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(54) **Title:** DIAZABICYCLO[3.3.1]NONANES, METHODS OF SYNTHESIS, AND USES THEREOF

(57) **Abstract:** The present invention relates to compounds that bind to and modulate the activity of neuronal nicotinic acetylcholine receptors, to processes for preparing these compounds, to pharmaceutical compositions containing these compounds, and to methods of using these compounds for treating a wide variety of conditions and disorders, including those associated with dysfunction of the central nervous system (CNS).



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DIAZABICYCLO[3.3.1]NONANES, METHODS OF SYNTHESIS, AND USES THEREOF**Field of the Invention**

The present invention relates to compounds that bind to and modulate the activity of neuronal nicotinic acetylcholine receptors, to processes for preparing these compounds, to pharmaceutical compositions containing these compounds, and to methods of using these compounds for treating a wide variety of conditions and disorders, including those associated with dysfunction of the central nervous system (CNS).

Background of the Invention

The therapeutic potential of compounds that target neuronal nicotinic receptors (NNRs), also known as nicotinic acetylcholine receptors (nAChRs), has been the subject of several reviews. See, for example, Breining et al., *Ann. Rep. Med. Chem.* 40: 3 (2005), Hogg and Bertrand, *Curr. Drug Targets: CNS Neurol. Disord.* 3: 123 (2004), Suto and Zacharias, *Expert Opin. Ther. Targets* 8: 61 (2004), Dani et al., *Bioorg. Med. Chem. Lett.* 14: 1837 (2004), Bencherif and Schmitt, *Curr. Drug Targets: CNS Neurol. Disord.* 1: 349 (2002), each incorporated by reference with regard to such teaching. Among the kinds of indications for which NNR ligands have been proposed as therapies are cognitive disorders, including Alzheimer's disease, attention deficit disorder, and schizophrenia (Newhouse et al., *Curr. Opin. Pharmacol.* 4: 36 (2004), Levin and Rezvani, *Curr. Drug Targets: CNS Neurol. Disord.* 1: 423 (2002), Graham et al., *Curr. Drug Targets: CNS Neurol. Disord.* 1: 387 (2002), Ripoll et al., *Curr. Med. Res. Opin.* 20(7): 1057 (2004), and McEvoy and Allen, *Curr. Drug Targets: CNS Neurol. Disord.* 1: 433 (2002)); pain and inflammation (Decker et al., *Curr. Top. Med. Chem.* 4(3): 369 (2004), Vincler, *Expert Opin. Invest. Drugs* 14(10): 1191 (2005), Jain, *Curr. Opin. Inv. Drugs* 5: 76 (2004), Miao et al., *Neuroscience* 123: 777 (2004)); depression and anxiety (Shytle et al., *Mol. Psychiatry* 7: 525 (2002), Damaj et al., *Mol. Pharmacol.* 66: 675 (2004), Shytle et al., *Depress. Anxiety* 16: 89 (2002)); neurodegeneration (O'Neill et al., *Curr. Drug Targets: CNS Neurol. Disord.* 1: 399 (2002), Takata et al., *J. Pharmacol. Exp. Ther.* 306: 772 (2003), Marrero et al., *J. Pharmacol. Exp. Ther.* 309: 16 (2004)); Parkinson's disease (Jonnala and Buccafusco, *J. Neurosci. Res.* 66: 565 (2001)); addiction (Dwoskin and Crooks, *Biochem. Pharmacol.* 63: 89 (2002), Coe et al., *Bioorg. Med. Chem. Lett.* 15(22): 4889 (2005)); obesity (Li et al., *Curr. Top. Med. Chem.* 3: 899 (2003)); and Tourette's syndrome (Sacco et al., *J. Psychopharmacol.* 18(4): 457 (2004), Young et al., *Clin. Ther.* 23(4): 532 (2001)), each of these references incorporated by reference with regard to the nexus of the receptor and the named indication(s).

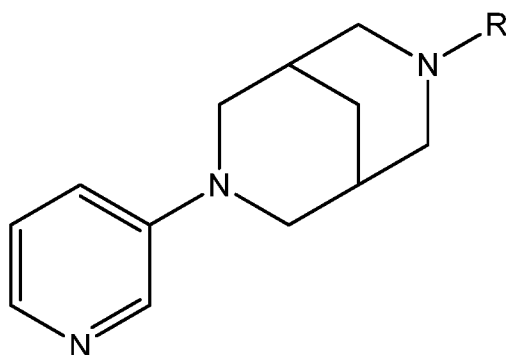
A limitation of some nicotinic compounds is that they are associated with various undesirable side effects due to non-specific binding to multiple nAChR subtypes. For example,

binding to and stimulation of muscle and ganglionic nAChR subtypes can lead to side effects which can limit the utility of a particular nicotinic binding compound as a therapeutic agent.

The compounds of the present invention exhibit a high degree of binding to the $\alpha 4\beta 2$ nAChR subtype and lower affinity for $\alpha 7$, ganglionic and muscle nAChR subtypes. Thus, these compounds can serve as therapeutic modulators of $\alpha 4\beta 2$ nAChRs in patients in need of such treatment, without producing side effects caused by non-specific nAChR subtype binding.

Summary of the Invention

The present invention includes compounds of Formula I:



Formula I

wherein

R is chosen from among the list of 3-azetidiny, 3-pyrrolidinyl, 3-piperidinyl, 4-piperidinyl, 4-azepanyl, and 4-azocanyl, each of which may be N-substituted with C_{1-6} alkyl, and 3-quinuclidinyl;

or a pharmaceutically acceptable salt thereof.

The compounds of the present invention bind with high affinity to NNRs of the $\alpha 4\beta 2$ subtype and exhibit selectivity for this subtype over the $\alpha 7$ NNR subtype, as well as ganglion and muscle subtypes.

The present invention also relates to pharmaceutically acceptable salts prepared from these compounds.

The present invention includes pharmaceutical compositions comprising a compound of the present invention or a pharmaceutically acceptable salt thereof. The pharmaceutical compositions of the present invention can be used for treating or preventing a wide variety of conditions or disorders, including those disorders characterized by dysfunction of nicotinic cholinergic neurotransmission or the degeneration of the nicotinic cholinergic neurons.

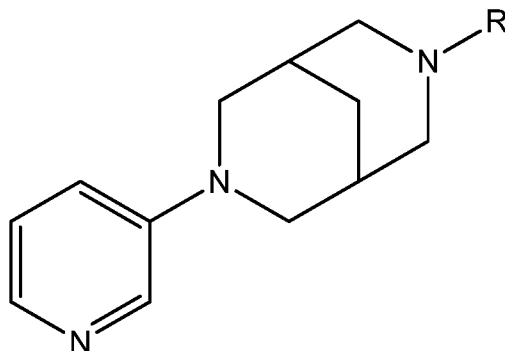
The present invention includes a method for treating or preventing disorders and dysfunctions, such as CNS disorders and dysfunctions, inflammation, inflammatory response associated with bacterial and/or viral infection, pain, metabolic syndrome, autoimmune disorders, or other disorders described in further detail herein. The present invention includes a method for modulating neovascularization. The methods involve administering to a subject a therapeutically effective amount of a compound of the present invention, including a salt thereof, or a pharmaceutical composition that includes such compounds. Additionally, the present invention includes compounds that have utility as diagnostic agents and in receptor binding studies as described herein.

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

Detailed Description

I. Compounds

One embodiment of the present invention includes a compound as represented by Formula I:



Formula I

wherein

R is chosen from among the list of 3-azetidiny, 3-pyrrolidinyl, 3-piperidinyl, 4-piperidinyl, 4-azepanyl, and 4-azocanyl, each of which may be N-substituted with C₁₋₆ alkyl, and 3-quinuclidinyl;

or a pharmaceutically acceptable salt thereof.

One embodiment of the present invention includes use of a compound of the present invention in the manufacture of a medicament. One embodiment of the present invention includes a method for the treatment or prevention of a variety of disorders and dysfunctions, comprising administering to a mammal in need of such treatment, a therapeutically effective

amount of the compound of the present invention. More specifically, the disorder or dysfunction may be selected from the group consisting of CNS disorders, inflammation, inflammatory response associated with bacterial and/or viral infection, pain, metabolic syndrome, autoimmune disorders or other disorders described in further detail herein. One embodiment of the present invention includes a method for modulating neovascularization. Another embodiment of the present invention includes compounds that have utility as diagnostic agents and in receptor binding studies as described herein. Additionally, these compounds may also have utility as diagnostic agents and in receptor binding studies as described herein.

One embodiment of the present invention includes a pharmaceutical composition comprising a therapeutically effective amount of a compound of the present invention and one or more pharmaceutically acceptable carrier.

One embodiment of the present invention includes the use of a compound of the present invention in the manufacture of a medicament for treatment of central nervous system disorders and dysfunctions.

Another embodiment of the present invention includes a compound as herein described with reference to any one of the Examples.

Another embodiment of the present invention includes a compound of the present invention for use as an active therapeutic substance.

Another embodiment of the present invention includes a compound of the present invention for use to modulate an NNR in a subject in need thereof.

Another embodiment of the present invention includes a compound of the present invention for use in the treatment or prevention of conditions or disorders mediated by NNR.

Another embodiment of the present invention includes a use of a compound of the present invention in the manufacture of a medicament for use of modulating NNR in a subject in need thereof.

Another embodiment of the present invention includes a use of a compound of the present invention in the manufacture of a medicament for use in the treatment or prevention of conditions or disorders mediated by NNR.

Another embodiment of the present invention includes a method of modulating NNR in a subject in need thereof through the administration of a compound of the present invention.

The scope of the present invention includes combinations of embodiments.

Unless otherwise stated, structures depicted herein are also meant to include compounds which differ only in the presence of one or more isotopically enriched atoms. For example, compounds having the present structure except for the replacement of a hydrogen

atom by a deuterium or tritium, or the replacement of a carbon atom by a ^{13}C - or ^{14}C -enriched carbon are within the scope of the invention.

The compounds of the present invention may crystallize in more than one form, a characteristic known as polymorphism, and such polymorphic forms ("polymorphs") are within the scope of the present invention. Polymorphism generally can occur as a response to changes in temperature, pressure, or both. Polymorphism can also result from variations in the crystallization process. Polymorphs can be distinguished by various physical characteristics known in the art such as x-ray diffraction patterns, solubility, and melting point.

Certain of the compounds described herein contain one or more chiral centers, or may otherwise be capable of existing as multiple stereoisomers. The scope of the present invention includes mixtures of stereoisomers as well as purified enantiomers or enantiomerically/diastereomerically enriched mixtures. Also included within the scope of the invention are the individual isomers of the compounds represented by the formulae of the present invention, as well as any wholly or partially equilibrated mixtures thereof. The present invention also includes the individual isomers of the compounds represented by the formulae above as mixtures with isomers thereof in which one or more chiral centers are inverted.

The present invention includes a salt or solvate of the compounds herein described, including combinations thereof such as a solvate of a salt. The compounds of the present invention may exist in solvated, for example hydrated, as well as unsolvated forms, and the present invention encompasses all such forms.

Typically, but not absolutely, the salts of the present invention are pharmaceutically acceptable salts. Salts encompassed within the term "pharmaceutically acceptable salts" refer to non-toxic salts of the compounds of this invention.

Examples of suitable pharmaceutically acceptable salts include inorganic acid addition salts such as chloride, bromide, 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 acidic amino acid such as aspartate and glutamate; alkali metal salts such as sodium salt and potassium salt; alkaline earth metal salts such as magnesium salt and calcium salt; ammonium salt; organic basic salts such as trimethylamine salt, triethylamine salt, pyridine salt, picoline salt, dicyclohexylamine salt, and N,N'-dibenzylethylenediamine salt; and salts with basic amino acid such as lysine salt and arginine salt. The salts may be in some cases hydrates or ethanol solvates. 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, each of which is herein

incorporated by reference with regard to such salts.

As noted herein, the present invention includes specific representative compounds, which are identified herein with particularity. The compounds of this invention may be made by a variety of methods, including well-known standard synthetic methods. Illustrative general synthetic methods are set out below and then specific compounds of the invention are prepared in the working Examples.

In all of the examples described below, protecting groups for sensitive or reactive groups are employed where necessary in accordance with general principles of synthetic chemistry. Protecting groups are manipulated according to standard methods of organic synthesis (T. W. Green and P. G. M. Wuts, *Protecting Groups in Organic Synthesis*, 3rd Edition, John Wiley & Sons, New York (1999), incorporated by reference with regard to protecting groups). These groups are removed at a convenient stage of the compound synthesis using methods that are readily apparent to those skilled in the art. The selection of processes as well as the reaction conditions and order of their execution shall be consistent with the preparation of compounds of the present invention.

Those skilled in the art will recognize if a stereocenter exists. As noted hereinabove, the present invention includes all possible stereoisomers and includes not only racemic compounds but the individual enantiomers as well. When a compound is desired as a single enantiomer, such may be obtained by stereospecific synthesis, by resolution of the final product or any convenient intermediate, or by chiral chromatographic methods as are known in the art. Resolution of the final product, an intermediate, or a starting material may be effected by any suitable method known in the art. See, for example, *Stereochemistry of Organic Compounds* (Wiley-Interscience, 1994), incorporated by reference with regard to stereochemistry.

The present invention also provides a method for the synthesis of compounds useful as intermediates in the preparation of compounds of the present invention along with methods for their preparation.

The compounds can be prepared according to the following methods using readily available starting materials and reagents. In these reactions, variants may be employed which are themselves known to those of ordinary skill in this art, but are not mentioned in greater detail.

II. General Synthetic Methods

Those skilled in the art of organic synthesis will appreciate that there exist multiple means of producing compounds of the present invention, as well as means for producing compounds of the present invention which are labeled with a radioisotope appropriate to various

uses.

For instance, PCTs WO 200/44755 and WO 2001/44243 describe the synthesis of 3-(pyridin-3-yl)-3,7-diazabicyclo[3.3.1]nonane, an intermediate useful in the preparation of compounds of Formula I. The secondary amine functionality (the 7-aza nitrogen) can participate in reductive amination reactions with a variety of aldehydes and ketones. When certain cyclic ketones are employed in these reductive aminations of 3-(pyridin-3-yl)-3,7-diazabicyclo[3.3.1]nonane, compounds of Formula I are formed. Thus, reaction of 3-(pyridin-3-yl)-3,7-diazabicyclo[3.3.1]nonane with N-(tert-butoxycarbonyl)-4-piperidone and sodium triacetoxyborohydride (as described in the Synthetic Examples section) produces tert-butyl 4-(7-(pyridin-3-yl)-3,7-diazabicyclo[3.3.1]nonan-3-yl)piperidine-1-carboxylate. Acid-catalyzed removal of the tert-butoxycarbonyl protecting group then produces 3-(piperidin-4-yl)-7-(pyridin-3-yl)-3,7-diazabicyclo[3.3.1]nonane, a compound of Formula I.

Cyclic ketones of a variety of ring sizes can be employed in the reductive amination procedure. Thus, N-(tert-butoxycarbonyl)-3-oxoazetidine, N-(tert-butoxycarbonyl)-3-oxopyrrolidine, N-methyl-3-oxopyrrolidine, N-(tert-butoxycarbonyl)-3-oxopiperidine, N-(tert-butoxycarbonyl)-4-oxoazepane, N-(tert-butoxycarbonyl)-4-oxoazocane and 3-quinuclidinone can also be employed as ketone components of the reductive amination reaction, leading, after acid-catalyzed de-protection (in those cases that require de-protection), to compounds of Formula I: 3-(azetidin-3-yl)-7-(pyridin-3-yl)-3,7-diazabicyclo[3.3.1]nonane, 3-(pyrrolidin-3-yl)-7-(pyridin-3-yl)-3,7-diazabicyclo[3.3.1]nonane, 3-(1-methylpyrrolidin-3-yl)-7-(pyridin-3-yl)-3,7-diazabicyclo[3.3.1]nonane, 3-(piperidin-3-yl)-7-(pyridin-3-yl)-3,7-diazabicyclo[3.3.1]nonane, 3-(azepan-4-yl)-7-(pyridin-3-yl)-3,7-diazabicyclo[3.3.1]nonane, 3-(azocan-4-yl)-7-(pyridin-3-yl)-3,7-diazabicyclo[3.3.1]nonane and 3-quinuclidinyl-7-(pyridin-3-yl)-3,7-diazabicyclo[3.3.1]nonane, respectively.

The incorporation of specific radioisotopes is also possible. For example, reductive aminations can utilize reducing agents that contain, and will transfer, deuterium and tritium atoms. Thus use of reducing agents generated, in situ, from sodium borodeuteride or sodium borotritide and acetic acid, can produce compounds of Formula I in which a deuterium or tritium atom has been incorporated. Alternatively, using a ketone, in which the carbonyl carbon is a ^{11}C , ^{13}C , or ^{14}C atom, in the reductive amination reaction will produce a compound of Formula I in which a ^{11}C , ^{13}C , or ^{14}C atom, respectively, has been incorporated. The incorporation of specific radioisotopes is often desirable in the preparation of compounds that are to be used in a diagnostic setting (e.g., as imaging agents) or in functional and metabolic studies.

Those skilled in the art of organic synthesis will appreciate that there exist multiple

means of producing compounds of the present invention which are labeled with a radioisotope appropriate to various diagnostic uses. Thus, condensation of a ^{11}C - or ^{18}F -labeled reactive derivative with either compound 5 or compound 6 followed by removal of the protecting group as described above will produce a compound suitable for use in positron emission tomography. Further derivatization of this compound is possible as described above by alkylation of the remaining basic nitrogen with an activated alkyl compound.

III. Pharmaceutical Compositions

The pharmaceutical compositions of the present invention include the salts described herein, in the pure state or in the form of a composition in which the compounds are combined with any other pharmaceutically compatible product, which can be inert or physiologically active. The resulting pharmaceutical compositions can be 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 I and/or pharmaceutically acceptable salts thereof.

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. Standard excipients include binders, fillers, colorants, solubilizers and the like. Compositions can 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 can be used. The use of such liquids and semisolids is well known to those of skill in the art.

The compositions can also be administered via injection, i.e., intravenously, intramuscularly, subcutaneously, intraperitoneally, intraarterially, intrathecally; and intracerebroventricularly. Intravenous administration is the 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 an infusion or injection (e.g., as a suspension or as an emulsion in a pharmaceutically acceptable liquid or mixture of liquids).

The formulations can 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); transdermally (e.g., using a transdermal patch) or iontophoretically; or by sublingual or buccal administration. 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.

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

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.

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., the contents of which are hereby incorporated by reference.

In an embodiment of the present invention and as will be appreciated by those skilled in the art, the compound of the present invention may be administered in combination with other therapeutic compounds. For example, a compound of this invention can be used in combination with other NNR ligands (such as varenicline), antioxidants (such as free radical scavenging agents), antibacterial agents (such as penicillin antibiotics), antiviral agents (such as nucleoside analogs, like zidovudine and acyclovir), anticoagulants (such as warfarin), anti-inflammatory agents (such as NSAIDs), anti-pyretics, analgesics, anesthetics (such as used in surgery), acetylcholinesterase inhibitors (such as donepezil and galantamine), antipsychotics (such as haloperidol, clozapine, olanzapine, and quetiapine), immuno-suppressants (such as cyclosporin and methotrexate), neuroprotective agents, steroids (such as steroid hormones), corticosteroids (such as dexamethasone, prednisone, and hydrocortisone), vitamins, minerals, nutraceuticals, anti-depressants (such as imipramine, fluoxetine, paroxetine, escitalopram, sertraline, venlafaxine, and duloxetine), anxiolytics (such as alprazolam and buspirone), anticonvulsants (such as phenytoin and gabapentin), vasodilators (such as prazosin and sildenafil), mood

stabilizers (such as valproate and aripiprazole), anti-cancer drugs (such as anti-proliferatives), antihypertensive agents (such as atenolol, clonidine, amlodipine, verapamil, and olmesartan), laxatives, stool softeners, diuretics (such as furosemide), anti-spasmodics (such as dicyclomine), anti-dyskinetic agents, and anti-ulcer medications (such as esomeprazole).

The compounds of the present invention may be employed alone or in combination with other therapeutic agents, including other compounds of the present invention. Such a combination of pharmaceutically active agents may be administered together or separately and, when administered separately, administration may occur simultaneously or sequentially, in any order. The amounts of the compounds or agents and the relative timings of administration will be selected in order to achieve the desired therapeutic effect. The administration in combination of a compound of the formulae of the present invention including salts or solvates thereof with other treatment agents may be in combination by administration concomitantly in: (1) a unitary pharmaceutical composition including both compounds; or (2) separate pharmaceutical compositions each including one of the compounds. Alternatively, the combination may be administered separately in a sequential manner wherein one treatment agent is administered first and the other second or vice versa. Such sequential administration may be close in time or remote in time. The compounds of the present invention may be used in the treatment of a variety of disorders and conditions and, as such, the compounds of the present invention may be used in combination with a variety of other suitable therapeutic agents useful in the treatment or prophylaxis of those disorders or conditions.

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.

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.

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 modulate the activity of relevant NNR 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.

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 modulate the activity of relevant NNRs, 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.

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, ameliorate symptoms of, and ameliorate to some degree of the recurrence of CNS or other 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 or ganglia. The compounds can be administered in a therapeutic window in which certain CNS and other 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 disorder 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 or other disorders but less than 1/5, and often less than 1/10, the amount required to elicit certain side effects to any significant degree. Most preferably, effective doses are at very low concentrations, where maximal effects are observed to occur, with a minimum of side effects. An effective dose of such compounds may require administering the compound in an amount of less than 5 mg/kg of patient weight. The compounds of the present invention may be administered in an amount from less than about 1 mg/kg patient weight and usually less than about 100 µg/kg of patient weight, but may be between about 10 µg to less than 100 µg/kg of patient weight. The foregoing doses typically represent that amount administered as a single dose, or as one or more doses administered over a 24-hour period. For human patients, an 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 100 mg/ 24 hr/ patient. For human patients, an 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 mg/ 24 hr/ patient. In addition, the compositions may be advantageously administered at an effective dose such that the concentration of the compound within the plasma of the patient normally does not exceed 50 ng/mL, often does not exceed 30 ng/mL, and frequently does not exceed 10 ng/mL.

IV. Method of Using Pharmaceutical Compositions

The compounds of the present invention can be used for the prevention or treatment of various conditions or disorders for which other types of nicotinic compounds have been proposed or are shown to be useful as therapeutics, such as CNS disorders, inflammation, inflammatory response associated with bacterial and/or viral infection, pain, metabolic syndrome, autoimmune disorders, addictions, obesity or other disorders described in further detail herein. This compound can also be used as a diagnostic agent in receptor binding studies (in vitro and in vivo). Such therapeutic and other teachings are described, for example, in references previously listed herein, including Williams et al., *Drug News Perspec.* 7(4): 205 (1994), Arneric et al., *CNS Drug Rev.* 1(1): 1-26 (1995), Arneric et al., *Exp. Opin. Invest. Drugs* 5(1): 79-100 (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), Holladay et al., *J. Med. Chem.* 40(28): 4169-94 (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.

CNS Disorders

The compounds and their pharmaceutical compositions are useful in the treatment or prevention of a variety of CNS disorders, including neurodegenerative disorders, neuropsychiatric disorders, neurologic disorders, and addictions. The compounds and their pharmaceutical compositions can be used to treat or prevent cognitive deficits and dysfunctions, age-related and otherwise; attentional disorders and dementias, including those due to infectious agents or metabolic disturbances; to provide neuroprotection; to treat convulsions and multiple cerebral infarcts; to treat mood disorders, compulsions and addictive behaviors; to provide analgesia; to control inflammation, such as mediated by cytokines and nuclear factor kappa B; to treat inflammatory disorders; to provide pain relief; and to treat infections, as anti-infectious agents for treating bacterial, fungal, and viral infections. Among the disorders, diseases and conditions that the compounds and pharmaceutical compositions of the present invention can be used to treat or prevent are: age-associated memory impairment (AAMI), mild

cognitive impairment (MCI), age-related cognitive decline (ARCD), pre-senile dementia, early onset Alzheimer's disease, senile dementia, dementia of the Alzheimer's type, Alzheimer's disease, cognitive impairment no dementia (CIND), Lewy body dementia, HIV-dementia, AIDS dementia complex, vascular dementia, Down syndrome, head trauma, traumatic brain injury (TBI), dementia pugilistica, Creutzfeld-Jacob Disease and prion diseases, stroke, central ischemia, peripheral ischemia, attention deficit disorder, attention deficit hyperactivity disorder, dyslexia, schizophrenia, schizophreniform disorder, schizoaffective disorder, cognitive dysfunction in schizophrenia, cognitive deficits in schizophrenia, Parkinsonism including Parkinson's disease, postencephalitic parkinsonism, parkinsonism-dementia of Gaum, frontotemporal dementia Parkinson's Type (FTDP), Pick's disease, Niemann-Pick's Disease, Huntington's Disease, Huntington's chorea, tardive dyskinesia, hyperkinesia, progressive supranuclear palsy, progressive supranuclear paresis, restless leg syndrome, Creutzfeld-Jakob disease, multiple sclerosis, amyotrophic lateral sclerosis (ALS), motor neuron diseases (MND), multiple system atrophy (MSA), corticobasal degeneration, Guillain-Barré Syndrome (GBS), and chronic inflammatory demyelinating polyneuropathy (CIDP), epilepsy, autosomal dominant nocturnal frontal lobe epilepsy, mania, anxiety, depression, premenstrual dysphoria, panic disorders, bulimia, anorexia, narcolepsy, excessive daytime sleepiness, bipolar disorders, generalized anxiety disorder, obsessive compulsive disorder, rage outbursts, conduct disorder, oppositional defiant disorder, Tourette's syndrome, autism, drug and alcohol addiction, tobacco addiction, obesity, cachexia, psoriasis, lupus, acute cholangitis, aphthous stomatitis, ulcers, asthma, ulcerative colitis, inflammatory bowel disease, Crohn's disease, irritable bowel syndrome, spastic dystonia, diarrhea, constipation, pouchitis, viral pneumonitis, arthritis, including, rheumatoid arthritis and osteoarthritis, endotoxaemia, sepsis, atherosclerosis, idiopathic pulmonary fibrosis, acute pain, chronic pain, neuropathies, urinary incontinence, diabetes, sexual dysfunction, neoplasias, and preeclampsia.

Cognitive impairments or dysfunctions may be associated with psychiatric disorders or conditions, such as schizophrenia and other psychotic disorders, including but not limited to psychotic disorder, schizophreniform disorder, schizoaffective disorder, delusional disorder, brief psychotic disorder, shared psychotic disorder, and psychotic disorders due to a general medical conditions, dementias and other cognitive disorders, including but not limited to mild cognitive impairment, pre-senile dementia, Alzheimer's disease, senile dementia, dementia of the Alzheimer's type, age-related memory impairment, Lewy body dementia, vascular dementia, AIDS dementia complex, dyslexia, Parkinsonism including Parkinson's disease, cognitive impairment and dementia of Parkinson's Disease, cognitive impairment of multiple sclerosis,

cognitive impairment caused by traumatic brain injury, dementias due to other general medical conditions, anxiety disorders, including but not limited to panic disorder without agoraphobia, panic disorder with agoraphobia, agoraphobia without history of panic disorder, specific phobia, social phobia, obsessive-compulsive disorder, post-traumatic stress disorder, acute stress disorder, generalized anxiety disorder and generalized anxiety disorder due to a general medical condition, mood disorders, including but not limited to major depressive disorder, dysthymic disorder, bipolar depression, bipolar mania, bipolar I disorder, depression associated with manic, depressive or mixed episodes, bipolar II disorder, cyclothymic disorder, and mood disorders due to general medical conditions, sleep disorders, including but not limited to dyssomnia disorders, primary insomnia, primary hypersomnia, narcolepsy, parasomnia disorders, nightmare disorder, sleep terror disorder and sleepwalking disorder, mental retardation, learning disorders, motor skills disorders, communication disorders, pervasive developmental disorders, attention-deficit and disruptive behavior disorders, attention deficit disorder, attention deficit hyperactivity disorder, feeding and eating disorders of infancy, childhood, or adults, tic disorders, elimination disorders, substance-related disorders, including but not limited to substance dependence, substance abuse, substance intoxication, substance withdrawal, alcohol-related disorders, amphetamine or amphetamine-like-related disorders, caffeine-related disorders, cannabis-related disorders, cocaine-related disorders, hallucinogen-related disorders, inhalant-related disorders, nicotine-related disorders, opioid-related disorders, phencyclidine or phencyclidine-like-related disorders, and sedative-, hypnotic- or anxiolytic-related disorders, personality disorders, including but not limited to obsessive-compulsive personality disorder and impulse-control disorders. Cognitive performance may be assessed with a validated cognitive scale, such as, for example, the cognitive subscale of the Alzheimer's Disease Assessment Scale (ADAS-cog). One measure of the effectiveness of the compounds of the present invention in improving cognition may include measuring a patient's degree of change according to such a scale.

Regarding compulsions and addictive behaviors, the compounds of the present invention may be used as a therapy for nicotine addiction and for other brain-reward disorders, such as substance abuse including alcohol addiction, illicit and prescription drug addiction, eating disorders, including obesity, and behavioral addictions, such as gambling, or other similar behavioral manifestations of addiction.

The above conditions and disorders are discussed in further detail, for example, in the American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision, Washington, DC, American Psychiatric Association, 2000. This Manual

may also be referred to for greater detail on the symptoms and diagnostic features associated with substance use, abuse, and dependence.

Preferably, the treatment or prevention of diseases, disorders and conditions occurs without appreciable adverse side effects, including, for example, significant increases in blood pressure and heart rate, significant negative effects upon the gastro-intestinal tract, and significant effects upon skeletal muscle.

The compounds of the present invention, when employed in effective amounts, are believed to modulate the activity of the $\alpha 4\beta 2$ and $\alpha 7$ NNRs without appreciable interaction with the nicotinic subtypes that characterize the human ganglia, as demonstrated by a lack of the ability to elicit nicotinic function in adrenal chromaffin tissue, or skeletal muscle, further demonstrated by a lack of the ability to elicit nicotinic function in cell preparations expressing muscle-type nicotinic receptors. Thus, these compounds are believed capable of treating or preventing diseases, disorders and conditions without eliciting significant side effects associated activity at ganglionic and neuromuscular sites. Thus, administration of the compounds is believed to provide a therapeutic window in which treatment of certain diseases, disorders and conditions is provided, and certain side effects are avoided. That is, an effective dose of the compound is believed sufficient to provide the desired effects upon the disease, disorder or condition, but is believed insufficient, namely is not at a high enough level, to provide undesirable side effects.

Thus, the present invention provides the use of a compound of the present invention, or a pharmaceutically acceptable salt thereof, for use in therapy, such as a therapy described above.

In yet another aspect the present invention provides the use of a compound of the present invention, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for use in the treatment of a CNS disorder, such as a disorder, disease or condition described hereinabove.

Inflammation

The nervous system, primarily through the vagus nerve, is known to regulate the magnitude of the innate immune response by inhibiting the release of macrophage tumor necrosis factor (TNF). This physiological mechanism is known as the “cholinergic anti-inflammatory pathway” (see, for example, Tracey, “The Inflammatory Reflex,” *Nature* 420: 853-9 (2002)). Excessive inflammation and tumor necrosis factor synthesis cause morbidity and even mortality in a variety of diseases. These diseases include, but are not limited to, endotoxemia,

rheumatoid arthritis, osteoarthritis, psoriasis, asthma, atherosclerosis, idiopathic pulmonary fibrosis, and inflammatory bowel disease.

Inflammatory conditions that can be treated or prevented by administering the compounds described herein include, but are not limited to, chronic and acute inflammation, psoriasis, endotoxemia, gout, acute pseudogout, acute gouty arthritis, arthritis, rheumatoid arthritis, osteoarthritis, allograft rejection, chronic transplant rejection, asthma, atherosclerosis, mononuclear-phagocyte dependent lung injury, idiopathic pulmonary fibrosis, atopic dermatitis, chronic obstructive pulmonary disease, adult respiratory distress syndrome, acute chest syndrome in sickle cell disease, inflammatory bowel disease, Crohn's disease, ulcerative colitis, acute cholangitis, aphthous stomatitis, pouchitis, glomerulonephritis, lupus nephritis, thrombosis, and graft vs. host reaction.

Inflammatory Response Associated with Bacterial and/or Viral Infection

Many bacterial and/or viral infections are associated with side effects brought on by the formation of toxins, and the body's natural response to the bacteria or virus and/or the toxins. As discussed above, the body's response to infection often involves generating a significant amount of TNF and/or other cytokines. The over-expression of these cytokines can result in significant injury, such as septic shock (when the bacteria is sepsis), endotoxic shock, urosepsis and toxic shock syndrome.

Cytokine expression is mediated by NNRs, and can be inhibited by administering agonists or partial agonists of these receptors. Those compounds described herein that are agonists or partial agonists of these receptors can therefore be used to minimize the inflammatory response associated with bacterial infection, as well as viral and fungal infections. Examples of such bacterial infections include anthrax, botulism, and sepsis. Some of these compounds may also have antimicrobial properties.

These compounds can also be used as adjunct therapy in combination with existing therapies to manage bacterial, viral and fungal infections, such as antibiotics, antivirals and antifungals. Antitoxins can also be used to bind to toxins produced by the infectious agents and allow the bound toxins to pass through the body without generating an inflammatory response. Examples of antitoxins are disclosed, for example, in U.S. Patent No. 6,310,043 to Bundle et al. Other agents effective against bacterial and other toxins can be effective and their therapeutic effect can be complemented by co-administration with the compounds described herein.

Pain

The compounds can be administered to treat and/or prevent pain, including acute, neurologic, inflammatory, neuropathic and chronic pain. The compounds can be used in

conjunction with opiates to minimize the likelihood of opiate addiction (e.g., morphine sparing therapy). The analgesic activity of compounds described herein can be demonstrated in models of persistent inflammatory pain and of neuropathic pain, performed as described in U.S. Published Patent Application No. 20010056084 A1 (Allgeier et al.) (e.g., mechanical hyperalgesia in the complete Freund's adjuvant rat model of inflammatory pain and mechanical hyperalgesia in the mouse partial sciatic nerve ligation model of neuropathic pain).

The analgesic effect is suitable for treating pain of various genesis or etiology, in particular in treating inflammatory pain and associated hyperalgesia, neuropathic pain and associated hyperalgesia, chronic pain (e.g., severe chronic pain, post-operative pain and pain associated with various conditions including cancer, angina, renal or biliary colic, menstruation, migraine, and gout). Inflammatory pain may be of diverse genesis, including arthritis and rheumatoid disease, teno-synovitis and vasculitis. Neuropathic pain includes trigeminal or herpetic neuralgia, diabetic neuropathy pain, causalgia, low back pain and deafferentation syndromes such as brachial plexus avulsion.

Neovascularization

The $\alpha 7$ NNR is associated with neovascularization. Inhibition of neovascularization, for example, by administering antagonists (or at certain dosages, partial agonists) of the $\alpha 7$ NNR can treat or prevent conditions characterized by undesirable neovascularization or angiogenesis. Such conditions can include those characterized by inflammatory angiogenesis and/or ischemia-induced angiogenesis. Neovascularization associated with tumor growth can also be inhibited by administering those compounds described herein that function as antagonists or partial agonists of $\alpha 7$ NNR.

Specific antagonism of $\alpha 7$ NNR-specific activity reduces the angiogenic response to inflammation, ischemia, and neoplasia. Guidance regarding appropriate animal model systems for evaluating the compounds described herein can be found, for example, in Heeschen, C. et al., "A novel angiogenic pathway mediated by non-neuronal nicotinic acetylcholine receptors," J. Clin. Invest. 110(4):527-36 (2002).

Representative tumor types that can be treated using the compounds described herein include NSCLC, ovarian cancer, pancreatic cancer, breast carcinoma, colon carcinoma, rectum carcinoma, lung carcinoma, oropharynx carcinoma, hypopharynx carcinoma, esophagus carcinoma, stomach carcinoma, pancreas carcinoma, liver carcinoma, gallbladder carcinoma, bile duct carcinoma, small intestine carcinoma, urinary tract carcinoma, kidney carcinoma, bladder carcinoma, urothelium carcinoma, female genital tract carcinoma, cervix carcinoma, uterus carcinoma, ovarian carcinoma, choriocarcinoma, gestational trophoblastic disease, male

genital tract carcinoma, prostate carcinoma, seminal vesicles carcinoma, testes carcinoma, germ cell tumors, endocrine gland carcinoma, thyroid carcinoma, adrenal carcinoma, pituitary gland carcinoma, skin carcinoma, hemangiomas, melanomas, sarcomas, bone and soft tissue sarcoma, Kaposi's sarcoma, tumors of the brain, tumors of the nerves, tumors of the eyes, tumors of the meninges, astrocytomas, gliomas, glioblastomas, retinoblastomas, neuromas, neuroblastomas, Schwannomas, meningiomas, solid tumors arising from hematopoietic malignancies (such as leukemias, chloromas, plasmacytomas and the plaques and tumors of mycosis fungoides and cutaneous T-cell lymphoma/leukemia), and solid tumors arising from lymphomas.

The compounds can also be administered in conjunction with other forms of anti-cancer treatment, including co-administration with antineoplastic antitumor agents such as cis-platin, adriamycin, daunomycin, and the like, and/or anti-VEGF (vascular endothelial growth factor) agents, as such are known in the art.

The compounds can be administered in such a manner that they are targeted to the tumor site. For example, the compounds can be administered in microspheres, microparticles or liposomes conjugated to various antibodies that direct the microparticles to the tumor. Additionally, the compounds can be present in microspheres, microparticles or liposomes that are appropriately sized to pass through the arteries and veins, but lodge in capillary beds surrounding tumors and administer the compounds locally to the tumor. Such drug delivery devices are known in the art.

Other Disorders

In addition to treating CNS disorders, inflammation, and neovascularization, and pain, the compounds of the present invention can be also used to prevent or treat certain other conditions, diseases, and disorders in which NNRs play a role. Examples include autoimmune disorders such as Lupus, disorders associated with cytokine release, cachexia secondary to infection (e.g., as occurs in AIDS, AIDS related complex and neoplasia), obesity, pemphitis, urinary incontinence, retinal diseases, infectious diseases, myasthenia, Eaton-Lambert syndrome, hypertension, preeclampsia, osteoporosis, vasoconstriction, vasodilatation, cardiac arrhythmias, type I diabetes, bulimia, anorexia as well as those indications set forth in published PCT application WO 98/25619. The compounds of this invention can also be administered to treat convulsions such as those that are symptomatic of epilepsy, and to treat conditions such as syphilis and Creutzfeld-Jakob disease.

Diagnostic Uses

The compounds can be used in diagnostic compositions, such as probes, particularly when they are modified to include appropriate labels. The probes can be used, for example, to determine the relative number and/or function of specific receptors, particularly the $\alpha 4\beta 2$ and $\alpha 7$ receptor subtypes. For this purpose the compounds of the present invention most preferably are labeled with a radioactive isotopic moiety such as ^{11}C , ^{18}F , ^{76}Br , ^{123}I or ^{125}I .

The administered compounds can be detected using known detection methods appropriate for the label used. Examples of detection methods include position emission topography (PET) and single-photon emission computed tomography (SPECT). The radiolabels described above are useful in PET (e.g., ^{11}C , ^{18}F or ^{76}Br) and SPECT (e.g., ^{123}I) imaging, with half-lives of about 20.4 minutes for ^{11}C , about 109 minutes for ^{18}F , about 13 hours for ^{123}I , and about 16 hours for ^{76}Br . A high specific activity is desired to visualize the selected receptor subtypes at non-saturating concentrations. The administered doses typically are below the toxic range and provide high contrast images. The compounds are expected to be capable of administration in non-toxic levels. Determination of dose is carried out in a manner known to one skilled in the art of radiolabel imaging. See, for example, U.S. Patent No. 5,969,144 to London et al.

The compounds can be administered using known techniques. See, for example, U.S. Patent No. 5,969,144 to London et al., as noted. The compounds can be administered in formulation compositions that incorporate other ingredients, such as those types of ingredients that are useful in formulating a diagnostic composition. Compounds useful in accordance with carrying out the present invention most preferably are employed in forms of high purity. See, U.S. Patent No. 5,853,696 to Elmalch et al.

After the compounds are administered to a subject (e.g., a human subject), the presence of that compound within the subject can be imaged and quantified by appropriate techniques in order to indicate the presence, quantity, and functionality of selected NNR subtypes. In addition to humans, the compounds can also be administered to animals, such as mice, rats, dogs, and monkeys. SPECT and PET imaging can be carried out using any appropriate technique and apparatus. See Villemagne et al., In: Arneric et al. (Eds.) *Neuronal Nicotinic Receptors: Pharmacology and Therapeutic Opportunities*, 235-250 (1998) and U.S. Patent No. 5,853,696 to Elmalch et al., each herein incorporated by reference, for a disclosure of representative imaging techniques.

The radiolabeled compounds bind with high affinity to selective NNR subtypes (e.g., $\alpha 4\beta 2$, $\alpha 7$) and preferably exhibit negligible non-specific binding to other nicotinic cholinergic receptor subtypes (e.g., those receptor subtypes associated with muscle and ganglia). As such,

the compounds can be used as agents for noninvasive imaging of nicotinic cholinergic receptor subtypes within the body of a subject, particularly within the brain for diagnosis associated with a variety of CNS diseases and disorders.

In one aspect, the diagnostic compositions can be used in a method to diagnose disease in a subject, such as a human patient. The method involves administering to that patient a detectably labeled compound as described herein, and detecting the binding of that compound to selected NNR subtypes (e.g., $\alpha 4\beta 2$ and $\alpha 7$ receptor subtypes). Those skilled in the art of using diagnostic tools, such as PET and SPECT, can use the radiolabeled compounds described herein to diagnose a wide variety of conditions and disorders, including conditions and disorders associated with dysfunction of the central and autonomic nervous systems. Such disorders include a wide variety of CNS diseases and disorders, including Alzheimer's disease, Parkinson's disease, and schizophrenia. These and other representative diseases and disorders that can be evaluated include those that are set forth in U.S. Patent No. 5,952,339 to Bencherif et al.

In another aspect, the diagnostic compositions can be used in a method to monitor selective nicotinic receptor subtypes of a subject, such as a human patient. The method involves administering a detectably labeled compound as described herein to that patient and detecting the binding of that compound to selected nicotinic receptor subtypes namely, the $\alpha 4\beta 2$ and $\alpha 7$ receptor subtypes.

Receptor Binding

The compounds of this invention can be used as reference ligands in binding assays for compounds which bind to NNR subtypes, particularly the $\alpha 4\beta 2$ and $\alpha 7$ receptor subtypes. For this purpose the compounds of this invention are preferably labeled with a radioactive isotopic moiety such as ^3H , or ^{14}C . Examples of such binding assays are described in detail below.

V. Synthetic Examples

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.

Example 1: 3-(Piperidin-4-yl)-7-(pyridin-3-yl)-3,7-diazabicyclo[3.3.1]nonane galactarate

To a round bottom flask was added 3-(pyridin-3-yl)-3,7-diazabicyclo[3.3.1]nonane (150 mg, 0.74 mmol; available as described in PCTs WO 200/44755 and WO 2001/44243), N,N-dimethylformamide (1.8 mL), 1,2-dichloroethane (6.0 mL), triethylamine (1.5 mL) and N-(tert-butoxycarbonyl)-4-piperidone (147 mg, 0.74 mmol). The mixture was stirred at 40°C for 1 h and cooled to ambient temperature. Sodium triacetoxymethylborohydride (312 mg, 1.48 mmol) was added,

and the reaction was stirred at ambient temperature for 2 h. Aqueous ammonium hydroxide (2.0 mL of 3 M, 6 mmol), and saturated aqueous sodium chloride (6.0 mL) were then added, and the contents of the flask were mixed well. The organic phase and a 1,2-dichloroethane (6.0 mL) wash of the aqueous phase were combined and passed through a phase separator. The resulting solution was concentrated, and the residue was purified on a silica gel column, eluting with a gradient of CMA90 (chloroform / methanol / ammonium hydroxide 90:9:1) in chloroform. Selected fractions were combined and concentrated in vacuo, leaving tert-butyl 4-(7-(pyridin-3-yl)-3,7-diazabicyclo[3.3.1]nonan-3-yl)piperidine-1-carboxylate (85 mg; 30% yield), as a light brown oil. This material was diluted with dichloromethane (10 mL), and combined with trifluoroacetic acid (2 mL). The resulting reaction mixture was stirred at ambient temperature for 16 h and concentrated in vacuo. The residue was dissolved in methanol and stirred with Amberlyst A-21 ion-exchange resin. The resin was removed by filtration washed with ammonium hydroxide solution (5 mL of 3 M in methanol). The filtrate was concentrated in vacuo, and the residue was purified on a silica gel column, eluting with a gradient of CMA90 (chloroform / methanol / ammonium hydroxide 90:9:1) in chloroform. Selected fractions were combined and concentrated in vacuo, leaving 3-(piperidin-4-yl)-7-(pyridin-3-yl)-3,7-diazabicyclo[3.3.1]nonane (60 mg, 95% yield), as a yellow oil.

To a solution of 3-(piperidin-4-yl)-7-(pyridin-3-yl)-3,7-diazabicyclo[3.3.1]nonane (60 mg, 0.21 mmol) in ethanol (2 mL) was added galactaric acid (220 mg, 1.05 mmol). The mixture was heated at 60°C and water (10 mL) was then added. The flask was heated at 60°C (water bath) for 5 min and filtered through a glass frit while still hot. Removal of solvent in vacuo gave the galactarate salt (90 mg, 88%) as a yellow solid. ¹H NMR (D₂O, 400 MHz): δ 8.15 (d, 1H), 7.95 (d, 1H), 7.43 (m, 1H), 7.24 (dd, 1H), 4.02 (s, 2H), 3.73 (s, 2H), 3.68 (d, 2H), 3.60 (d, 2H), 3.37 (m, 5H), 2.91 (m, 4H), 2.32 (s, 2H), 2.13 (d, 2H), 1.83 (m, 4H); LCMS (m/z): 287 (M+1).

The above illustrated procedures were used as a basis to make the compounds shown in Table 1. Reagents and conditions will be readily apparent to those skilled in the art. In some cases, compounds were characterized by nuclear magnetic resonance (NMR) data. In other cases, compounds were structurally characterized by LCMS.

VI. Biological Assays

Example 2: Radioligand Binding at CNS nAChRs

α4β2 nAChR Subtype

Preparation of membranes from rat cortex: Rats (female, Sprague-Dawley), weighing 150-250 g, were maintained on a 12 h light/dark cycle and were allowed free access to water and food supplied by PMI Nutrition International, Inc. Animals were anesthetized with 70% CO₂,

and then decapitated. Brains were removed and placed on an ice-cold platform. The cerebral cortex was removed and placed in 20 volumes (weight:volume) of ice-cold preparative buffer (137 mM NaCl, 10.7 mM KCl, 5.8 mM KH_2PO_4 , 8 mM Na_2HPO_4 , 20 mM HEPES (free acid), 5 mM iodoacetamide, 1.6 mM EDTA, pH 7.4); PMSF, dissolved in methanol to a final concentration of 100 μM , was added and the suspension was homogenized by Polytron. The homogenate was centrifuged at 18,000 x g for 20 min at 4 °C and the resulting pellet was re-suspended in 20 volumes of ice-cold water. After 60 min incubation on ice, a new pellet was collected by centrifugation at 18,000 x g for 20 min at 4 °C. The final pellet was re-suspended in 10 volumes of buffer and stored at -20 °C.

Preparation of membranes from SH-EP1/human $\alpha 4\beta 2$ clonal cells: Cell pellets from 40 150 mm culture dishes were pooled, and homogenized by Polytron (Kinematica GmbH, Switzerland) in 20 milliliters of ice-cold preparative buffer. The homogenate was centrifuged at 48,000 g for 20 minutes at 4 °C. The resulting pellet was re-suspended in 20 mL of ice-cold preparative buffer and stored at -20 °C.

On the day of the assay, the frozen membranes were thawed and spun at 48,000 x g for 20 min. The supernatant was decanted and discarded. The pellet was resuspended in Dulbecco's phosphate buffered saline (PBS, Life Technologies) pH 7.4 and homogenized with the Polytron for 6 seconds. Protein concentrations were determined using a Pierce BCA Protein Assay Kit, with bovine serum albumin as the standard (Pierce Chemical Company, Rockford, IL).

Assay: Membrane preparations (approximately 50 μg for human and 200-300 μg protein for rat $\alpha 4\beta 2$) were incubated in PBS (50 μL and 100 μL respectively) in the presence of competitor compound (0.01 nM to 100 μM) and 5 nM [^3H]nicotine for 2-3 hours on ice. Incubation was terminated by rapid filtration on a multi-manifold tissue harvester (Brandel, Gaithersburg, MD) using GF/B filters presoaked in 0.33% polyethyleneimine (w/v) to reduce non-specific binding. Tissue was rinsed 3 times in PBS, pH 7.4. Scintillation fluid was added to filters containing the washed tissue and allowed to equilibrate. Filters were then counted to determine radioactivity bound to the membranes by liquid scintillation counting (2200CA Tri-Carb LSC, Packard Instruments, 50% efficiency or Wallac Trilux 1450 MicroBeta, 40% efficiency, Perkin Elmer).

Data were expressed as disintegrations per minute (DPMs). Within each assay, each point had 2-3 replicates. The replicates for each point were averaged and plotted against the log of the drug concentration. IC_{50} , which is the concentration of the compound that produces 50% inhibition of binding, was determined by least squares non-linear regression. K_i values

were calculated using the Cheng-Prusoff equation (1973):

$$K_i = IC_{50} / (1 + N/K_d)$$

where N is the concentration of [³H]nicotine and K_d is the affinity of nicotine (3 nM, determined in a separate experiment).

α 7 nAChR Subtype

Preparation of membranes from rat hippocampus: Rats (female, Sprague-Dawley), weighing 150-250 g, were maintained on a 12 h light/dark cycle and were allowed free access to water and food supplied by PMI Nutrition International, Inc. Animals were anesthetized with 70% CO₂, then decapitated. Brains were removed and placed on an ice-cold platform. The hippocampus was removed and placed in 10 volumes (weight:volume) of ice-cold preparative buffer (137 mM NaCl, 10.7 mM KCl, 5.8 mM KH₂PO₄, 8 mM Na₂HPO₄, 20 mM HEPES (free acid), 5 mM iodoacetamide, 1.6 mM EDTA, pH 7.4); PMSF, dissolved in methanol to a final concentration of 100 μ M, was added and the tissue suspension was homogenized by Polytron. The homogenate was centrifuged at 18,000 x g for 20 min at 4 °C and the resulting pellet was re-suspended in 10 volumes of ice-cold water. After 60 min incubation on ice, a new pellet was collected by centrifugation at 18,000 x g for 20 min at 4 °C. The final pellet was re-suspended in 10 volumes of buffer and stored at -20 °C.

On the day of the assay, tissue was thawed, centrifuged at 18,000 x g for 20 min, and then re-suspended in ice-cold PBS (Dulbecco's Phosphate Buffered Saline, 138 mM NaCl, 2.67 mM KCl, 1.47 mM KH₂PO₄, 8.1 mM Na₂HPO₄, 0.9 mM CaCl₂, 0.5 mM MgCl₂, Invitrogen/Gibco, pH 7.4) to a final concentration of approximately 2 mg protein/mL. Protein was determined by the method of Lowry et al., J. Biol. Chem. 193: 265 (1951), herein incorporated by reference, using bovine serum albumin as the standard.

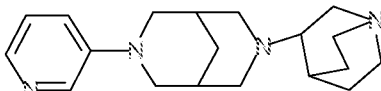
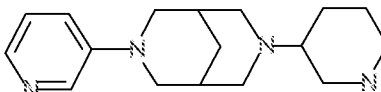
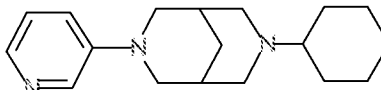
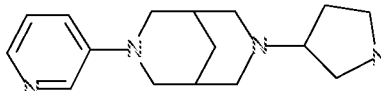
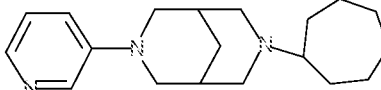
Assay: The binding of [³H]MLA was measured using a modification of the methods of Davies et al., Neuropharmacol. 38: 679 (1999), herein incorporated by reference. [³H]MLA (Specific Activity = 25-35 Ci/mmol) was obtained from Tocris. The binding of [³H]MLA was determined using a 2 h incubation at 21 °C. Incubations were conducted in 48-well micro-titre plates and contained about 200 μ g of protein per well in a final incubation volume of 300 μ L. The incubation buffer was PBS and the final concentration of [³H]MLA was 5 nM. The binding reaction was terminated by filtration of the protein containing bound ligand onto glass fiber filters (GF/B, Brandel) using a Brandel Tissue Harvester at room temperature. Filters were soaked in de-ionized water containing 0.33% polyethyleneimine to reduce non-specific binding. Each filter was washed with PBS (3 x 1 mL) at room temperature. Non-specific binding was determined by inclusion of 50 μ M non-radioactive MLA in selected wells.

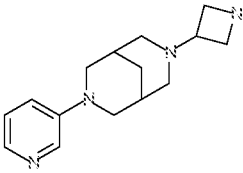
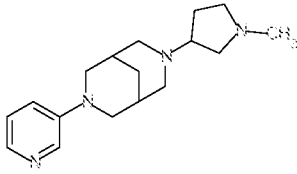
The inhibition of [^3H]MLA binding by test compounds was determined by including seven different concentrations of the test compound in selected wells. Each concentration was replicated in triplicate. IC_{50} values were estimated as the concentration of compound that inhibited 50 percent of specific [^3H]MLA binding. Inhibition constants (K_i values), reported in nM, were calculated from the IC_{50} values using the method of Cheng et al., Biochem. Pharmacol. 22: 3099-3108 (1973), herein incorporated by reference.

Example 3: Tabular Receptor Binding Data

Receptor binding data for compounds of the present invention are shown in Table 1.

Table 1

Structure	Human $\alpha 4\beta 2$ K_i (nM)	Human $\alpha 7$ K_i (nM)
	42	510
	0.79	62
	14	790
	0.16	24
	0.45	20

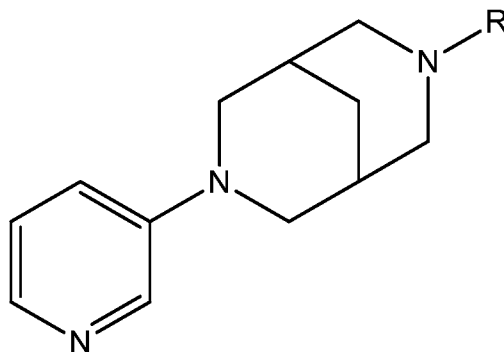
	5.8	550
	11	790

The specific pharmacological responses observed may vary according to and depending on the particular active compound selected or whether there are present pharmaceutical carriers, as well as the type of formulation and mode of administration employed, and such expected variations or differences in the results are contemplated in accordance with practice of the present invention.

Although specific embodiments of the present invention are herein illustrated and described in detail, the invention is not limited thereto. The above detailed descriptions are provided as exemplary of the present invention and should not be construed as constituting any limitation of the invention. Modifications will be obvious to those skilled in the art, and all modifications that do not depart from the spirit of the invention are intended to be included with the scope of the appended claims.

WHAT IS CLAIMED IS:

1.



Formula I

wherein

R is selected from the group consisting of 3-azetidiny, 3-pyrrolidiny, 3-piperidiny, 4-piperidiny, 4-azepany, and 4-azocany, each of which may be N-substituted with C₁₋₆ alkyl, and 3-quinuclidiny;

or a pharmaceutically acceptable salt thereof.

2. Use of the compound according to claim 1 in the manufacture of a medicament.
3. A method for treatment of central nervous system disorders and dysfunctions, comprising administering to a mammal in need of such treatment, a therapeutically effective amount of the compound according to claim 1.
4. The method of claim 3, wherein the disorder is selected from the group consisting of age-associated memory impairment, mild cognitive impairment, pre-senile dementia, early onset Alzheimer's disease, senile dementia, dementia of the Alzheimer's type, Lewy body dementia, vascular dementia, Alzheimer's disease, stroke, AIDS dementia complex, attention deficit disorder, attention deficit hyperactivity disorder, dyslexia, schizophrenia, schizophreniform disorder, schizoaffective disorder, cognitive deficits in schizophrenia, and cognitive dysfunction in schizophrenia.
5. The method of claim 4, wherein the disorder is selected from the group consisting of mild to moderate dementia of the Alzheimer's type, attention deficit disorder, attention deficit hyperactivity disorder, mild cognitive impairment, age-associated memory impairment, cognitive deficits in schizophrenia, and cognitive dysfunction in schizophrenia.
6. A pharmaceutical composition comprising a compound according to claim 1, and one or more pharmaceutically acceptable carrier.

7. Use of the pharmaceutical composition according to claim 6 in the manufacture of a medicament for treatment of central nervous system disorders and dysfunctions.
8. A method of treating inflammation, the inflammatory response associated with bacterial and/or viral infection, pain, metabolic syndrome, autoimmune disorders, addictions, and obesity, comprising administering to a mammal in need of such treatment, a therapeutically effective amount of the compound according to claim 1.

A. CLASSIFICATION OF SUBJECT MATTER**C07D 471/04(2006.01)i, A61K 31/4375(2006.01)i, A61P 25/00(2006.01)i**

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

C07D 471/04

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

Korean utility models and applications for utility models

Japanese utility models and applications for utility models

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

eKOMPASS(KIPO internal) & Keywords: NNR, α4β2 subtype

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 2010-0173968 A1 (HAMMOND, P. S. et al.) 08 July 2010 See abstract and pages 1-2.	1-2,6-7
A	WO 00-44755 A1 (ABBOTT LABORATORIES) 03 August 2000 See abstract and pages 6-8.	1-2,6-7
A	US 2006-0167039 A1 (NGUYEN T. M. et al.) 27 July 2006 See abstract and pages 1-3.	1-2,6-7
A	JP 2002-302490 A (PFIZER PROD. INC.) 18 October 2002 See abstract and the claims.	1-2,6-7



Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

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Name and mailing address of the ISA/KR

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.

PCT/US2013/023968

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Information on patent family members

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2013/023968

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 3-5,8
because they relate to subject matter not required to be searched by this Authority, namely:
Claims 3-5 and 8 are directed to a treatment method of the human body by therapy, and thus relate to a subject matter which this International Searching Authority is not required to search under Article 17(2)(a)(i) of the PCT and Rule 39.1(iv) of the Regulations under the PCT.
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
- ☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- ☐ No protest accompanied the payment of additional search fees.