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(54) **ARYL FUSED AZAPOLYCYCLIC COMPOUNDS**

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(51) **Int. Cl.**[7] **A61K 31/44**; A61K 31/505; C07D 221/22; C07D 413/00; A61P 1/00

(52) **U.S. Cl.** **514/289**; 514/210.21; 514/228.2; 514/232.8; 514/253.02; 514/253.03; 514/256; 514/281; 514/295; 546/43; 546/74; 546/97; 544/58.2; 544/60; 544/125; 544/126; 544/242; 544/361

(58) **Field of Search** 546/43, 74, 97; 544/58.2, 60, 125, 126, 242, 361; 514/210.21, 228.2, 232.8, 253.02, 253.03, 256, 281, 289, 295

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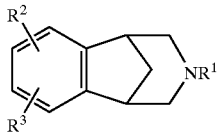
(57) **ABSTRACT**

Compounds of the formula

(I)



and their pharmaceutically acceptable salts, wherein R^1, R^2, and R^3 are defined as in the specification, intermediates in the synthesis of such compounds. pharmaceutical compositions containing such compounds and methods of using such compounds, in the treatment of neurological and psychological disorders.

15 Claims, No Drawings

ARYL FUSED AZAPOLYCYCLIC COMPOUNDS

This application is a national stage entry under 35 U.S.C. §371 of PCT/IB98/01813, filed Nov. 13, 1998 which claims the benefit of U.S. Provisional Application Ser. No. 60/070,245, filed Dec. 31, 1997.

BACKGROUND OF THE INVENTION

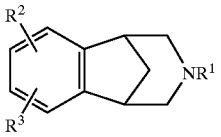
This invention relates to aryl fused azapolycyclic compounds, as defined more specifically by formula I below. Compounds of formula I bind to neuronal nicotinic acetylcholine specific receptor sites and are useful in modulating cholinergic function. Such compounds are useful in the treatment of inflammatory bowel disease (including but not limited to ulcerative colitis, pyoderma gangrenosum and Crohn's disease), irritable bowel syndrome, spastic dystonia, chronic pain, acute pain, celiac sprue, pouchitis, vasoconstriction, anxiety, panic disorder, depression, bipolar disorder, autism, sleep disorders, jet lag, amyotrophic lateral sclerosis (ALS), cognitive dysfunction, hypertension, bulimia, anorexia, obesity, cardiac, arrythmias, gastric acid hypersecretion, ulcers, pheochromocytoma, progressive supranuclear palsy, chemical dependencies and addictions (e.g., dependencies on, or addictions to nicotine (and/or tobacco products), alcohol, benzodiazepines, barbiturates, opioids or cocaine), headache, stroke, traumatic brain injury (TBI), obsessive-compulsive disorder, psychosis, Huntington's Chorea, tardive dyskinesia, hyperkinesia, dyslexia, schizophrenia, multi-infarct dementia, age related cognitive decline, epilepsy, including petit mal absence epilepsy, senile dementia of the Alzheimer's type (AD), Parkinson's disease (PD), attention deficit hyperactivity disorder (ADHD) and Tourette's Syndrome.

The compounds of this invention may also be used in combination with an antidepressant such as, for example, a tricyclic antidepressant or a serotonin reuptake inhibiting antidepressant (SRI), in order to treat both the cognitive decline and depression associated with AD, PD, stroke, Huntington's Chorea or traumatic brain injury (TBI): in combination with muscarinic agonists in order to stimulate both central muscarinic and nicotinic receptors for the treatment, for example, of ALS, cognitive dysfunction, age related cognitive decline, AD, PD, stroke, Huntington's Chorea and TBI; in combination with neurotrophic factors such as NGF in order to maximize cholinergic enhancement for the treatment, for example, of ALS, cognitive dysfunction, age related cognitive decline, AD, PD stroke, Huntington's Chorea and TBI; or in combination with agents that slow or arrest AD such as cognition enhancers, amyloid aggregation inhibitors, secretase inhibitors, tau kinase inhibitors, neuronal antiinflammatory agents and estrogen-like therapy.

Other compounds that bind to neuronal nicotinic receptor sites are referred to in U.S. patent application Ser. No. 08/963,852, which was filed on Nov. 4, 1997 now U.S. Pat. No. 6,020,335. The foregoing application is owned in common with the present application, and is incorporated herein by reference in its entirety.

SUMMARY OF THE INVENTION

This invention relates to aryl fused azapolycyclic compounds of the formula



(I)

R^1 is hydrogen, $(C_1–C_6)$alkyl, unconjugated $(C_3–C_6)$ alkenyl, benzyl, $XC(=O)R^{13}$ or $—CH_2CH_2—O—(C_1–C_4)$alkyl;

R^2 and R^3 are selected, independently, from hydrogen, $(C_2–C_6)$alkenyl, $(C_2–C_6)$alkynyl, hydroxy, nitro, amino, halo, cyano, $—SO_q(C_1–C_6)$alkyl wherein q is zero, one or two, $(C_1–C_6)$alkylamino-, $[(C_1–C_6)\text{alkyl}]_2$amino-, $—CO_2R^4$, $—CONR^5R^6$, $—SO_2NR^7R^8$, $—C(=O)R^{13}$ $—XC(=O)R^{13}$, aryl-$(C_0–C_3)$alkyl- or aryl-$(C_0–C_3)$alkyl-O—, wherein said aryl is selected from phenyl and naphthyl, heteroaryl-$(C_0–C_3)$alkyl- or heteroaryl-$(C_0–C_3)$alkyl-O—, wherein said heteroaryl is selected from five to seven membered aromatic rings containing from one to four heteroatoms selected from oxygen, nitrogen and sulfur, and $X^2(C_0–C_6)$alkoxy-$(C_0–C_6)$alkyl-, wherein X^2 is absent or X^2 is $(C_1–C_6)$ alkylamino- or $[(C_1–C_6)\text{alkyl}]_2$amino-, and wherein the $(C_0–C_6)$alkoxy-$(C_0–C_6)$alkyl- moiety of said $X^2(C_0–C_6)$alkoxy-$(C_0–C_6)$alkyl- contains at least one carbon atom, and wherein from one to three of the carbon atoms of said $(C_0–C_6)$alkoxy-$(C_0–C_6)$alkyl- moiety may optionally be replaced by an oxygen, nitrogen or sulfur atom, with the proviso that any two such heteroatoms must be separated by at least two carbon atoms, and wherein any of the alkyl moieties of said $(C_0–C_6)$alkoxy-$(C_0–C_6)$alkyl- may be optionally substituted with from two to seven fluonne atoms, and wherein one of the carbon atoms of each of the alkyl moieties of said aryl-$(C_0–C_3)$alkyl- and said heteroaryl-$(C_0–C_3)$alkyl- may optionally be replaced by an oxygen, nitrogen or sulfur atom, and wherein each of the foregoing aryl and heteroaryl groups may optionally be substituted with one or more substituents, preferably from zero to two substituents, independently selected from $(C_1–C_6)$alkyl optionally substituted with from one to seven fluonne atoms, $(C_1–C_6)$alkoxy optionally substituted with from two to seven fluorine atoms, halo (e.g., chloro, fluoro, bromo or iodo), $(C_2–C_6)$alkenyl, $(C_2–C_6)$alkynyl, hydroxy, nitro, cyano, amino, $(C_1–C_6)$-, $[(C_1–C_6)\text{alkyl}]_2$amino-, $—CO_2R^4$, $—CONR^5R^6$, $—SO_2NR^7R^8$, $—C(=O)R^{13}$ and $—XC(=O)R^{13}$;

or R^2 and R^3, together with the carbons to which they are attached, form a four to seven membered monocyclic, or a ten to fourteen membered bicyclic, carbocyclic ring that can be saturated or unsaturated, wherein from one to three of the nonfused carbon atoms of said monocyclic rings, and from one to five of the carbon atoms of said bicyclic rings that are not part of the benzo ring shown in formula I, may optionally and independently be replaced by a nitrogen, oxygen or sulfur, and wherein said monocyclic and bicyclic rings may optionally be substituted with one or more substituents, preferably from zero to two substituents for the monocyclic rings and from zero to three substituents for the bicyclic rings, that are selected, independently, from $(C_0–C_6)$alkoxy-$(C_0–C_6)$alkyl-, wherein the total number of carbon atoms does not

exceed six and wherein any of the alkyl moieties may optionally be substituted with from one to seven fluorine atoms; nitro, oxo, cyano, halo, $(C_2–C_6)$alkenyl, $(C_2–C_6)$alkynyl, hydroxy, amino, $(C_1–C_6)$alkylamino-, $[(C_1–C_6)alkyl]_2$amino-, $—CO_2R^4$, $—CONR^5R^6$, $—SO_2NR^7R^8$, $—C(=O)R^{13}$, and $—XC(=O)R^{13}$;

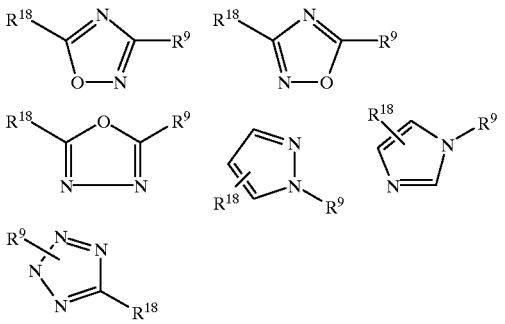
each R^4, R^5, R^6, R^7, R^8 and R^{13} is selected, independently, from hydrogen and $(C_1–C_6)$ alkyl, or R^5 and R^6, or R^7 and R^8 together with the nitrogen to which they are attached, form a pyrrolidine, piperidine, morpholine, azetidine, piperazine, —N—$(C_1–C_6)$alkylpiperazine or thiomorpholine ring, or a thiomorpholine ring wherein the ring sulfur is replaced with a sulfoxide or sulfone; and

each X is, independently, $(C_1–C_6)$alkylene:

with the proviso that: (a) at least one of R^1, R^2 and R^3 must be the other than hydrogen, and (b) when R^2 and R^3 are hydrogen, R^1 cannot be methyl or hydrogen;

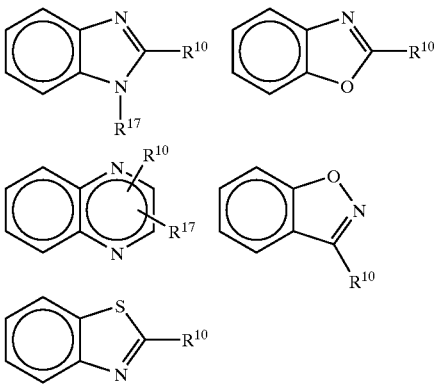
and the pharmaceutically acceptable salts of such compounds.

Examples of heteroaryl groups that each of R^2 and R^3 can be are the following: thienyl, oxazoyl, isoxazolyl, pyridyl, pyrimidyl, thiazolyl, tetrazolyl, isothiazolyl, triazolyl, imidazolyl, tetrazolyl, pyrroyl and the following groups:



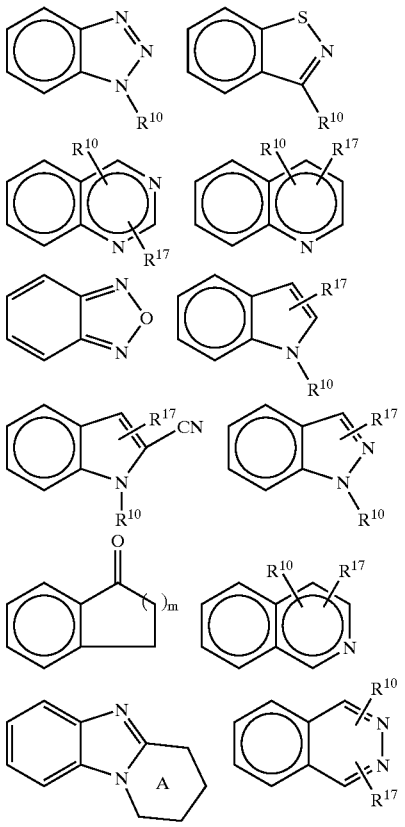
wherein one of R^9 and R^{18} is hydrogen or $(C_1–C_6)$alkyl, and the other is a bond to the benzo ring of formula I.

Examples of compounds of this invention are compounds of the formula I, and their pharmaceutically acceptable salts, wherein R^2 and R^3, together with the benzo ring of formula I, form a bicyclic ring system selected from the following:



wherein R^{10} and R^{17} are selected, independently, from $(C_0–C_6)$alkoxy-$(C_0–C_6)$alkyl- wherein the total number of carbon atoms does not exceed six and wherein any of the alkyl moieties may optionally be substituted with from one to seven fluorine atoms; nitro, cyano, halo, amino, $(C_1–C_6)$ alkylamino-, $[(C_1–C_6)$ alkyl$]_2$amino-, $—CO_2R^4$, $—CONR^5R^6$, $—SO_2NR^7R^8$, $—C(=O)R^{13}$ $—XC(=O)R^{13}$, phenyl and monocyclic heteroaryl wherein said heteroaryl is defined as R^2 and R^3 are defined in the definition of compounds of the formula I above;

Other embodiments of this invention relate to compounds of the formula I, and their pharmaceutically acceptable salts, wherein R^2 and R^3, together with the benzo ring of formula I, form a bicyclic or tricyclic ring system selected from the following:



wherein R^{10} and R^{17} are defined as above and m is zero, one or two, and wherein one of the carbon atoms of ring A can optionally be replaced with oxygen or $—N(C_1–C_6)$alkyl.

Other embodiments of this invention relate to compounds of the formula I, and their pharmaceutically acceptable salts, wherein neither R^2 nor R^3 is attached to the benzo ring of formula I via an oxygen atom.

Other embodiments of this invention relate to compounds of the formula I, and their pharmaceutically acceptable salts, wherein R^2 and R^3 do not, together with the benzo ring of formula I, form a bicyclic or tricyclic ring system.

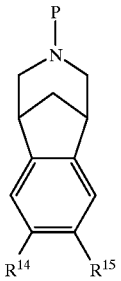
Other embodiments of this invention relate to compounds of the formula I wherein one or both of R^2 and R^3 are $—C(=O)R^{13}$, wherein R^{13} is $(C_1–C_6)$alkyl. Further embodiments of this invention relate to compounds of the formula I wherein one or both of R^2 and R^3 are $—C(=O)R^{13}$, wherein R^{13} is $(C_1–C_6)$alkyl or $(C_1–C_3)$alkyl optionally substituted with from one to seven fluorine atoms. Other embodiments relate to compounds of the formula I wherein one of R^2 and R^3 is CF_3, fluoro, cyano or C_2F_5.

Other embodiments of this invention relate to compounds of the formula I wherein R^1 is not methyl.

Examples of specific compounds of the formula I are the following:

6-methyl-5,7-dioxo-6,13-diazatetracyclo[9.3 1.0^{2,10}.0^{4,8}] pentadeca-2(10),3,8-triene hydrochloride;
6-methyl-5-oxo-6,13-diazatetracyclo[9.3.1.0^{2,10}.0^{4,8}] pentadeca-2(10),3,8-triene hydrochloride;
5,7-dimethyl-6-oxo-5,7,13-triazatetracyclo[9.3.1.0^{2,10}.0^{4,8}] pentadeca-2(10),3,8-triene hydrochloride;
5,7-dioxo-6,13-diazatetracyclo[9.3.1.0^{2,10}.0^{4,8}]pentadeca-2 (10),3,8-triene hydrochloride;
5-oxo-6,13-diazatetracyclo[9.3.1.0^{2,10}.0^{4,8}]pentadeca-2 (10),3,8-triene hydrochloride:
6-oxo-5,7,13-triazatetracyclo[9.3.1.0^{2,10}.0^{4,8}]pentadeca-2 (10),3,8-triene hydrochloride;
4,5-difluoro-10-aza-tricyclo[6.3.1.0^{2,7}]dodeca-2(7),3,5-triene hydrochloride;
5-fluoro-10-aza-tricyclo[6.3.1.0^{2,7}]dodeca-2(7),3,5-triene-4-carbonitrile hydrochloride;
4-ethynyl-5-fluoro-10-aza-tricyclo[6.3.1.0^{2,7}]dodeca-2(7), 3,5-triene hydrochloride;
5-ethynyl-10-aza-tricyclo[6.3.1.0^{2,7}]dodeca-2(7),3,5-triene-4-carbonitrile hydrochloride;
4-ethynyl-5-chloro-10-aza-tricyclo[6.3.1.0^{2,7}]dodeca-2(7), 3,5-triene-4-carbonitrile hydrochloride;
4-ethynyl-5-chloro-10-aza-tricyclo[6.3.1.0^{2,7}]dodeca-2(7), 3,5-triene hydrochloride.
5-oxa-7-methyl-6-oxo-7,13-diazatetracyclo[9.3.1.0^{2,10}.0^{4,8}] pentadeca-2(10),3,8-triene hydrochloride;
4-fluoro-5-trifluoromethyl-10-aza-tricyclo[6.3.1.0^{2,7}] dodeca-2(7),3,5-triene hydrochloride;
4-chloro-5-trifluoromethyl-10-aza-tricyclo[6.3.1.0^{2,7}] dodeca-2(7),3,5-triene hydrochloride;
5-trifluoromethyl-10-aza-tricyclo[6.3.1.0^{2,7}]dodeca-2(7),3, 5-triene-4-carbonitrile hydrochloride:
4-ethynyl-5-trifluoromethyl-10-aza-tricyclo[6.3.1.0^{2,7}] dodeca-2(7),3,5-triene hydrochloride.
6-methyl-5-thia-5-dioxa-6,13-Diazatetracyclo[9.3.1.0^{2,10}.0^{4,8}]pentadeca-2(10),3,8-triene hydrochloride;
7-dimethylamino-5-thia-5-dioxa-6,13-Diazatetracyclo [9.3.1.0^{2,10}.0^{4,8}]pentadeca-2(10),3,8-triene hydrochloride;
6,7-dioxa-5,8,14-triazatetracyclo[10.3.1.0^{2,11}.0^{4,9}] hexadeca-2(11),3,9-triene hydrochloride; and
5,8-dimethyl-6,7-dioxa-5,8,14-triazatetracyclo[10.3.1.0^{2,11}.0^{4,9}]hexadeca-2(11),3,9-triene hydrochloride.

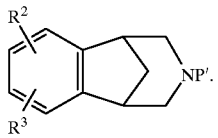
This invention also relates to compounds of the formula



wherein P is hydrogen, methyl, COOR^{16} wherein R^{16} is (C_1–C_6)alkyl, allyl, 2^{2,2,2}-trichloroethyl or (C_1–C_6)alkyl; —C(═O)NR^{5}R^6 wherein R^5 and R^6 are defined as in formula I above; —C(═O)H, —C(═O)(C_1–C_6)alkyl wherein the alkyl moiety may optionally be substituted with from 1 to 3 halo atoms, preferably with from 1 to 3 fluoro or chloro atoms; benzyl or t-butoxycarbonyl (t-Boc); and R^{14} and R^{15} are selected independently from hydrogen (C_1–C_6)alkyl optionally substituted with from one to seven fluorine atoms; —C(═O)(C_1–C_6)alkyl, cyano, hydroxy, nitro, amino, —O(C_1–C_6)alkyl or halo: with the proviso that R^{14} and R^{15} can not both be hydrogen when P is hydrogen or methyl. Such compounds are useful as intermediates in the synthesis of compounds of the formula I.

The invention also relates to a compound of the formula

(I′)



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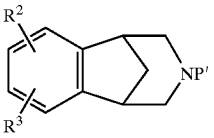


wherein R^2 and R^3 are defined above; and P' is COOR^{16} wherein R^{16} is allyl, 2,2,2-trichloroethyl or (C_1–C_6)alkyl; —C(═O)NR^{5}R^6 wherein R^5 and R^6 are defined as in claim 2; —C(═O)H, —C(═O)(C_1–C_6)alkyl wherein the alkyl moiety may optionally be substituted with from 1 to 3 halo atoms, preferably with from 1 to 3 fluoro or chloro atoms; benzyl, or t-butoxycarbonyl (t-Boc).

Unless otherwise indicated, the term "halo", as used herein, includes fluoro, chloro, bromo and iodo.

Unless otherwise indicated, the term "alkyl", as used herein, includes straight, branched or cyclic, and may include straight and cyclic alkyl moieties as well as branched and cyclic moieties.

The term "alkoxy", as used herein, means "alkyl-O—", wherein "alkyl" is defined as above.

The term "alkylene, as used herein, means an alkyl radical having two available bonding sites (i.e., -alkyl-), wherein "alkyl" is defined as above.

Unless otherwise indicated, the term "one or more substituents", as used herein, refers to from one to the maximum number of substituents possible based on the number of available bonding sites.

The term "treatment", as used herein, refers to reversing, alleviating, inhibiting the progress of, or preventing the disorder or condition to which such term applies, or one or more symptoms of such condition or disorder. The term "treatment", as used herein, refers to the act of treating, as "treating" is defined immediately above.

The compounds of formula I may have optical centers and therefore may occur in different enantiomeric configurations. The invention includes all enantiomers, diastereomers, and other stereoisomers of such compounds of formula I, as well as racemic and other mixtures thereof.

The present invention also relates to all radiolabeled forms of the compounds of the formula I. Preferred radiolabeled compounds of formula I are those wherein the radiolabels are selected from as ^{3}H, ^{11}C, ^{14}C, ^{18}F, ^{123}I and ^{125}I. Such radiolabeled compounds are useful as research and diagnostic tools in metabolism pharmacokinetics studies and in binding assays in both animals and man.

The present invention also relates to a pharmaceutical composition for use in reducing nicotine addiction or aiding in the cessation or lessening of tobacco use in a mammal, including a human, comprising an amount of a compound of the formula I or a pharmaceutically acceptable salt thereof

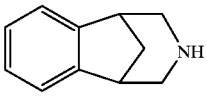
that is effective in reducing nicotine addiction or aiding in the cessation or lessening of tobacco use and a pharmaceutically acceptable carrier.

The present invention also relates to a method for reducing nicotine addiction or aiding in the cessation or lessening of tobacco use in a mammal, including a human, comprising administering to said mammal an amount of a compound of the formula I, or a pharmaceutically acceptable salt thereof, that is effective in reducing nicotine addiction or aiding in the cessation or lessening of tobacco use.

The present invention also relates to a method of treating a disorder or condition selected from inflammatory bowel disease (including but not limited to ulcerative colitis, pyoderma gangrenosum and Crohn's disease), irritable bowel syndrome, spastic dystonia, chronic pain, acute pain, celiac sprue, pouchitis, vasoconstriction, anxiety, panic disorder, depression, bipolar disorder, autism, sleep disorders, jet lag, amyotrophic lateral sclerosis (ALS), cognitive dysfunction, hypertension, bulimia, anorexia, obesity, cardiac arrythmias, gastric acid hypersecretion, ulcers, pheochromocytoma, progressive supranuclear, palsy, chemical dependencies and addictions (e.g., dependencies on, or addictions to nicotine (and/or tobacco products), alcohol, benzodiazepines, barbiturates, opioids or cocaine), headache, stroke, traumatic brain injury (TBI), obsessive-compulsive disorder (OCD), psychosis, Huntingon's Chorea, tardive dyskinesia, hyperkinesia, dyslexia, schizophrenia, multi-infarct dementia, age related cognitive decline, epilepsy, including petit mal absence epilepsy, senile dementia of the Alzheimer's type (AD), Parkinson's disease (PD), attention deficit hyperactivity disorder (ADHD) and Tourette's Syndrome in a mammal, comprising administering to a mammal in need of such treatment an amount of a compound of the formula I, or a pharmaceutically acceptable salt thereof, that is effective in treating such disorder or condition.

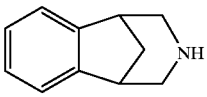
The present invention also relates to a pharmaceutical composition for treating a disorder or condition selected from inflammatory bowel disease (including but not limited to ulcerative colitis, pyoderma gangrenosum and Crohn's disease), irritable bowel syndrome, spastic dystonia, chronic pain, acute pain, celiac sprue, pouchitis, vasoconstriction, anxiety, panic disorder, depression, bipolar disorder, autism, sleep disorders, jet lag, amyotropic lateral sclerosis (ALS), cognitive dysfunction, hypertension, bulimia, anorexia, obesity, cardiac arrythmias, gastric acid hypersecretion, ulcers, pheochromocytoma, progressive supranuclear palsy, chemical dependencies and addictions (e.g., dependencies on, or addictions to nicotine (and/or tobacco products), alcohol, benzodiazepines, barbiturates, opioids or cocaine), headache, stroke, traumatic brain injury (TBI) obsessive-compulsive disorder (OCD), psychosis, Huntington's Chorea, tardive dyskinesia, hyperkinesia, dyslexia, schizophrenia, multi-infarct dementia, age related cognitive decline, epilepsy, including petit mal absence epilepsy, senile dementia of the Alzheimer's type (AD), Parkinson's disease (PD), attention deficit hyperactivity disorder (ADHD) and Tourette's Syndrome in a mammal, comprising an amount of a compound of the formula I, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

The present invention also relates to a method for reducing nicotine addiction or aiding in the cessation or lessening of tobacco use in a mammal, comprising administering to said mammal an amount of a compound comprising an amount of a compound of the formula



or a pharmaceutically acceptable salt thereof, that is effective in reducing nicotine addiction or aiding in the cessation or lessening of tobacco use.

The present invention also relates to a method for treating a disorder or condition selected from inflammatory bowel disease (including but not limited to ulcerative colitis, pyoderma gangrenosum and Crohn's disease), irritable bowel syndrome, spastic dystonia, chronic pain, acute pain, celiac sprue, pouchitis, vasoconstriction, anxiety, panic disorder, depression, bipolar disorder, autism, sleep disorders, jet lag, amyotrophic latera sclerosis (ALS), cognitive dysfunction, hypertension, bulimia, anorexia, obesity, cardiac arrythmias, gastric acid hypersecretion, ulcers, pheochromocytoma, progressive supranuclear palsy, chemical dependencies and addictions (e.g., dependencies on, or addictions to nicotine (and/or tobacco products), alcohol, benzodiazepines, barbituates, opioids or cocaine), headache, stroke, traumatic brain injury (TBI) obsessive-compulsive disorder (OCD), psychosis, Huntington's Chorea, tardive dyskinesia, hyperkinesia, dyslexia, schizophrenia, multi-infarct dementia, age related cognitive decline, epilepsy, including petit mal absence epilepsy, senile dementia of the Alzheimer's type (AD), Parkinson's disease (PD), attention deficit hyperactivity disorder (ADHD) and Tourette's Syndrome in a mammal, comprising administering to a mammal in need of such treatment an amount of a compound of the formula



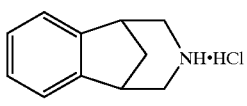
or a pharmaceutically acceptable salt thereof, that is effective in treating such disorder or condition.

This invention also relates to the pharmaceutically acceptable acid addition salts of the compounds of formula I. Examples of pharmaceutically acceptable acid addition salts of the compounds of formula I are the salts of hydrochlonc acid, p-toluenesulfonic acid, fumaric acid, citric acid, succinic acid, salicylic acid, oxalic acid, hydrobromic acid, phosphoric acid, methanesulfonic acid, tartaric acid, malate, di-p-toluoyl tartaric acid, and mandelic acid.

DETAILED DESCRIPTION OF THE INVENTION

Except where otherwise stated, R^1 through R^{18}, m and P, and structural formula I in the reaction schemes and discussion that follow are defined as above.

Scheme 1



III

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