NOVEL QUINUCLIDINE DERIVATIVES AND THEIR USE

TECHNICAL FIELD

This invention relates to novel quinuclidine derivatives and their use as pharmaceuticals. Due to their pharmacological profile the compounds of the invention may be useful for the treatment of diseases or disorders as diverse as those related to the cholinergic system of the central nervous system (CNS), the peripheral nervous system (PNS), diseases or disorders related to smooth muscle contraction, endocrine diseases or disorders, diseases or disorders related to neuro-degeneration, diseases or disorders related to inflammation, pain, and withdrawal symptoms caused by the termination of abuse of chemical substances.

BACKGROUND ART

The endogenous cholinergic neurotransmitter, acetylcholine, exerts its biological effect via two types of cholinergic receptors, the muscarinic Acetyl Choline Receptors (mAChR) and the nicotinic Acetyl Choline Receptors (nAChR).

It is well established that muscarinic acetylcholine receptors are of importance in relation to memory and cognition, and much research aimed at the development of agents for the treatment of memory related disorders have focused on the synthesis of muscarinic acetylcholine receptor modulators.

Indeed several CNS disorders can be attributed to a cholinergic deficiency, a dopaminergic deficiency, an adrenergic deficiency or a serotonergic deficiency.

Brown et al. [*Brown et al.*: Quinuclidine Inhibitors of 2,3-Oxidosqualene Cyclase-Lanosterol Synthase: Optimization from Lipid Profiles; J. Med. Chem. 1999 **42** 1306-1311] describe the synthesis of 3-substituted quinuclidine derivatives useful as inhibitors of the cholesterol biosynthesis. An effect on the nicotinic and/or the monoamine receptors is not reported.

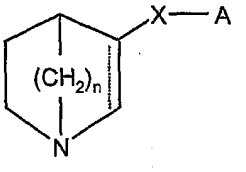
SUMMARY OF THE INVENTION

The present invention is devoted to the provision of new quinuclidine derivatives that are modulators of the nicotinic and/or of the monoamine receptors, and which modulators are useful for the treatment of diseases or disorders related to the cholinergic receptors, and in particular the nicotinic acetylcholine receptor, the monoamine receptors, in particular the serotonin receptor (5-HTR), the dopamine receptor (DAR) and the norepinephrine receptor (NER), and of the biogenic amine transporters for serotonin (5-HT), dopamine (DA) and norepinephrine (NE).

Due to their pharmacological profile the compounds of the invention may be useful for the treatment of diseases or disorders as diverse as those related to the cholinergic system of the central nervous system (CNS), the peripheral nervous system (PNS), diseases or disorders related to smooth muscle contraction, endocrine diseases or disorders, diseases or disorders related to neuro-degeneration, diseases or disorders related to inflammation, pain, and withdrawal symptoms caused by the termination of abuse of chemical substances.

The compounds of the invention may also be useful as diagnostic tools or monitoring agents in various diagnostic methods, and in particular for *in vivo* receptor imaging (neuroimaging), and they may be used in labelled or unlabelled form.

Accordingly, in its first aspect the invention provides quinuclidine derivatives represented by Formula I



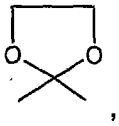
(I)

an enantiomer thereof, or a mixture of its enantiomers, or a pharmaceutically-acceptable addition salt thereof, or an onium salt thereof, wherein,

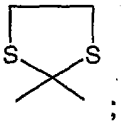
----- represents an optional double bond;

n is 1, 2 or 3;

X represents a linker selected from -O-, -O-CH_2-, -O-CH_2-CH_2-, -S-, -SO-, -SO_2-, -CH_2-, -S-CH_2-CH_2-, -CH_2-, -C(=CH_2)-,-NH-, -N(alkyl)-, -C(=O)-, -C(=S)-,



, and



; and

A represents a monocyclic or polycyclic, carbocyclic or heterocyclic group, optionally substituted one or more times with substituents selected from the group consisting of alkyl, cycloalkyl, cycloalkyl-alkyl, alkoxy, hydroxyalkoxy, alkoxy-alkyl, alkoxy-alkoxy, cycloalkoxy, cycloalkoxy-alkyl, cycloalkoxy-alkoxy, halo, CF_3, CN, NO_2, NH_2, carboxy, carbamoyl, amido, sulfamoyl, and phenyl, or with another monocyclic or polycyclic, carbocyclic or heterocyclic group, which additional monocyclic or polycyclic, carbocyclic or heterocyclic group may optionally be substituted one or more times with substituents selected from the group consisting of alkyl, cycloalkyl, cycloalkyl-alkyl, alkoxy, hydroxyalkoxy, alkoxy-alkyl, alkoxy-alkoxy, cycloalkoxy, cycloalkoxy-alkyl, cycloalkoxy-alkoxy, halo, CF_3, CN, NO_2, NH_2, carboxy, carbamoyl, amido, sulfamoyl, and phenyl;

provided, however,

if X represents O or S;

then A is not phenyl or phenyl substituted with anything other than a phenyl group (i.e. a biphenyl group).

In another aspect the invention provides pharmaceutical compositions comprising a therapeutically effective amount of the quinuclidine derivative of the invention.

In a third aspect the invention relates to the use of the quinuclidine derivative of the invention, or a pharmaceutically-acceptable addition salt thereof, for the manufacture of a pharmaceutical composition/medicament for the treatment, prevention or alleviation of a disease or a disorder or a condition of a mammal, including a human, which disease, disorder or condition is responsive to the action of a nicotinic acetylcholine receptor modulator.

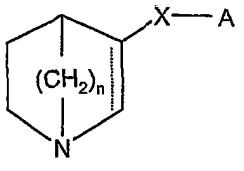
In a further aspect the invention provides a method of the treatment or alleviation of a disease or disorder of a living animal body, including a human, which disease or disorder is responsive to the action of a nicotinic acetylcholine receptor modulator, which method comprises the step of administering to such a living animal body, including a human, in need thereof a therapeutically effective amount of the quinuclidine derivative of the invention.

Other objects of the invention will be apparent to the person skilled in the art from the following detailed description and examples.

DETAILED DISCLOSURE OF THE INVENTION

Quinuclidine Derivatives

In its first aspect, the present invention provides novel quinuclidine derivatives represented by Formula I



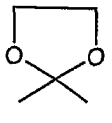
(I)

an enantiomer thereof, or a mixture of its enantiomers, or a pharmaceutically-acceptable addition salt thereof, or an onium salt thereof, wherein,

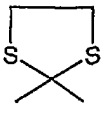
------ represents an optional double bond;

n is 1, 2 or 3;

X represents a linker selected from -O-, -O-CH_2-, -O-CH_2-CH_2-, -S-, -SO-, -SO_2-, -CH_2-, -S-CH_2-CH_2-, -CH_2-, -C(=CH_2)-,-NH-, -N(alkyl)-, -C(=O)-, -C(=S)-,



, and



; and

A represents a monocyclic or polycyclic, carbocyclic or heterocyclic group, optionally substituted one or more times with substituents selected from the group consisting of alkyl, cycloalkyl, cycloalkyl-alkyl, alkoxy, hydroxyalkoxy, alkoxy-alkyl, alkoxy-alkoxy, cycloalkoxy, cycloalkoxy-alkyl, cycloalkoxy-alkoxy, halo, CF_3, CN, NO_2, NH_2, carboxy, carbamoyl, amido, sulfamoyl, and phenyl, or with another monocyclic or polycyclic, carbocyclic or heterocyclic group, which additional monocyclic or polycyclic, carbocyclic or heterocyclic group may optionally be substituted one or more times with substituents selected from the group consisting of alkyl, cycloalkyl, cycloalkyl-alkyl, alkoxy, hydroxyalkoxy, alkoxy-alkyl, alkoxy-alkoxy, cycloalkoxy, cycloalkoxy-alkyl, cycloalkoxy-alkoxy, halo, CF_3, CN, NO_2, NH_2, carboxy, carbamoyl, amido, sulfamoyl, and phenyl;

provided, however,

if X represents O or S;

then A is not phenyl or phenyl substituted with anything other than a phenyl group (i.e. if X represents O or S, and A represents a phenyl group, then this phenyl group must be a biphenyl group only).

In a preferred embodiment the quinuclidine derivative of the invention is a compound of Formula I, wherein ----- represents a single (covalent) bond.

In another preferred embodiment the quinuclidine derivative of the invention is a compound of Formula I, wherein n is 1, 2 or 3.

In a third preferred embodiment the quinuclidine derivative of the invention is a compound of Formula I, wherein X represents a linker selected from -O-, $-O-CH_2-$, $-O-CH_2-CH_2-$, -S-, and $-CH_2-$. In a more preferred embodiment X represents a linker selected from -O-, $-O-CH_2-$, and $-O-CH_2-CH_2-$.

In a fourth preferred embodiment the quinuclidine derivative of the invention is a compound of Formula I, wherein A represents a monocyclic or polycyclic carbocyclic group selected from phenyl; indanyl, in particular 4-indanyl and 5-indanyl; indenyl, in particular 1-indenyl, 2-indenyl and 3-indenyl; naphthyl, in particular 1-naphthyl and 2-naphthyl; 5,6,7,8-tetrahydro-naphthyl, in particular 5,6,7,8-tetrahydro-1-naphthyl and 5,6,7,8-tetrahydro-2-naphthyl; azulenyl, in particular 1-azulenyl, 2-azulenyl and 3-azulenyl; and fluorenyl, in particular 1-fluorenyl, 2-fluorenyl, 3-fluorenyl and 4-fluorenyl; and anthracenyl, in particular 1-anthracenyl and 2-anthracenyl; which carbocyclic group is optionally substituted one or two times with substituents selected from the group consisting of alkyl, cycloalkyl, cycloalkyl-alkyl, alkoxy, hydroxyalkoxy, alkoxy-alkyl, alkoxy-alkoxy, cycloalkoxy, cycloalkoxy-alkyl, cycloalkoxy-alkoxy, halo, CF_3, CN, NO_2, NH_2, carboxy, carbamoyl, amido, sulfamoyl, and phenyl.

In a fifth preferred embodiment the quinuclidine derivative of the invention is a compound of Formula I, wherein A represents an aromatic monocyclic or polycyclic carbocyclic group selected from phenyl; indenyl, in particular 1-indenyl, 2-indenyl and

3-indenyl; naphthyl, in particular 1-naphthyl and 2-naphthyl; azulenyl, in particular 1-azulenyl, 2-azulenyl and 3-azulenyl; and anthracenyl, in particular 1-anthracenyl and 2-anthracenyl; which aromatic carbocyclic group is optionally substituted one or two times with substituents selected from the group consisting of alkyl, cycloalkyl, cycloalkyl-alkyl, alkoxy, hydroxyalkoxy, alkoxy-alkyl, alkoxy-alkoxy, cycloalkoxy, cycloalkoxy-alkyl, cycloalkoxy-alkoxy, halo, CF_3, CN, NO_2, NH_2, carboxy, carbamoyl, amido, sulfamoyl, and phenyl.

In a most preferred embodiment the quinuclidine derivative of the invention of Formula I is

(±)-3-(2-Phenylphenyloxy)-1-aza-bicyclo[2.2.2]octane;
(±)-3-(3-Phenylphenyloxy)-1-aza-bicyclo[2.2.2]octane;
(±)-3-(4-Phenylphenyloxy)-1-aza-bicyclo[2.2.2]octane;
(±)-3-(4-Phenylphenyl-methoxy)-1-aza-bicyclo[2.2.2]octane;
(±)-3-(Naphthalen-2-yloxy)-1-aza-bicyclo[2.2.2]octane;
(±)-3-(5,6,7,8-Tetrahydro-2-naphthyloxy)-1-aza-bicyclo[2.2.2]octane; or
(±)-3-(5-Indanyloxy)-1-aza-bicyclo[2.2.2]octane;

or an enantiomer thereof, or a pharmaceutically-acceptable addition salt thereof, or an onium salt thereof.

In a sixth preferred embodiment the quinuclidine derivative of the invention is a compound of Formula I, wherein A represents a monocyclic or polycyclic heterocyclic group selected from pyridyl, in particular pyrid-2-yl, pyrid-3-yl and pyrid-4-yl; thienyl, in particular thien-2-yl and thien-3-yl; furanyl, in particular furan-2-yl and furan-3-yl; pyridazinyl, in particular pyridazin-3-yl and pyridazin-4-yl; thiazolyl, in particular thiazol-2-yl, thiazol-4-yl and thiazol-5-yl; thiadiazolyl, in particular 1,3,4-thiadiazol-2-yl, 1,3,4-thiadiazol-5-yl, 1,2,4-thiadiazol-3-yl and 1,2,4-thiadiazol-5-yl; quinolinyl, in particular quinolin-2-yl, quinolin-3-yl, quinolin-4-yl, quinolin-5-yl and quinolin-6-yl; quinoxalinyl, in particular quinoxalin-2-yl and quinoxalin-3-yl; benzimidazolyl, in particular benzimidazol-2-yl; benzoxazolyl, in particular benzoxazol-2-yl; benzthiazolyl, in particular benzthiazol-2-yl; which monocyclic or polycyclic heterocyclic group is optionally substituted one or more times with substituents selected from the group consisting of alkyl, cycloalkyl, cycloalkyl-alkyl, alkoxy, hydroxyalkoxy, alkoxy-alkyl, alkoxy-alkoxy, cycloalkoxy, cycloalkoxy-alkyl, cycloalkoxy-alkoxy, halo, CF_3, CN, NO_2, NH_2, carboxy, carbamoyl, amido, sulfamoyl, and phenyl, or with another monocyclic or polycyclic, carbocyclic or heterocyclic group, which additional monocyclic or polycyclic, carbocyclic or heterocyclic group may optionally be substituted one or more times with substituents selected from the group consisting of alkyl, cycloalkyl, cycloalkyl-alkyl, alkoxy, hydroxyalkoxy, alkoxy-alkyl, alkoxy-alkoxy, cycloalkoxy, cycloalkoxy-alkyl, cycloalkoxy-alkoxy, halo, CF_3, CN, NO_2, NH_2, carboxy, carbamoyl, amido, sulfamoyl, and phenyl.

In a seventh preferred embodiment the quinuclidine derivative of the invention is a compound of Formula I, wherein A represents a monocyclic heterocyclic group selected from pyridyl, in particular pyrid-2-yl, pyrid-3-yl and pyrid-4-yl; thienyl, in particular thien-2-yl and thien-3-yl; furanyl, in particular furan-2-yl and furan-3-yl; pyridazinyl, in particular pyridazin-3-yl and pyridazin-4-yl; thiazolyl, in particular thiazol-2-yl, thiazol-4-yl and thiazol-5-yl; thiadiazolyl, in particular 1,3,4-thiadiazol-2-yl, 1,3,4-thiadiazol-5-yl, 1,2,4-thiadiazol-3-yl and 1,2,4-thiadiazol-5-yl; which monocyclic heterocyclic group is optionally substituted one or more times with substituents selected from the group consisting of alkyl, cycloalkyl, alkoxy, cycloalkoxy, halo, CF_3, CN, NO_2, NH_2, phenyl, 2-thienyl, 3-thienyl, 2-furanyl, 3-furanyl, and 3-pyridinyl, which phenyl, 2-thienyl, 3-thienyl, 2-furanyl, 3-furanyl, and 3-pyridinyl groups may optionally be substituted one or two times with substituents selected from the group consisting of alkyl, cycloalkyl, alkoxy, halo, CF_3, CN, NO_2, NH_2, and phenyl.

In a most preferred embodiment the quinuclidine derivative of the invention of Formula I is

(±)-3-(3,4,5-Trichloro-thien-2-yloxy)-1-aza-bicyclo[2.2.2]octane;
(±)-3-(5-Bromo-thiazol-2-yloxy)-1-aza-bicyclo[2.2.2]octane;
(±)-3-(5-Phenyl-thiazol-2-yloxy)-1-aza-bicyclo[2.2.2]octane;
(±)-3-[5-(2,4-Difluoro-phenyl)-thiazol-2-yloxy]-1-aza-bicyclo[2.2.2]octane;
(±)-3-[5-(3-Thienyl)-thiazol-2-yloxy]-1-aza-bicyclo[2.2.2]octane;
(±)-3-[5-(2-Thienyl)-thiazol-2-yloxy]-1-aza-bicyclo[2.2.2]octane;
(±)-3-[5-(3-Furanyl)-thiazol-2-yloxy]-1-aza-bicyclo[2.2.2]octane;
(±)-3-[5-(3-Pyridyl)-thiazol-2-yloxy]-1-aza-bicyclo[2.2.2]octane;
(±)-3-(6-Chloro-pyridazin-3-yloxy)-1-aza-bicyclo[2.2.2]octane;
(±)-3-(6-Bromo-pyridazin-3-yloxy)-1-aza-bicyclo[2.2.2]octane;
(±)-3-(6-Phenyl-pyridazin-3-yloxy)-1-aza-bicyclo[2.2.2]octane;
(±)-3-[6-(3-Thienyl)-pyridazin-3-yloxy]-1-aza-bicyclo[2.2.2]octane;
(±)-3-[6-(2-Thienyl)-pyridazin-3-yloxy]-1-aza-bicyclo[2.2.2]octane;
(±)-3-[6-(2-Furanyl)-pyridazin-3-yloxy]-1-aza-bicyclo[2.2.2]octane;
(±)-3-[6-(3-Furanyl)-pyridazin-3-yloxy]-1-aza-bicyclo[2.2.2]octane;
(±)-3-[6-(3-Pyridyl)-pyridazin-3-yloxy]-1-aza-bicyclo[2.2.2]octane;
(±)-3-(5-Phenyl-1,3,4-thiadiazol-2-yloxy)-1-aza-bicyclo[2.2.2]octane;
(±)-3-(5-Phenyl-1,2,4-thiadiazol-3-yloxy)-1-aza-bicyclo[2.2.2]octane; or
(±)-3-[5-(2-Thienyl)-1,3,4-thiadiazol-2-yloxy]-1-aza-bicyclo[2.2.2]octane;

or an enantiomer thereof, or a pharmaceutically-acceptable addition salt thereof, or an onium salt thereof.

In an eight preferred embodiment the quinuclidine derivative of the invention is a compound of Formula I, wherein A represents a polycyclic heterocyclic group selected from indolyl, in particular indol-2-yl and indol-3-yl; isoindolyl, in particular

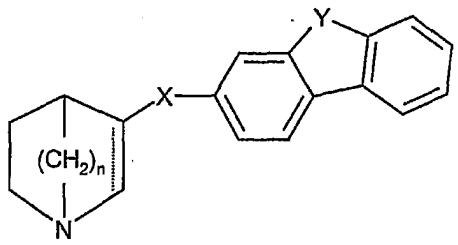
isoindol-2-yl; quinolinyl, in particular quinolin-2-yl, quinolin-3-yl, quinolin-4-yl, quinolin-5-yl and quinolin-6-yl; quinoxalinyl, in particular quinoxalin-2-yl and quinoxalin-3-yl; benzimidazolyl, in particular benzimidazol-2-yl; benzoxazolyl, in particular benzoxazol-2-yl; benzthiazolyl, in particular benzthiazol-2-yl; benzisothiazolyl, in particular benzisothiazol-3-yl; benztriazolyl, in particular 1,2,3-benztriazol-1-yl; imidazo[1,2-b]pyridazinyl, in particular imidazo[1,2-b]pyridazin-6-yl; dibenzofuranyl, in particular dibenzofuran-2-yl; which monocyclic or polycyclic heterocyclic group is optionally substituted one or more times with substituents selected from the group consisting of alkyl, cycloalkyl, alkoxy, cycloalkoxy, halo, CF_3, CN, NO_2, NH_2, and phenyl, which phenyl group may optionally be substituted one or more times with substituents selected from the group consisting of alkyl, cycloalkyl, alkoxy, halo, CF_3, CN, NO_2, NH_2, and phenyl.

In a most preferred embodiment the quinuclidine derivative of the invention of Formula I is

(±)-3-[(1,3-Dione)-2-isoindolyl-methoxy]-1-azabicyclo[2.2.2]octane;
(±)-3-[(1,3-Dione)-2-isoindolyl-ethoxy]-1-azabicyclo[2.2.2]octane;
(±)-3-(2-Quinolinyloxy)-1-aza-bicyclo[2.2.2]octane;
(±)-3-(2-Quinolinyloxy)-1-aza-bicyclo[2.2.2]octane methylium iodide;
(±)-3-(6-Quinolinyloxy)-1-aza-bicyclo[2.2.2]octane;
(±)-3-(2-Quinoxalinyloxy)-1-aza-bicyclo[2.2.2]octane;
(±)-3-(2-Quinoxalinyloxy)-1-aza-bicyclo[2.2.2]octane methylium iodide;
(±)-3-(3-Chloro-2-quinoxalinyloxy)-1-aza-bicyclo[2.2.2]octane;
(±)-3-(3-Methoxy-2-quinoxalinyloxy)-1-aza-bicyclo[2.2.2]octane;
(±)-3-(Benzoxazol-2-yloxy)-1-aza-bicyclo[2.2.2]octane;
(±)-3-(Benzothiazol-2-yloxy)-1-aza-bicyclo[2.2.2]octane;
(±)-3-(6-Chloro-benzothiazol-2-yloxy)-1-aza-bicyclo[2.2.2]octane;
(±)-3-(1,2-Benzoisothiazol-3-yloxy)-1-aza-bicyclo[2.2.2]octane;
(±)-3-(1,2-Benzoisothiazol-3-yloxy)-1-aza-bicyclo[2.2.2]octane;
(±)-3-(1-Methyl-benzoimidazol-2-yloxy)-1-aza-bicyclo[2.2.2]octane; or
(±)-3-(Benzotriazol-1-yloxy)-1-azabicyclo[2.2.2]octane;

or an enantiomer thereof, or a pharmaceutically-acceptable addition salt thereof, or an onium salt thereof.

In another preferred embodiment the quinuclidine derivative of the invention is a compound of Formula II



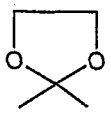
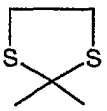
(II)

wherein

------ represents an optional double bond;

n is 1, 2 or 3;

X represents a linker selected from -O-, -O-CH_2-, -O-CH_2-CH_2-, -S-, -SO-, -SO_2-, -CH_2-, -S-CH_2-CH_2-, -CH_2-, -C(=CH_2)-,-NH-, -N(alkyl)-, -C(=O)-, -C(=S)-,

 , and  ; and

Y represents O, S, SO_2, or NR', wherein R' represents hydrogen or alkyl.

In a more preferred embodiment of this aspect the quinuclidine derivative of the invention is a compound of Formula II, wherein ----- represents a single (covalent) bond.

In another preferred embodiment of this aspect the quinuclidine derivative of the invention is a compound of Formula II, wherein n is 1, 2 or 3.

In a third preferred embodiment of this aspect the quinuclidine derivative of the invention is a compound of Formula II, wherein X represents a linker selected from -O-, -O-CH_2-, -O-CH_2-CH_2-, -S-, and -CH_2-.

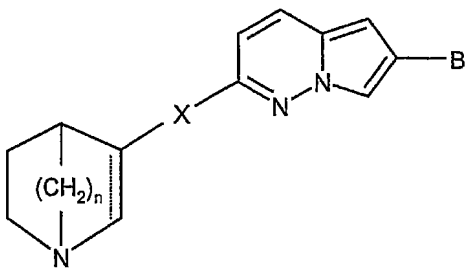
In a fourth preferred embodiment of this aspect the quinuclidine derivative of the invention is a compound of Formula II, wherein Y represents O, S, SO_2, or NR', wherein R' represents hydrogen or alkyl.

In a most preferred embodiment the quinuclidine derivative of the invention of Formula II is

(±)-3-(Dibenzofuran-2-yloxy)-1-azabicyclo[2.2.2]octane;

or an enantiomer thereof, or a pharmaceutically-acceptable addition salt thereof, or an onium salt thereof.

In yet another preferred embodiment the quinuclidine derivative of the invention is a compound of Formula III



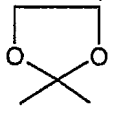
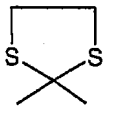
(III)

wherein

------ represents an optional double bond;

n is 1, 2 or 3;

X represents a linker selected from -O-, -O-CH_2-, -O-CH_2-CH_2-, -S-, -SO-, -SO_2-, -CH_2-, -S-CH_2-CH_2-, -CH_2-, -C(=CH_2)-,-NH-, -N(alkyl)-, -C(=O)-, -C(=S)-,

 , and  ; and

B represents a monocyclic or polycyclic, carbocyclic or heterocyclic group, optionally substituted one or more times with substituents selected from the group consisting of alkyl, cycloalkyl, cycloalkyl-alkyl, alkoxy, hydroxyalkoxy, alkoxy-alkyl, alkoxy-alkoxy, cycloalkoxy, cycloalkoxy-alkyl, cycloalkoxy-alkoxy, halo, CF_3, CN, NO_2, NH_2, carboxy, carbamoyl, amido, sulfamoyl, and phenyl, or with another monocyclic or polycyclic, carbocyclic or heterocyclic group, which additional monocyclic or polycyclic, carbocyclic or heterocyclic group may optionally be substituted one or more times with substituents selected from the group consisting of alkyl, cycloalkyl, cycloalkyl-alkyl, alkoxy, hydroxyalkoxy, alkoxy-alkyl, alkoxy-alkoxy, cycloalkoxy, cycloalkoxy-alkyl, cycloalkoxy-alkoxy, halo, CF_3, CN, NO_2, NH_2, carboxy, carbamoyl, amido, sulfamoyl, and phenyl.

In a more preferred embodiment of this aspect the quinuclidine derivative of the invention is a compound of Formula III, wherein ----- represents a single (covalent) bond.

In another preferred embodiment of this aspect the quinuclidine derivative of the invention is a compound of Formula III, wherein n is 1, 2 or 3.

In a third preferred embodiment of this aspect the quinuclidine derivative of the invention is a compound of Formula III, wherein X represents a linker selected from -O-, -O-CH_2-, -O-CH_2-CH_2-, -S-, and -CH_2-.

In a fourth preferred embodiment of this aspect the quinuclidine derivative of the invention is a compound of Formula III, wherein B represents a monocyclic or polycyclic, carbocyclic or heterocyclic group, optionally substituted one or more times with substituents selected from the group consisting of alkyl, cycloalkyl, cycloalkyl-alkyl, alkoxy, hydroxyalkoxy, alkoxy-alkyl, alkoxy-alkoxy, cycloalkoxy, cycloalkoxy-alkyl,

cycloalkoxy-alkoxy, halo, CF_3, CN, NO_2, NH_2, carboxy, carbamoyl, amido, sulfamoyl, and phenyl, or with another monocyclic or polycyclic, carbocyclic or heterocyclic group, which additional monocyclic or polycyclic, carbocyclic or heterocyclic group may optionally be substituted one or more times with substituents selected from the group consisting of alkyl, cycloalkyl, cycloalkyl-alkyl, alkoxy, hydroxyalkoxy, alkoxy-alkyl, alkoxy-alkoxy, cycloalkoxy, cycloalkoxy-alkyl, cycloalkoxy-alkoxy, halo, CF_3, CN, NO_2, NH_2, carboxy, carbamoyl, amido, sulfamoyl, and phenyl.

In a fifth preferred embodiment of this aspect the quinuclidine derivative of the invention is a compound of Formula III, wherein B represents a phenyl group, which phenyl is optionally substituted one or two times with substituents selected from the group consisting of alkyl, cycloalkyl, alkoxy, cycloalkoxy, halo, CF_3, CN, NO_2, NH_2, and phenyl.

In a most preferred embodiment the quinuclidine derivative of the invention of Formula III is

(±)-3-(2-Phenyl-imidazo[1,2-b]pyridazin-6-yloxy)-1-azabicyclo[2.2.2]octane;

or an enantiomer thereof, or a pharmaceutically-acceptable addition salt thereof, or an onium salt thereof.

Any combination of two or more of the embodiments described herein is considered within the scope of the present invention.

Definition of Substituents

In the context of this invention halo represents fluoro, chloro, bromo or iodo. Thus a trihalomethyl group represents e.g. a trifluoromethyl group, a trichloromethyl group, and similar trihalo-substituted methyl groups.

In the context of this invention an alkyl group designates a univalent saturated, straight or branched hydrocarbon chain. The hydrocarbon chain preferably contain of from one to eighteen carbon atoms (C_{1-18}-alkyl), more preferred of from one to six carbon atoms (C_{1-6}-alkyl; lower alkyl), including pentyl, isopentyl, neopentyl, tertiary pentyl, hexyl and isohexyl. In a preferred embodiment alkyl represents a C_{1-4}-alkyl group, including butyl, isobutyl, secondary butyl, and tertiary butyl. In another preferred embodiment of this invention alkyl represents a C_{1-3}-alkyl group, which may in particular be methyl, ethyl, propyl or isopropyl.

In the context of this invention a cycloalkyl group designates a cyclic alkyl group, preferably containing of from three to seven carbon atoms (C_{3-7}-cycloalkyl), including cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl.

In the context of this invention a cycloalkyl-alkyl group designates a cycloalkyl group as defined above, which cycloalkyl group is substituted on an alkyl group as also defined above. Examples of preferred cycloalkyl-alkyl groups of the invention include cyclopropylmethyl and cyclopropylethyl.

In the context of this invention an alkoxy group designates an "alkyl-O-" group, wherein alkyl is as defined above. Examples of preferred alkoxy groups of the invention include methoxy and ethoxy.

In the context of this invention a hydroxy-alkoxy group designates an alkoxy group as defined above, which alkoxy group is substituted with one or more hydroxy groups. Preferred hydroxy-alkoxy groups of the invention include 2-hydroxy-ethoxy, 3-hydroxy-propoxy, 4-hydroxy-butoxy, 5-hydroxy-pentoxy and 6-hydroxy-hexoxy.

In the context of this invention a cycloalkoxy group designates a "cycloalkyl-O-" group, wherein cycloalkyl is as defined above.

In the context of this invention an alkoxy-alkyl group designates an "alkyl-O-alkyl-" group, wherein alkyl is as defined above. Examples of preferred alkoxy-alkyl groups of the invention include methoxy-methyl, methoxy-ethyl, ethoxy-methyl, and ethoxy-ethyl.

In the context of this invention an alkoxy-alkoxy group designates an "alkyl-O-alkyl-O-" group, wherein alkyl is as defined above. Examples of preferred alkoxy-alkoxy groups of the invention include methoxy-methoxy, methoxy-ethoxy, ethoxy-methoxy, and ethoxy-ethoxy.

In the context of this invention a cycloalkoxy-alkyl group designates a "cycloalkyl-O-alkyl" group, wherein cycloalkyl and alkyl are as defined above.

In the context of this invention a cycloalkoxy-alkoxy group designates a "cycloalkyl-O-alkyl-O-" group, wherein cycloalkyl and alkyl are as defined above.

In the context of this invention a mono- or polycyclic carbocyclic group is a mono- or polycyclic carbocyclic group holding carbon only as ring atom. The ring structure may in particular be aromatic (i.e. an aryl group), or saturated or partially saturated.

Preferred mono- or polycyclic carbocyclic groups of the invention include phenyl; indanyl, in particular 4-indanyl and 5-indanyl; indenyl, in particular 1-indenyl, 2-indenyl and 3-indenyl; naphthyl, in particular 1-naphthyl and 2-naphthyl; 5,6,7,8-tetrahydro-naphthyl, in particular 5,6,7,8-tetrahydro-1-naphthyl and 5,6,7,8-tetrahydro-2-naphthyl; azulenyl, in particular 1-azulenyl, 2-azulenyl and 3-azulenyl; fluorenyl, in particular 1-fluorenyl, 2-fluorenyl, 3-fluorenyl and 4-fluorenyl; and anthracenyl, in particular 1-anthracenyl and 2-anthracenyl.

The mono- or polycyclic carbocyclic group may in particular be an aromatic group (aryl). Preferred aryl groups of the invention include phenyl; indenyl, in particular 1-indenyl, 2-indenyl and 3-indenyl; naphthyl, in particular 1-naphthyl and 2-naphthyl; azulenyl, in particular 1-azulenyl, 2-azulenyl and 3-azulenyl; and anthracenyl, in particular 1-anthracenyl and 2-anthracenyl.

In the context of this invention a mono- or polycyclic heterocyclic group is a mono- or polycyclic compound, which holds one or more heteroatoms in its ring

structure. The term poly-heterocyclic groups includes benzo-fused five- and six-membered heterocyclic rings containing one or more heteroatoms. Preferred heteroatoms include nitrogen (N), oxygen (O), and sulphur (S). One or more of the ring structures may in particular be aromatic (i.e. a heteroaryl).

Preferred monocyclic heterocyclic groups of the invention include pyridyl, in particular pyrid-2-yl, pyrid-3-yl and pyrid-4-yl; thienyl, in particular thien-2-yl and thien-3-yl; furanyl, in particular furan-2-yl and furan-3-yl; pyridazinyl, in particular pyridazin-3-yl and pyridazin-4-yl; thiazolyl, in particular thiazol-2-yl, thiazol-4-yl and thiazol-5-yl; and thiadiazolyl, in particular 1,3,4-thiadiazol-2-yl, 1,3,4-thiadiazol-5-yl, 1,2,4-thiadiazol-3-yl and 1,2,4-thiadiazol-5-yl.

Preferred polycyclic heterocyclic of the invention include indolyl, in particular indol-2-yl and indol-3-yl; isoindolyl, in particular isoindol-2-yl; quinolinyl, in particular quinolin-2-yl, quinolin-3-yl, quinolin-4-yl, quinolin-5-yl and quinolin-6-yl; quinoxalinyl, in particular quinoxalin-2-yl and quinoxalin-3-yl; benzimidazolyl, in particular benzimidazol-2-yl; benzoxazolyl, in particular benzoxazol-2-yl; benzthiazolyl, in particular benzthiazol-2-yl; benzisothiazolyl, in particular benzisothiazol-3-yl; benztriazolyl, in particular 1,2,3-benztriazol-1-yl; imidazo[1,2-b]pyridazinyl, in particular imidazo[1,2-b]pyridazin-6-yl; and dibenzofuranyl, in particular dibenzofuran-2-yl.

Pharmaceutically Acceptable Salts

The quinuclidine derivative of the invention may be provided in any form suitable for the intended administration. Suitable forms include pharmaceutically (i.e. physiologically) acceptable salts, and pre- or prodrug forms of the quinuclidine derivative of the invention.

Examples of pharmaceutically acceptable addition salts include, without limitation, the non-toxic inorganic and organic acid addition salts such as the hydrochloride derived from hydrochloric acid, the hydrobromide derived from hydrobromic acid, the nitrate derived from nitric acid, the perchlorate derived from perchloric acid, the phosphate derived from phosphoric acid, the sulphate derived from sulphuric acid, the formate derived from formic acid, the acetate derived from acetic acid, the aconate derived from aconitic acid, the ascorbate derived from ascorbic acid, the benzenesulphonate derived from benzensulphonic acid, the benzoate derived from benzoic acid, the cinnamate derived from cinnamic acid, the citrate derived from citric acid, the embonate derived from embonic acid, the enantate derived from enanthic acid, the fumarate derived from fumaric acid, the glutamate derived from glutamic acid, the glycolate derived from glycolic acid, the lactate derived from lactic acid, the maleate derived from maleic acid, the malonate derived from malonic acid, the mandelate derived from mandelic acid, the methanesulphonate derived from methane sulphonic acid, the naphthalene-2-sulphonate derived from naphtalene-2-sulphonic

acid, the phthalate derived from phthalic acid, the salicylate derived from salicylic acid, the sorbate derived from sorbic acid, the stearate derived from stearic acid, the succinate derived from succinic acid, the tartrate derived from tartaric acid, the toluene-p-sulphonate derived from p-toluene sulphonic acid, and the like. Such salts may be formed by procedures well known and described in the art.

Other acids such as oxalic acid, which may not be considered pharmaceutically acceptable, may be useful in the preparation of salts useful as intermediates in obtaining a chemical compound of the invention and its pharmaceutically acceptable acid addition salt.

Examples of pharmaceutically acceptable cationic salts of a chemical compound of the invention include, without limitation, the sodium, the potassium, the calcium, the magnesium, the zinc, the aluminium, the lithium, the choline, the lysine, and the ammonium salt, and the like, of a chemical compound of the invention containing an anionic group. Such cationic salts may be formed by procedures well known and described in the art.

In the context of this invention the "onium salts" of N-containing compounds are also contemplated as pharmaceutically acceptable salts (aza-onium salts). Preferred aza-onium salts include the alkyl-onium salts, in particular the methyl- and the ethyl-onium salts; the cycloalkyl-onium salts, in particular the cyclopropyl-onium salts; and the cycloalkylalkyl-onium salts, in particular the cyclopropyl-methyl-onium salts.

Steric Isomers

The quinuclidine derivatives of the present invention may exist in (+) and (-) forms as well as in racemic forms (±). The racemates of these isomers and the individual isomers themselves are within the scope of the present invention.

Racemic forms can be resolved into the optical antipodes by known methods and techniques. One way of separating the diastereomeric salts is by use of an optically active acid, and liberating the optically active amine compound by treatment with a base. Another method for resolving racemates into the optical antipodes is based upon chromatography on an optical active matrix. Racemic compounds of the present invention can thus be resolved into their optical antipodes, e.g., by fractional crystallisation of d- or l- (tartrates, mandelates, or camphorsulphonate) salts for example.

The quinuclidine derivatives of the present invention may also be resolved by the formation of diastereomeric amides by reaction of the chemical compounds of the present invention with an optically active activated carboxylic acid such as that derived from (+) or (-) phenylalanine, (+) or (-) phenylglycine, (+) or (-) camphanic acid

or by the formation of diastereomeric carbamates by reaction of the chemical compound of the present invention with an optically active chloroformate or the like.

Additional methods for the resolving the optical isomers are known in the art. Such methods include those described by *Jaques J, Collet A, & Wilen S* in "Enantiomers, Racemates, and Resolutions", John Wiley and Sons, New York (1981).

Optical active compounds can also be prepared from optical active starting materials.

Methods of Preparation

The quinuclidine derivatives of the invention may be prepared by conventional methods for chemical synthesis, e.g. those described in the working examples. The starting materials for the processes described in the present application are known or may readily be prepared by conventional methods from commercially available chemicals.

Also one compound of the invention can be converted to another compound of the invention using conventional methods.

The end products of the reactions described herein may be isolated by conventional techniques, e.g. by extraction, crystallisation, distillation, chromatography, etc.

Biological Activity

The present invention relates to novel quinuclidine derivatives, which are found to be cholinergic ligands at the nicotinic acetylcholine receptors (nAChR), and modulators of the monoamine receptors, in particular the biogenic amine transporters such as the serotonin receptor (5-HTR), the dopamine receptor (DAR) and the norepinephrine receptor (NER), and of the biogenic amine transporters for serotonin (5-HT), dopamine (DA) and norepinephrine (NE). Also preferred quinuclidine derivatives of the invention show selective α7 activity, as shown in the working examples. The compounds of the present invention may in particular be agonists, partial agonists, antagonists and allosteric modulators of the receptor.

Due to their pharmacological profile the quinuclidine derivatives of the invention may be useful for the treatment of diseases or conditions as diverse as CNS related diseases, PNS related diseases, diseases related to smooth muscle contraction, endocrine disorders, diseases related to neuro-degeneration, diseases related to inflammation, pain, and withdrawal symptoms caused by the termination of abuse of chemical substances.

In a preferred embodiment the quinuclidine derivatives of the invention are used for the treatment of diseases, disorders, or conditions relating to the central nervous system. Such diseases or disorders includes anxiety, cognitive disorders,

learning deficit, memory deficits and dysfunction, Alzheimer's disease, attention deficit, attention deficit hyperactivity disorder (ADHD), Parkinson's disease, Huntington's disease, Amyotrophic Lateral Sclerosis, Gilles de la Tourette's syndrome, psychosis, depression, mania, manic depression, schizophrenia, obsessive compulsive disorders (OCD), panic disorders, eating disorders such as anorexia nervosa, bulimia and obesity, narcolepsy, nociception, AIDS-dementia, senile dementia, periferic neuropathy, autism, dyslexia, tardive dyskinesia, hyperkinesia, epilepsy, bulimia, post-traumatic syndrome, social phobia, sleeping disorders, pseudodementia, Ganser's syndrome, pre-menstrual syndrome, late luteal phase syndrome, chronic fatigue syndrome, mutism, trichotillomania, and jet-lag.

In a preferred embodiment diseases, disorders, or conditions relating to the central nervous system for which the quinuclidine derivatives of the invention are used are cognitive disorders, psychosis, schizophrenia and/or depression.

In another preferred embodiment the quinuclidine derivatives of the invention may be useful for the treatment of diseases, disorders, or conditions associated with smooth muscle contractions, including convulsive disorders, angina pectoris, premature labour, convulsions, diarrhoea, asthma, epilepsy, tardive dyskinesia, hyperkinesia, premature ejaculation, and erectile difficulty.

In yet another preferred embodiment the quinuclidine derivatives of the invention may be useful for the treatment of endocrine disorders, such as thyrotoxicosis, pheochromocytoma, hypertension and arrhythmias.

In still another preferred embodiment the quinuclidine derivatives of the invention may be useful for the treatment of neurodegenerative disorders, including transient anoxia and induced neurodegeneration.

In even another preferred embodiment the quinuclidine derivatives of the invention may be useful for the treatment of inflammatory diseases, disorders, or conditions, including inflammatory skin disorders such as acne and rosacea, Chron's disease, inflammatory bowel disease, ulcerative colitis, and diarrhoea.

In still another preferred embodiment the quinuclidine derivatives of the invention may be useful for the treatment of mild, moderate or even severe pain of acute, chronic or recurrent character, as well as pain caused by migraine, postoperative pain, and phantom limb pain. The pain may in particular be neuropathic pain, chronic headache, central pain, pain related to diabetic neuropathy, to post therapeutic neuralgia, or to peripheral nerve injury.

Finally the quinuclidine derivatives of the invention may be useful for the treatment of withdrawal symptoms caused by termination of use of addictive substances. Such addictive substances include nicotine containing products such as tobacco, opioids such as heroin, cocaine and morphine, benzodiazepines and benzodiazepine-like drugs, and alcohol. Withdrawal from addictive substances is in

general a traumatic experience characterised by anxiety and frustration, anger, anxiety, difficulties in concentrating, restlessness, decreased heart rate and increased appetite and weight gain.

In this context "treatment" covers treatment, prevention, prophylactics and alleviation of withdrawal symptoms and abstinence as well as treatment resulting in a voluntary diminished intake of the addictive substance.

In another aspect, the quinuclidine derivatives of the invention are used as diagnostic agents, e.g. for the identification and localisation of nicotinic receptors in various tissues.

Pharmaceutical Compositions

In another aspect the invention provides novel pharmaceutical compositions comprising a therapeutically effective amount of the quinuclidine derivatives of the invention.

While a chemical compound of the invention for use in therapy may be administered in the form of the raw chemical compound, it is preferred to introduce the active ingredient, optionally in the form of a physiologically acceptable salt, in a pharmaceutical composition together with one or more adjuvants, excipients, carriers, buffers, diluents, and/or other customary pharmaceutical auxiliaries.

In a preferred embodiment, the invention provides pharmaceutical compositions comprising the quinuclidine derivative together with one or more pharmaceutically acceptable carriers therefore, and, optionally, other therapeutic and/or prophylactic ingredients, know and used in the art. The carrier(s) must be "acceptable" in the sense of being compatible with the other ingredients of the formulation and not harmful to the recipient thereof.

The pharmaceutical composition of the invention may be administered by any convenient route, which suits the desired therapy. Preferred routes of administration include oral administration, in particular in tablet, in capsule, in dragé, in powder, or in liquid form, and parenteral administration, in particular cutaneous, subcutaneous, intramuscular, or intravenous injection. The pharmaceutical composition of the invention can be manufactured by a person skilled in the art by use of standard methods and conventional techniques appropriate to the desired formulation. When desired, compositions adapted to give sustained release of the active ingredient may be employed.

Further details on techniques for formulation and administration may be found in the latest edition of Remington's Pharmaceutical Sciences (Maack Publishing Co., Easton, PA).

The actual dosage depend on the nature and severity of the disease being treated, and is within the discretion of the physician, and may be varied by titration of

the dosage to the particular circumstances of this invention to produce the desired therapeutic effect. However, it is presently contemplated that pharmaceutical compositions containing of from about 0.1 to about 500 mg of active ingredient per individual dose, preferably of from about 1 to about 100 mg, most preferred of from about 1 to about 10 mg, are suitable for therapeutic treatments.

The active ingredient may be administered in one or several doses per day. A satisfactory result can, in certain instances, be obtained at a dosage as low as 0.1 µg/kg i.v. and 1 µg/kg p.o. The upper limit of the dosage range is presently considered to be about 10 mg/kg i.v. and 100 mg/kg p.o. Preferred ranges are from about 0.1 µg/kg to about 10 mg/kg/day i.v., and from about 1 µg/kg to about 100 mg/kg/day p.o.

Methods of Therapy

Due to their pharmacological profile the compounds of the invention may be useful for the treatment of diseases or conditions as diverse as CNS related diseases, PNS related diseases, diseases related to smooth muscle contraction, endocrine disorders, diseases related to neuro-degeneration, diseases related to inflammation, pain, and withdrawal symptoms caused by the termination of abuse of chemical substances.

In another aspect the invention provides methods of the treatment, prevention or alleviation of diseases or disorders or conditions of a living animal body, including a human, which disease or disorder is responsive to the action of a monoamine receptor modulator, and which method comprises the step of administering to such a living animal body, including a human, in need thereof a therapeutically effective amount of the quinuclidine derivative of the invention.

In the context of this invention the term "treating" covers treatment, prevention, prophylaxis or alleviation, and the term "disease" covers illnesses, diseases, disorders and conditions related to the disease in question.

It is at present contemplated that a suitable dosage lies within the range of from about 0.1 to about 500 milligram of active substance daily, more preferred of from about 10 to about 70 milligram of active substance daily, administered once or twice a day, dependent as usual upon the exact mode of administration, form in which administered, the indication toward which the administration is directed, the subject involved and the body weight of the subject involved, and further the preference and experience of the physician or veterinarian in charge.

EXAMPLES

The invention is further illustrated with reference to the following examples, which are not intended to be in any way limiting to the scope of the invention as claimed.

General remarks: All reactions involving air sensitive reagents or intermediates were performed under nitrogen and in anhydrous solvents. Magnesium sulfate was used as drying agent in the workup-procedures and solvents were evaporated under reduced pressure.

Method A

(±)-3-(Naphthalen-2-yloxy)-1-aza-bicyclo[2.2.2]octane fumaric acid salt (Compound A1)

To a mixture of 2-naphthol (5.0 g, 34.5 mmol), (±)-3-quinuclidinol (2.94 g, 23.1 mmol), triphenylphosphine (9.0 g, 34.5 mmol) and tetrahydrofuran (100 ml) was added: diethylazodicarboxylate (5.4 ml, 34.5 mmol) at room temperature during 30 minutes. The reaction mixture was allowed to stir for 20 hours at 50°C. Aqueous sodium hydroxide (100 ml, 1 M) was added. The mixture was extracted with dichloromethane (3 x 100 ml). Chromatography on silica gel with dichloromethane, methanol and conc. ammonia (89:10:1) gave the title compound. The corresponding salt was obtained by addition of a diethyl ether and methanol mixture (9:1) saturated with fumaric acid. Yield 3.7 g (43%). Mp 140.9-141.6°C.

(±)-3-(4-Phenylphenyloxy)-1-aza-bicyclo[2.2.2]octane fumaric acid salt (Compound A2)

Was prepared according to method A from 4-phenylphenol. Mp 173.5-185.1°C.

(±)-3-(3-Phenylphenyloxy)-1-aza-bicyclo[2.2.2]octane free base (Compound A3)

Was prepared according to method A from 3-phenylphenol. The product was isolated as an oil.

(±)-3-(2-Phenylphenyloxy)-1-aza-bicyclo[2.2.2]octane fumaric acid salt (Compound A4)

Was prepared according to method A from 2-phenylphenol. Mp 125.4°C.

(±)-3-(6-Quinolinoxy)-1-aza-bicyclo[2.2.2]octane fumaric acid salt (Compound A5)

Was prepared according to method A from 6-hydroxyquinoline. Mp 146.0-147.0°C.

(±)-3-(5-Indanyloxy)-1-aza-bicyclo[2.2.2]octane fumaric acid salt (Compound A6)

Was prepared according to method A from 5-indanol. Mp 149.3-150.5°C.

(±)-3-(5,6,7,8-Tetrahydro-2-naphthyloxy)-1-aza-bicyclo[2.2.2]octane fumaric acid salt (Compound A7)

Was prepared according to method A from 5,6,7,8-tetrahydro-2-naphthol. Mp 109.7-111.3°C.

Method B

(±)-2-(1-Aza-bicyclo[2.2.2]oct-3-yloxy)-quinoline fumaric acid salt (Compound B1)

A mixture of (±)-3-quinuclidinol (2.0 g, 15.7 mmol), 2-chloroquinoline (2.6 g, 15.7 mmol) and DMF (30 ml) was stirred at room temperature. Sodium hydride (0.94 g, 23.6 mmol, 60% in oil) was added in small portions. The reaction mixture was stirred for 1.5 hours at 50°C. Aqueous sodium hydroxide (50 ml, 1 M) was added followed by extraction with diethyl ether (3 x 50 ml). The combined ethereal phases were washed with aqueous sodium hydroxide (2 x 50 ml, 1 M). The corresponding salt was obtained by addition of a diethyl ether and methanol mixture (9:1) saturated with fumaric acid. Yield 4.62 g (79%). Mp 160.0-160.5°C.

(±)-3-(6-Chloro-benzothiazol-2-yloxy)-1-aza-bicyclo[2.2.2]octane fumaric acid salt (Compound B2)

Was prepared according to procedure B from 2,6-dichlorobenzothiazole. Mp 203-205°C.

(±)-3-(Benzothiazol-2-yloxy)-1-aza-bicyclo[2.2.2]octane fumaric acid salt (Compound B3)

Was prepared according to procedure B from 2-chlorobenzothiazole. Mp 173.7-174.2°C.

(±)-2-(1-Aza-bicyclo[2.2.2]oct-3-yloxy)-3-chloro-quinoxaline fumaric acid salt (Compound B4)

Was prepared according to procedure B from 2.3-dichloroquinoxaline. Mp 120.8-122.1°C.

(±)-3-(1-Methyl-benzoimidazol-2-yloxy)-1-aza-bicyclo[2.2.2]octane fumaric acid salt (Compound B5)

Was prepared according to procedure B from 2-chloro-1-methylbenzoimidazole. Mp 184.9-185.9°C.

(±)-3-(Benzoxazol-2-yloxy)-1-aza-bicyclo[2.2.2]octane fumaric acid salt (Compound B6)

Was prepared according to procedure B from 2-chlorobenzoxazole. Mp 187.2-188.8°C.

(±)-2-(1-Aza-bicyclo[2.2.2]oct-3-yloxy)-quinoxaline fumaric acid salt (Compound B7)

Was prepared according to procedure B from 2-chloroquinoxaline. Mp 127.7-128.5°C.

(±)-3-(6-Phenylpyridazin-3-yloxy)-1-aza-bicyclo[2.2.2]octane fumaric acid salt (Compound B8)

Was prepared according to procedure B from 3-chloro-6-phenylpyridazine. Mp 168.5-172.0°C.

(±)-3-(5-Phenyl-1,3,4-thiadiazol-2-yloxy)-1-aza-bicyclo[2.2.2]octane fumaric acid salt (Compound B9)

Was prepared according to procedure B from 2-chloro-5-phenyl-1,3,4-thiadiazole. Mp 168.5-172.0°C.

(±)-3-(5-Bromo-thiazol-2-yloxy)-1-aza-bicyclo[2.2.2]octane fumaric acid salt (Compound B10)

Was prepared according to procedure B from 2,5-dibromothiazole, using 0°C as reaction temperature. Mp 157.8-162.1°C.

(±)-3-(1,2-Benzoisothiazol-3-yloxy)-1-aza-bicyclo[2.2.2]octane fumaric acid salt (Compound B11)

Was prepared according to procedure B from 3-chloro-1,2-benzoisothiazole. Mp 172.3-173.6°C.

(±)-3-(5-Phenyl-1,2,4-thiadiazol-3-yloxy)-1-aza-bicyclo[2.2.2]octane fumaric acid salt (Compound B12)

Was prepared according to procedure B 3-chloro-5-phenyl-1,2,4,-thiadiazole. Mp 155.0-159.3°C.

(±)-3-(6-Bromo-pyridazin-3-yloxy)-1-aza-bicyclo[2.2.2]octane fumaric acid salt (Compound B13)

Was prepared according to procedure B from 3,6-dibromopyridazine. Mp 152.8°C.

(±)-3-(6-Chloro-pyridazin-3-yloxy)-1-aza-bicyclo[2.2.2]octane fumaric acid salt (Compound B14)

Was prepared according to procedure B from 3,6-dichloropyridazine. Mp 164-164.5°C.

(±)-3-(3,4,5-Trichloro-2-yloxy)-1-aza-bicyclo[2.2.2]octane fumaric acid salt (Compound B15)

Was prepared according to procedure B, using the conditions: potassium *tert*-butoxide, crown ether (18:6), from tetrachlorothiophene. Mp 188-189.4°C.

(±)-3-(3-Methoxy-2-quinoxalinyloxy)-1-aza-bicyclo[2.2.2]octane fumaric acid salt (Compound B16)

A mixture of (±)-2-(1-Aza-bicyclo[2.2.2]oct-3-yloxy)-3-chloro-quinoxaline (Compound B4; 1.38 g, 4.76 mmol), cecium carbonate (1.55 g, 4.76 mmol) and methanol (15 ml) was stirred for 3 hours at 45°C. Aqueous sodium hydroxide (50 ml, 1 M) was added followed by extraction with diethyl ether (3 x 50 ml). The corresponding salt was obtained by addition of a diethyl ether and methanol mixture (9:1) saturated with fumaric acid. Yield 0.51 g, 27%. Mp 168.5-170.0°C.

(±)-3-[5-(3-Thienyl)-1,3,4-thiadiazol-2-yloxy]-1-aza-bicyclo[2.2.2]octane fumaric acid salt (Compound B17)

Was prepared according to procedure B from 2-chloro-5-(3-thienyl)-1,3,4-thiadiazole. Mp 186-188°C.

(±)-3-[(1,3-Dione)-2-isoindolyl-methoxy]-1-azabicyclo[2.2.2]octane fumaric acid salt (Compound B18)

Was prepared according to procedure B from *N*-(2-bromomethyl)-phtalimid. Mp 212-213°C.

(±)-3-[(1,3-Dione)-2-isoindolyl-ethoxy]-1-azabicyclo[2.2.2]octane free base (Compound B19)

Was prepared according to procedure B from *N*-(2-bromoethyl)-phtalimid. Isolated as free base, oil.

(±)-3-(Benzotriazol-1-yloxy)-1-azabicyclo[2.2.2]octane fumaric acid salt (Compound B20)

Was prepared according to procedure B from 1-(chloromethyl)-1*H*-benzotriazole Mp 163.3-164.5°C.

Method C

(±)-2-(1-Aza-bicyclo[2.2.2]oct-3-yloxy)-quinoxaline methylium iodide salt (Compound C1)

A mixture of (±)-3-(quinoxalin-2-yloxy)-1-aza-bicyclo[2.2.2]octane (1.27 g, 5.0 mmol) dichloromethane (10 ml) was added at -70°C: methyliodide (0.31 g, 5.0 mmol) solved in dichloromethane (1.5 ml) was added over 10 minutes. The reaction was stirred at -70°C for 40 minutes. The reaction mixture was allowed to stir at room temperature for 3 hours. The precipitate was isolated by filtration. Mp 229-230°C.

(±)-2-(1-Aza-bicyclo[2.2.2]oct-3-yloxy)-quinoline methylium iodide (Compound C2)

Was prepared according to method C from (±)-2-(1-Aza-bicyclo[2.2.2]oct-3-yloxy)-quinoline. Mp 156.6-175.2°C.

(±)-3-(1,2-Benzoisothiazol-3-yloxy)-1-aza-bicyclo[2.2.2]octane methylium iodide (Compound C3)

Was prepared according to method C from (±)-3-(1,2-benzoisothiazol-3-yloxy)-1-aza-bicyclo[2.2.2]octane. Mp 180.1-186.4°C.

Method D

(±)-3-(5-Phenyl-thiazol-2-yloxy)-1-aza-bicyclo[2.2.2]octane fumaric acid salt (Compound D1)

A mixture of (±)-3-(5-bromo-thiazol-2-yloxy)-1-aza-bicyclo[2.2.2]octane (1.25 g, 4.32 mmol), phenylboronic acid (0.791 g, 6.48 mmol), $Pd(PPh_3)_4$ (0.150 g, 0.13 mmol), aqueous potassium carbonate (6.5 ml, 2 M), 1,3-propanediol (0.97 ml, 13.0 mmol) and 1,2-dimethoxyethane (30 ml) was stirred at reflux for 15 hours. Aqueous sodium hydroxide (50 ml, 1 M) was added, the mixture was extracted with ethyl acetate (3 x 50 ml). Chromatography on silica gel with dichloromethane, methanol and conc. ammonia (89:10:1) gave the title compound. Yield 3.7 g (43%). The corresponding salt was obtained by addition of a diethyl ether and methanol mixture (9:1) saturated with fumaric acid. Mp 170.9-172.2°C.

(±)-3-[5-(2,4-Difluoro-phenyl)-thiazol-2-yloxy]-1-aza-bicyclo[2.2.2]octane fumaric acid salt (Compound D2)

Was prepared according to method D. Mp 84.3-86.3°C.

(±)-3-[5-(3-Thienyl)-thiazol-2-yloxy]-1-aza-bicyclo[2.2.2]octane fumaric acid salt (Compound D3)

Was prepared according to method D. Mp 68.5-74.3°C.

(±)-3-[5-(2-Thienyl)-thiazol-2-yloxy]-1-aza-bicyclo[2.2.2]octane fumaric acid salt (Compound D4)

Was prepared according to method D. Mp 152.6-154.9°C.

(±)-3-[5-(3-Furanyl)-thiazol-2-yloxy]-1-aza-bicyclo[2.2.2]octane fumaric acid salt (Compound D5)

Was prepared according to method D. Mp 127.6-136.2°C.

(±)-3-[5-(3-Pyridyl)-thiazol-2-yloxy]-1-aza-bicyclo[2.2.2]octane fumaric acid salt (Compound D6)

Was prepared according to method D. Mp 82.7-86.0°C.

(±)-3-[6-(3-Thienyl)-pyridazin-3-yloxy]-1-aza-bicyclo[2.2.2]octane fumaric acid salt (Compound D7)

Was prepared according to method D from (±)-3-(6-bromo-pyridazin-3-yloxy)-1-aza-bicyclo[2.2.2]octane. Mp 197.9°C.

(±)-3-[6-(2-Thienyl)-pyridazin-3-yloxy]-1-aza-bicyclo[2.2.2]octane fumaric acid salt (Compound D8)

Was prepared according to method D from (±)-3-(6-bromo-pyridazin-3-yloxy)-1-aza-bicyclo[2.2.2]octane. Mp 180.3-191.1°C.

(±)-3-[6-(2-Furanyl)-pyridazin-3-yloxy]-1-aza-bicyclo[2.2.2]octane fumaric acid salt (Compound D9)

Was prepared according to method D from (±)-3-(6-bromo-pyridazin-3-yloxy)-1-aza-bicyclo[2.2.2]octane. Mp 175.8-178.2°C.

(±)-3-[6-(3-Furanyl)-pyridazin-3-yloxy]-1-aza-bicyclo[2.2.2]octane fumaric acid salt (Compound D10)

Was prepared according to method D from (±)-3-(6-bromo-pyridazin-3-yloxy)-1-aza-bicyclo[2.2.2]octane. Mp 224.8-225.4°C.

(±)-3-[6-(3-Pyridyl)-pyridazin-3-yloxy]-1-aza-bicyclo[2.2.2]octane fumaric acid salt (Compound D11)

Was prepared according to method D from (±)-3-(6-bromo-pyridazin-3-yloxy)-1-aza-bicyclo[2.2.2]octane. Mp 137.2-143.2°C.

Method E

(±)-3-(4-Phenylphenyl-methoxy)-1-aza-bicyclo[2.2.2]octane fumaric acid salt (Compound E1)

A mixture of (±)-3-quinuclidinol (2.0 g, 15.7 mmol), 4-phenylbenzylchloride (3.2 g, 15.7 mmol), sodium hydride, 60% with oil (1.26 g, 31.4 mmol) and DMF (30 ml) was at 50°C for 4.5 hours. Aqueous sodium hydroxide (100 ml, 1 M) was added. The mixture was extracted with diethyl ether (3 x 50 ml). Chromatography on silica gel with dichloromethane, methanol and conc. ammonia (89:10:1) gave the title compound. Yield 2.0 g (29%).

The corresponding salt was obtained by addition of a diethyl ether and methanol mixture (9:1) saturated with fumaric acid. Mp 159.8-160.4°C.

The compound may also be named (±)-3-(biphenyl-4-yl-methoxy)-quinuclidine.

Method F

(±)-3-(2-Phenyl-imidazo[1,2-b]pyridazin-6-yloxy)-1-aza-bicyclo[2.2.2]octane fumaric acid salt (Compound F1)

To a mixture of 6-chloro-2-phenyl-imidazo[1,2-b]pyridazin (prepared according to J. Heterocycl. Chem. 39, 737, 2002) (3.6 g, 15.7 mmol), (±)-3-quinuclidinol 2.0 g, 15.7 mmol) in DMF (30 ml): sodium hydride (1.26 g, 31.4 mmol) was added over 20 min, at room temperature, followed by stirring at 50°C for 4 hours. Aqueous sodium hydroxide (100 ml, 1 M) was added. The mixture was extracted with diethyl ether (3 x 100 ml). Chromatography on silica gel with dichloromethane, methanol and conc. ammonia (89:10:1) gave the title compound. Yield 2.9 g (57%).

The corresponding salt was obtained by addition of a diethyl ether and methanol mixture (9:1) saturated with fumaric acid. Mp 211-216°C.

Method G

(±)-3-(Dibenzofuran-2-yloxy)-1-azabicyclo[2.2.2]octane fumaric acid salt (Compound G1)

To a mixture of (±)-3-quinuclidinol (3.0 g, 23.6 mmol), 2-hydroxydibenzofuran (4.3 g, 23.6 mmol), triphenylphosphine (9.29 g, 35.4 mmol) and THF, was added: diethylazodicarboxylate (6.3 ml, 35.4 mmol) over a time period of 40 min at room temperature. The mixture was stirred at 50°C for 7 days. Aqueous sodium hydroxide (100 ml, 1 M) was added. The mixture was extracted with dichloromethane (3 x 100 ml). Chromatography on silica gel with dichloromethane, methanol and conc. ammonia (89:10:1) gave the title compound. Yield 2.0 g (29%).

The corresponding fumaric acid salt was obtained by addition of a diethyl ether and methanol mixture (9:1) saturated with fumaric acid. Mp 131.3-133.8°C.

The compound also may be named (±)-3-(Dibenzofuran-2-yloxy)-quinuclidine.

Biological Activity

***In vitro* Inhibition of ^{3}H-α-Bungarotoxine Binding in Rat Brain**

In this example the affinity of the compounds of the invention for binding to α_7-subtype of nicotinic receptors is determined.

α-Bungarotoxine is a peptide isolated from the venom of the Elapidae snake *Bungarus multicinctus*. It has high affinity for neuronal and neuromuscular nicotinic receptors, where it acts as a potent antagonist.

^{3}H-α-Bungarotoxine labels nicotinic acetylcholine receptors formed by the α_7 subunit isoform found in brain and the α_1 isoform in the neuromuscular junction.

Tissue preparation

Preparations are performed at 0-4°C. Cerebral cortices from male Wistar rats (150-250 g) are homogenised for 10 seconds in 15 ml of 20 mM Hepes buffer containing 118 mM NaCl, 4.8 mM KCl, 1.2 mM $MgSO_4$ and 2.5 mM $CaCl_2$ (pH 7.5) using an Ultra-Turrax homogeniser. The tissue suspension is subjected to centrifugation at 27,000 x g for 10 minutes. The supernatant is discarded and the pellet is washed twice by centrifugation at 27,000 x g for 10 minutes in 20 ml of fresh buffer, and the final pellet is then re-suspended in fresh buffer containing 0.01% BSA (35 ml per g of original tissue) and used for binding assays.

Assay

Aliquots of 500 µl of homogenate are added to 25 µl of test solution and 25 µl of ^{3}H-α-bungarotoxine (2 nM, final concentration) and mixed and incubated for 2 hours at 37°C. Non-specific binding is determined using (-)-nicotine (1 mM, final concentration). After incubation, the samples are added 5 ml of ice-cold Hepes buffer containing 0.05% PEI and poured directly onto Whatman GF/C glass fibre filters (pre-soaked in 0.1% PEI for at least 6 hours) under suction, and immediately washed with 2 x 5 ml ice-cold buffer.

The amount of radioactivity on the filters is determined by conventional liquid scintillation counting. Specific binding is total binding minus non-specific binding.

The test value is given as an IC_{50} (the concentration of the test substance which inhibits the specific binding of ^{3}H-α-bungarotoxin by 50%).

The results of these experiments are presented in Table 1 below.

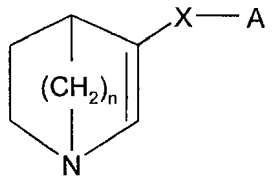
Table 1

Inhibition of ^{3}H-α-Bungarotoxine Binding

Compound No.	IC_{50} (µM)
A2	0.16
B2	0.18
B3	0.17
B17	0.15
D1	0.052
D3	0.11
D4	0.020
D5	0.048
D6	0.18
D7	0.13
D8	0.053

CLAIMS

1. A quinuclidine derivative represented by Formula I



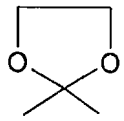
(I)

an enantiomer thereof, or a mixture of its enantiomers, or a pharmaceutically-acceptable addition salt thereof, or an onium salt thereof, wherein,

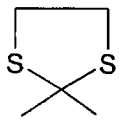
------ represents an optional double bond;

n is 1, 2 or 3;

X represents a linker selected from -O-, -O-CH_2-, -O-CH_2-CH_2-, -S-, -SO-, -SO_2-, -CH_2-, -S-CH_2-CH_2-, -CH_2-, -C(=CH_2)-,-NH-, -N(C_{1-6}-alkyl)-, -C(=O)-, -C(=S)-,



, and



; and

A represents

a monocyclic or polycyclic carbocyclic group selected from indanyl; indenyl; naphthyl; 5,6,7,8-tetrahydro-naphthyl; azulenyl; and anthracenyl;

or a monocyclic heterocyclic group selected from pyridazinyl; and thiazolyl;

or a polycyclic heterocyclic group selected from indolyl; isoindolyl; quinolinyl; quinoxalinyl; benzoxazolyl; benzthiazolyl; benzisothiazolyl; benztriazolyl; and imidazo[1,2-b]pyridazinyl;

which mono or polycyclic, carbocyclic or heterocyclic groups are optionally substituted one or more times with substituents selected from the group consisting of C_{1-6}-alkyl, C_{3-7}-cycloalkyl, C_{3-7}-cycloalkyl-C_{1-6}-alkyl, C_{1-6}-alkoxy, hydroxy-C_{1-6}-alkoxy, C_{1-6}-alkoxy-C_{1-6}-alkyl, C_{1-6}-alkoxy-C_{1-6}-alkoxy, C_{3-7}-cycloalkoxy,

C_{3-7}-cycloalkoxy-C_{1-6}-alkyl, C_{3-7}-cycloalkoxy-C_{1-6}-alkoxy, halo, CF_3, CN, NO_2, NH_2, carboxy, carbamoyl, amido, sulfamoyl, and phenyl, or with another monocyclic or polycyclic, carbocyclic or heterocyclic group, which additional monocyclic or polycyclic, carbocyclic or heterocyclic group may optionally be substituted one or more times with substituents selected from the group consisting of C_{1-6}-alkyl, C_{3-7}-cycloalkyl, C_{3-7}-cycloalkyl-C_{1-6}-alkyl, C_{1-6}-alkoxy, hydroxy-C_{1-6}-alkoxy, C_{1-6}-alkoxy-C_{1-6}-alkyl, C_{1-6}-alkoxy-C_{1-6}-alkoxy, C_{3-7}-cycloalkoxy, C_{3-7}-cycloalkoxy-C_{1-6}-alkyl, C_{3-7}-cycloalkoxy-C_{1-6}-alkoxy, halo, CF_3, CN, NO_2, NH_2, carboxy, carbamoyl, amido, sulfamoyl, and phenyl.

2. The quinuclidine derivative of claim 1, wherein ------ represents a single (covalent) bond.

3. The quinuclidine derivative of either one of claims 1-2, wherein n is 1, 2 or 3.

4. The quinuclidine derivative of claim 3, wherein n is 2.

5. The quinuclidine derivative of any one of claims 1-4, wherein X represents a linker selected from -O-, -O-CH_2-, -O-CH_2-CH_2-, -S-, and -CH_2-.

6. The quinuclidine derivative of claim 5, wherein X represents -O-, -O-CH_2- or -O-CH_2-CH_2-.

7. The quinuclidine derivative of claim 5, wherein X represents -O-.

8. The quinuclidine derivative of any one of claims 1-7, wherein A represents a monocyclic or polycyclic carbocyclic group selected from

indanyl;
indenyl;
naphthyl;
5,6,7,8-tetrahydro-naphthyl;
azulenyl; and
anthracenyl;

which carbocyclic group is optionally substituted one or two times with substituents selected from the group consisting of C_{1-6}-alkyl, C_{3-7}-cycloalkyl, C_{3-7}-

cycloalkyl-C_{1-6}-alkyl, C_{1-6}-alkoxy, hydroxy-C_{1-6}-alkoxy, C_{1-6}-alkoxy-C_{1-6}-alkyl, C_{1-6}-alkoxy-C_{1-6}-alkoxy, C_{3-7}-cycloalkoxy, C_{3-7}-cycloalkoxy-C_{1-6}-alkyl, C_{3-7}-cycloalkoxy-C_{1-6}-alkoxy, halo, CF_3, CN, NO_2, NH_2, carboxy, carbamoyl, amido, sulfamoyl, and phenyl.

9. The quinuclidine derivative of claim 8, wherein A represents a monocyclic or polycyclic carbocyclic group selected from 4-indanyl and 5-indanyl; 1-indenyl, 2-indenyl and 3-indenyl; 1-naphthyl and 2-naphthyl; 5,6,7,8-tetrahydro-1-naphthyl and 5,6,7,8-tetrahydro-2-naphthyl; 1-azulenyl, 2-azulenyl and 3-azulenyl; and 1-anthracenyl and 2-anthracenyl; which carbocyclic group is optionally substituted one or two times with substituents selected from the group consisting of C_{1-6}-alkyl, C_{3-7}-cycloalkyl, C_{3-7}-cycloalkyl-C_{1-6}-alkyl, C_{1-6}-alkoxy, hydroxy-C_{1-6}-alkoxy, C_{1-6}-alkoxy-C_{1-6}-alkyl, C_{1-6}-alkoxy-C_{1-6}-alkoxy, C_{3-7}-cycloalkoxy, C_{3-7}-cycloalkoxy-C_{1-6}-alkyl, C_{3-7}-cycloalkoxy-C_{1-6}-alkoxy, halo, CF_3, CN, NO_2, NH_2, carboxy, carbamoyl, amido, sulfamoyl, and phenyl.

10. The quinuclidine derivative of claim 9, which is

(±)-3-(Naphth-2-yloxy)-1-aza-bicyclo[2.2.2]octane;

(±)-3-(5,6,7,8-Tetrahydro-2-naphthyloxy)-1-aza-bicyclo[2.2.2]octane; or

(±)-3-(5-Indanyloxy)-1-aza-bicyclo[2.2.2]octane;

or an enantiomer thereof, or a pharmaceutically-acceptable addition salt thereof, or an onium salt thereof.

11. The quinuclidine derivative of any one of claims 1-7, wherein A represents a monocyclic or polycyclic heterocyclic group selected from

pyridazinyl;

thiazolyl;

quinolinyl;

quinoxalinyl;

benzoxazolyl; and

benzthiazolyl;

which monocyclic or polycyclic heterocyclic group is optionally substituted one or more times with substituents selected from the group consisting of C_{1-6}-alkyl, C_{3-7}-cycloalkyl, C_{3-7}-cycloalkyl-C_{1-6}-alkyl, C_{1-6}-alkoxy, hydroxy-C_{1-6}-alkoxy, C_{1-6}-alkoxy-C_{1-6}-alkyl, C_{1-6}-alkoxy-C_{1-6}-alkoxy, C_{3-7}-cycloalkoxy, C_{3-7}-cycloalkoxy-C_{1-6}-alkyl, C_{3-7}-cycloalkoxy-C_{1-6}-alkoxy, halo, CF_3, CN, NO_2, NH_2,

carboxy, carbamoyl, amido, sulfamoyl, and phenyl, or with another monocyclic or polycyclic, carbocyclic or heterocyclic group, which additional monocyclic or polycyclic, carbocyclic or heterocyclic group may optionally be substituted one or more times with substituents selected from the group consisting of C_{1-6}-alkyl, C_{3-7}-cycloalkyl, C_{3-7}-cycloalkyl-C_{1-6}-alkyl, C_{1-6}-alkoxy, hydroxy-C_{1-6}-alkoxy, C_{1-6}-alkoxy-C_{1-6}-alkyl, C_{1-6}-alkoxy-C_{1-6}-alkoxy, C_{3-7}-cycloalkoxy, C_{3-7}-cycloalkoxy-C_{1-6}-alkyl, C_{3-7}-cycloalkoxy-C_{1-6}-alkoxy, halo, CF_3, CN, NO_2, NH_2, carboxy, carbamoyl, amido, sulfamoyl, and phenyl.

12. The quinuclidine derivative of claim 11, wherein A represents a monocyclic or polycyclic heterocyclic group selected from pyridazin-3-yl and pyridazin-4-yl; thiazol-2-yl, thiazol-4-yl and thiazol-5-yl; quinolin-2-yl, quinolin-3-yl, quinolin-4-yl, quinolin-5-yl and quinolin-6-yl; quinoxalin-2-yl and quinoxalin-3-yl; benzoxazol-2-yl; and benzthiazol-2-yl; which monocyclic or polycyclic heterocyclic group is optionally substituted one or more times with substituents selected from the group consisting of C_{1-6}-alkyl, C_{3-7}-cycloalkyl, C_{3-7}-cycloalkyl-C_{1-6}-alkyl, C_{1-6}-alkoxy, hydroxy-C_{1-6}-alkoxy, C_{1-6}-alkoxy-C_{1-6}-alkyl, C_{1-6}-alkoxy-C_{1-6}-alkoxy, C_{3-7}-cycloalkoxy, C_{3-7}-cycloalkoxy-C_{1-6}-alkyl, C_{3-7}-cycloalkoxy-C_{1-6}-alkoxy, halo, CF_3, CN, NO_2, NH_2, carboxy, carbamoyl, amido, sulfamoyl, and phenyl, or with another monocyclic or polycyclic, carbocyclic or heterocyclic group, which additional monocyclic or polycyclic, carbocyclic or heterocyclic group may optionally be substituted one or more times with substituents selected from the group consisting of C_{1-6}-alkyl, C_{3-7}-cycloalkyl, C_{3-7}-cycloalkyl-C_{1-6}-alkyl, C_{1-6}-alkoxy, hydroxy-C_{1-6}-alkoxy, C_{1-6}-alkoxy-C_{1-6}-alkyl, C_{1-6}-alkoxy-C_{1-6}-alkoxy, C_{3-7}-cycloalkoxy, C_{3-7}-cycloalkoxy-C_{1-6}-alkyl, C_{3-7}-cycloalkoxy-C_{1-6}-alkoxy, halo, CF_3, CN, NO_2, NH_2, carboxy, carbamoyl, amido, sulfamoyl, and phenyl.

13. The quinuclidine derivative of claim 11, wherein A represents pyridazin-3-yl or pyridazin-4-yl; optionally substituted one or more times with substituents selected from the group consisting of C_{1-6}-alkyl, C_{3-7}-cycloalkyl, C_{3-7}-cycloalkyl-C_{1-6}-alkyl, C_{1-6}-alkoxy, hydroxy-C_{1-6}-alkoxy, C_{1-6}-alkoxy-C_{1-6}-alkyl, C_{1-6}-alkoxy-C_{1-6}-alkoxy, C_{3-7}-cycloalkoxy, C_{3-7}-cycloalkoxy-C_{1-6}-alkyl, C_{3-7}-cycloalkoxy-C_{1-6}-alkoxy, halo, CF_3, CN, NO_2, NH_2, carboxy, carbamoyl, amido, sulfamoyl, and phenyl, or with another monocyclic or polycyclic, carbocyclic or heterocyclic group, which additional monocyclic or polycyclic, carbocyclic or heterocyclic group may optionally be substituted one or more times with substituents selected from the

group consisting of C_{1-6}-alkyl, C_{3-7}-cycloalkyl, C_{3-7}-cycloalkyl-C_{1-6}-alkyl, C_{1-6}-alkoxy, hydroxy-C_{1-6}-alkoxy, C_{1-6}-alkoxy-C_{1-6}-alkyl, C_{1-6}-alkoxy-C_{1-6}-alkoxy, C_{3-7}-cycloalkoxy, C_{3-7}-cycloalkoxy-C_{1-6}-alkyl, C_{3-7}-cycloalkoxy-C_{1-6}-alkoxy, halo, CF_3, CN, NO_2, NH_2, carboxy, carbamoyl, amido, sulfamoyl, and phenyl.

14. The quinuclidine derivative of claim 13, wherein A represents pyridazin-3-yl or pyridazin-4-yl; optionally substituted with a polycyclic heterocyclic group.

15. The quinuclidine derivative of claim 14, wherein A represents pyridazin-3-yl or pyridazin-4-yl; optionally substituted with indolyl; isoindolyl; quinolinyl; quinoxalinyl; benzoxazolyl; benzthiazolyl; benzisothiazolyl; benztriazolyl; or imidazo[1,2-b]pyridazinyl.

16. The quinuclidine derivative of claim 15, wherein A represents pyridazin-3-yl or pyridazin-4-yl; optionally substituted with indolyl.

17. The quinuclidine derivative of claim 16, wherein A represents pyridazin-3-yl substituted with indolyl.

18. The quinuclidine derivative of any one of claims 1-7, wherein A represents a monocyclic heterocyclic group selected from

pyridazinyl; and

thiazolyl;

which monocyclic heterocyclic group is optionally substituted one or more times with substituents selected from the group consisting of C_{1-6}-alkyl, C_{3-7}-cycloalkyl, C_{1-6}-alkoxy, C_{3-7}-cycloalkoxy, halo, CF_3, CN, NO_2, NH_2, phenyl, 2-thienyl, 3-thienyl, 2-furanyl, 3-furanyl, and 3-pyridinyl, which phenyl, 2-thienyl, 3-thienyl, 2-furanyl, 3-furanyl, and 3-pyridinyl groups may optionally be substituted one or two times with substituents selected from the group consisting of C_{1-6}-alkyl, C_{3-7}-cycloalkyl, C_{1-6}-alkoxy, halo, CF_3, CN, NO_2, NH_2, and phenyl.

19. The quinuclidine derivative of any one of claims 1-7, wherein A represents a monocyclic heterocyclic group selected from pyridazin-3-yl and pyridazin-4-yl; and thiazol-2-yl, thiazol-4-yl and thiazol-5-yl; which monocyclic heterocyclic group is optionally substituted one or more times with substituents

selected from the group consisting of C_{1-6}-alkyl, C_{3-7}-cycloalkyl, C_{1-6}-alkoxy, C_{3-7}-cycloalkoxy, halo, CF_3, CN, NO_2, NH_2, phenyl, 2-thienyl, 3-thienyl, 2-furanyl, 3-furanyl, and 3-pyridinyl, which phenyl, 2-thienyl, 3-thienyl, 2-furanyl, 3-furanyl, and 3-pyridinyl groups may optionally be substituted one or two times with substituents selected from the group consisting of C_{1-6}-alkyl, C_{3-7}-cycloalkyl, C_{1-6}-alkoxy, halo, CF_3, CN, NO_2, NH_2, and phenyl.

20. The quinuclidine derivative of any one of claims 1-7, wherein A represents a monocyclic heterocyclic group selected from pyridazin-3-yl and pyridazin-4-yl; and thiazol-2-yl, thiazol-4-yl and thiazol-5-yl; which monocyclic heterocyclic group is optionally substituted one or more times with substituents selected from the group consisting of halo, phenyl, 2-thienyl, 3-thienyl, 2-furanyl, 3-furanyl, and 3-pyridinyl, which phenyl, 2-thienyl, 3-thienyl, 2-furanyl, 3-furanyl, and 3-pyridinyl groups may optionally be substituted one or two times with halo.

21. The quinuclidine derivative of claim 18, which is
(±)-3-(5-Bromo-thiazol-2-yloxy)-1-aza-bicyclo[2.2.2]octane;
(±)-3-(5-Phenyl-thiazol-2-yloxy)-1-aza-bicyclo[2.2.2]octane;
(±)-3-[5-(2,4-Difluoro-phenyl)-thiazol-2-yloxy]-1-aza-bicyclo[2.2.2]octane;
(±)-3-[5-(3-Thienyl)-thiazol-2-yloxy]-1-aza-bicyclo[2.2.2]octane;
(±)-3-[5-(2-Thienyl)-thiazol-2-yloxy]-1-aza-bicyclo[2.2.2]octane;
(±)-3-[5-(3-Furanyl)-thiazol-2-yloxy]-1-aza-bicyclo[2.2.2]octane;
(±)-3-[5-(3-Pyridyl)-thiazol-2-yloxy]-1-aza-bicyclo[2.2.2]octane;
(±)-3-(6-Chloro-pyridazin-3-yloxy)-1-aza-bicyclo[2.2.2]octane;
(±)-3-(6-Bromo-pyridazin-3-yloxy)-1-aza-bicyclo[2.2.2]octane;
(±)-3-(6-Phenyl-pyridazin-3-yloxy)-1-aza-bicyclo[2.2.2]octane;
(±)-3-[6-(3-Thienyl)-pyridazin-3-yloxy]-1-aza-bicyclo[2.2.2]octane;
(±)-3-[6-(2-Thienyl)-pyridazin-3-yloxy]-1-aza-bicyclo[2.2.2]octane;
(±)-3-[6-(2-Furanyl)-pyridazin-3-yloxy]-1-aza-bicyclo[2.2.2]octane;
(±)-3-[6-(3-Furanyl)-pyridazin-3-yloxy]-1-aza-bicyclo[2.2.2]octane; or
(±)-3-[6-(3-Pyridyl)-pyridazin-3-yloxy]-1-aza-bicyclo[2.2.2]octane;
or an enantiomer thereof, or a pharmaceutically-acceptable addition salt thereof, or an onium salt thereof.

22. The quinuclidine derivative of any one of claims 1-7, wherein A represents a polycyclic heterocyclic group selected from

indolyl;
isoindolyl;
quinolinyl;
quinoxalinyl;
benzoxazolyl;
benzthiazolyl;
benzisothiazolyl;
benztriazolyl; and
imidazo[1,2-b]pyridazinyl;

which monocyclic or polycyclic heterocyclic group is optionally substituted one or more times with substituents selected from the group consisting of C_{1-6}-alkyl, C_{3-7}-cycloalkyl, C_{1-6}-alkoxy, C_{3-7}-cycloalkoxy, halo, CF_3, CN, NO_2, NH_2, and phenyl, which phenyl group may optionally be substituted one or more times with substituents selected from the group consisting of C_{1-6}-alkyl, C_{3-7}-cycloalkyl, C_{1-6}-alkoxy, halo, CF_3, CN, NO_2, NH_2, and phenyl.

23. The quinuclidine derivative of claim 22, wherein A represents a polycyclic heterocyclic group selected from indol-2-yl and indol-3-yl; isoindol-2-yl; quinolin-2-yl, quinolin-3-yl, quinolin-4-yl, quinolin-5-yl and quinolin-6-yl; quinoxalin-2-yl and quinoxalin-3-yl; benzoxazol-2-yl; benzthiazol-2-yl; benzisothiazol-3-yl; 1,2,3-benztriazol-1-yl; and imidazo[1,2-b]pyridazin-6-yl; which monocyclic or polycyclic heterocyclic group is optionally substituted one or more times with substituents selected from the group consisting of C_{1-6}-alkyl, C_{3-7}-cycloalkyl, C_{1-6}-alkoxy, C_{3-7}-cycloalkoxy, halo, CF_3, CN, NO_2, NH_2, and phenyl, which phenyl group may optionally be substituted one or more times with substituents selected from the group consisting of C_{1-6}-alkyl, C_{3-7}-cycloalkyl, C_{1-6}-alkoxy, halo, CF_3, CN, NO_2, NH_2, and phenyl.

24. The quinuclidine derivative of claim 23, wherein A represents a polycyclic heterocyclic group selected from isoindol-2-yl; quinolin-2-yl, quinolin-3-yl, quinolin-4-yl, quinolin-5-yl and quinolin-6-yl; quinoxalin-2-yl and quinoxalin-3-yl; benzoxazol-2-yl; benzthiazol-2-yl; benzisothiazol-3-yl; 1,2,3-benztriazol-1-yl; and imidazo[1,2-b]pyridazin-6-yl; which monocyclic or polycyclic heterocyclic group is optionally substituted one or more times with substituents selected from the group consisting of C_{1-6}-alkyl, C_{1-6}-alkoxy and halo.

25. The quinuclidine derivative of claim 24, which is
(±)-3-[(1,3-Dione)-2-isoindolyl-methoxy]-1-azabicyclo[2.2.2]octane;
(±)-3-[(1,3-Dione)-2-isoindolyl-ethoxy]-1-azabicyclo[2.2.2]octane;
(±)-3-(2-Quinolinyloxy)-1-aza-bicyclo[2.2.2]octane;
(±)-3-(2-Quinolinyloxy)-1-aza-bicyclo[2.2.2]octane methylium iodide;
(±)-3-(6-Quinolinyloxy)-1-aza-bicyclo[2.2.2]octane;
(±)-3-(2-Quinoxalinyloxy)-1-aza-bicyclo[2.2.2]octane;
(±)-3-(2-Quinoxalinyloxy)-1-aza-bicyclo[2.2.2]octane methylium iodide;
(±)-3-(3-Chloro-2-quinoxalinyloxy)-1-aza-bicyclo[2.2.2]octane;
(±)-3-(3-Methoxy-2-quinoxalinyloxy)-1-aza-bicyclo[2.2.2]octane;
(±)-3-(Benzoxazol-2-yloxy)-1-aza-bicyclo[2.2.2]octane;
(±)-3-(Benzthiazol-2-yloxy)-1-aza-bicyclo[2.2.2]octane;
(±)-3-(6-Chloro-benzthiazol-2-yloxy)-1-aza-bicyclo[2.2.2]octane;
(±)-3-(1,2-Benzisothiazol-3-yloxy)-1-aza-bicyclo[2.2.2]octane;
(±)-3-(1,2-Benzisothiazol-3-yloxy)-1-aza-bicyclo[2.2.2]octane;
(±)-3-(Benztriazol-1-yloxy)-1-azabicyclo[2.2.2]octane; or
(±)-3-(2-Phenyl-imidazo[1,2-b]pyridazin-6-yloxy)-1-azabicyclo[2.2.2]octane;
or an enantiomer thereof, or a pharmaceutically-acceptable addition salt thereof, or an onium salt thereof.

26. A pharmaceutical composition comprising a therapeutically effective amount of a quinuclidine derivative of any one of claims 1-25, or a pharmaceutically-acceptable addition salt thereof.

27. Use of a quinuclidine derivative of any one of claims 1-25, or a pharmaceutically-acceptable addition salt thereof, for the manufacture of a pharmaceutical composition/medicament for the treatment, prevention or alleviation of a disease or a disorder or a condition of a mammal, including a human, which disease, disorder or condition is responsive to modulation of cholinergic receptors and/or monoamine receptors.

28. The use according to claim 27, wherein the disease, disorder or condition relates to the central nervous system.

29. The use according to claim 28, wherein the disease, disorder or condition is anxiety, cognitive disorders, learning deficit, memory deficits and dysfunction, Alzheimer's disease, attention deficit, attention deficit hyperactivity disorder (ADHD), Parkinson's disease, Huntington's disease, Amyotrophic Lateral Sclerosis, Gilles de la Tourette's syndrome, psychosis, depression, mania, manic depression, schizophrenia, obsessive compulsive disorders (OCD), panic disorders, eating disorders, anorexia nervosa, bulimia and obesity, narcolepsy, nociception, AIDS-dementia, senile dementia, periferic neuropathy, autism, dyslexia, tardive dyskinesia, hyperkinesia, epilepsy, bulimia, post-traumatic syndrome, social phobia, sleeping disorders, pseudodementia, Ganser's syndrome, pre-menstrual syndrome, late luteal phase syndrome, chronic fatigue syndrome, mutism, trichotillomania, and jet-lag.

30. The use according to claim 27, wherein the disease, disorder or condition are associated with smooth muscle contractions, convulsive disorders, angina pectoris, premature labour, convulsions, diarrhoea, asthma, epilepsy, tardive dyskinesia, hyperkinesia, premature ejaculation, and erectile difficulty.

31. The use according to claim 27, wherein the disease, disorder or condition is thyrotoxicosis, pheochromocytoma, hypertension and arrhythmias.

32. The use according to claim 27, wherein the disease, disorder or condition is a neurodegenerative disorders, transient anoxia, or induced neuro-degeneration.

33. The use according to claim 27, wherein the disease, disorder or condition is an inflammatory disorder, inflammatory skin disorders, acne, rosacea, Chron's disease, inflammatory bowel disease, ulcerative colitis, and diarrhoea.

34. The use according to claim 27, wherein the disease, disorder or condition is mild, moderate or even severe pain of acute, chronic or recurrent character, pain caused by migraine, postoperative pain, phantom limb pain, neuropathic pain, chronic headache, central pain, pain related to diabetic neuropathy, to post therapeutic neuralgia, or to peripheral nerve injury.

35. The use according to claim 27, wherein the disease, disorder or condition is associated with withdrawal symptoms caused by termination of use of addictive substances, nicotine containing products, tobacco, opioids, heroin, cocaine and morphine, benzodiazepines and benzodiazepine-like drugs, and alcohol.