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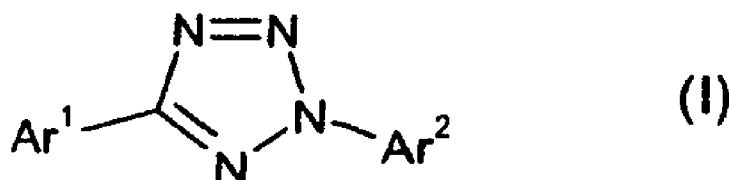
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(54) Title: 2, 5-DISUBSTITUTED TETRAZOLE DERIVATIVES AND THEIR USE AS NICOTINIC ACETYLCHOLINE RECEPTOR MODULATORS



(57) Abstract: This invention relates to novel tetrazole derivatives of formula (I), which are found to be modulators of the nicotinic acetylcholine receptors. Due to their pharmacological profile the compounds of the invention may be useful for the treatment of diseases or disorders as diverse as those related to the cholinergic system of the central nervous system (CNS), the peripheral nervous system (PNS), diseases or disorders related to smooth muscle contraction, endocrine diseases or disorders, diseases or disorders related to neuro- degeneration, diseases or disorders related to inflammation, pain, and withdrawal symptoms caused by the termination of abuse of chemical substances.

2,5-DISUBSTITUTED TETRAZOLE DERIVATIVES AND THEIR USE AS NICOTINIC ACETYLCHOLINE RECEPTOR MODULATORS

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TECHNICAL FIELD

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

BACKGROUND ART

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

Nicotinic acetylcholine receptors (nAChRs) are pentameric ligand gated ion channels and widely distributed throughout the central (CNS) and peripheral (PNS) nervous systems. At least 12 subunit proteins, i.e. $\alpha 2$ - $\alpha 10$ and $\beta 2$ - $\beta 4$, have been identified in neuronal tissue. These subunits provide for a great variety of homomeric and heteromeric combinations that account for the diverse receptor subtypes. For example, the predominant receptor that is responsible for high affinity binding of nicotine in brain tissue has composition $\alpha 4\beta 2$, while another major population of receptors is comprised of the homomeric $\alpha 7$.

Discovery of the important role played by nAChRs in several CNS disorders has called attention to these membrane proteins and to ligands able to modulate their functions. The existence of different subtypes at multiple levels has complicated the understanding of this receptor's physiological role, but at the same time has increased the efforts to discover selective compounds in order to improve the pharmacological characterization of this kind of receptor and to make safer the possible therapeutic use of its modulators.

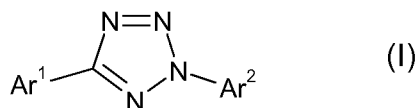
SUMMARY OF THE INVENTION

The present invention is devoted to the provision modulators of the nicotinic receptors, which modulators are useful for the treatment of diseases or disorders related to the nicotinic acetylcholine receptor (nAChR).

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 abuse liability and withdrawal symptoms caused by the termination of abuse of chemical substances, in particular nicotine.

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 a tetrazole derivative represented by Formula I



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or a pharmaceutically acceptable addition salt thereof, wherein one of Ar¹ and Ar² represents phenyl, substituted one or two times with substituents selected from trifluoromethyl, trifluoromethoxy and cyano; and the other one of Ar¹ and Ar² represents pyridinyl, optionally substituted one or two times with substituents selected from halo, trifluoromethyl, trifluoromethoxy and cyano.

In a second aspect the invention provides pharmaceutical compositions comprising a therapeutically effective amount of the tetrazole derivative of the invention, or a pharmaceutically acceptable addition salt thereof, together with at least one pharmaceutically acceptable carrier or diluent.

Viewed from another aspect the invention relates to the use of the tetrazole derivative of the invention, or a pharmaceutically acceptable addition salt thereof, for the manufacture of pharmaceutical compositions/medicaments for the treatment, prevention or alleviation of a disease or a disorder or a condition of a mammal, including a human, which disease, disorder or condition is responsive to modulation of cholinergic receptors.

In yet another aspect the invention provides a method for 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 which method comprises the step of
5 administering to such a living animal body in need thereof a therapeutically effective amount of the tetrazole derivative of the invention.

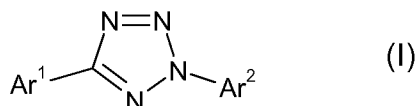
Other objects of the invention will be apparent to the person skilled in the art from the following detailed description and examples.

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DETAILED DISCLOSURE OF THE INVENTION

Tetrazole derivatives

In its first aspect the invention provides a tetrazole derivative represented by Formula I



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or a pharmaceutically acceptable addition salt thereof, wherein one of Ar¹ and Ar² represents phenyl, substituted one or two times with substituents selected from trifluoromethyl, trifluoromethoxy and cyano; and the other one of Ar¹ and Ar² represents pyridinyl, optionally substituted one or two times with
20 substituents selected from halo, trifluoromethyl, trifluoromethoxy and cyano.

In a preferred embodiment the tetrazole derivative of the invention is a compound of Formula I, or a pharmaceutically acceptable addition salt thereof, wherein Ar¹ represents phenyl, substituted one or two times with substituents selected from trifluoromethyl, trifluoromethoxy and cyano.

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In a more preferred embodiment Ar¹ represents phenyl, substituted with trifluoromethyl, trifluoromethoxy or cyano.

In a third more preferred embodiment Ar¹ represents phenyl substituted with cyano. In a special embodiment Ar¹ represents 3-cyanophenyl.

In another preferred embodiment the tetrazole derivative of the
30 invention is a compound of Formula I, or a pharmaceutically acceptable addition salt thereof, wherein Ar² represents phenyl, substituted one or two times with substituents selected from trifluoromethyl, trifluoromethoxy and cyano.

In a more preferred embodiment Ar² represents phenyl, substituted with trifluoromethyl, trifluoromethoxy or cyano.

In another more preferred embodiment Ar^2 represents phenyl, substituted with cyano. In a special embodiment Ar^2 represents 3-cyanophenyl. In a further embodiment Ar^2 represents 3,4-dicyanophenyl.

In a third preferred embodiment the tetrazole derivative of the invention
5 is a compound of Formula I, or a pharmaceutically acceptable addition salt thereof, wherein Ar^1 represents pyridinyl, optionally substituted one or two times with substituents selected from halo, trifluoromethyl, trifluoromethoxy and cyano.

In a more preferred embodiment Ar^1 represents pyridinyl, optionally substituted with halo, trifluoromethyl, trifluoromethoxy or cyano.

10 In another more preferred embodiment Ar^1 represents pyridinyl, optionally substituted with cyano.

In a third more preferred embodiment Ar^1 represents pyridinyl substituted with cyano.

In a fourth more preferred embodiment pyridinyl is an optionally
15 substituted pyridinyl group selected from pyridin-2-yl, pyridin-3-yl and pyridin-4-yl.

In a fourth preferred embodiment the tetrazole derivative of the invention is a compound of Formula I, or a pharmaceutically acceptable addition salt thereof, wherein Ar^2 represents pyridinyl, optionally substituted one or two times with substituents selected from halo, trifluoromethyl, trifluoromethoxy and
20 cyano.

In a more preferred embodiment Ar^2 represents pyridinyl, optionally substituted with halo, trifluoromethyl, trifluoromethoxy or cyano.

In another more preferred embodiment Ar^2 represents pyridinyl, optionally substituted with cyano.

25 In a third more preferred embodiment Ar^2 represents pyridinyl substituted with cyano.

In a fourth more preferred embodiment the pyridinyl group is an optionally substituted pyridinyl group selected from pyridin-2-yl, pyridin-3-yl and pyridin-4-yl.

30 In a further embodiment the tetrazole derivative of the invention is a compound of Formula I, or a pharmaceutically acceptable addition salt thereof, wherein one of Ar^1 and Ar^2 represents phenyl, substituted one or two times with substituents selected from trifluoromethyl, trifluoromethoxy and cyano; and the other one of Ar^1 and Ar^2 represents pyridin-3-yl, optionally substituted one or two
35 times with substituents selected from halo, trifluoromethyl, trifluoromethoxy and cyano.

In a further embodiment the tetrazole derivative of the invention is a compound of Formula I, or a pharmaceutically acceptable addition salt thereof,

wherein one of Ar¹ and Ar² represents phenyl, substituted one or two times with cyano; and the other one of Ar¹ and Ar² represents pyridin-3-yl, optionally substituted one or two times with substituents selected from halo, trifluoromethyl, trifluoromethoxy and cyano. In a further embodiment the one of Ar¹ and Ar² represents phenyl, substituted one or two times with cyano; and the other one of Ar¹ and Ar² represents pyridin-3-yl, optionally substituted one or two times with substituents selected from halo and cyano.

In a further embodiment one of Ar¹ and Ar² represents cyanophenyl, such as 3-cyanophenyl. In a further embodiment one of Ar¹ and Ar² represents dicyanophenyl, such as 3,4-dicyanophenyl.

In a further embodiment the other one of Ar¹ and Ar² represents pyridin-3-yl. In a further embodiment the other one of Ar¹ and Ar² represents pyridin-3-yl substituted with halo, such as pyridin-3-yl substituted with chloro, pyridin-3-yl substituted with fluoro and pyridin-3-yl substituted with bromo. In a further embodiment, the other one of Ar¹ and Ar² represents 6-chloro-pyridin-3-yl, 2-fluoro-pyridin-3-yl, 6-fluoro-pyridin-3-yl, 5-bromo-pyridin-3-yl, 5-fluoro-pyridin-3-yl or 5-chloro-pyridin-3-yl.

In a most preferred embodiment the tetrazole derivative of the invention is

3-(5-Pyridin-3-yl-tetrazol-2-yl)-benzonitrile;
3-(2-Pyridin-3-yl-2H-tetrazol-5-yl)-benzonitrile;
3-[2-(6-Fluoro-3-pyridyl)tetrazol-5-yl]benzonitrile;
3-[2-(2-Fluoro-3-pyridyl)tetrazol-5-yl]benzonitrile;
3-[2-(5-Bromo-3-pyridyl)tetrazol-5-yl]benzonitrile;
3-[2-(5-Fluoro-3-pyridyl)tetrazol-5-yl]benzonitrile;
3-[5-(6-Chloro-3-pyridyl)tetrazol-2-yl]benzonitrile;
3-[5-(2-Fluoro-3-pyridyl)tetrazol-2-yl]benzonitrile;
3-[5-(5-Fluoro-3-pyridyl)tetrazol-2-yl]benzonitrile;
3-[5-(6-Fluoro-3-pyridyl)tetrazol-2-yl]benzonitrile;
3-[2-(6-Chloro-3-pyridyl)tetrazol-5-yl]benzonitrile;
3-[5-(5-Chloro-3-pyridyl)tetrazol-2-yl]benzonitrile;
3-[2-(5-chloro-3-pyridyl)tetrazol-5-yl]benzonitrile;
4-[5-(3-pyridyl)tetrazol-2-yl]phthalonitrile;
or a pharmaceutically acceptable addition 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.

5 Pharmaceutically acceptable salts

The tetrazole 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.

10 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 benzene-sulphonate, the benzoate, the cinnamate, the citrate, the embonate, the enantate,
15 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.

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

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

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

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

 Examples of pre- or prodrug forms of the chemical compound of the invention include examples of suitable prodrugs of the substances according to

the invention, including compounds modified at one or more reactive or derivatizable groups of the parent compound. Of particular interest are compounds modified at a carboxyl group, a hydroxyl group, or an amino group. Examples of suitable derivatives are esters or amides.

5 The chemical compound of the invention may be provided in dissoluble or indissoluble forms together with a pharmaceutically acceptable solvent such as water, ethanol, and the like. Dissoluble forms may also include hydrated forms such as the monohydrate, the dihydrate, the hemihydrate, the trihydrate, the tetrahydrate, and the like. In general, the dissoluble forms are considered
10 equivalent to indissoluble forms for the purposes of this invention.

Steric isomers

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

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

Additional methods for the resolving the optical isomers are known in the art. Such methods include those described by *Jaques J, Collet A, & Wilen S* in "Enantiomers, Racemates, and Resolutions", John Wiley and Sons, New York
30 (1981).

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

Labelled Compounds

35 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), and Computed Axial X-ray Tomography (CAT), or combinations thereof.

Methods of producing tetrazole derivatives

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

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

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

Biological activity

The present invention is devoted to the provision modulators of the nicotinic receptors, which modulators are useful for the treatment of diseases or disorders related to the nicotinic acetylcholine receptor (nAChR). Preferred compounds of the invention show a positive allosteric modulation of the nicotinic acetylcholine $\alpha 4\beta 2$ receptor subtypes.

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 abuse liability and withdrawal symptoms caused by the termination of abuse of chemical substances, in particular nicotine.

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

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.

10 In another preferred embodiment 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
15 schizophrenia, obsessive compulsive disorders (OCD), panic disorders, eating disorders, in particular anorexia nervosa, bulimia and obesity, narcolepsy, nociception, AIDS-dementia, senile dementia, autism, Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis (ALS), anxiety, non-OCD anxiety disorders, convulsive disorders, convulsions, epilepsy, neurodegenerative
20 disorders, transient anoxia, induced neuro-degeneration, neuropathy, diabetic neuropathy, peripheral dyslexia, tardive dyskinesia, hyperkinesia, pain, 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
25 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, chronic fatigue syndrome, mutism, trichotillomania, jet-lag, arrhythmias, smooth muscle contractions, angina pectoris, premature labour, diarrhoea, asthma, tardive
30 dyskinesia, hyperkinesia, premature ejaculation, erectile difficulty, hypertension, inflammatory disorders, inflammatory skin disorders, acne, rosacea, Crohn's disease, inflammatory bowel disease, ulcerative colitis, diarrhoea, or abuse liability and withdrawal symptoms caused by termination of use of addictive substances, including nicotine containing products, in particular tobacco, opioids,
35 in particular heroin, cocaine and morphine, benzodiazepines and benzodiazepine-like drugs, and alcohol.

In a more preferred embodiment the compounds of the invention are used 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.

5 In another more preferred embodiment the compounds of the invention are used for the treatment, prevention or alleviation of smooth muscle contractions, convulsive disorders, angina pectoris, premature labour, convulsions, diarrhoea, asthma, epilepsy, tardive dyskinesia, hyperkinesia, premature ejaculation, or erectile difficulty.

10 In a third more preferred embodiment the compounds of the invention are used for the treatment, prevention or alleviation of a neurodegenerative disorder, transient anoxia, or induced neuro-degeneration.

 In a fourth more preferred embodiment the compounds of the invention are used for the treatment, prevention or alleviation of an inflammatory disorder,
15 inflammatory skin disorder, acne, rosacea, Crohn's disease, inflammatory bowel disease, ulcerative colitis, or diarrhoea.

 In a fifth more preferred embodiment the compounds of the invention are used for the treatment, prevention or alleviation of diabetic neuropathy, schizophrenia, cognitive or attention deficits related to schizophrenia, or
20 depression.

 In a sixth more preferred embodiment the compounds of the invention are used for the treatment, prevention or alleviation of pain, in particular neuropathic pain, diabetic neuropathy, schizophrenia and cognitive or attentional deficits related to schizophrenia, depression, and for assisting in obtaining
25 smoking cessation.

 In a seventh more preferred embodiment the compounds of the invention are used the treatment of abuse liability and withdrawal symptoms caused by termination of use of addictive substances, in particular nicotine containing products, in particular tobacco, opioids, in particular heroin, cocaine
30 and morphine, cannabis, benzodiazepines, benzodiazepine-like drugs, and alcohol.

 In an eight more preferred embodiment the compounds of the invention are used for the treatment of anxiety, cognitive disorders, learning deficit, memory deficits and dysfunction, Down's syndrome, Alzheimer's disease, attention deficit,
35 attention deficit hyperactivity disorder (ADHD), Parkinson's disease, Huntington's disease, Amyotrophic Lateral Sclerosis, Gilles de la Tourette's syndrome, psychosis, depression, mania, manic depression, schizophrenia, obsessive compulsive disorders (OCD), panic disorders, eating disorders, in particular

anorexia nervosa, bulimia and obesity, narcolepsy, nociception, AIDS-dementia, senile dementia, peripheral neuropathy, autism, dyslexia, tardive dyskinesia, hyperkinesia, epilepsy, bulimia, post-traumatic syndrome, social phobia, sleeping disorders, pseudodementia, Ganser's syndrome, pre-menstrual syndrome, late
5 luteal phase syndrome, chronic fatigue syndrome, mutism, trichotillomania, and jet-lag.

In a ninth more preferred embodiment the compounds of the invention are used for the treatment of cognitive disorders, psychosis, schizophrenia and/or depression.

10 In a further more preferred embodiment the compounds of the invention are used for the treatment of endocrine disorders, in particular thyrotoxicosis, pheochromocytoma, hypertension and arrhythmias.

In a further more preferred embodiment the compounds of the invention are used for the treatment of inflammatory diseases, disorders, or conditions,
15 including inflammatory skin disorders, in particular acne and rosacea, Crohn's disease, inflammatory bowel disease, ulcerative colitis, and diarrhoea.

Finally, in a most preferred embodiment, the compounds of the invention may be useful for the treatment of cognition, schizophrenia, attention deficit hyperactivity disorder (ADHD) and neuropathic pain..

20 In this context "treatment" covers treatment, prevention, prophylactics and alleviation of abuse liability and 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
25 in various tissues.

Pharmaceutical compositions

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

In a preferred embodiment the pharmaceutical composition of the invention comprises a therapeutically effective amount of the tetrazole derivative of the invention, any of its isomers or any mixture of isomers, or a pharmaceutically acceptable addition salt thereof.

35 While a compound 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 tetrazole derivative of the invention, or a
5 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 the 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, 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,
25 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 chemical compound of the invention, together with a conventional
30 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
35 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 chemical compound 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 chemical compound of the invention or a pharmaceutically acceptable salt of a chemical compound of the invention.

For preparing pharmaceutical compositions from a chemical compound 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 chemical compound 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
10 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 chemical compound of the invention may be formulated as ointments, creams or lotions, or as a
30 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.

35 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
10 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
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 In a preferred embodiment, when the pharmaceutical composition of the invention is intended for treating patients with abuse liability and withdrawal symptoms caused by nicotine addiction, formulations such as gums, patches, sprays, inhalers, aerosols, etc., are contemplated.

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 $0.1 \mu\text{g/kg}$ 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 100 mg/kg/day p.o.

Methods of therapy

The tetrazole derivatives of the present invention are valuable nicotinic 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 which method comprises administering to

such a living animal body, including a human, in need thereof an effective amount of a tetrazole derivative of the invention.

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

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

It is at present contemplated that suitable dosage ranges are 0.1 to 1000 milligrams daily, 10-500 milligrams daily, and especially 30-100 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 and the body weight of the subject involved, and further the preference and experience of the physician or veterinarian in charge.

A satisfactory result can, in certain instances, be obtained at a dosage as low as 0.005 mg/kg i.v. and 0.01 mg/kg p.o. The upper limit of the dosage range is about 10 mg/kg i.v. and 100 mg/kg p.o. Preferred ranges are from about 0.001 to about 1 mg/kg i.v. and from about 0.1 to about 10 mg/kg p.o.

EXAMPLES

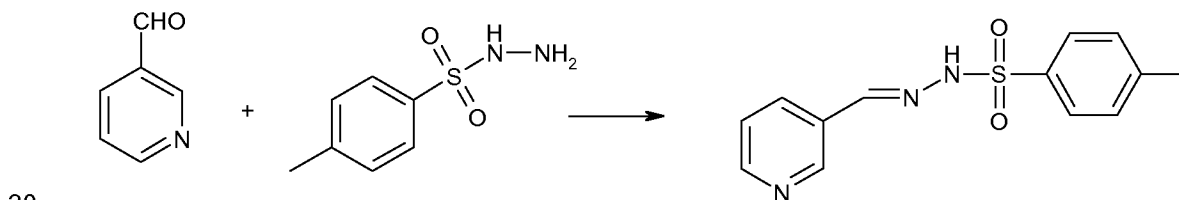
20

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.

25 Preparatory examples

Example 1

1-[Pyridin-3-yl-meth-(Z)-ylidene]-2-toluene-4-sulfone)-hydrazine
(Intermediate compound)



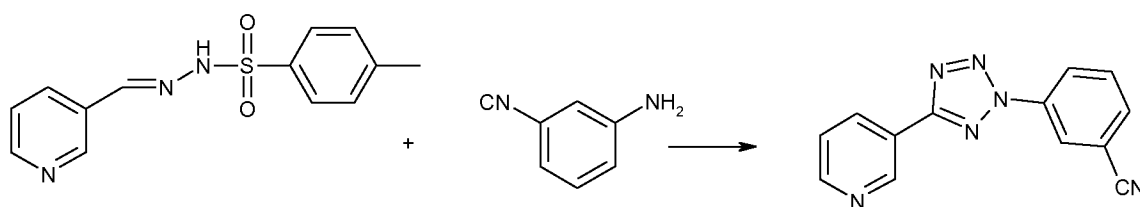
A boiling solution of 3.5 g (18.3 mmol) tolylsulfonyl hydrazide in 20 ml of ethanol (96%), was acidified with a few drops of 1 N hydrochloric acid. A solution of 2 g pyridine-3-carbaldehyde (18.3 mmol, 1 eq.) was added drop wise.

After the addition the heating power was turned off, the product crystallized out of the solution. The white crystals was isolated by filtration, washed with cold water, dried and re-crystallized from ethanol. Yield 4.5 g (90%)

- 5 In analogy herewith the following compound was made:
1-[Benzonitril-3-yl-meth-(Z)-ylidene]-2-(toluene-4-sulfone)-hydrazine
(Intermediate compound)

Example 2

- 10 3-(5-Pyridin-3-yl-tetrazol-2-yl)-benzonitrile (Compound 2.1)



In 5 ml of water and 5 ml of concentrated hydrochloric acid, was suspended 3-amino benzonitrile, the mixture was cooled to 0°C a solution of 1.5 g sodium nitrite was slowly added. The reaction mixture was stirred for 15 minutes, the added dropwise to a cold (0°C) solution of 2 g of 1-[pyridine-3-yl-meth-(Z)-ylidene]-2-(toluene-4-sulfone)-hydrazine in 20 ml of pyridine. The reaction mixture was stirred overnight at room temperature.

The reaction mixture was poured into 100 ml of water. The mixture was stirred for 30 minutes. The solid was isolated by filtration, washed with water and dried in vacuo. The solid was stirred in 1 N hydrochloric acid, the product was isolated by filtration. Yield 0.9 g (54%). Mp. 208-209°C.

- In analogy herewith the following compound was made:
25 3-(2-Pyridin-3-yl-2H-tetrazol-5-yl)-benzonitrile (Compound 2.2)
Mp. 185-205°C.

- 3-[2-(6-Fluoro-3-pyridyl)tetrazol-5-yl]benzonitrile hydrochloride (Compound 2.3)
LC-ESI-HRMS of [M+H]⁺ shows 267.0782 Da. Calc. 267.078902 Da, dev. -2.6
30 ppm. Mp. 168-170°C.

3-[2-(2-Fluoro-3-pyridyl)tetrazol-5-yl]benzonitrile hydrochloride (Compound 2.4)
LC-ESI-HRMS of [M+H]⁺ shows 267.07895 Da. Calc. 267.078902 Da, dev. 0.2
ppm. Mp. 138-140°C.

3-[2-(5-Bromo-3-pyridyl)tetrazol-5-yl]benzonitrile free base (Compound 2.5)

Mp. 175-191 °C

5 3-[2-(5-Fluoro-3-pyridyl)tetrazol-5-yl]benzonitrile free base (Compound 2.6)

LC-ESI-HRMS of [M+H]⁺ shows 267.07899 Da. Calc. 267.078902 Da, dev. 0.3 ppm

3-[5-(6-Chloro-3-pyridyl)tetrazol-2-yl]benzonitrile hydrochloride (Compound 2.7)

10 LC-ESI-HRMS of [M+H]⁺ shows 283.0491 Da. Calc. 283.049352 Da, dev. -0.9 ppm. Mp. 188.3-191.4°C.

3-[5-(2-Fluoro-3-pyridyl)tetrazol-2-yl]benzonitrile hydrochloride (Compound 2.8)

15 LC-ESI-HRMS of [M+H]⁺ shows 267.07974 Da. Calc. 267.078902 Da, dev. 3.1 ppm. Mp. 198-200°C.

3-[5-(5-Fluoro-3-pyridyl)tetrazol-2-yl]benzonitrile free base (Compound 2.9)

20 LC-ESI-HRMS of [M+H]⁺ shows 267.07901 Da. Calc. 267.078902 Da, dev. 0.4 ppm

3-[5-(6-Fluoro-3-pyridyl)tetrazol-2-yl]benzonitrile free base (Compound 2.10)

LC-ESI-HRMS of [M+H]⁺ shows 239.07302 Da. Calc. 239.07278 Da, dev. 1 ppm. Confirmed with N₂ loss.

25 3-[2-(6-Chloro-3-pyridyl)tetrazol-5-yl]benzonitrile free base (Compound 2.11)

LC-ESI-HRMS of [M+H]⁺ shows 255.0429 Da. Calc. 255.04318 Da, dev. -1.1 ppm. Confirmed with N₂ loss.

3-[5-(5-Chloro-3-pyridyl)tetrazol-2-yl]benzonitrile free base (Compound 2.12)

30 LC-ESI-HRMS of [M+H]⁺ shows 255.04315 Da. Calc. 255.04318 Da, dev. -0.1 ppm. Confirmed with N₂ loss.

3-[2-(5-chloro-3-pyridyl)tetrazol-5-yl]benzonitrile free base (Compound 2.13)

35 LC-ESI-HRMS of [M+H]⁺ shows 255.0439 Da. Calc. 255.04318 Da, dev. 2.8 ppm. Confirmed with N₂ loss.

4-[5-(3-pyridyl)tetrazol-2-yl]phthalonitrile free base (Compound 2.14)

LC-ESI-HRMS of [M+H]⁺ shows 246.07768 Da. Calc. 246.07738 Da, dev. 1.2 ppm. Confirmed with N₂ loss.

5 Example 3

Biological activity

Characterization of $\alpha 4\beta 2$ positive allosteric modulators using FLIPR

This experiment shows the modulating activity of compounds of the invention by the ability to positively modulate the response induced by a range of concentrations of nicotine (0.1 nM-100 mM) in human HEK-293 cells stably expressing the human nicotinic acetylcholine receptor subtype $\alpha 4\beta 2$. The modulator activity is determined as a fluorescence-based assay using a Fluorometric Imaging Plate Reader (FLIPR) as described below in more detail.

Full concentration-response curves of nicotine +/- test compound are generated and delta pEC₅₀ values are calculated based on EC₅₀ values for nicotine +/- test compound. EC₅₀ values (Effective Concentration 50%) represent the concentration of the nicotine, at which the nicotine-induced response is 50% of the maximal nicotine-induced response.

Compounds of the invention showing an activity determined as delta pEC₅₀ values of above 1 in the presence of 10 μ M of the test compound compared to nicotine alone are presented in Table 1 below.

Table 1

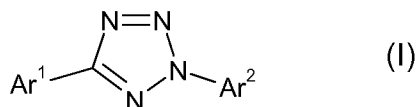
FLIPR nAChR $\alpha 4\beta 2$ positive allosteric modulator activity

25

Compound	Delta pEC ₅₀
2.1	1.9
2.2	1.9
2.3	1.7
2.6	1.8
2.9	1.6
2.10	1.3
2.11	1.1
2.14	1.1

CLAIMS

1. A tetrazole derivative represented by Formula I:



or a pharmaceutically acceptable addition salt thereof, wherein

one of Ar¹ and Ar² represents phenyl, substituted one or two times with
10 substituents selected from trifluoromethyl, trifluoromethoxy and cyano; and

the other one of Ar¹ and Ar² represents pyridinyl, optionally substituted
one or two times with substituents selected from halo, trifluoromethyl,
trifluoromethoxy and cyano.

15 2. The tetrazole derivative of claim 1, or a pharmaceutically acceptable
addition salt thereof, wherein Ar¹ represents phenyl, substituted one or two times
with substituents selected from trifluoromethyl, trifluoromethoxy and cyano.

20 3. The tetrazole derivative of claim 1, or a pharmaceutically acceptable
addition salt thereof, wherein Ar² represents phenyl, substituted one or two times
with substituents selected from trifluoromethyl, trifluoromethoxy and cyano.

4. The tetrazole derivative of claim 1, or a pharmaceutically acceptable
addition salt thereof, wherein Ar¹ represents pyridinyl, optionally substituted one
25 or two times with substituents selected from halo, trifluoromethyl, trifluoromethoxy
and cyano.

5. The tetrazole derivative of claim 1, or a pharmaceutically acceptable
addition salt thereof, wherein Ar² represents pyridinyl, optionally substituted one
30 or two times with substituents selected from halo, trifluoromethyl, trifluoromethoxy
and cyano.

6. The tetrazole derivative of claim 1, or a pharmaceutically acceptable
addition salt thereof, wherein one of Ar¹ and Ar² represents phenyl, substituted
35 one or two times with cyano; and the other one of Ar¹ and Ar² represents pyridin-
3-yl, optionally substituted one or two times with substituents selected from halo
and cyano.

7. The tetrazole derivative compound of claim 1, which is
3-(5-Pyridin-3-yl-tetrazol-2-yl)-benzonitrile; or
3-(2-Pyridin-3-yl-2H-tetrazol-5-yl)-benzonitrile;
5 3-[2-(6-Fluoro-3-pyridyl)tetrazol-5-yl]benzonitrile;
3-[2-(2-Fluoro-3-pyridyl)tetrazol-5-yl]benzonitrile;
3-[2-(5-Bromo-3-pyridyl)tetrazol-5-yl]benzonitrile;
3-[2-(5-Fluoro-3-pyridyl)tetrazol-5-yl]benzonitrile;
3-[5-(6-Chloro-3-pyridyl)tetrazol-2-yl]benzonitrile;
10 3-[5-(2-Fluoro-3-pyridyl)tetrazol-2-yl]benzonitrile;
3-[5-(5-Fluoro-3-pyridyl)tetrazol-2-yl]benzonitrile;
3-[5-(6-Fluoro-3-pyridyl)tetrazol-2-yl]benzonitrile;
3-[2-(6-Chloro-3-pyridyl)tetrazol-5-yl]benzonitrile;
3-[5-(5-Chloro-3-pyridyl)tetrazol-2-yl]benzonitrile;
15 3-[2-(5-chloro-3-pyridyl)tetrazol-5-yl]benzonitrile;
4-[5-(3-pyridyl)tetrazol-2-yl]phthalonitrile;
or a pharmaceutically acceptable addition salt thereof.
8. A pharmaceutical composition comprising a therapeutically effective
20 amount of a tetrazole derivative of any one of claims 1-7, or a pharmaceutically
acceptable addition salt thereof, together with at least one pharmaceutically
acceptable carrier or diluent.
9. The tetrazole derivative of any one of claims 1-7, or a
25 pharmaceutically acceptable salt thereof, for use as a medicament.
10. Use of a tetrazole derivative of any one of claims 1-7, or a
pharmaceutically acceptable addition salt thereof, for the manufacture of a
pharmaceutical composition/medicament for the treatment, prevention or
30 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.
11. The use according to claim 10, wherein the disease, disorder or
35 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 (ALS), anxiety, non-
5 OCD anxiety disorders, convulsive disorders, convulsions, epilepsy, neurodegenerative disorders, transient anoxia, induced neuro-degeneration, neuropathy, diabetic neuropathy, peripheral dyslexia, tardive dyskinesia, hyperkinesia, pain, mild pain, moderate or severe pain, pain of acute, chronic or recurrent character, pain caused by migraine, postoperative pain, phantom limb
10 pain, inflammatory pain, neuropathic pain, chronic headache, central pain, pain related to diabetic neuropathy, to postherpetic neuralgia, or to peripheral nerve injury, post-traumatic syndrome, social phobia, sleeping disorders, pseudodementia, Ganser's syndrome, pre-menstrual syndrome, late luteal phase syndrome, chronic fatigue syndrome, mutism, trichotillomania, jet-lag, arrhythmias,
15 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 abuse liability and withdrawal symptoms caused by termination of use of addictive
20 substances, including nicotine containing products such as tobacco, opioids such as heroin, cocaine and morphine, cannabis, benzodiazepines and benzodiazepine-like drugs, and alcohol.

12. A method of treatment, prevention or alleviation of a disease or a
25 disorder or a condition of a living animal body, including a human, which disorder, disease or condition is responsive to modulation of cholinergic receptors, which method comprises the step of administering to such a living animal body in need thereof a therapeutically effective amount of a tetrazole derivative of any one of claims 1-6, or a pharmaceutically acceptable addition salt thereof.

INTERNATIONAL SEARCH REPORT

International application No

PCT/EP2010/053472

A. CLASSIFICATION OF SUBJECT MATTER

INV. C07D401/04 A61K31/4439 A61P25/28
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 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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 03/029210 A2 (MERCK & CO INC [US]; COSFORD NICHOLAS D [US]; ROPPE JEFFREY [US]; CHEN) 10 April 2003 (2003-04-10) claims 1,30; examples 2,8,11,28,55,118,123,144,180,193,194 -----	1-6,8,9
X	ROPPE JEFFREY ET AL: "Discovery of Novel Heteroarylazoles That Are Metabotropic Glutamate Subtype 5 Receptor Antagonists with Anxiolytic Activity" JOURNAL OF MEDICINAL CHEMISTRY, AMERICAN CHEMICAL SOCIETY, WASHINGTON, US LNKD- DOI:10.1021/JM049828C, vol. 47, no. 19, 14 August 2004 (2004-08-14), pages 4645-4648, XP002518935 ISSN: 0022-2623 table 1; compounds 45,47 ----- -/-	1-5,8,9

☒ 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

4 May 2010

Date of mailing of the international search report

12/05/2010

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INTERNATIONAL SEARCH REPORT

International application No

PCT/EP2010/053472

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2005/066155 A1 (ASTRAZENECA AB [SE]; NPS PHARMA INC [US]; WENSBO DAVID [SE]; EDWARDS L) 21 July 2005 (2005-07-21) page 9, line 12; claims 1,5,6,7-17 -----	1-5,8,9
X	TEHRANI L R ET AL: "3-[Substituted]-5-(5-pyridin-2-yl-2H-tetr azol-2-yl)benzonitriles: Identification of highly potent and selective metabotropic glutamate subtype 5 receptor antagonists" BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, PERGAMON, ELSEVIER SCIENCE, GB LNKD- DOI:10.1016/J.BMCL.2005.07.062, vol. 15, no. 22, 15 November 2005 (2005-11-15), pages 5061-5064, XP025313888 ISSN: 0960-894X [retrieved on 2005-11-15] table 1; compounds 2,8 -----	1,3,4,8, 9
A	WO 2006/114400 A1 (NEUROSEARCH AS [DK]; DAHL BJARNE H [DK]; PETERS DAN [DK]; OLSEN GUNNAR) 2 November 2006 (2006-11-02) page 1, paragraph 1; claim 1 -----	1-12

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/EP2010/053472

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