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(54) Title: NOVEL 1,4-DIAZA-BICYCLO[3.2.2]NONANE DERIVATIVES AND THEIR MEDICAL USE

(57) Abstract: This invention relates to novel 1,4-diaza-bicyclo[3.2.2]nonane derivatives, which are found to be cholinergic ligands at the nicotinic acetylcholine receptors and modulators of the monoamine receptors and transporters. 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.

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NOVEL 1,4-DIAZA-BICYCLO[3.2.2]NONANE DERIVATIVES AND THEIR MEDICAL USE

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TECHNICAL FIELD

This invention relates to novel 1,4-diaza-bicyclo[3.2.2]nonane derivatives, which are found to be cholinergic ligands at the nicotinic acetylcholine receptors and modulators of the monoamine receptors and transporters. 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, exert its biological effect via two types of cholinergic receptors, the muscarinic Acetyl Choline Receptors (mAChR) and the nicotinic Acetyl Choline Receptors (nAChR).

As it is well established that muscarinic acetylcholine receptors dominate quantitatively over nicotinic acetylcholine receptors in the brain area important 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.

Recently, however, an interest in the development of nAChR modulators has emerged. Several diseases are associated with degeneration of the cholinergic system i.e. senile dementia of the Alzheimer type, vascular dementia and cognitive impairment due to the organic brain damage disease related directly to alcoholism. Indeed several CNS disorders can be attributed to a cholinergic deficiency, a dopaminergic deficiency, an adrenergic deficiency or a serotonergic deficiency.

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SUMMARY OF THE INVENTION

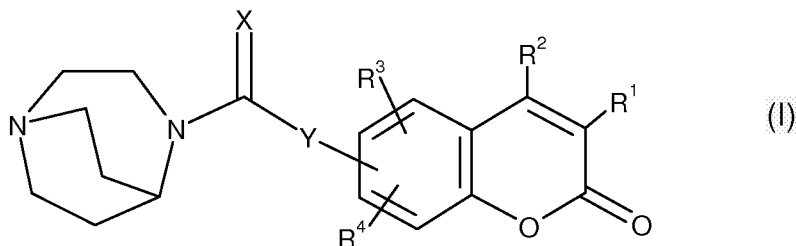
The present invention is devoted to the provision novel modulators of the nicotinic and/or of the monoamine receptors, which modulators are useful for the treatment of diseases or disorders related to the cholinergic receptors, and in particular the nicotinic acetylcholine receptor (nAChR), the serotonin receptor (5-HT₂), 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.

In its first aspect the invention provides novel 1,4-diaza-bicyclo[3.2.2]nonane derivatives of Formula I



or a pharmaceutically acceptable salt thereof, wherein

X represents O, S, or NR', wherein R' represents hydrogen or alkyl;

Y represents O, S, or NR'', wherein R'' represents hydrogen or alkyl; and

R¹, R², R³ and R⁴, independently of each other, represent hydrogen, alkyl,

cycloalkyl, cycloalkyl-alkyl, hydroxy, alkoxy, halo, haloalkyl, haloalkoxy, cyano, nitro, amino, oxo, carboxy, alkyl-carbonyl, alkoxy-carbonyl, alkyl-carbonyl-oxy, carbamoyl, amido, sulfamoyl, phenyl and/or benzyl.

In its second aspect the invention provides pharmaceutical compositions comprising a therapeutically effective amount of the 1,4-diaza-bicyclo[3.2.2]nonane derivatives of the invention, or a pharmaceutically-acceptable addition salt thereof, or a prodrug thereof, together with at least one pharmaceutically-acceptable carrier or diluent.

In a further aspect the invention relates to the use of the 1,4-diaza-bicyclo[3.2.2]nonane derivatives 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 modulation of cholinergic receptors and/or monoamine receptors.

In a final aspect the invention provides methods of treatment, prevention or alleviation of diseases, disorders or conditions of a living animal body, including a human, which disorder, disease or condition is responsive to modulation of cholinergic receptors and/or monoamine receptors, which method comprises the step of
 5 administering to such a living animal body in need thereof a therapeutically effective amount of the 1,4-diaza-bicyclo[3.2.2]nonane derivatives of the invention.

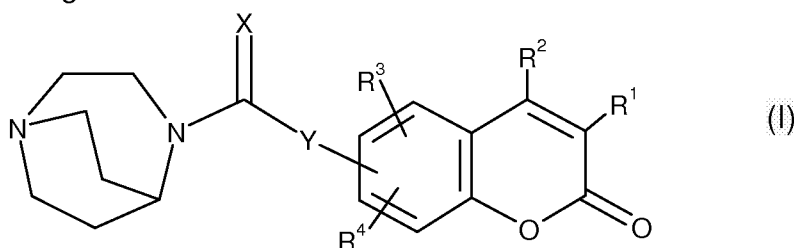
Other objects of the invention will be apparent to the person skilled in the art from the following detailed description and examples.

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DETAILED DISCLOSURE OF THE INVENTION

1,4-Diaza-bicyclo[3.2.2]nonane Derivatives

In a first aspect novel 1,4-diaza-bicyclo[3.2.2]nonane derivatives are provided. The 1,4-diaza-bicyclo[3.2.2]nonane derivatives of the invention may be
 15 represented by the general Formula I



or a pharmaceutically acceptable salt thereof, wherein

X represents O, S, or NR', wherein R' represents hydrogen or alkyl;

Y represents O, S, or NR'', wherein R'' represents hydrogen or alkyl; and

20 R¹, R², R³ and R⁴, independently of each other, represent hydrogen, alkyl, cycloalkyl, cycloalkyl-alkyl, hydroxy, alkoxy, halo, haloalkyl, haloalkoxy, cyano, nitro, amino, oxo, carboxy, alkyl-carbonyl, alkoxy-carbonyl, alkyl-carbonyl-oxy, carbamoyl, amido, sulfamoyl, phenyl and/or benzyl.

In a first more preferred embodiment the 1,4-diaza-bicyclo[3.2.2]nonane derivative of the invention is a compound of Formula I, wherein X represents O, S, or NR', wherein R' represents hydrogen or alkyl, and in particular methyl or ethyl.

In an even more preferred embodiment X represents O.

In a second more preferred embodiment the 1,4-diaza-bicyclo[3.2.2]nonane derivative of the invention is a compound of Formula I, wherein Y represents O, S, or
 30 NR'', wherein R'' represents hydrogen or alkyl, and in particular methyl or ethyl.

In an even more preferred embodiment Y represents O.

In a third more preferred embodiment the 1,4-diaza-bicyclo[3.2.2]nonane derivative of the invention is a compound of Formula I, wherein R¹, R², R³ and R⁴, independently of each other, represent hydrogen, alkyl, cycloalkyl, cycloalkyl-alkyl,

hydroxy, alkoxy, halo, haloalkyl, haloalkoxy, cyano, nitro, amino, oxo, carboxy, alkyl-carbonyl, alkoxy-carbonyl, alkyl-carbonyl-oxy, carbamoyl, amido, sulfamoyl, phenyl and/or benzyl.

In a more preferred embodiment R^1 and R^2 , independently of each other,
5 represent hydrogen, alkyl, cycloalkyl, cycloalkyl-alkyl, hydroxy, alkoxy, halo, haloalkyl, haloalkoxy, cyano, nitro, amino, oxo, carboxy, alkyl-carbonyl, alkoxy-carbonyl, alkyl-carbonyl-oxy, carbamoyl, amido, sulfamoyl, phenyl and/or benzyl; and R^3 and R^4 both represent hydrogen.

In another more preferred embodiment R^1 and R^2 , independently of each
10 other, represent hydrogen, alkyl, cycloalkyl, hydroxy, alkoxy, halo or trifluoromethyl; and R^3 and R^4 both represent hydrogen.

In a third more preferred embodiment one of R^1 and R^2 represents hydrogen, alkyl, cycloalkyl, hydroxy, alkoxy, halo or trifluoromethyl; and the other of R^1 and R^2 , together with R^3 and R^4 all represent hydrogen.

15 In a fourth more preferred embodiment R^1 and R^2 , independently of each other, represent hydrogen, halo or trifluoromethyl; and R^3 and R^4 both represent hydrogen.

In a fifth more preferred embodiment one of R^1 and R^2 represents hydrogen, halo or trifluoromethyl; and the other of R^1 and R^2 , together with R^3 and R^4 all
20 represent hydrogen.

In a sixth more preferred embodiment R^1 , R^2 , R^3 and R^4 all represent hydrogen.

In a seventh more preferred embodiment R^1 represents halo; and R^2 , R^3 and R^4 all represent hydrogen.

25 In a most preferred embodiment the 1,4-diaza-bicyclo[3.2.2]nonane derivative of the invention is

1,4-Diaza-bicyclo[3.2.2]nonane-4-carboxylic acid 2-oxo-2*H*-chromen-7-yl ester;

1,4-Diaza-bicyclo[3.2.2]nonane-4-carboxylic acid 2-oxo-2*H*-chromen-6-yl
30 ester; or

1,4-Diaza-bicyclo[3.2.2]nonane-4-carboxylic acid 3-bromo-2-oxo-2*H*-chromen-7-yl ester;

or a pharmaceutically acceptable salt thereof.

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

Definition of Substituents

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.

10 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 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.

20 In the context of this invention a haloalkyl group designates an alkyl group as defined herein, which alkyl group is substituted one or more times with halo. Preferred haloalkyl groups of the invention include trihalomethyl, preferably trifluoromethyl.

In the context of this invention a haloalkoxy group designates an alkoxy group as defined herein, which alkoxy group is substituted one or more times with halo. Preferred haloalkoxy groups of the invention include trihalomethoxy, preferably trifluoromethoxy.

In the context of this invention an alkyl-carbonyl group designates an "alkyl-CO- group", wherein alkyl is as defined above. Examples of preferred alkyl-carbonyl groups of the invention include acetyl and propionyl.

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

35 In the context of this invention an alkyl-carbonyl-oxy group designates an "alkyl-CO-O-" group, wherein alkyl is as defined above. Examples of preferred alkyl-carbonyl-oxy groups of the invention include acetoxyl and propionyloxy.

Pharmaceutically Acceptable Salts

The 1,4-diaza-bicyclo[3.2.2]nonane 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 chemical compound 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, the hydrobromide, the nitrate, the perchlorate, the phosphate, the sulphate, the formate, the acetate, the aconate, the ascorbate, the benzenesulphonate, the benzoate, the cinnamate, the citrate, the embonate, the enantate, the fumarate, the glutamate, the glycolate, the lactate, the maleate, the malonate, the mandelate, the methanesulphonate, the naphthalene-2-sulphonate derived, the phthalate, the salicylate, the sorbate, the stearate, the succinate, the tartrate, the toluene-p-sulphonate, and the like. Such salts may be formed by procedures well known and described in the art.

Metal salts of a chemical compound of the invention include alkali metal salts, such as the sodium salt of a chemical compound of the invention containing a carboxy group.

In the context of this invention the "onium salts" of N-containing compounds are also contemplated as pharmaceutically acceptable salts. Preferred "onium salts" include the alkyl-onium salts, the cycloalkyl-onium salts, and the cycloalkylalkyl-onium salts.

Labelled Compounds

The compounds of the invention may be used in their labelled or unlabelled form. In the context of this invention the labelled compound has one or more atoms replaced by an atom having an atomic mass or mass number different from the atomic mass or mass number usually found in nature. The labelling will allow easy quantitative detection of said compound.

The labelled compounds of the invention may be useful as diagnostic tools, radio tracers, or monitoring agents in various diagnostic methods, and for *in vivo* receptor imaging.

The labelled isomer of the invention preferably contains at least one radio-nuclide as a label. Positron emitting radionuclides are all candidates for usage. In the context of this invention the radionuclide is preferably selected from ^2H (deuterium), ^3H (tritium), ^{13}C , ^{14}C , ^{131}I , ^{125}I , ^{123}I , and ^{18}F .

The physical method for detecting the labelled isomer of the present invention may be selected from Position Emission Tomography (PET), Single Photon Imaging Computed Tomography (SPECT), Magnetic Resonance Spectroscopy (MRS),

Magnetic Resonance Imaging (MRI), and Computed Axial X-ray Tomography (CAT), and combinations thereof.

Methods of Producing 1,4-Diaza-bicyclo[3.2.2]nonane Derivatives

5 The 1,4-diaza-bicyclo[3.2.2]nonane derivative 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.

10 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.

15 Biological Activity

The present invention is devoted to the provision novel ligands and modulators of the nicotinic receptors, which ligands and modulators are useful for the treatment of diseases or disorders related to the cholinergic receptors, and in particular
20 the nicotinic acetylcholine receptor (nAChR). Preferred compounds of the invention show a pronounced nicotinic acetylcholine $\alpha 7$ receptor subtype selectivity.

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
25 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 compounds of the present invention may be useful for the treatment, prevention or alleviation of a cognitive disorder, learning
30 deficit, memory deficits and dysfunction, Down's syndrome, Alzheimer's disease, attention deficit, attention deficit hyperactivity disorder (ADHD), Tourette's syndrome, psychosis, depression, Bipolar Disorder, mania, manic depression, schizophrenia, cognitive or attention deficits related to schizophrenia, obsessive compulsive disorders (OCD), panic disorders, eating disorders such as anorexia nervosa, bulimia and
35 obesity, narcolepsy, nociception, AIDS-dementia, senile dementia, autism, Parkinson's disease, Huntington's disease, Amyotrophic Lateral Sclerosis, anxiety, non-OCD anxiety disorders, convulsive disorders, epilepsy, neurodegenerative disorders, transient anoxia, induced neuro-degeneration, neuropathy, diabetic neuropathy, periferic dyslexia, tardive dyskinesia, hyperkinesia, mild pain, moderate or severe pain,

pain of acute, chronic or recurrent character, pain caused by migraine, postoperative pain, phantom limb pain, inflammatory pain, neuropathic pain, chronic headache, central pain, pain related to diabetic neuropathy, to post therapeutic neuralgia, or to peripheral nerve injury, bulimia, post-traumatic syndrome, social phobia, sleeping disorders, pseudodementia, Ganster's syndrome, pre-menstrual syndrome, late luteal phase syndrome, fibromyalgia, chronic fatigue syndrome, mutism, trichotillomania, jet-lag, arrhythmias, smooth muscle contractions, angina pectoris, premature labour, diarrhoea, asthma, tardive dyskinesia, hyperkinesia, premature ejaculation, erectile difficulty, hypertension, inflammatory disorders, inflammatory skin disorders, acne, rosacea, Chron's disease, inflammatory bowel disease, ulcerative colitis, diarrhoea, or withdrawal symptoms caused by termination of use of addictive substances, including nicotine containing products such as tobacco, opioids such as heroin, cocaine and morphine, benzodiazepines and benzodiazepine-like drugs, and alcohol.

In a more preferred embodiment the compounds of the invention may be useful for the treatment, prevention or alleviation of pain, mild or moderate or severe pain, pain of acute, chronic or recurrent character, pain caused by migraine, postoperative pain, phantom limb pain, inflammatory pain, neuropathic pain, chronic headache, central pain, pain related to diabetic neuropathy, to post therapeutic neuralgia, or to peripheral nerve injury.

In an even more preferred embodiment the compounds of the invention may be useful for the treatment, prevention or alleviation of diseases, disorders or conditions associated with smooth muscle contractions, convulsive disorders, angina pectoris, premature labour, convulsions, diarrhoea, asthma, epilepsy, tardive dyskinesia, hyperkinesia, premature ejaculation, or erectile difficulty.

In a still more preferred embodiment the compounds of the invention may be useful for the treatment, prevention or alleviation of a neurodegenerative disorder, transient anoxia, or induced neuro-degeneration.

In a yet more preferred embodiment the compounds of the invention may be useful for the treatment, prevention or alleviation of an inflammatory disorder, inflammatory skin disorder, acne, rosacea, Chron's disease, inflammatory bowel disease, ulcerative colitis, or diarrhoea.

In a further preferred embodiment the compounds of the invention may be useful for the treatment, prevention or alleviation of diabetic neuropathy, schizophrenia, cognitive or attentional deficits related to schizophrenia, or depression.

Finally the compounds 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, 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
5 voluntary diminished intake of the addictive substance.

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

It is at present contemplated that a suitable dosage of the active
10 pharmaceutical ingredient (API) is within the range of from about 0.1 to about 1000 mg API per day, more preferred of from about 10 to about 500 mg API per day, most preferred of from about 30 to about 100 mg API per day, dependent, however, upon the exact mode of administration, the form in which it is administered, the indication considered, the subject and in particular the body weight of the subject involved, and
15 further the preference and experience of the physician or veterinarian in charge.

Preferred compounds of the invention show a biological activity in the sub-micromolar and micromolar range, i.e. of from below 1 to about 100 μ M.

Pharmaceutical Compositions

20 In another aspect the invention provides novel pharmaceutical compositions comprising a therapeutically effective amount of the 1,4-diaza-bicyclo[3.2.2]nonane derivatives, derivative 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
25 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 1,4-diaza-bicyclo[3.2.2]nonane derivative of the invention,
30 or a pharmaceutically acceptable salt or derivative thereof, together with one or more pharmaceutically acceptable carriers therefore, and, optionally, other therapeutic and/or prophylactic ingredients, known 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.

35 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 any skilled person 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.

5 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 depends 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
10 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.

15 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.

20

Methods of Therapy

The 1,4-diaza-bicyclo[3.2.2]nonane derivatives of the present invention are valuable nicotinic and monoamine receptor modulators, and therefore useful for the treatment of a range of ailments involving cholinergic dysfunction as well as a range of
25 disorders responsive to the action of nAChR modulators.

In another aspect the invention provides a method for the treatment, prevention or alleviation of a disease or a disorder or a condition of a living animal body, including a human, which disease, disorder or condition is responsive to modulation of cholinergic receptors and/or monoamine receptors, and which method
30 comprises administering to such a living animal body, including a human, in need thereof an effective amount of a 1,4-diaza-bicyclo[3.2.2]nonane derivative of the invention.

In a preferred embodiment, the disease, disorder or condition relates to the central nervous system.

35 The preferred medical indications contemplated according to the invention are those stated above.

It is at present contemplated that suitable dosage ranges are within 0.1 to 1000 milligrams daily, preferably 10 to 500 milligrams daily, and more preferred of from 30 to 100 milligrams daily, dependent as usual upon the exact mode of administration,

form in which administered, the indication toward which the administration is directed, the subject involved, the body weight of the subject involved, and further the preference and experience of the physician or veterinarian in charge.

5

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.

10 Example 1

Preparatory Example

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
15 pressure.

1,4-Diazabicyclo[3.2.2]nonane (Intermediate compound)

The title compound was prepared according to J. Med. Chem. 1993 **36** 2311-2320 (and according to a slightly modified method below).

20

1,4-Diazabicyclo[3.2.2]nonane (Intermediate compound)

To the solution of 1,4-diazabicyclo[3.2.2]nonan-3-one (15.8 g; 113 mmol) in absolute dioxane (130 ml) LiAlH₄ (4.9 g; 130 mmol) was added under argon. The mixture was refluxed for 6 h and then allowed to reach room temperature. To the
25 reaction mixture water (5 ml in 10 ml of dioxane) was added by drops, the mixture was stirred for 0.5 hour and then filtered off via glass filter. The solvent was evaporated and the residue was distilled using Kugelrohr apparatus at 90°C (0.1 mbar) to yield 1,4-diazabicyclo[3.2.2]nonane (11.1 g; 78%) as colourless hygroscopic material.

30 1,4-Diazabicyclo[3.2.2]nonan-3-one (Intermediate compound)

To the solution of 3-quinuclidinone hydrochloride (45 g; 278 mmol) in 90 ml of water hydroxylamine hydrochloride (21 g; 302 mmol) and sodium acetate (CH₃COOHx3H₂O; 83 g; 610 mmol) were added, the mixture was stirred at 70°C for 1 hour and then cooled to 0°C. The separated crystalline material was filtered off
35 (without washing) and dried *in vacuo* to yield 40.0 g of oxime.

The 3-quinuclidinone oxime (40.0 g) was added during 2 hours by small portions to preheated to 120°C polyphosphoric acid (190 g). The temperature of the solution during the reaction was kept at 130°C. After addition of all oxime the solution was stirred for 20 minutes at the same temperature, then transferred to an enamelled
40 vessel and allowed to reach room temperature. The acidic mixture was neutralized by

a solution of potassium carbonate (500 g in 300 ml of water), transferred into 2000 ml flask, diluted with 300 ml of water and extracted with chloroform (3 x 600 ml). The combined organic extracts were dried with sodium sulphate, the solvent evaporated and the solid residue dried up *in vacuo* to yield 30.0 g (77%) of the mixture of lactams.

- 5 Crystallization of the obtained mixture from 1,4-dioxane (220 ml) gave 15.8 g (40.5%) of 1,4-diazabicyclo[3.2.2]nonan-3-one as colourless large crystals with mp. 211-212°C.

Method A

- 10 1,4-Diaza-bicyclo[3.2.2]nonane-4-carboxylic acid 2-oxo-2*H*-chromen-7-yl ester free base (Compound A1)

Phosgen, 20% in toluene (3.05 g, 30.8 mmol) was solved in anhydrous dichloromethane (15 ml) at 0°C. A mixture of 7-hydroxy-chromen-2-one (1.00 g, 6.17 mmol), pyridine (0.63 g, 8.01 mmol), and dichloromethane (40 ml) was added to the
15 mixture at 0°C. The mixture was stirred for 30 minutes at 0°C. The mixture was allowed reach room-temperature and was stirred over-night. The reaction-mixture was evaporated and was then co-evaporated with toluene (25 ml). The crude chlorocarbonylated intermediate, 1,4-diazabicyclo[3.2.2]nonane (0.78 g 6.17 mmol) and 1,2-dimethoxyethane (20 ml) was stirred at room-temperature for 20 hours. The
20 mixture was filtered. The free base was obtained by adding a mixture of sodium methoxide (2 eq.), methanol (20 ml) and silica gel (5 g), followed by evaporation. The crude mixture was separated by column chromatography on silica gel with dichloromethane, 10% methanol and 1% aqueous ammonia as solvent gave the title compound as a solid. Yield 140 mg, 7%. LC-ESI-HRMS of [M+H]⁺ shows 315.1332
25 Da. Calc. 315.134483 Da, dev. -4.1 ppm.

1,4-Diaza-bicyclo[3.2.2]nonane-4-carboxylic acid 2-oxo-2*H*-chromen-6-yl ester free base (Compound A2)

Was prepared according to Method A from 6-hydroxy-chromen-2-one. LC-
30 ESI-HRMS of [M+H]⁺ shows 315.1336 Da. Calc. 315.134483 Da, dev. -2.8 ppm.

Method B

1,4-Diaza-bicyclo[3.2.2]nonane-4-carboxylic acid 3-bromo-2-oxo-2*H*-chromen-7-yl ester hydrobromide salt (Compound B1)

- 35 1,4-Diaza-bicyclo[3.2.2]nonane-4-carboxylic acid 2-oxo-2*H*-chromen-7-yl ester (0.75 g, 2.39 mmol), sodium acetate (1.17 g, 14.3 mmol), acetic acid (25 ml) and bromine (0.84 g, 5.23 mmol) was stirred at room temperature for 15 h. Water (25 ml) was added, the mixture was stirred and filtered. The crystalline product was washed

with water, methanol and diethylether. Yield 550 mg (42%). LC-ESI-HRMS of [M+H]⁺ shows 393.0464 Da. Calc. 393.044996 Da, dev. 3.6 ppm.

1,4-Diaza-bicyclo[3.2.2]nonane-4-carboxylic acid 3-bromo-2-oxo-2*H*-chromen-6-yl

5 ester (Compound B2)

Is prepared according to Method B.

1,4-Diaza-bicyclo[3.2.2]nonane-4-carboxylic acid 3-chloro-2-oxo-2*H*-chromen-7-yl

ester (Compound B3)

10 Is prepared according to Method B using chlorine, solved in acetic acid.

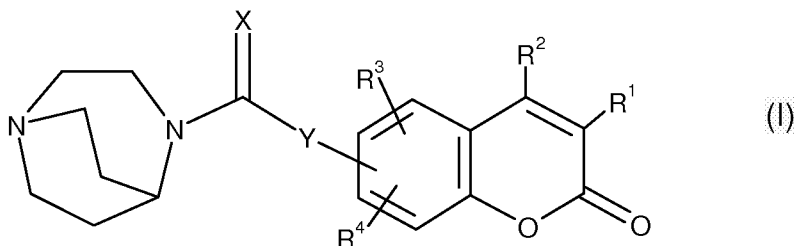
1,4-Diaza-bicyclo[3.2.2]nonane-4-carboxylic acid 3-chloro-2-oxo-2*H*-chromen-6-yl

ester (Compound B4)

Is prepared according to Method B using chlorine, solved in acetic acid.

CLAIMS

1. A 1,4-diaza-bicyclo[3.2.2]nonane derivative represented by Formula I



or a pharmaceutically acceptable salt thereof, wherein

X represents O, S, or NR', wherein R' represents hydrogen or alkyl;

Y represents O, S, or NR'', wherein R'' represents hydrogen or alkyl; and

R¹, R², R³ and R⁴, independently of each other, represent hydrogen, alkyl, cycloalkyl, cycloalkyl-alkyl, hydroxy, alkoxy, halo, haloalkyl, haloalkoxy, cyano, nitro, amino, oxo, carboxy, alkyl-carbonyl, alkoxy-carbonyl, alkyl-carbonyl-oxy, carbamoyl, amido, sulfamoyl, phenyl and/or benzyl.

2. The 1,4-diaza-bicyclo[3.2.2]nonane derivative of claim 1, or a pharmaceutically acceptable salt thereof, wherein X represents O, S, or NR', wherein R' represents hydrogen or alkyl.

3. The 1,4-diaza-bicyclo[3.2.2]nonane derivative of either one of claims 1-2, or a pharmaceutically acceptable salt thereof, wherein Y represents O, S, or NR'', wherein R'' represents hydrogen or alkyl.

4. The 1,4-diaza-bicyclo[3.2.2]nonane derivative of any one of claims 1-3, or a pharmaceutically acceptable salt thereof, wherein R¹, R², R³ and R⁴, independently of each other, represent hydrogen, alkyl, cycloalkyl, cycloalkyl-alkyl, hydroxy, alkoxy, halo, haloalkyl, haloalkoxy, cyano, nitro, amino, oxo, carboxy, alkyl-carbonyl, alkoxy-carbonyl, alkyl-carbonyl-oxy, carbamoyl, amido, sulfamoyl, phenyl and/or benzyl.

5. The 1,4-diaza-bicyclo[3.2.2]nonane derivative of claim 1, which is
1,4-Diaza-bicyclo[3.2.2]nonane-4-carboxylic acid 2-oxo-2*H*-chromen-7-yl ester;
1,4-Diaza-bicyclo[3.2.2]nonane-4-carboxylic acid 2-oxo-2*H*-chromen-6-yl ester;

or

1,4-Diaza-bicyclo[3.2.2]nonane-4-carboxylic acid 3-bromo-2-oxo-2*H*-chromen-7-yl ester;

or a pharmaceutically acceptable salt thereof.

5 6. A pharmaceutical composition comprising a therapeutically effective amount of the 1,4-diaza-bicyclo[3.2.2]nonane derivative of any one of claims 1-5, or a pharmaceutically-acceptable addition salt thereof, or a prodrug thereof, together with at least one pharmaceutically-acceptable carrier or diluent.

10 7. Use of the 1,4-diaza-bicyclo[3.2.2]nonane derivative of any one of claims 1-5, 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
15 monoamine receptors.

8. The use according to claim 7, wherein the disease, disorder or condition is a cognitive disorder, learning deficit, memory deficits and dysfunction, Down's syndrome, Alzheimer's disease, attention deficit, attention deficit hyperactivity disorder (ADHD),
20 Tourette's syndrome, psychosis, depression, Bipolar Disorder, mania, manic depression, schizophrenia, cognitive or attention deficits related to schizophrenia, obsessive compulsive disorders (OCD), panic disorders, eating disorders such as anorexia nervosa, bulimia and obesity, narcolepsy, nociception, AIDS-dementia, senile dementia, autism, Parkinson's disease, Huntington's disease, Amyotrophic Lateral
25 Sclerosis, anxiety, non-OCD anxiety disorders, convulsive disorders, epilepsy, neurodegenerative disorders, transient anoxia, induced neuro-degeneration, neuropathy, diabetic neuropathy, periferic dyslexia, tardive dyskinesia, hyperkinesia, mild pain, moderate or severe pain, pain of acute, chronic or recurrent character, pain caused by migraine, postoperative pain, phantom limb pain, inflammatory pain,
30 neuropathic pain, chronic headache, central pain, pain related to diabetic neuropathy, to post therapeutic neuralgia, or to peripheral nerve injury, bulimia, post-traumatic syndrome, social phobia, sleeping disorders, pseudodementia, Ganser's syndrome, pre-menstrual syndrome, late luteal phase syndrome, fibromyalgia, chronic fatigue syndrome, mutism, trichotillomania, jet-lag, arrhythmias, smooth muscle contractions,
35 angina pectoris, premature labour, diarrhoea, asthma, tardive dyskinesia, hyperkinesia, premature ejaculation, erectile difficulty, hypertension, inflammatory disorders, inflammatory skin disorders, acne, rosacea, Chron's disease, inflammatory bowel disease, ulcerative colitis, diarrhoea, or withdrawal symptoms caused by termination of use of addictive substances, including nicotine containing products such

as tobacco, opioids such as heroin, cocaine and morphine, benzodiazepines and benzodiazepine-like drugs, and alcohol.

9. A method of treatment, prevention or alleviation of a disease or a disorder or
5 a condition of a living animal body, including a human, which disorder, disease or condition is responsive to modulation of cholinergic receptors and/or monoamine receptors, which method comprises the step of administering to such a living animal body in need thereof a therapeutically effective amount of the 1,4-diaza-bicyclo[3.2.2]nonane derivative of any one of claims 1-5.

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2007/054871

A. CLASSIFICATION OF SUBJECT MATTER

INV. C07D471/08 A61K31/551 A61P25/00 A61P25/28

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

C07D A61K A61P

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

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

EPO-Internal, WPI Data, BIOSIS, EMBASE, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 1 231 212 A1 (PFIZER PROD INC [US]) 14 August 2002 (2002-08-14) the whole document	1-9
Y	in particular: paragraph [0024] - paragraph [0029]; claims 1-3,5,7-9,13-16; examples 7,18 paragraph [0035] - paragraph [0043]	1-9
Y	US 2003/130305 A1 (WALKER DANIEL PATRICK [US] ET AL WALKER DANIEL PATRICK [US] ET AL) 10 July 2003 (2003-07-10) abstract paragraph [0002] paragraphs [0127], [0158] - [0161], [0255] - [0274], [0327] - [0340], [0350] - [0357]; claims 1-64; examples 14-17 paragraphs [0472] - [0523], [0690] - [0702]	1-9
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☒ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents :

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- * & * document member of the same patent family

Date of the actual completion of the international search

23 August 2007

Date of mailing of the international search report

29/08/2007

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INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2007/054871

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	<p>WO 2005/111038 A (MEMORY PHARMACEUTICALS CORP [US]; XIE WENGE [US]; HERBERT BRIAN [US];) 24 November 2005 (2005-11-24) abstract page 88, line 5 - page 89, line 14; examples 34-36 page 46, line 3 - page 60, line 22; claims 1-67</p> <p>-----</p>	1-9

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP2007/054871

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 9
because they relate to subject matter not required to be searched by this Authority, namely:
Although claim 9 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

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

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

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/EP2007/054871

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
EP 1231212	A1	14-08-2002	AT 348829 T	15-01-2007
			BR 0200283 A	08-10-2002
			CA 2370411 A1	06-08-2002
			DE 60216830 T2	14-06-2007
			ES 2275808 T3	16-06-2007
			JP 2002302490 A	18-10-2002
			MX PA02001306 A	22-06-2004
<hr/>				
US 2003130305	A1	10-07-2003	NONE	
<hr/>				
WO 2005111038	A	24-11-2005	AU 2005243147 A1	24-11-2005
			CA 2565984 A1	24-11-2005
			EP 1745046 A2	24-01-2007
			KR 20070015607 A	05-02-2007
			US 2005272735 A1	08-12-2005
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