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Remarks:
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(54) Spyrocyclic quiniclidinic ether derivatives

(57) Compounds of formula (I) wherein n1 is 0, 1, or 2; n2 is 0, 1, or 2; X is a bond, O, S, or NR1; and Ar1 is a 5-membered aromatic ring, 6-membered aromatic ring, or a fused bicycloheterocycle. The compounds are useful in treating conditions or disorders prevented by or ameliorated by $\alpha7$ nAChR ligands. Also disclosed are pharmaceutical compositions having compounds of formula (I) and methods for using such compounds and compositions.

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Description

BACKGROUND OF THE INVENTION

Technical Field

[0001] The invention relates to spirocyclic quinuclidinic ether derivatives, compositions comprising such compounds, and methods of treating conditions and disorders using such compounds and compositions.

Description of Related Technology

[0002] Nicotinic acetylcholine receptors (nAChRs) are widely distributed throughout the central (CNS) and peripheral (PNS) nervous systems. Such receptors play an important role in regulating CNS function, particularly by modulating release of a wide range of neurotransmitters, including, but not necessarily limited to acetylcholine, norepinephrine, dopamine, serotonin and GABA. Consequently, nicotinic receptors mediate a very wide range of physiological effects, and have been targeted for therapeutic treatment of disorders relating to cognitive function, learning and memory, neurodegeneration, pain and inflammation, psychosis and sensory gating, mood and emotion, among others.

[0003] Many subtypes of the nAChR exist in the CNS and periphery. Each subtype has a different effect on regulating the overall physiological function.

Typically, nAChRs are ion channels that are constructed from a pentameric assembly of subunit proteins. At least 12 subunit proteins, α2-α10 and β2-β4, have been identified in neuronal tissue. These subunits provide for a great variety of homomeric and heteromeric combinations that account for the diverse receptor subtypes. For example, the predominant receptor that is responsible for high affinity binding of nicotine in brain tissue has composition $(\alpha4)_2(\alpha2)_3$ (the $\alpha4\beta2$ subtype), while another major population of receptors is comprised of the homomeric $(\alpha7)_5$ (the α7 subtype).

[0004] Certain compounds, like the plant alkaloid nicotine, interad with all subtypes of the nAChRs, accounting for the profound physiological effects of this compound. While nicotine has been demonstrated to have many beneficial properties, not all of the effects mediated by nicotine are desirable. For example, nicotine exerts gastrointestinal and cardiovascular side effects that interfere at therapeutic doses, and its addictive nature and acute toxicity are well-known. Ligands that are selective for interaction with only certain subtypes of the nAChR offer potential for achieving beneficial therapeutic effects with an improved margin for safety.

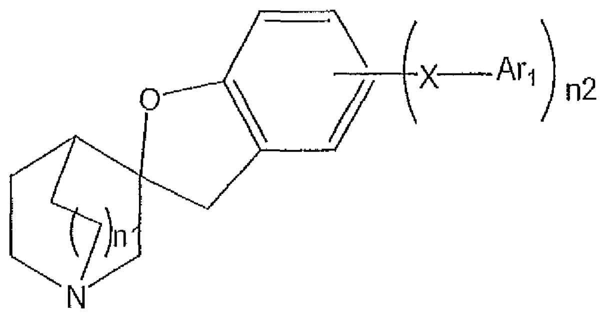
[0005] The α7 nAChRs have been shown to play a significant role in enhancing cognitive function, including aspects of learning, memory and attention (Levin, E.D., J. Neurobiol. 53: 633-640, 2002). For example, α7nAChRs have been linked to conditions and disorders related to attention deficit disorder, attention deficit hyperactivity disorder (ADHD), Alzheimer's disease (AD), mild cognitive impairment, senile dementia, dementia associated with Lewy bodies, dementia associated with Down's syndrome, AIDS dementia, Pick's Disease, as well as cognitive deficits associated with schizophrenia, among other systemic activities.

The activity at the α7 nAChRs can be modified or regulated by the administration of α7 nAChR ligands. The ligands can exhibit antagonist, agonist, partial agonist, or inverse agonist properties. Thus, α7 ligands have potential in treatment of various cognitive disorders.

[0006] Although various classes of compounds demonstrating α7 nAChR-modulating activity exist, it would be beneficial to provide additional compounds demonstrating activity at the α7 nAChRs that can be incorporated into pharmaceutical compositions useful for therapeutic methods. Specifically, it would be beneficial to provide compounds that interact selectively with α7-containing neuronal nAChRs compared to other subtypes.

SUMMARY OF THE INVENTION

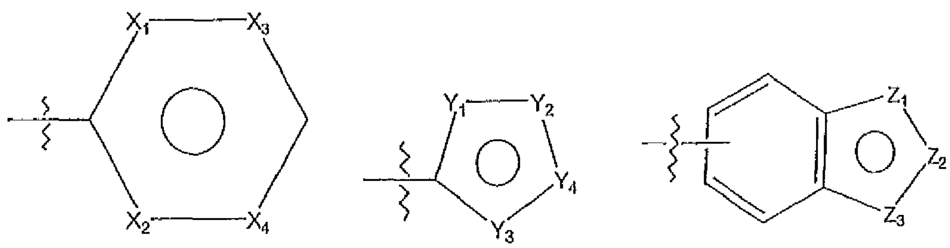
[0007] The invention is directed to spirocyclic quinuclidinic ether derivative compounds as well as compositions comprising such compounds, and method of using the same. Compounds of the invention have the formula:



(I)

or a pharmaceutically acceptable salt, ester, amide, or prodrug thereof, wherein:

n1 is 0, 1, or 2;
n2 is 0, 1, or 2;
X is selected from the group consisting of O, S, or NR_1, or X is a bond;
Ar_1 is a group of the formula:



(a) , (b) , or (c) ;

X_1, X_2, X_3, and X_4 are each independently selected from the group consisting of N and $-CR_2$;
Y_1, Y_2, and Y_3 are each independently selected from the group consisting of N, O, S, and $-CR_2$;
Y_4 is C or N, provided that when Y_4 is C at least one of Y_1, Y_2, and Y_3, is other than $-CR_2$;
Z_1, Z_2, and Z_3 are each independently selected from the group consisting of N, O, S, and $-CR_2$;
R_1 is independently selected from the group consisting of hydrogen, alkyl, alkoxycarbonyl, alkylsulfonyl, and arylsulfonyl;
R_2 at each occurrence is independently selectedfrom the group consisting of hydrogen, halogen, alkyl, alkoxy, alkylcarbonyl, and-NR_3R_4; and
R_3 and R_4 are each independently selected from the group consisting of hydrogen and alkyl.

[0008] Another aspect of the invention relates to pharmaceutical compositions comprising compounds of the invention. Such compositions can be administered in accordance with a method of the invention, typically as part of a therapeutic regimen for treatment or prevention of conditions and disorders related to nAChR activity, and more particularly α7 nAChR activity.

[0009] Yet another aspect of the invention relates to a method of selectively modulating to nAChR activity, for example α7 nAChR activity. The method is useful for treating and/or preventing conditions and disorders related to α7 nAChR activity modulation in mammals. More particularly, the method is useful for conditions and disorders related to attention deficit disorder, attention deficit hyperactivity disorder (ADHD), Alzheimer's disease (AD), mild cognitive impairment, senile dementia, AIDS dementia, Pick's Disease, dementia associated with Lewy bodies, dementia associated with Down's syndrome, amyotrophic lateral sclerosis, Huntington's disease, diminished CNS function associated with traumatic brain injury, acute pain, post-surgical pain, chronic pain, inflammatory pain, neuropathic pain, infertility, need for new blood vessel growth associated with wound healing, need for new blood vessel growth associated with vascularization of skin grafts, and lack of circulation, more particularly circulation around a vascular occlusion, among other systemic activities.

[0010] The compounds, compositions comprising the compounds, and methods for treating or preventing conditions and disorders by administering the compounds are further described herein.

DETAILED DESCRIPTION OF THE INVENTION

Definition of Terms

[0011] Certain terms as used in the specification are intended to refer to the following definitions, as detailed below.

[0012] The term "acyl", as used herein, means an alkyl group, as defined herein, appended to the parent molecular moiety through a carbonyl group, as defined herein. Representative examples of acyl include, but are not limited to, acetyl, 1-oxopropyl, 2,2-dimethyl-1-oxopropyl, 1-oxobutyl, and 1-oxopentyl.

[0013] The term "acyloxy", as used herein, means an acyl group, as defined herein, appended to the parent molecular moiety through an oxygen atom. Representative examples of acyloxy include, but are not limited to, acetyloxy, propionyloxy, and isobutyryloxy.

[0014] The term "alkenyl", as used herein, means a straight or branched chain hydrocarbon containing from 2 to 10 carbons and containing at least one carbon-carbon double bond formed by the removal of two hydrogens. Representative examples of alkenyl include, but are not limited to, ethenyl, 2-propenyl, 2-methyl2-propenyl, 3-butenyl, 4-pentenyl, 5-hexenyl, 2-heptenyl, 2-methyl-1-heptenyl, and 3-decenyl.

[0015] The term "alkoxy", as used herein, means an alkyl group as defined herein, appended to the parent molecular moiety through an oxygen atom. Representative examples of alkoxy include, but are not limited to, methoxy, ethoxy, propoxy, 2-propoxy, butoxy, tert-butoxy, pentyloxy, and hexyloxy.

[0016] The term "alkoxyalkoxy", as used herein, means an alkoxy group, as defined herein, appended to the parent molecular moiety through another alkoxy group, as defined herein. Representative examples of alkoxyalkoxy include, but are not limited to, tert-butoxymethoxy, 2-ethoxyethoxy, 2-methoxyethoxy, and methoxymethoxy.

[0017] The term "alkoxyalkyl", as used herein, means an alkoxy group, as defined herein, appended to the parent molecular moiety through an alkyl group, as defined herein. Representative examples of alkoxyalkyl include, but are not limited to, tert-butoxymethyl, 2-ethoxyethyl, 2-methoxyethyl, and methoxymethyl.

[0018] The term "alkoxycarbonyl", as used herein, means an alkoxy group, as defined herein, appended to the parent molecular moiety through a carbonyl group, represented by-C(O)-, as defined herein. Representative examples of akoxycarbonyl include, but are not limited to, methoxycarbonyl, ethoxycarbonyl, and tertbutoxycarbonyl.

[0019] The term "alkoxyimino", as used herein, means an alkoxy group, as defined herein, appended to the parent molecular moiety through an imino group, as defined herein. Representative examples of alkoxyimino include, but are not limited to, ethoxy(imino)methyl and methoxy(imino)methyl.

[0020] The term "alkoxysulfonyl", as used herein, means an alkoxy group, as defined herein, appended to the parent molecularmoiety through a sulfonyl group, as defined herein. Representative examples of alkoxysulfonyl include, but are not limited to, methoxysulfonyl, ethoxysulfonyl and propoxysulfonyl.

[0021] The term "alkyl", as used herein, means a straight or branched chain hydrocarbon containing from 1 to 6 carbon atoms. Representative examples of alkyl include, but are not limited to, methyl, ethyl, n-propyl, iso-propyl, n-butyl, sec-butyl, isobutyl, tert-butyl, n-pentyl, isopentyl, neopentyl, and n-hexyl.

[0022] The term "alkylcarbonyl", as used herein, means an alkyl group, as defined herein, appended to the parent molecular moiety through a carbonyl group, as defined herein. Representative examples of alkylcarbonyl include, but are not limited to, acetyl, 1-oxopropyl, 2,2-dimethyl-1-oxopropyl, 1-oxobutyl, and 1-oxopentyl.

[0023] The term "alkylcarbonyloxy", as used herein, means an alkylcarbonyl group, as defined herein, appended to the parent molecular moiety through an oxygen atom. Representative examples of alkylcarbonyloxy include, but are not limited to, acetyloxy, ethylcarbonyloxy, and tert-butylcarbonyloxy.

[0024] The term "alkylsulfonyl", as used herein, means an alkyl group, as defined herein, appended to the parent molecular moiety through a sulfonyl group, as defined herein. Representative examples of alkylsulfonyl include, but are not limited to, methylsulfonyl and ethylsulfonyl.

[0025] The term "alkylthio", as used herein, means an alkyl group, as defined herein, appended to the parent molecular moiety through a sulfur atom. Representative examples of alkylthio include, but are not limited, methylthio, ethylthio, tert-butylthio, and hexylthio.

[0026] The term "alkynyl", as used herein, means a straight or branched chain hydrocarbon group containing from 2 to 10 carbon atoms and containing at least one carbon-carbon triple bond. Representative examples of alkynyl include, but are not limited, to acetylenyl, 1-propynyl, 2-propynyl, 3-butynyl, 2-pentynyl, and 1-butynyl.

[0027] The term "amido", as used herein, means an amino, alkylamino, or dialkylamino group appended to the parent molecular moiety through a carbonyl group, as defined herein. Representative examples of amido include, but are not limited to, aminocarbonyl, methylaminocarbonyl, dimethylaminocarbonyl, and ethylmethylaminocarbonyl.

[0028] The term "aryl", as used herein, means a monocyclic or bicyclic aromatic ring system. Representative examples of aryl include, but are not limited to, phenyl and naphthyl.

[0029] The aryl groups of this invention are substituted with 0, 1, 2, 3, 4, or 5 substituents independently selected from acyl, acyloxy, alkenyl, alkoxy, alkoxyalkoxy, alkoxyalkyl, alkoxycarbonyl, alkoxyimino, alkoxysulfonyl, alkyl, alkylsulfonyl, alkynyl, amino, carboxy, cyano, formyl, haloalkoxy, haloalkyl, halo, hydroxy, hydroxyalkyl, mercapto, nitro, thioalkoxy, -NR_AR_B, (NR_AR_B)alkyl, (NR_AR_B)alkoxy, (NR_AR_B)carbonyl, and (NR_AR_B)sulfonyl.

[0030] The term "arylsulfonyl", as used herein, means an aryl group, as defined herein, appended to the parent molecular moiety through a sulfonyl group, as defined herein. Representative examples of arylsulfonyl include, but are not limited to, phenylsulfonyl, (methylaminophenyl)sulfonyl, (dimethylaminophenyl)sulfonyl, and (naphthyl)sulfonyl.

[0031] The term "carbonyl", as used herein, means a -C(O)- group.

[0032] The term "carboxy", as used herein, means a -CO_2H group.

[0033] The term "cyano", as used herein, means a -CN group.

[0034] The term "formyl", as used herein, means a -C(O)H group.

[0035] The term "halo" or "halogen", as used herein, means -Cl,-Br, -I or -F.

[0036] The term "haloalkoxy", as used herein, means at least one halogen, as defined herein, appended to the parent molecular moiety through an alkoxy group, as defined herein. Representative examples of haloalkoxy include, but are not limited to, chloromethoxy, 2-fluoroethoxy, trifluoromethoxy, and pentafluoroethoxy.

[0037] The term "haloalkyl", as used herein, means at least one halogen, as defined herein, appended to the parent molecular moiety through an alkyl group, as defined herein. Representative examples of haloalkyl include, but are not limited to, chloromethyl, 2-fluoroethyl, trifluoromethyl, pentafluoroethyl, and 2-chloro-3 fluoropentyl.

[0038] The term "heteroaryl" means an aromatic five- or six-membered ring containing 1, 2, 3, or 4 heteroatoms independently sdected from nitrogen, oxygen, or sulfur. The heteroaryl groups are connected to the parent molecular moiety through a carbon or nitrogen atom. Representative examples of heteroaryl include, but are not limited to, furyl, imidazolyl, isoxazolyl, isothiazolyl, oxadiazolyl, oxazolyl, pyrazinyl, pyrazolyl, pyridazinyl, pyridinyl, pyrimidinyl, pyrrolyl, tetrazolyl, thiadiazolyl, thiazolyl, thienyl, triazinyl, and triazolyl.

[0039] The heteroaryl groups of the invention are substituted with 0, 1, 2, or 3 substituents independently selected from alkenyl, alkoxy, alkoxyalkoxy, alkoxyalkyl, alkoxycarbonyl, alkoxysulfonyl, alkyl, alkylcarbonyl, alkylcarbonyloxy, alkylsulfonyl, alkylthio, alkynyl, carboxy, cyano, formyl, haloalkoxy, haloalkyl, halo, hydroxy, hydroxyalkyl, mercapto, nitro,-NR_AR_B, (NR_AR_B)alkyl, (NR_AR_B)alkoxy, (NR_AR_B)carbonyl, and (NR_AR_B)sulfonyl.

[0040] The term "bicyclic heteroaryl" refers to fused aromatic nine- and ten-membered bicyclic rings containing 1, 2, 3, or 4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or a tautomer thereof. The bicyclic heteroaryl groups are connected to the parent molecular moiety through a carbon or nitrogen atom. Representative examples of bicyclic heteroaryl rings include, but are not limited to, indolyl, benzothiazolyl, benzofuranyl, isoquinolinyl, and quinolinyl. Bicyclic heteroaryl groups of the invention are substituted with 0, 1, 2, or 3 substituents independently selected from alkenyl, alkoxy, alkoxyalkoxy, alkoxyalkyl, alkoxycarbonyl, alkoxysulfonyl, alkyl, alkylcarbonyl, alkylcarbonyloxy, alkylsulfonyl, alkylthio, alkynyl, carboxy, cyano, formyl, haloalkoxy, haloalkyl, halo, hydroxy, hydroxyalkyl, mercapto, nitro, NR_AR_B, (NR_AR_B)alkyl, (NR_AR_B)alkoxy, (NR_AR_B)carbonyl, and (NR_AR_B)sulfonyl.

[0041] The term "hydroxy", as used herein, means an OH group.

[0042] The term "hydroxyalkyl", as used herein, means at least one hydroxy group, as defined herein, is appended to the parent molecular moiety through an alkyl group, as defined herein. Representative examples of hydroxyalkyl include, but are not limited to, hydroxymethyl, 2-hydroxyethyl, 3-hydroxypropyl, 2,3-dihydroxypentyl, and 2-ethyl-4-hydroxyheptyl.

[0043] The term "mercapto", as used herein, means a -SH group.

[0044] The term "nitro", as used herein, means a -NO_2 group.

[0045] The term "-NR_AR_B", as used herein, means two groups, R_A and R_B, which are appended to the parent molecular moiety through a nitrogen atom. R_A and R_B are each independently hydrogen, alkyl, alkylcarbonyl, or formyl. Representative examples of - NR_AR_B include, but are not limited to, amino, methylamino, acetylamino, and acetylmethylamino.

[0046] The term "(NR_AR_B)alkyl", as used herein, means a -NR_AR_B group, as defined herein, appended to the parent molecular moiety through an alkyl group, as defined herein. Representative examples of (NR_AR_B)alkyl include, but are not limited to, (amino)methyl, (dimethylamino)methyl, and (ethylamino)methyl.

[0047] The term "(NR_AR_B)alkoxy", as used herein, means a -NR_AR_B group, as defined herein, appended to the parent molecularmoiety through an alkoxy group, as defined herein. Representative examples of (NR_AR_B)alkoxy include, but are not limited to, (amino)methoxy, (dimethylamino)methoxy, and (diethylamino)ethoxy.

[0048] The term "(NR_AR_B)carbonyl", as used herein, means a -NR_AR_B group, as defined herein, appended to the parent molecular moiety through a carbonyl group, as defined herein. Representative examples of (NR_AR_B)carbonyl include, but are not limited to, aminocarbonyl, (methylamino)carbonyl, (dimethylamino)carbonyl, and (ethylmethylamino) carbonyl.

[0049] The term "(NR_AR_B)sulfonyl", as used herein, means a -NR_AR_B group, as defined herein, appended to the parent molecular moiety through a sulfonyl group, as defined herein. Representative examples of (NR_AR_B)sulfonyl include, but are not limited to, aminosulfonyl, (methylamino)sulfonyl, (dimethylamino)sulfonyl, and (ethylmethylamino) sulfonyl.

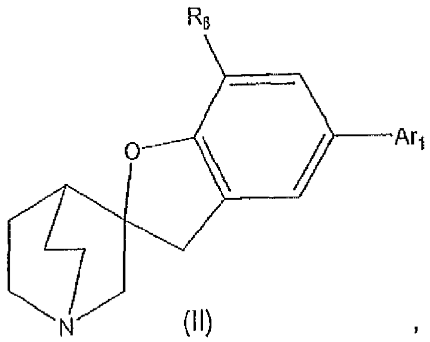
[0050] The term "sulfonyl", as used herein, means a -$S(O)_2$- group.

[0051] The term "thioalkoxy", as used herein, means an alkyl group, as defined herein appended to the parent molecular moiety through a sulfur atom. Representative examples of thioalkoxy include, but are no limited to, methylthio, ethylthio, and propylthio.

[0052] Although typically it may be recognized that an asterisk is used to indicate that the exact subunit composition of a receptor is uncertain, for exampleα3b4* indicates a receptor that contains the α3 and β4 proteins in combination with other subunits, the term α7 as used herein is intended to include receptors wherein the exact subuit composition is both certain and uncertain. For example, as used herein α7 includes homomeric $(\alpha 7)_5$ receptors and α7* receptors, which denote a nAChR containing at least one α7 subunit.

Compounds of the Invention

[0053] Compounds of the invention can have the formula (I) as described above. More particularly, compounds of formula (I) can have the formula:



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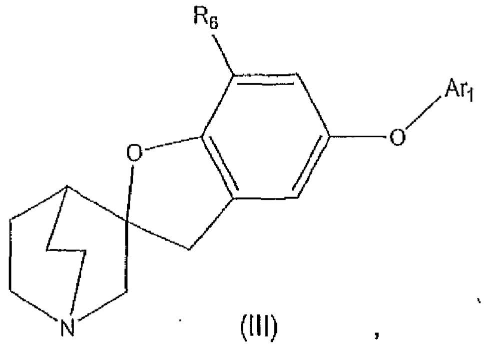

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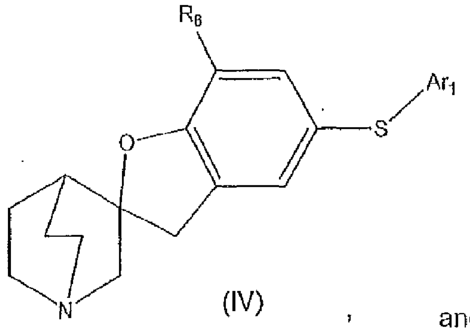

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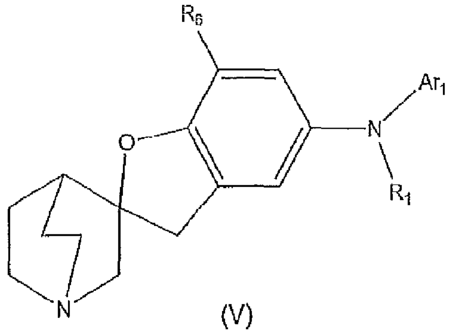
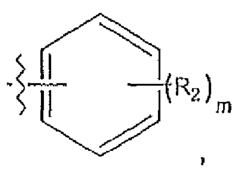


(V) ,

wherein Ar_1 is as previously defined for compounds of formula (I) and R_6 is selected from the group consisting of hydrogen, halogen, alkyl, phenyl,-O-R_7 and -NH-R_7, wherein R_7 is hydrogen, alkyl and aryl.

[0054] Specific examples of rings suitable for Ar_1 include, but are not limited to,



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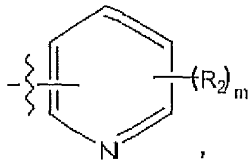

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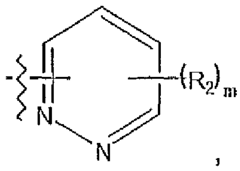

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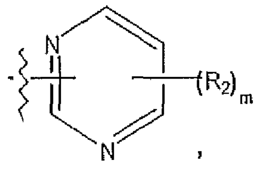

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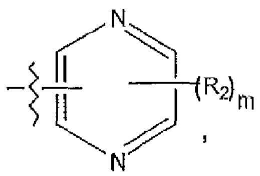

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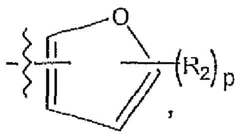

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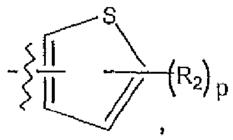

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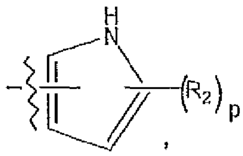

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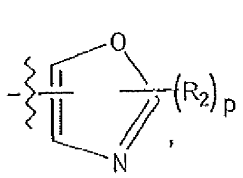

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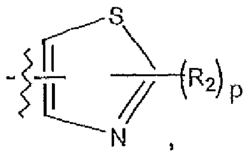

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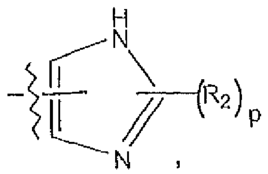

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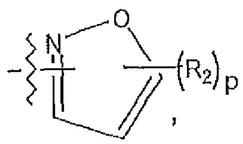

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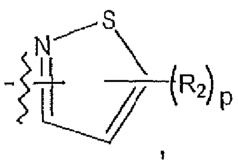

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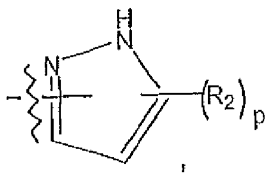

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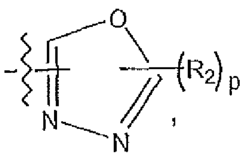

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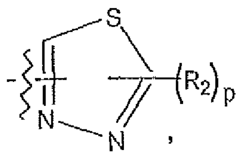

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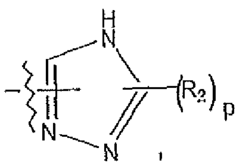

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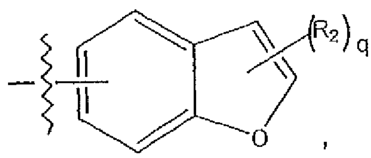

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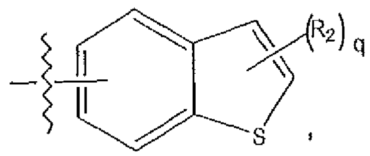

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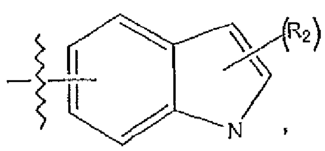
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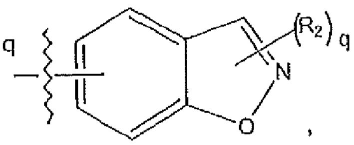
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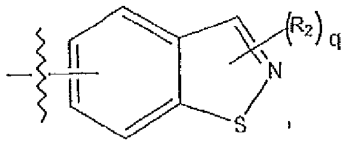
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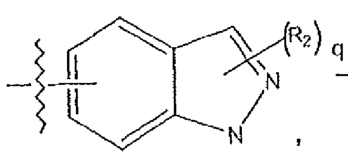
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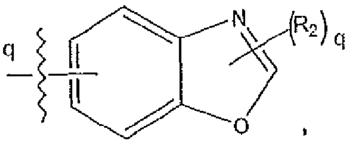
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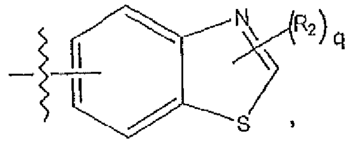
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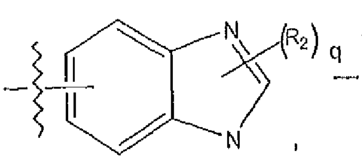
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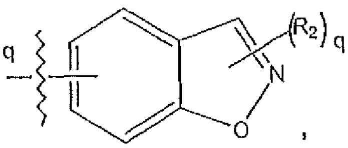
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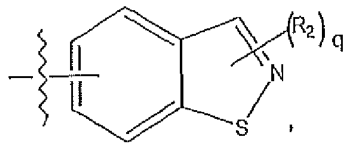
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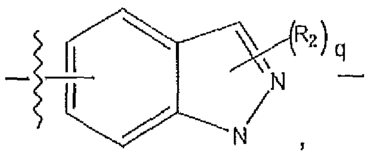
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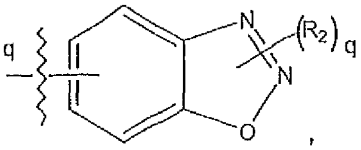
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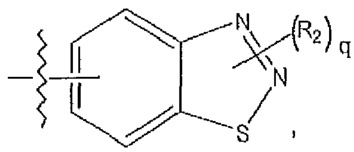
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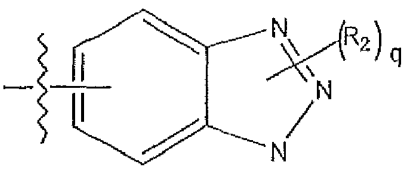
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wherein R_2 at each occurrence is as defined for compounds of formula (I); m at each occurrence is 0, 1, 2, or 3; p at each occurrence is 0, 1, or 2; and q at each occurrence is 0, 1, or 2. Preferably, R_2 is hydrogen.

[0055] The preferred moiety for Ar_1 is phenyl or phenyl substituted with amino.

[0056] Typically, the compound of formula (I) contains one moiety represented by-X-Ar_1, such that n2 is 1. However, embodiments wherein zero or two moieties represented by -X-Ar_1 are incorporated into compounds of formula (1) also are contemplated. Particularly, in compounds wherein two -XAr_1 moieties are included, the groups represented by-X-Ar_1 at each occurrence can be the same or different moieties. Generally, it is preferred that such substitution occurs at the 4- and 6-positions.

[0057] Specific embodiments contemplated as part of the invention include, but are not limited to, compounds of formula (I), as defined, wherein:

5'-phenyl-3'H-spiro[4-azabicyclo[2.2.2]octane-2,2'-[1]benzofuran];
5',7'-diphenyl-3'H-spiro[4-azabicyclo[2.2.2]octane-2,2'-[1]benzofuran];
3-(3'H-spiro[4-azabicyclo[2.2.2]octane-2,2'-[1]benzofuran]-5'-yl)aniline;
5'-phenoxy-3'H-spiro[4-azabicyclo[2.2.2]octane-2,2'[1]benzofuran];
5',7'-diphenoxy-3'H-spiro[4-azabicyclo[2.2.2]octane-2,2'-[1]benzofuran];
7'-bromo-5'-phenoxy-3'H-spiro[4-azabicyclo[2.2.2]octane-2,2'-[1]benzofuran];
N-phenyl-3'H-spiro[4-azabicyclo[2.2.2]octane-2,2'-[1]benzofuran]-5'-amine;
N,N'-diphenyl-3'H-spiro[4-azabicyclo[2.2.2]octane-2,2'-[1]benzofuran]-5',7'-diamine; and , 5'-(1H-indol-5-yl)-3'H-spiro[4-azabicyclo[2.2.2]octane-2,2'[1]benzofuran];

or pharmaceutically acceptable salts, esters, amides, and prodrugs thereof.

[0058] Compound names are assigned by using AUTCNOM naming software, which is provided by MDL Information Systems GmbH (formerly known as Beilstein Informationssysteme) of Frankfurt, Germany, and is part of the CHEM-DRAW® ULTRA v. 6.0.2 software suite.

[0059] Compounds of the invention may exist as stereoisomers wherein, asymmetric or chiral centers are present. These stereoisomers are "R" or "S" depending on the configuration of substituents around the chiral element. The terms "R" and "S" used herein are configurations as defined in IUPAC 1974 Recommendations for Section E, Fundamental Stereochemistry, Pure Appl. Chem., 1976, 45: 13-30. The invention contemplates various stereoisomers and mixtures thereof and are specifically included within the scope of this invention. Stereoisomers include enantiomers and diastereomers, and mixtures of enantiomers or diastereomers. Individualstereoisomers of compounds of the invention may be prepared synthetically from commercially available starting materials which contain asymmetric or chiral centers or by preparation of racemic mixtures followed by resolution well-known to those of ordinary skill in the art. These methods of resolution are exemplified by (1) attachment of a mixture of enantiomers to a chiral auxiliary, separation of the resulting mixture of diastereomers by recrystallization or chromatography and optional liberation of the optically pure product from the auxiliary as described in Furniss, Hannaford, Smith, and Tatchell, "Vogel's Textbook of Practical Organic Chemistry", 5th edition (1989), Longman Scientific & Technical, Essex CM20 2JE, England, or (2) direct separation of the mixture of optical enantiomers on chiral chromatographic columns or (3) fractional recrystallization methods.

Methods for Preparing Compounds of the Invention

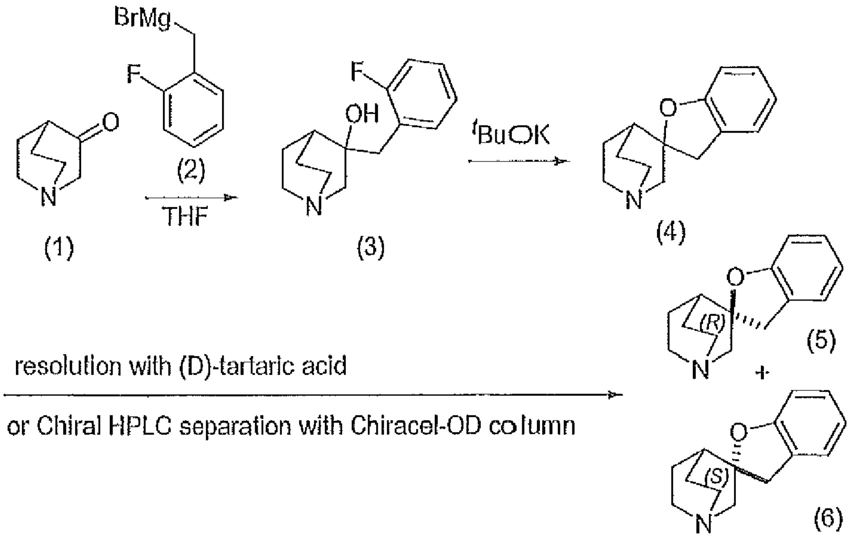
[0060] As used in the descriptions of the schemes and the examples, certain abbreviations are intended to have the following meanings: Ac for acetyl; Bu for n-butyl; Bn for benzyl; dba for dibenzylidene acetone; EtOH for ethanol; Et_3N for triethylamine; EtOAc for ethyl acetate; HPLC for high pressure liquid chromatography;'Pr for isopropyl; ^{i}PrOAc for isopropyl acetate; LAH for lithium aluminum hydride; Me for methyl; MeOH for methanol; NBS for N-bromosuccinimide; NMP for N-methylpyrrolidine; OAc for acetoxy; Pd/L for palladium/ligand; Ph for phenyl; Bu for tert-butyl; ^{t}BuO for tert-butoxide; and THF for tetrahydrofuran.

[0061] The reactions exemplified in the schemes are performed in a solvent appropriate to the reagents and materials employed and suitable for the transformations being effected. The described transformations may require modifying the order of the synthetic steps or selecting one particular process scheme over another in order to obtain a desired compound of the invention, depending on the functionality present on the molecule.

[0062] Nitrogen protecting groups can be used for protecting amine groups present in the described compounds. Such methods, and some suitable nitrogen protecting groups, are described in Greene and Wuts (Protective Groups In Organic Synthesis, Wiley and Sons, 1999). For example, suitable nitrogen protecting groups include, but are not limited to, tert-butoxycarbonyl (Boc), benzyloxycarbonyl (Cbz), benzyl (Bn), acetyl, and trifluoracetyl. More particularly, the BOC protecting group may be removed by treatment with an acid such as trifluoroacetic acid or hydrochloric acid. The Cbz and Bn protecting groups may be removed by catalytic hydrogenation. The acetyl and trifluoracetyl protecting groups may be removed by a hydroxide ion.

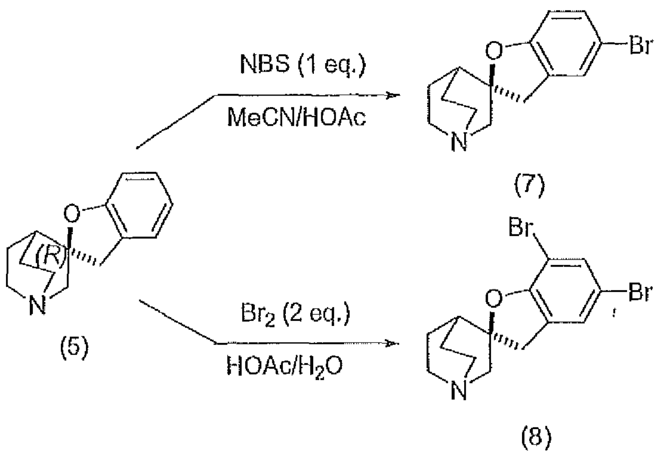
[0063] The methods described below can entail use of various enantiomers. Where the stereochemistry is shown in the Schemes, it is intended for illustrative purposes only.

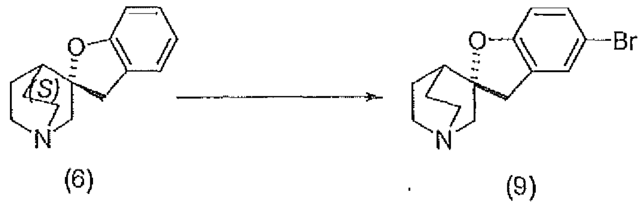
Scheme 1



[0064] Fused quinuclidine ethers of formula (5) and (6) can be prepared as described in Scheme 1. 3-Quinuclidinones (1) can be treated with a substituted Grignard reagent of formula (2) in an organic solvent, for example tetrahydrofuran, to provide 3(2-fluorobenzyl)-1-aza-bicyclo[2.2.2]octan-3-ol of formula (3), which is treated with potassium tert-butoxide to provide a racemic mixture of spiro[1-azabicyclo[2.2.2]octane-(3,2')]-(2',3')-dihydrobenzofuran of formula (4). The racemate can be resolved into its respective isomers by resolution with D-tartaric acid or via chiral HPLC chromatography on a Chiracel®-OD chromatography column using methods well-known in the art to provide the (R)- and (S)-isomers of formulas (5) and (6), respectively.

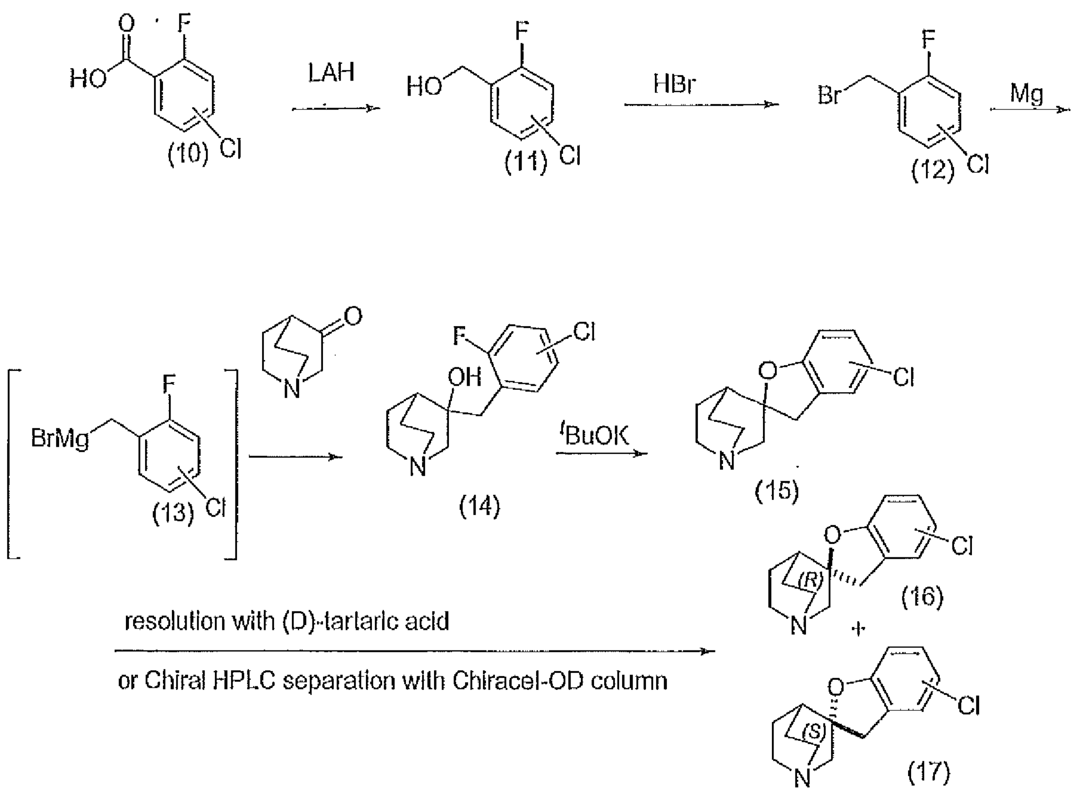
Scheme 2





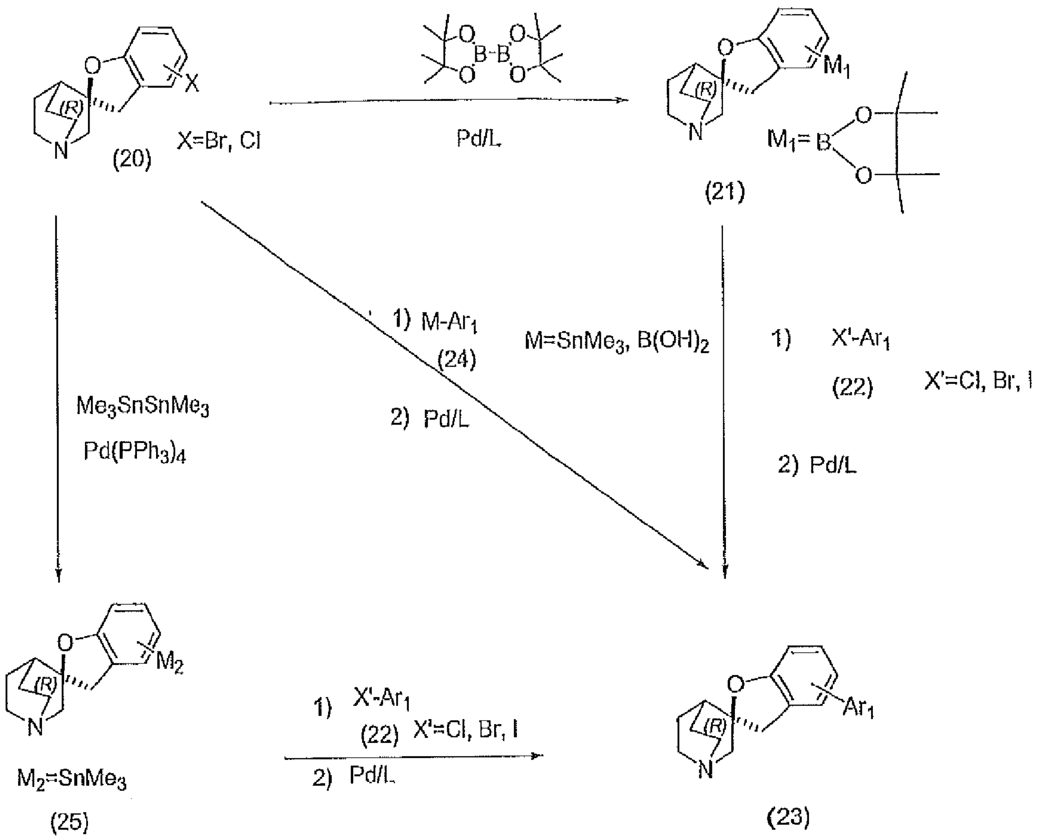
[0065] 5'-Bromo-spiro[1-azabicyclo[2.2.2]octane-(3,2')]-2(2',3')-didhydrobenzofuran compounds (7) and 5',7'-dibromo-spiro[1-azabicyclo[2.2.2]octane-(3,2')]-2(2',3')-didhydrobenzofuran (8) can be prepared as shown in Scheme 2. In one method, compounds of formula (5) are treated with N-bromosuccinimide in acetic acid and acetonitrile, to provide compounds of formula (7). Alternatively, compounds of formula (5) can be reacted with bromine in a weak acid, for example acetic acid, to provide compounds of formula (8). Likewise, (S)-enantiomer compounds of formula (6) from Scheme 1 can be substituted for compounds of formula (5) to provide the corresponding brominated compounds of formula (9).

Scheme 3



[0066] Chloro-substituted fused quinuclidine ethers of formula (16) and (17) can be prepared as described in Scheme 3. A fluoro-chloro-substituted phenylcarboxylic acid of formula (10) is reduced with lithium aluminum hydride to provide a corresponding alcohol of formula (11). The alcohol of formula (11) is treated with HBr to provide the compounds of formula (12), which are treated with magnesium to provide a Grignard reagent of formula (13). 3-Quinuclidinone can be reacted with the Grignard reagent of formula (13) to provide 3-(2-fluoro-4-chloro-benzyl)-1-aza-bicyclo[2.2.2]octan-3-ol of formula (14), which is treated with potassium tert-butoxide to provide a racemic mixture of spiro[1-azabicyclo[2.2.2] octane-(3,2')]-(2',3')-dihydrobenzofuran of formula (15). The racemate can be resolved into its respective isomers by resolution with Dtartaric acid or via chiral HPLC chromatography on a Chiracel®-OD chromatography column as described for Scheme 1 to provide the (R)- and (S)isomers of formulas (16) and (17), respectively.

Scheme 4

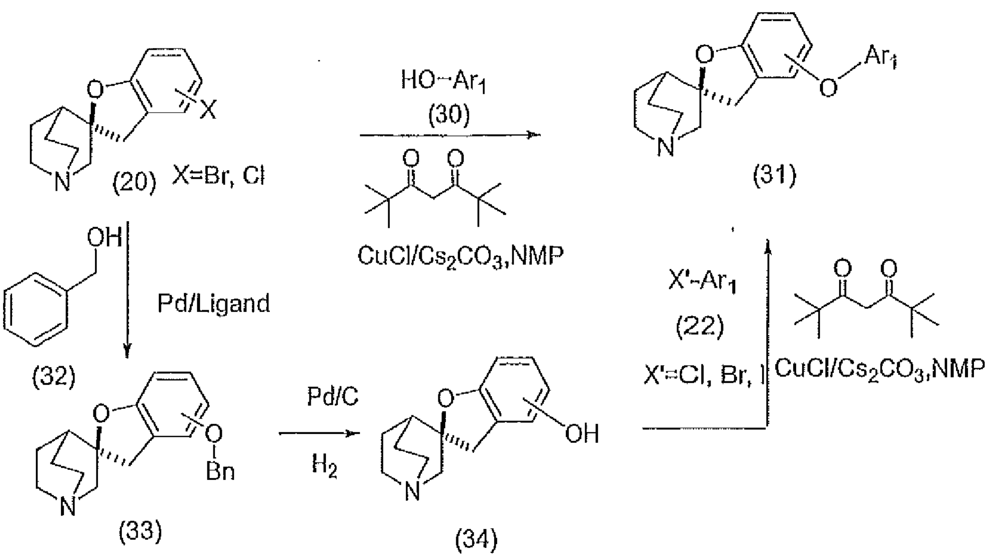


[0067] Compounds of formula (I) wherein X is a bond as represented by formula (23) can be prepared according to methods described in Scheme 4. Compounds of formula (20), which encompass compounds of formulas (5), (6), (16), and (17), as shown in the previous Schemes 1-3, can be reacted with bis(pinacolato)diboron in the presence of a palladium ligand to provide boronic acid esters of formula (21). The boronic acid esters of formula (21) are treated with a halide of a desired group Ar_1, wherein Ar_1 can be any group as defined for formula (I) and X' is chloride, bromide, or iodide, of formula (22) in the presence of palladium/ligand to provide compounds of formula (23).

[0068] Alternatively, compounds of formula (20) can be reacted with the corresponding tin or boron reagent of the desired group Ar_1, as defined for formula (I), in the presence of a palladium catalyst to provide compounds of formula (23).

[0069] Compounds of formula (20) also can be reacted with a hexamethylditin in the presence of tetrakis(triphenylphosphine)palladium (0) to provide the corresponding compound of formula (25), which can be reacted with a chloride, bromide, or iodide of a desired Ar_1 group to provide compounds of formula (23).

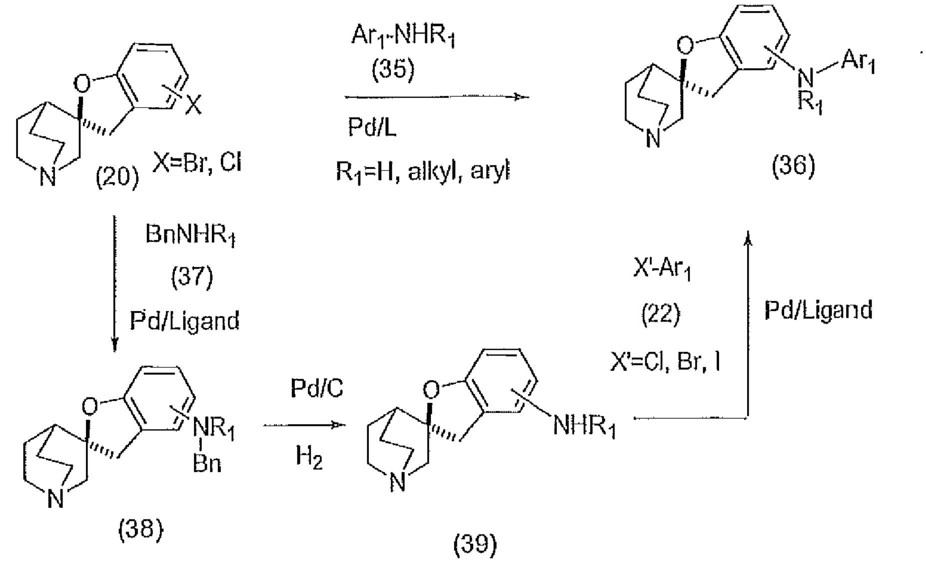
Scheme 5



[0070] Compounds of formula (I) wherein X is O, as represented by compounds of formula (31), can be prepared according to Scheme 5. Compounds of formula (20) can be treated with the compound of formula (30), wherein Ar_i is as defined for formula (I), 2,2,6,6-tetramethyl-heptane-3,5-dione and Cs_2CO_3 in the presence of a CuCl to provide compounds of formula (31) as described in Org. Lett. 2002, 4, 1623.

[0071] Alternatively, compounds of formula (20) can be treated with benzyl alcohol of formula (32) to provide a compound of formula (33). Compounds of formula (33) can be hydrogenated to provide compounds of formula (34), which are treated with a halide of a desired group Ar_1 of formula (22), 2,2,6,6-tetramethyl-heptane-3,5-dione and Cs_2CO_3 in the presence of CuCl to provide the desired compound of formula (31).

Scheme 6



[0072] Compounds of formula (I), wherein X is NR_1, as defined in formula (36) can be prepared as described in Scheme 6. Compounds of formula (20) can be treated with compounds of formula (35), wherein Ar_1 and R_1 are as defined for formula (I), in the presence of a palladium catalyst and a ligand to provide compounds of formula (36) as described in

Org. Lett. 2002, 4, 3481.

[0073] Alternatively, compounds of formula (20) can be treated with a compound of formula (37), wherein R_1 is as defined for compounds of formula (I), in the presence of a palladium catalyst and a ligand to afford compounds of formula (38). Compounds of formula (38) can be hydrogenated to afford compounds of formula (39), which can be reacted with a compound of formula (22) to provide a compound of formula (36).

[0074] The compounds and intermediates of the invention may be isolated and purified by methods well-known to those skilled in the art of organic synthesis. Examples of conventional methods for isolating and purifying compounds can include, but are not limited to, chromatography on solid supports such as silica gel, alumina, or silica derivatized with alkylsilane groups, by recrystallization at high or low temperature with an optional pretreatment with activated carbon, thin-layer chromatography, distillation at various pressures, sublimation under vacuum, and trituration, as described for instance in "Vogel's Textbook of Practical Organic Chemistry", 5th edition (1989), by Furniss, Hannaford, Smith, and Tatchell, pub. Longman Scientific & Technical, Essex CM20 2JE, England.

[0075] The compounds of the invention have at least one basic nitrogen whereby the compound can be treated with an acid to form a desired salt. For example, a compound may be reacted with an acid at or above room temperature to provide the desired salt, which is deposited, and collected by filtration after cooling. Examples of acids suitable for the reaction include, but are not limited to tartaric acid, lactic acid, succinic acid, as well as mandelic, atrolactic, methanesulfonic, ethanesulfonic, toluenesulfonic, naphthalenosulfonic, carbonic, fumaric, gluconic, acetic, propionic, salicylic, hydrochloric, hydrobromic, phosphoric, sulfuric, citric, or hydroxybutyric acid, camphorsulfonic, malic, phenylacetic, aspartic, glutamic, and the like.

Compositions of the Invention

[0076] The invention also provides pharmaceutical compositions comprising a therapeutically effective amount of a compound of formula (I) in combination with a pharmaceutically acceptable carrier. The compositions comprise compounds of the invention formulated together with one or more non-toxic pharmaceutically acceptable carriers. The pharmaceutical compositions can be formulated for oral administration in solid or liquid form, for parenteral injection or for rectal administration.

[0077] The term "pharmaceutically acceptable carrier," as used herein, means a non-toxic, inert solid, semi-solid or liquid filler, diluent, encapsulating material or formulation auxiliary of any type. Some examples of materials which can serve as pharmaceutically acceptable carriers are sugars such as lactose, glucose and sucrose; starches such as corn starch and potato starch; cellulose and its derivatives such as sodium carboxymethyl cellulose, ethyl cellulose and cellulose acetate; powdered tragacanth; malt; gelatin; talc; cocoa butter and suppository waxes; oils such as peanut oil, cottonseed oil, safflower oil, sesame oil, olive oil, corn oil and soybean oil; glycols; such a propylene glycol; esters such as ethyl oleate and ethyl laurate; agar; buffering agents such as magnesium hydroxide and aluminum hydroxide; alginic acid; pyrogen-free water; isotonic saline; Ringer's solution; ethyl alcohol, and phosphate buffer solutions, as well as other non-toxic compatible lubricants such as sodium lauryl sulfate and magnesium stearate, as well as coloring agents, releasing agents, coating agents, sweetening, flavoring and perfuming agents, preservatives and antioxidants can also be present in the composition, according to the judgment of one skilled in the art of formulations.

[0078] The pharmaceutical compositions of this invention can be administered to humans and other mammals orally, rectally, parenterally, intracisternally, intravaginally, intraperitoneally, topically (as by powders, ointments or drops), bucally or as an oral or nasal spray. The term "parenterally," as used herein, refers to modes of administration, including intravenous, intramuscular, intraperitoneal, intrasternal, subcutaneous, intraarticular injection and infusion.

[0079] Pharmaceutical compositions for parenteral injection comprise pharmaceutically acceptable sterile aqueous or nonaqueous solutions, dispersions, suspensions or emulsions and sterile powders for reconstitution into sterile injectable solutions or dispersions. Examples of suitable aqueous and nonaqueous carriers, diluents, solvents or vehicles include water, ethanol, polyols (propylene glycol, polyethylene glycol, glycerol, and the like, and suitable mixtures thereof), vegetable oils (such as olive oil) and injectable organic esters suchas ethyl oleate, or suitable mixtures thereof. Suitable fluidity of the composition may be maintained, for example, by the use of a coating such as lecithin, by the maintenance of the required particle size in the case of dispersions, and by the use of surfactants.

[0080] These compositions can also contain adjuvants such as preservative agents, wetting agents, emulsifying agents, and dispersing agents. Prevention of the action of microorganisms can be ensured by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, sorbic acid, and the like. It also can be desirable to include isotonic agents, for example, sugars, sodium chloride and the like. Prolonged absorption of the injectable pharmaceutical form can be brought about by the use of agents delaying absorption, for example, aluminum monostearate and gelatin.

[0081] In some cases, in order to prolong the effect of a drug, it is often desirable to slow the absorption of the drug from subcutaneous or intramuscular injection. Thiscan be accomplished by the use of a liquid suspension of crystalline or amorphous material with poor water solubility. The rate of absorption of the drug can depend upon its rate of dissolution, which, in turn, may depend upon crystal size and crystalline form. Alternatively, a parenterally administered drug form can be administered by dissolving or suspending the drug in an oil vehicle.

[0082] Suspensions, in addition to the active compounds, can contain suspending agents, for example, ethoxylated isostearyl alcohols, polyoxyethylene sorbitol and sorbitan esters, microcrystalline cellulose, aluminum metahydroxide, bentonite, agar-agar, tragacanth, and mixtures thereof.

[0083] If desired, and for more effective distribution, the compounds of the invention can be incorporated into slow-release or targeted-delivery systems such as polymer matrices, liposomes, and microspheres. They may be sterilized, for example, by filtration through a bacteria-retaining filter or by incorporation of sterilizing agents in the form of sterile solid compositions, which may be dissolved in sterile water or some other sterile injectable medium immediately before use.

[0084] Injectable depot forms are made by forming microencapsulated matrices of the drug in biodegradable polymers such as polylactidepolyglycolide. Depending upon the ratio of drug to polymer and the nature of the particular polymer employed, the rate of drug release can be controlled. Examples of other biodegradable polymers include poly(orthoesters) and poly(anhydrides) Depot injectable formulations also are prepared by entrapping the drug in liposomes or microemulsions which are compatible with body tissues.

[0085] The injectable formulations can be sterilized, for example, by filtration through a bacterial-retaining filter or by incorporating sterilizing agents in the form of sterile solid compositions which can be dissolved or dispersed in sterile water or other sterile injectable medium just prior to use.

[0086] Injectable preparations, for example, sterile injectable aqueous or oleaginous suspensions can be formulated according to the known art using suitable dispersing or wetting agents and suspending agents. The sterile injectable preparation also can be a sterile injectable solution, suspension or emulsion in a nontoxic, parenterally acceptable diluent or solvent such as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that can be employed are water, Ringer's solution, U.S.P. and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil can be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid are used in the preparation of injectables.

[0087] Solid dosage forms for oral administration include capsules, tablets, pills, powders, and granules. In such solid dosage forms, one or more compounds of the invention is mixed with at least one inert pharmaceutically acceptable carrier such as sodium citrate or dicalcium phosphate and/or a) fillers or extenders such as starches, lactose, sucrose, glucose, mannitol, and salicylic acid; b) binders such as carboxymethylcellulose, alginates, gelatin, polyvinylpyrrolidinone, sucrose, and acacia; c) humectants such as glycerol; d) disintegrating agents such as agar-agar, calcium carbonate, potato or tapioca starch, alginic acid, certain silicates, and sodium carbonate; e) solution retarding agents such as paraffin; f) absorption accelerators such as quaternary ammonium compounds; g) wetting agents such as cetyl alcohol and glycerol monostearate; h) absorbents such as kaolin and bentonite clay; and i) lubricants such as talc, calcium stearate, magnesium stearate, solid polyethylene glycols, sodium lauryl sulfate, and mixtures thereof. In the case of capsules, tablets and pills, the dosage form may also comprise buffering agents.

[0088] Solid compositions of a similar type may also be employed as fillers in soft and hard-filled gelatin capsules using lactose or milk sugar as well as high molecular weight polyethylene glycols.

[0089] The solid dosage forms of tablets, dragees, capsules, pills, and granules can be prepared with coatings and shells such as enteric coatings and other coatings well-known in the pharmaceutical formulating art. They can optionally contain opacifying agents and can also be of a composition that they release the active ingredient(s) only, or preferentially, in a certain part of the intestinal tract in a delayed manner. Examples of materials useful for delaying release of the active agent can include polymeric substances and waxes.

[0090] Compositions for rectal or vaginal administration are preferably suppositories which can be prepared by mixing the compounds of this invention with suitable non irritating carriers such as cocoa butter, polyethylene glycol or a suppository wax which are solid at ambient temperature but liquid at body temperature and therefore melt in the rectum or vaginal cavity and release the active compound.

[0091] Liquid dosage forms for oral administration include pharmaceutically acceptable emulsions, microemulsions, solutions, suspensions, syrups and elixirs. In addition to the active compounds, the liquid dosage forms may contain inert diluents commonly used in the art such as, for example, water or other solvents, solubilizing agents and emulsifiers such as ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propylene glycol, 1,3butylene glycol, dimethylformamide, oils (in particular, cottonseed, groundnut, corn, germ, olive, castor, and sesame oils), glycerol, tetrahydrofurfuryl alcohol, polyethylene glycols and fatty acid esters of sorbitan, and mixtures thereof.

[0092] Besides inert diluents, the oral compositions can also include adjuvants such as wetting agents, emulsifying and suspending agents, sweetening, flavoring, and perfuming agents.

[0093] Dosage forms for topical or transdermal administration of a compound of this invention include ointments, pastes, creams, lotions, gels, powders, solutions, sprays, inhalants or patches. A desired compound of the invention is admixed under sterile conditions with a pharmaceutically acceptable carrier and any needed preservatives or buffers as may be required. Ophthalmic formulation, eardrops, eye ointments, powders and solutions are also contemplated as being within the scope of this invention.

[0094] The ointments, pastes, creams and gels may contain, in addition to an active compound of this invention, animal and vegetable fats, oils, waxes, paraffins, starch, tragacanth, cellulose derivatives, polyethylene glycols, silicones, bentonites, silicic acid, talc and zinc oxide, or mixtures thereof.

[0095] Powders and sprays can contain, in addition to the compounds of this invention, lactose, talc, silicic acid, aluminum hydroxide, calcium silicates and polyamide powder, or mixtures of these substances. Sprays can additionally contain customary propellants such as chlorofluorohydrocarbons.

[0096] Compounds of the invention also can be administered in the form of liposomes. As is known in the art, liposomes are generally derived from phospholipids or other lipid substances. Liposomes are formed by mono- or multilamellar hydrated liquid crystals that are dispersed in an aqueous medium. Any non-toxic, physiologically acceptable and metabolizable lipid capable of forming liposomes may be used. The present compositions in liposome form may contain, in addition to the compounds of the invention, stabilizers, preservatives, and the like. The preferred lipids are the natural and synthetic phospholipids and phosphatidylcholines (lecithins) used separately or together.

[0097] Methods to form liposomes are known in the art. See, for example, Prescott, Ed., Methods in Cell Biology, Volume XIV, Academic Press, New York, N. Y., (1976), p 33 et seq.

[0098] Dosage forms for topical administration of a compound of this invention include powders, sprays, ointments and inhalants. The active compound is mixed under sterile conditions with a pharmaceutically acceptable carrier and any needed preservatives, buffers or propellants. Ophthalmic formulations, eye ointments, powders and solutions are also contemplated as being within the scope of this invention. Aqueous liquid compositions of the invention also are particularly useful.

[0099] The compounds of the invention can beused in the form of pharmaceutically acceptable salts, esters, or amides derived from inorganic or organic acids. The term "pharmaceutically acceptable salts, esters and amides," as used herein, include salts, zwitterions, esters and amides of compounds of formula (I) which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of humans and lower animals without undue toxicity, irritation, allergic response, and the like, are commensurate with a reasonable benefit/risk ratio, and are effective for their intended use.

[0100] The term "pharmaceutically acceptable salt" refers to those salts which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of humans and lower animals without undue toxicity, irritation, allergic response, and the like, and are commensurate with a reasonable benefit/risk ratio. Pharmaceutically acceptable salts are well-known in the art. The salts can be prepared in situ during the final isolation and purification of the compounds of the invention or separately by reacting a free base function with a suitable organic acid.

[0101] Representative acid addition salts include, but are not limited to acetate, adipate, alginate, citrate, aspartate, benzoate, benzenesulfonate, bisulfate, butyrate, camphorate, camphorsulfonate, digluconate, glycerophosphate, hemisulfate, heptanoate, hexanoate, fumarate, hydrochloride, hydrobromide, hydroiodide, 2 hydroxyethansulfonate (isethionate), lactate, maleate, methanesulfonate, nicoinate, 2-naphthalenesulfonate, oxalate, pamoate, pectinate, persulfate, 3phenylpropionate, picrate, pivalate, propionate, succinate, tartrate, thiocyanate, phosphate, glutamate, bicarbonate, p-toluenesulfonate and undecanoate.

[0102] Also, the basic nitrogen-containing groups can be quaternized with such agents as lower alkyl halides such as methyl, ethyl, propyl, and butyl chlorides, bromides and iodides; dialkyl sulfates such as dimethyl, diethyl, dibutyl and diamyl sulfates; long chain halides such as decyl, lauryl, myristyl and stearyl chlorides, bromides and iodides; arylalkyl halides such as benzyl and phenethyl bromides and others. Water or oil soluble or dispersible products are thereby obtained.

[0103] Examples of acids which can be employed to form pharmaceutically acceptable acid addition salts include such inorganic acids as hydrochloric acid, hydrobromic acid, sulphuric acid and phosphoric acid and such organic acids as oxalic acid, maleic acid, succinic acid, and citric acid.

[0104] Basic addition salts can be prepared in situ during the final isolation and purification of compounds of this invention by reacting a carboxylic acidcontaining moiety with a suitable base such as the hydroxide, carbonate or bicarbonate of a pharmaceutically acceptable metal cation or with ammonia or an organic primary, secondary or tertiary amine. Pharmaceutically acceptable salts include, but are not limited to, cations based on alkali metals or alkaline earth metals such as lithium, sodium, potassium, calcium, magnesium, and aluminum salts, and the like, and nontoxic quaternary ammonia and amine cations including ammonium, tetramethylammonium, tetraethylammonium, methylamine, dimethylamine, trimethylamine, triethylamine, diethylamine, ethylamine and the such as. Other representative organic amines useful for the formation of base addition salts include ethylenediamine, ethanolamine, diethanolamine, piperidine, and piperazine.

[0105] The term "pharmaceutically acceptable ester," as used herein, refers to esters of compounds of the invention which hydrolyze in vivo and include those that break down readily in the human body to leave the parent compound or a salt thereof. Examples of pharmaceutically acceptable, non-toxic esters of the invention include C_1-to-C_6 alkyl esters and C_5-to-C_7 cycloalkyl esters, although C_1-to-C_4 alkyl esters are preferred. Esters of the compounds of formula (I) can be prepared according to conventional methods. Pharmaceutically acceptable esters can be appended onto hydroxy groups by reaction of the compound that contains the hydroxy group with acid and an alkylcarboxylic acid such as acetic acid, or with acid and an arylcarboxylic acid such as benzoic acid. In the case of compounds containing carboxylic acid groups, the pharmaceutically acceptable esters are prepared from compounds containing the carboxylic acid groups by reaction of the compound with base such as triethylamine and an alkyl halide, alkyl trifilate, for example with methyl iodide, benzyl iodide, cyclopentyl iodide. They also can be prepared by reaction of the compound with an acid such as hydrochloric acid and an alkylcarboxylic acid such as acetic acid, or with acid and an arylcarboxylic acid such as benzoic acid.

[0106] The term "pharmaceutically acceptable amide," as used herein, refers to non-toxic amides of the invention derived from ammonia, primary C_1-to-C_6 alkyl amines and secondary C_1-to-C_6 dialkyl amines. In the case of secondary amines, the amine can also be in the form of a 5- or 6-membered heterocycle containing one nitrogen atom. Amides derived from ammonia, C_1-to-C_3 alkyl primary amides and C_1-to-C_2 dialkyl secondary amides are preferred. Amides of the compounds of formula (I) can be prepared according to conventional methods. Pharmaceutically acceptable amides can be prepared from compounds containing primary or secondary amine groups by reaction of the compound that contains the amino group with an alkyl anhydride, aryl anhydride, acyl halide, or aroyl halide. In the case of compounds containing carboxylic acid groups, the pharmaceutically acceptable esters are prepared from compounds containing the carboxylic acid groups by reaction of the compound with base such as triethylamine, a dehydrating agent such as dicyclohexyl carbodiimide or carbonyl diimidazole, and an alkyl amine, dialkylamine, for example with methylamine, diethylamine, piperidine. They also can be prepared by reaction of the compound with an acid such as sulfuric acid and an alkylcarboxylic acid such as acetic acid, or with acid and an arylcarboxylic acid such as benzoic acid under dehydrating conditions as with molecular sieves added. The composition can contain a compound of the invention in the form of a pharmaceutically acceptable prodrug.

[0107] The term "pharmaceutically acceptable prodrug" or "prodrug," as usedherein, represents those prodrugs of the compounds of the invention which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of humans and lower animals without undue toxicity, irritation, allergic response, and the like, commensurate with a reasonable benefit/risk ratio, and effective for their intended use. Prodrugs of the invention can be rapidly transformed in vivo to a parent compound of formula (I), for example, by hydrolysis in blood. A thorough discussionis provided in T. Higuchi and V. Stella, Pro-drugs as Novel Delivery Systems, V. 14 of the A.C.S. Symposium Series, and in Edward B. Roche, ed., Bioreversible Carriers in Drug Design, American Pharmaceutical Association and Pergamon Press (1987).

[0108] The invention contemplates pharmaceutically active compounds either chemically synthesized or formed by in vivo biotransformation to compounds of formula (I).

Methods of the invention

[0109] Compounds and compositions of the invention are useful for modulating the effects of nAChRs, and more particularlyα7 nAChRs. In particular, the compounds and compositions of the invention can be used for treating and preventing disorders modulated by α7 nAChRs. Typically, such disorders can be ameliorated by selectively modulating the α7 nAChRs in a mammal, preferably by administering a compound or composition of the invention, either alone or in combination with another active agent, for example, as part of a therapeutic regimen.

[0110] The compounds of the invention, including but not limited to those specified in the examples, possess an affinity for nAChRs, and more particularlyα7 nAChRs. As α7 nAChRs ligands, the compounds of the invention can be useful for the treatment and prevention of a number of α7 nAChR-mediated diseases or conditions.

[0111] For example, α7 nAChRs have been shown to play a significant role in enhancing cognitive function, including aspects of learning, memory and attention (Levin, E.D., J. Neurobiol. 53: 633-640, 2002). As such, α7 ligands are suitable for the treatment of cognitive disorders including, for example, attention deficit disorder, attention deficit hyperactivity disorder (ADHD), Alzheimer's disease (AD), mild cognitive impairment, senile dementia, AIDS dementia, Pick's Disease, dementia associated with Lewy bodies, and dementia associated with Down's syndrome, as well as cognitive deficits associated with schizophrenia.

[0112] In addition, α7-containing nAChRs have been shown to be involved in the neuroprotective effects of nicotine both in vitro (Jonnala, R. B. and Buccafusco, J. J., J. Neurosci. Res. 66: 565-572, 2001) and in vivo (Shimohama, S. et al., Brain Res. 779: 359-363, 1998). More particularly, neurodegeneration underlies several progressive CNS disorders, including, but not limited to, Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, Huntington's disease, dementia with Lewy bodies, as well as diminished CNS function resulting from traumatic brain injury. For example, the impaired function of α7 nAChRs by β-amyloid peptides linked to Alzheimer's disease has been implicated as a key factor in development of the cognitive deficits associated with the disease (Liu, Q.-S., Kawai, H., Berg, D. K., PNAS 98: 4734-4739, 2001). The activation of α7 nAChRs has been shown to block this neurotoxicity (Kihara, T. et al., J. Biol. Chem. 276: 13541-13546, 2001). As such, selective ligands that enhance α7 activity can counter the deficits of Alzheimer's and other neurodegenerative diseases.

[0113] Schizophrenia is a complex disease that is characterized by abnormalities in perception, cognition, and emotions. Significant evidence implicates the involvement of α7 nAChRs in this disease, including a measured deficit of these receptors in post-mortem patients (Leonard, S. Eur. J. Pharmacol. 393: 237-242, 2000). Deficits in sensory processing (gating) are one of the hallmarks of schizophrenia. These deficits can be normalized by nicotinic ligands that operate at the α7 nAChR (Adler L. E. et al., Schizophrenia Bull. 24: 189-202, 1998; Stevens, K. E. et al., Psychopharmacology 136: 320-327, 1998). Thus, α7 ligands demonstrate potential in the treatment schizophrenia.

[0114] Angiogenesis, a process involved in the growth of new blood vessels, is important in beneficial systemic functions, such as wound healing, vascularization of skin grafts, and enhancement of circulation, for example, increased circulation around a vascular occlusion. Non-selective nAChR agonists like nicotine have been shown to stimulate angiogenesis (Heeschen, C. et al., Nature Medicine 7: 833-839, 2001). Improved angiogenesis has been shown to involve activation of theα7 nAChR (Heeschen, C. et al, J. Clin. Invest. 110: 527-536, 2002). Therefore, nAChR ligands that are selective for the α7 subtype offer improved potential for stimulating angiogenesis with an improved side effect profile.

[0115] A population of α7 nAChRs in the spinal cord modulate serotonergic transmission that have been associated with the pain-relieving effects of nicotinic compounds (Cordero-Erausquin, M. and Changeux, J.-P. PNAS 98:2803-2807, 2001). The α7 nAChR ligands demonstrate therapeutic potential for the treatment of pain states, including acute pain, post-surgical pain, as well as chronic pain states including inflammatory pain and neuropathic pain. Moreover, α7nAChRs are expressed on the surface of primary macrophages that are involved in the inflammation response, and that activation of the α7 receptor inhibits release of TNF and other cytokines that trigger the inflammation response (Wang, H. et al Nature 421: 384388, 2003). Therefore, selective α7 ligands demonstrate potential for treating conditions involving inflammation and pain.

[0116] The mammalian sperm acrosome reaction is an exocytosis process important in fertilization of the ovum by sperm. Activation of an α7 nAChR on the sperm cell has been shown to be essential for the acrosome reactbn (Son, J.-H. and Meizel, S. Biol. Reproduct. 68: 1348-1353 2003). Consequently, selective α7agents demonstrate utility for treating fertility disorders.

[0117] Compounds of the invention are particularly useful for treating and preventing a condition or disorder affecting cognition, neurodegeneration, and schizophrenia.

[0118] Cognitive impairment associated with schizophrenia often limits the ability of patients to function normally, a symptom not adequately treated by commonly available treatments, for example, treatment with an atypical antipsychotic. (Rowley, M. et al., J. Med. Chem. 44: 477-501, 2001). Such cognitive deficit has been linked to dysfunction of the nicotinic cholinergic system, in particular with decreased activity at α7 receptors. (Friedman, J. I. et al., Biol Psychiatry, 51: 349-357, 2002). Thus, activators ofα7 receptors can provide useful treatment for enhancing cognitive function in schizophrenic patients who are being treated with atypical antipsychotics. Accordingly, the combination of an α7 nAChR ligand and an atypical antipsychotic would offer improved therapeutic utility. Specific examples of suitable atypical antipsychotics include, but are not limited to, clozapine, risperidone, olanzapine, quietapine, ziprasidone, zotepine, iloperidone, and the like.

[0119] Actual dosage levels of active ingredients in the pharmaceutical compositions of this invention can be varied so as to obtain an amount of the active compound(s) that is effective to achieve the desired therapeutic response for a particular patient, compositions and mode of administration. The selected dosage level will depend upon the activity of the particular compound, the route of administration, the severity of the condition being treated and the condition and prior medical history of the patient being treated. However, it is within the skill of the art to start doses of the compound at levels lower than required to achieve the desired therapeutic effect and to gradually increase the dosage until the desired effect is achieved.

[0120] When used in the above or other treatments, a therapeutically effective amount of one of the compounds of the invention can be employed in pure form or, where such forms exist, in pharmaceutically acceptable salt, ester, amide or prodrug form. Alternatively, the compound can be administered as a pharmaceutical composition containing the compound of interest in combination with one or more pharmaceutically acceptable carriers. The phrase "therapeutically effective amount" of the compound of the invention means a sufficient amount of the compound to treat disorders, at a reasonable benefit/risk ratio applicable to any medical treatment. It will be understood, however, that the total daily usage of the compounds and compositions of the invention will be decided by the attending physician within the scope of sound medical judgment. The specific therapeutically effective dose level for any particular patient will depend upon a variety of factors including the disorder being treated and the severity of the disorder; activity of the specific compound employed; the specific composition employed; the age, body weight, general health, sex and diet of the patient; the time of administration, route of administration, and rate of excretion of the specific compound employed; the duration of the treatment; drugs used in combination or coincidental with the specific compound employed; and like factors well-known in the medical arts. For example, it is well within the skill of the art to start doses of the compound at levels lower than required to achieve the desired therapeutic effect and to gradually increase the dosage until the desired effect is achieved.

[0121] The total daily dose of the compounds of this invention administered to a human or lower animal range from about 0.10 mg/kg body weight to about 1 g/kg body weight. More preferable doses can be in the range of from about 0.10 mg/kg body weight to about 100 mg/kg body weight. If desired, the effective daily dose can be divided into multiple doses for purposes of administration. Consequently, single dose compositions may contain such amounts or submultiples thereof to make up the daily dose.

[0122] The compounds and processes of the invention will be better understood by reference to the following examples and reference examples, which are intended as an illustration of and not a limitation upon the scope of the invention.

Example 1

5'-phenyl-3'H-spiro[4-azabicyclo[2.2.2]octane-2,2'-[1]benzofuran] hydrochloride

Example 1A

3-Quinuclidinone

[0123] 3-Quinuclidinone hydrochloride (Aldrich, 16.1 g, 100 mol) was treated with saturated with $NaHCO_3$ (20 mL) at ambient temperature for 10 minutes. It was then extracted with diethyl ether (4 x 100 mL). The extracts were combined, washed with brine (2 x 20 mL) and dried over $MgSO_4$ (Aldrich, anhydrous). The drying reagents were removed by filtration and the filtrate was concentrated under reduced pressure at ambient temperature to give the title compound as white solid (11.0 g, 88% yield). MS (DCI/NH_3) m/z 126 $(M+H)^+$.

Example 1B

3-(2-fluorobenzyl)quinuclidin-3-ol

[0124] Magnesium turnings (Aldrich, 1.20 g, 50 mmol) and I_2 (Aldrich, 10 mg) were combined in diethyl ether (Aldrich, anhydrous, 20 mL.) and treated with 2-fluorobenzyl bromide [Aldrich, 5.70 g, 50 mmol, in diethyl ether (200 mL)] at ambient temperature. After the reaction was initiated (discharge of brown color), the addition of 2-fluorobenzyl bromide ether solution was continued to maitain the reaction temperature ≤ 30 °C. After the addition was complete, the mixture was stirred at ambient temperature for 4 hours. The product of Example 1A (3.75 g, 30 mmol, in diethyl ether (20 mL) was added at 05 °C. The reaction mixture was then stirred at room temperature for 10 h. It was then quenched with water (20 mL) at 0 °C and ether was removed under reduced pressure. The residue was extracted with $CHCl_3$:isopropyl alcohol (10:1, 3 X 300 mL). The extracts were combined and concentrated. The title compound was purified by chromatography (SiO_2, CH_2Cl_2 : MeOH : $NH_3{\cdot}H_2O$, 90:10:1, R_f. 0.10) as oil (4.72 g, 67% yield). ^1H NMR (MeOH-d_4, 300 MHz) δ 1.42-1.50 (m, 1H), 1.64-1.78 (m, 2H), 1.88-1.10(m, 2H), 2.64 (d, J=13.9 Hz, 1H), 2.70-2.91 (m, 6H), 3.00 (d, J=13.9 Hz, 1H), 7.01-7.12 (m, 2H), 7.19-7.27 (m, 1H), 7.36 (td, J=7.8, 2.0 Hz, 1H) ppm. MS (DCI/NH_3) m/z 236 $(M+H)^+$.

Example 1C

3'H-spiro[4-azabicyclo[2.2.2]octane-2,2'-[1]benzofuran]

[0125] The product of 1B (4.48 g, 19 mmol) in tetrahydrofuran (100 mL) was treated with potssium tert-butoxide (Aldrich, 4.26 g, 38 mmol) at 65 °C for 6 hours. The reaction was monitored with TLC. After the reaction was complete, it was concentrated and the residue was diluted with $CHCl_3$ (100 mL) and washed with brine (2 x 20 mL). The organic solution was concentrated and the title compound was purified by chromatography (SiO_2, CH_2Cl_2 : MeOH : $NH_3{\cdot}H_2O$, 90:10:1, R_f. 0.30) as oil (3.12 g, 76% yield). ^1H NMR (MeOH-d_4, 300 MHz) δ 1.52-1.64 (m, 1H), 1.69-1.90 (m, 2H), 1.96-2.08 (m, 1H), 2.14-2.25 (m, 1H), 2.80-3.08 (m, 6H), 3.20 (d, J=14.3 Hz, 1H), 3.40 (d, J=15.0 Hz, 1H), 6.70 (d, J=7.8 Hz, 1H), 6.80 (t, J=7.4 Hz, 1H), 7.07 (t, J=7.5 Hz, 1H), 7.14 (d, J=7.1 Hz, 1H) ppm. MS (DCI/NH_3) m/z 216 $(M+H)^+$.

Example 1D

3'H-spiro[4-azabicyclo[2.2.2]octane-2,2'-[1]benzofuran] hydrochloride

[0126] The product of Example 1C (180 mg, 0.84 mmol) was treated with HCl (Aldrich, in dioxane, 4M, 0.5 mL, 2 mmol) in EtOAc (5 mL) at ambient temperature for 10 h. The title compound was obtained as solid (200 mg, 95% yield). ^1H NMR (MeOH-d_4, 300 MHz) δ 1.85-2.11 (m, 2H), 2.25-2.34 (m, 1H), 2.40-2.52 (m, 1H), 3.23-3.71-3.45 (m, 8H), 6.76 (d, J=7.8 Hz, 1H), 6.89 (t, J=7.5 Hz, 1H), 7.13 (t, J=7.8 Hz, 1H), 7.21 (d, J=7.4 Hz, 1H) ppm. MS (DCI/NH_3) m/z 216 $(M+H)^+$.

Anal. Calculated for $C_{14}H_{17}NO\cdot1.00\ HCl\cdot0.62\ H_2O$: C, 63.96; H, 7.38; N, 5.33. Found: C, 63.56; H, 6.97; N, 5.30.

Example 1E

5'-bromo-3'H-spiro[4-azabicyclo[2.2.2]octane-2,2'-[1]benzofuran]

[0127] The product of 1C (2.80 g, 13 mmol) was treated with N-bromosuccinimide (NBS) (Aldrich, 3.56 g, 20 mmol) in MeCN/HOAc (v. 5:1, 120 mL) at 0 °C to room temperature for 20 h. After the reaction was complete, it was concentrated under reduced pressure at ambient temperature. The residue was diluted with EtOAc (200 mL) and washed with brine (2 x 20 mL). The organic solution was concentrated under reduced pressure and the title compound was purified by chromatography (SiO_2, CH_2Cl_2 : MeOH : $NH_3\cdot H_2O$, 90:10:1, R_f. 0.35) as oil (2.9 g, 70% yield). ^1H NMR (MeOH-d_4, 300 MHz) δ 1.52-1.62 (m, 1H), 1.68-1.90 (m, 2H), 2.00-2.08 (m, 1H), 2.10-2.25 (m, 1H), 2.81-3.35 (m, 7H), 3.47 (d, J=15.9 Hz, 1H), 6.71 (d, J=8.6 Hz, 1H), 7.22 (ddt, J=8.6, 2.2, 0.8 Hz, 1H), 7.32 (dt, J=2.1, 0.8 Hz, 1H) ppm. MS (DCI/NH_3) m/z 294 $(M+H)^+$, 296 $(M+H)^+$.

Example 1F

5'-bromo-3'H-spiro[4-azabicyclo[2.2.2]octane-2,2'-[1]benzofuran] hydrochloride

[0128] The product of Example 1E (230 mg, 0.78 mmol) was treated with HCl (Aldrich, in dioxane, 4M, 0.5 mL, 2 mmol) in EtOAc (5 mL) at ambient temperature for 10 hours. The title compound was obtained asa solid (140 mg, 54% yield): ^1H NMR (MeOH-d_4, 300 MHz) 1.89-1.98 (m, 1H), 2.02-2.11 (m, 2H), 2.30-2.33 (m, 1H), 2.35-2.43 (m, 1H), 3.28-3.53 (m, 6H), 3.62 (dd, J=13.8, 2.1 Hz, 1H), 3.68 (d, J=13.9 Hz, 1H), 6.72 (d, J=8.6 Hz, 1H), 7.25 (ddt, J=8.6, 2.2, 0.8 Hz, 1H), 7.35 (dt, J=2.1, 0.8 Hz, 1H) ppm. MS (DCI/NH_3) m/z 294 $(M+H)^+$, 296 $(M+H)^+$. Anal. Calculated for $C_{14}H_{16}BrNO\cdot1.0\ HCl\cdot0.5\ H_2O$: C, 49.51; H, 5.34; N, 4.12. Found: C, 49.46; H, 5.07; N, 4.05.

Example 1G

5'-phenyl-3'H-spiro[4-azabicyclo[2.2.2]octane-2,2'-[1]benzofuran]

[0129] Under N_2, the mixture of the product of 1 E (200 mg, 0.68 mmol), phenylboronic acid (Aldrich, 276 mg, 1.36 mmol), $Pd_2(dba)_3$ (Strem Chemicals, 12.4 mg, 0.014 mmol) and 1,3-bis(2,6-di-*i*-propylphenyl)imidazolium chloride, (Strem Chemicals, 95%, 18.3 mg, 0.041 mmol) in Na_2CO_3 (aqueous, 2M, 2 mL, 4 mmol) and ethanol (8 mL) was stirred at 80 °C for 15 hours. The reaction was monitored with TLC. After the reaction was complete, it was concentrated under reduced pressure and the residue was diluted with EtOAc (30 mL). It was then washed with brine (2 x 5 mL). The organic solution was concentrated and the title compound was purified by chromatography (SiO_2, CH_2Cl_2 : MeOH : $NH_3\cdot H_2O$, 90:10:2, R_f. 0.40) as oil (90 mg, 45% yield). ^1H NMR (MeOH-d_4, 300 MHz) δ 1.52-1.62 (m, 1H), 1.68-1.89 (m, 2H), 2.00-2.06 (m, 1H), 2.14-2.25 (m, 1H), 2.81-3.32 (m, 7H), 3.47 (d, J=15.9 Hz, 1H), 6.76 (d, J=8.6 Hz, 1H), 7.24 (tt, J=7.1, 1.2 Hz, 1H), 7.32-7.42 (m, 4H), 7.49-53 (m, 1H) ppm. MS (DCI/NH_3) m/z 292 $(M+H)^+$.

Example 1H

5'-phenyl-3'H-spiro[4-azabicyclo[2.2.2]octane-2,2'-[1]benzofuran] hydrochloride

[0130] The product of Example 1 G (90 mg, 0.31 mmol) was treated with HCl (Aldrich, in dioxane, 4M, 0.2 mL, 0.8 mmol) in EtOAc (5 mL) at ambient temperature for 10 hours. The title compound was obtained as a solid (60 mg, 59% yield): ^1H NMR (MeOH-d_4, 300 MHz) 1.89-2.00 (m, 1H), 2.06-2.13 (m, 2H), 2.35-2.39 (m, 1H), 2.41-2.51 (m, 1H), 3.28-3.54 (m, 6H), 3.63 (dd, J=13.8, 2.1 Hz, 1H), 3.73 (d, J=13.9 Hz, 1H), 6.84 (d, J=8.5 Hz, 1H), 7.27 (tt, J=7.1, 1.2 Hz, 1H), 7.36-7.42 (m, 3H), 7.49-53 (m, 3H) ppm. MS (DCI/NH_3) m/z 292 $(M+H)^+$. Anal. Calculated for $C_{20}H_{21}NO\cdot1.00\ HCl\cdot1.40\ H_2O$: C, 68.04; H, 7.08; N, 3.97. Found: C, 67.86; H, 6.61; N, 3.92.

Example 2

5',7'-diphenyl-3'H-spiro[4-azabicyclo[2.2.2]octane-2,2'-[1]benzofuran] trifluoroacetate

Example 2A

5',7'-dibromo-3'H-spiro[4-azabicyclo[2.2.2]octane-2,2'-[1]benzofuran]

[0131] The product of 1C (1.50 g, 7.0 mmol) and $NaOAc{\cdot}3H_2O$ (Aldrich, 9.52 g, 70 mmol) was dissolved in aqueous HOAc solution (50%, 60 mL) and warmed up to 60 °C. Meanwhile, bromine (Aldrich, 0.73 mL, 2.28 g, 14.3 mmol) was dissolved in aqueous HOAc (50%, 10 mL) and added slowly to the above mixture at 60 °C. After the addition was complete, the reaction was stirred at 60 °C for additional 30 min. The reaction mixture was then cooled down to room temperature. Saturated Na_2CO_3 aqueous solution was added slowly to adjust the pH to pH=10. The resulting mixture was then extracted with EtOAc (3 x 100 mL). The extracts were combined and concentrated. The title compound was purified by chromatography (SiO_2 CH_2Cl_2: MeOH : $NH_3{\cdot}H_2O$, 90:10:1, R_f. 0.40) as oil (1.18 g, 45% yield). ^1H NMR (MeOH-d_4, 300 MHz) δ 1.52-1.62 (m, 1H), 1.69-1.89 (m, 2H), 2.00-2.10 (m, 1H), 2.14-2.34 (m, 1H), 2.80-3.25 (m, 7H), 3.54 (d, J=16.2 Hz, 1H), 7.28 (dt, J=2.0, 1.0Hz, 1H), 7.41 (dt, J=2.0, 1.0Hz, 1H) ppm. MS (DCI/NH_3) m/z 372 $(M+H)^+$, 374 $(M+H)^+$, 376 $(M+H)^+$.

Example 2B

5',7'-dibromo-3'H-spiro[4-azablcyclo[2.2.2]octane-2,2'-[1]benzofuran hydrochloride

[0132] The product of Example 2A (100 mg, 0.27 mmol) was treated with HCl (Aldrich, in dioxane, 4M, 0.2 mL, 0.8 mmol) in EtCAc (5 mL) at ambient temperature for 10 h. The title compound was obtained as solid (70 mg, 63% yield). ^1H NMR (MeOH-d_4, 300 MHz) 1.89-2.13(m, 3H), 2.35-2.48 (m, 2H), 3.28-3.48 (m, 4H), 3.61-3.67 (m, 2H), 3.78 (d, J=14.5 Hz, 1H), 7.36 (dt, J=2.1, 1.0Hz, 1H), 7.48 (dt, J=2.0, 1.0Hz, 1H) ppm. MS (DCI/NH_3) m/z 372 $(M+H)^+$, 374 $(M+H)^+$, 376 $(M+H)^+$. Anal. Calculated for $C_{14}H_{15}Br_2NO{\cdot}1.00$ HCl: C, 41.06; H, 3.94; N, 3.42. Found: C, 40.90; H, 3.51; N, 3.33.

Example 2C

5',7'-diphenyl-3'H-spiro[4-azabicyclo[2.2.2]octane-2,2'-[1]benzofuran trifluoroacetate

[0133] The product of 2B (250 mg, 0.68 mmol) was coupled with phenylboronic acid (Aldrich, 550 mg, 4.50 mmol) according to the procedure of Example 1G. The title compound was purified by preparative HPLC (Gilson, column, Symmetry® G8 7 μm, 40 x 100 mm. Solvent, MeCN / H_2O (with 0.2% v. TFA) (v. 90/10 to 10/90 over 20 min.) Flow rate, 75 mL/min. uv, 250 nM) as solid (60 mg, 18% yield). ^1H NMR (MeOH-d_4, 300 MHz) 1.89-2.00 (m, 1H), 2.06-2.14 (m, 2H), 2.27-2.53 (m, 2H), 3.30-3.46 (m, 5H), 3.62-3.69 (m, 2H), 3.78 (d, J=14.3 Hz, 1H), 7.27-7.36 (m, 2H),7.35-7.50 (m, 5H), 7.55-7.61 (m, 3H), 7.70-7.76 (m, 2H). ppm. MS (DCI/NH_3) m/z 368 $(M+H)^+$. Anal. Calculated for $C_{26}H_{25}NO{\cdot}1.0$ $CF_3CO_2H{\cdot}1.0$ H_2O: C, 67.32; H, 5.65; N, 2.80. Found: C, 67.60; H, 5.74; N, 2.86.

Example 3

3-(3'H-spiro[4-azabicyclo[2.2.2]octane-2,2'-[1]benzofuran]-5'-yl)aniline trifluoroacetate

Example 3A

3-(3'H-spiro[4-azabicyclo[2.2.2]octane-2,2'-[1]benzofuran]-5'-yl)aniline

[0134] The product of 1 E (200 mg, 0.68 mmol) was coupled with 3-aminophonylboronic acid (Lancaster, 183 mg, 1.40 mmol) according to the procedure of Example 1G. The title compound was purified by chromatography (SiO_2, CH_2Cl_2: MeOH : $NH_3{\cdot}H_2O$, 90:10:1, R_f. 0.10) as oil (100 mg, 45% yield). ^1H NMR (MeOH-d_4, 300 MHz) δ 1.59-1.69 (m, 1H), 1.76-1.93 (m, 2H), 2.07-2.12 (m, 1H), 2.17-2.29 (m, 1H), 2.92-3.34 (m, 7H), 3.47 (d, J=16.2 Hz, 1H), 6.65 (ddd, J=7.8, 2.4, 1.0 Hz, 1H), 6.75 (d, J=8.2 Hz, 1H), 6.86 (dt, J=7.8, 1.3 Hz, ^1H), 6.90 (t, J=2.4 Hz, 1H), 7.11 (t, J=7.8 Hz, 1H), 7.21 (dd, J=8.1, 2.0 Hz, 1H), 7.38 (d, J=1.0 Hz, 1H) ppm. MS (DCI/NH_3) m/z 307 $(M+H)^+$.

Example 3B

3-(3'H-spiro[4-azabicyclo[2.2.2]octane-2,2'-[1]benzofuran]-5'-yl)aniline trifluoroacetate

[0135] The product of Example 3A (100 mg, 0.33 mmol) was treated with trifluroacetic acid (Aldrich, 114 mg, 78 μL, 1.0 mmol) in MeCN/PrOAc (v. 1 ; 4, 5 mL) at ambient temperature for 10 h. The title compound was obtained as solid (60 mg, 43% yield): ^{1}H NMR (MeOH-d_4, 300 MHz) 1.89-2.02 (m, 1H), 2.06-2.13 (m, 2H), 2.35-2.51 (m, 2H), 3.28-3.68 (m, 7H), 3.75 (d, J=14.3 Hz, 1H), 6.92 (d, J=8.2 Hz, 1H), 7.33 (ddd, J=7.8, 2.4, 1.0 Hz, 1H), 7.46 (dd, J=8.5, 2.0 Hz, 1H), 7.53-7.57 (m, 3H), 7.59 (d, J=7.8 Hz, 1H0, 7.69 (dt, J=8.1, 1.3 Hz, 1H) ppm. MS (DCI/NH_3) m/z 307 $(M+H)^+$. Anal. Calculated for $C_{20}H_{22}NO{\cdot}1.1\ CF_3CO_2H{\cdot}2.0\ H_2O$: C, 56.99; H, 5.84; N, 5.99. Found: C, 56.95; H, 6.14; N, 6.17.

Example 4

5'-phenoxy-3'H-spiro[4-azabicyclo[2.2.2]octane-2,2'-[1]benzofuran] trifluoroacetate

Example 4A

5'-phenoxy-3'H-spiro[4-azabicyclo[2.2.2]octane-2,2'-[1]benzofuran]

[0136] The product of 1 E (200 mg, 0.68 mmol) was coupled with phenol (Aldrich, 132 mg, 1.4 mmol) catalyzed by CuCl (Strem Chemicals, 34 mg, 0.34 mmol) 2,2,6,6-tetramethyl-heptane-3,5-dione (Strem Chemicals, 11 mg, 0.07 mmol) with Cs_2CO_3 (Strem Chemicals, 456 mg, 1.4 mmol) in NMP (2 mL) at 160 °C for 6 hours. After the reaction went to completion, it was then cooled down to room temperature and diluted with CH_2Cl_2 (5 mL). The solid was filtered off and the filtrate was directly purified by chromatography (SiO_2, CH_2Cl_2: MeOH : $NH_3{\cdot}H_2O$, 90:10:1, R_f. 0.30) to give the title product as oil (110 mg, 48% yield). ^{1}H NMR (MeOH-d_4, 300 MHz) δ 1.65-1.76 (m, 1H), 1.84-1.93 (m, 2H), 2.13-2.17 (m, 1H), 2.22-2.32 (m, 1H), 3.00-3.38 (m, 7H), 3.44 (d, J=16.3 Hz, 1H), 6.71-6.80 (m, 2H), 6.82-6.90 (m, 3H), 6.98-7.05 (m, 1H), 7.20-7.32 (m, 2H) ppm. MS (DCI/NH_3) m/z 308 $(M+H)^+$.

Example 4B

5'-phenoxy-3'H-spiro[4-azabicyclo[2.2.2]octane-2,2'-[1]benzofuran] trifluoroacetate

[0137] The product of Example 4A (110 mg, 0.36 mmol) was treated with trifluroacetic acid (Aldrich, 114 mg, 78 μL, 1.0 mmol) in PrOAc (5 mL) at ambient temperature for 10 hours. The title compound was obtained as solid (110 mg, 73% yield). ^{1}H NMR (MeOH-d_4, 300 MHz) 1.89-1.99 (m, 1H), 2.03-2.10 (m, 2H), 2.33-2.49 (m, 2H), 3.23-3.52 (m, 6H), 3.60 (dd, J=13.9, 1.7 Hz, 1H), 3.71 (d, J=13.9 Hz, 1H), 6.76-6.91 (m, 5H), 7.03 (t, J=7.4 Hz, 1H), 7.24-7.35 (m, 2H) ppm. MS (DCI/NH_3) m/z 308$(M+H)^+$. Anal. Calculated for $C_{20}H_{22}NO{\cdot}1.15\ CF_3CO_2H{\cdot}2.0\ H_2O$: C, 56.44; H, 5.55; N, 2.95. Found: C, 56.07; H, 5.43; N, 3.20.

Example 5

5',7'-diphenoxy-3'H-spiro[4-azabicyclo[2.2.2]octane-2,2'-[1]benzofuran] hydrochloride

Example 5A

5',7'-diphenoxy-3'H-spiro[4-azabicyclo[2.2.2]octane-2,2'-[1]benzofuran]

[0138] The product of 2A (190 mg, 0.5 mmol) was coupled with phenol (Aldrich, 97 mg, 1.0 mmol) according to the procedure of Example 4A. The title compound was purified by chromatography (SiO_2, CH_2Cl_2 : MeOH : $NH_3{\cdot}H_2O$, 90: 10:1, R_f. 0.45) as major product (100 mg, 50% yield). ^{1}H NMR (MeOH-d_4, 300 MHz) δ 1.29-1.41 (m, 1H) 1.65-1.83 (m, 3H), 1.94-2.00 (m, 1H), 2.57-2.79 (m, 4H), 2.97 (dd, J=14.5, 2.1 Hz, 1H), 3.05-3.10 (m, 2H), 3.40 (d, J=16.2 Hz, 1H), 6.52 (d, J=2.3 Hz, 1H), 6.71 (d, J=2.3 Hz, 1H), 6.90-6.96 (m, 4H), 7.00-7.07 (m, 2H), 7.25-7.34 (m, 4H) ppm. MS (DCI/NH_3) m/z 400 $(M+H)^+$.

Example 5B

5',7'-diphenoxy-3'H-spiro[4-azabicyclo[2.2.2]octane-2,2'-[1]benzofuran] hydrochloride

[0139] The product of Example 5A (100 mg, 0.25 mmol) was treated with HCl (Aldrich, in dioxane, 4M, 0.5 mL 2.0 mmol) in ^{i}PrOAc (5 mL) at ambient temperature for 10 h. The title compound was obtained as solid (90 mg, 83% yield). ^{1}H NMR (MeOH-d_4, 300 MHz) 1.68-1.80 (m, 1H), 1.88-2.06 (m, 3H), 2.28-2.36 (m, 1H), 2.95-3.08 (m, 1H), 3.24 3.34 (m, 3H), 3.52 (d, J=16.3 Hz, 1H), 3.58 (s, 2H), 6.57 (d, J=23 Hz, 1H), 6.74 (d, J=2.3 Hz, 1H), 6.90-7.02 (m, 4H), 7.01-7.12 (m, 2H), 7.25-7.38 (m, 4H) ppm. MS (DCI/NH_3) m/z 400(M+H)$^+$. Anal. Calculated for $C_{26}H_{25}NO_3$·1.0 HCl·0.1 H_2O: C, 71.34; H, 6.03; N, 3.20. Found: C, 71.24; H, 6.14; N, 3.14.

Example 6

7'-bromo-5'-phenoxy-3'H-spiro[4-azabicyclo[2.2.2]octane-2,2'-[1]benzofuran] trifluoroacetate

[0140] The product of 2A (190 mg, 0.5 mmol) was coupled with phenol (Aldrich, 97 mg, 1.0 mmol) according to the procedure of Example 5A. The title compound was purified by preparative HPLC (Gilson, column, Symmetry® C-8 7 µm, 40 x 100 mm. Solvent, MeCN / H_2O (with 0.2% v. TFA) (v. 90/10 to 10/90 over 20 min.) Flow rate, 75 mL/min. uv, 250 nM)) as solid (30 mg, 12% yield). ^{1}H NMR (MeOH-d_4, 300 MHz) 1.90-2.13 (m, 3H), 2.35-2.51 (m, 2H), 3.26-3.66 (m, 7H), 3.78 (dd, J=13.9, 1.3 Hz, 1H), 6.89-6.98 (m, 4H), 7.06-7.12 (m, 1H), 7.30-7.37 (m, 2H) ppm. MS (DCI/NH_3) m/z 386 (M+H)$^+$, 388 (M+H)$^+$. Anal. Calculated for $C_{20}H_{20}BrNO_2$·1.0 CF_3CO_2H: C, 52.82; H, 4.23; N, 2.80. Found: C, 52.58; H, 4.47; N, 2.69.

Example 7

N-phenyl-3'H-spiro[4-azabicyclo[2.2.2]octane-2,2'-[1]benzofuran]-5'-amine dihydrochloride

Example 7A

N-phenyl-3'H-spiro[4-azabicyclo[2.2.2]octane-2,2'-[1]benzofuran]-5'-amine

[0141] The product of 1 E (200 mg, 0.68 mmol) was coupled with aniline (Aldrich, 130 mg, 1.40 mmol) catalyzed by $Pd_2(dba)_3$ (Strem Chemicals, 12.4 mg, 0.014 mmol) and Xantphos (Strem Chemicals, 24.3 mg, 0.042 mmol) with Cs_2CO_3 (Aldrich, 460 mg, 1.4 mmol) in toluene (Aldrich, anhydrous, 10 mL) at 110 °C for 20 h. The reaction was monitored with TLC. After the reaction was complete, it was diluted with EtOAc (30 mL) and washed with brine (2 x 5 mL). The organic solution was concentrated and the title compound was purified by chromatography (SiO_2, CH_2Cl_2 : MeOH : NH_3·H_2O, 90:10:2, R_f. 0.20) as oil (120 mg, 58% yield). ^{1}H NMR (MeOH-d_4, 300 MHz) δ 1.52-1.63 (m, 1H), 1.73-1.85 (m, 2H), 1.99-2.06 (m, 1H), 2.13-2.25 (m, 1H), 2.84-3.43 (m, 8H), 6.63 (d, J=8.6 Hz, 1H), 6.70 (tt, J=7.1, 1.2 Hz, 1H), 6.80-7.90 (m, 2H), 6.96-6.99 (m, 1H), 7.06-7.16 (m, 2H) ppm. MS (DCI/NH_3) m/z 307 (M+H)$^+$.

Example 7B

N-phenyl-3'H-spiro[4-azabicyclo[2.2.2]octane-2,2'-[1]benzofuran]-5'-amine dihydrochloride

[0142] The product of Example 7A (120 mg, 0.39 mmol) was treated with HCl (Aldrich, in dioxane, 4M, 0.5 mL, 2.0 mmol) in EtOAc (5 mL) at ambient temperature for 10 hours. The title compound was obtained as solid (110 mg, 75% yield): ^{1}H NMR (MeOH-d_4, 300 MHz) 1.89-2.13 (m, 3H), 2.30-2.6 (m, 2H), 3.22-3.72 (m, 8H), 6.73 (d, J=8.5 Hz, 1H), 6.84 (t, J=7.8 Hz, 1H), 6.92-7.00 (m, 2H), 7.04-7.07 (m, 1H), 7.15-7.25 (m, 2H) ppm. MS (DCI/NH_3) m/z 307 (M+H)$^+$. Anal. Calculated for $C_{20}H_{22}N_2O$·2.00 HCl·0.40 H_2O: C, 62.15; H, 6.47; N, 7.25. Found: C, 62.50; H, 6.86; N, 6.84.

Example 8

N,N'-diphenyl-3'H-spiro[4-azabicyclo[2.2.2]octane-2,2'-[1]benzofuran]-5',7'-diamine dihydrochloride

[0143] The product of 2A (190 mg, 0.5 mmol) was coupled with aniline (Aldrich, 97 mg, 1.0 mmol) according to the procedure of Example 7A. The free base of the title compound was purified by chromatography (SiO_2, CH_2Cl_2 : MeOH : NH_3·H_2O, 90:10:2, R_f. 0.10) as major product (50 mg, 25% yield). MS (DCI/NH_3) m/z 398 (M+H)$^+$. The free base (50 mg, 0.12 mmol) was treated with HCl (Aldrich, in dioxane, 4M, 0.2 mL 2.0 mmol) in EtOAc (3 mL) at ambient temperature for 10 hours. The title compound was obtained as solid (50 mg, 89% yield): ^{1}H NMR (MeOH-d_4, 300 MHz) 1.83-1.94 (m, 1H), 2.01-2.13 (m, 2H), 2.34-2.50 (m, 2H), 3.28-3.45 (m, 4H), 3.52 (d, J=16.3 Hz, 1H), 3.62 (dd, J=13.9, 1.3 Hz, 1H), 3.66 (s, 2H), 3.70 (d, J=13.9 Hz, 1H), 6.89-6.91 (m, 1H), 7.02-7.07 (m, 2H), 7.14-7.27 (m, 6H), 7.30-7,40 (m, 3H) ppm. MS (DCl/NH_3) m/z 398 $(M+H)^+$. Anal. Calculated for $C_{26}H_{27}N_3O{\cdot}2.0\ HCl{\cdot}0.9\ EtOAc{\cdot}2.0\ H_2O$: C, 60.69; H, 6.92; N, 7.17. Found: C, 60.92; H, 6.90; N, 6.81.

Example 9

5'-(1H-indol-5-yl)-3'H-spiro[4-azabicyclo[2.2.2]octane-2,2'[1]benzofuran] trifluoroacetate

[0144] The product of 1 E (200 mg, 0.68 mmol) was coupled with 5-indolylboronic acid (Frontier, 161 mg, 1.00 mmol) according to the procedure of Example 1G. The title compound was purified by preparative HPLC (Gilson, column, Symmetry® G8 7 µm, 40 x 100 mm. Solvent, MeCN / H_2O (with 0.2% v. TFA) (v. 90/10 to 10/90 over 20 min. uv, 250 nM)) as solid (30 mg, 12% yield). ^{1}H NMR (MeOH-d_4, 300 MHz) 1.89-2.00 (m, 1H), 2.06-2.13 (m, 2H), 2.35-2.51 (m, 2H), 3.24-3.40 (m, 5H), 3.54-3.64 (m, 2H), 3.74 (d, J=13.9 Hz, 1H), 6.45 (dd, J=3.0, 0.7 Hz, 1H), 6.83 (d, J=8.1 Hz, 1H), 7.23 (d, J=3.0 Hz, 1H), 7.28 (dd, J=8.3, 2.0Hz, 1H), 7.36-7.43 (m, 2H), 7.48 (d, J=0.8 Hz, 1H), 7.68 (d, J=0.7 Hz, 1H) ppm. MS (DCl/NH_3) m/z 331 $(M+H)^+$. Anal. Calculated for $C_{22}H_{22}N_2O{\cdot}1.29\ CF_3CO_2H$: C, 61.83; H, 4.92; N, 5.87. Found: C, 62.21; H, 4.44; N, 5.73.

Example 10

DETERMINATION OF BIOLOGICAL ACTIVITY

[0145] To determine the effectiveness of representative compounds of this invention as α7 nAChRs, the compounds of the invention were evaluated according to the [3H] methyllycaconitine (MLA) binding assay and considering the [3H] cytisine binding assay, which were performed as described below.

[3H]-Cytisine binding

[0146] Binding conditions were modified from the procedures described inPabreza LA, Dhawan, S, Kellar KJ, [3H]-Cytisine Binding to Nicotinic Cholinergic Receptors in Brain, Mol. Pharm. 39: 9-12, 1991. Membrane enriched fractions from rat brain minus cerebellum (ABS Inc., Wilmington, DE) were slowly thawed at 4 °C, washed and resuspended in 30 volumes of BSS-Tris buffer (120 mM NaCl/5mM KCl/2 mM $CaCl_2$/2 mM $MgCl_2$/50 mM Tris-Cl, pH 7.4, 4 °C). Samples containing 100-200 µg of protein and 0.75 nM [3H]-cytisine (30 C/mmol; Perkin Elmer-/NEN Life Science Products, Boston, MA) were incubated in a final volume of 500 µL for 75 minutes at 4 °C. Seven log-dilution concentrations of each compound were tested induplicate. Non-specific binding was determined in the presence of 10 µM ()-nicotine. Bound radioactivity was isolated by vacuum filtration onto prewetted glass fiber filter plates (Millipore, Bedford, MA) using a 96-well filtration apparatus (Packard Instruments, Meriden, CT) and were then rapidly rinsed with 2 mL of ice-cold BSS buffer (120 mM NaCl/5 mM KCl/2 mM $CaCl_2$/2 mM $MgCl_2$). Packard MicroScint20® scintillation cocktail (40 µL) was added to each well and radioactivity determined using a Packard TapCount® instrument. The IC_{50} values were determined by nonlinear regression in Microsoft Excel® software. K_1 values were calculated from the IC_{50}s using the Cheng-Prusoff equation, where $K_{1=}$ IC_{50}/1+[Ligand]/K_D].

[3H]-Methyllycaconitine (MLA) binding

[0147] Binding conditions were similar to those for [3H]-cytisine binding. Membrane enriched fractions from rat brain minus cerebellum (ABS Inc., Wilmington, DE) were slowly thawed at 4 °C, washed and resuspended in 30 volumes of BSS-Tris buffer (120 mM NaCl, 5 mM KCl, 2 mM $CaCl_2$, 2 mM $MgCl_2$, and 50 mM Tris-Cl, pH 7.4, 22 °C). Samples containing 100-200 µg of protein, 5 nM [3H]-MLA (25 C_i/mmol; Perkin Elmer/NEN Life Science Products, Boston, MA) and 0.1% bovine serum albumin (BSA, Millipore, Bedford, MA) were incubated in a final volume of 500 µL for 60 minutes at 22 °C. Seven log-dilution concentrations of each compound were tested in duplicate. Non-specific binding was determined in the presence of 10 µM MLA. Bound radioactivity was isolated by vacuum filtration onto glass fiber filter plates prewetted with 2% BSA using a 96-well filtration apparatus (Packard Instruments, Meriden, CT) and were then rapidly rinsed with 2 mL of ice-cold BSS. Packard MicroScint-20® scintillation cocktail (40 µL) was added to each well and radioactivity was determined using a Packard TopCount® instrument. The IC_{50} values were determined by nonlinear regression in Microsoft Excel® software. K_i values were calculated from the IC_{50}s using the Cheng-Prusoff equation, where K_I = IC_{50}/1+[Ligand]/K_D].

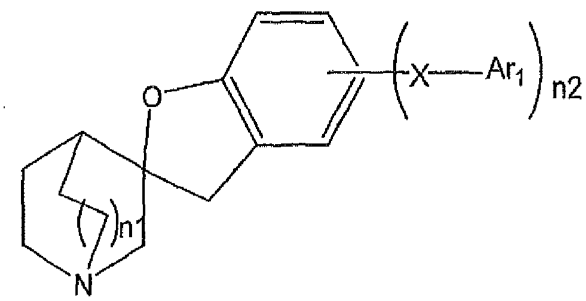
[0148] Compounds of the invention had K_i values of from about 1 nanomolar to about 10 micromolar when tested by the MLA assay, many having a K_i of less than 1 micromolar. [3H]-Cytisine binding values of compounds of the invention ranged from about 50 nanomolar to at least 100 micromolar. The determination of preferred compounds typically considered the K_i value as measured by MLA assay in view of the K_i value as measured by [3H]-cytisine binding, such that in the formula D = K_i 3H-cytisine/ K_i MLA, D is about 50. Preferred compounds typically exhibited greater potency at α7receptors compared to α4β2 receptors.

[0149] Compounds of the invention are α7nAChRs ligands that modulate function of α7 nAChRs by altering the activity of the receptor. The compounds can be inverse agonists that inhibit the basal activity of the receptor or antagonists that completely block the action of receptor-activating agonists. The compounds also can be partial agonists that partially block or partially activate the α7 nAChRreceptor or agonists that activate the receptor.

[0150] It is understood that the foregoing detailed description and accompanying examples are merely illustrative and are not to be taken as limitations upon the scope of the invention, which is defined solely by the appended claims and their equivalents. Various changes and modifications to the disclosed embodiments will be apparent to those skilled in the art. Such changes and modifications, including without limitation those relating to the chemical structures, substituents, derivatives, intermediates, syntheses, formulations and/or methods of use of the invention, may be made without departing from the spirit and scope thereof.

Claims

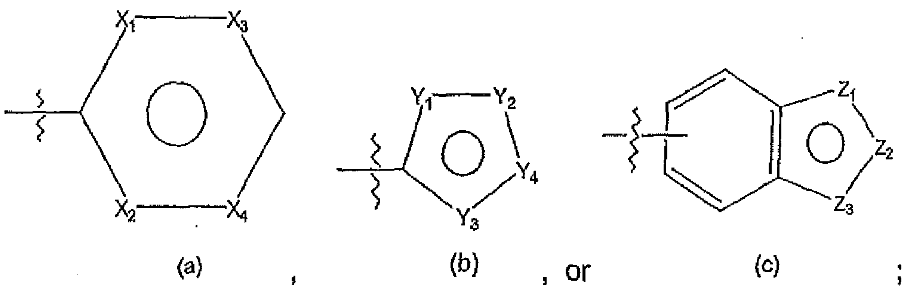
1. A compound of the formula (1):



(I)

or a pharmaceutically acceptable salt, ester, amide, or prodrug thereof, wherein:

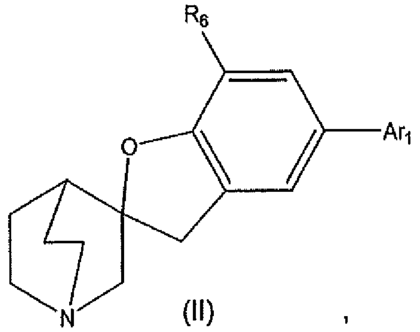
n1 is 0, 1, or 2;
n2 is 0, 1, or 2;
X is selected from the group consisting of O, S, or NR_1, or X is a bond;
Ar_1 is a group of the formula:



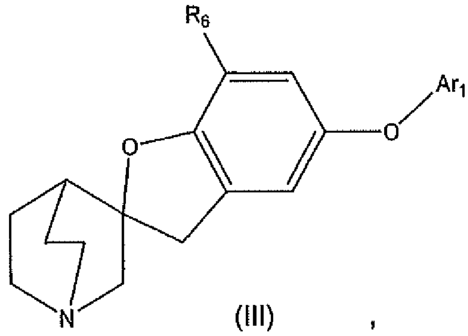
$X1$, X_2, X_3, and X_4 are each independently selected from the group consisting of N and $-CR_2$;
Y_1, Y_2, and Y_3 are each independently selected from the group consisting of N, O, S, and $-CR_2$;

Y_4 is C or N, provided that when Y_4 is C at least one of Y_1, Y_2, and Y_3, is other than $-CR_2$;
Z_1, Z_2, and Z_3 are each independently selected from the group consisting of N, O, S, and $-CR_2$;
R_1 is independently selected from the group consisting of hydrogen, alkyl, alkoxycarbonyl, alkylsulfonyl, and arylsulfonyl;
R_2 at each occurrence is independently selected from the group consisting of hydrogen, halogen, alkyl, alkoxy, alkylcarbonyl, and-NR_3R_4; and
R_3 and R_4 are each independently selected from the group consisting of hydrogen and alkyl.

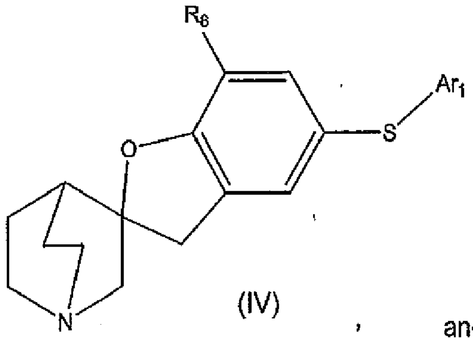
2. The compound of claim 1, selected from the group consisting of:



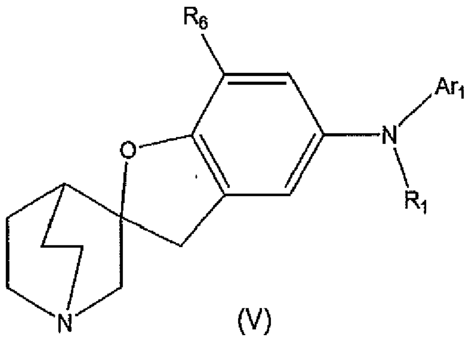
(II) ,



(III) ,



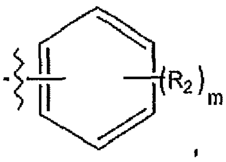
(IV) , and



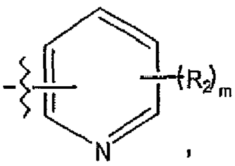
(V) ,

wherein Ar_1 is as previously defined for compounds of formula (I) and R_6 is selected from the group consisting of hydrogen, halogen, alkyl, phenyl,-O-R_7 and -NH-R_7, wherein R_7 is hydrogen, alkyl, and aryl.

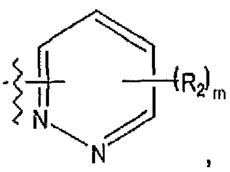
3. The compound of claim 1, wherein Ar_1 is selected from the group consisting of:



, (i)



, (ii)



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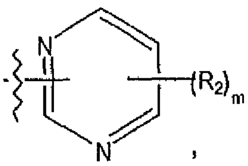

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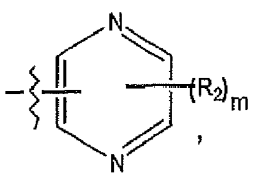
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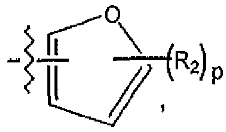
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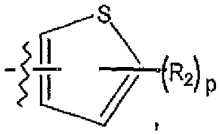
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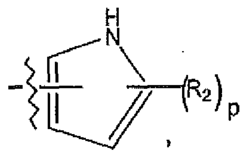
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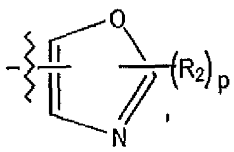
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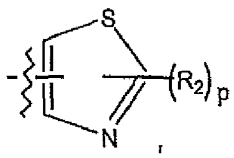
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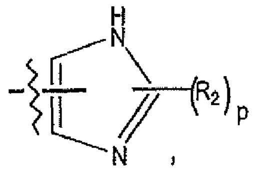
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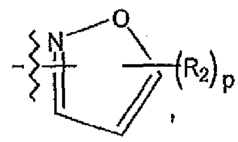
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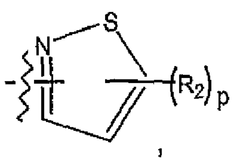
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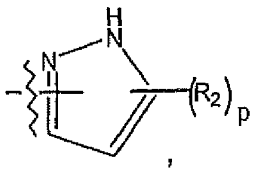
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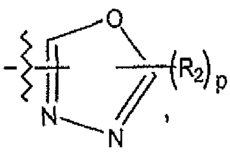
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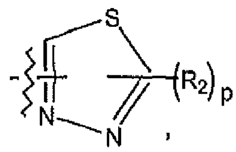
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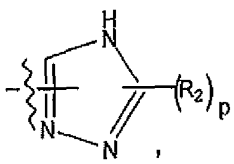
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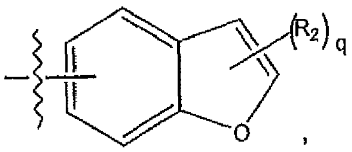
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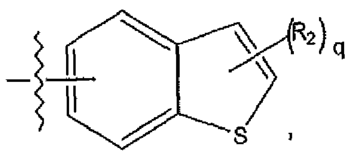
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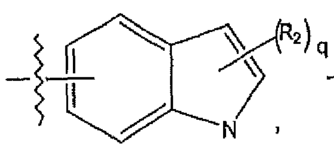
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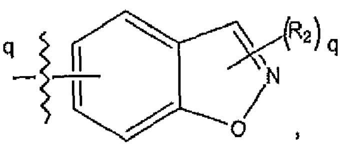
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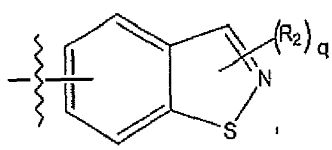
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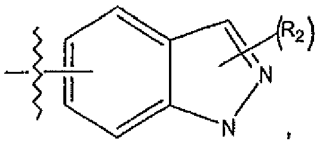

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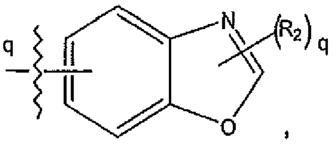

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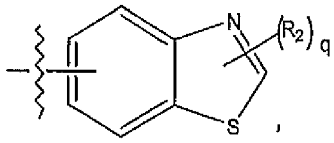

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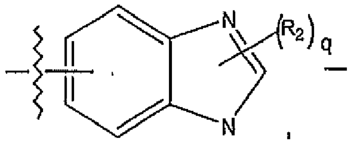

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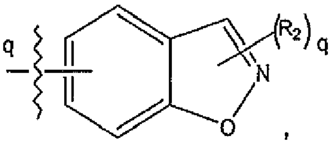

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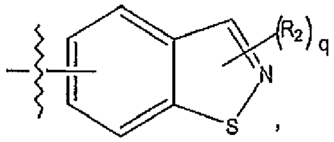

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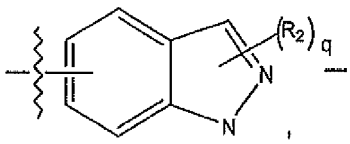

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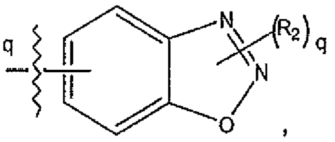

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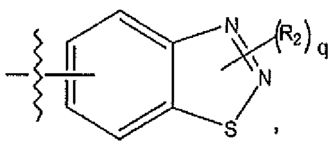

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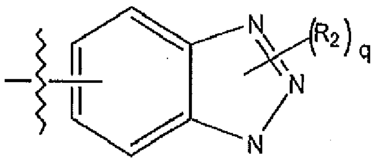

(xxxii) ;

wherein R_2 at each occurrence is as defined in claim 1; m at each occurrence is 0, 1, 2, or 3; p at each occurrence is 0, 1, or 2; and q at each occurrence is 0, 1, or 2.

4. The compound of claim 1 wherein Ar_1 is phenyl or phenyl substituted with amino,

5. The compound of claim 1, wherein n2 is 1.

6. The compound of claim 1, or a pharmaceutically acceptable salt, ester, amide, or prodrug thereof, selected from the group consisting of:

5'-phenyl-3'H-spiro[4-azabicycio[2.2.2]octane-2,2'-[1]benzofuran];
5',7'-diphenyl-3'H-spiro[4-azabicyclo[2.2.2]octane-2,2'-[1]benzofuran];
3-(3'H-spiro[4-azabicyclo[2.2.2]octane-2,2'-[1]benzofuranl-5'-yl)aniline;
5'-phenoxy-3'H-spiro[4-azabicyclo[2.2.2]octane-2,2'-[1]benzofuran];
5',7'-diphenoxy-3'H-spiro[4-azabicyclo[2.2.2]octane-2,2-[1]benzofuran];
7'-bromo-5'-phenoxy-3'H-spiro[4-azabicyclo[2.2.2]octane-2,2'-[1]benzofuran];

N-phenyl-3'H-spiro[4-azabicyclo[2.2.2]octane-2,2'-[1]benzofuran]-5'-amine;
N,N'-diphenyl-3'H-spiro[4-azabicyclo[2.2.2]octane-2,2'[1]benzofuran]-5',7'-diamine; and
5'-(1H-indol-5-yl)-3'H-spiro[4-azabicyclo[2.2.2]octane-2,2'-[1]benzofuran].

7. A pharmaceutical composition comprising a therapeutically effective amount of a compound of claim 1 in combination with a pharmaceutically acceptable carrier.

8. A compound of claim 1 for use in selectively modulating the effects of $\alpha 7$ nicotinic acetylcholine receptors in a mammal by administering an effective amount of said compound of claim 1.

9. A compound of claim 1 for use in treating a condition or disorder modulated by an $\alpha 7$ nicotinic acetylcholine receptor by administering said compound of claim 1.

10. The compound according to claim 9, wherein the condition or disorder is selected from the group consisting of attention deficit disorder, attention deficit hyperactivity disorder (ADHD), Alzheimer's disease (AD), mild cognitive impairment, senile dementia, AIDS dementia, Pick's Disease, dementia associated with Lewy bodies, dementia associated with Down's syndrome, amyotrophic lateral sclerosis, Huntington's disease, diminished CNS function associated with traumatic brain injury, acute pain, post-surgical pain, chronic pain, inflammatory pain, neuropathic pain, infertility, need for new blood vessel growth associated with wound healing, need for new blood vessel growth associated with vascularization of skin grafts, and lack of circulation, more particularly circulation around a vascular occlusion.

11. The compound according to claim 9, wherein the condition or disorder is selected from the group consisting of a cognitive disorder, neurodegeneration, and schizophrenia.

12. The compound according to claim 9, wherein said compound of claim 1 is in combination with an atypical antipsychotic.

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EUROPEAN SEARCH REPORT

Application Number
EP 10 17 5488

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Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (IPC)
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The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
Munich	15 October 2010	Bakboord, Joan

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