can cross the blood-brain barrier, and thus enter the central nervous system of the patient. Log P values provide a measure of the ability of a compound to pass across a diffusion barrier, such as a biological membrane, including the blood brain barrier. See, for example, Hansch et al., *J. Med. Chem.* 11:1 (1968). Typical log P values for the compounds described herein are generally greater than about -0.5, often are greater than about 0, and frequently are greater than about 0.5, and are typically less than about 3, often are less than about 2, and frequently are less than about 1.

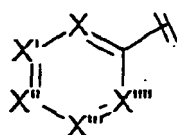
[0020] The compounds of the invention have the structure represented by Formula 1 below:



[0021] In the formula, Q<sup>I</sup> is (CZ<sub>2</sub>)<sub>u</sub>, Q<sup>II</sup> is (CZ<sub>2</sub>)<sub>v</sub>, Q<sup>III</sup> is (CZ<sub>2</sub>)<sub>w</sub>, and Q<sup>IV</sup> is (CZ<sub>2</sub>)<sub>x</sub> where u, v, w and x are individually 0, 1, 2, 3 or 4, preferably 0, 1, 2 or 3 and are selected such that the diazaspicyclic ring of the compound of Formula 1 contains 7, 8 or 9 members. R is hydrogen, lower alkyl, acyl, alkoxycarbonyl or aryloxycarbonyl, preferably hydrogen or lower alkyl. When the value of u is 0, the value of v must be greater than 0, and, when the value of w is 0, the value of x must be greater than 0. In addition, the values of u, v, w and x are selected such that the diazaspicyclic ring contains 7, 8 or 9 members.

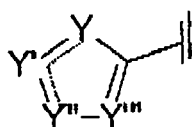
[0022] Each individual Z represents either hydrogen or lower alkyl or aryl.

[0023] Cy represents a suitable five- or six-membered heteroaromatic ring. In one embodiment, Cy is a six membered ring of the formula:



[0024] Each of X, X', X'', X''' and X'''' is individually nitrogen, nitrogen bonded to oxygen (e.g., an N-oxide or N-O functionality) or carbon bonded to a substituent species. No more than three of X, X', X'', X''' and X'''' are nitrogen or nitrogen bonded to oxygen, and it is preferred that only one or two of X, X', X'', X''' and X'''' be nitrogen or nitrogen bonded to oxygen. In addition, it is highly preferred that not more than one of X, X', X'', X''' and X'''' be nitrogen bonded to oxygen; and it is preferred that if one of those species is nitrogen bonded to oxygen, that species is X'''. Most preferably, X''' is nitrogen. In certain preferred circumstances, both X' and X'' are nitrogen. Typically, X, X'' and X'''' are carbon bonded to a substituent species, and it is typical that the substituent species at X, X'' and X'''' are hydrogen. For certain other preferred compounds where X''' is carbon bonded to a substituent species such as hydrogen. X and X'' are both nitrogen. In certain other preferred compounds where X' is carbon bonded to a substituent species such as hydrogen, X and X'' are both nitrogen.

[0025] In another embodiment, Cy is a five 5-membered heteroaromatic ring, such as pyrrole, furan, thiophene, isoxazole, isothiazole, oxazole, thiazole, pyrazole, 1,2,4-oxadiazole, 1,3,4-oxadiazole and 1,2,4-triazole. Other examples of such rings are described in U.S. Patent No. 6,022,868 to Olesen et al. One way of depicting Cy is as follows:



where Y and Y'' are individually nitrogen, nitrogen bonded to a substituent species, oxygen, sulfur or carbon bonded to a substituent species, and Y' and Y''' are nitrogen or carbon bonded to a substituent species. The dashed lines indicate that the bonds (between Y and Y' and between Y' and Y'') can be either single or double bonds.

[0026] However, when the bond between Y and Y' is a single bond, the bond between Y' and Y'' must be a double bond and vice versa. In cases in which Y or Y'' is oxygen or sulfur, only one of Y and Y'' is either oxygen or sulfur. At least one of Y, Y', Y'' and Y''' must be oxygen, sulfur, nitrogen or nitrogen bonded to a substituent species. It is preferred that no more than three of Y, Y', Y'' and Y''' be oxygen, sulfur, nitrogen or nitrogen bonded to a substituent species. It is further preferred that at least one, but no more than three, of Y, Y', Y'' and Y''' be nitrogen.

[0027] Substituent species associated with any of X, X', X'', X''', X'''', Y, Y', Y'' and Y''' (when any is carbon bonded to a substituent species or nitrogen bonded to a substituent species) typically have a sigma m value between about -0.3 and about 0.75, frequently between about -0.25 and about 0.6; and each sigma m value individually can be 0 or not equal to zero; as determined in accordance with Hansch et al., Chem. Rev. 91:165 (1991).

[0028] Examples of suitable substituent species associated with any of X, X', X'', X''', X'''', Y, Y', Y'' and Y''' (when any is carbon bonded to a substituent species or nitrogen bonded to a substituent species), include hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, heterocyclyl, substituted heterocyclyl, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, alkylaryl, substituted alkylaryl, arylalkyl, substituted arylalkyl, halo (e.g., F, Cl, Br, or I), -OR', -NR'R'', -CF<sub>3</sub>, -CN, -NO<sub>2</sub>, -C<sub>2</sub>R', -SR', -N<sub>3</sub>, -C(=O)NR'R'', -NR'C(=O)R'', -C(=O)R', -C(=O)OR', -OC(=O)R', -O(CR'R''), C(=O)R', -O(CR'R''), NR''C(=O)R', -O(CR'R''), NR''SO<sub>2</sub>R', -OC(=O)NR'R'', -NR'C(=O)O R'', -SO<sub>2</sub>R', -SO<sub>2</sub>NR'R'', and -NR'SO<sub>2</sub>R'', where R' and R'' are individually hydrogen, lower alkyl (e.g., straight chain or branched alkyl including C<sub>1</sub>-C<sub>8</sub>, preferably C<sub>1</sub>-C<sub>5</sub>, such as methyl, ethyl, or isopropyl), cycloalkyl, heterocyclyl, aryl, or arylalkyl (such as benzyl), and r is an integer from 1 to 6. R' and R'' can combine to form a cyclic functionality. The term "substituted" as applied to alkyl, aryl, cycloalkyl and the like refers to the substituents described above, starting with halo and ending with -NR'SO<sub>2</sub>R''.

[0029] Examples of suitable Cy groups include 3-pyridyl (unsubstituted or substituted in the 5 and/or 6 position(s) with any of the aforementioned substituents), 5-pyrimidinyl (unsubstituted or substituted in the 2 position with any of the aforementioned substituents), 4 and 5-isoxazolyl, 4 and 5-isothiazolyl, 5-oxazolyl, 5-thiazolyl, 5-(1,2,4-oxadiazolyl), 2-(1,3,4-oxadiazolyl) or 3-(1,2,4-triazolyl).

[0030] Representative aryl groups include phenyl, naphthyl, furanyl, thienyl, pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, quinolinyl, and indolyl. Other representative aromatic ring systems are set forth in Gibson et al., J. Med. Chem. 39: 4065 (1996). Any of these aromatic group containing species can be substituted with at least one substituent group, such as those described above that are associated with x' and the like. Representative substituents include alkyl, aryl, halo, hydroxy, alkoxy, aryloxy or amino substituents.

[0031] Adjacent substituents of X, X', X'', X''', X'''', Y, Y', Y'' and Y''' (when substituents are present) can combine to form one or more saturated or unsaturated, substituted or unsubstituted carbocyclic or heterocyclic rings containing, but not limited to, ether, acetal, ketal, amine, ketone, lactone, lactam, carbamate, or urea functionalities.

[0032] The compounds can occur in stereoisomeric forms, including both single enantiomers and racemic mixtures of such compounds, as well as mixtures of varying degrees of enantiomeric excess.

**[0033]** The compounds can be in a free base form or in a salt form (e.g., as pharmaceutically acceptable salts). Examples of suitable pharmaceutically acceptable salts include inorganic acid addition salts such as sulfate, phosphate, and nitrate; organic acid addition salts such as acetate, galactarate, propionate, succinate, lactate, glycolate, malate, tartrate, citrate, maleate, fumarate, methanesulfonate, p-toluenesulfonate, and ascorbate; salts with an acidic amino acid such as aspartate and glutamate; alkali metal salts such as sodium and potassium; alkaline earth metal salts such as magnesium and calcium; ammonium salt; organic basic salts such as trimethylamine, triethylamine, pyridine, picoline, dicyclohexylamine, and N,N'-dibenzylethylenediamine; and salts with a basic amino acid such as lysine and arginine. The salts can be in some cases hydrates or ethanol solvates. The stoichiometry of the salt will vary with the nature of the components. Representative salts are provided as described in U.S. Patent Nos. 5,597,919 to Dull et al., 5,616,716 to Dull et al. and 5,663,356 to Ruecroft et al.

**[0034]** Representative compounds of the invention include the following:

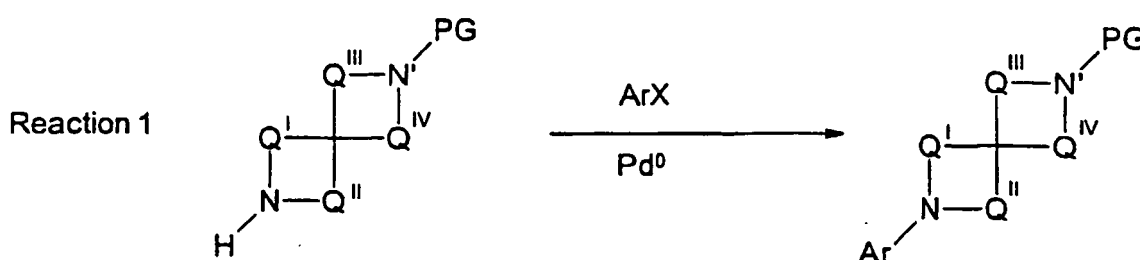
7-(3-pyridyl)-1,7-diazaspiro[4.4]nonane  
 7-(5-pyrimidinyl)-1,7-diazaspiro[4.4]nonane  
 7-(5-isoxazolyl)-1,7-diazaspiro[4.4]nonane  
 7-(5-isothiazolyl)-1,7-diazaspiro[4.4]nonane  
 7-(5-(1,2,4-oxadiazolyl))-1,7-diazaspiro[4.4]nonane  
 7-(2-(1,3,4-oxadiazolyl))-1,7-diazaspiro[4.4]nonane  
 7-(2-pyrazinyl)-1,7-diazaspiro[4.4]nonane  
 7-(3-pyridazinyl)-1,7-diazaspiro[4.4]nonane  
 7-(5-methoxy-3-pyridyl)-1,7-diazaspiro[4.4]nonane  
 7-(5-cyclopentyloxy-3-pyridyl)-1,7-diazaspiro[4.4]nonane  
 7-(5-phenoxy-3-pyridyl)-1,7-diazaspiro[4.4]nonane  
 7-(5-(4-hydroxyphenoxy)-3-pyridyl)-1,7-diazaspiro[4.4]nonane  
 7-(5-ethynyl-3-pyridyl)-1,7-diazaspiro[4.4]nonane  
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 1-(5-(1,2,4-oxadiazolyl))-1,7-diazaspiro[4.4]nonane  
 1-(2-(1,3,4-oxadiazolyl))-1,7-diazaspiro[4.4]nonane  
 1-(2-pyrazinyl)-1,7-diazaspiro[4.4]nonane  
 1-(3-pyridazinyl)-1,7-diazaspiro[4.4]nonane  
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 1-methyl-7-(5-pyrimidinyl)-1,7-diazaspiro[4.4]nonane  
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 1-methyl-7-(5-cyclopentyloxy-3-pyridyl)-1,7-diazaspiro[4.4]nonane  
 1-methyl-7-(5-phenoxy-3-pyridyl)-1,7-diazaspiro[4.4]nonane  
 1-methyl-7-(5-(4-hydroxyphenoxy)-3-pyridyl)-1,7-diazaspiro[4.4]nonane  
 1-methyl-7-(5-ethynyl-3-pyridyl)-1,7-diazaspiro[4.4]nonane  
 1-methyl-7-(6-chloro-3-pyridyl)-1,7-diazaspiro[4.4]nonane  
 1-methyl-7-(6-methoxy-3-pyridazinyl)-1,7-diazaspiro[4.4]nonane  
 7-methyl-1-(3-pyridyl)-1,7-diazaspiro[4.4]nonane  
 7-methyl-1-(5-pyrimidinyl)-1,7-diazaspiro[4.4]nonane  
 7-methyl-1-(5-isoxazolyl)-1,7-diazaspiro[4.4]nonane  
 7-methyl-1-(5-isothiazolyl)-1,7-diazaspiro[4.4]nonane  
 7-methyl-1-(5-(1,2,4-oxadiazolyl))-1,7-diazaspiro[4.4]nonane  
 7-methyl-1-(2-(1,3,4-oxadiazolyl))-1,7-diazaspiro[4.4]nonane  
 7-methyl-1-(2-pyrazinyl)-1,7-diazaspiro[4.4]nonane  
 7-methyl-1-(3-pyridazinyl)-1,7-diazaspiro[4.4]nonane

- 2-(3-pyridyl)-2,7-diazaspiro[4.4]nonane  
 2-(5-pyrimidinyl)-2,7-diazaspiro[4.4]nonane  
 2-(5-isoxazolyl)-2,7-diazaspiro[4.4]nonane  
 2-(5-isothiazolyl)-2,7-diazaspiro[4.4]nonane  
 5 2-(5-(1,2,4-oxadiazolyl)-2,7-diazaspiro[4.4]nonane  
 2-(2-(1,3,4-oxadiazolyl)-2,7-diazaspiro[4.4]nonane  
 2-(2-pyrazinyl)-2,7-diazaspiro[4.4]nonane  
 2-(3-pyridazinyl)-2,7-diazaspiro[4.4]nonane  
 2-(5-methoxy-3-pyridyl)-2,7-diazaspiro[4.4]nonane  
 10 2-(5-cyclopentyloxy-3-pyridyl)-2,7-diazaspiro[4.4]nonane  
 2-(5-phenoxy-3-pyridyl)-2,7-diazaspiro[4.4]nonane  
 2-(5-(4-hydroxyphenoxy)-3-pyridyl)-2,7-diazaspiro[4.4]nonane  
 2-(5-ethynyl-3-pyridyl)-2,7-diazaspiro[4.4]nonane  
 2-(6-chloro-3-pyridyl)-2,7-diazaspiro[4.4]nonane  
 15 2-(6-methoxy-3-pyridazinyl)-2,7-diazaspiro[4.4]nonane  
 2-methyl-7-(3-pyridyl)-2,7-diazaspiro[4.4]nonane  
 2-methyl-7-(5-methoxy-3-pyridyl)-2,7-diazaspiro[4.4]nonane  
 2-methyl-7-(5-phenoxy-3-pyridyl)-2,7-diazaspiro[4.4]nonane  
 6-(3-pyridyl)-1,6-diazaspiro[3.4]octane  
 20 1-methyl-6-(3-pyridyl)-1,6-diazaspiro[3.4]octane  
 2-(3-pyridyl)-2,5-diazaspiro[3.4]octane  
 5-methyl-2-(3-pyridyl)-2,5-diazaspiro[3.4] octane  
 6-(3-pyridyl)-1,6-diazaspiro[3.5]nonane  
 1-methyl-6-(3-pyridyl)-1,6-diazaspiro[3.5]nonane  
 25 2-(3-pyridyl)-2,5-diazaspiro[3.5]nonane  
 5-methyl-2-(3-pyridyl)-2,5-diazaspiro[3.5]nonane  
 2-(3-pyridyl)-2,6-diazaspiro[4.5]decane  
 6-methyl-2-(3-pyridyl)-2,6-diaaspiro[4.5]decane  
 7-(3-pyridyl)-1,7-diazaspiro[4.5]decane  
 30 1-methyl-7-(3-pyridyl)-1,7-diazaspiro[4.5]decane

## II. Methods of Preparing the Compounds

[0035]

Scheme 1



- [0036] The compounds of Formula 1 can be prepared using a general method involving arylation of one amino group of an optionally protected diazaspiroalkane (Scheme 1). Arylation at N with an appropriate aryl, or preferably heteroaryl, halide or triflate can be performed according to methods known to those skilled in the art, for example, employing metal (e.g., copper or palladium compounds) catalysis. The preferred general method in the present invention utilizes the teachings of Buchwald or Hartwig (Buchwald et al, J. Org. Chem., 61: 7240 (1996); Hartwig et al., J. Org. Chem., 64: 5575 (1999); see also Old et al., J. Am. Chem. Soc. 120: 9722 (1998)), wherein an amine is treated with a palladium(0) catalyst, a phosphine ligand and base. Thus, 1-benzyl-1,7-diazaspiro[4.4]nonane is reacted with 3-bromopyridine in the presence of tris(dibenzylideneacetone)dipalladium(0); 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl and sodium tert-butoxide in toluene, to give 1-benzyl-7-(3-pyridyl)diazaspiro[4.4]nonane. Removal of the benzyl group by hydrogenation,

over 10% palladium on carbon, provides 7-(3-pyridyl)-diazaspiro[4.4]nonane. Alternatively, one skilled in the art will recognize that various protecting group strategies can be employed to provide products bearing an aryl group on nitrogen N', as opposed to N (Reaction 1, Scheme 1). A particularly useful combination of protecting groups in the present invention is benzyl and a carbamate, specifically, tert-butylcarbamate. Thus, 1-benzyl-1,7-diazaspiro[4.4]nonane is converted into 1-benzyl-7-(tert-butoxycarbonyl)-1,7-diazaspiro[4.4]nonane by treatment with di-tert-butyl dicarbonate. Subsequent hydrogenation and palladium-catalyzed arylation, with 3-bromopyridine, gives 7-(tert-butoxycarbonyl)-1-(3-pyridyl)diazaspiro[4.4]nonane. Removal of the tert-butoxycarbonyl group, with hydrochloric acid, provides 1-(3-pyridyl)-diazaspiro[4.4]nonane. Finally, in many cases where N and N' are sterically dissimilar, selective arylation of N can be accomplished without first protecting N'. Thus, reaction of 1,7-diazaspiro[4.4]nonane with 3-bromopyridine, under the palladium-catalyzed conditions reported previously, gives almost exclusively 7-(3-pyridyl)-diazaspiro[4.4]nonane.

**[0037]** It will be obvious to those skilled in the art that incorporation of substituents on the heteroaryl ring introduced onto the diazaspiroalkane can be readily realized. Such substituents can provide useful properties in and of themselves or serve as a handle for further synthetic elaboration. A suitably protected heteroaryl diazaspiroalkane can be elaborated to give a number of useful compounds possessing substituents on the heteroaryl ring. For example, 1-benzyl-7-(5-bromo-3-pyridyl)-1,7-diazaspiro[4.4]nonane can be made by reacting 3,5-dibromopyridine with 1-benzyl-1,7-diazaspiro[4.4]nonane according to procedures described previously. The conversion of 1-benzyl-7-(5-bromo-3-pyridyl)diazaspiro[4.4]nonane into the corresponding 5-amino-substituted compound can be accomplished by the general method of Zwart et al., *Recueil Trav. Chim. Pays-Bas* 74: 1062 (1955), in which the bromo compound heated with aqueous ammonia in the presence of a copper catalyst. 5-Alkylamino substituted compounds can be prepared in a similar manner. 5-Ethynyl-substituted compounds can be prepared from the 5-bromo compound by palladium catalyzed coupling using 2-methyl-3-butyne-2-ol, followed by base-catalyzed (sodium hydride) removal of the acetone unit, according to the general techniques described in Cosford et al., *J. Med. Chem.* 39: 3235 (1996). The 5-ethynyl analogs can be converted into the corresponding 5-ethenyl, and subsequently to the corresponding 5-ethyl analogs by successive catalytic hydrogenation reactions. The 5-azido-substituted analogs can be prepared from the 5-bromo compound by reaction with lithium azide in N,N-dimethylformamide. 5-Alkylthio-substituted analogs can be prepared from the 5-bromo compound by reaction with an appropriate sodium alkylmercaptide (sodium alkanethiolate), using techniques known to those skilled in the art of organic synthesis.

**[0038]** A number of other analogs, bearing substituents in the 5 position of the pyridine ring, can be synthesized from the corresponding amino compounds, *vide supra*, via a 5-diazonium salt intermediate. Examples of other 5-substituted analogs that can be produced from 5-diazonium salt intermediates include, but are not limited to: 5-hydroxy, 5-alkoxy, 5-fluoro, 5-chloro, 5-iodo, 5-cyano, and 5-mercapto. These compounds can be synthesized using the general techniques set forth in Zwart et al., *supra*. For example, 1-benzyl-7-(5-hydroxy-3-pyridyl)-1,7-diazaspiro[4.4]nonane can be prepared from the reaction of the corresponding 5-diazonium salt intermediate with water. Likewise, 1-benzyl-7-(5-alkoxy-3-pyridyl)-1,7-diazaspiro[4.4]nonanes can be made from the reaction of the diazonium salt with alcohols. Appropriate 5-diazonium salts can be used to synthesize cyano or halo compounds, as will be known to those skilled in the art. 5-Mercapto substitutions can be obtained using techniques described in Hoffman et al., *J. Med. Chem.* 36: 953 (1993). The 5-mercaptan so generated can, in turn, be converted to a 5-alkylthio substituent by reaction with sodium hydride and an appropriate alkyl bromide. Subsequent oxidation would then provide a sulfone. 5-Acylamido analogs of the aforementioned compounds can be prepared by reaction of the corresponding 5-amino compounds with an appropriate acid anhydride or acid chloride using techniques known to those skilled in the art of organic synthesis.

**[0039]** 5-Hydroxy-substituted analogs of the aforementioned compounds can be used to prepare corresponding 5-alkanoyloxy-substituted compounds by reaction with the appropriate acid, acid chloride, or acid anhydride. Likewise, the 5-hydroxy compounds are precursors of both the 5-aryloxy and 5-heteroaryloxy via nucleophilic aromatic substitution at electron deficient aromatic rings (e.g., 4-fluorobenzonitrile and 2,4-dichloropyrimidine). Such chemistry is well known to those skilled in the art of organic synthesis. Ether derivatives can also be prepared from the 5-hydroxy compounds by alkylation with alkyl halides and a suitable base or via Mitsunobu chemistry, in which a trialkyl- or triarylphosphine and diethyl azodicarboxylate are typically used. See Hughes, *Org. React. (N.Y.)* 42: 335 (1992) and Hughes, *Org. Prep. Proced. Int.* 28: 127 (1996) for typical Mitsunobu conditions.

**[0040]** 5-Cyano-substituted analogs of the aforementioned compounds can be hydrolyzed to afford the corresponding 5-carboxamido-substituted compounds. Further hydrolysis results in formation of the corresponding 5-carboxylic acid-substituted analogs. Reduction of the 5-cyano-substituted analogs with lithium aluminum hydride yields the corresponding 5-aminomethyl analogs. 5-Acyl-substituted analogs can be prepared from corresponding 5-carboxylic acid-substituted analogs by reaction with an appropriate alkyllithium using techniques known to those skilled in the art of organic synthesis.

**[0041]** 5-Carboxylic acid-substituted analogs of the aforementioned compounds can be converted to the corresponding esters by reaction with an appropriate alcohol and acid catalyst. Compounds with an ester group at the 5-pyridyl position can be reduced with sodium borohydride or lithium aluminum hydride to produce the corresponding 5-hydroxymethyl-substituted analogs. These analogs in turn can be converted to compounds bearing an ether moiety at the 5-pyridyl position by reaction with sodium hydride and an appropriate alkyl halide, using conventional techniques. Alternatively,

the 5-hydroxymethyl-substituted analogs can be reacted with tosyl chloride to provide the corresponding 5-tosyloxymethyl analogs. The 5-carboxylic acid-substituted analogs can also be converted to the corresponding 5-alkylaminoacyl analogs by sequential treatment with thionyl chloride and an appropriate alkylamine. Certain of these amides are known to readily undergo nucleophilic acyl substitution to produce ketones. Thus, the so-called Weinreb amides (N-methoxy-N-methyl-

amides) react with aryllithium reagents to produce the corresponding diaryl ketones. For example, see Selnick et al., Tet. Lett. 34: 2043 (1993).  
**[0042]** 5-Tosyloxymethyl-substituted analogs of the aforementioned compounds can be converted to the corresponding 5-methyl-substituted compounds by reduction with lithium aluminum hydride. 5-Tosyloxymethyl-substituted analogs of the aforementioned compounds can also be used to produce 5-alkyl-substituted compounds via reaction with an alkyllithium reagent. 5-Hydroxy-substituted analogs of the aforementioned compounds can be used to prepare 5-N-alkyl- or 5-N-arylcabamoyloxy-substituted compounds by reaction with N-alkyl- or N-arylisocyanates. 5-Amino-substituted analogs of the aforementioned compounds can be used to prepare 5-alkoxycarboxamido-substituted compounds and 5-urea derivatives by reaction with alkyl chloroformate esters and N-alkyl- or N-arylisocyanates, respectively, using techniques known to those skilled in the art of organic synthesis.

**[0043]** Chemistries analogous to those described hereinbefore for the preparation of 5-substituted pyridine analogs of diazaspiro compounds can be devised for the synthesis of analogs bearing substituents in the 2, 4, and 6 positions of the pyridine ring. For example, a number of 2-, 4-, and 6-aminopyridyldiazaspiroalkanes can be converted to the corresponding diazonium salt intermediates, which can be transformed to a variety of compounds with substituents at the 2, 4, and 6 positions of the pyridine ring as was described for the 5-substituted analogs above. The requisite 2-, 4-, and 6-aminopyridyl diazaspiroalkanes are available via the Chichibabin reaction of unsubstituted pyridyl diazaspiroalkanes (e.g., 1-benzyl-7-(3-pyridyl)-1,7-diazaspiro[4.4]nonane, described previously) with sodium amide. Similar reactions are described in Chemistry of Heterocyclic Compounds, Volume 14, part 3, pp.3-5 (Interscience Publishers, 1962) and by Lahti et al., J. Med. Chem. 42: 2227 (1999).

**[0044]** After the desired heteroaryl ring functional group manipulation has been accomplished, the optional protecting group can be removed from the diazabicyclo using appropriate conditions. Thus, for example, hydrogenolysis of 1-benzyl-7-(5-alkoxy-3-pyridyl)-1,7-diazaspiro[4.4]nonane will generate 7-(5-alkoxy-3-pyridyl)-1,7-diazaspiro[4.4]nonane. Those skilled in the art of organic chemistry will appreciate the necessity of pairing protecting groups with the chemistries required to generate particular functionalities. In some cases it can be necessary, to retain a particular functionality, to replace one protecting group with another.

**[0045]** In an alternative approach to the synthesis of pyridine-substituted pyridyl diazaspiroalkanes, 3,5-dibromopyridine can be converted into the corresponding 5-alkoxy-3-bromo- and 5-aryloxy-3-bromopyridines by the action of sodium alkoxides or sodium aryloxides. Procedures such as those described by Comins et al., J. Org. Chem. 55: 69 (1990) and Hertog et al., Recueil Trav. Chim. Pays-Bas 74: 1171 (1955) are used. This is exemplified by the preparation 7-(5-(4-methoxyphenoxy)-3-pyridyl)-1,7-diazaspiro[4.4]nonane. Reaction of 3,5-dibromopyridine with sodium 4-methoxyphenoxide in N,N-dimethylformamide gives 3-bromo-5-(4-methoxyphenoxy)pyridine. Coupling of 3-bromo-5-(4-methoxyphenoxy)pyridine with 1-benzyl-7-(3-pyridyl)-1,7-diazaspiro[4.4]nonane in the presence of sodium tert-butoxide, and a catalytic amount of tris(dibenzylideneacetone)dipalladium(0) and 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl, in toluene, followed by hydrogenolysis of the benzyl protecting group, will provide 7-(5-(4-methoxyphenoxy)-3-pyridyl)-1,7-diazaspiro[4.4]nonane.

**[0046]** Other aryl halides undergo the palladium-catalyzed coupling reaction described previously. Thus 7-(5-pyrimidinyl)-1,7-diazaspiro[4.4]nonane is prepared in a similar manner from 5-bromopyrimidine and optionally 1-position protected 1,7-diazaspiro[4.4]nonane followed by deprotection, if necessary. This technology is especially applicable in cases, such as 3-bromopyridine, 3,5-dibromopyridine, and 5-bromopyrimidine, where the aromatic ring is not activated toward nucleophilic aromatic substitution.

**[0047]** In some cases, coupling of the heteroaromatic ring to the diazaspirocycle can be accomplished without the use of palladium catalysis. Examples of both five- and six-membered heteroaromatic ring compounds, which are activated toward nucleophilic aromatic substitution, are known by those skilled in the art of organic synthesis. For example, 7-(6-chloro-3-pyridazinyl)-1,7-diazaspiro[4.4]nonane can be synthesized from 3,6-dichloropyridazine and 1,7-diazaspiro[4.4]nonane. Likewise, 2,6-dichloropyrazine, and 2-bromothiazole will react with 1,7-diazaspiro[4.4]nonane to give 7-(6-chloro-2-pyrazinyl)-1,7-diazaspiro[4.4]nonane and 7-(2-thiazoyl)-1,7-diazaspiro[4.4]nonane, respectively.

**[0048]** The coupling reactions described in this application, whether palladium catalyzed or not, are amenable to high through-put synthetic techniques. Thus a library of compounds of the present invention can be produced by coupling, in a 96-well plate format, for instance, various haloarenes with various diazaspiro compounds.

### Specific Diazaspiro Ring Systems

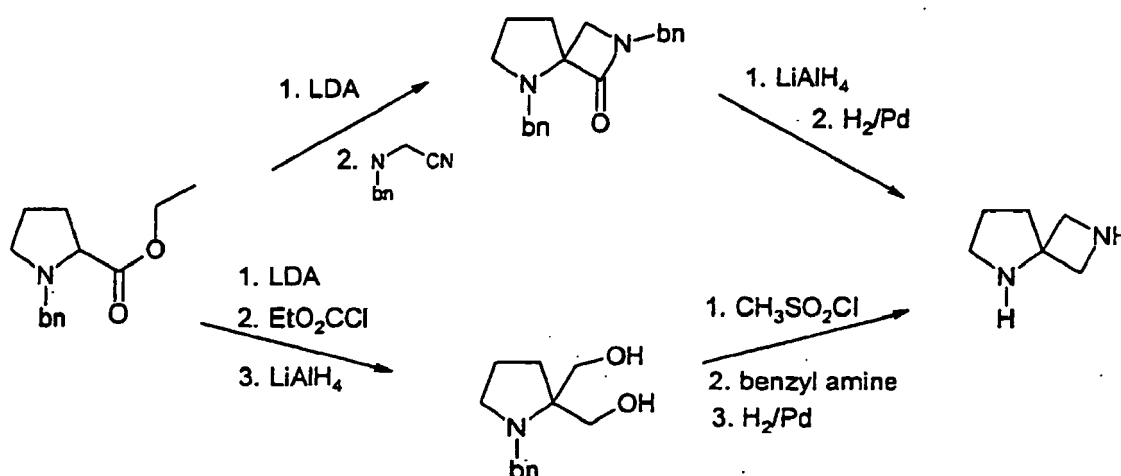
**[0049]** Optionally protected diazaspiroalkane intermediates used to prepare the compounds of Formula 1 can be prepared by numerous methods. Several of these diazaspiroalkane intermediates are known and can be prepared using

prior art methods. However, the synthesis of the intermediates using palladium chemistry is new to the art, and the pharmaceutical activity of the intermediates was not appreciated in the prior art.

[0050] The compounds of Formula 1, where  $u=v=1$ ,  $w=0$  and  $x=3$ , possess a 2,5-diazaspiro[3,4]octane core which can be prepared as depicted in Scheme 2.

[0051] Alkylation of N-benzyl-L-proline ethyl ester (Aldrich Chemical), using a strong base such as lithium diisopropylamide (LDA) and the aminomethyl equivalent cyanomethylbenzylamine, provides a beta-lactam, according to the procedure reported by Overman, J. Am. Chem. Soc. 107:1698 (1985) and Tet. Lett. 25: 1635 (1985). This can subsequently be reduced with lithium aluminum hydride to provide the 2,5-dibenzyl derivative of 2,5-diazaspiro[3,4]octane. Removal of the benzyl protecting groups, by either hydrogenation or oxidative cleavage with, for example, ceric ammonium nitrate, will produce 2,5-diazaspiro[3,4]octane. Alternatively, chemistry similar to that described in EP patent application 90117078.7 (publication number EP 0 417 631) can be used to produce a geminal bis(hydroxymethyl) derivative and subsequently convert it to the desired 2,5-diazaspiro[3,4]octane (Scheme 2). The subsequent palladium-catalyzed arylation, as described previously, would be expected to proceed with selectivity for the less sterically hindered azetidinyll nitrogen, producing 2-aryl-2,5-diazaspiro[3,4]octanes. The isomeric 5-aryl-2,5-diazaspiro[3,4]octanes can be made by first protecting the azetidinyll nitrogen (with, for instance, a carbamate) and then performing the arylation, followed by deprotection.

Scheme 2



[0052] The compounds of Formula 1, wherein  $u=2$ ,  $v=1$ ,  $w=0$  and  $x=3$ , possess the 1,7-diazaspiro[4.4]nonane system which can be prepared according to numerous methods, several of which are shown in Scheme 3. In one embodiment (Method A), a suitably protected proline ester, for example N-benzyl-L-proline ethyl ester, can be deprotonated with lithium diisopropylamide and allowed to react by Michael addition to nitroethylene. This provides methyl 2-(2-nitroethyl)-1-benzylpyrrolidine-2-carboxylate. Subsequent reduction of the nitro group using Raney nickel, followed by lactamization by methods known to those skilled in the art (for example, heating in a suitable solvent with or without an acidic or basic catalyst), provides 1-benzyl-1,7-diazaspiro[4.4]nonan-6-one.

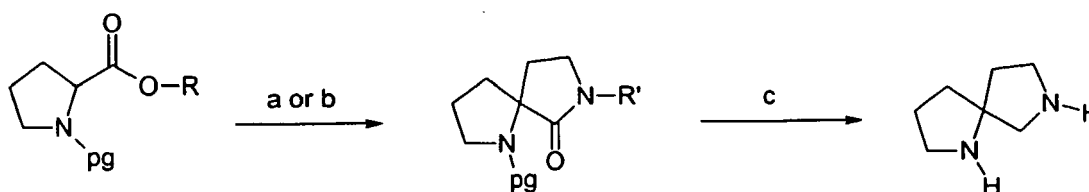
[0053] The 1,7-diazaspiro[4.4]nonane-6-one can alternatively be prepared according to one of several other methods reported in the literature. Such teachings indicate that a suitably protected proline ester can be deprotonated with lithium diisopropylamide and allowed to react with an alkylating agent such as chloroacetonitrile, then subjected to nitrile reduction and cyclization (Method B, Scheme 3) as reported by Culbertson et al., J. Med. Chem. 33:2270 (1990).

[0054] Other teachings indicate that a suitably protected proline ester can be deprotonated with lithium diisopropylamide and allowed to react with an alkylating agent such as allyl bromide (Method C, Scheme 3). The resulting olefin can then be oxidatively cleaved to an aldehyde, as reported by Genin et al., J. Org. Chem. 58:2334 (1993); Hinds et al., J. Med. Chem. 34:1777 (1991); Kim et al., J. Org. Chem. 61:3138 (1996); EP 0 360 390 and U.S. Patent No. 5,733,912. The aldehyde can then be subjected to reductive amination with an ammonium salt or primary aliphatic or aromatic amine, according to methods known to those skilled in the art. Alternatively, the aldehyde can be reduced to the corresponding alcohol and the alcohol then transformed to an amine by conversion to a leaving group, followed by displacement with the appropriate amine. This can also be achieved by displacing the leaving group with an azide ion and subsequently reduction to the primary amine using methods known to those skilled in the art. The alcohol can be converted to an

amine using Mitsunobu conditions, as discussed previously. The alkyl 2-aminoethyl pyrrolidine-2-carboxylate, obtained according to one of the methods described above, can be cyclized to a spirolactam by methods known to those skilled in the art, such as heating in a suitable solvent with or without an acidic or basic catalyst.

**[0055]** The lactam obtained by any one of the above methods (Methods A, B or C) can be treated with a suitable reducing agent, such as lithium aluminum hydride, to provide the protected 1,7-diazaspiro[4.4]nonane, in this example, 1-benzyl-1,7-diazaspiro[4.4]nonane. The protecting group can be removed using methods known those skilled in the art to provide the desired 1,7-diazaspiro[4.4]nonane. Arylation at either nitrogen can be accomplished using methods described herein.

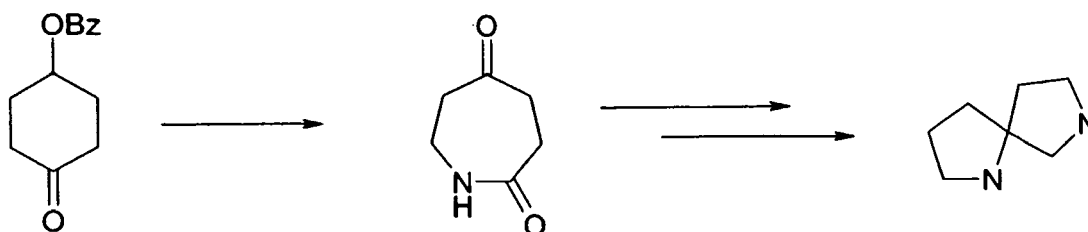
Scheme 3



- a) (i) LDA; (ii) nitroethylene (Method A) or ClCH<sub>2</sub>CN (Method B); (iii) RaNi; (iv) PhCH<sub>3</sub>, heat  
 b) (i) LDA; (ii) allyl bromide; (iii) O<sub>3</sub> or OsO<sub>4</sub>, NaIO<sub>4</sub>; (iv) NH<sub>4</sub>Cl, NaBH(OAc)<sub>3</sub> (Method C)  
 c) (i) LiAlH<sub>4</sub> or BH<sub>3</sub>; (ii) [-PG]

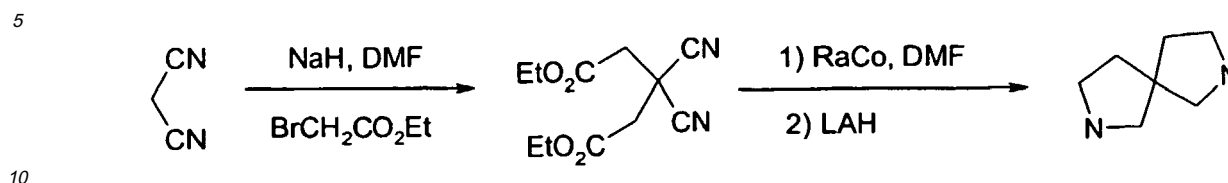
**[0056]** Alternatively, the 1,7-diazaspiro[4.4]nonane core can also be prepared according to Scheme 4. The conversion of 1,4-dioxaspiro[4.5]decan-8-one to 4-benzoyloxycyclohexanone can be readily achieved by those skilled in the art. Subsequent transformation of 4-benzoyloxycyclohexanone to 1,7-diazaspiro[4.4]nonane (through the intermediacy of 4-oxocaprolactam, as shown) can be performed according to the teachings of Majer et al., Coll. Czech. Chem. Comm. 47:950 (1982).

Scheme 4



**[0057]** The compounds of Formula 1, wherein u=2, v=1, w=1 and x=2, possess the symmetrical 2,7-diazaspiro[4,4]nonane system which can be prepared according to Scheme 5. This method is reported by Overman et al., J. Org. Chem. 46: 2757 (1981) and Culbertson et al., J. Med. Chem. 33:2270 (1990).

## Scheme 5



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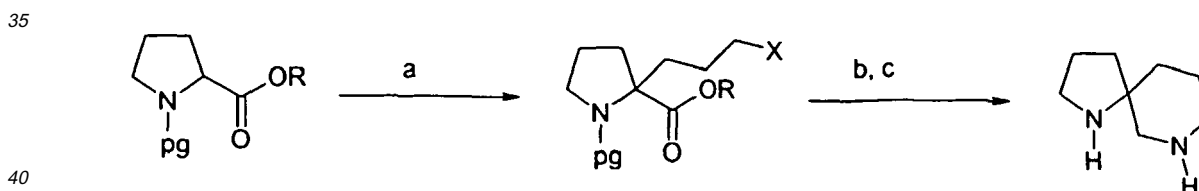
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**[0058]** The compounds of Formula 1, wherein  $u=3$ ,  $v=1$ ,  $w=0$  and  $x=3$ , possess the 1,7-diazaspiro[4.5]decane system which can be prepared according to Scheme 6. The teachings of Kim et al., J. Org. Chem. 61:3138 (1996), patent EP360390 and US patent 5,733,912 indicate that a suitably protected proline ester (e.g., N-benzyl-L-proline ethyl ester) can be deprotonated with lithium diisopropylamide and allowed to react with an alkylating agent such as allyl bromide. US patent 5,733,912 also teaches that hydroboration/oxidation of the allyl side chain can be performed to provide the 2-(3-hydroxypropyl) group. Those skilled in the art will appreciate that the hydroxyl group can then be converted to an amino group by a number of methods, for example oxidation followed by reductive amination. Alternatively, a suitably protected proline ester can be deprotonated with lithium diisopropylamide and allowed to react with an alkylating agent such as diiodopropane. Conversion of the primary iodide to an amine can then be performed according to known methods, for example treatment with ammonia in the presence of a copper catalyst. The resulting amino ester can be cyclized to afford a protected 1,7-diazaspiro[4.5]decan-6-one using any number of known procedures, for example heating in a suitable solvent in the presence or absence of an acidic or basic catalyst, as discussed previously. Alternatively, the known 1,7-diazaspiro[4.5]decan-6-one can be prepared according to the teachings of Loefas et al., J. Het. Chem. 21: 583 (1984), in which the ring contraction of 2,10-diazabicyclo[4.4.0]dec-1-ene is used.

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**[0059]** The 1,7-diazaspiro[4.5]decan-6-one, obtained by any of the above methods, can then be treated with a reducing agent, such as lithium aluminum hydride, followed by removal of the protecting group, to provide the desired 1,7-diazaspiro[4.5]decane. Arylation can then be carried out at either nitrogen using methods described herein.

## Scheme 6



- 45
- a)  $X=OH$ : (i) LDA, allyl bromide; (ii)  $BH_3$ ,  $H_2O_2$   
 $X=I$ : LDA, 1,3-diiodopropane  
 b)  $X=OH$ : (i) PCC or Swern; (ii)  $NH_4Cl$ ,  $NaBH(OAc)_3$ ; (iii) heat (+catalyst?)  
 $X=I$ : (i)  $NH_3$ , CuI; (ii) heat (+catalyst?)  
 c) (i)  $BH_3$  or  $LiAlH_4$ ; (ii) [-PG]

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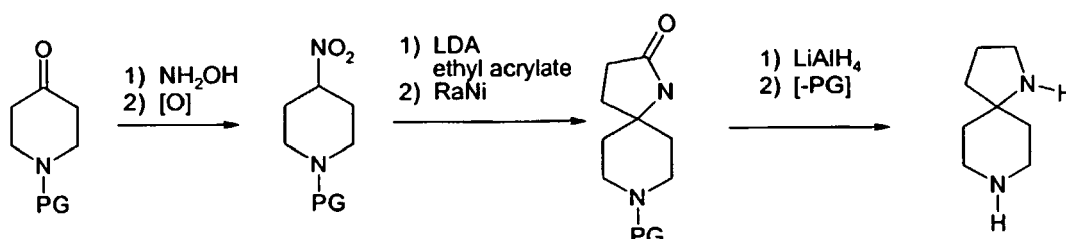
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**[0060]** The compounds of Formula 1, wherein  $u=2$ ,  $v=1$ ,  $w=0$ , and  $x=4$ , possess the 2,6-diazaspiro[4.5]decane core which can be prepared according to the method of Ciblat, et al., Tet. Lett. 42: 4815 (2001). Thus, commercially available 1-benzyl-3-pyrrolidinone can be reacted with 2-methyl-2-(2-aminoethyl)-1,3-dioxolane (Islam and Raphael, J. Chem. Soc. 3151 (1955)) in an intramolecular Mannich reaction. The product, the ethylene ketal of 2-benzyl-2,10-diazaspiro[4,5]decan-7-one, can then be hydrolyzed to the ketone, using aqueous hydrochloric acid. Deoxygenation of the ketone can then be accomplished by standard methods, such as conversion to the corresponding 1,3-dithiane, followed by treatment with Raney nickel. The 2-benzyl-2,6-diazaspiro[4,5]decane thus produced can be directly arylated on the 6-position nitrogen or converted into 6-(tert-butoxycarbonyl)-2,6-diazaspiro[4,5]decane by treatment with di-tert-butyl dicarbonate, followed by hydrogenation. The latter derivative can then be arylated at the 2-position nitrogen. Similar chemistry can be used to convert other azacyclic ketones into the corresponding spirodiaz compounds. Thus, reaction

of any of various N-protected 3-azetidionones (the synthesis of which is described by Lall, et al., J. Org. Chem. 67: 1536 (2002) and Marchand, et al., Heterocycles 49: 149 (1998)) with 2-methyl-2-(2-aminoethyl)-1,3-dioxolane, followed by deoxygenation (as described above), will produce the corresponding protected 2,5-diazaspiro[3.5]nonane (Formula 1, wherein  $u=1$ ,  $v=1$ ,  $w=0$ , and  $x=4$ ).

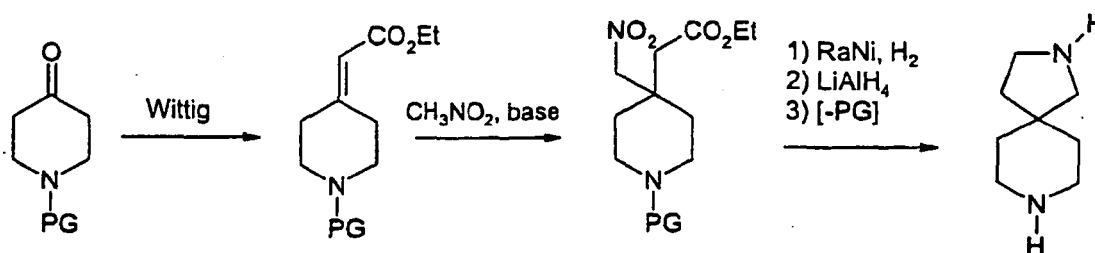
**[0061]** The compounds of Formula 1, wherein  $u=v=2$ ,  $w=0$ , and  $x=3$ , possess the 1,8-diazaspiro[4.5]decane core which can be prepared according to Scheme 7. According to the teachings reported by Wittekind et al., J. Het. Chem. 9:11 (1972), a protected 4-piperidone can be converted to the 4-nitropiperidine. Subsequent Michael addition with ethyl acrylate, for example, followed by reduction of the nitro group with Raney nickel, provides the 1,8-diazaspiro[4.5]decan-2-one. This lactam can be reduced with an appropriate reducing agent, such as lithium aluminum hydride, followed by removal of the protecting group, to provide the optionally substituted 1,8-diazaspiro[4.5]decane. Arylation on either nitrogen can be accomplished using methods described herein.

Scheme 7



**[0062]** The compounds of Formula 1, wherein  $u=2$ ,  $v=1$ , and  $w=x=2$ , possess the 2,8-diazaspiro[4.5]decane core which can be prepared according to Scheme 8. According to various teachings (Helv. Chim. Acta 60: 1650 (1977); Smith et al., J. Med. Chem. 19:3772 (1995); Elliott et al., Biorg. Med. Chem. Lett. 8:1851 (1998)), a protected 4-piperidone can be converted to the 4-piperidinylidene acetic acid ester via Wittig olefination. Subsequent Michael addition with the anion of nitromethane, followed by reduction of the nitro group and spontaneous cyclization with Raney nickel, provides the protected 2,8-diazaspiro[4.5]decan-3-one. Treatment of the protected 2,8-diazaspiro[4.5]decan-3-one with a reducing agent, such as lithium aluminum hydride, followed by removal of the protecting group, provides the 2,8-diazaspiro[4.5]decane. Arylation can be accomplished on either nitrogen using the methods described herein.

Scheme 8



**[0063]** The compounds of Formula 1, wherein  $u=2$ ,  $v=1$ ,  $w=4$  and  $x=0$ , possess the 1,8-diazaspiro[5.5]decane core and can be prepared according to the procedures utilized for the analogous 1,7-diazaspiro[4.4]nonanes by substituting pipercolinate ester for proline ester. Alternatively, the procedure reported in Zhu et al., J. Org. Chem. 58:6451 (1993) can be employed.

**[0064]** Single enantiomer compounds of the present invention can be made by various methods. One method, well known to those skilled in the art of organic synthesis, involves resolution using diastereomeric salts. Compounds of the present invention contain basic nitrogen atoms and will react with acids to form crystalline salts. Various acids, carboxylic and sulfonic, are commercially available in enantiomerically pure form. Examples include tartaric, dibenzoyl- and di-p-toluoyltartaric, and camphorsulfonic acids. When any one of these or other single enantiomer acids is reacted with a

racemic amine base, diastereomeric salts result. Fractional crystallization of the salts, and subsequent regeneration of the bases, results in enantiomeric resolution thereof.

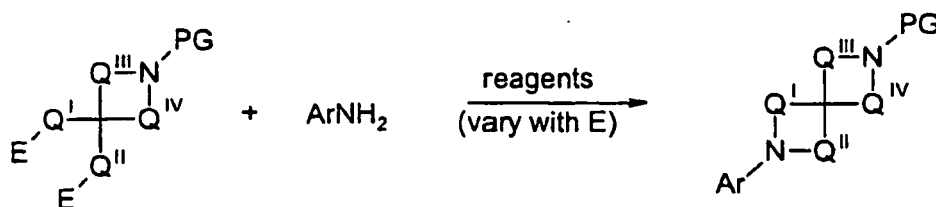
[0065] Another means of separation of involves conversion of the enantiomeric mixture into diastereomeric amides or carbamates, using a chiral acid or chloroformate. Thus, when racemic 7-(3-pyridyl)-1,7-diazaspiro[4.4]nonane is coupled with N-(tert-butoxycarbonyl)-S-proline, using diphenyl chlorophosphate, and the protecting group removed (with trifluoroacetic acid), the resulting diastereomeric proline amides of 7-(3-pyridyl)-1,7-diazaspiro[4.4]nonane are separable by liquid chromatography. The separated amides are then transformed into (+) and (-) 7-(3-pyridyl)-1,7-diazaspiro[4.4]nonane by the Edman degradation.

[0066] Selective synthesis of single enantiomers can also be accomplished by methods known to those skilled in the art. Such methods will vary as the chemistry used for construction of the diazaspiro rings varies. For instance, for the syntheses in which the alkylation of a proline derivative is used to form the diazaspiro system (such as described for the 1,7-diazaspiro[4.4]nonane system), the alkylation of proline can be carried out in a stereospecific manner. Thus, methods such as those described by Beck et al., *Org. Synth.* 72: 62 (1993) or Wang and Germanas, *Synlett* : 33 (1999) (and references therein) can be used to control the stereochemistry of the alkylation step. When enantiomerically pure proline ester (commercially available from Aldrich) is used as the starting material for such a process, the alkylation product is also a single enantiomer. A variety of electrophiles can be used in such alkylations, including allyl halides, which have been useful in assembling spiro systems related to compounds of the present invention Genin and Johnson, *J. Amer. Chem. Soc.* 114: 8778 (1992).

### Alternate Synthetic Methods

[0067] The compounds can be produced using varying methods. Alternatives to the palladium catalyzed coupling protocol described above can be used. For instance, those skilled in the art of organic synthesis will recognize that one or more of the nitrogen containing rings can be formed by any one of many common amine syntheses. Thus, an arylamine can be reacted with a protected cyclic amine derivative (see scheme 9), which contains two reactive electrophiles, to generate an N-aryldiazaspiro compound. A variety of electrophiles participate in such chemistry (e.g., halides and sulfonates via nucleophilic displacement, aldehydes *via* reductive amination, esters and other acid derivatives *via* acyl substitution, followed by reduction).

Scheme 9



E = CH<sub>2</sub>Z (where Z = X or sulfonate), CHO, CO<sub>2</sub>R

[0068] The requisite bis-electrophiles can be synthesized by many diverse methods. Schemes 2, 3 and 6 all incorporate such intermediates (in reaction with benzylamine or ammonia). Pedersen, et al., *J. Org. Chem.* 58: 6966 (1993) and Berkowitz, et al., *J. Org. Chem.* 60: 1233 (1995) both report the alkylation of dianions of N-acyl  $\alpha$ -aminoesters. These alkylations also can be used for synthesis of N-aryldiazaspiro compounds. Thus, dianion of commercially available (Acros) ethyl 2-pyrrolidone-5-carboxylate can be alkylated with ethyl bromoacetate to generate ethyl 5-(carboethoxymethyl)-2-pyrrolidone-5-carboxylate. The second spiro ring can be formed by reacting ethyl 5-(carboethoxymethyl)-2-pyrrolidone-5-carboxylate with an arylamine. The resulting 2-aryl-2,6-diazaspiro[4.4]nonane-1,3,7-trione can be reduced with diborane to give 7-aryl-1,7-diazaspiro[4.4]nonane. Depending on the nature of the aryl group, the order of the synthetic steps can be changed. Likewise, it can be necessary to incorporate protection/deprotection steps into particular methods.

[0069] A wide variety of arylamines are available for use in the approach outlined in Scheme 9. In addition to aminopyridines and aminopyrimidines, 3-aminoisoxazole is commercially available (Aldrich). This provides a means of synthesizing N-isoxazolyldiazaspiro compounds. The isomeric 4-aminoisoxazole can be made by reducing the corresponding nitro compound using the method described by Reiter, *J. Org. Chem.* 52: 2714 (1987). Examples of other amino derivatives of 5-membered aromatic rings include 3-aminoisothiazole, made according to Holland, et al., *J. Chem. Soc.*, 7277 (1965), and 4-aminoisothiazole, made according to Avalos, et al., *An. Quim.* 72: 922 (1976). Thus, a variety

of N-aryldiazaspiro compounds of the present invention, in which the aryl group is a five-membered heterocycle, can be produced.

### III. Pharmaceutical Compositions

5 [0070] The compounds of the invention can be incorporated into pharmaceutical compositions and used to prevent a condition or disorder in a subject susceptible to such a condition or disorder, and/or to treat a subject suffering from the condition or disorder. The pharmaceutical compositions described herein include one or more compounds of Formula 1 and/or pharmaceutically acceptable salts thereof. Optically active compounds can be employed as racemic mixtures or as pure enantiomers.

10 [0071] The manner in which the compounds are administered can vary. The compositions are preferably administered orally (e.g., in liquid form within a solvent such as an aqueous or non-aqueous liquid, or within a solid carrier). Preferred compositions for oral administration include pills, tablets, capsules, caplets, syrups, and solutions, including hard gelatin capsules and time-release capsules. Compositions may be formulated in unit dose form, or in multiple or subunit doses. Preferred compositions are in liquid or semisolid form. Compositions including a liquid pharmaceutically inert carrier such as water or other pharmaceutically compatible liquids or semisolids may be used. The use of such liquids and semisolids is well known to those of skill in the art.

15 [0072] The compositions can also be administered via injection, i.e., intravenously, intramuscularly, subcutaneously, intraperitoneally, intraarterially, intrathecally; and intracerebroventricularly. Intravenous administration is a preferred method of injection. Suitable carriers for injection are well known to those of skill in the art, and include 5% dextrose solutions, saline, and phosphate buffered saline. The compounds can also be administered as all infusion or injection (e.g., as a suspension or as an emulsion in a pharmaceutically acceptable liquid or mixture of liquids).

20 [0073] The formulations may also be administered using other means, for example, rectal administration. Formulations useful for rectal administration, such as suppositories, are well known to those of skill in the art. The compounds can also be administered by inhalation (e.g., in the form of an aerosol either nasally or using delivery articles of the type set forth in U.S. Patent No. 4,922,901 to Brooks et al., the disclosure of which is incorporated herein in its entirety); topically (e.g., in lotion form); or transdermally (e.g., using a transdermal patch, using technology that is commercially available from Novartis and Alza Corporation). Although it is possible to administer the compounds in the form of a bulk active chemical, it is preferred to present each compound in the form of a pharmaceutical composition or formulation for efficient and effective administration.

25 [0074] Exemplary methods for administering such compounds will be apparent to the skilled artisan. The usefulness of these formulations may depend on the particular composition used and the particular subject receiving the treatment. These formulations may contain a liquid carrier that may be oily, aqueous, emulsified or contain certain solvents suitable to the mode of administration.

30 [0075] The compositions can be administered intermittently or at a gradual, continuous, constant or controlled rate to a warm-blooded animal (e.g., a mammal such as a mouse, rat, cat, rabbit, dog, pig, cow, or monkey), but advantageously are administered to a human being. In addition, the time of day and the number of times per day that the pharmaceutical formulation is administered can vary.

35 [0076] Preferably, upon administration, the active ingredients interact with receptor sites within the body of the subject that affect the functioning of the CNS. More specifically, in treating a CNS disorder, preferable administration is designed to optimize the effect upon those relevant receptor subtypes that have an effect upon the functioning of the CNS, while minimizing the effects upon muscle-type receptor subtypes. Other suitable methods for administering the compounds of the present invention are described in U.S. Patent No. 5,604,231 to Smith et al.

40 [0077] Preferably, the compositions are administered such that active ingredients interact with regions where cytokine production is affected or occurs. The compounds described herein are very potent at treating these conditions or disorders (i.e., they affect cytokine production and/or secretion at very low concentrations) and are very efficacious (i.e., they inhibit cytokine production and/or secretion to a relatively high degree).

45 [0078] In certain circumstances, the compounds described herein can be employed as part of a pharmaceutical composition with other compounds intended to prevent or treat a particular disorder. In addition to effective amounts of the compounds described herein, the pharmaceutical compositions can also include various other components as additives or adjuncts. Exemplary pharmaceutically acceptable components or adjuncts which are employed in relevant circumstances include antioxidants, free-radical scavenging agents, peptides, growth factors, antibiotics, bacteriostatic agents, immunosuppressives, anticoagulants, buffering agents, anti-inflammatory agents, anti-pyretics, time-release binders, anaesthetics, steroids, vitamins, minerals and corticosteroids. Such components can provide additional therapeutic benefit, act to affect the therapeutic action of the pharmaceutical composition, or act towards preventing any potential side effects which can be imposed as a result of administration of the pharmaceutical composition.

50 [0079] The appropriate dose of the compound is that amount effective to prevent occurrence of the symptoms of the disorder or to treat some symptoms of the disorder from which the patient suffers. By "effective amount", "therapeutic

amount" or "effective dose" is meant that amount sufficient to elicit the desired pharmacological or therapeutic effects, thus resulting in effective prevention or treatment of the disorder.

5 [0080] When treating a CNS disorder, an effective amount of compound is an amount sufficient to pass across the blood-brain barrier of the subject, to bind to relevant receptor sites in the brain of the subject and to activate relevant nicotinic receptor subtypes (e.g., provide neurotransmitter secretion, thus resulting in effective prevention or treatment of the disorder). Prevention of the disorder is manifested by delaying the onset of the symptoms of the disorder. Treatment of the disorder is manifested by a decrease in the symptoms associated with the disorder or an amelioration of the recurrence of the symptoms of the disorder. Preferably, the effective amount is sufficient to obtain the desired result, but insufficient to cause appreciable side effects.

10 [0081] The effective dose can vary, depending upon factors such as the condition of the patient, the severity of the symptoms of the disorder, and the manner in which the pharmaceutical composition is administered. For human patients, the effective dose of typical compounds generally requires administering the compound in an amount sufficient to activate relevant receptors to effect neurotransmitter (e.g., dopamine) release, but the amount should be insufficient to induce effects on skeletal muscles and ganglia to any significant degree. The effective dose of compounds will of course differ from patient to patient, but in general includes amounts starting where CNS effects or other desired therapeutic effects occur but below the amount where muscular effects are observed.

15 [0082] The compounds, when employed in effective amounts in accordance with the method described herein, are selective to certain relevant nicotinic receptors, but do not significantly activate receptors associated with undesirable side effects at concentrations at least greater than those required for eliciting the release of dopamine or other neurotransmitters. By this is meant that a particular dose of compound effective in preventing and/or treating a CNS disorder is essentially ineffective in eliciting activation of certain ganglionic-type nicotinic receptors at concentration higher than 5 times, preferably higher than 100 times, and more preferably higher than 1,000 times than those required for activation of dopamine release. This selectivity of certain compounds described herein against those ganglionic-type receptors responsible for cardiovascular side effects is demonstrated by a lack of the ability of those compounds to activate nicotinic function of adrenal chromaffin tissue at concentrations greater than those required for activation of dopamine release.

20 [0083] For human patients, the effective dose of typical compounds generally requires administering the compound in an amount of at least about 1, often at least about 10, and frequently at least about 25  $\mu\text{g}/24 \text{ hr}$ / patient. The effective dose generally does not exceed about 500, often does not exceed about 400, and frequently does not exceed about 300  $\mu\text{g}/24 \text{ hr}$ / patient. In addition, administration of the effective dose is such that the concentration of the compound within the plasma of the patient normally does not exceed 500 ng/mL and frequently does not exceed 100 ng/mL.

25 [0084] The compounds described herein, when employed in effective amounts in accordance with the methods described herein, can provide some degree of prevention of the progression of CNS disorders, ameliorate symptoms of CNS disorders, and ameliorate to some degree of the recurrence of CNS disorders. The effective amounts of those compounds are typically below the threshold concentration required to elicit any appreciable side effects, for example those effects relating to skeletal muscle. The compounds can be administered in a therapeutic window in which certain CNS disorders are treated and certain side effects are avoided. Ideally, the effective dose of the compounds described herein is sufficient to provide the desired effects upon the CNS but is insufficient (i.e., is not at a high enough level) to provide undesirable side effects. Preferably, the compounds are administered at a dosage effective for treating the CNS disorders but less than 1/5, and often less than 1/10, the amount required to elicit certain side effects to any significant degree.

30 [0085] Most preferably, effective doses are at very low concentrations, where maximal effects are observed to occur, with a minimum of side effects. Concentrations, determined as the amount of compound per volume of relevant tissue, typically provide a measure of the degree to which that compound affects cytokine production. Typically, the effective dose of such compounds generally requires administering the compound in an amount of less than 5 mg/kg of patient weight. Often, the compounds of the present invention are administered in an amount from less than about 1 mg/kg patient weight and usually less than about 100  $\mu\text{g}/\text{kg}$  of patient weight, but frequently between about 10  $\mu\text{g}$  to less than 100  $\mu\text{g}/\text{kg}$  of patient weight. For compounds that do not induce effects on muscle-type nicotinic receptors at low concentrations, the effective dose is less than 5 mg/kg of patient weight; and often such compounds are administered in an amount from 50  $\mu\text{g}$  to less than 5 mg/kg of patient weight. The foregoing effective doses typically represent that amount administered as a single dose, or as one or more doses administered over a 24-hour period.

35 [0086] For human patients, the effective dose of typical compounds generally requires administering the compound in an amount of at least about 1, often at least about 10, and frequently at least about 25  $\mu\text{g}/24 \text{ hr}$ / patient. For human patients, the effective dose of typical compounds requires administering the compound which generally does not exceed about 500, often does not exceed about 400, and frequently does not exceed about 300  $\mu\text{g}/24 \text{ hr}$ / patient. In addition, the compositions are advantageously administered at an effective dose such that the concentration of the compound within the plasma of the patient normally does not exceed 500 pg/mL, often does not exceed 300 pg/mL, and frequently does not exceed 100 pg/mL. When employed in such a manner, the compounds are dose dependent, and, as such, inhibit cytokines production and/or secretion when employed at low concentrations but do not exhibit those inhibiting

effects at higher concentrations. The compounds exhibit inhibitory effects on cytokines production and/or secretion when employed in amounts less than those amounts necessary to elicit activation of relevant nicotinic receptor subtypes to any significant degree.

#### 5 IV Methods of Using the Compounds and/or Pharmaceutical Compositions

10 **[0087]** The compounds can be used in the treatment of those types of conditions and disorders for which other types of nicotinic compounds have been proposed as therapeutics. See, for example, Williams et al., *Drug News Perspec.* 7 (4):205 (1994), Arneric et al., *CNS Drug Rev.* 1(1):1 (1995), Arneric et al., *Exp. Opin. Invest. Drugs* 5(1):79 (1996), Bencherif et al., *J Pharmacol, Exp. Ther.* 279: 1413 (1996), Lippiello et al., *J. Pharmacol, Exp. Ther.* 279: 1422 (1996), Damaj et al., *J. Pharmacol. Exp. Ther.* 291:390 (1999); Chiari et al., *Anesthesiology* 91:1447 (1999); Lavand'homme and Eisenbach, *Anesthesiology* 91:1455 (1999); *Neuroscience* (1997), Holladay et al., *J. Med. Chem* 40(28):4169 (1997), Bannon et al., *Science* 279:77 (1998), PCT WO 94/08992, PCT WO 96/31475, and U.S. Patent Nos. 5,583,140 to Bencherif et al., 5,597,919 to Dull et al., and 5,604,231 to Smith et al.

15 **[0088]** The compounds can also be used as adjunct therapy in combination with existing therapies in the management of the aforementioned types of diseases and disorders. In such situations, it is preferably to administer the active ingredients to in a manner that optimizes effects upon abnormal cytokine production, while minimizing effects upon receptor subtypes such as those that are associated with muscle and ganglia This can be accomplished by targeted drug delivery and/or by adjusting the dosage such that a desired effect is obtained without meeting the threshold dosage required to achieve significant side effects.

#### 20 Treatment of CNS Disorders

25 **[0089]** The compounds describe herein are effective at treating a wide variety of CNS disorders. Examples of CNS disorders that can be treated in accordance with the present invention include pre-senile dementia (early onset Alzheimer's disease), senile dementia (dementia of the Alzheimer's type), Lewy Body dementia, HIV-dementia, multiple cerebral infarcts, Parkinsonism including parkinson's disease, Pick's disease, Huntington's chorea, tardive dyskinesia, hyperkinesia, mania, attention deficit disorder, anxiety, depression, mild cognitive impairment, dyslexia, schizophrenia and Tourette's syndrome.

30 **[0090]** CNS Disorders can be treated and/or prevented by administering to a patient an amount of a compound or pharmaceutical composition effective for providing some degree of prevention of the progression of a CNS disorder (i.e., provide protective effects), amelioration of the symptoms of a CNS disorder, and amelioration of the recurrence of a CNS disorder. The method involves administering an effective amount of a compound selected from the general formulae, which are set forth hereinbefore.

#### 35 Other Disorders

40 **[0091]** In addition to treating CNS disorders, the pharmaceutical compositions can be used to prevent or treat certain other conditions, diseases and disorders. Examples include neurodegenerative diseases, autoimmune disorders such as Lupus, disorders associated with cytokine release, anti-inflammatory uses, as well as those indications set forth in PCT WO 98/25619. The pharmaceutical compositions can ameliorate many of the symptoms associated with those conditions, diseases and disorders.

45 **[0092]** Inhibition of cytokine release is desirable in the treatment of cachexia, inflammation, neurodegenerative diseases, viral infection, and neoplasia. The cachexia is often secondary to infection (e.g., as occurs in AIDS, AIDS-related complex and neoplasia) or to cancer therapy. Examples of inflammatory disorders that can be treated include acute cholangitis, aphthous stomatitis, asthma, ulcerative colitis, inflammatory bowel disease, pouchitis, viral pneumonitis and arthritis (e.g., rheumatoid arthritis and osteoarthritis).

**[0093]** The pharmaceutical compositions can also be used as anti-infectious agents (e.g, for treating bacterial, fungal and viral infections, as well as the effects, such as sepsis, of other types of toxins).

50 **[0094]** The compounds can be used as analgesics, to treat convulsions such as those that are symptomatic of epilepsy, to treat conditions such as syphilis and Creutzfeld-Jakob disease.

**[0095]** The compounds can also be appropriately synthesized and used as or within pharmaceutical compositions that are used as diagnostic probes.

55 **[0096]** The compounds useful according to the method of the present invention have the ability to bind to, and in most circumstances, cause activation of, nicotinic cholinergic receptors of the brain of the patient (e.g., such as those receptors that modulate dopamine release). As such, such compounds have the ability to express nicotinic pharmacology, and in particular, to act as nicotinic agonists. The receptor binding constants of typical compounds useful in carrying out the present invention generally exceed about 0.1 nM, often exceed about 1 nM, and frequently exceed about 10 nM. The

receptor binding constants of such typical compounds generally are less than about 1  $\mu$ M often are less than about 100 nM, and frequently are less than about 50 nM. Receptor binding constants provide a measure of the ability of the compound to bind to half of the relevant receptor sites of certain brain cells of the patient. See, Cheng, et al., *Biochem. Pharmacol.* 22: 3099 (1973). The compounds useful according to the method of the present invention have the ability to demonstrate a nicotinic function by effectively eliciting ion flux through, and/or neurotransmitter secretion from, nerve ending preparations (e.g., thalamic or striatal synaptosomes). As such, such compounds have the ability to cause relevant neurons to become activated, and to release or secrete acetylcholine, dopamine, or other neurotransmitters. Generally, typical compounds useful in carrying out the present invention effectively provide for relevant receptor activation in amounts of at least about 30 percent, often at least about 50 percent, and frequently at least about 75 percent, of that maximally provided by (S)-(-)-nicotine. Generally, typical compounds useful in carrying out the present invention are more potent than (S)-(-)-nicotine in eliciting relevant receptor activation. Generally, typical compounds useful in carrying out the present invention effectively provide for the secretion of dopamine in amounts of at least about 50 percent, often at least about 75 percent, and frequently at least about 100 percent, of that maximally provided by (S)-(-)-nicotine. Certain compounds of the present invention can provide secretion of dopamine in an amount which can exceed that maximally provided by (S)-(-)-nicotine. Generally, typical compounds useful in carrying out the present invention are less potent than (S)-(-)-nicotine in eliciting neurotransmitter secretion, such as dopamine secretion.

**[0097]** The compounds of the present invention, when employed in effective amounts in accordance with the method of the present invention, lack the ability to elicit activation of nicotinic receptors of human muscle to any significant degree. In that regard, the compounds of the present invention demonstrate poor ability to cause isotopic rubidium ion flux through nicotinic receptors in cell preparations expressing muscle-type nicotinic acetylcholine receptors. Thus, such compounds exhibit receptor activation constants or EC50 values (i.e., which provide a measure of the concentration of compound needed to activate half of the relevant receptor sites of the skeletal muscle of a patient) which are extremely high (i.e., greater than about 100  $\mu$ M). Generally, typical preferred compounds useful in carrying the present invention activate isotopic rubidium ion flux by less than 10 percent, often by less than 5 percent, of that maximally provided by S(-) nicotine.

**[0098]** The compounds of the present invention, when employed in effective amounts in accordance with the method of the present invention, are selective to certain relevant nicotinic receptors, but do not cause significant activation of receptors associated with undesirable side effects. By this is meant that a particular dose of compound resulting in prevention and/or treatment of a CNS disorder, is essentially ineffective in eliciting activation of certain ganglionic-type nicotinic receptors. This selectivity of the compounds of the present invention against those receptors responsible for cardiovascular side effects is demonstrated by a lack of the ability of those compounds to activate nicotinic function of adrenal chromaffin tissue. As such, such compounds have poor ability to cause isotopic rubidium ion flux through nicotinic receptors in cell preparations derived from the adrenal gland. Generally, typical preferred compounds useful in carrying out the present invention activate isotopic rubidium ion flux by less than 10 percent, often by less than 5 percent, of that maximally provided by S(-) nicotine.

**[0099]** Compounds of the present invention, when employed in effective amounts in accordance with the method of the present invention, are effective towards providing some degree of prevention of the progression of CNS disorders, amelioration of the symptoms of CNS disorders, and amelioration to some degree of the recurrence of CNS disorders. However, such effective amounts of those compounds are not sufficient to elicit any appreciable side effects, as is demonstrated by decreased effects on preparations believed to reflect effects on the cardiovascular system, or effects to skeletal muscle. As such, administration of compounds of the present invention provides a therapeutic window in which treatment of certain CNS disorders is provided, and side effects are avoided. That is, an effective dose of a compound of the present invention is sufficient to provide the desired effects upon the CNS, but is insufficient (i.e., is not at a high enough level) to provide undesirable side effects. Preferably, effective administration of a compound of the present invention resulting in treatment of CNS disorders occurs upon administration of less 1/3, frequently less than 1/5, and often less than 1/10, that amount sufficient to cause any side effects to a significant degree.

**[0100]** The following examples are provided to illustrate the present invention, and should not be construed as limiting thereof. In these examples, all parts and percentages are by weight, unless otherwise noted. Reaction yields are reported in mole percentages. Several commercially available starting materials are used throughout the following examples. 3-Bromopyridine, 3,5-dibromopyridine, 5-bromonicotinic acid, 5-bromopyrimidine, and 4-penten-2-ol were obtained from Aldrich Chemical Company or Lancaster Synthesis Inc. 2-Amino-5-bromo-3-methylpyridine was purchased from Maybridge Chemical Company Ltd. (R)-(+)-propylene oxide was obtained from Fluka Chemical Company, and (S)-(-)-propylene oxide was obtained from Aldrich Chemical Company. Column chromatography was done using either Merck silica gel 60 (70-230 mesh) or aluminum oxide (activated, neutral, Brockmann I, standard grade, about 150 mesh). Pressure reactions were done in a heavy wall glass pressure tube (185 mL capacity), with Ace-Thread, and plunger valve available from Ace Glass Inc. Reaction mixtures were typically heated using a high-temperature silicon oil bath, and temperatures refer to those of the oil bath. The following abbreviations are used in the following examples:  $\text{CHCl}_3$  for chloroform,  $\text{CH}_2\text{Cl}_2$  for dichloromethane,  $\text{CH}_3\text{OH}$  for methanol, DMF for N,N-dimethylformamide, and EtOAc for ethyl

acetate, THF for tetrahydrofuran, and Et<sub>3</sub>N for triethylamine.

## V. Assays

### 5 Binding Assay

[0101] The ability of the compounds to bind to relevant receptor sites was determined in accordance with the techniques described in U.S. Patent No. 5,597,919 to Dull et al. Inhibition constants ( $K_i$  values) were calculated from the  $IC_{50}$  values using the method of Cheng et al., Biochem. Pharmacol. 22:3099 (1973). For the  $\alpha 4\beta 2$  subtype, the  $K_i$  value for each of  
10 the examples in this application was less than 1  $\mu$ M, indicating that compounds of the present invention bind tightly to the receptor.

### Determination of Log P Value

15 [0102] Log P values, which have been used to assess the relative abilities of compounds to pass across the blood-brain barrier (Hansch, et al., J. Med. Chem. 11: 1 (1968)), were calculated using the Cerius<sup>2</sup> software package Version 3.5 by Molecular Simulations, Inc.

### Determination of Dopamine Release

20 [0103] Dopamine release was measured using the techniques described in U.S. Pat. No. 5,597,919 to Dull et al. Release is expressed as a percentage of release obtained with a concentration of (S)-(-)-nicotine resulting in maximal effects. Reported  $EC_{50}$  values are expressed in nM, and  $E_{max}$  values represent the amount released relative to (S)-(-)-nicotine on a percentage basis.

### Determination of Rubidium Ion Release

25 [0104] Rubidium release was measured using the techniques described in Bencherif et al., JPET 279: 1413-1421 (1996). Reported  $EC_{50}$  values are expressed in nM, and  $E_{max}$  values represent the amount of rubidium ion released relative to 300 $\mu$ M tetramethylammonium ion, on a percentage basis.

### Determination of Interaction with Muscle Receptors

35 [0105] The determination of the interaction of the compounds with muscle receptors was carried out in accordance with the techniques described in U.S. Pat. No. 5,597,919 to Dull et al. The maximal activation for individual compounds ( $E_{max}$ ) was determined as a percentage of the maximal activation induced by (S)-(-)-nicotine. Reported  $E_{max}$  values represent the amount released relative to (S)-(-)-nicotine on a percentage basis.

### Determination of Interaction with Ganglion Receptors

40 [0106] The determination of the interaction of the compounds with ganglionic receptors was carried out in accordance with the techniques described in U.S. Pat. No. 5,597,919 to Dull et al. The maximal activation for individual compounds ( $E_{max}$ ) was determined as a percentage of the maximal activation induced by (S)-(-)-nicotine. Reported  $E_{max}$  values represent the amount released relative to (S)-(-)-nicotine on a percentage basis.

### 45 Selectivity

[0107] The selectivity of the compounds for a given receptor can be evaluated by comparing the binding of the compounds to different receptors using known methodology.

## VI. Synthetic Examples

55 [0108] The following synthetic examples are provided to illustrate the present invention and should not be construed as limiting the scope thereof. In these examples, all parts and percentages are by weight, unless otherwise noted. Reaction yields are reported in mole percentage.

## Example 1

[0109] Sample No. 1 is 7-(3-pyridyl)-1,7-diazaspiro[4.4]nonane dihydrochloride, which was prepared according to the following techniques:

5 **Nitroethylene**

[0110] Nitroethylene was prepared accordingly to the procedure reported by Ranganathan, et al., J. Org. Chem. 45: 1185 (1980).

10 **Ethyl 2-(2-nitroethyl)-1-benzylpyrrolidine-2-carboxylate**

[0111] Under a nitrogen atmosphere, a solution of diisopropylamine (4.34 g, 6.01 mL, 42.9 mmol) in dry THF (50 mL) was cooled in an ice bath as n-butyllithium (17.1 mL of 2.5 M in hexane, 42.8 mmol) was added by syringe. The ice bath was removed and the solution of lithium diisopropylamide was first warmed to ambient temperature and then transferred by cannula into a stirred solution of ethyl (S)-N-benzyl pyrrolidine-2-carboxylate (10.0 g, 42.9 mmol) (Fluka) in dry THF (50 mL), held at -78°C under nitrogen. The addition took 10 min. After stirring an additional 30 min at -78°C, the enolate solution was treated (via cannula) with a solution of nitroethylene (3.13 g, 42.9 mmol) in dry THF (20 mL). The mixture was then stirred for 1 h at -78°C. Saturated aqueous ammonium chloride solution was then added (at -78°C), and the mixture was warmed to ambient temperature and extracted the ethyl acetate (4 x 30 mL). The extracts were dried (K<sub>2</sub>CO<sub>3</sub>) and concentrated by rotary evaporation. The residue was purified by chromatography on a Merck silica gel 60 (70-230 mesh) column with 9:1 (v/v) hexane/ethyl acetate. Concentration of selected fractions gave 10.0 g (76.3%) of viscous, tan oil.

25 **6-Benzyl-2,6-diazaspiro[4.4] nonan-1-one**

[0112] Raney nickel (-2 g) was added to a solution of ethyl 2-(2-nitroethyl)-1-benzylpyrrolidine-2-carboxylate (6.00 g, 19.6 mmol) in absolute ethanol (200 mL) in a hydrogenation bottle. The mixture was shaken for 12 h under a hydrogen atmosphere (50 psi) in a Parr hydrogenation apparatus, filtered through a Celite pad and concentrated by rotary evaporation. GCMS analysis indicated that the hydrogenation product was a mixture of the primary amine and the lactam resulting from cyclization of the amine onto the ester. The mixture was dissolved in toluene (150 mL). A catalytic amount of p-toluenesulfonic acid (~30 mg) was added and the mixture was heated at reflux under a nitrogen atmosphere for 24 h. Upon evaporation of the toluene, the residue (now entirely lactam, by GCMS) crystallized to give 4.20 g (93.1%) of tan solid (mp 152-153°C).

35 **1-Benzyl-1,7-diazaspiro [4.4] nonane**

[0113] Lithium aluminum hydride (1.98 g, 52.2 mmol) was added in portions, under argon, to a ice bath cooled solution of 6-benzyl-2,6-diazaspiro[4.4]nonan-1-one (4.00 g, 17.4 mmol) in dry THF (100 mL). The addition funnel was replaced with a reflux condenser, and the mixture was heated at reflux for 24 h. The mixture was cooled to 0°C and treated dropwise (caution: exothermic reaction) with 10 M aqueous sodium hydroxide until hydrogen evolution ceased and the aluminate salts were granular. The mixture was stirred 1 h at 0°C and filtered through Celite. The filtrate was dried (K<sub>2</sub>CO<sub>3</sub>) and concentrated, leaving 3.60 g (95.7%) of viscous, colorless liquid.

45 **1-Benzyl-7-(3-pyridyl)-1,7-diazaspiro[4.4]nonane**

[0114] A mixture of 1-benzyl-1,7-diazaspiro[4.4]nonane (2.00 g, 9.26 mmol), 3-bromopyridine (1.38 g, 8.73 mmol), potassium tert-butoxide (2.50 g, 22.3 mmol), tris(dibenzylideneacetone)dipalladium(0) (0.318 g, 0.347 mmol), 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (0.324 g, 0.520 mmol) and dry toluene (50 mL) was placed in a pressure tube under argon. The mixture was stirred and heated at 90°C (bath temperature) for 24 h and cooled. Water (20 mL) was added and the mixture was extracted with ethyl acetate (6 x 25 mL). The extracts were dried (K<sub>2</sub>CO<sub>3</sub>) and concentrated. Column chromatography of the residue on Merck silica gel 60 (70-230 mesh), with 6:4 (v/v) chloroform/acetone, gave 1.80 g (66.2%) of light brown oil, after concentration of selected fractions.

55 **7-(3-Pyridyl)-1,7-diazaspiro[4.4]nonane dihydrochloride**

[0115] Aqueous hydrochloric acid (0.5 mL of 12 M) and 10% palladium on carbon (0.100 g) were added to a solution of 1-benzyl-7-(3-pyridyl)-1,7-diazaspiro[4.4]nonane (1.0 g, 3.41 mmol) in methanol (30 mL). The mixture was shaken

under a hydrogen atmosphere (50 psi) in a Parr hydrogenation apparatus for 24 h and filtered through Celite. The filtrate was concentrated by rotary evaporation and column chromatographed on Merck silica gel 60 (70-230 mesh). Elution with 0.01:1:9 (v/v) aqueous ammonia/methanol/chloroform, and concentration of selected fractions, gave 0.650 g (93.8%) of viscous, brown oil. A portion (300 mg, 1.48 mmol) of this material was treated with aqueous hydrochloric acid (2 mL). The water was azeotropically removed by repeated treatment with small volumes of ethanol (~ 5 mL) and rotary evaporation. The resulting solid was recrystallized from hot isopropanol to give 360 mg (88.2%) of fine tan crystals.

#### Example 2

**[0116]** Sample 2 is 1-(3-pyridyl)-1,7-diaza-spiro[4.4]nonane dihydrochloride, which was prepared according to the following techniques:

#### **tert-Butyl 6-benzyl-2,6-diazaspiro[4.4]nonane-2-carboxylate**

**[0117]** Di-*t*-butyl dicarbonate (1.45 g, 6.64 mmol) was added to a solution of 1-benzyl-1,7-diazaspiro[4.4]nonane (1.30 g, 6.01 mmol) and triethylamine (1 mL) in dichloromethane (25 mL), and the mixture was stirred at ambient temperature overnight. The mixture was poured into saturated aqueous sodium bicarbonate (10 mL) and extracted with chloroform (4 x 25 mL). The extracts were dried ( $K_2CO_3$ ) and concentrated by rotary evaporation. The residue was column chromatographed on Merck silica gel 60 (70-230 mesh), eluting with, to give 1.85 g (97.4%) of viscous, colorless oil, after concentration of selected fractions.

#### **tert-Butyl 2,6-diazaspiro[4.4]nonane-2-carboxylate**

**[0118]** A solution of *t*-butyl 6-benzyl-2,6-diazaspiro[4.4]nonane-2-carboxylate (1.70 g, 5.37 mmol) in methanol (30 mL) was mixed with 10% palladium on carbon (50 mg). The mixture was shaken under a hydrogen atmosphere (50 psi) in a Parr hydrogenation apparatus for 8 h and filtered through Celite. The filtrate was concentrated by rotary evaporation and high vacuum treatment, leaving 1.26 g of viscous, light brown oil (>100%), which was of sufficient purity to be used in the subsequent reaction.

#### **tert-Butyl 6-(3-pyridyl)-2,6-diazaspiro[4.4]nonane-2-carboxylate**

**[0119]** A mixture of *tert*-butyl 2,6-diazaspiro[4.4]nonane-2-carboxylate (1.00 g, -4.4 mmol), 3-bromopyridine (0.736 g, 4.66 mmol), potassium *tert*-butoxide (1.22 g, 10.9 mmol), tris(dibenzylideneacetone)dipalladium(0) (0.155 g, 0.169 mmol), 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (0.158 g, 0.254 mmol) and dry toluene (25 mL) was placed in a pressure tube under argon. The mixture was stirred and heated at 180°C (bath temperature) for 8 h and cooled. Thin layer analysis indicated that very little conversion had taken place. A second charge, equal in quantity to the first, of all reagents except the *tert*-butyl 2,6-diazaspiro[4.4]nonane-2-carboxylate was added to pressure tube and the tube was returned to the bath for another 8 h. Again relatively little reaction seemed to have occurred, so a third charge of reagents was added and heating (at 180°C) was continued for a third 8 h period. Water (20 mL) was added and the mixture was extracted with ethyl acetate (6 x 25 mL). The extracts were dried ( $K_2CO_3$ ) and concentrated. Column chromatography of the residue on Merck silica gel 60 (70-230 mesh), with 6:4 (v/v) chloroform/acetone, gave 150 mg (~11 %) of light brown oil, after concentration of selected fractions.

#### **1-(3-Pyridyl)-1,7-diazaspiro[4.4]nonane dihydrochloride**

**[0120]** A solution of *tert*-butyl 6-(3-pyridyl)-2,6-diazaspiro[4.4]nonane-2-carboxylate (100 mg, 0.330 mmol) in dichloromethane (5 mL) was rapidly stirred with 1 mL of 12 M hydrochloric acid at ambient temperature for 1 h, during which time the biphasic mixture became monophasic. The dichloromethane was evaporated, and the residue was dissolved in water (3 mL) and made strongly basic (pH 9) with potassium carbonate. The mixture was saturated with sodium chloride and extracted with chloroform (4x10 mL). The extracts were dried ( $K_2CO_3$ ) and concentrated, first by rotary evaporation and then by high vacuum treatment. The viscous brown oil which resulted was 98% pure by GCMS and weighed 50 mg (73%). A sample of this free base (40 mg, 0.20 mmol) was dissolved in 10 drops of 12 M hydrochloric acid. The water was azeotropically removed by repeated treatment with small volumes of ethanol (~ 5 mL) and rotary evaporation. The resulting solid was recrystallized from hot isopropanol to give 40 mg (72%) of fine tan crystals (mp 170-175°C).

## Example 3

[0121] Sample 3 is 1-methyl-7-(3-pyridyl)-1,7-diazaspiro[4.4]nonane, which was prepared according to the following techniques:

5  
**1-Methyl-7-(3-pyridyl)-1,7-diazaspiro[4.4]nonane**

[0122] 7-(3-Pyridyl)-1,7-diazaspiro[4.4]nonane (30 mg, 0.15 mmol) was dissolved in 98% formic acid (0.5 mL) and formaldehyde (1 mL, 28% aqueous solution). The reaction mixture was heated to reflux for 8 h. The reaction mixture was cooled to room temperature, basified with saturated aqueous sodium bicarbonate to pH 9-10 and extracted with chloroform (4 x 3mL). The combined chloroform extracts were dried ( $K_2CO_3$ ), filtered and concentrated on a rotary evaporator to afford 30 mg of the desired compound (93.6%) as a light brown liquid.

15  
**Example 4**

[0123] Sample 4 is 1-methyl-7-(5-ethoxy-3-pyridyl)-1,7-diazaspiro[4.4]nonane, which was prepared according to the following techniques:

20  
**5-bromo-3-ethoxypyridine**

[0124] Under a nitrogen atmosphere, sodium (4.60 g, 200 mmol) was added to absolute ethanol (100 mL) at 0-5°C, and the stirring mixture was allowed to warm to ambient temperature over 18 h. To the resulting solution was added 3,5-dibromopyridine (31.5 g, 133 mmol), followed by DMF (100 mL). The mixture was heated at 70°C for 48 h. The brown mixture was cooled, poured into water (600 mL), and extracted with ether (3 x 500 mL). The combined ether extracts were dried ( $Na_2SO_4$ ), filtered, and concentrated by rotary evaporation. Purification by vacuum distillation afforded 22.85 g (85.0%) of an oil, bp 89-90°C at 2.8 mm Hg (lit. bp 111 °C at 5 mm Hg, see K. Clarke, et al., *J. Chem. Soc.* 1885 (1960)).

25  
**1-Benzyl-7-(5-ethoxy-3-pyridyl)-1,7-diazaspiro[4.4]nonane**

[0125] 1-Benzyl-1,7-diazaspiro[4.4]nonane (500.0 mg, 2.4 mmol) was dissolved in dry toluene (15 mL) in a 50 mL round bottom flask equipped with a magnetic stirring bar. Nitrogen was bubbled through the solution in a slow stream. To the stirring solution was added 3-bromo-5-ethoxypyridine (513.8 mg, 2.55 mmol), potassium tert-butoxide (1039.0 mg, 9.26 mmol), rac-2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (86.4 mg, 0.14 mmol) and tris(dibenzylideneacetone) dipalladium(0) (63.6 mg, 0.06 mmol), while continuing to purge with nitrogen. Nitrogen flow was discontinued and the flask was sealed and heated at 90°C for 8 h. The reaction was cooled and the solvent was removed by rotary evaporation. The resulting residue was suspended in saturated aqueous sodium bicarbonate (10 mL) and extracted with chloroform (4 x 25 mL). The combined organic extracts were dried ( $Na_2SO_4$ ), filtered, and concentrated by rotary evaporation to a thick dark mass. Purification by column chromatography, using methanol/chloroform (2:98, v/v) as the eluent, gave 0.54 g of the desired compound as a light brown viscous liquid (69%).

30  
**7-(5-Ethoxy-3-pyridyl)-1,7-diazaspiro[4.4]nonane**

[0126] To a solution of 1-benzyl-7-(5-ethoxy-3-pyridyl)-1,7-diazaspiro[4.4]nonane (540 mg, 1.6 mmol) in ethanol (25 mL) in a pressure bottle was added concentrated HCl (1 mL) and Pearlman's catalyst ( $Pd(OH)_2$ , 20% on carbon, 50 mg). The solution was shaken under 50 psi of hydrogen gas for 8 h. The catalyst was removed by filtration through Celite, and the filter cake was washed with ethanol (20 mL). The solvent was removed by rotary evaporation, and the residue was basified with saturated aqueous sodium bicarbonate to pH 8-9. Solid sodium chloride (2 g) was added, and the mixture was extracted with chloroform (4 x 20 mL). The combined chloroform extracts were dried ( $Na_2SO_4$ ), filtered and concentrated by rotary evaporation to afford 360.7 mg of the desired compound as a light brown viscous liquid (91.1%).

35  
**1-Methyl-7-(5-ethoxy-3-pyridyl)-1,7-diazaspiro[4.4]nonane**

[0127] To a stirring solution of 7-(5-ethoxy-3-pyridyl)-1,7-diazaspiro[4.4]nonane (360.4mg, 1.4 mmol) in 37% aqueous solution of formaldehyde (4 mL) was added 98 % formic acid (2 mL) under nitrogen. The reaction mixture was heated to reflux for 8 h. The reaction mixture was cooled to room temperature, then basified with saturated aqueous sodium bicarbonate to pH 8-9 and extracted with chloroform (4 x 15mL). The combined chloroform extracts were dried ( $Na_2SO_4$ ), filtered and concentrated by rotary evaporation to afford a viscous brown liquid. This was distilled using a Kugelrohr

apparatus (2mm, 180°C) to give a very light cream-colored syrup (340 mg, 89.3%).

#### Example 5

5 **[0128]** Sample 5 is 1-methyl-7-(5-phenoxy-3-pyridyl)-1,7-diazaspiro[4.4]nonane, which was prepared according to the following techniques:

#### 3-Bromo-5-phenoxy pyridine

10 **[0129]** Sodium hydride (1.35 g of 80% in mineral oil, 45.0 mmol) was added to a stirred solution of phenol (4.26 g, 45.3 mmol) in DMF (30 mL) at 0°C, under nitrogen. The mixture was stirred at room temperature for 3 h, treated with 3,5-dibromopyridine (4.0 g, 16.9 mmol) and heated at 100°C for 48 h. The reaction mixture was cooled to room temperature, poured into a mixture of water (100 mL) and 5M sodium hydroxide (10 mL), and extracted with ether (3 x 60 mL). The combined ether extracts were dried (Na<sub>2</sub>SO<sub>4</sub>), filtered, and rotary evaporated to a pale yellow semi-solid (4.9 g).  
15 This was chromatographed on a silica gel (200 g) column with hexane/ethyl acetate/chloroform (8:1:1, v/v) as eluant to give 2.86 g (68% yield) of a colorless oil.

#### 1-Benzyl-7-(5-phenoxy-3-pyridyl)-1,7-diazaspiro[4.4]nonane

20 **[0130]** 1-Benzyl-1,7-diazaspiro[4.4]nonane (500.0 mg, 2.4 mmol) was dissolved in dry toluene (15 mL) in a 50 mL round bottom flask equipped with a magnetic stirring bar. Nitrogen was bubbled through the solution in a slow stream. To the stirring solution was added 3-bromo-5-phenoxy pyridine (636.8 mg, 2.55 mmol), potassium tert-butoxide (1039.0 mg, 9.26 mmol), rac-2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (86.4 mg, 0.14 mmol) and tris(dibenzylideneacetone) dipalladium(0) (63.6 mg, 0.06 mmol), while continuing to purge with nitrogen. Nitrogen flow was discontinued and the  
25 flask was sealed and heated at 90°C for 8 h. The reaction was cooled and the solvent was removed by rotary evaporation. The resulting residue was suspended in saturated aqueous sodium bicarbonate (10 mL) and extracted with chloroform (4 x 25 mL). The combined organic extracts were dried (Na<sub>2</sub>SO<sub>4</sub>), filtered, concentrated by rotary evaporation to a thick dark mass. This was purified by column chromatography, using methanol/chloroform (2:98, v/v) as the eluent, to afford 0.70 g of the desired compound as a light brown viscous liquid (78.6%).

#### 7-(5-Phenoxy-3-pyridyl)-1,7-diazaspiro[4.4]nonane

30 **[0131]** To a solution of 1-benzyl-7-(5-phenoxy-3-pyridyl)-1,7-diazaspiro[4.4]nonane (690 mg, 1.79 mmol) in ethanol (25 mL) in a pressure bottle was added concentrated HCL (1mL) and Pearlman's catalyst (Pd(OH)<sub>2</sub>, 20% on carbon, 50 mg). The solution was shaken under 50 psi of hydrogen gas for 8 h. The catalyst was removed by filtration through Celite, and the filter cake was washed with ethanol (20 mL). The solvent was removed by rotary evaporation, and the residue was basified with saturated aqueous sodium bicarbonate to pH 8-9. Solid sodium chloride (2 g) was added, and the solution was extracted with chloroform (4 x 20 mL). The combined chloroform extracts were dried (Na<sub>2</sub>SO<sub>4</sub>), filtered and concentrated by rotary evaporation to afford 490 mg of the desired compound as a light brown viscous liquid (92.7 %).  
35

#### 1-Methyl-7-(5-phenoxy-3-pyridyl)-1,7-diazaspiro[4.4]nonane

40 **[0132]** To a stirring solution of 7-(5-phenoxy-3-pyridyl)-1,7-diazaspiro[4.4]nonane (420 mg, 1.42 mmol) in 37% aqueous solution of formaldehyde (5 mL) was added 98% formic acid (3 mL) under nitrogen. The reaction mixture was heated to reflux for 8 h. The reaction mixture was cooled to room temperature, then basified with saturated aqueous sodium bicarbonate to pH 8-9 and extracted with chloroform (4 x 15 mL). The combined chloroform extracts were dried (Na<sub>2</sub>SO<sub>4</sub>), filtered and concentrated by rotary evaporation to afford a thick brown viscous liquid. This was distilled using a Kugelrohr apparatus (2mm, 180°C) to give a very pale cream-colored syrup (400 mg, 90.9 %).  
45

#### 1-Methyl-7-(5-phenoxy-3-pyridyl)-1,7-diazaspiro[4.4]nonane dihydrochloride

50 **[0133]** 1-Methyl-7-(5-phenoxy-3-pyridyl)-1,7-diazaspiro[4.4]nonane (200 mg, 0.65 mmol) was dissolved in concentrated HCl (1 mL) and sonicated for 5 min. The excess acid and water were removed by repeated azeotropic evaporation with small portions of ethanol. A pale yellow solid was obtained. The solid was dissolved in the minimum amount of absolute ethanol (~ 1 mL), and then ether was added drop-wise until the solution became opaque. Cooling in the refrigerator overnight produced cream-colored crystals, which were filtered, washed with ether and dried in a vacuum oven to yield 210 mg (85.4 %) of pure dihydrochloride salt, m.p. 180-191°C.  
55

Examples 12 and 13

[0134] Samples 12 and 13 are (+) and (-) 7-(3-pyridyl)-1,7-diazaspiro[4.4]nonane respectively, which were prepared according to the following techniques:

#### Diastereomeric 7-(3-pyridyl)-1,7-diazaspiro[4.4]nonane S-proline amides

[0135] Triethylamine (6.0 mL, 43 mmol) and diphenyl chlorophosphate (4.0 mL, 19 mmol) were added, in that order, to a stirred suspension of N-(tert-butoxycarbonyl)-S-proline (4.67 g, 21.7 mmol) in dichloromethane (100 mL) under a nitrogen atmosphere. After stirring for 1.5 h at ambient temperature, the reaction mixture was treated with a solution of 7-(3-pyridyl)-1,7-diazaspiro[4.4]nonane (4.40 g, 21.6 mmol) in dichloromethane (10 mL). The mixture was stirred 3 days at ambient temperature. Sodium hydroxide solution (30 mL of 5 M) was then added. After stirring an additional hour, the mixture was poured into a separatory funnel with chloroform (30 mL) and water (30 mL). The mixture was shaken vigorously, and the layers were separated. The organic layer and a 30 mL chloroform extract of the aqueous layer were combined, dried (MgSO<sub>4</sub>) and concentrated by rotary evaporation. The residue (7.2 g) was dissolved in dichloromethane (100 mL) and combined with trifluoroacetic acid (50 mL). The mixture was stirred at ambient temperature for 1 h. The volatiles were evaporated, first by rotary evaporation and then on the vacuum pump. The residue was purified by preparative HPLC, using 10% acetonitrile, 0.1% trifluoroacetic acid in water as eluent. Selected fractions were combined and concentrated, leaving 3.13 g (79% yield) of the diastereomer which elutes at 11.4 min and 2.90 g (74% yield) of the diastereomer that elutes at 13.2 min, both as white foams (presumably mono trifluoroacetate salts).

#### (+) and (-) 7-(3-pyridyl)-1,7-diazaspiro[4.4]nonane

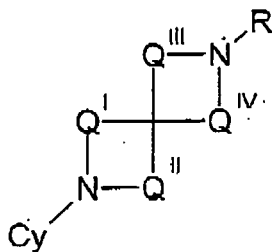
[0136] Each of the two diastereomeric S-proline amides was dissolved in dichloromethane (50 mL) and triethylamine (2-3 mL), and then combined with phenylisothiocyanate (1.73 g, 12.8 mmol for the earlier eluting diastereomer and 1.57 g, 11.6 mmol for the later eluting diastereomer). The two reactions were stirred at ambient temperature for 16 h, at which point thin layer chromatography indicated that the reactions were complete. The mixtures were concentrated by rotary evaporation, and each of the residues was taken up in dichloromethane (10 mL) and treated with trifluoroacetic acid (10 mL). These reactions were held at 50°C for 16 h and concentrated to dryness. Column chromatography on silica gel with 80:20:2 chloroform/methanol/ammonia gave 620 mg (derived from the earlier eluting diastereomer, 40.5% yield) and 720 mg (derived from the later eluting diastereomer, 50.7% yield), as light brown oils. Chiral HPLC analysis was performed on a Chiralcel OD® column, using 7:3 hexane/ethanol. The isomer derived from the earlier eluting diastereomer had the longer retention time on the chiral column (10.9 min); that derived from the later eluting isomer exhibited a retention time of 8.7 min on the chiral column. The samples were enantiomerically pure within the limits of detection (~2%).

[0137] Having hereby disclosed the subject matter of the present invention, it should be apparent that many modifications, substitutions, and variations of the present invention are possible in light thereof. It is to be understood that the present invention can be practiced other than as specifically described. Such modifications, substitutions and variations are intended to be within the scope of the present application.

#### Claims

1. A compound having the following formula:

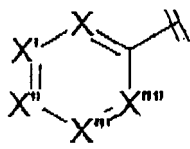
Formula 1



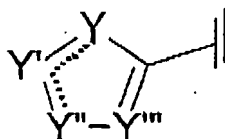
EP 1 519 939 B9

and pharmaceutically acceptable salts thereof,  
 wherein Q<sup>I</sup> is (CZ<sub>2</sub>)<sub>u</sub>, Q<sup>II</sup> is (CZ<sub>2</sub>)<sub>v</sub>, Q<sup>III</sup> is (CZ<sub>2</sub>)<sub>w</sub>, and Q<sup>IV</sup> is (CZ<sub>2</sub>)<sub>x</sub>

u, v, w and x are individually 0, 1, 2, 3 or 4, preferably 0, 1, 2 or 3 and are selected such that the diazaspirocyclic ring of the compound of Formula 1 contains 7, 8 or 9 members,  
 R is hydrogen, lower alkyl, acyl, alkoxy carbonyl or aryloxy carbonyl,  
 Z is, individually, selected from the group consisting of hydrogen, lower alkyl and aryl;  
 Cy is a six membered heteroaromatic ring of the formula:



where each of X, X', X'', X''' and X'''' is individually nitrogen, nitrogen bonded to oxygen or carbon bonded to a substituent species, wherein no more than three of X, X', X'', X''' and X'''' are nitrogen or nitrogen bonded to oxygen, or Cy is a five 5-membered heteroaromatic ring of the formula:



where Y and Y'' are individually nitrogen, nitrogen bonded to a substituent species, oxygen, sulfur or carbon bonded to a substituent species and Y' and Y''' are nitrogen or carbon bonded to a substituent species, wherein "substituent species" are, individually, selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, heterocyclyl, substituted heterocyclyl, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, alkylaryl, substituted alkylaryl, arylalkyl, substituted arylalkyl, halo, -OR', -NR'R'', -CF<sub>3</sub>, -CN, -NO<sub>2</sub>, -C<sub>2</sub>R', -SR', -N<sub>3</sub>, -C(=O)NR'R'', -NR'C(=O)R'', -C(=O)R', -C(=O)OR', -OC(=O)R', -O(CR'R'')<sub>r</sub>C(=O)R', -O(CR'R'')<sub>r</sub>NR'C(=O)R', -O(CR'R'')<sub>r</sub>NR''SO<sub>2</sub>R', -OC(=O)NR'R'', -NR'C(=O)OR'', -SO<sub>2</sub>R', -SO<sub>2</sub>NR'R'', and -NR'SO<sub>2</sub>R'',

where R' and R'' are individually hydrogen, C<sub>1</sub>-C<sub>8</sub> alkyl, cycloalkyl, heterocyclyl, aryl, or arylalkyl, and r is an integer from 1 to 6, or R' and R'' can combine to form a cyclic functionality,

wherein the term "substituted" as applied to alkyl, aryl, cycloalkyl, alkenyl, heterocyclyl, alkylaryl and aryl alkyl refers to the substituents described above, starting with halo and ending with -NR'SO<sub>2</sub>R'', and

wherein the dashed lines indicate that the bonds (between Y and Y' and between Y'' and Y''') can be either single or double bonds, with the proviso that when the bond between Y and Y' is a single bond, the bond between Y'' and Y''' must be a double bond and vice versa, where Y or Y'' is oxygen or sulfur, only one of Y and Y'' is either oxygen or sulfur, and at least one of Y, Y', Y'' and Y''' must be oxygen, sulfur, nitrogen or nitrogen bonded to a substituent species.

2. The compound of claim 1, wherein only one or two of X, X', X'', X''' and X'''' are nitrogen or nitrogen bonded to oxygen.

3. The compound of claim 1, wherein not more than one of X, X', X'', X''' and X'''' are nitrogen bonded to oxygen.

4. The compound of claim 1, wherein X''' is nitrogen or nitrogen bonded to oxygen.

5. The compound of claim 1, wherein both X' and X''' are nitrogen.

6. The compound of claim 1, wherein X, X'' and X'''' are carbon bonded to a substituent species.

7. The compound of claim 6, where the substituent species at X, X'' and X'''' are hydrogen.

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8. The compound of claim 1, wherein X<sup>'''</sup> is carbon bonded to a substituent species and X and X' are both nitrogen, or X' is carbon bonded to a substituent species and X and X<sup>'''</sup> are both nitrogen.
- 5 9. The compound of claim 1, wherein no more than three of Y, Y', Y'' and Y<sup>'''</sup> are oxygen, sulfur, nitrogen or nitrogen bonded to a substituent species.
10. The compound of claim 1, wherein between one and three of Y, Y', Y'' and Y<sup>'''</sup> are nitrogen.
- 10 11. A pharmaceutical composition including a compound of any one of claims 1 to 10.
12. Use of an effective amount of a compound of any one of claims 1 to 10 in the manufacture of a medicament for treating or preventing a CNS disorder associated with the release of neurotransmitters mediated by nicotinic receptors.
- 15 13. The compound of any one of claims 1 to 10 for use in treating or preventing a CNS disorder associated with the release of neurotransmitters mediated by nicotinic receptors.
- 20 14. The use of claim 12 or compound of claim 13, wherein the CNS disorder is selected from the group consisting of pre-senile dementia (early onset Alzheimer's disease), senile dementia (dementia of the Alzheimer's type), Lewy Body dementia, HIV-dementia, multiple cerebral infarcts, Parkinsonism including Parkinson's disease, Pick's disease, Huntington's chorea, tardive dyskinesia, hyperkinesia, mania, attention deficit disorder, anxiety, depression, mild cognitive impairment, dyslexia, schizophrenia and Tourette's syndrome.
- 25 15. The use of claim 12 or compound of claim 13, wherein the compound or medicament is for administering the compound at a dosage effective at treating or preventing the CNS disorder but at a dosage that does not result in appreciable amounts of side effects associated with stimulation of muscle or ganglionic receptors.
- 30 16. Use of an effective amount of a compound of any one of claims 1 to 10 in the manufacture of a medicament for causing analgesia, reducing inflammation, treating ulcerative colitis, inflammatory and auto-immune diseases, treating neurodegenerative diseases, and/or treating convulsions.
- 35 17. The compound of any one of claims 1 to 10 for use in causing analgesia, reducing inflammation, treating ulcerative colitis, inflammatory and auto-immune diseases, treating neurodegenerative diseases, and/or treating convulsions.
- 40 18. Use of an effective amount of a compound of any one of claims 1 to 10 in the manufacture of a medicament for treating bacterial, fungal and/or viral infections, and/or the effects of toxins produced by such infections.
- 45 19. The compound of any one of claims 1 to 10 for use in treating bacterial, fungal and/or viral infections, and/or the effects of toxins produced by such infections.
- 50 20. Use of an effective amount of a compound of any one of claims 1 to 10 in the manufacture of a medicament for treating inflammatory bowel disease, pouchitis, acute cholangitis, aphthous stomatitis, arthritis, neurodegenerative diseases, Creutzfeldt-Jakob disease, cachexia secondary to infection, genetic diseases and disorders, and/or auto-immune disorders.
- 55 21. The compound of any one of claims 1 to 10 for use in treating inflammatory bowel disease, pouchitis, acute cholangitis, aphthous stomatitis, arthritis, neurodegenerative diseases, Creutzfeldt-Jakob disease, cachexia secondary to infection, genetic diseases and disorders, and/or auto-immune disorders.
22. Use of an effective amount of a compound of any one of claims 1 to 10 in the manufacture of a medicament for treating ulcerative colitis.
23. The compound of any one of claims 1 to 10 for use in treating ulcerative colitis.
24. Use of an effective amount of a compound of any one of claims 1 to 10 in the manufacture of a medicament for causing analgesia.
25. The compound of any one of claims 1 to 10 for use in causing analgesia.

26. A compound of claim 1 selected from the group consisting of:

- 7-(3-pyridyl)-1,7-diazaspiro[4.4]nonane  
 7-(5-pyrimidinyl)-1,7-diazaspiro[4.4]nonane  
 5 7-(5-isoxazolyl)-1,7-diazaspiro[4.4]nonane  
 7-(5-isothiazolyl)-1,7-diazaspiro[4.4]nonane  
 7-(5-(1,2,4-oxadiazol)yl)-1,7-diazaspiro[4.4]nonane  
 7-(2-(1,3,4-oxadiazol)yl)-1,7-diazaspiro[4.4]nonane  
 10 7-(2-pyrazinyl)-1,7-diazaspiro[4.4]nonane  
 7-(3-pyridazinyl)-1,7-diazaspiro[4.4]nonane  
 7-(5-methoxy-3-pyridyl)-1,7-diazaspiro[4.4]nonane  
 7-(5-cyclopentyloxy-3-pyridyl)-1,7-diazaspiro[4.4]nonane  
 7-(5-phenoxy-3-pyridyl)-1,7-diazaspiro[4.4]nonane  
 7-(5-(4-hydroxyphenoxy)-3-pyridyl)-1,7-diazaspiro[4.4]nonane  
 15 7-(5-ethynyl-3-pyridyl)-1,7-diazaspiro[4.4]nonane  
 7-(6-chloro-3-pyridyl)-1,7-diazaspiro[4.4]nonane  
 7-(6-methoxy-3-pyridazinyl)-1,7-diazaspiro[4.4]nonane  
 1-(3-pyridyl)-1,7-diazaspiro[4.4]nonane  
 1-(5-pyrimidinyl)-1,7-diazaspiro[4.4]nonane  
 20 1-(5-isoxazolyl)-1,7-diazaspiro[4.4]nonane  
 1-(5-isothiazolyl)-1,7-diazaspiro[4.4]nonane  
 1-(5-(1,2,4-oxadiazol)yl)-1,7-diazaspiro[4.4]nonane  
 1-(2-(1,3,4-oxadiazol)yl)-1,7-diazaspiro[4.4]nonane  
 1-(2-pyrazinyl)-1,7-diazaspiro[4.4]nonane  
 25 1-(3-pyridazinyl)-1,7-diazaspiro[4.4]nonane  
 1-methyl-7-(3-pyridyl)-1,7-diazaspiro[4.4]nonane  
 1-methyl-7-(5-pyrimidinyl)-1,7-diazaspiro[4.4]nonane  
 1-methyl-7-(5-isoxazolyl)-1,7-diazaspiro[4.4]nonane  
 1-methyl-7-(5-isothiazolyl)-1,7-diazaspiro[4.4]nonane  
 30 1-methyl-7-(5-(1,2,4-oxadiazol)yl)-1,7-diazaspiro[4.4]nonane  
 1-methyl-7-(2-(1,3,4-oxadiazol)-1,7-diazaspiro[4.4]nonane  
 1-methyl-7-(2-pyrazinyl)-1,7-diazaspiro[4.4]nonane  
 1-methyl-7-(3-pyridazinyl)-1,7-diazaspiro[4.4]nonane  
 1-methyl-7-(5-methoxy-3-pyridyl)-1,7-diazaspiro[4.4]nonane  
 35 1-methyl-7-(5-cyclopentyloxy-3-pyridyl)-1,7-diazaspiro[4.4]nonane  
 1-methyl-7-(5-phenoxy-3-pyridyl)-1,7-diazaspiro[4.4]nonane  
 1-methyl-7-(5-(4-hydroxyphenoxy)-3-pyridyl)-1,7-diazaspiro[4.4]nonane  
 1-methyl-7-(5-ethynyl-3-pyridyl)-1,7-diazaspiro[4.4]nonane  
 1-methyl-7-(6-chloro-3-pyridyl)-1,7-diazaspiro[4.4]nonane  
 40 1-methyl-7-(6-methoxy-3-pyridazinyl)-1,7-diazaspiro[4.4]nonane  
 7-methyl-1-(3-pyridyl)-1,7-diazaspiro[4.4]nonane  
 7-methyl-1-(5-pyrimidinyl)-1,7-diazaspiro[4.4]nonane  
 7-methyl-1-(5-isoxazolyl)-1,7-diazaspiro[4.4]nonane  
 7-methyl-1-(5-isothiazolyl)-1,7-diazaspiro[4.4]nonane  
 45 7-methyl-1-(5-(1,2,4-oxadiazol)yl)-1,7-diazaspiro[4.4]nonane  
 7-methyl-1-(2-(1,3,4-oxadiazol)yl)-1,7-diazaspiro[4.4]nonane  
 7-methyl-1-(2-pyrazinyl)-1,7-diazaspiro[4.4]nonane  
 7-methyl-1-(3-pyridazinyl)-1,7-diazaspiro[4.4]nonane  
 2-(3-pyridyl)-2,7-diazaspiro[4.4]nonane  
 50 2-(5-pyrimidinyl)-2,7-diazaspiro[4.4]nonane  
 2-(5-isoxazolyl)-2,7-diazaspiro[4.4]nonane  
 2-(5-isothiazolyl)-2,7-diazaspiro[4.4]nonane  
 2-(5-(1,2,4-oxadiazol)yl)-2,7-diazaspiro[4.4]nonane  
 2-(2-(1,3,4-oxadiazol)yl)-2,7-diazaspiro[4.4]nonane  
 55 2-(2-pyrazinyl)-2,7-diazaspiro[4.4]nonane  
 2-(3-pyridazinyl)-2,7-diazaspiro[4.4]nonane  
 2-(5-methoxy-3-pyridyl)-2,7-diazaspiro[4.4]nonane  
 2-(5-cyclopentyloxy-3-pyridyl)-2,7-diazaspiro[4.4]nonane

2-(5-phenoxy-3-pyridyl)-2,7-diazaspiro[4.4]nonane  
 2-(5-(4-hydroxyphenoxy)-3-pyridyl)-2,7-diazaspiro[4.4]nonane  
 2-(5-ethynyl-3-pyridyl)-2,7-diazaspiro[4.4]nonane  
 2-(6-chloro-3-pyridyl)-2,7-diazaspiro[4.4]nonane  
 2-(6-methoxy-3-pyridazinyl)-2,7-diazaspiro[4.4]nonane  
 2-methyl-7-(3-pyridyl)-2,7-diazaspiro[4.4]nonane  
 2-methyl-7-(5-methoxy-3-pyridyl)-2,7-diazaspiro[4.4]nonane  
 2-methyl(-7-(5-phenoxy-3-pyridyl)-2,7-diazaspiro[4.4]nonane  
 6-(3-pyridyl)-1,6-diazaspiro[3.4]octane  
 1-methyl-6-(3-pyridyl)-1,6-diazaspiro[3.4]octane  
 2-(3-pyridyl)-2,5-diazaspiro [3.4]octane  
 5-methyl-2-(3-pyridyl)-2,5-diazaspiro[3,4]octane  
 6-(3-pyridyl)-1,6-diazaspiro[3.5]nonane  
 1-methyl-6-(3-pyridyl)-1,6-diazaspiro[3.5]nonane  
 2-(3-pyridyl)-2,5-diazaspiro[3.5]nonane  
 5-methyl-2-(3-pyridyl)-2,5-diazaspiro[3.5]nonane and  
 pharmaceutically acceptable salts thereof.

27. A compound of claim 26, wherein the compound is 7-(3-pyridyl)-1,7-diazaspiro[4.4]nonane.

28. A pharmaceutical composition comprising an effective amount of a compound of claim 26 or 27.

29. A compound as defined in any one of claims 1 to 10, 26 or 27 for use in medicine.

30. Use of a compound of claim 26 or 27 in the manufacture of a medicament for treating or preventing a CNS disorder associated with the release of neurotransmitters mediated by nicotinic receptors.

31. The compound of claim 26 or 27 for use in treating or preventing a CNS disorder associated with the release of neurotransmitters mediated by nicotinic receptors.

32. Use of a compound of claim 26 or 27 in the manufacture of a medicament for causing analgesia, reducing inflammation, treating ulcerative colitis, inflammatory and auto-immune diseases, treating neurodegenerative diseases, and/or treating convulsions.

33. The compound of claim 26 or 27 for use in causing analgesia, reducing inflammation, treating ulcerative colitis, inflammatory and auto-immune diseases, treating neurodegenerative diseases, and/or treating convulsions.

34. Use of a compound of claim 26 or 27 in the manufacture of a medicament for treating bacterial, fungal and/or viral infections, and/or the effects of toxins produced by such infections.

35. The compound of claim 26 or 27 for use in treating bacterial, fungal and/or viral infections, and/or the effects of toxins produced by such infections.

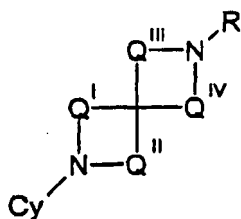
36. Use of a compound of claim 26 or 27 in the manufacture of a medicament for treating inflammatory bowel disease, pouchitis, acute cholangitis, aphthous stomatitis, arthritis, neurodegenerative diseases, Creutzfeld-Jakob disease, cachexia secondary to infection, genetic diseases and disorders, and/or auto-immune disorders.

37. The compound of claim 26 or 27 for use in treating inflammatory bowel disease, pouchitis, acute cholangitis, aphthous stomatitis, arthritis, neurodegenerative diseases, Creutzfeld-Jakob disease, cachexia secondary to infection, genetic diseases and disorders, and/or auto-immune disorders.

## Patentansprüche

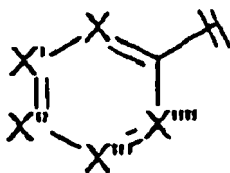
1. Verbindung mit der folgenden Formel:

Formel 1

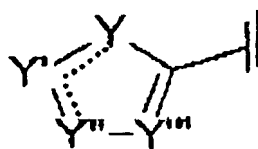


und pharmazeutisch akzeptable Salze davon,  
wobei Q<sup>I</sup>(CZ<sub>2</sub>)<sub>u</sub> ist, Q<sup>II</sup>(CZ<sub>2</sub>)<sub>v</sub> ist, Q<sup>III</sup>(CZ<sub>2</sub>)<sub>w</sub> ist, und Q<sup>IV</sup>(CZ<sub>2</sub>)<sub>x</sub> ist,

u, v, w und x unabhängig voneinander 0, 1, 2, 3 oder 4, vorzugsweise 0, 1, 2 oder 3, sind und derart ausgewählt sind, dass der diazaspironische Ring der Verbindung der Formel 1 7, 8 oder 9 Glieder enthält,  
R Wasserstoff, niedriges Alkyl, Acyl, Alkoxy-carbonyl oder Aryloxy-carbonyl ist,  
Z unabhängig aus der Gruppe ausgewählt ist, die aus Wasserstoff, niedrigem Alkyl und Aryl besteht;  
Cy ein sechsgliedriger heteroaromatischer Ring der Formel:



ist, wobei X, X', X'', X''' und X'''' jeweils unabhängig voneinander Stickstoff, Stickstoff gebunden an Sauerstoff oder Sauerstoff gebunden an eine Substituenten-Spezies ist, wobei nicht mehr als drei von X, X', X'', X''' und X'''' Stickstoff oder Stickstoff gebunden an Sauerstoff sind,  
oder Cy ein fünfgliedriger heteroaromatischer Ring der Formel:



ist, wobei Y und Y'' unabhängig voneinander Stickstoff, Stickstoff gebunden an eine Substituenten-Spezies, Sauerstoff, Schwefel oder Kohlenstoff gebunden an eine Substituenten-Spezies sind und Y' und Y''' Stickstoff oder Kohlenstoff gebunden an eine Substituenten-Spezies sind,  
wobei "Substituenten-Spezies" unabhängig voneinander aus der Gruppe ausgewählt sind, die aus Wasserstoff, Alkyl, substituiertem Alkyl, Alkenyl, substituiertem Alkenyl, Heterozykl, substituiertem Heterozykl, Zyloalkyl, substituiertem Zyloalkyl, Aryl, substituiertem Aryl, Alkylaryl, substituiertem Alkylaryl, Arylalkyl, substituiertem Arylalkyl, Halogen, -OR', -NR'R'', -CF<sub>3</sub>, -CN, -NO<sub>2</sub>, -C<sub>2</sub>R', SR', -N<sub>3</sub>, -C(=O)NR'R'', -NR'C(=O)R'', -C(=O)R', -C(=O)OR', -OC(=O)R', -O(CR'R'')<sub>r</sub>C(=O)R', -O(CR'R'')<sub>r</sub>NR''C(=O)R', -O(CR'R'')<sub>r</sub>NR''SO<sub>2</sub>R', -OC(=O)NR'R'', -NR'C(=O)OR'', -SO<sub>2</sub>R', -SO<sub>2</sub>NR'R'' und -NR'SO<sub>2</sub>R'' besteht,  
wobei R' und R'' unabhängig voneinander Wasserstoff, C<sub>1</sub>-C<sub>3</sub> Alkyl, Zyloalkyl, Heterozykl, Aryl oder Arylalkyl sind und r eine ganze Zahl von 1 bis 6 ist oder R' und R'' kombinieren können, um eine zyklische Funktionalität auszubilden,  
wobei sich der Begriff "substituiert", wie er hier auf Alkyl, Aryl, Zyloalkyl, Alkenyl, Heterozykl, Alkylaryl und Arylalkyl angewandt wird, auf die oben beschriebenen Substituenten, beginnend mit Halogen und endend mit -NR'SO<sub>2</sub>R'' bezieht und  
wobei die gestrichelten Linien anzeigen, dass die Bindungen (zwischen Y und Y' und zwischen Y' und Y''')

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- entweder einfache oder Doppelbindungen sein können, unter der Voraussetzung, dass dann, wenn die Bindung zwischen Y und Y' eine Einfachbindung ist, die Bindung zwischen Y' und Y'' eine Doppelbindung sein muss, und umgekehrt, wobei Y oder Y'' Sauerstoff oder Schwefel ist, nur eins von Y oder Y'' entweder Sauerstoff oder Schwefel ist und wobei mindestens eines von Y, Y', Y'' und Y''' Sauerstoff, Schwefel, Stickstoff oder Stickstoff gebunden an eine Substituenten-Spezies sein muss.
- 5
2. Verbindung nach Anspruch 1, wobei nur eins oder zwei von X, X', X'', X''' und X'''' Stickstoff oder Stickstoff gebunden an Sauerstoff ist/sind.
- 10
3. Verbindung nach Anspruch 1, wobei nicht mehr als eins von X, X', X'', X''' und X'''' Stickstoff gebunden an Sauerstoff ist.
4. Verbindung nach Anspruch 1, wobei X''' Stickstoff oder Stickstoff gebunden an Sauerstoff ist.
5. Verbindung nach Anspruch 1, wobei sowohl X' als auch X''' Stickstoff sind.
- 15
6. Verbindung nach Anspruch 1, wobei X, X'' und X'''' Kohlenstoff gebunden an eine Substituenten-Spezies sind.
7. Verbindung nach Anspruch 6, wobei die Substituenten-Spezies bei X, X'' und X'''' Wasserstoff ist.
- 20
8. Verbindung nach Anspruch 1, wobei X''' Kohlenstoff gebunden an eine Substituenten-Spezies ist und X und X' beide Stickstoff sind oder X' Kohlenstoff gebunden an eine Substituenten-Spezies ist und X und X''' beide Stickstoff sind.
9. Verbindung nach Anspruch 1, wobei nicht mehr als drei von Y, Y', Y'' und Y''' Sauerstoff, Schwefel, Stickstoff oder Stickstoff gebunden an eine Substituenten-Spezies sind.
- 25
10. Verbindung nach Anspruch 1, wobei zwischen einem und drei von Y, Y', Y'' und Y''' Stickstoff sind.
11. Pharmazeutische Zusammensetzung, die eine Verbindung nach einem der Ansprüche 1 bis 10 umfasst.
- 30
12. Verwendung einer wirksamen Menge einer Verbindung nach einem der Ansprüche 1 bis 10, bei der Herstellung eines Medikaments zur Behandlung oder Vorbeugung einer ZNS-Störung verbunden mit der Freisetzung von Neurotransmittern ausgelöst durch Nikotinrezeptoren.
- 35
13. Verbindung nach einem der Ansprüche 1 bis 10 zur Verwendung bei der Behandlung oder Vorbeugung einer ZNS-Störung, verbunden mit der Freisetzung von Neurotransmittern ausgelöst durch Nikotinrezeptoren.
- 40
14. Verwendung nach Anspruch 12 oder Verbindung nach Anspruch 13, wobei die ZNS-Störung aus der Gruppe ausgewählt ist, die aus präseniler Demenz (früh einsetzender Alzheimer-Krankheit), seniler Demenz (Demenz vom Alzheimerstyp), Lewy-Körperchen Demenz, HIV-Demenz, multizerebralen Infarkten, Parkinsonismus einschließlich Parkinson-Krankheit, Pick-Krankheit, Chorea Huntington, tardiver Dyskinesie, Hypokinesie, Manie, Aufmerksamkeitsdefizit, Angst, Depression, milder kognitiver Beeinträchtigung, Dyslexie, Schizophrenie und Tourette-Syndrom besteht.
- 45
15. Verwendung nach Anspruch 12 oder Verbindung nach Anspruch 13, wobei die Verbindung oder das Medikament zur Verabreichung der Verbindung in einer Dosierung vorgesehen ist, die zur Behandlung oder Vorbeugung der ZNS-Störung wirksam ist, aber mit einer Dosierung, die nicht in merklichem Umfang in Nebenwirkungen resultiert, die mit der Stimulation von Muskel- oder Ganglienrezeptoren verbunden ist.
- 50
16. Verwendung einer wirksamen Menge einer Verbindung nach einem der Ansprüche 1 bis 10 bei der Herstellung eines Medikaments zum Verursachen von Analgesie, zum Reduzieren von Entzündung, zum Behandeln von Colitis ulcerosa, entzündlichen und Autoimmun-Krankheiten, zum Behandeln von neurodegenerativen Störungen und/oder zum Behandeln von Konvulsionen.
- 55
17. Verbindung nach einem der Ansprüche 1 bis 10 zur Verwendung beim Verursachen von Analgesie, Reduzieren von Entzündung, Behandeln von Colitis ulcerosa, entzündlichen und Autoimmun-Krankheiten, Behandeln von neurodegenerativen Störungen und/oder zum Behandeln von Konvulsionen.
18. Verwendung einer wirksamen Menge einer Verbindung nach einem der Ansprüche 1 bis 10 bei der Herstellung

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eines Medikaments zum Behandeln von Bakterien-, Pilz- oder Virusinfektionen und/oder den Auswirkungen von Toxinen, die durch solche Infektionen produziert werden.

- 5 19. Verbindung nach einem der Ansprüche 1 bis 10 zur Verwendung bei der Behandlung von Bakterien-, Pilz- und/oder Virusinfektionen und/oder den Auswirkungen von Toxinen, die durch solche Infektionen produziert werden.
- 10 20. Verwendung einer wirksamen Menge einer Verbindung nach einem der Ansprüche 1 bis 10 bei der Herstellung eines Medikaments zur Behandlung von entzündlicher Darmkrankheit, Pouchitis, akuter Cholangitis, aphtöser Stomatitis, Arthritis, neurodegenerativen Krankheiten, Creutzfeld-Jakob-Krankheit, Kachexie infolge von Infektion, genetischen Erkrankungen und Störungen und/oder Autoimmun-Störungen.
- 15 21. Verbindung nach einem der Ansprüche 1 bis 10 zur Verwendung bei der Behandlung von entzündlicher Darmkrankheit, Pouchitis, akuter Cholangitis, aphtöser Stomatitis, Arthritis, neurodegenerativen Krankheiten, Creutzfeld-Jakob-Krankheit, Kachexie infolge von Infektion, genetischen Erkrankungen und Störungen und/oder Autoimmun-Störungen.
- 20 22. Verwendung einer wirksamen Menge einer Verbindung nach einem der Ansprüche 1 bis 10 bei der Herstellung eines Medikaments zur Behandlung von Colitis ulcerosa.
23. Verbindung nach einem der Ansprüche 1 bis 10 zur Verwendung bei der Behandlung von Colitis ulcerosa.
24. Verwendung einer wirksamen Menge einer Vergütung nach einem der Ansprüche 1 bis 10 bei der Herstellung eines Medikaments zum Verursachen von Analgesie.
- 25 25. Verbindung nach einem der Ansprüche 1 bis 10 zur Verwendung beim Verursachen von Analgesie.
26. Verbindung nach Anspruch 1, ausgewählt aus der Gruppe, die besteht aus:

- 30 7-(3-Pyridyl)-1,7-diazaspiro[4.4]nonan  
7-(5-Pyrimidinyl)-1,7-diazaspiro[4.4]nonan  
7-(5-Isioxazolyl)-1,7-diazaspiro[4.4]nonan  
7-(5-Isouthiazolyl)-1,7-diazaspiro[4.4]nonan  
7-(5-(1,2,4-Oxadiazol)yl)-1,7-diazaspiro[4.4]nonan  
7-(2-(1,3,4-Oxadiazol)yl)-1,7-diazaspiro[4.4]nonan  
35 7-(2-Pyrazinyl)-1,7-diazaspiro[4.4]nonan  
7-(3-Pyridazinyl)-1,7-diazaspiro[4.4]nonan  
7-(5-Methoxy-3-pyridyl)-1,7-diazaspiro[4.4] nonan  
7-(5-Zyklopentyloxy-3-pyridyl)-1,7-diazaspiro[4.4]nonan  
7-(5-Phenoxy-3-pyridyl)-1,7-diazaspiro[4.4]nonan  
40 7-(5-(4-Hydroxyphenoxy)-3-pyridyl)-1,7-diazaspiro[4.4]nonan  
7-(5-Ethynyl-3-pyridyl)-1,7-diazaspiro[4.4]nonan  
7-(6-Chlor-3-pyridyl)-1,7-diazaspiro[4.4]nonan  
7-(6-Methoxy-3-pyridazinyl)-1,7-diazaspiro[4.4]nonan  
1-(3-Pyridyl)-1,7-diazaspiro[4.4]nonan  
45 1-(5-Pyrimidinyl)-1,7-diazaspiro[4.4]nonan  
1-(5-Isioxazolyl)-1,7-diazaspiro[4.4]nonan  
1-(5-Isouthiazolyl)-1,7-diazaspiro[4.4]nonan  
1-(5-(1,2,4-Oxadiazol)yl)-1,7-diazaspiro[4.4]nonan  
1-(2-(1,3,4-Oxadiazol)yl)-1,7-diazaspiro[4.4]nonan  
50 1-(2-Pyrazinyl)-1,7-diazaspiro[4.4]nonan  
1-(3-Pyridazinyl)-1,7-diazaspiro[4.4]nonan  
1-Methyl-7-(3-pyridyl)-1,7-diazaspiro[4.4]nonan  
1-Methyl-7-(5-pyrimidinyl)-1,7-diazaspiro[4.4]nonan  
1-Methyl-7-(5-isioxazolyl)-1,7-diazaspiro[4.4]nonan  
55 1-Methyl-7-(5-isouthiazolyl)-1,7-diazaspiro[4.4]nonan  
1-Methyl-7-(5-(1,2,4-oxadiazol)yl)-1,7-diazaspiro[4.4]nonan  
1-Methyl-7-(2-(1,3,4-oxadiazol)yl)-1,7-diazaspiro[4.4]nonan  
1-Methyl-7-(2-pyrazinyl)-1,7-diazaspiro[4.4]nonan

- 1-Methyl-7-(3-pyridazinyl)-1,7-diazaspiro[4.4]nonan  
 1-Methyl-7-(5-methoxy-3-pyridyl)-1,7-diazaspiro[4.4]nonan  
 1-Methyl-7-(5-zyklopentylloxy-3-pyridyl)-1,7-diazaspiro[4.4]nonan  
 1-Methyl-7-(5-phenoxy-3-pyridyl)-1,7-diazaspiro[4.4]nonan  
 5 1-Methyl-7-(5-(4-hydroxyphenoxy)-3-pyridyl)-1,7-diazaspiro[4.4]nonan  
 1-Methyl-7-(5-ethynyl-3-pyridyl)-1,7-diazaspiro[4.4]nonan  
 1-Methyl-7-(6-chlor-3-pyridyl)-1,7-diazaspiro[4.4]nonan  
 1-Methyl-7-(6-methoxy-3-pyridazinyl)-1,7-diazaspiro[4.4]nonan  
 7-Methyl-1-(3-pyridyl)-1,7-diazaspiro[4.4]nonan  
 10 7-Methyl-1-(5-pyrimidinyl)-1,7-diazaspiro[4.4]nonan  
 7-Methyl-1-(5-isoxazolyl)-1,7-diazaspiro[4.4]nonan  
 7-Methyl-1-(5-isothiazolyl)-1,7-diazaspiro[4.4]nonan  
 7-Methyl-1-(5-(1,2,4-oxadiazolyl))-1,7-diazaspiro[4.4]nonan  
 7-Methyl-1-(2-(1,3,4-oxadiazolyl))-1,7-diazaspiro[4.4]nonan  
 15 7-Methyl-1-(2-pyrazinyl)-1,7-diazaspiro[4.4]nonan  
 7-Methyl-1-(3-pyridazinyl)-1,7-diazaspiro[4.4]nonan  
 2-(3-Pyridyl)-2,7-diazaspiro[4.4]nonan  
 2-(5-Pyrimidinyl)-2,7-diazaspiro[4.4]nonan  
 2-(5-Isioxazolyl)-2,7-diazaspiro[4.4]nonan  
 20 2-(5-Isouthiazolyl)-2,7-diazaspiro[4.4]nonan  
 2-(5-(1,2,4-Oxadiazolyl))-2,7-diazaspiro[4.4]nonan  
 2-(2-(1,3,4-Oxadiazolyl))-2,7-diazaspiro[4.4]nonan  
 2-(2-Pyrazinyl)-2,7-diazaspiro[4.4]nonan  
 2-(3-Pyridazinyl)-2,7-diazaspiro[4.4]nonan  
 25 2-(5-Methoxy-3-pyridyl)-2,7-diazaspiro[4.4]nonan  
 2-(5-Zyklopentylloxy-3-pyridyl)-2,7-diazaspiro[4.4]nonan  
 2-(5-Phenoxy-3-pyridyl)-2,7-diazaspiro[4,4]nonan  
 2-(5-(4-Hydroxyphenoxy)-3-pyridyl)-2,7-diazaspi-ro[4.4]nonan  
 2-(5-Ethynyl-3-Pyridyl)-2,7-diazaspiro[4.4]nonan  
 30 2-(6-Chlor-3-pyridyl)-2,7-diazaspiro[4.4]nonan  
 2-(6-Methoxy-3-pyridazinyl)-2,7-diazaspiro[4.4]nonan  
 2-Methyl-7-(3-pyridyl)-2,7-diazaspiro[4.4]nonan  
 2-Methyl-7-(5-methoxy-3-pyridyl)-2,7-diazaspiro[4.4]nonan  
 2-Methyl-7-(5-Phenoxy-3-pyridyl)-2,7-diazaspiro[4,4]nonan  
 35 6-(3-Pyridyl)-1,6-diazaspiro[3.4]octan  
 1-Methyl-6-(3-pyridyl)-1,6-diazaspiro[3.4]octan  
 2-(3-Pyridyl)-2,5-diazaspiro[3.4]octan  
 5-Methyl-2-(3-pyridyl)-2,5-diazaspiro[3.4]octan  
 6-(3-Pyridyl)-1,6-diazaspiro[3.5]nonan  
 40 1-Methyl-6-(3-pyridyl)-1,6-diazaspiro[3.5]nonan  
 2-(3-Pyridyl)-2,5-diazaspiro[3.5]nonan  
 5-Methyl-2-(3-pyridyl)-2,5-diazaspiro[3.5]nonan und  
 pharmazeutisch akzeptablen Salzen davon.
- 45 **27.** Verbindung nach Anspruch 26, wobei die Verbindung 7-(3-Pyridyl)-1,7-diazaspiro[4.4] nonan ist.
- 28.** Pharmazeutische Zusammensetzung, die eine wirksame Menge einer Verbindung nach Anspruch 26 oder 27 aufweist.
- 50 **29.** Verbindung wie in einem der Ansprüche 1 bis 10, 26 oder 27 definiert zur Verwendung in der Medizin.
- 30.** Verwendung einer Verbindung nach Anspruch 26 oder 27 bei der Herstellung eines Medikaments für die Behandlung oder Vorbeugung einer ZNS-Störung verbunden mit der Freisetzung von Neurotransmittern ausgelöst durch Nikotinrezeptoren.
- 55 **31.** Verbindung nach Anspruch 26 oder 27 zur Verwendung bei der Behandlung oder Vorbeugung einer ZNS-Störung verbunden mit der Freisetzung von Neurotransmittern ausgelöst durch Nikotinrezeptoren.

32. Utilisation d'une Verbindung nach Anspruch 26 oder 27 bei der Herstellung eines Medikaments zum Verursachen von Analgesie, Reduzieren von Entzündung, Behandeln von Colitis ulcerosa, entzündlichen und Autoimmun-Krankheiten, Behandeln von neurodegenerativen Störungen und/oder zum Behandeln von Krampfanfällen.

5 33. Verbindung nach Anspruch 26 oder 27 zur Verwendung beim Verursachen von Analgesie, Reduzieren von Entzündung, Behandeln von Colitis ulcerosa, entzündlichen und Autoimmun-Krankheiten, Behandeln von neurodegenerativen Störungen und/oder zum Behandeln von Krampfanfällen.

10 34. Utilisation d'une Verbindung nach Anspruch 26 oder 27 bei der Herstellung eines Medikaments zum Behandeln von Bakterien-, Pilz- und/oder Virusinfektionen und/oder den Effekten von Toxinen, die durch solche Infektionen produziert werden.

15 35. Verbindung nach Anspruch 26 oder 27 zur Verwendung beim Behandeln von Bakterien-, Pilz- oder Virusinfektionen und/oder den Effekten von Toxinen, die durch solche Infektionen produziert werden.

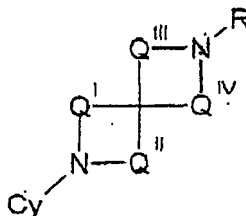
20 36. Utilisation d'une Verbindung nach Anspruch 26 oder 27 bei der Herstellung eines Medikaments zum Behandeln von entzündlicher Darmerkrankung, Pouchitis, akuter Cholangitis, aphtöser Stomatitis, Arthritis, neurodegenerativen Erkrankungen, Creutzfeld-Jakob-Krankheit, Kachexie infolge von Infektion, genetischen Erkrankungen und Störungen und/oder Autoimmun-Störungen.

25 37. Verbindung nach Anspruch 26 oder 27 zur Verwendung beim Behandeln von entzündlicher Darmerkrankung, Pouchitis, akuter Cholangitis, aphtöser Stomatitis, Arthritis, neurodegenerativen Erkrankungen, Creutzfeld-Jakob-Krankheit, Kachexie infolge von Infektion, genetischen Erkrankungen und Störungen und/oder Autoimmun-Störungen.

Revendications

1. Composé ayant la formule suivante :

Formule 1



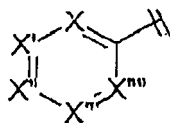
et les sels pharmaceutiquement acceptables de celui-ci, dans lequel Q<sup>I</sup> est (CZ<sub>2</sub>)<sub>u</sub>, Q<sup>II</sup> est (CZ<sub>2</sub>)<sub>v</sub>, Q<sup>III</sup> est (CZ<sub>2</sub>)<sub>w</sub> et Q<sup>IV</sup> est (CZ<sub>2</sub>)<sub>x</sub>,

u, v, w et x sont individuellement 0, 1, 2, 3 ou 4, de préférence 0, 1, 2 ou 3, et sont choisis de sorte que le noyau diazaspicyclic du composé de formule 1 contienne 7, 8 ou 9 chaînons,

R est un hydrogène, un alkyle inférieur, un acyle, un alcoxycarbonyle ou un aryloxy-carbonyle,

Z est, individuellement, choisi dans le groupe constitué par un hydrogène, un alkyle inférieur et un aryle ;

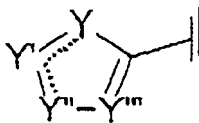
Cy est un noyau hétéroaromatique à six chaînons de formule :



où chacun parmi X, X', X'', X''' et X'''' est individuellement un azote, un azote lié à de l'oxygène ou un carbone lié à une espèce substituante, où pas plus de trois parmi X, X', X'', X''' et X'''' sont un azote ou un azote lié à de

l'oxygène,  
ou Cy est un noyau hétéroaromatique à 5 chaînons de formule :

5



10 où Y et Y'' sont individuellement un azote, un azote lié à une espèce substituante, un oxygène, un soufre ou un carbone lié à une espèce substituante, et Y' et Y''' sont un azote ou un carbone lié à une espèce substituante, où les "espèces substituantes" sont, individuellement, choisies dans le groupe constitué par un hydrogène, un alkyle, un alkyle substitué, un alcényle, un alcényle substitué, un hétérocyclyle, un hétérocyclyle substitué, un cycloalkyle, un cycloalkyle substitué, un aryle, un aryle substitué, un alkylaryle, un alkylaryle substitué, un arylalkyle, un arylalkyle substitué, un halogéno, -OR', -NR'R'', -CF<sub>3</sub>, -CN, -NO<sub>2</sub>, -C<sub>2</sub>R', -SR', -N<sub>3</sub>, -C(=O)NR'R'', -NR'C(=O)R'', -C(=O)R', -C(=O)OR', -OC(=O)R', -O(CR'R'')<sub>r</sub>C(=O)R', -O(CR'R'')<sub>r</sub>NR''C(=O)R', -O(CR'R'')<sub>r</sub>NR''SO<sub>2</sub>R', -OC(=O)NR'R'', -NR'C(=O)OR'', -SO<sub>2</sub>R', -SO<sub>2</sub>NR'R'' et -NR'SO<sub>2</sub>R'',

15 où R' et R'' sont individuellement un hydrogène, un alkyle en C<sub>1</sub>-C<sub>8</sub>, un cycloalkyle, un hétérocyclyle, un aryle ou un arylalkyle, et r est un entier de 1 à 6, ou R' et R'' peuvent se combiner pour former une fonctionnalité cyclique, où le terme "substitué" tel qu'appliqué à un alkyle, un aryle, un cycloalkyle, un alcényle, un hétérocyclyle, un alkylaryle et un arylalkyle désigne les substituants décrits ci-dessus, en partant de halogéno et en finissant par -NR'SO<sub>2</sub>R'', et

20 où les traits en pointillés indiquent que les liaisons (entre Y et Y' et entre Y' et Y''') peuvent être des liaisons soit simples soit doubles, avec pour condition que lorsque la liaison entre Y et Y' est une liaison simple, la liaison entre Y' et Y''' doit être une liaison double et *vice versa*, lorsque Y ou Y''' est un oxygène ou un soufre, seulement l'un parmi Y et Y''' est soit un oxygène soit un soufre, et au moins l'un parmi Y, Y', Y'' et Y''' doit être un oxygène, un soufre, un azote ou un azote lié à une espèce substituante.

25

30 2. Composé selon la revendication 1, dans lequel seulement un ou deux parmi X, X', X'', X''' et X'''' sont un azote ou un azote lié à de l'oxygène.

3. Composé selon la revendication 1, dans lequel pas plus d'un parmi X, X', X'', X''' et X'''' est un azote lié à de l'oxygène.

35

4. Composé selon la revendication 1, dans lequel X'''' est un azote ou un azote lié à de l'oxygène.

5. Composé selon la revendication 1, dans lequel X' que X'''' sont tous les deux un azote.

6. Composé selon la revendication 1, dans lequel X, X'' et X'''' sont un carbone lié à une espèce substituante.

40

7. Composé selon la revendication 6, dans lequel les espèces substituantes à X, X'' et X'''' sont de l'hydrogène.

8. Composé selon la revendication 1, dans lequel X'''' est un carbone lié à une espèce substituante et X et X' sont tous les deux un azote, ou X' est un carbone lié à une espèce substituante et X et X'''' sont tous les deux un azote.

45

9. Composé selon la revendication 1, dans lequel pas plus de trois parmi Y, Y', Y'' et Y''' sont un oxygène, un soufre, un azote ou un azote lié à une espèce substituante.

10. Composé selon la revendication 1, dans lequel entre un et trois parmi Y, Y', Y'' et Y''' sont un azote.

50

11. Composition pharmaceutique incluant un composé selon l'une quelconque des revendications 1 à 10.

12. Utilisation d'une quantité efficace d'un composé selon l'une quelconque des revendications 1 à 10, dans la fabrication d'un médicament pour traiter ou prévenir un trouble du SNC associé à la libération de neurotransmetteurs médiée par les récepteurs nicotiniques.

55

13. Composé selon l'une quelconque des revendications 1 à 10, pour une utilisation dans le traitement ou la prévention d'un trouble du SNC associé à la libération de neurotransmetteurs médiée par les récepteurs nicotiniques.

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- 5 14. Utilisation selon la revendication 12 ou composé selon la revendication 13, dans lesquels le trouble du SNC est choisi dans le groupe constitué par une démence présénile (maladie d'Alzheimer à début précoce), une démence sénile (démence du type Alzheimer), une démence à corps de Lewy, une démence liée au VIH, des infarctus cérébraux multiples, un parkinsonisme incluant la maladie de Parkinson, une maladie de Pick, une chorée de Huntington, une dyskinésie tardive, une hyperkinésie, une manie, un trouble de déficit de l'attention, une anxiété, une dépression, une détérioration cognitive légère, une dyslexie, une schizophrénie et un syndrome de Tourette.
- 10 15. Utilisation selon la revendication 12 ou composé selon la revendication 13, dans lesquels le composé ou le médicament est destiné à l'administration du composé à une posologie efficace pour traiter ou prévenir le trouble du SNC mais à une posologie qui ne conduit pas à des degrés appréciables d'effets secondaires associés à une stimulation des récepteurs musculaires ou ganglionnaires.
- 15 16. Utilisation d'une quantité efficace d'un composé selon l'une quelconque des revendications 1 à 10, dans la fabrication d'un médicament pour provoquer une analgésie, réduire une inflammation, traiter une recto-colite hémorragique, des maladies inflammatoires et auto-immunes, traiter des maladies neurodégénératives et/ou traiter des convulsions.
- 20 17. Composé selon l'une quelconque des revendications 1 à 10, pour une utilisation afin de provoquer une analgésie, réduire une inflammation, traiter une recto-colite hémorragique, des maladies inflammatoires et auto-immunes, traiter des maladies neurodégénératives et/ou traiter des convulsions.
- 25 18. Utilisation d'une quantité efficace d'un composé selon l'une quelconque des revendications 1 à 10, dans la fabrication d'un médicament pour traiter des infections bactériennes, fongiques et/ou virales, et/ou les effets de toxines produites par de telles infections.
- 30 19. Composé selon l'une quelconque des revendications 1 à 10, pour une utilisation dans le traitement d'infections bactériennes, fongiques et/ou virales, et/ou les effets de toxines produites par de telles infections.
- 35 20. Utilisation d'une quantité efficace d'un composé selon l'une quelconque des revendications 1 à 10 dans la fabrication d'un médicament pour traiter une maladie intestinale inflammatoire, une pochite, une cholangite aiguë, une stomatite aphteuse, une arthrite, des maladies neurodégénératives, une maladie de Creutzfeld-Jakob, une cachexie secondaire à une infection, des maladies et des troubles génétiques et/ou des troubles auto-immuns.
- 40 21. Composé selon l'une quelconque des revendications 1 à 10, pour une utilisation dans le traitement d'une maladie intestinale inflammatoire, d'une pochite, d'une cholangite aiguë, d'une stomatite aphteuse, d'une arthrite, de maladies neurodégénératives, d'une maladie de Creutzfeld-Jakob, d'une cachexie secondaire à une infection, de maladies et de troubles génétiques et/ou de troubles auto-immuns.
- 45 22. Utilisation d'une quantité efficace d'un composé selon l'une quelconque des revendications 1 à 10, dans la fabrication d'un médicament pour traiter une recto-colite hémorragique.
- 50 23. Composé selon l'une quelconque des revendications 1 à 10, pour une utilisation dans le traitement d'une recto-colite hémorragique.
- 55 24. Utilisation d'une quantité efficace d'un composé selon l'une quelconque des revendications 1 à 10, dans la fabrication d'un médicament pour provoquer une analgésie.
25. Composé selon l'une quelconque des revendications 1 à 10, pour une utilisation afin de provoquer une analgésie.
26. Composé selon la revendication 1, choisi dans le groupe constitué par les :
- 7-(3-pyridyl)-1,7-diazaspiro[4.4]nonane
  - 7-(5-pyrimidinyl)-1,7-diazaspiro[4.4]nonane
  - 7-(5-isoxazolyl)-1,7-diazaspiro[4.4]nonane
  - 7-(5-isothiazolyl)-1,7-diazaspiro[4.4]nonane
  - 7-(5-(1,2,4-oxadiazol)yl)-1,7-diazaspiro[4.4]nonane
  - 7-(2-(1,3,4-oxadiazol)yl)-1,7-diazaspiro[4.4]nonane
  - 7-(2-pyrazinyl)-1,7-diazaspiro[4.4]nonane
  - 7-(3-pyridazinyl)-1,7-diazaspiro[4.4]nonane

7-(5-méthoxy-3-pyridyl)-1,7-diazaspiro[4.4]nonano  
 7-(5-cyclopentyloxy-3-pyridyl)-1,7-diazaspiro[4.4]nonane  
 7-(5-phénoxy-3-pyridyl)-1,7-diazaspiro[4.4]nonane  
 7-(5-(4-hydroxyphénoxy)-3-pyridyl)-1,7-diazaspiro[4.4]nonane  
 5 7-(5-éthynyl-3-pyridyl)-1,7-diazaspiro[4.4]nonane  
 -7-(6-chloro-3-pyridyl)-1,7-diazaspiro[4.4]nonane  
 7-(6-méthoxy-3-pyridazinyl)-1,7-diazaspiro[4.4]nonane  
 1-(3-pyridyl)-1,7-diazaspiro[4.4]nonane  
 1-(5-pyrimidinyl)-1,7-diazaspiro[4.4]nonane  
 10 1-(5-isoxazolyl)-1,7-diazaspiro[4.4]nonane  
 1-(5-isothiazolyl)-1,7-diazaspiro[4.4]nonane  
 1-(5-(1,2,4-oxadiazolyl)-1,7-diazaspiro[4.4]nonane  
 1-(2-(1,3,4-oxadiazolyl)-1,7-diazaspiro[4.4]nonane  
 1-(2-pyrazinyl)-1,7-diazaspiro[4.4]nonane  
 15 1-(3-pyridazinyl)-1,7-diazaspiro[4.4]nonane  
 1-méthyl-7-(3-pyridyl)-1,7-diazaspiro[4.4]nonane  
 1-méthyl-7-(5-pyrimidinyl)-1,7-diazaspiro[4.4]nonane  
 1-méthyl(-7-(5-isoxazolyl)-1,7-diazaspiro[4.4]nonane  
 1-méthyl-7-(5-isothiazolyl)-1,7-diazaspiro[4.4]nonane  
 20 1-méthyl-7-(5-(1,2,4-oxadiazolyl)-1,7-diazaspiro[4.4]nonane  
 1-méthyl-7-(2-(1,3,4-oxadiazolyl)-1,7-diazaspiro[4.4]nonane  
 1-méthyl-7-(2-pyrazinyl)-1,7-diazaspiro[4.4]nonane  
 1-méthyl-7-(3-pyridazinyl)-1,7-diazaspiro[4.4]nonane  
 1-méthyl-7-(5-méthoxy-3-pyridyl)-1,7-diazaspiro[4.4]nonane  
 25 1-méthyl-7-(5-cyclopentyloxy-3-pyridyl)-1,7-diazaspiro[4.4]nonane  
 1-méthyl-7-(5-phénoxy-3-pyridyl)-1,7-diazaspiro[4.4]nonane  
 1-méthyl-7-(5-(4-hydroxyphénoxy)-3-pyridyl)-1,7-diazaspiro[4.4]nonane  
 1-méthyl-7-(5-éthynyl-3-pyridyl)-1,7-diazaspiro[4.4]nonane  
 1-méthyl-7-(6-chloro-3-pyridyl)-1,7-diazaspiro[4.4]nonane  
 30 1-méthyl-7-(6-méthoxy-3-pyridazinyl)-1,7-diazaspiro[4.4]nonane  
 7-méthyl-1-(3-pyridyl)-1,7-diazaspiro[4.4]nonane  
 7-méthyl-1-(5-pyrimidinyl)-1,7-diazaspiro[4.4]nonane  
 7-méthyl-1-(5-isoxazolyl)-1,7-diazaspiro[4.4]nonane  
 7-méthyl-1-(5-isothiazolyl)-1,7-diazaspiro[4.4]nonane  
 35 7-méthyl-1-(5-(1,2,4-oxadiazolyl)-1,7-diazaspiro[4.4]nonane  
 7-méthyl-1-(2-(1,3,4-oxadiazolyl)-1,7-diazaspiro[4.4]nonane  
 7-méthyl-1-(2-pyrazinyl)-1,7-diazaspiro[4.4]nonane  
 7-méthyl-1-(3-pyridazinyl)-1,7-diazaspiro[4.4]nonane  
 2-(3-pyridyl)-2,7-diazaspiro[4.4]nonane  
 40 2-(5-pyrimidinyl)-2,7-diazaspiro[4.4]nonane  
 2-(5-isoxazolyl)-2,7-diazaspiro[4.4]nonane  
 2-(5-isothiazolyl)-2,7-diazaspiro[4.4]nonane  
 2-(5-(1,2,4-oxadiazolyl)-2,7-diazaspiro[4.4]nonane  
 2-(2-(1,3,4-oxadiazolyl)-2,7-diazaspiro[4.4]nonane  
 45 2-(2-pyrazinyl)-2,7-diazaspiro[4.4]nonane  
 2-(3-pyridazinyl)-2,7-diazaspiro[4.4]nonane  
 2-(5-méthoxy-3-pyridyl)-2,7-diazaspiro[4.4]nonane  
 2-(5-cyclopentyloxy-3-pyridyl)-2,7-diazaspiro[4.4]nonane  
 2-(5-phénoxy-3-pyridyl)-2,7-diazaspiro[4.4]nonane  
 50 2-(5-(4-hydroxyphénoxy)-3-pyridyl)-2,7-diazaspiro[4.4]nonane  
 2-(5-éthynyl-3-pyridyl)-2,7-diazaspiro[4.4]nonane  
 2-(6-chloro-3-pyridyl)-2,7-diazaspiro[4.4]nonane  
 2-(6-méthoxy-3-pyridazinyl)-2,7-diazaspiro[4.4]nonane  
 2-méthyl-7-(3-pyridyl)-2,7-diazaspiro[4.4]nonane  
 55 2-méthyl-7-(5-méthoxy-3-pyridyl)-2,7-diazaspiro[4.4]nonane  
 2-méthyl-7-(5-phénoxy-3-pyridyl)-2,7-diazaspiro[4.4]nonane  
 6-(3-pyridyl)-1,6-diazaspiro[3.4]octane  
 1-méthyl-6-(3-pyridyl)-1,6-diazaspiro[3.4]octane

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2-(3-pyridyl)-2,5-diazaspiro[3.4]octane  
5-méthyl-2-(3-pyridyl)-2,5-diazaspiro[3.4]octane  
6-(3-pyridyl)-1,6-diazaspiro[3.5]nonane  
1-méthyl-6-(3-pyridyl)-1,6-diazaspiro[3.5]nonane  
2-(3-pyridyl)-2,5-diazaspiro[3.5]nonane  
5-méthyl-2-(3-pyridyl)-2,5-diazaspiro[3.5]nonane  
et les sels pharmaceutiquement acceptables de ceux-ci.

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- 27.** Composé selon la revendication 26, lequel composé est le 7-(3-pyridyl)-1,7-diazaspiro[4.4]nonane.
- 28.** Composition pharmaceutique comprenant une quantité efficace d'un composé selon la revendication 26 ou 27.
- 29.** Composé selon l'une quelconque des revendications 1 à 10, 26 ou 27, pour une utilisation en médecine.
- 30.** Utilisation d'un composé selon la revendication 26 ou 27, dans la fabrication d'un médicament pour traiter ou prévenir un trouble du SNC associé à la libération de neurotransmetteurs médiée par les récepteurs nicotiques.
- 31.** Composé selon la revendication 26 ou 27, pour une utilisation dans le traitement ou la prévention d'un trouble du SNC associé à la libération de neurotransmetteurs médiée par les récepteurs nicotiques.
- 32.** Utilisation d'un composé selon la revendication 26 ou 27, dans la fabrication d'un médicament pour provoquer une analgésie, réduire une inflammation, traiter une recto-colite hémorragique, des maladies inflammatoires et auto-immunes, traiter des maladies neurodégénératives et/ou traiter des convulsions.
- 33.** Composé selon la revendication 26 ou 27, pour une utilisation afin de provoquer une analgésie, réduire une inflammation, traiter une recto-colite hémorragique, des maladies inflammatoires et auto-immunes, traiter des maladies neurodégénératives et/ou traiter des convulsions.
- 34.** Composé selon la revendication 26 ou 27, dans la fabrication d'un médicament pour traiter des infections bactériennes, fongiques et/ou virales, et/ou les effets de toxines produites par de telles infections.
- 35.** Composé selon la revendication 26 ou 27, pour une utilisation afin de traiter des infections bactériennes, fongiques et/ou virales, et/ou les effets de toxines produites par de telles infections.
- 36.** Utilisation d'un composé selon la revendication 26 ou 27, dans la fabrication d'un médicament pour traiter une maladie intestinale inflammatoire, une pochite, une cholangite aiguë, une stomatite aphteuse, une arthrite, des maladies neurodégénératives, une maladie de Creutzfeld-Jakob, une cachexie secondaire à une infection, des maladies et des troubles génétiques et/ou des troubles auto-immuns.
- 37.** Composé selon la revendication 26 ou 27, pour une utilisation afin de traiter une maladie intestinale inflammatoire, une pochite, une cholangite aiguë, une stomatite aphteuse, une arthrite, des maladies neurodégénératives, une maladie de Creutzfeld-Jakob, une cachexie secondaire à une infection, des maladies et des troubles génétiques et/ou des troubles auto-immuns.

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