



(51) International Patent Classification:

C07D 471/08 (2006.01) *A61P 29/00* (2006.01)
A61K 31/551 (2006.01) *A61P 1/12* (2006.01)
A61P 25/00 (2006.01) *A61P 9/00* (2006.01)

(21) International Application Number:

PCT/EP2010/050609

(22) International Filing Date:

20 January 2010 (20.01.2010)

(25) Filing Language:

English

(26) Publication Language:

English

(30) Priority Data:

PA 2009 00091 21 January 2009 (21.01.2009) DK
61/146,486 22 January 2009 (22.01.2009) US

(71) Applicant (for all designated States except US): **NEUROSEARCH A/S** [DK/DK]; Pederstrupvej 93, DK-2750 Ballerup (DK).

(72) Inventors; and

(75) Inventors/Applicants (for US only): **PETERS, Dan** [SE/DK]; c/o NeuroSearch A/S, Pederstrupvej 93, DK-2750 Ballerup (DK). **TIMMERMANN, Daniel, B.** [DK/DK]; c/o NeuroSearch A/S, Pederstrupvej 93, DK-2750 Ballerup (DK). **NIELSEN, Elsebet, Østergaard** [DK/DK]; c/o NeuroSearch A/S, Pederstrupvej 93, DK-2750 Ballerup (DK). **DYHRING, Tino** [DK/DK]; c/o NeuroSearch A/S, Pederstrupvej 93, DK-2750 Ballerup (DK). **CHRISTENSEN, Jeppe, Kejser** [DK/DK]; c/o NeuroSearch A/S, Pederstrupvej 93, DK-2750 Ballerup (DK).

(74) Common Representative: **NEUROSEARCH A/S**; Pederstrupvej 93, DK-2750 Ballerup (DK).

(81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PE, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:

— as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))

Published:

— with international search report (Art. 21(3))

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

(57) Abstract: This invention relates to novel 1,4-diaza-bicyclo[3.2.2]nonyl pyrimidine 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-PYRIMIDINYL DERIVATIVES AND THEIR MEDICAL USE

TECHNICAL FIELD

5

This invention relates to novel 1,4-diaza-bicyclo[3.2.2]nonyl pyrimidine 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
10 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
15 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

20

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
25 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
30 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
35 serotonergic deficiency.

WO 2004/029053 and WO 2005/074940 describe diazabicyclic aryl derivatives useful as modulators of the nicotinic receptors. However, the 1,4-diaza-

bicyclo[3.2.2]nonyl pyrimidinyl derivatives of the present invention have not been described.

SUMMARY OF THE INVENTION

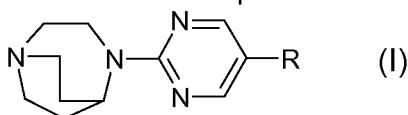
5

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-
10 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
15 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.

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

In its first aspect the invention provides novel 1,4-diaza-
25 bicyclo[3.2.2]nonyl pyrimidine derivatives represented by Formula I



a stereoisomer thereof or a mixture of its stereoisomers, or a pharmaceutically acceptable salt thereof; wherein R represents alkyl, halo, trifluoromethyl, trifluoromethoxy or cyano.

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

35 In a further aspect the invention relates to the use of the 1,4-diaza-bicyclo[3.2.2]nonyl pyrimidine 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.

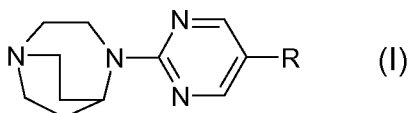
In a final aspect the invention provides methods of treatment, prevention or alleviation of diseases, disorders or conditions of a living animal body, including a human, which disorder, disease or condition is responsive to modulation of cholinergic receptors and/or monoamine receptors, which method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

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

In a first aspect novel 1,4-diaza-bicyclo[3.2.2]nonyl pyrimidine derivatives represented by Formula I



a stereoisomer thereof or a mixture of its stereoisomers, or a pharmaceutically acceptable salt thereof; wherein R represents alkyl, halo, trifluoromethyl, trifluoromethoxy or cyano.

In a preferred embodiment the 1,4-diaza-bicyclo[3.2.2]nonyl pyrimidine derivative of the invention is a compound of Formula I, or a pharmaceutically acceptable salt thereof, wherein R represents halo, trifluoromethyl, trifluoromethoxy or cyano.

In another preferred embodiment the 1,4-diaza-bicyclo[3.2.2]nonyl pyrimidine derivative of the invention is a compound of Formula I, or a pharmaceutically acceptable salt thereof, wherein R represents halo, and in particular chloro, bromo or iodo.

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

4-(5-Bromo-pyrimidin-2-yl)-1,4-diaza-bicyclo[3.2.2]nonane;
4-(5-Iodopyrimidin-2-yl)-1,4-diazabicyclo[3.2.2]nonane; or

4-(5-Chloropyrimidin-2-yl)-1,4-diazabicyclo[3.2.2]nonane;

a stereoisomer thereof or a mixture of its stereoisomers, or a pharmaceutically acceptable salt thereof.

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

Definition of Substituents

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

10 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 (C₁₋₁₈-alkyl), more preferred of from one to six carbon atoms (C₁₋₆-alkyl; lower alkyl), including pentyl, isopentyl, neopentyl, hexyl and isohexyl. In a preferred embodiment alkyl
15 represents a C₁₋₄-alkyl group, including butyl, isobutyl, secondary butyl, and tertiary butyl. In another preferred embodiment of this invention alkyl represents a C₁₋₃-alkyl group, which may in particular be methyl, ethyl, propyl or isopropyl.

Steric Isomers

20 It will be appreciated by those skilled in the art that the compounds of the present invention may exist in different stereoisomeric forms, including enantiomers, diastereomers, as well as geometric isomers (cis-trans isomers). The invention includes all such stereoisomers and any mixtures thereof including racemic mixtures.

25 Racemic forms can be resolved into the optical antipodes by known methods and techniques. One way of separating the enantiomeric compounds (including enantiomeric intermediates) is – in the case the compound being a chiral acid – by use of an optically active amine, and liberating the diastereomeric, resolved salt by treatment with an acid. Another method for resolving racemates
30 into the optical antipodes is based upon chromatography on an optical active matrix. Racemic compounds of the present invention can thus be resolved into their optical antipodes, e.g., by fractional crystallisation of D- or L- (tartrates, mandelates, or camphorsulphonate) salts for example.

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

Optical active compounds can also be prepared from optically active starting materials or intermediates.

Pharmaceutically Acceptable Salts

5 The 1,4-diaza-bicyclo[3.2.2]nonyl pyrimidine 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
10 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
15 acetic acid, the aconate derived from aconitic acid, the ascorbate derived from ascorbic acid, the benzenesulphonate derived from benzenesulphonic 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
20 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 naphthalene-2-sulphonic acid, the phthalate derived from
25 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.

30 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 1,4-diaza-bicyclo[3.2.2]nonyl pyrimidine derivative of the invention and its pharmaceutically acceptable acid addition salt.

 Examples of pharmaceutically acceptable cationic salts of an 1,4-diaza-
35 bicyclo[3.2.2]nonyl pyrimidine 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 1,4-diaza-bicyclo[3.2.2]nonyl pyrimidine 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.

20

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 ^2H (deuterium), ^3H (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 1,4-Diaza-bicyclo[3.2.2]nonyl Pyrimidine Derivatives

5 The 1,4-diaza-bicyclo[3.2.2]nonyl pyrimidine derivative of the invention may be prepared by conventional methods for chemical synthesis, e.g. those described in the working examples. The starting materials for the processes described in the present application are known or may readily be prepared by conventional methods from commercially available chemicals.

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

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

15

Biological Activity

 The 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.

25 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.

30 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 postherpetic 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 postherpetic 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 attention deficits related to schizophrenia, or depression.

5 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
10 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
15 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
20 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
25 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 μ M.

30 **Pharmaceutical Compositions**

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

While an 1,4-diaza-bicyclo[3.2.2]nonyl pyrimidine derivative of the
35 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 pyrimidine derivative of
5 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, known and used in the art. The carrier(s) must be "acceptable" in the sense of being compatible with the other ingredients of the formulation and not harmful to the recipient thereof.

10 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
15 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
20 oral, rectal, bronchial, nasal, pulmonary, 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
25 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 pyrimidine derivative of the invention,
30 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
35 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 pyrimidine 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 1,4-diaza-bicyclo[3.2.2]nonyl pyrimidine 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 homogeneous 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.

5 The 1,4-diaza-bicyclo[3.2.2]nonyl pyrimidine 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
10 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.

15 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
20 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
25 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 pyrimidine derivative of the invention may be formulated as
30 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
35 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
5 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,
10 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
15 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.

20 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
25 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
30 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.

35 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
5 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
10 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
15 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.

20 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 $\mu\text{g/kg}$ i.v. and 1 $\mu\text{g/kg}$ 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 $\mu\text{g/kg}$ to about 10 mg/kg/day i.v., and from about 1 $\mu\text{g/kg}$ to about
25 100 mg/kg/day p.o.

Methods of Therapy

The 1,4-diaza-bicyclo[3.2.2]nonyl pyrimidine derivatives of the present invention are valuable nicotinic and monoamine receptor modulators, and
30 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
35 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 1,4-diaza-bicyclo[3.2.2]nonyl pyrimidine derivative of the invention.

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

5 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
10 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.

15

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.

20

Example 1

Preparatory Example

All reactions involving air sensitive reagents or intermediates were performed under nitrogen and in anhydrous solvents. Magnesium sulfate was
25 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**
30 2311-2320 (and according to a slightly modified method below).

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
35 (CH₃COONa x 3H₂O; 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.

15 1,4-Diazabicyclo[3.2.2]nonane (Intermediate compound)

To the solution of 1,4-diazabicyclo[3.2.2]nonan-3-one (15.8 g; 113 mmol) in absolute dioxane (130 ml) LiAlH₄ (4.9 g; 130 mmol) was added under argon. The mixture was refluxed for 6 hours 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.

25 4-(5-Bromo-pyrimidin-2-yl)-1,4-diaza-bicyclo[3.2.2]nonane fumaric acid salt (Compound 1)

A mixture of 5-bromo-2-chloropyrimidine (2.5 g, 12.92 mmol), 1,4-diazabicyclo[3.2.2]nonane (1.4 g, 18.09 mmol), triethylamine (1.3 g, 12.92 mmol) and dioxane (100 ml) was stirred for 3 hours at room-temperature. Water (100 ml) was added. The mixture was extracted with ethyl acetate (3 x 100 ml). The organic phase was washed with sodium carbonate (100 ml, 1%) and saturated sodium chloride (75 ml). The product was isolated as an oil. The corresponding salt was obtained by addition of a diethyl ether and methanol mixture (9:1) saturated with fumaric acid.

35 LC-ESI-HRMS of [M+H]⁺ shows 283.0543557 Da. Calc. 283.055289 Da, dev. -3.3 ppm.

4-(5-Iodopyrimidin-2-yl)-1,4-diazabicyclo[3.2.2]nonane fumaric acid salt
(Compound 2)

Was prepared according to Method A. LC-ESI-HRMS of [M+H]⁺ shows 331.04023 Da. Calc. 331.041451 Da, dev. -3.7 ppm.

5

4-(5-Chloropyrimidin-2-yl)-1,4-diazabicyclo[3.2.2]nonane fumaric acid salt
(Compound 3)

Was prepared according to Method A. LC-ESI-HRMS of [M+H]⁺ shows 239.10515 Da. Calc. 239.105804 Da, dev. -2.7 ppm.

10

Example 2

In vitro Inhibition of ³H- 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 IC₅₀ (the concentration of the test substance which inhibits the specific binding of ³H- α -bungarotoxin by 50%).

Compounds of the invention tested in this assay show activities in the sub-micromolar range (i.e. having an IC₅₀ of below 1 μ M).

20

Table 1

Inhibition of ³H- α -Bungarotoxine Binding

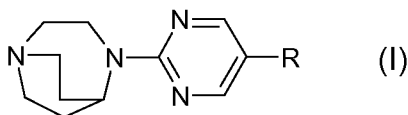
Compound No.	IC ₅₀ (μ M)
Compound 1	0.28
Compound 2	0.038
Compound 3	0.19

25

CLAIMS

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

5



a stereoisomer thereof or a mixture of its stereoisomers, or a pharmaceutically acceptable salt thereof; wherein R represents alkyl, halo, trifluoromethyl, trifluoromethoxy or cyano.

2. The 1,4-diaza-bicyclo[3.2.2]nonyl pyrimidine derivative of claim 1, a stereoisomer thereof or a mixture of its stereoisomers, or a pharmaceutically acceptable salt thereof, wherein R represents halo, trifluoromethyl, trifluoromethoxy or cyano.

3. The 1,4-diaza-bicyclo[3.2.2]nonyl pyrimidine derivative of claim 1, a stereoisomer thereof or a mixture of its stereoisomers, or a pharmaceutically acceptable salt thereof, wherein R represents halo.

20

4. The 1,4-diaza-bicyclo[3.2.2]nonyl pyrimidine derivative of claim 1, which is

4-(5-Bromo-pyrimidin-2-yl)-1,4-diaza-bicyclo[3.2.2]nonane;

4-(5-Iodopyrimidin-2-yl)-1,4-diazabicyclo[3.2.2]nonane; or

25 4-(5-Chloropyrimidin-2-yl)-1,4-diazabicyclo[3.2.2]nonane;

a stereoisomer thereof or a mixture of its stereoisomers, or a pharmaceutically acceptable salt thereof.

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

30

6. The 1,4-diaza-bicyclo[3.2.2]nonyl pyrimidine derivative of any one of claims 1-4, a stereoisomer thereof or a mixture of its stereoisomers, or a pharmaceutically-acceptable addition salt thereof, for use as a medicament.

5 7. Use of the 1,4-diaza-bicyclo[3.2.2]nonyl pyrimidine derivative of any one of claims 1-4, 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
10 human, which disease, disorder or condition is responsive to modulation of cholinergic receptors and/or monoamine receptors.

8. The use according to claim 7, wherein the disease, disorder or condition is a cognitive disorder, learning deficit, memory deficits and dysfunction,
15 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,
20 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
25 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 postherpetic neuralgia, or to peripheral nerve injury, bulimia, post-traumatic syndrome, social phobia, sleeping disorders, pseudodementia, Ganser's
30 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
35 disease, inflammatory bowel disease, ulcerative colitis, diarrhoea, or withdrawal symptoms caused by termination of use of addictive substances, including nicotine containing products such as tobacco, opioids such as heroin, cocaine and morphine, benzodiazepines and benzodiazepine-like drugs, and alcohol.

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

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2010/050609

A. CLASSIFICATION OF SUBJECT MATTER

INV. C07D471/08 A61K31/551 A61P25/00 A61P29/00 A61P1/12
A61P9/00

ADD.

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

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, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 00/34279 A1 (SANOFI SYNTHELABO [FR]; LOCHEAD ALISTAIR [FR]; JEGHAM SAMIR [FR]; NEDE) 15 June 2000 (2000-06-15) the whole document, in particular claims 1,4,5; pages 13-17; entries 2 and 6 in the table	1-9
Y	WO 2007/138039 A1 (NEUROSEARCH AS [DK]; PETERS DAN [DK]; OLSEN GUNNAR M [DK]; NIELSEN ELS) 6 December 2007 (2007-12-06) in particular the claims	1-9
Y	WO 2005/074940 A1 (NEUROSEARCH AS [DK]; PETERS DAN [DK]; OLSEN GUNNAR M [DK]; NIELSEN ELS) 18 August 2005 (2005-08-18) cited in the application in particular claims 1-4,20-30 and page 8, lines 4-8	1-9
	----- -/--	

☒ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

26 April 2010

Date of mailing of the international search report

06/05/2010

Name and mailing address of the ISA/

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040,
Fax: (+31-70) 340-3016

Authorized officer

Hanisch, Inken

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2010/050609

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X,P	WO 2009/024515 A1 (NEUROSEARCH AS [DK]; PETERS DAN [DK]; TIMMERMANN DANIEL B [DK]; OLSEN) 26 February 2009 (2009-02-26)	1-4
Y,P	the whole document, in particular the claims and the intermediate bromo-compound prepared on page 16 -----	1-9

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2010/050609

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 0034279	A1	15-06-2000	AT 249460 T 15-09-2003
		AU 1393000 A 26-06-2000	
		DE 69911241 D1 16-10-2003	
		DE 69911241 T2 01-07-2004	
		EP 1135389 A1 26-09-2001	
		FR 2786770 A1 09-06-2000	
		JP 2002531565 T 24-09-2002	
		US 6407095 B1 18-06-2002	
WO 2007138039	A1	06-12-2007	AU 2007267176 A1 06-12-2007
			AU 2007267177 A1 06-12-2007
			AU 2007267178 A1 06-12-2007
			CA 2653371 A1 06-12-2007
			CA 2653460 A1 06-12-2007
			CA 2653681 A1 06-12-2007
			EP 2041134 A1 01-04-2009
			EP 2049538 A1 22-04-2009
			EP 2029595 A1 04-03-2009
			WO 2007138040 A1 06-12-2007
			WO 2007138041 A1 06-12-2007
			JP 2009538868 T 12-11-2009
			JP 2009538869 T 12-11-2009
			JP 2009538870 T 12-11-2009
			US 2009181984 A1 16-07-2009
			US 2009197872 A1 06-08-2009
			US 2009270403 A1 29-10-2009
WO 2005074940	A1	18-08-2005	AT 450263 T 15-12-2009
			AU 2005210166 A1 18-08-2005
			BR PI0506890 A 17-07-2007
			CA 2554050 A1 18-08-2005
			DK 1713487 T3 06-04-2010
			EP 1713487 A1 25-10-2006
			EP 2172469 A1 07-04-2010
			JP 2007520526 T 26-07-2007
			KR 20060125885 A 06-12-2006
			US 2008227773 A1 18-09-2008
WO 2009024515	A1	26-02-2009	AU 2008290647 A1 26-02-2009