NOVEL 1,4-DIAZA-BICYCLO[3.2.2]NONYL OXADIAZOLYL DERIVATIVES USEFUL AS MODULATOR OF NICOTINIC ACETYLCHOLINE RECEPTORS

TECHNICAL FIELD

This invention relates to novel N-oxides of a 1,4-diaza-bicyclo[3.2.2]nonyl oxadiazolyl derivative and their use in the manufacture of pharmaceutical compositions. The compounds of the invention are found to be cholinergic ligands at the nicotinic acetylcholine receptors.

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.

WO 2007/138038 describes 1,4-diazabicycloalkane derivatives useful as modulators of the nicotinic receptors. However, the N-oxide of the 1,4-diaza-bicyclo[3.2.2]nonyl oxadiazolyl derivative of the present invention have not been described.

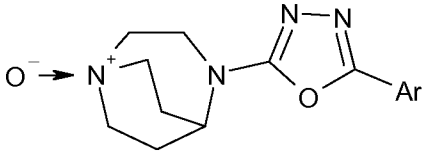
SUMMARY OF THE INVENTION

The present invention is devoted to the provision novel modulators of the nicotinic, which modulators are useful for the treatment of diseases or disorders related to the cholinergic receptors.

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 N-oxides of a 1,4-diaza-bicyclo[3.2.2]nonyl oxadiazolyl derivative of Formula I



(I)

or a pharmaceutically acceptable salt thereof; wherein

Ar represents a phenyl group, which phenyl is substituted with methylenedioxy or ethylenedioxy.

In its second aspect the invention provides pharmaceutical compositions comprising a therapeutically effective amount of the N-oxides of the 1,4-diaza-bicyclo[3.2.2]nonyl oxadiazolyl derivative 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 N-oxides of the 1,4-diaza-bicyclo[3.2.2]nonyl oxadiazolyl 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 modulation of cholinergic 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, which method comprises the step of administering to such a living animal

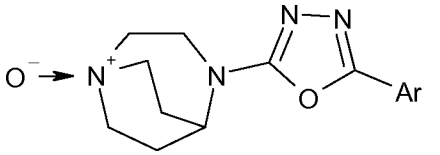
body in need thereof a therapeutically effective amount of the N-oxides of the 1,4-diaza-bicyclo[3.2.2]nonyl oxadiazolyl derivative of the invention.

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

1,4-Diaza-bicyclo[3.2.2]nonyl Oxadiazolyl Derivatives

In a first aspect novel N-oxides of 1,4-diaza-bicyclo[3.2.2]nonyl oxadiazolyl derivatives are provided. The N-oxide of the 1,4-diaza-bicyclo[3.2.2]nonyl oxadiazolyl derivative of the invention may be represented by the general Formula I



(I)

or a pharmaceutically acceptable salt thereof; wherein Ar represents a phenyl group, which phenyl is substituted with methylenedioxy or ethylenedioxy.

In a more preferred embodiment the N-oxides of the 1,4-diaza-bicyclo[3.2.2]nonyl oxadiazolyl derivative of the invention is a compound of Formula I, or a pharmaceutically acceptable salt thereof, wherein Ar represents a phenyl group substituted with methylenedioxy.

In another more preferred embodiment the N-oxides of the 1,4-diaza-bicyclo[3.2.2]nonyl oxadiazolyl derivative of the invention is a compound of Formula I, or a pharmaceutically acceptable salt thereof, wherein Ar represents a phenyl group substituted with ethylenedioxy.

In a most preferred embodiment the N-oxide of the 1,4-diaza-bicyclo[3.2.2]nonyl oxadiazolyl derivative of the invention is

4-(5-Benzo[1,3]dioxol-5-yl-[1,3,4]oxadiazol-2-yl)-1,4-diazabicyclo[3.2.2]-nonane-1-oxide;

or a pharmaceutically acceptable salt thereof.

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

Pharmaceutically Acceptable Salts

The N-oxides of the 1,4-diaza-bicyclo[3.2.2]nonyl oxadiazolyl 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 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 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 1,4-diaza-bicyclo[3.2.2]nonyl oxadiazolyl derivative of the invention and its pharmaceutically acceptable acid addition salt.

Examples of pharmaceutically acceptable cationic salts of a 1,4-diaza-bicyclo[3.2.2]nonyl oxadiazolyl derivative 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 compound of the invention containing an anionic group. Such cationic salts may be formed by procedures well known and described in the art.

Additional 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 1,4-diaza-bicyclo[3.2.2]nonyl oxadiazolyl derivative of the invention include alkali metal salts, such as the sodium salt of a 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 radionuclide as a label. Positron emitting radionuclides are all candidates for usage. In the context of this invention the radionuclide is preferably selected from ^{2}H (deuterium), ^{3}H (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]nonyl Oxadiazolyl Derivatives

The N-oxides of the 1,4-diaza-bicyclo[3.2.2]nonyl oxadiazolyl 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.

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 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 the nicotinic acetylcholine receptor (nAChR). Preferred compounds of the invention show a pronounced nicotinic acetylcholine $\alpha 7$ receptor subtype selectivity, and show a promising in vivo profile.

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 a preferred embodiment the compounds of the present invention may be useful for the treatment, prevention or alleviation of a cognitive disorder, learning 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 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, peripheral 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, Ganser'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, Crohn'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, Crohn'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 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 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 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 μM.

Pharmaceutical Compositions

In another aspect the invention provides novel pharmaceutical compositions comprising a therapeutically effective amount of the N-oxide of the 1,4-diaza-bicyclo[3.2.2]nonyl oxadiazolyl derivative of the invention.

While a 1,4-diaza-bicyclo[3.2.2]nonyl oxadiazolyl derivative of the invention for use in therapy may be administered in the form of the raw 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 1,4-diaza-bicyclo[3.2.2]nonyl oxadiazolyl derivative of the invention, 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, 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 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.

Pharmaceutical compositions of the invention may be those suitable for oral, rectal, bronchial, nasal, pulmonal, topical (including buccal and sub-lingual), transdermal, vaginal or parenteral (including cutaneous, subcutaneous, intramuscular, intraperitoneal, intravenous, intraarterial, intracerebral, intraocular injection or

infusion) administration, or those in a form suitable for administration by inhalation or insufflation, including powders and liquid aerosol administration, or by sustained release systems. Suitable examples of sustained release systems include semipermeable matrices of solid hydrophobic polymers containing the compound of the invention, which matrices may be in form of shaped articles, e.g. films or microcapsules.

The 1,4-diaza-bicyclo[3.2.2]nonyl oxadiazolyl derivative of the invention, together with a conventional adjuvant, carrier, or diluent, may thus be placed into the form of pharmaceutical compositions and unit dosages thereof. Such forms include solids, and in particular tablets, filled capsules, powder and pellet forms, and liquids, in particular aqueous or non-aqueous solutions, suspensions, emulsions, elixirs, and capsules filled with the same, all for oral use, suppositories for rectal administration, and sterile injectable solutions for parenteral use. Such pharmaceutical compositions and unit dosage forms thereof may comprise conventional ingredients in conventional proportions, with or without additional active compounds or principles, and such unit dosage forms may contain any suitable effective amount of the active ingredient commensurate with the intended daily dosage range to be employed.

The 1,4-diaza-bicyclo[3.2.2]nonyl oxadiazolyl derivative of the present invention can be administered in a wide variety of oral and parenteral dosage forms. It will be obvious to those skilled in the art that the following dosage forms may comprise, as the active component, either a compound of the invention or a pharmaceutically acceptable salt of a compound of the invention.

For preparing pharmaceutical compositions from a 1,4-diaza-bicyclo[3.2.2]nonyl oxadiazolyl derivative of the present invention, pharmaceutically acceptable carriers can be either solid or liquid. Solid form preparations include powders, tablets, pills, capsules, cachets, suppositories, and dispersible granules. A solid carrier can be one or more substances which may also act as diluents, flavouring agents, solubilizers, lubricants, suspending agents, binders, preservatives, tablet disintegrating agents, or an encapsulating material.

In powders, the carrier is a finely divided solid, which is in a mixture with the finely divided active component.

In tablets, the active component is mixed with the carrier having the necessary binding capacity in suitable proportions and compacted in the shape and size desired.

The powders and tablets preferably contain from five or ten to about seventy percent of the active compound. Suitable carriers are magnesium carbonate, magnesium stearate, talc, sugar, lactose, pectin, dextrin, starch, gelatin, tragacanth, methylcellulose, sodium carboxymethylcellulose, a low melting wax, cocoa butter, and the like. The term “preparation” is intended to include the formulation of the active

compound with encapsulating material as carrier providing a capsule in which the active component, with or without carriers, is surrounded by a carrier, which is thus in association with it. Similarly, cachets and lozenges are included. Tablets, powders, capsules, pills, cachets, and lozenges can be used as solid forms suitable for oral administration.

For preparing suppositories, a low melting wax, such as a mixture of fatty acid glyceride or cocoa butter, is first melted and the active component is dispersed homogeneously therein, as by stirring. The molten homogenous mixture is then poured into convenient sized moulds, allowed to cool, and thereby to solidify.

Compositions suitable for vaginal administration may be presented as pessaries, tampons, creams, gels, pastes, foams or sprays containing in addition to the active ingredient such carriers as are known in the art to be appropriate.

Liquid preparations include solutions, suspensions, and emulsions, for example, water or water-propylene glycol solutions. For example, parenteral injection liquid preparations can be formulated as solutions in aqueous polyethylene glycol solution.

The 1,4-diaza-bicyclo[3.2.2]nonyl oxadiazolyl derivative according to the present invention may thus be formulated for parenteral administration (e.g. by injection, for example bolus injection or continuous infusion) and may be presented in unit dose form in ampoules, pre-filled syringes, small volume infusion or in multi-dose containers with an added preservative. The compositions may take such forms as suspensions, solutions, or emulsions in oily or aqueous vehicles, and may contain formulation agents such as suspending, stabilising and/or dispersing agents. Alternatively, the active ingredient may be in powder form, obtained by aseptic isolation of sterile solid or by lyophilization from solution, for constitution with a suitable vehicle, e.g. sterile, pyrogen-free water, before use.

Aqueous solutions suitable for oral use can be prepared by dissolving the active component in water and adding suitable colorants, flavours, stabilising and thickening agents, as desired.

Aqueous suspensions suitable for oral use can be made by dispersing the finely divided active component in water with viscous material, such as natural or synthetic gums, resins, methylcellulose, sodium carboxymethylcellulose, or other well known suspending agents.

Also included are solid form preparations, intended for conversion shortly before use to liquid form preparations for oral administration. Such liquid forms include solutions, suspensions, and emulsions. In addition to the active component such preparations may comprise colorants, flavours, stabilisers, buffers, artificial and natural sweeteners, dispersants, thickeners, solubilizing agents, and the like.

For topical administration to the epidermis the 1,4-diaza-bicyclo[3.2.2]nonyl oxadiazolyl derivative of the invention may be formulated as ointments, creams or lotions, or as a transdermal patch. Ointments and creams may, for example, be formulated with an aqueous or oily base with the addition of suitable thickening and/or gelling agents. Lotions may be formulated with an aqueous or oily base and will in general also contain one or more emulsifying agents, stabilising agents, dispersing agents, suspending agents, thickening agents, or colouring agents.

Compositions suitable for topical administration in the mouth include lozenges comprising the active agent in a flavoured base, usually sucrose and acacia or tragacanth; pastilles comprising the active ingredient in an inert base such as gelatin and glycerine or sucrose and acacia; and mouthwashes comprising the active ingredient in a suitable liquid carrier.

Solutions or suspensions are applied directly to the nasal cavity by conventional means, for example with a dropper, pipette or spray. The compositions may be provided in single or multi-dose form.

Administration to the respiratory tract may also be achieved by means of an aerosol formulation in which the active ingredient is provided in a pressurised pack with a suitable propellant such as a chlorofluorocarbon (CFC) for example dichlorodifluoromethane, trichlorofluoromethane, or dichlorotetrafluoroethane, carbon dioxide, or other suitable gas. The aerosol may conveniently also contain a surfactant such as lecithin. The dose of drug may be controlled by provision of a metered valve.

Alternatively the active ingredients may be provided in the form of a dry powder, for example a powder mix of the compound in a suitable powder base such as lactose, starch, starch derivatives such as hydroxypropylmethyl cellulose and polyvinylpyrrolidone (PVP). Conveniently the powder carrier will form a gel in the nasal cavity. The powder composition may be presented in unit dose form for example in capsules or cartridges of, e.g., gelatin, or blister packs from which the powder may be administered by means of an inhaler.

In compositions intended for administration to the respiratory tract, including intranasal compositions, the compound will generally have a small particle size for example of the order of 5 microns or less. Such a particle size may be obtained by means known in the art, for example by micronization.

When desired, compositions adapted to give sustained release of the active ingredient may be employed.

The pharmaceutical preparations are preferably in unit dosage forms. In such form, the preparation is subdivided into unit doses containing appropriate quantities of the active component. The unit dosage form can be a packaged preparation, the package containing discrete quantities of preparation, such as packaged tablets, capsules, and powders in vials or ampoules. Also, the unit dosage

form can be a capsule, tablet, cachet, or lozenge itself, or it can be the appropriate number of any of these in packaged form.

Tablets or capsules for oral administration and liquids for intravenous administration and continuous infusion are preferred compositions.

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).

A therapeutically effective dose refers to that amount of active ingredient, which ameliorates the symptoms or condition. Therapeutic efficacy and toxicity, e.g. ED_{50} and LD_{50}, may be determined by standard pharmacological procedures in cell cultures or experimental animals. The dose ratio between therapeutic and toxic effects is the therapeutic index and may be expressed by the ratio LD_{50}/ED_{50}. Pharmaceutical compositions exhibiting large therapeutic indexes are preferred.

The dose administered must of course be carefully adjusted to the age, weight and condition of the individual being treated, as well as the route of administration, dosage form and regimen, and the result desired, and the exact dosage should of course be determined by the practitioner.

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 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

The 1,4-diaza-bicyclo[3.2.2]nonyl oxadiazolyl derivatives of the present invention are valuable nicotinic, and therefore useful for the treatment of a range of ailments involving cholinergic dysfunction as well as a range of 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 which method 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]nonyl oxadiazolyl derivative of the invention.

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

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.

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.

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 pressure.

4-(5-Benzo[1,3]dioxol-5-yl-[1,3,4]oxadiazol-2-yl)-1,4-diazabicyclo[3.2.2]-nonane-1-oxide
(Compound 1)

4-(5-Benzo[1,3]dioxol-5-yl-[1,3,4]oxadiazol-2-yl)-1,4-diaza-bicyclo[3.2.2]nonane (1.0 g, 3.2 mmol) was solved in ethanol (10 ml, 99%). Hydrogenperoxide (10 ml, 31.82 mmol, 30 wt %) was added dropwise and was stirred for 15 h at room-temperature. The precipitated product was filtered and was washed with ethanol. The product was dried under vacuum for 15 h. Yield 0.50 g (48%). LC-ESI-HRMS of [M+H]+ shows 331.1391 Da. Calc. 331.140631 Da, dev. -4.6 ppm.

4-(5-Benzo[1,3]dioxol-5-yl-[1,3,4]oxadiazol-2-yl)-1,4-diaza-bicyclo[3.2.2]nonane fumaric acid salt (Intermediate compound)

A mixture of 1,4-diazabicyclo[3.2.2]nonane (6.36 g, 50.4 mmol), 2-benzo[1,3]dioxol-5-yl-5-benzylsulfanyl-[1,3,4]oxadiazole (15.0 g, 48.0 mmol), DMF (20 ml) and N,N-diisopropylethylamine (13.0 g, 100.8 mmol) was stirred at 100°C for 20 hours. Chromatography on silica gel with chloroform, 10% methanol and 1% aqueous ammonia as solvent gave a crude product (7.9 g). Repeated chromatography on silica gel with chloroform, 10% methanol and 1% aqueous ammonia as solvent gave the product as an amorphous solid. Yield 4.4 g (29%). The corresponding salt was obtained by addition of a diethyl ether and methanol mixture (9:1) saturated with fumaric acid. The product fumarate salt was recrystalized from isopropanol. Yield from free base 3.2 g (61%). LC-ESI-HRMS of [M+H]+ shows 315.1463 Da. Calc. 315.145716 Da, dev. 1.9 ppm.

2-Benzo[1,3]dioxol-5-yl-5-benzylsulfanyl-[1,3,4]oxadiazole (Intermediate compound)

Benzylbromide (20.2 g, 118.1 mmol) was added over 5 minutes time-period to a mixture of 5-benzo[1,3]dioxol-5-yl-[1,3,4]oxadiazole-2-thiol (25 g, 112.5 mmol), trietylamine (22.8 g, 225 mmol) and ethanol (200 ml, 99%). The reaction mixture was stirred at room-temperature for 2 hours. Aqueous sodium hydroxide (150 ml, 1 M) and water (100 ml) was added followed by filtration. The product was isolated as a solid. Yield 31.0 g (94%).

5-Benzo[1,3]dioxol-5-yl-[1,3,4]oxadiazole-2-thiol (Intermediate compound)

Benzo[1,3]dioxole-5-carboxylic acid hydrazide (45.8 g, 254 mmol) was added to a mixture of potassium hydroxide (15.7 g, 280 mmol) and methanol (350 ml). The mixture was stirred for 30 minutes at room temperature. Carbon disulfide (38.7 g, 508 mmol) was added. The mixture was stirred at reflux for 20 hours, followed by another portion of carbon disulfide (12.7 g, 167 mmol) and reflux for 4 h. Water (300 ml) was added and the excess of carbon disulfide and methanol was evaporated. The aqueous suspension was acidified by adding concentrated hydrochloric acid to pH 3-4. The product precipitated, filtered and was washed with water (50 ml). Yield 53.5 g (95%) as yellow powder.

Benzo[1,3]dioxole-5-carboxylic acid hydrazide (Intermediate compound)

A mixture of benzo[1,3]dioxole-5-carboxylic acid (42.7 g, 257.0 mmol) and thionylchloride (163 g, 1.36 mol) was stirred at 65°C for 6 days. The mixture of benzo[1,3]dioxole-5-carbonyl chloride was evaporated, solved in tetrahydrofuran (200 ml) and added to a mixture of hydrazine monohydrate (154.4 g, 3.08 mol) and tetrahydrofuran (250 ml) at -25°C, followed by stirring for 0.5 hours at -25°C. Water (200 ml) was added followed by filtration. Solid material (35.0 g) was isolated by

filtration and another portion of solid material (10.8 g) was isolated by extraction of the filtrate with ethyl acetate, followed by drying and evaporation. Yield 45.8 g (99%).

Example 2

***Ex vivo* inhibition of ^{3}H-α-bungarotoxine binding in hippocampal membranes**

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

At a predetermined time point after injection mice are killed by decapitation, the hippocampi rapidly dissected on ice and the tissue per animal is weighed. Preparations are performed at 0-4°C unless otherwise indicated. The individual hippocampi (2 per animal) are homogenized for 10 sec in 75 volumes of ice-cold 20 mM Hepes buffer containing 118 mM NaCl, 4.8 mM KCl, 1.2 mM $MgSO_4$ and 2.5 mM $CaCl_2$ containing 0.01% BSA (pH 7.5) using an Ultra-Turrax homogenizer. The tissue suspension is used for binding assays.

Assay

Aliquots of 500 µl homogenate are added to 25 µl of test solution and 25 µl of ^{3}H-α-bungarotoxin (1 nM, final concentration), mixed and incubated for 2 h 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 ½ h) under suction and immediately washed with 2 × 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 ED_{50} (the dose (mg/kg) of the test substance which inhibits the specific binding of ^{3}H-α-bungarotoxin by 50%). Three doses of test substance are used to determine the dose response curve from which the ED_{50} value is determined. If a full curve is not available a 25-75% inhibition of specific binding must be obtained before calculation of an ED_{50} value.

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

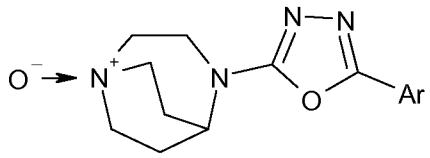
Table 1

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

Compound	EC_{50} (mg/kg)
1	1.5

CLAIMS

1. An N-oxide of a 1,4-diaza-bicyclo[3.2.2]nonyl oxadiazolyl derivative represented by Formula I



(I)

or a pharmaceutically acceptable salt thereof; wherein

Ar represents a phenyl group, which phenyl is substituted with methylenedioxy or ethylenedioxy.

2. The N-oxide of the 1,4-diaza-bicyclo[3.2.2]nonyl oxadiazolyl derivative of claim 1, or a pharmaceutically acceptable salt thereof, wherein Ar represents a phenyl group substituted with methylenedioxy.

3. The N-oxide of the 1,4-diaza-bicyclo[3.2.2]nonyl oxadiazolyl derivative of claim 1, or a pharmaceutically acceptable salt thereof, wherein Ar represents a phenyl group substituted with ethylenedioxy.

4. The N-oxide of the 1,4-diaza-bicyclo[3.2.2]nonyl oxadiazolyl derivative of claim 1, which is

4-(5-Benzo[1,3]dioxol-5-yl-[1,3,4]oxadiazol-2-yl)-1,4-diazabicyclo[3.2.2]-nonane-1-oxide;

or a pharmaceutically acceptable salt thereof.

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

6. Use of the N-oxide of the 1,4-diaza-bicyclo[3.2.2]nonyl oxadiazolyl derivative of any one of claims 1-4, 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.

7. The use according to claim 6, 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), 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 Sclerosis, anxiety, non-OCD anxiety disorders, convulsive disorders, epilepsy, neurodegenerative disorders, transient anoxia, induced neuro-degeneration, neuropathy, diabetic neuropathy, peripheral 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, Ganser'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, Crohn'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.

8. A method of treatment, prevention or alleviation of a disease or a disorder or a condition of a living animal body, including a human, which disorder, disease or condition is responsive to modulation of cholinergic receptors, which method comprises the step of administering to such a living animal body in need thereof a therapeutically effective amount of the N-oxide of the 1,4-diaza-bicyclo[3.2.2]nonyl oxadiazolyl derivative of any one of claims 1-4, or a pharmaceutically acceptable addition salt thereof.