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(54) **Title**: NOVEL DIAZA-BICYCLONONYL-PHENYL DERIVATIVES AND THEIR MEDICAL USE

(57) **Abstract**: This invention relates to novel diazabicyclononyl-phenyl derivatives 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 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.

NOVEL DIAZA-BICYCLONONYL-PHENYL DERIVATIVES AND THEIR MEDICAL USE

TECHNICAL FIELD

This invention relates to novel diazabicyclononyl-phenyl derivatives 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 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.

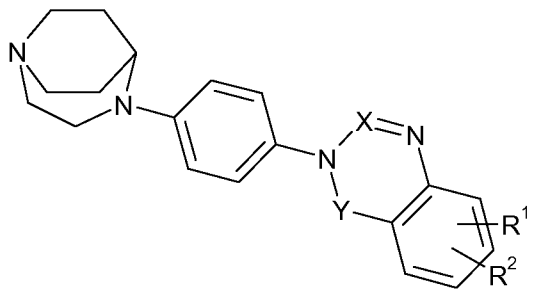
SUMMARY OF THE INVENTION

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-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.

In its first aspect the invention provides novel diazabicyclononyl-phenyl derivative represented by Formula I



(I)

or an *N*-oxide thereof, or a pharmaceutically acceptable salt thereof; wherein

X represents N or CH;

Y represents CH_2 or CO; and

R^1 and R^2, independently of each other, represent hydrogen, halo, trifluoromethyl, trifluoromethoxy, cyano, nitro, hydroxy, alkoxy, alkyl-sulfonyl, phenyl or phenoxy.

In its second aspect the invention provides pharmaceutical compositions comprising a therapeutically effective amount of the diazabicyclononyl-phenyl derivatives of the invention, a stereoisomer thereof or a mixture of its stereoisomers, 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 diazabicyclononyl-phenyl derivatives of the invention, a stereoisomer thereof or a mixture of its stereoisomers, 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.

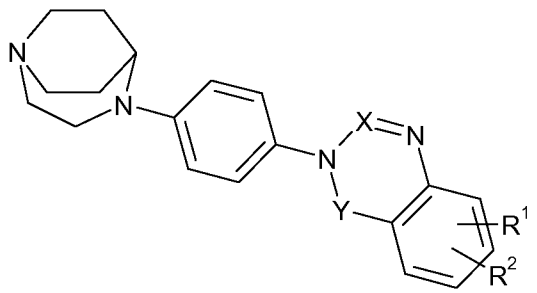
In a final aspect the invention provides methods of treatment, prevention or alleviation of diseases, disorders or conditions of a living animal body, including a human, which disorder, disease or condition is responsive to modulation of cholinergic receptors and/or monoamine receptors, which method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

DETAILED DISCLOSURE OF THE INVENTION

Diazabicyclononyl-phenyl Derivatives

In a first aspect novel diazabicyclononyl-phenyl derivatives are provided. The diazabicyclononyl-phenyl derivatives of the invention may be represented by the general Formula I



(I)

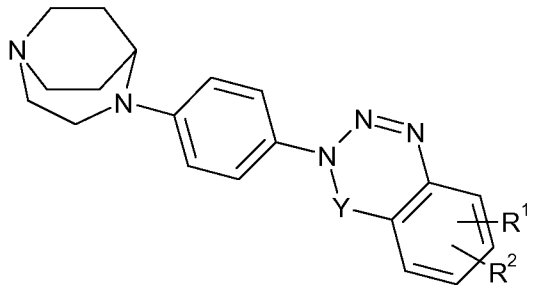
or an *N*-oxide thereof, or a pharmaceutically acceptable salt thereof; wherein

X represents N or CH;

Y represents CH_2 or CO; and

R^1 and R^2, independently of each other, represent hydrogen, halo, trifluoromethyl, trifluoromethoxy, cyano, nitro, hydroxy, alkoxy, alkyl-sulfonyl, phenyl or phenoxy.

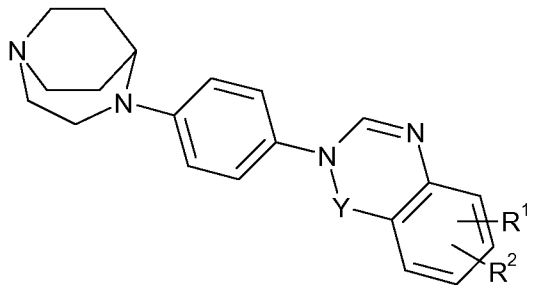
In a more preferred embodiment the diazabicyclononyl-phenyl derivative of the invention is a diazabicyclononyl-phenyl benzotriazinyl derivative represented by Formula IA



(IA)

or an *N*-oxide thereof, or a pharmaceutically acceptable salt thereof; wherein Y, R^1 and R^2, are as defined above.

In another more preferred embodiment the diazabicyclononyl-phenyl derivative of the invention is a diazabicyclononyl-phenyl quinazoline derivative represented by Formula IB



(IB)

or an *N*-oxide thereof, or a pharmaceutically acceptable salt thereof; wherein Y, R^1 and R^2 are as defined above.

In another preferred embodiment the diazabicyclononyl-phenyl derivative of the invention is a compound of Formula I, or an *N*-oxide thereof, or a pharmaceutically acceptable salt thereof, wherein X represents N or CH.

In a more preferred embodiment the diazabicyclononyl-phenyl derivative of the invention is a compound of Formula I, wherein X represents N.

In another more preferred embodiment the diazabicyclononyl-phenyl derivative of the invention is a compound of Formula I, wherein X represents CH.

In a third preferred embodiment the diazabicyclononyl-phenyl derivative of the invention is a compound of Formula I, IA or IB, or an *N*-oxide thereof, or a pharmaceutically acceptable salt thereof, wherein Y represents CH_2 or CO.

In a more preferred embodiment the diazabicyclononyl-phenyl derivative of the invention is a compound of Formula I, IA or IB, wherein Y represents CH_2.

In another more preferred embodiment the diazabicyclononyl-phenyl derivative of the invention is a compound of Formula I, IA or IB, wherein Y represents CO.

In a fourth preferred embodiment the diazabicyclononyl-phenyl derivative of the invention is a compound of Formula I, IA or IB, or an *N*-oxide thereof, or a pharmaceutically acceptable salt thereof, wherein R^1 and R^2, independently of each other, represent hydrogen, halo, trifluoromethyl, trifluoromethoxy, cyano, nitro, hydroxy, alkoxy, alkyl-sulfonyl, phenyl or phenoxy.

In a more preferred embodiment the diazabicyclononyl-phenyl derivative of the invention is a compound of Formula I, IA or IB, wherein R^1 and R^2, independently of each other, represent hydrogen, halo, trifluoromethyl, trifluoromethoxy, cyano or nitro.

In another more preferred embodiment the diazabicyclononyl-phenyl derivative of the invention is a compound of Formula I, IA or IB, wherein one of R^1 and R^2 represents hydrogen; and the other one of R^1 and R^2 represents hydrogen, halo, trifluoromethyl, trifluoromethoxy, cyano, nitro, hydroxy, alkoxy, alkyl-sulfonyl, phenyl or phenoxy.

In a third more preferred embodiment the diazabicyclononyl-phenyl derivative of the invention is a compound of Formula I, IA or IB, wherein one of R^1 and R^2 represents hydrogen; and the other one of R^1 and R^2 represents hydrogen, halo, trifluoromethyl, trifluoromethoxy, cyano or nitro.

In a fourth more preferred embodiment the diazabicyclononyl-phenyl derivative of the invention is a compound of Formula I, IA or IB, wherein both of R^1 and R^2 represent hydrogen.

In a most preferred embodiment the diazabicyclononyl-phenyl derivative of the invention is

3-[4-(1,4-Diaza-bicyclo[3.2.2]non-4-yl)-phenyl]-3H-benzo[d][1,2,3]triazin-4-one; or

3-[4-(1,4-Diaza-bicyclo[3.2.2]non-4-yl)-phenyl]-3H-quinazolin-4-one;

or an *N*-oxide thereof, 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.

Definition of Substituents

In the context of this invention halo represents fluoro, chloro, bromo or iodo.

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

Pharmaceutically Acceptable Salts

The diazabicyclononyl-phenyl 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 an diazabicyclononyl-phenyl derivative of the invention and its pharmaceutically acceptable acid addition salt.

Examples of pharmaceutically acceptable cationic salts of an diazabicyclononyl-phenyl 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 an diazabicyclononyl-phenyl 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), ^{11}C, ^{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), Computed Axial X-ray Tomography (CAT), Computed Tomography (CT), Functional Magnetic Resonance Imaging (fMRI), and combinations thereof.

Methods of Producing Diazabicyclononyl-phenyl Derivatives

The diazabicyclononyl-phenyl 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 compounds of the invention are found to be cholinergic ligands at the nicotinic acetylcholine receptors and modulators of the monoamine receptors and transporters. In a more preferred embodiment the 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.

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, 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 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 diazabicyclononyl-phenyl derivative of the invention.

While an diazabicyclononyl-phenyl 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 diazabicyclononyl-phenyl 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 diazabicyclononyl-phenyl 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 diazabicyclononyl-phenyl 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 an diazabicyclononyl-phenyl 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 diazabicyclononyl-phenyl 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 diazabicyclononyl-phenyl 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 diazabicyclononyl-phenyl 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 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 comprises administering to such a living animal body, including a human, in need thereof an effective amount of an diazabicyclononyl-phenyl 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 sulphate was used as drying agent in the workup-procedures and solvents were evaporated under reduced 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).

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) $LiAlH_4$ (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 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.

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 ($CH_3COOHx3H_2O$; 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 (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 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.

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.

The filtrate was evaporated and the residue was chromatographed on a silica gel (Merck, 9385, 230-400 mesh) column with acetone as eluent. The solvent was evaporated and the residue recrystallized from ethyl etanoate to yield 1,3-diazabicyclo[3.2.2]nonan-4-one (10.2 g; 26%) as colourless fine crystals with mp. 125-126°C.

Method A

4-(4-Nitro-phenyl)-1,4-diaza-bicyclo[3.2.2]nonane hydrofluoric acid salt (Intermediate compound)

A mixture of 1,4-diazabicyclo[3.2.2]nonane (20.2 g, 160 mmol), 1-fluoro-4-nitrobenzene (17.5 ml, 163.3 mmol) and ethylene glycol diethyl ether (160 ml) was stirred at 135°C for 18 hours. The mixture was cooled to room-temperature and diethyl ether (100 ml) was added. The mixture was filtered and the product was isolated by filtration. Yield 24.8 g (58%). Mp. 122-129°C.

Method B

4-(1,4-Diaza-bicyclo[3.2.2]non-4-yl)-phenylamine (Intermediate compound)

A mixture of 4-(4-nitro-phenyl)-1,4-diaza-bicyclo[3.2.2]nonane (0.50 g, 2.0 mmol), palladium on carbon (100 mg, 10%) and methanol (60 ml) was stirred for 15 minutes under hydrogen (130 ml of hydrogen was consumed). The crude mixture was filtered through celite and the product was isolated as an oil in quantitative yield.

2-Amino-N-[4-(1,4-diaza-bicyclo[3.2.2]non-4-yl)-phenyl]-benzamide (Intermediate compound)

Was prepared from N-[4-(1,4-Diaza-bicyclo[3.2.2]non-4-yl)-phenyl]-2-nitro-benzamide according to Method B.

Method C

N-[4-(1,4-Diaza-bicyclo[3.2.2]non-4-yl)-phenyl]-2-nitro-benzamide

4-(1,4-Diaza-bicyclo[3.2.2]non-4-yl)-phenylamine (4.40 g, 20.2 mmol) solved in DME (50 ml) was added to a mixture of 2-nitrobenzoyl chloride (5.4 g 26.3 mmol) and DME(100 ml). The mixture was stirred at room temperature for 15 h. Aqueous sodium hydroxide (1 M) was added and the mixture was extracted with chloroform. Chromatography on silica gel with chloroform, 10% methanol and 1% aqueous ammonia as solvent gave the title compound. The product was isolated, yield 4.0 g (54%).

Method D

3-[4-(1,4-Diaza-bicyclo[3.2.2]non-4-yl)-phenyl]-3H-benzo[d][1,2,3]triazin-4-one fumaric acid salt (Compound D1)

A mixture of 2-amino-N-[4-(1,4-diaza-bicyclo[3.2.2]non-4-yl)-phenyl]-benzamide (1.0 g 2.97 mmol), acetic acid (10 ml), water (5 ml) and sodium nitrite (0.22 g 3.3 mmol) was stirred at 80°C for 1.5 h. Aqueous ammonia (1 M) was

added and the mixture was extracted with chloroform. Chromatography on silica gel with chloroform, 10% methanol and 1% aqueous ammonia as solvent gave the title compound. The product was isolated. Yield 330 mg (32%). The corresponding salt was obtained by addition of a diethyl ether and methanol mixture (9:1) saturated with fumaric acid. Yield 300 mg (68%). LC-ESI-HRMS of [M+H]+ shows 348.1823 Da. Calc. 348.18189 Da, dev. 1.2 ppm.

Method E

3-[4-(1,4-Diaza-bicyclo[3.2.2]non-4-yl)-phenyl]-3H-quinazolin-4-one fumaric acid salt (Compound E1)

A mixture of 2-amino-N-[4-(1,4-diaza-bicyclo[3.2.2]non-4-yl)-phenyl]-benzamide (1.0 g 2.97 mmol) and formic acid (5 ml) was stirred at reflux for 15 h. The mixture was evaporated. Aqueous sodium hydroxide (1 M) was added and the mixture was extracted with chloroform. Chromatography on silica gel with chloroform, 10% methanol and 1% aqueous ammonia as solvent gave the title compound. The product was isolated and yielded 600 mg (58%). The corresponding salt was obtained by addition of a diethyl ether and methanol mixture (9:1) saturated with fumaric acid. Yield 690 mg (86%). LC-ESI-HRMS of [M+H]+ shows 347.187864 Da. Calc. 347.186641 Da, dev. 3.5 ppm.

Example 2

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

The affinity of a compound for binding to α_7-subtype of nicotinic receptors may be determined in a standard assay carried out essentially as described in e.g. WO 2006/087306. In this assay the test value is presented as an IC_{50} (the concentration of the test substance which inhibits the specific binding of ^{3}H-α-bungarotoxin by 50%).

Compounds of the invention tested in this assay show activities in the low sub-micromolar range, i.e. having an IC_{50} of below 1 μM, bee Table 1 below.

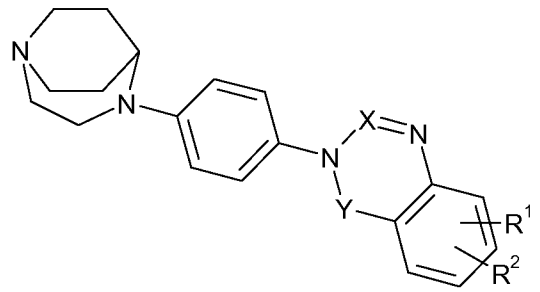
Table 1

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

Compound No.	IC_{50} (μM)
(Compound D1)	0.022
(Compound E1)	0.13

CLAIMS

1. An diazabicyclononyl-phenyl derivative represented by Formula I



(I)

or an *N*-oxide thereof, or a pharmaceutically acceptable salt thereof; wherein

X represents N or CH;

Y represents CH_2 or CO; and

R^1 and R^2, independently of each other, represent hydrogen, halo, trifluoromethyl, trifluoromethoxy, cyano, nitro, hydroxy, alkoxy, alkyl-sulfonyl, phenyl or phenoxy.

2. The diazabicyclononyl-phenyl derivative of claim 1, or an *N*-oxide thereof, or a pharmaceutically acceptable salt thereof, wherein X represents N or CH.

3. The diazabicyclononyl-phenyl derivative of claim 1, or an *N*-oxide thereof, or a pharmaceutically acceptable salt thereof, wherein Y represents CH_2 or CO.

4. The diazabicyclononyl-phenyl derivative of claim 1, or an *N*-oxide thereof, or a pharmaceutically acceptable salt thereof, wherein R^1 and R^2, independently of each other, represent hydrogen, halo, trifluoromethyl, trifluoromethoxy, cyano, nitro, hydroxy, alkoxy, alkyl-sulfonyl, phenyl or phenoxy.

5. The diazabicyclononyl-phenyl derivative of claim 1, which is

3-[4-(1,4-Diaza-bicyclo[3.2.2]non-4-yl)-phenyl]-3H-benzo[d][1,2,3]triazin-4-one; or

3-[4-(1,4-Diaza-bicyclo[3.2.2]non-4-yl)-phenyl]-3H-quinazolin-4-one;

or an *N*-oxide thereof, or a pharmaceutically acceptable salt thereof.

6. A pharmaceutical composition comprising a therapeutically effective amount of the diazabicyclononyl-phenyl derivative of any one of claims 1-5, or an *N*-oxide thereof, or a pharmaceutically-acceptable addition salt thereof, or a prodrug thereof, together with at least one pharmaceutically-acceptable carrier or diluent.

7. The diazabicyclononyl-phenyl derivative of any one of claims 1-5, or an *N*-oxide thereof, or a pharmaceutically-acceptable addition salt thereof, for use as a medicament.

8. Use of the diazabicyclononyl-phenyl derivative of any one of claims 1-5, or an *N*-oxide thereof, 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.

9. The use according to claim 8, 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.

10. 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 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 diazabicyclononyl-phenyl derivative of any one of claims 1-5, or an *N*-oxide thereof, or a pharmaceutically acceptable salt thereof.

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2009/066288

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D471/08 A61K31/55

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, BEILSTEIN Data, CHEM ABS Data, WPI Data, BIOSIS

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[X] Further documents are listed in the continuation of Box C.

[X] 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	Date of mailing of the international search report
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Name and mailing address of the ISA/	Authorized officer
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