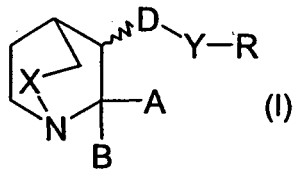
NOVEL 1-AZA BICYCLOALKYL DERIVATIVES FOR THE TREATMENT OF PSYCHOTIC AND NEURODEGENERATIVE DISORDERS

The present invention relates to novel 1-aza-bicycloalkyl derivatives, to processes for their production, their use as pharmaceuticals and to pharmaceutical compositions comprising them.

WO2004/022556 discloses Aza-bicycloethers and their use as nic-alpha 7 agonists. The compounds disclosed in this patent application have valuable properties, but also show disadvantages. Thus, there is a need to provide further compounds having valuable properties as nic-alpha 7 agonists.

In a first aspect, the present invention provides a compound of formula (I)

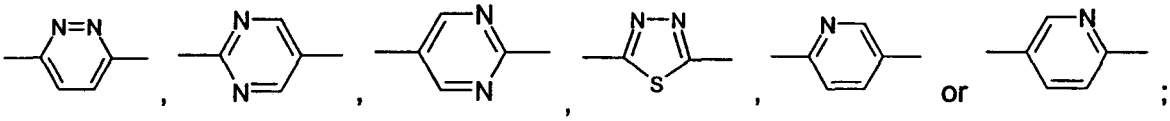

(I)

wherein

X represents CH_2 or a single bond ;

R represents a substituted or unsubstituted C_5-C_{10}aryl or a substituted or unsubstituted C_5-C_{10}heteroaryl, or a group $N(R^1)(R^5)$, or a group $N(R^2)(CHR^3R^4)$;

Y represents a group of formula



D represents NH,NR^6, S, S(O), SO_2

A and B represent, independently of each other, hydrogen or C_1-C_7alkyl under the proviso that not both A and B can represent hydrogen at the same time, or

A and B represent together with the carbon atom to which they are attached form a C_3-C_7cycloalkyl group,

R^1 represents hydrogen, C_1-C_4alkyl, or CF_3;

R^2 represents hydrogen, C_1-C_4alkyl, or CF_3;

R^3 represents hydrogen, C_1-C_4alkyl, or CF_3;

R^4 represents a substituted or unsubstituted C_5-C_{10}aryl or substituted or unsubstituted C_5-C_{10}heteroaryl;

R^5 represents a substituted or unsubstituted C_5-C_{10}aryl or substituted or unsubstituted C_5-C_{10}heteroaryl;

R^6 represents C_1-C_4alkyl, benzyl or benzyl substituted by one or more substituents selected from the group consisting of halogen, C_1-C_4alkyl, C_1-C_4alkoxy;

in free base or acid addition salt form.

The general terms used hereinbefore and hereinafter preferably have within the context of this disclosure the following meanings, unless otherwise indicated:

Where the plural form is used for compounds, salts, and the like, this is taken to mean also a single compound, salt, or the like.

Unless otherwise mentioned, the terms as used in this specification shall have the following meaning:

The term "unsubstituted or substituted" as used herein means that the respective radical can by substituted by one or more, preferably up to three, especially one or two substituents, especially selected from amino, C_1-C_4alkyl amino, di(C_1-C_4alky)-amino, C_3-C_5cycloalkyl amino, di(C_3-C_5)cycloalkyl amino, N-C_1-C_4alkyl-N-C_3-C_5cycloalkyl amino, halogen, C_1-C_4alkyl, C_4-C_6cycloalkyl, hydroxy, C_1-C_4alkoxy, C_3-C_5cycloalkyloxy, C_1-C_4alkoxy C_1-C_4alkoxy, di(C_1-C_4alkyl)-amino C_1-C_4alkoxy, carbamoyl, N-C_1-C_4alkyl-carbamoyl, N,N-di(C_1-C_4alkyl)-carbamoyl, nitro, cyano, carboxy, C_1-C_4alkoxy carbonyl, C_1-C_4alkanoyl, C_1-C_4alkanoyloxy, benzoyl, amidino, guanidino, ureido, mercapto, C_1-C_4alkylthio, pyridyl, phenyl, phenoxy, C_1-C_4alkoxy phenyl, phenylthio, phenyl-C_1-C_4alkylthio, C_1-C_4alkylsulfonyl, phenylsulfonyl, C_1-C_4alkylphenylsulfonyl, C_1-C_4alkenyl, C_1-C_4alkanoyl, C_1-C_4alkylene dioxy bound at adjacent C-atoms of the ring, and C_1-C_4alkyl, which is substituted by halogen, hydroxy, C_1-C_4alkoxy, nitro, cyano, carboxy, C_1-C_4alkoxy carbonyl, C_1-C_4alkanoyl or C_1-C_4alkanoyloxy.

C_5-C_{10}aryl or C_5-C_{10}heteroaryl residues are to be understood as aromatic residues which are in each case unsubstituted or substituted by the substituents provided above, preferably in each case unsubstituted or substituted by one or more substituents selected from halogen, e.g. F, Cl, Br, I; CN, or alkyl, which can be unsubstituted or substituted by halogen, e.g. trifluoromethyl; or C_1-C_4alkoxy, or condensed, e.g. to a benzo[1,3]dioxole or 2,3-dihydrobenzo[1,4]dioxine and/or to a further heterocyclic ring. C_5-C_{10}heteroaryl is an aromatic heterocyclic system comprising one, two or three hetero atoms selected from N, O, S, e.g. a 5 or 7 membered aromatic heterocyclic residue optionally condensed, e.g. to 1 or 2 phenyl rings and/or to a further heterocyclic ring. Examples of C_5-C_{10}aryl or C_5-C_{10}heteroaryl residues as mentioned above include phenyl, naphthyl and isobenzofuranyl.

Alkyl is especially alkyl with from and including 1 up to and including 7, preferably from and including 1 to and including 4 C atoms, more preferably C_1-C_2alkyl, and is linear or branched; preferably, alkyl is methyl, ethyl, propyl, such as n-propyl or isopropyl, butyl, such as n-butyl, sec-butyl, isobutyl or tert-butyl, more preferably methyl or ethyl.

Alkoxy is especially C_1-C_4alkoxy, in particular methoxy, ethoxy or n-propoxy.

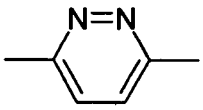
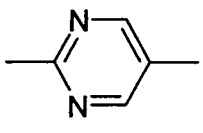
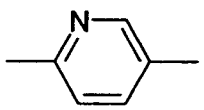
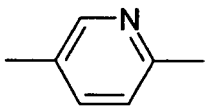
On account of the asymmetrical carbon atom(s) present in the compounds of formula (I) and their salts as well as the corresponding intermediates, may exist in optically active form or in form of mixtures of optical isomers, e.g. in form of racemic mixtures. All optical isomers and their mixtures including racemic mixtures, entantiomers, enantiopure diastereomers, diastereomeric mixtures are part of the present invention.

Compounds of formula (I) exist in free or acid addition salt form. In this specification, unless otherwise indicated, language such as "compounds of formula (I)" is to be understood as embracing the compounds in any form, for example free base or acid addition salt form. Salts which are unsuitable for pharmaceutical uses but which can be employed, for example, for the isolation or purification of free compounds of formula (I) , such as picrates or perchlorates, are also included. For therapeutic use, only pharmaceutically acceptable salts or free compounds are employed (where applicable in the form of pharmaceutical preparations), and are therefore preferred.

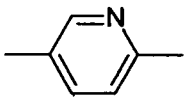
In view of the close relationship between the novel compounds in free form and those in the form of their salts, including those salts that can be used as intermediates, for example in the purification or identification of the novel compounds, any reference to the free compounds hereinbefore and hereinafter is to be understood as referring also to the corresponding salts, as appropriate and expedient.

for compounds of formula (I) and the corresponding intermediates, the following significances are preferred independently, collectively or in any combination or sub-combination:

Y preferably represents one of the following groups:




or


Y particularly preferably represents one of the following groups:



R preferably represents phenyl or substituted phenyl, the substituents being selected from the group consisiting of halogen, nitro, cyano, C_1-C_4alkyl, C_1-C_4alkoxy, C_1-C_4halogenalkyl,

C_1-C_4halogenalkoxy, C_1-C_4alkylsulfonyl, C_1-C_4alkylcarbonyl, C_1-C_4alkylcarbonylamino, phenyl, C_1-C_4alkylphenyl, C_1-C_4alkoxyphenyl, benzyl.

R preferably represents C_5-C_{10} heteroaryl or substituted C_5-C_{10} heteroaryl, the substituents being selected from the cgroup consisiting of halogen, nitro, cyano, C_1-C_4alkyl, C_1-C_4alkoxy, C_1-C_4halogenalkyl, C_1-C_4halogenalkoxy, C_1-C_4alkylsulfonyl, C_1-C_4alkylcarbonyl, C_1-C_4alkylcarbonylamino, phenyl, C_1-C_4alkylphenyl, C_1-C_4alkoxyphenyl, benzyl.

R particularly preferably represents substituted phenyl, the substituents being selected from the cgroup consisiting of halogen, nitro, cyano, C_1-C_4alkyl, C_1-C_4alkoxy, C_1-C_4halogenalkyl, C_1-C_4halogenalkoxy, C_1-C_4alkylsulfonyl, C_1-C_4alkylcarbonyl, C_1-C_4alkylcarbonylamino, phenyl, C_1-C_4alkylphenyl, C_1-C_4alkoxyphenyl, benzyl.

R particularly preferably represents C_5-C_{10} heteroaryl or substituted C_5-C_{10} heteroaryl, the substituents being selected from the cgroup consisiting of halogen, nitro, cyano, C_1-C_4alkyl, C_1-C_4alkoxy, C_1-C_4halogenalkyl, C_1-C_4halogenalkoxy, C_1-C_4alkylsulfonyl, C_1-C_4alkylcarbonyl, C_1-C_4alkylcarbonylamino, phenyl, C_1-C_4alkylphenyl, C_1-C_4alkoxyphenyl, benzyl and the C_5-C_{10} heteroaryl being selected from the group consisting of indolyl, thiophenyl, benzo[1,3]dioxolyl, furanyl, benzathiazolyl, pyrrolo[2,3-b]pyridinyl, dibenzothiophenyl, benzo[b]thiophenyl, pyridinyl, dibenzofuranyl, quinolinyl.

A preferably represents C_1-C_4alkyl, more preferably methyl or ethyl, most preferably methyl.

B preferably represents hydrogen, C_1-C_4alkyl, more preferably hydrogen, methyl or ethyl, most preferably hydrogen.

A and B preferably represent with the carbon atom to which they are attached a cycloporpyl group.

X preferably represents CH_2.

D preferably represents NH.

R^1 preferably represents H, C_1-C_4alkyl or CF_3.

R^2 preferably represents H, C_1-C_4alkyl or CF_3.

R^3 preferably represents H, C_1-C_4alkyl or CF_3.

R^4 preferably represents C_5-C_{10}aryl, which is unsubstituted or substituted by one or more substituents selected from halogen, C_1-C_4alkoxy, CN or C_1-C_2alkyl which is unsubstituted or substituted by halogen; or hetero-C_5-C_{10}aryl, which which is unsubstituted or substituted by one or more substituents selected from halogen, C_1-C_4alkoxy, CN or C_1-C_2alkyl which is unsubstituted or substituted by halogen.

R^6 preferably represents hydrogen, C_1-C_4alkyl or benzyl, more preferably hydrogen, methyl, ethyl or benzyl.

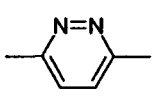
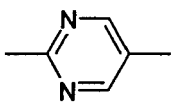
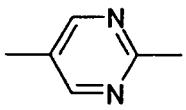
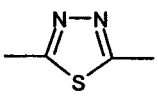
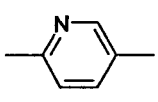
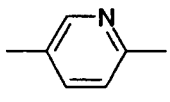
R^6 particularly referably represents Hydrogen, Methyl or Benzyl.

A preferred embodiment of the invention relates to compounds of formula (I) wherein

X represent CH_2,

R represents C_5-C_{10}aryl, which is substituted by one or more substituents selected from halogen, NO_2, CN, C_1-C_4alkoxy which is unsubstituted or substituted by halogen, or C_1-C_4alkyl which is unsubstituted or substituted by halogen, C_1-C_4alkylsulfonyl, C_1-C_4alkylcarbonylamino;

Y represents a group of formula






or

;

D represents NH;

A represents hydrogen or C_1-C_7alkyl and B represents hydrogen, C_1-C_7alkyl or

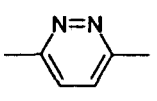
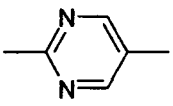
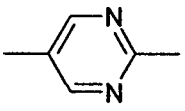
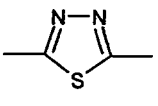
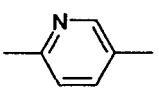
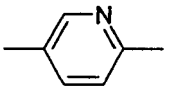
A and B represent together with the carbon atom to which they are attached form a cyclopropyl, cyclopentyl or cyclohexyl group,

A further preferred embodiment of the invention relates to compounds of formula (I) wherein

X represents CH_2,

R represents hetero-C_5-C_{10}aryl, which which is unsubstituted or substituted by one or more substituents selected from halogen, C_1-C_4alkoxy, CN or C_1-C_4alkyl which is unsubstituted or substituted by halogen, phenyl which is unsubstituted or substituted by phenyl, C_1-C_4alkoxy or benzyl;

Y represents a group of formula






or

;

D represents NH;

A represents hydrogen or C_1-C_7alkyl and B represents hydrogen, C_1-C_7alkyl or

A and B represent together with the carbon atom to which they are attached form a cyclopropyl, cyclopentyl or cyclohexyl group,

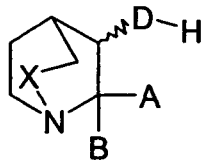
Particularly preferred compounds of the invention are the compounds of the Examples.

In a further aspect, the present invention provides a processes for the production of a compound of formula (I).

A first process comprises the step of reacting a compound of formula (II)

Z-Y-R (II)

wherein Y and R are as defined above for a compound of formula (I) and Z is a leaving group, e.g. F, Cl, Br, I or OSO_2CF_3, with a compound of formula (III)



(III)

wherein A, B, D, X have the meanings as defined for a compound of formula (I), and recovering the so obtained compound of formula (I) in free base or acid addition salt form and optionally oxidizing the so obtained compound.

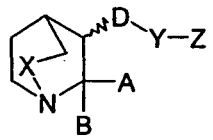
The above described processes for production may be carried out in accordance with standard procedures, for example as illustrated in the Examples.

Compounds of formula (II) are known or may be prepared from corresponding known compounds, e.g. as described in the Examples, e.g. in analogy to Coates WJ, McKillop A (1992) Synthesis 334-342. The compounds of formula (III) are known (Vorob'eva, V. Ya.; Bondarenko, V. A.; Mikhlina, E. E.; Turchin, K. F.; Linberg, L. F.; Yakhontov, L. N. Reaction of 2-methylene-3-oxoquinuclidine with nucleophilic reagents. Khimiya Geterotsiklicheskikh Soedinenii (1977), (10), 1370-6).

Compounds of formula (III) are known or may be prepared from corresponding known compounds

A second process for manufacturing the copounds of formula (I) comprises the step of reacting a compound of formula (IV)

(IV)



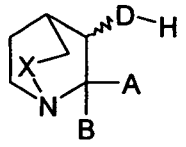
wherein A, B,D and Y are as defined above for a compound of formula (I) and Z represents a leaving group, e.g. F, Cl, Br, I or OSO_2CF_3, with a compound of formula V

$R\text{-}B(OH)_2$ (V)

wherein R is as defined above for a compound of formula (I), and recovering the so obtained compound of formula (I) in free base or acid addition salt form.

Compounds of formula (IV) are novel and subject to the present invention. Compounds of formula (IV) may be prepared by reacting compounds of formula (III)

(III)



wherein A, B, D, X have the meanings as defined for a compound of formula (I), with compounds of formula (IIX)

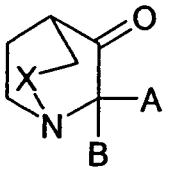
Z-Y-Z (IIX)

wherein Y and Z are as defined for a compound of formula (II).

In this process, reaction auxiliaries such as arylboronic acids may be used.

Compounds of formula (IIX) are known or may be prepared from corresponding known compounds.

A third process, for manufacturing the copounds of formula (I), wherein D represents NH or NR^6, comprises the step of reacting a compound of formula (VI)



(VI)

wherein A, B and X are as defined above for compounds of formula (I) with a compound (VII)

H_2N-Y-R (VII)

wherein Y and R are as defined above for compounds of formula (I) and recovering the so obtained compound of formula (I) in free base or acid addition salt form.

In this process, reaction auxiliaries, such as aryl and/or heteroarylamines may be used.

Compounds of formula (VI) are known or may be prepared from corresponding known compounds.

Compounds of formula (VII) are known or may be prepared from corresponding known compounds.

The following consideration may apply to all processes as described above, as the case may be:

Purifiacation / Isolation: Working up the reaction mixtures according to the above processes and purification of the compounds thus obtained may be carried out in accordance to known procedures.

Salt formation: Acid addition salts may be produced from the free bases in known manner, and vice-versa. Suitable acid addition salts for use in accordance with the present invention include for example the hydrochloride.

Optical pure isomers: Compounds of formula (I) in optically pure form can be obtained from the corresponding racemates according to well-known procedures, e.g. HPLC with chiral matrix. Alternatively, optically pure starting materials can be used.

Protecting groups: If one or more other functional groups, for example carboxy, hydroxy, amino, or mercapto, may need to be protected in the starting materials by protecting groups. The

protecting groups employed may already be present in precursors and should protect the functional groups concerned against unwanted secondary reactions, such as acylations, etherifications, esterifications, oxidations, solvolysis, and similar reactions. It is a characteristic of protectiAng groups that they lend themselves readily, i.e. without undesired secondary reactions, to removal, typically by solvolysis, reduction, photolysis or also by enzyme activity, for example under conditions analogous to physiological conditions, and that they are not present in the end-products. The specialist knows, or can easily establish, which protecting groups are suitable with the reactions mentioned hereinabove and hereinafter.

The protection of such functional groups by such protecting groups, the protecting groups themselves, and their removal reactions are described for example in standard reference works, such as J. F. W. McOmie, "Protective Groups in Organic Chemistry", Plenum Press, London and New York 1973, in T. W. Greene, "Protective Groups in Organic Synthesis", Wiley, New York 1981, in "The Peptides"; Volume 3 (editors: E. Gross and J. Meienhofer), Academic Press, London and New York 1981, in "Methoden der organischen Chemie" (*Methods of organic chemistry*), Houben Weyl, 4th edition, Volume 15/I, Georg Thieme Verlag, Stuttgart 1974, in H.-D. Jakubke and H. Jescheit, "Aminosäuren, Peptide, Proteine" (*Amino acids, peptides, proteins*), Verlag Chemie, Weinheim, Deerfield Beach, and Basel 1982, and in Jochen Lehmann, "Chemie der Kohlenhydrate: Monosaccharide und Derivate" (*Chemistry of carbohydrates: monosaccharides and derivatives*), Georg Thieme Verlag, Stuttgart 1974.

Oxidation: In case D represents S, an oxidation to S(O) or SO_2 is possible using standard oxidizing agents, e.g. H_2O_2, MCPBA or the like in conventional inert diluent, e.g. benzene or chlorinated solvent such as dichlormethane.

The compounds of the invention and their pharmaceutically acceptable acid addition salts, hereinafter referred to as compounds of the invention, exhibit valuable pharmacological properties when tested in vitro and in animals, and are therefore useful as pharmaceuticals.

Thus, the compounds of the invention are found to be cholinergic ligands of the nAChR. In addition preferred compounds of the invention show selective α7-nAChR activity. The compounds of the present invention may in particular be found to be agonists, partial agonists, antagonists or allosteric modulators of the receptor.

Due to their pharmacological profiles, compound of the invention are anticipated to be useful for the treatment of diseases or conditions as diverse as CNS related diseases, PNS related diseases, diseases related to inflammation, pain and withdrawal symptoms caused by an abuse of chemical substances. Diseases or disorders related to the CNS include general anxiety disorders, cognitive disorders, learning and memory deficits and dysfunctions, Alzheimer`s

disease (AD), prodromal AD, mild cognitive impairment in the elderly (MCI), amnestic MCI, age associated memory impairment, attention deficit and hyperactivity disorder (ADHD), Parkinson's disease, Huntington's disease, ALS, prionic neurodegenerative disorders such as Creutzfeld-Jacob disease and kuru disease, Gilles de la Tourette's syndrome, psychosis, depression and depressive disorders, mania, manic depression, schizophrenia, the cognitive deficits in schizophrenia, obsessive compulsive disorders, panic disorders, eating disorders, narcolepsy, nociception, AIDS-dementia, senile dementia, mild cognitive dysfunctions related to age, autism, dyslexia, tardive dyskinesia, epilepsy, and convulsive disorders, post-traumatic stress disorders, transient anoxia, pseudodementia, pre-menstrual syndrome, late luteal phase syndrome, chronic fatigue syndrome and jet lag. Furthermore, compound of the invention may be useful for the treatment of endocrine disorders, such as thyrotoxicosis, pheochromocytoma, hypertension and arrhythmias as well as angina pectoris, hyperkinesia, premature ejaculation and erectile difficulty. Still further, compound of the invention may be useful in the treatment of inflammatory disorders (Wang et al., Nature 2003, 421, 384; de Jonge et al., Nature Immunology 2005, 6, 844; Saeed et al., JEM 2005, 7, 1113), disorders or conditions including inflammatory skin disorders, rheumatoid arthritis, post-operative ileus, Crohn's diesease, inflammatory bowel disease, ulcerative colitis, sepsis, fibromyalgia, pancreatitis and diarrhoea. Compounds of the invention may further be useful for the treatment of withdrawal symptoms caused by termination of the use of addictive substances, like heroin, cocaine, tobacco, nicotine, opioids, benzodiazepines and alcohol. Finally, compound of the invention may be useful for the treatment of pain, e.g. caused by migraine, postoperative pain, phantom limb pain or pain associated with cancer. The pain may comprise inflammatory or neuropathic pain, central pain, chronic headache, pain related to diabetic neuropathy, to post therapeutic neuralgia or to peripheral nerve injury.

Furthermore, degenerative ocular disorders which may be treated include ocular diseases which may directly or indirectly involve the degeneration of retinal cells, including ischemic retinopathies in general, anterior ischemic optic neuropathy, all forms of optic neuritis, age-related macular degeneration (AMD), in its dry forms (dry AMD) and wet forms (wet AMD), diabetic retinopathy, cystoid macular edema (CME), retinal detachment, retinitis pigmentosa, Stargardt's disease, Best's vitelliform retinal degeneration, Leber's congenital amaurosis and other hereditary retinal degenerations, pathologic myopia, retinopathy of prematurity,and Leber's hereditary optic neuropathy.

It has been found that the effect of a combination which comprises at least one nicotinic-alpha 7 receptor agonist and at least one compound selected from the group consisting of (a) conventional antipsychotics and (b) atypical antipsychotics is greater than the additive effect of the combined drugs in the treatment of psychiatric disorders. In particular, the combinations

disclosed herein can be used to treat schizophrenia which is refractory to monotherapy employing one of the combination partners alone.

Therefore, in one aspect of the present invention, there is provided a combination, such as a combined preparation or pharmaceutical composition, which comprises at least one nicotinic-alpha 7 receptor agonist and at least one compound selected from the group consisting of
(a) conventional antipsychotics; and
(b) atypical antipsychotics,
in which the active ingredients are present in each case in free form or in the form of a pharmaceutically acceptable salt and optionally at least one pharmaceutically acceptable carrier.

Any such combuination may be administered for simultaneous, separate or sequential use.

The term "psychiatric disorders" as used herein includes, but is not limited to schizophrenia, anxiety disorders, depression and bipolar disorders. Preferably, the psychiatric disorder to be treated with the combination disclosed herein is schizophrenia, more preferably schizophrenia which is refractory to monotherapy employing one of the combination partners alone.

The term "conventional antipsychotics" as used herein includes, but is not limited to haloperidol, fluphenazine, thiotixene and flupentixol.

The term "atypical antipsychotics" as used herein includes, but is not limited to clozaril, risperidone, olanzapine, quetiapine, ziprasidone and aripiprazol.

In another aspect, the compounds of the invention are used as diagnostic agents and/or PET ligands and / or SPECT ligands, e.g. for the identification and localization of nicotine receptors in various tissues.

In particular, the agents of the invention are α7 nicotinic acetylcholine receptor (α7 nAChR) agonists.

In functional assays, the agents of the invention display high affinity at the α7 nAChR as shown in the following tests:

a) A functional assay for affinity at the α7 nAChR is carried out with a rat pituitary cell line stably expressing the α7 nAChR (Feuerbach et al., Neuropharmacology, 2005, 48, 215). Briefly, GH3 cells recombinantly expressing the nAChR α7 were seeded 72 h prior to the experiment on

black 96-well plates and incubated at 37°C in a humidified atmosphere (5 % CO_2/95 % air). On the day of the experiment medium was removed by flicking the plates and replaced with 100 µl growth medium containing af fluorescent calcium sensitve dye, in the presence of 2.5 mM probenicid (Sigma). The cells were incubated at 37°C in a humidified atmosphere (5 % CO_2/95 % air) for 1 h. Plates were flicked to remove excess of Fluo-4, washed twice with Hepes-buffered salt solution (in mM: NaCl 130, KCl 5.4, $CaCl_2$ 2, $MgSO_4$ 0.8, NaH_2PO_4 0.9, glucose 25, Hepes 20, pH 7.4; HBS) and refilled with 100 µl of HBS containing antagonists when appropriate. The incubation in the presence of the antagonist lasted between 3 and 5 minutes. Plates were then placed into an imaging plate reader and fluorescence signal recordedd In this assay, compounds of the invention exhibit pEC_{50} values of about 5 to about 9. Partial and potent agonists in this test are preferred.

b) To assess the antagonist activity of the compounds of the invention on the human neuronal nAChR α4β2, a similar functional assay is carried out using a human epithelial cell line stably expressing the human α4β2 subtype (Michelmore et al., Naunyn-Schmiedeberg's Arch. Pharmacol. (2002) 366, 235) In this assay, the preferred compounds of the invention show selectivity for the α7 nAChR subtypes.

c) To assess the antagonist activity of the compounds of the invention on the "ganglionic subtype" (α3β4), the muscle type of nicotinic receptor (α1β1γδ) and the 5-HT_3 receptor, similar functional tests as just described under a) are carried out with a human epithelial cell line stably expressing the human ganglionic subtype, a cell line endogenously expressing the human muscle type of nicotinic receptors or a cell line endogenously expressing the murine 5-HT_3 receptor (Michelmore et al., Naunyn-Schmiedeberg's Arch. Pharmacol. (2002) 366, 235. Compounds which display little or no activity on the α3β4 nAChR, the muscle subtype of nicotinic receptor as well as the 5-HT_3 receptor are especially preferred.

In the model of mice showing sensory gating deficit (DBA/2-mice) described by S. Leonard et al. in Schizophrenia Bulletin 22, 431-445 (1996), the compounds of the invention may induce significant sensory gating at concentrations of about 10 to about 40 µM.

The compounds of the invention may be shown to increase attention in a test of attention for rodents (Robbins, J. Neuropsychiatry Clin. Neurosci. (2001) 13, 326-35), namely the 5-choice serial reaction time test (5-CSRTT). In this test, the rat must observe a wall containing 5 holes. When a light flash appears in one of them, the rat must respond with a nose-poke into the correct hole within 5 sec. in order to receive a food pellet reward, delivered to a feeder in the opposite wall.

Compounds of the invention may also show learning/memory enhancing effects in the social recognition test in mice and rats (Ennaceur and Delacour, Behav. Brain Res. (1988) 31, 47-59). Compounds of the invention may also show learning/memory enhancing effects in the object recognition test in mice and rats (Ennaceur and Delacour, Behav. Brain Res. (1988) 31, 47-59). The compounds of the invention are therefore useful for the prevention, treatment and delay of progression(including mitigation and prevention) of various disorders, especially those mentioned above. The usefulness of α7 nAChR agonists in neurodegeneration is documented in the literature, e.g. in Wang et al., J. Biol. Chem. 275, 5626-5632 (2000).

For the treatment of the above and other disorders, the appropriate dosage of a compound (active ingredient) of the invention will, of course, vary depending upon, for example, the host, the mode of administration and the nature and severity of the condition being treated as well as the relative potency of the particular agent of the invention employed. For example, the amount of active agent required may be determined on the basis of known in vitro and in vivo techniques, determining how long a particular active agent concentration in the blood plasma remains at an acceptable level for a therapeutic effect. In general, satisfactory results in animals are indicated to be obtained at daily dosages of from about 0.01 to about 30.0 mg/kg p.o. In humans, an indicated daily dosage is in the range of from about 0.7 to about 1400 mg/day p.o., e.g. from about 50 to 200 mg (70 kg man), conveniently administered once or in divided doses up to 4 x per day or in sustained release form.

Pharmaceutical compositions contain, for example, from about 0.1 % to about 99.9 %, preferably from about 20 % to about 60 %, of the active ingredient(s).

Examples for compositions comprising a compound of the invention include, for example, a solid dispersion, an aqueous solution, e.g. containing a solubilising agent, a microemulsion and a suspension of, e.g. a salt of a compound of formula (I) or a free compound of the formula (I) in the range of from 0.1 to 1 %, e.g. 0.5 %. The composition may be buffered to a pH in the range of, e.g. from 3.5 to 9.5, e.g. to pH 4.5, by a suitable buffer.

The compounds of the invention are also commercially useful as research chemicals.

For use according to the invention, a compound of the formula (I) and/or a pharmaceutically acceptable salt thereof may be administered as single active agent or in combination with one or more other active agents of the formula (I) and/or a pharmaceutically acceptable salt thereof or especially other active agents commonly employed especially for the treatment of the disorders mentioned herein or further other disorders, in any customary manner, e.g. orally, for example in the form of tablets, capsules, or as nasal spray, or parenterally, for example in the

form of injection solutions or suspensions. Such other active agents employed in such combinations are preferably selected from the group consisting of benzodiazepines, selective serotonin reuptake inhibitors (SSRIs), selective serotonin and norepinephrine reuptake inhibitors (SNRIs), conventional antipsychotics, atypical antipsychotics, buspirone, carbamazepine, oxcarbazepine, gabapentin and pregabalin.

An SSRI suitable for the present invention is especially selected from fluoxetine, fuvoxamine, sertraline, paroxetine, citalopram and escitalopram. An SNRI suitable for the present invention is especially selected from venlafaxine and duloxetine. The term "benzodiazepines" as used herein includes, but is not limited to clonazepam, diazepam and lorazepam. The term "conventional antipsychotics" as used herein includes, but is not limited to haloperidol, fluphenazine, thiotixene and flupentixol. The term "atypical antipsychotics" as used herein relates to clozaril, risperidone, olanzapine, quetiapine, ziprasidone and aripiprazol.

Buspirone can be administered in free form or as a salt, e.g. as its hydrochloride, e.g., in the form as marketed, e.g. under the trademark Buspar™ or Bespar™. It can be prepared and administered, e.g., as described in US 3,717,634. Fluoxetine can be administered, e.g., in the form of its hydrochloride as marketed, e.g. under the trademark Prozac™. It can be prepared and administered, e.g., as described in CA 2002182. Paroxetine ((3S,4R)-3-[(1,3-benzodioxol-5-yloxy)methyl]-4-(4-fluorophenyl)piperidine) can be administered, e.g., in the form as marketed, e.g. under the trademark Paxil™. It can be prepared and administered, e.g., as described in US 3,912,743. Sertraline can be administered, e.g., in the form as marketed, e.g. under the trademark Zoloft™. It can be prepared and administered, e.g., as described in US 4,536,518. Clonazepam can be administered, e.g., in the form as marketed, e.g. under the trademark Antelepsin™. Diazepam can be administered, e.g., in the form as marketed, e.g. under the trademark Diazepam Desitin™. Lorazepam can be administered, e.g., in the form as marketed, e.g. under the trademark Tavor™. Citalopram can be administered in free form or as a salt, e.g. as its hydrobromide, e.g., in the form as marketed, e.g. under the trademark Cipramil™. Escitalopram can be administered, e.g., in the form as marketed, e.g. under the trademark Cipralex™. It can be prepared and administered, e.g., as described in AU623144. Venlafaxine can be administered, e.g., in the form as marketed, e.g. under the trademark Trevilor™. Duloxetine can be administered, e.g., in the form as marketed, e.g. under the trademark Cymbalta™. It may be prepared and administered, e.g., as described in CA 1302421. Carbamazepine can be administered, e.g., in the form as marketed, e.g. under the trademark Tegretal™ or Tegretol™. Oxcarbazepine can be administered, e.g., in the form as marketed, e.g. under the trademark Trileptal™. Oxcarbazepine is well known from the literature [see for example Schuetz H. et al., Xenobiotica (GB), 16(8), 769-778 (1986)]. Gabapentin can be administered, e.g., in the form as marketed, e.g. under the trademark Neurontin™.

Haloperidol can be administered, e.g., in the form as marketed, e.g. under the trademark Haloperidol STADA™. Fluphenazine can be administered, e.g., in the form of its dihydrochloride as marketed, e.g. under the trademark Prolixin™. Thiothixene can be administered, e.g., in the form as marketed, e.g. under the trademark Navane™. It can be prepared, e.g., as described in US 3,310,553. Flupentixol can be administered for instance in the form of its dihydrochloride, e.g., in the form as marketed, e.g. under the trademark Emergil™ or in the form of its decanoate, e.g., in the form as marketed, e.g. under the trademark Depixol™. It can be prepared, e.g., as described in BP 925,538. Clozaril can be administered, e.g., in the form as marketed, e.g. under the trademark Leponex™. It can be prepared, e.g., as described in US 3,539,573. Risperidone can be administered, e.g., in the form as marketed, e.g. under the trademark Risperdal™. Olanzapine can be administered, e.g., in the form as marketed, e.g. under the trademark Zyprexa™. Quetiapine can be administered, e.g., in the form as marketed, e.g. under the trademark Seroquel™. Ziprasidone can be administered, e.g., in the form as marketed, e.g. under the trademark Geodon™. It can be prepared, e.g., as described in GB 281,309. Aripiprazole can be administered, e.g., in the form as marketed, e.g. under the trademark Abilify™. It can be prepared, e.g., as described in US 5,006,528.

The structure of the active ingredients identified by code nos., generic or trade names may be taken from the actual edition of the standard compendium "The Merck Index" or from databases, e.g. Patents International (e.g. IMS World Publications). The corresponding content thereof is hereby incorporated by reference. Any person skilled in the art is fully enabled to identify the active ingredients and, based on these references, likewise enabled to manufacture and test the pharmaceutical indications and properties in standard test models, both *in vitro* and *in vivo*.

In the case of a combination, the pharmaceutical compositions for separate administration of the combination partners and/or those for administration in a fixed combination, i.e. a single galenical composition comprising at least two combination partners, according to the inventtion can be prepared in a manner known per se and are those suitable for enteral, such as oral or rectal, and parenteral administration to mammals, including man, comprising a therapeutically effective amount of at least one pharmacologically active combination partner alone or in combination with one or more pharmaceutically acceptable carriers, especially suitable for enteral or parenteral application. When the combination partners employed are applied in the form as marketed as single drugs, their dosage and mode of administration can take place in accordance with the information provided on the packet leaflet of the respective marketed drug in order to result in the beneficial effect described herein, if not mentioned herein otherwise.

Pharmaceutical preparations for the combination therapy for enteral or parenteral administration are, for example, those in unit dosage forms, such as sugar-coated tablets, tablets, capsules or suppositories, or furthermore ampoules. If not indicated otherwise, these are prepared in a manner known per se, for example by means of conventional mixing, granulating, sugar-coating, dissolving or lyophilizing processes. It will be appreciated that the unit content of a combination partner contained in an individual dose of each dosage form need not in itself constitute an effective amount since the necessary effective amount can instead with a single dosage unit also be reached by administration of a two or more dosage units.

In particular, a therapeutically effective amount of each of the combination partners may be administered simultaneously or sequentially and in any order, and the components may be administered separately (e.g. sequentially after fixed or variable periods of time), or as a fixed combination. For example, the method of treatment (including mitigation) of a disorder according to the invention may comprise (i) administration of the combination partner (a) (a compound of the present invention) in free or pharmaceutically acceptable salt form and (ii) administration of a combination partner (b) (e.g. a different compound of the present inventtion or an active ingredient of a different formula) in free or pharmaceutically acceptable salt form, simultaneously or sequentially in any order, in jointly therapeutically effective amounts, preferably in synergistically effective amounts, e.g. in daily dosages corresponding to the amounts described herein. The individual combination partners can be administered separately at different times during the course of therapy or concurrently in divided or single combination forms. Furthermore, the term "administering" also encompasses the use of a pro-drug of a combination partner that convert *in vivo* to the combination partner as such. The instant invention is therefore to be understood as embracing all such regimes of simultaneous and/ or alternating treatment and the term "administering" is to be interpreted accordingly.

The effective dosage of the combination partners employed may vary, for example depending on the particular compound or pharmaceutical composition employed, the mode of administration, the disorder being treated, and/or the severity of the disorder being treated. Thus, the dosage regimen is selected in accordance with a variety of factors including the route of administration, metabolism by and the renal and hepatic function of the patient. A physician, clinician or veterinarian of ordinary skill can readily determine and prescribe the effective amount of the single active ingredients required to prevent, mitigate, counter or arrest the disorder. Optimal precision in achieving concentration of the active ingredients within the range that yields efficacy without toxicity requires a regimen based on the kinetics of the active ingredients' availability to target sites.

In accordance with the foregoing, the present invention also provides:

(1) A compound of the formula (I), and/or a salt thereof, for use in the diagnostic or therapeutic treatment of a mammal, especially a human; especially for use as an alpha-7 receptor agonist, for example for use in the treatment (including mitigation) of any one or more disorders, especially of any one or more of the particular disorders set forth hereinbefore and hereinafter.

(2) A pharmaceutical composition comprising a compound of the formula (I), and/or a pharmaceutically acceptable salt thereof, as active ingredient together with a pharmaceutically acceptable diluent or carrier.

(2') A pharmaceutical composition for the treatment or prevention of a disorder in the treatment of which alpha-7 receptor activation plays a role or is involved and/or in which alpha-7 receptor activity is involved, especially any one or more of the disorders mentioned hereinbefore or hereinafter, comprising a compound of the formula (I), and/or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable diluent or carrier.

(3) A method for the treatment of a disorder, especially any one or more of the particular disorders set forth hereinbefore, in a subject in need of such treatment, comprising administering a pharmaceutically effective amount of a compound of the formula (I), or a pharmaceutically acceptable salt thereof.

(3') A method for treating or preventing a disorder in the treatment of which alpha-7 receptor activation plays a role or is involved and/or in which alpha-7 receptor activity is involved, comprising administering to a mammal in need thereof a therapeutically effective amount of a compound of the formula (I), and/or a pharmaceutically acceptable salt thereof.

(4) The use of a compound of the formula (I), and/or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for the treatment or prevention of a disease or condition in the treatment of which alpha-7 receptor activation plays a role or is involved and/or in which alpha-7 receptor activity is involved, especially one or more of the disorders mentioned above.

(5) A method as defined above comprising co-administration, e.g. concomitantly or in sequence, of a therapeutically effective amount of an alpha-7 agonist of the formula (I), and/or a pharmaceutically acceptable salt thereof, and a second pharmaceutically active compound and/or a pharmaceutically acceptable salt thereof, said second pharmaceutically active compound and/or salt thereof being especially for use in the treatment of any one or more of the disorders set forth hereinbefore or hereinafter.

(6) A combination comprising a therapeutically effective amount of an alpha-7 agonist of the formula (I), and/or a pharmaceutically acceptable salt thereof, and a second pharmaceutically active compound and/or a pharmaceutically acceptable salt thereof, said second pharmaceutically active compound being especially for use or of use in the treatment of any one or more of the particular disorders set forth hereinbefore.

The Examples which follow serve to illustrate the invention without limiting the scope thereof. The following abbrevieations are used in the examples:

AcOEt	ethyl acetate
aq.	aqueous
DMF	dimethylformamide
EtOH	ethanol
FC	flash chromatography
HV	high vacuum
MeOH	MeOH
RP-HPLC	reversed-phase high performance liquid chromatography
rt	room temperature
rac.	racemate
soln.	solution
TFA	trifluoroacetic acid
THF	tetrahydrofuran

Temperatures are measured in degrees Celsius. Unless indicated otherwise, reactions are carried out at room temperature. The structure of final products, intermediates and starting materials is confirmed by standard analytical methods, e.g. microanalysis and spectroscopic characteristics (e.g. MS, IR, NMR).

Example 1: Preparation of Rac.-trans-2-Methyl-1-aza-bicyclo[2.2.2]oct-3-yl)-(6-phenyl-pyridin-3-yl)-amine

A solution of 2-methyl-1-aza-bicyclo[2.2.2]octan-3-one (1.33 g , 9.5 mmol), 6-phenyl-pyridin-3-ylamine (1.25 g, 7.3 mmol) and p-toluene sulfonic acid monohydrate (139 mg, 0.73 mmol) in toluene (40 ml) is heated under reflux for 18 hours using a Dean-Stark apparatus. The toluene is evaporated and the residue is dissolved in ethyl acetate and washed with brine. The organic layer is dried over anhydrous magnesium sulfate, filtered and evaporated to dryness, and the residual oil purified by silica gel column chromatography (eluent: EtOAc: CH_3OH:NH_4OH; 9:1:0.1) to afford [2-Methyl-1-aza-bicyclo[2.2.2]oct-(3Z)-ylidene]-(6-phenyl-pyridin-3-yl)-amine. A solution of $LiAlH_4$ (1.03 ml, 1M) in THF is added to a solution of [2-Methyl-1-aza-bicyclo[2.2.2]oct-(3Z)-ylidene]-(6-phenyl-pyridin-3-yl)-amine (300mg, 1.02 mmol) in THF (10 ml). The resulting mixture is stirred at room temperature for 18 hours and then quenched with a saturated aqueous solution of sodium sulfate (1 ml). The solvents are removed by evaporation and the residue is redissolved in ethyl acetate and filtered. The filtrate is evaporated and purified by silica gel column chromatography (eluent: EtOAc: CH_3OH: NH_4OH; 8.5:1.5:0.1) to afford Rac.-trans-2-Methyl-1-aza-bicyclo[2.2.2]oct-3-yl)-(6-phenyl-pyridin-3-yl)-amine. MS (ES^+): m/e = 294.4 (MH^+); preparative enantiomer separation (column: Chiralpak AD-H 10 um; (4.6x250 mm), eluent: n-hexane : EtOH 50:50, flow: 1.0 ml / min, detector: UV 210 nm): peak 1: 6.29 min; peak 2: 20.16 min.

Example 2:

The following compounds are prepared in a similar manner using the appropriate starting materials:

2a) Rac.-trans-2-Methyl-1-aza-bicyclo[2.2.2]oct-3-yl)-(6-p-tolyl-pyridin-3-yl)-amine. MS (ES^+): m/e = 308 (MH^+).

2b) Rac.-trans- (2-Methyl-1-aza-bicyclo[2.2.2]oct-3-yl)-(6-phenyl-pyridazin-3-yl)-amine

2c) Rac.-trans- (2-Methyl-1-aza-bicyclo[2.2.2]oct-3-yl)-(5-phenyl-pyridin-2-yl)-amine

2d) Rac.-trans- (2-Methyl-1-aza-bicyclo[2.2.2]oct-3-yl)-(5-phenyl-pyrimidin-2-yl)-amine

Example 3:

The following compounds are prepared in a similar manner using the appropriate starting materials:

3a) Rac.-trans -[6-(1H-Indol-5-yl)-pyridin-3-yl]-(2-methyl-1-aza-bicyclo[2.2.2]oct-3-yl)-amine; preparative enantiomer separation (column: Chiralpak AD 20 um; (50 x 500 mm), eluent: n-hexane : CHCl3 : EtOH 80:20, flow: 100 ml / min, detector: UV 200 - 400 nm): peak 1: 40.46 min; peak 2: 78.96 min.3b) Rac.-trans -[6-(1H-Indol-5-yl)-pyridazin-3-yl]-(2-methyl-1-aza-bicyclo[2.2.2]oct-3-yl)-amine

3c) Rac.-trans- [5-(1H-Indol-5-yl)-pyridin-2-yl]-(2-methyl-1-aza-bicyclo[2.2.2]oct-3-yl)-amine

3d) Rac.-trans- [5-(1H-Indol-5-yl)-pyrimidin-2-yl]-(2-methyl-1-aza-bicyclo[2.2.2]oct-3-yl)-amine

3e) Rac.-trans- (2-Methyl-1-aza-bicyclo[2.2.2]oct-3-yl)-[6-(5-methyl-thiophen-2-yl)-pyridin-3-yl]-amine

3f) Rac.-trans- (2-Methyl-1-aza-bicyclo[2.2.2]oct-3-yl)-[6-(5-methyl-thiophen-2-yl)-pyridazin-3-yl]-amine

3g) Rac.-trans- (2-Methyl-1-aza-bicyclo[2.2.2]oct-3-yl)-[5-(5-methyl-thiophen-2-yl)-pyridin-2-yl]-amine

3h) Rac.-trans- (2-Methyl-1-aza-bicyclo[2.2.2]oct-3-yl)-[5-(5-methyl-thiophen-2-yl)-pyrimidin-2-

3i) Rac.-trans- [6-(2,3-Dimethyl-1H-indol-5-yl)-pyridin-3-yl]-(2-methyl-1-aza-bicyclo[2.2.2]oct-3-yl)-amine

3j) Rac.-trans- [6-(2,3-Dimethyl-1H-indol-5-yl)-pyridazin-3-yl]-(2-methyl-1-aza-bicyclo [2.2.2]oct-3-yl)-amine

3k) Rac.-trans- [5-(2,3-Dimethyl-1H-indol-5-yl)-pyridin-2-yl]-(2-methyl-1-aza-bicyclo [2.2.2]oct-3-yl)-amine

3l) Rac.-trans- [5-(2,3-Dimethyl-1H-indol-5-yl)-pyrimidin-2-yl]-(2-methyl-1-aza-bicyclo [2.2.2]oct-3-yl)-amine

3m) Rac.-trans- [6-(1H-Indol-6-yl)-pyridin-3-yl]-(2-methyl-1-aza-bicyclo[2.2.2]oct-3-yl)-amine

3n) Rac.-trans- [6-(1H-Indol-6-yl)-pyridazin-3-yl]-(2-methyl-1-aza-bicyclo[2.2.2]oct-3-yl)-amine

3o) Rac.-trans- [5-(1H-Indol-6-yl)-pyridin-2-yl]-(2-methyl-1-aza-bicyclo[2.2.2]oct-3-yl)-amine

3p) Rac.-trans- [5-(1H-Indol-6-yl)-pyrimidin-2-yl]-(2-methyl-1-aza-bicyclo[2.2.2]oct-3-yl)-amine

3q) Rac.-trans- [6-(2,5-Difluoro-4-methyl-phenyl)-pyridin-3-yl]-(2-methyl-1-aza-bicyclo [2.2.2]oct-3-yl)-amine

3r) Rac.-trans- [6-(2,5-Difluoro-4-methyl-phenyl)-pyridazin-3-yl]-(2-methyl-1-aza-bicyclo [2.2.2]oct-3-yl)-amine

3s) Rac.-trans- [5-(2,5-Difluoro-4-methyl-phenyl)-pyridin-2-yl]-(2-methyl-1-aza-bicyclo [2.2.2]oct-3-yl)-amine

3t) Rac.-trans- [5-(2,5-Difluoro-4-methyl-phenyl)-pyrimidin-2-yl]-(2-methyl-1-aza-bicyclo [2.2.2]oct-3-yl)-amine

3u) 3q) Rac.-trans- [6-(2-fluoro-4-methyl-phenyl)-pyridin-3-yl]-(2-methyl-1-aza-bicyclo [2.2.2]oct-3-yl)-amine

3v) Rac.-trans- [6-(2-fluoro-4-methyl-phenyl)-pyridazin-3-yl]-(2-methyl-1-aza-bicyclo [2.2.2]oct-3-yl)-amine
3w) Rac.-trans- [5-(2-fluoro-4-methyl-phenyl)-pyridin-2-yl]-(2-methyl-1-aza-bicyclo [2.2.2]oct-3-yl)-amine
3x) Rac.-trans- [5-(2-fluoro-4-methyl-phenyl)-pyrimidin-2-yl]-(2-methyl-1-aza-bicyclo [2.2.2]oct-3-yl)-amine
3y) Rac.-trans- (2-Methyl-1-aza-bicyclo[2.2.2]oct-3-yl)-(6-m-tolyl-pyridin-3-yl)-amine
3z) Rac.-trans- (2-Methyl-1-aza-bicyclo[2.2.2]oct-3-yl)-(6-m-tolyl-pyridazin-3-yl)-amine
3aa) Rac.-trans- (2-Methyl-1-aza-bicyclo[2.2.2]oct-3-yl)-(5-m-tolyl-pyridin-2-yl)-amine
3ab) (2-Methyl-1-aza-bicyclo[2.2.2]oct-3-yl)-(5-m-tolyl-pyrimidin-2-yl)-amine
3ac) Rac.-trans- (2-Methyl-1-aza-bicyclo[2.2.2]oct-3-yl)-[6-(3-nitro-phenyl)-pyridin-3-yl]-amine
3ad) Rac.-trans- (2-Methyl-1-aza-bicyclo[2.2.2]oct-3-yl)-[6-(3-nitro-phenyl)-pyridazin-3-yl]-amine
3ae) Rac.-trans- (2-Methyl-1-aza-bicyclo[2.2.2]oct-3-yl)-[5-(3-nitro-phenyl)-pyridin-2-yl]-amine
3af) Rac.-trans- (2-Methyl-1-aza-bicyclo[2.2.2]oct-3-yl)-[5-(3-nitro-phenyl)-pyrimidin-2-yl]-amine
3ak) Rac.-trans- [6-(5-Ethyl-2-fluoro-phenyl)-pyridin-3-yl]-(2-methyl-1-aza-bicyclo[2.2.2]oct-3-yl)-amine
3al) Rac.-trans- [6-(5-Ethyl-2-fluoro-phenyl)-pyridazin-3-yl]-(2-methyl-1-aza-bicyclo[2.2.2]oct-3-yl)-amine
3am) Rac.-trans- [5-(5-Ethyl-2-fluoro-phenyl)-pyridin-2-yl]-(2-methyl-1-aza-bicyclo[2.2.2]oct-3-yl)-amine
3an) Rac.-trans- [5-(5-Ethyl-2-fluoro-phenyl)-pyrimidin-2-yl]-(2-methyl-1-aza-bicyclo [2.2.2] oct-3-yl)-amine
3ao) Rac.-trans- (6-Benzo[1,3]dioxol-5-yl-pyridin-3-yl)-(2-methyl-1-aza-bicyclo[2.2.2]oct-3-yl)-amine
3ap) Rac.-trans- (6-Benzo[1,3]dioxol-5-yl-pyridazin-3-yl)-(2-methyl-1-aza-bicyclo[2.2.2]oct-3-yl)-amine
3aq) Rac.-trans- (5-Benzo[1,3]dioxol-5-yl-pyridin-2-yl)-(2-methyl-1-aza-bicyclo[2.2.2]oct-3-yl)-amine
3ar) Rac.-trans- (5-Benzo[1,3]dioxol-5-yl-pyrimidin-2-yl)-(2-methyl-1-aza-bicyclo[2.2.2]oct-3-yl)-amine
3as) Rac.-trans- [6-(3-Methoxy-phenyl)-pyridin-3-yl]-(2-methyl-1-aza-bicyclo[2.2.2]oct-3-yl)-amine
3at) Rac.-trans- [6-(3-Methoxy-phenyl)-pyridazin-3-yl]-(2-methyl-1-aza-bicyclo[2.2.2]oct-3-yl)-amine
3au) Rac.-trans- [5-(3-Methoxy-phenyl)-pyridin-2-yl]-(2-methyl-1-aza-bicyclo[2.2.2]oct-3-yl)-amine
3av) Rac.-trans- [5-(3-Methoxy-phenyl)-pyrimidin-2-yl]-(2-methyl-1-aza-bicyclo[2.2.2]oct-3-yl)-amine
3bd) Rac.-trans- N-{4-[2-(2-Methyl-1-aza-bicyclo[2.2.2]oct-3-yloxy)-pyrimidin-5-yl]-phenyl}-acetamide
3be) Rac.-trans- [6-(2-Fluoro-5-methoxy-4-methyl-phenyl)-pyridin-3-yl]-(2-methyl-1-aza-bicyclo[2.2.2]oct-3-yl)-amine
3bf) Rac.-trans- [6-(2-Fluoro-5-methoxy-4-methyl-phenyl)-pyridazin-3-yl]-(2-methyl-1-aza-bicyclo[2.2.2]oct-3-yl)-amine
3bg) Rac.-trans- [5-(2-Fluoro-5-methoxy-4-methyl-phenyl)-pyridin-2-yl]-(2-methyl-1-aza-bicyclo[2.2.2]oct-3-yl)-amine
3bh) Rac.-trans- [5-(2-Fluoro-5-methoxy-4-methyl-phenyl)-pyrimidin-2-yl]-(2-methyl-1-aza-bicyclo[2.2.2]oct-3-yl)-amine
3bi) Rac.-trans- [6-(3,5-Dimethyl-phenyl)-pyridin-3-yl]-(2-methyl-1-aza-bicyclo[2.2.2]oct-3-yl)-amine; preparative enantiomer separation (column: Chiralpak AD-H 10 um; (4.6x250 mm), eluent: n-hexane : EtOH : DEA 50:50:0.5 (v:v:v), flow: 1.0 ml / min, detector: UV 220 nm): peak 1: 8.25 min; peak 2: 23.57 min.3bj) Rac.-trans- [6-(3,5-Dimethyl-phenyl)-pyridazin-3-yl]-(2-methyl-1-aza-bicyclo[2.2.2]oct-3-yl)-amine
3bk) Rac.-trans- [5-(3,5-Dimethyl-phenyl)-pyridin-2-yl]-(2-methyl-1-aza-bicyclo[2.2.2]oct-3-yl)-amine
3bl) Rac.-trans- [5-(3,5-Dimethyl-phenyl)-pyrimidin-2-yl]-(2-methyl-1-aza-bicyclo[2.2.2]oct-3-yl)-amine
3bm) Rac.-trans- (2-Methyl-1-aza-bicyclo[2.2.2]oct-3-yl)-[6-(1-methyl-1H-indol-5-yl)-pyridin-3-yl]-amine
3bn) Rac.-trans- (2-Methyl-1-aza-bicyclo[2.2.2]oct-3-yl)-[6-(1-methyl-1H-indol-5-yl)-pyridazin -3-yl]-amine
3bo) Rac.-trans- (2-Methyl-1-aza-bicyclo[2.2.2]oct-3-yl)-[5-(1-methyl-1H-indol-5-yl)-pyrimidin-2-yl]-amine
3bp) Rac.-trans- (2-Methyl-1-aza-bicyclo[2.2.2]oct-3-yl)-[5-(1-methyl-1H-indol-5-yl)-pyridin-2-yl]-amine

3bq) Rac.-trans- [6-(3,4-Difluoro-phenyl)-pyridin-3-yl]-(2-methyl-1-aza-bicyclo[2.2.2]oct-3-yl)-amine
3br) Rac.-trans- [6-(3,4-Difluoro-phenyl)-pyridazin-3-yl]-(2-methyl-1-aza-bicyclo[2.2.2]oct-3-yl)-amine
3bs) Rac.-trans- [5-(3,4-Difluoro-phenyl)-pyridin-2-yl]-(2-methyl-1-aza-bicyclo[2.2.2]oct-3-yl)-amine
3bt) Rac.-trans- [5-(3,4-Difluoro-phenyl)-pyrimidin-2-yl]-(2-methyl-1-aza-bicyclo[2.2.2]oct-3-yl)-amine
3bu) Rac.-trans- [6-(3,4-Dimethyl-phenyl)-pyridin-3-yl]-(2-methyl-1-aza-bicyclo[2.2.2]oct-3-yl)-amine
3bv) Rac.-trans- [6-(3,4-Dimethyl-phenyl)-pyridazin-3-yl]-(2-methyl-1-aza-bicyclo[2.2.2]oct-3-yl)-amine
3bw) Rac.-trans- [5-(3,4-Dimethyl-phenyl)-pyrimidin-2-yl]-(2-methyl-1-aza-bicyclo[2.2.2]oct-3-yl)-amine
3bx) Rac.-trans- [5-(3,4-Dimethyl-phenyl)-pyridin-2-yl]-(2-methyl-1-aza-bicyclo[2.2.2]oct-3-yl)-amine
3by) Rac.-trans- [6-(4-Fluoro-phenyl)-pyridin-3-yl]-(2-methyl-1-aza-bicyclo[2.2.2]oct-3-yl)-amine
3bz) Rac.-trans- [6-(4-Fluoro-phenyl)-pyridazin-3-yl]-(2-methyl-1-aza-bicyclo[2.2.2]oct-3-yl)-amine
3ca) Rac.-trans- [5-(4-Fluoro-phenyl)-pyridin-2-yl]-(2-methyl-1-aza-bicyclo[2.2.2]oct-3-yl)-amine
3cb) Rac.-trans- [5-(4-Fluoro-phenyl)-pyrimidin-2-yl]-(2-methyl-1-aza-bicyclo[2.2.2]oct-3-yl)-amine
3cc) Rac.-trans- (2-Methyl-1-aza-bicyclo[2.2.2]oct-3-yl)-[6-(3-trifluoromethoxy-phenyl)-pyridin -3-yl]-amine
3cd) Rac.-trans- (2-Methyl-1-aza-bicyclo[2.2.2]oct-3-yl)-[6-(3-trifluoromethoxy-phenyl)-pyridazin-3-yl]-amine
3ce) Rac.-trans- (2-Methyl-1-aza-bicyclo[2.2.2]oct-3-yl)-[5-(3-trifluoromethoxy-phenyl)-pyridin-2-yl]-amine
3cf) Rac.-trans- (2-Methyl-1-aza-bicyclo[2.2.2]oct-3-yl)-[5-(3-trifluoromethoxy-phenyl)-pyrimidin-2-yl]-amine
3cg) Rac.-trans- [6-(1H-Indol-4-yl)-pyridin-3-yl]-(2-methyl-1-aza-bicyclo[2.2.2]oct-3-yl)-amine
3ch) Rac.-trans- [6-(1H-Indol-4-yl)-pyridazin-3-yl]-(2-methyl-1-aza-bicyclo[2.2.2]oct-3-yl)-amine
3ci) Rac.-trans- [5-(1H-Indol-4-yl)-pyridin-2-yl]-(2-methyl-1-aza-bicyclo[2.2.2]oct-3-yl)-amine
3cj) Rac.-trans- [5-(1H-Indol-4-yl)-pyrimidin-2-yl]-(2-methyl-1-aza-bicyclo[2.2.2]oct-3-yl)-amine
3ck) Rac.-trans- [6-(4-Ethyl-phenyl)-pyridin-3-yl]-(2-methyl-1-aza-bicyclo[2.2.2]oct-3-yl)-amine
3cl) Rac.-trans- [6-(4-Ethyl-phenyl)-pyridazin-3-yl]-(2-methyl-1-aza-bicyclo[2.2.2]oct-3-yl)-amine
3cm) Rac.-trans- [5-(4-Ethyl-phenyl)-pyridin-2-yl]-(2-methyl-1-aza-bicyclo[2.2.2]oct-3-yl)-amine
3cn) Rac.-trans- [5-(4-Ethyl-phenyl)-pyrimidin-2-yl]-(2-methyl-1-aza-bicyclo[2.2.2]oct-3-yl)-amine
3co) Rac.-trans- [6-(3,4-Dimethoxy-phenyl)-pyridin-3-yl]-(2-methyl-1-aza-bicyclo[2.2.2]oct-3-yl)-amine
3cp) Rac.-trans- [6-(3,4-Dimethoxy-phenyl)-pyridazin-3-yl]-(2-methyl-1-aza-bicyclo[2.2.2]oct-3-yl)-amine
3cq) Rac.-trans- [5-(3,4-Dimethoxy-phenyl)-pyridin-2-yl]-(2-methyl-1-aza-bicyclo[2.2.2]oct-3-yl)-amine
3cr) Rac.-trans- [5-(3,4-Dimethoxy-phenyl)-pyrimidin-2-yl]-(2-methyl-1-aza-bicyclo[2.2.2]oct-3-yl)-amine
3cs) Rac.-trans- [6-(3-Fluoro-4-methyl-phenyl)-pyridin-3-yl]-(2-methyl-1-aza-bicyclo [2.2.2] oct-3-yl)-amine
3ct) Rac.-trans- [6-(3-Fluoro-4-methyl-phenyl)-pyridazin-3-yl]-(2-methyl-1-aza-bicyclo [2.2.2] oct-3-yl)-amine
3cu) Rac.-trans [5-(3-Fluoro-4-methyl-phenyl)-pyridin-2-yl]-(2-methyl-1-aza-bicyclo[2.2.2] oct-3-yl)-amine
3cv) Rac.-trans- [5-(3-Fluoro-4-methyl-phenyl)-pyrimidin-2-yl]-(2-methyl-1-aza-bicyclo[2.2.2] oct-3-yl)-amine
3cw) Rac.-trans- [6-(2,5-Dimethoxy-phenyl)-pyridin-3-yl]-(2-methyl-1-aza-bicyclo[2.2.2]oct-3-yl)-amine
3cx) Rac.-trans- [6-(2,5-Dimethoxy-phenyl)-pyridazin-3-yl]-(2-methyl-1-aza-bicyclo[2.2.2]oct-3-yl)-amine
3cy) Rac.-trans- [5-(2,5-Dimethoxy-phenyl)-pyridin-2-yl]-(2-methyl-1-aza-bicyclo[2.2.2]oct-3-yl)-amine
3cz) Rac.-trans- [5-(2,5-Dimethoxy-phenyl)-pyrimidin-2-yl]-(2-methyl-1-aza-bicyclo[2.2.2]oct-3-yl)-amine
3da) Rac.-trans- [6-(3-Chloro-phenyl)-pyridin-3-yl]-(2-methyl-1-aza-bicyclo[2.2.2]oct-3-yl)-amine
3db) Rac.-trans- [6-(3-Chloro-phenyl)-pyridazin-3-yl]-(2-methyl-1-aza-bicyclo[2.2.2]oct-3-yl)-amine

3dc) Rac.-trans- [5-(3-Chloro-phenyl)-pyridin-2-yl]-(2-methyl-1-aza-bicyclo[2.2.2]oct-3-yl)-amine

3dd) Rac.-trans- [5-(3-Chloro-phenyl)-pyrimidin-2-yl]-(2-methyl-1-aza-bicyclo[2.2.2]oct-3-yl)-amine

3de) Rac.-trans- (6-Furan-3-yl-pyridin-3-yl)-(2-methyl-1-aza-bicyclo[2.2.2]oct-3-yl)-amine

3df) Rac.-trans- (6-Furan-3-yl-pyridazin-3-yl)-(2-methyl-1-aza-bicyclo[2.2.2]oct-3-yl)-amine

3dg) Rac.-trans- (5-Furan-3-yl-pyridin-2-yl)-(2-methyl-1-aza-bicyclo[2.2.2]oct-3-yl)-amine

3dh) Rac.-trans- (5-Furan-3-yl-pyrimidin-2-yl)-(2-methyl-1-aza-bicyclo[2.2.2]oct-3-yl)-amine

3di) Rac.-trans- (2-Methyl-1-aza-bicyclo[2.2.2]oct-3-yl)-[6-(4-methyl-thiophen-3-yl)-pyridin-3-yl]-amine

3dj) Rac.-trans- (2-Methyl-1-aza-bicyclo[2.2.2]oct-3-yl)-[6-(4-methyl-thiophen-3-yl)-pyridazin-3-yl]-amine

3dk) Rac.-trans- (2-Methyl-1-aza-bicyclo[2.2.2]oct-3-yl)-[5-(4-methyl-thiophen-3-yl)-pyridin-2-yl]-amine

3dl) Rac.-trans- (2-Methyl-1-aza-bicyclo[2.2.2]oct-3-yl)-[5-(4-methyl-thiophen-3-yl)-pyrimidin-2-yl]-amine

3dm) Rac.-trans- (2-Methyl-1-aza-bicyclo[2.2.2]oct-3-yl)-[6-(1-phenyl-1H-indol-5-yl)-pyridin-3-yl]-amine

3dn) Rac.-trans- (2-Methyl-1-aza-bicyclo[2.2.2]oct-3-yl)-[6-(1-phenyl-1H-indol-5-yl)-pyridazin-3-yl]-amine

3do) Rac.-trans- (2-Methyl-1-aza-bicyclo[2.2.2]oct-3-yl)-[5-(1-phenyl-1H-indol-5-yl)-pyridin-2-yl]-amine

3dp) Rac.-trans- (2-Methyl-1-aza-bicyclo[2.2.2]oct-3-yl)-[5-(1-phenyl-1H-indol-5-yl)-pyrimidin-2-yl]-amine

3dq) Rac.-trans- (2-Methyl-1-aza-bicyclo[2.2.2]oct-3-yl)-[6-(2-methyl-benzothiazol-5-yl)-pyridin-3-yl]-amine

3dr) Rac.-trans- (2-Methyl-1-aza-bicyclo[2.2.2]oct-3-yl)-[6-(2-methyl-benzothiazol-5-yl)-pyridazin-3-yl]-amine

3ds) Rac.-trans- (2-Methyl-1-aza-bicyclo[2.2.2]oct-3-yl)-[5-(2-methyl-benzothiazol-5-yl)-pyridin-2-yl]-amine

3dt) Rac.-trans- (2-Methyl-1-aza-bicyclo[2.2.2]oct-3-yl)-[5-(2-methyl-benzothiazol-5-yl)-pyrimidin-2-yl]-amine

3du) Rac.-trans- [6-(3,4-Dichloro-phenyl)-pyridin-3-yl]-(2-methyl-1-aza-bicyclo[2.2.2]oct-3-yl)-amine

3dv) Rac.-trans- [6-(3,4-Dichloro-phenyl)-pyridazin-3-yl]-(2-methyl-1-aza-bicyclo[2.2.2]oct-3-yl)-amine

3dw) Rac.-trans- [5-(3,4-Dichloro-phenyl)-pyridin-2-yl]-(2-methyl-1-aza-bicyclo[2.2.2]oct-3-yl)-amine

3dx) Rac.-trans- [5-(3,4-Dichloro-phenyl)-pyrimidin-2-yl]-(2-methyl-1-aza-bicyclo[2.2.2]oct-3-yl)-amine

3dy) Rac.-trans- [6-(2-Fluoro-phenyl)-pyridin-3-yl]-(2-methyl-1-aza-bicyclo[2.2.2]oct-3-yl)-amine

3dz) Rac.-trans- [6-(2-Fluoro-phenyl)-pyridazin-3-yl]-(2-methyl-1-aza-bicyclo[2.2.2]oct-3-yl)-amine

3ea) Rac.-trans- [5-(2-Fluoro-phenyl)-pyridin-2-yl]-(2-methyl-1-aza-bicyclo[2.2.2]oct-3-yl)-amine

3eb) Rac.-trans- [5-(2-Fluoro-phenyl)-pyrimidin-2-yl]-(2-methyl-1-aza-bicyclo[2.2.2]oct-3-yl)-amine

3ec) Rac.-trans- (2-Methyl-1-aza-bicyclo[2.2.2]oct-3-yl)-[6-(1H-pyrrolo[2,3-b]pyridin-5-yl)-pyridin-3-yl]-amine

3ed) Rac.-trans- (2-Methyl-1-aza-bicyclo[2.2.2]oct-3-yl)-[6-(1H-pyrrolo[2,3-b]pyridin-5-yl)-pyridazin-3-yl]-amine

3ee) Rac.-trans- (2-Methyl-1-aza-bicyclo[2.2.2]oct-3-yl)-[5-(1H-pyrrolo[2,3-b]pyridin-5-yl)-pyridin-2-yl]-amine

3ef) Rac.-trans- (2-Methyl-1-aza-bicyclo[2.2.2]oct-3-yl)-[5-(1H-pyrrolo[2,3-b]pyridin-5-yl)-pyrimidin-2-yl]-amine

3eg) Rac.-trans- (2-Methyl-1-aza-bicyclo[2.2.2]oct-3-yl)-(6-thiophen-2-yl-pyridin-3-yl)-amine

3eh) Rac.-trans- (2-Methyl-1-aza-bicyclo[2.2.2]oct-3-yl)-(6-thiophen-2-yl-pyridazin-3-yl)-amine

3ei) Rac.-trans- (2-Methyl-1-aza-bicyclo[2.2.2]oct-3-yl)-(5-thiophen-2-yl-pyridin-2-yl)-amine

3ej) Rac.-trans- (2-Methyl-1-aza-bicyclo[2.2.2]oct-3-yl)-(5-thiophen-2-yl-pyrimidin-2-yl)-amine

3ek) Rac.-trans- (6-Dibenzothiophen-4-yl-pyridin-3-yl)-(2-methyl-1-aza-bicyclo[2.2.2]oct-3-yl)-amine

3el) Rac.-trans- (6-Dibenzothiophen-4-yl-pyridazin-3-yl)-(2-methyl-1-aza-bicyclo[2.2.2]oct-3-yl)-amine

3em) Rac.-trans- (5-Dibenzothiophen-4-yl-pyridin-2-yl)-(2-methyl-1-aza-bicyclo[2.2.2]oct-3-yl)-amine

3en) Rac.-trans- (5-Dibenzothiophen-4-yl-pyrimidin-2-yl)-(2-methyl-1-aza-bicyclo[2.2.2]oct-3-yl)-amine

3eo) Rac.-trans- (6-Benzo[b]thiophen-3-yl-pyridin-3-yl)-(2-methyl-1-aza-bicyclo[2.2.2]oct-3-yl)-amine

3ep) Rac.-trans- (6-Benzo[b]thiophen-3-yl-pyridazin-3-yl)-(2-methyl-1-aza-bicyclo[2.2.2]oct-3-yl)-amine

3eq) Rac.-trans- (5-Benzo[b]thiophen-3-yl-pyridin-2-yl)-(2-methyl-1-aza-bicyclo[2.2.2]oct-3-yl)-amine

3er) Rac.-trans- (5-Benzo[b]thiophen-3-yl-pyrimidin-2-yl)-(2-methyl-1-aza-bicyclo[2.2.2]oct-3-yl)-amine

3es) Rac.-trans- (6'-Methoxy-[2,3']bipyridinyl-5-yl)-(2-methyl-1-aza-bicyclo[2.2.2]oct-3-yl)-amine

3et) Rac.-trans- [6-(6-Methoxy-pyridin-3-yl)-pyridazin-3-yl]-(2-methyl-1-aza-bicyclo[2.2.2] oct-3-yl)-amine

3eu) Rac.-trans- (6'-Methoxy-[3,3']bipyridinyl-6-yl)-(2-methyl-1-aza-bicyclo[2.2.2]oct-3-yl)-amine

3ev) Rac.-trans- [5-(6-Methoxy-pyridin-3-yl)-pyrimidin-2-yl]-(2-methyl-1-aza-bicyclo[2.2.2] oct-3-yl)-amine

3ew) Rac.-trans- [6-(1-Benzyl-1H-indol-5-yl)-pyridin-3-yl]-(2-methyl-1-aza-bicyclo[2.2.2]oct-3-yl)-amine

3ex) Rac.-trans- [6-(1-Benzyl-1H-indol-5-yl)-pyridazin-3-yl]-(2-methyl-1-aza-bicyclo[2.2.2]oct-3-yl)-amine

3ey) Rac.-trans- [5-(1-Benzyl-1H-indol-5-yl)-pyridin-2-yl]-(2-methyl-1-aza-bicyclo[2.2.2]oct-3-yl)-amine

3ez) Rac.-trans- [5-(1-Benzyl-1H-indol-5-yl)-pyrimidin-2-yl]-(2-methyl-1-aza-bicyclo[2.2.2]oct-3-yl)-amine

3fa) Rac.-trans- (6-Dibenzofuran-4-yl-pyridin-3-yl)-(2-methyl-1-aza-bicyclo[2.2.2]oct-3--yl)-amine

3fb) Rac.-trans- (6-Dibenzofuran-4-yl-pyridazin-3-yl)-(2-methyl-1-aza-bicyclo[2.2.2]oct
-3-yl)-amine

3fc) Rac.-trans- (5-Dibenzofuran-4-yl-pyridin-2-yl)-(2-methyl-1-aza-bicyclo[2.2.2]oct-3
-yl)-amine

3fd) Rac.-trans- (5-Dibenzofuran-4-yl-pyrimidin-2-yl)-(2-methyl-1-aza-bicyclo[2.2.2]oct
-3-yl)-amine

3fe) Rac.-trans- [6-(2,3-Difluoro-4-methyl-phenyl)-pyridin-3-yl]-(2-methyl-1-aza-bicyclo [2.2.2]oct-3-yl)-amine

3ff) Rac.-trans- [6-(2,3-Difluoro-4-methyl-phenyl)-pyridazin-3-yl]-(2-methyl-1-aza-bicyclo [2.2.2] oct-3-yl)-amine

3fg) Rac.-trans- [5-(2,3-Difluoro-4-methyl-phenyl)-pyridin-2-yl]-(2-methyl-1-aza-bicyclo [2.2.2]oct-3-yl)-amine

3fh) Rac.-trans- [5-(2,3-Difluoro-4-methyl-phenyl)-pyrimidin-2-yl]-(2-methyl-1-aza-bicyclo [2.2.2]oct-3-yl)-amine

3fi) Rac.-trans- {6-[1-(4-Methoxy-phenyl)-1H-indol-5-yl]-pyridin-3-yl}-(2-methyl-1-aza-bicyclo [2.2.2]oct-3-yl)-amine

3fj) Rac.-trans- {6-[1-(4-Methoxy-phenyl)-1H-indol-5-yl]-pyridazin-3-yl}-(2-methyl-1-aza-bicyclo [2.2.2]oct-3-yl)-amine

3fk) Rac.-trans- {5-[1-(4-Methoxy-phenyl)-1H-indol-5-yl]-pyridin-2-yl}-(2-methyl-1-aza-bicyclo [2.2.2]oct-3-yl)-amine

3fl) Rac.-trans- {5-[1-(4-Methoxy-phenyl)-1H-indol-5-yl]-pyrimidin-2-yl}-(2-methyl-1-aza-bicyclo[2.2.2]oct-3-yl)-amine

3fm) Rac.-trans-[6-(4-Methoxy-phenyl)-pyridin-3-yl]-(2-methyl-1-aza-bicyclo[2.2.2]oct-3-yl)-amine

3fn) Rac.-trans-[6-(4-Methoxy-phenyl)-pyridazin-3-yl]-(2-methyl-1-aza-bicyclo[2.2.2]oct-3-yl)-amine

3fo) Rac.-trans-[5-(4-Methoxy-phenyl)-pyridin-2-yl]-(2-methyl-1-aza-bicyclo[2.2.2]oct-3-yl)-amine

3fp) Rac.-trans-[5-(4-Methoxy-phenyl)-pyrimidin-2-yl]-(2-methyl-1-aza-bicyclo[2.2.2]oct-3-yl)-amine

3fq) Rac.-trans- (6-Biphenyl-4-yl-pyridin-3-yl)-(2-methyl-1-aza-bicyclo[2.2.2]oct-3-yl)-amine

3fr) Rac.-trans- (6-Biphenyl-4-yl-pyridazin-3-yl)-(2-methyl-1-aza-bicyclo[2.2.2]oct-3-yl)-amine

3fs) Rac.-trans- (5-Biphenyl-4-yl-pyridin-2-yl)-(2-methyl-1-aza-bicyclo[2.2.2]oct-3-yl)-amine

3ft) Rac.-trans- (5-Biphenyl-4-yl-pyrimidin-2-yl)-(2-methyl-1-aza-bicyclo[2.2.2]oct-3-yl)-amine

3fu) Rac.-trans- (2-Methyl-1-aza-bicyclo[2.2.2]oct-3-yl)-[6-(3-trifluoromethyl-phenyl)-pyridin-3-yl]-amine

3fv) Rac.-trans- (2-Methyl-1-aza-bicyclo[2.2.2]oct-3-yl)-[6-(3-trifluoromethyl-phenyl)-pyridazin -3-yl]-amine

3fw) Rac.-trans- (2-Methyl-1-aza-bicyclo[2.2.2]oct-3-yl)-[5-(3-trifluoromethyl-phenyl)-pyridin-2-yl]-amine

3fX) Rac.-trans- (2-Methyl-1-aza-bicyclo[2.2.2]oct-3-yl)-[5-(3-trifluoromethyl-phenyl)-pyrimidin-2-yl]-amine

3fy) Rac.-trans- (2-Methyl-1-aza-bicyclo[2.2.2]oct-3-yl)-(6-quinolin-5-yl-pyridin-3-yl)-amine

3fz) Rac.-trans- (2-Methyl-1-aza-bicyclo[2.2.2]oct-3-yl)-(6-quinolin-5-yl-pyridazin-3-yl)-amine

3ga) Rac.-trans- (2-Methyl-1-aza-bicyclo[2.2.2]oct-3-yl)-(5-quinolin-5-yl-pyridin-2-yl)-amine

3gb) Rac.-trans- (2-Methyl-1-aza-bicyclo[2.2.2]oct-3-yl)-(5-quinolin-5-yl-pyrimidin-2-yl)-amine

3gc) Rac.-trans- [6-(2,2-Difluoro-benzo[1,3]dioxol-5-yl)-pyridin-3-yl]-(2-methyl-1-aza-bicyclo [2.2.2]oct-3-yl)-amine

3gd) Rac.-trans- [6-(2,2-Difluoro-benzo[1,3]dioxol-5-yl)-pyridazin-3-yl]-(2-methyl-1-aza-bicyclo[2.2.2]oct-3-yl)-amine

3ge) Rac.-trans- [5-(2,2-Difluoro-benzo[1,3]dioxol-5-yl)-pyridin-2-yl]-(2-methyl-1-aza-bicyclo [2.2.2]oct-3-yl)-amine

3gf) Rac.-trans- [5-(2,2-Difluoro-benzo[1,3]dioxol-5-yl)-pyrimidin-2-yl]-(2-methyl-1-aza-bicyclo[2.2.2]oct-3-yl)-amine

3gg) Rac.-trans- (6-Benzo[b]thiophen-2-yl-pyridin-3-yl)-(2-methyl-1-aza-bicyclo[2.2.2]oct-3-yl)-amine

3gh) Rac.-trans- (6-Benzo[b]thiophen-2-yl-pyridazin-3-yl)-(2-methyl-1-aza-bicyclo[2.2.2]oct-3-yl)-amine

3gi) Rac.-trans- (5-Benzo[b]thiophen-2-yl-pyridin-2-yl)-(2-methyl-1-aza-bicyclo[2.2.2]oct-3-yl)-amine

3gj) Rac.-trans- (5-Benzo[b]thiophen-2-yl-pyrimidin-2-yl)-(2-methyl-1-aza-bicyclo[2.2.2]oct-3-yl)-amine

3gk) Rac.-trans- [6-(1H-Indol-2-yl)-pyridin-3-yl]-(2-methyl-1-aza-bicyclo[2.2.2]oct-3-yl)-amine

3gl) Rac.-trans- [6-(1H-Indol-2-yl)-pyridazin-3-yl]-(2-methyl-1-aza-bicyclo[2.2.2]oct-3-yl)-amine

3gm) Rac.-trans- [5-(1H-Indol-2-yl)-pyridin-2-yl]-(2-methyl-1-aza-bicyclo[2.2.2]oct-3-yl)-amine

3gn) Rac.-trans- [5-(1H-Indol-2-yl)-pyrimidin-2-yl]-(2-methyl-1-aza-bicyclo[2.2.2]oct-3-yl)-amine

3go) Rac.-trans- 5-[5-(2-Methyl-1-aza-bicyclo[2.2.2]oct-3-ylamino)-pyridin-2-yl]-thiophene-2-carbonitrile

3gp) Rac.-trans- 5-[6-(2-Methyl-1-aza-bicyclo[2.2.2]oct-3-ylamino)-pyridazin-3-yl]-thiophene-2-carbonitrile

3gq) Rac.-trans- 5-[6-(2-Methyl-1-aza-bicyclo[2.2.2]oct-3-ylamino)-pyridin-3-yl]-thiophene-2-carbonitrile

3gr) Rac.-trans- 5-[2-(2-Methyl-1-aza-bicyclo[2.2.2]oct-3-ylamino)-pyrimidin-5-yl]-thiophene-2-carbonitrile

3gs) Rac.-trans- [6-(4-Methanesulfonyl-phenyl)-pyridin-3-yl]-(2-methyl-1-aza-bicyclo [2.2.2]oct-3-yl)-amine

3gt) Rac.-trans- [6-(4-Methanesulfonyl-phenyl)-pyridazin-3-yl]-(2-methyl-1-aza-bicyclo [2.2.2]oct-3-yl)-amine

3gu) Rac.-trans- [5-(4-Methanesulfonyl-phenyl)-pyridin-2-yl]-(2-methyl-1-aza-bicyclo [2.2.2]oct-3-yl)-amine

3gv) Rac.-trans- [5-(4-Methanesulfonyl-phenyl)-pyrimidin-2-yl]-(2-methyl-1-aza-bicyclo [2.2.2]oct-3-yl)-amine

3gw) Rac.-trans-[6-(4-Chloro-phenyl)-pyridin-3-yl]-(-2-methyl-1-aza-bicyclo[2.2.2]oct-3-yl)-amine; preparative enantiomer separation (column: Chiralcel OD-H 5 um; (4.6x250 mm), solvent A: n-hexane : EtOH 95:5 (v:v) + 0.1% DEA, solvent B: EtOH, solvent composition: 85% A, 15% B (v:v), flow: 1.0 ml / min, detector: UV 270 nm): peak 1: 7.85 min; peak 2: 17.56 min.

Example 4: (2,4-dimethoxy-benzyl)-(2-methyl-1-aza-bicyclo[2.2.2]oct-3-yl)-(5-phenyl-pyrimidin-2-yl)-amine

2-Methyl-1-aza-bicyclo[2.2.2]octan-3-one (500 mg, 3.59 mmol) and 2,4-diemthoxybenzyl amine (1.2 g, 7.18 mmol) were dissolved in anhydrous 1,2-dichloroethane (10 ml). Sodium triacetoxyborohydride (1.1 g, 5.0 mmol) followed by glacial acetic acid (0.21 ml, 3.59 mmol) and the resultant foamy suspension was stirred at ambient temperature for 12 hours. The reaction was quenched by the addition of 1M NaOH, and the layers wee separated. The aqueous phase was extracted further with ethyl acetate. The organic portions were combined, dried (Na_2SO_4), filtered and concentrated in vacuo. The crude reaction mixture was purified by chromatography [eluent gradient: 10-30% MeOH/Et_3N (9:1) in EtOAc) to give pure (2,4-dimethoxy-benzyl)-(2-methyl-1-aza-bicyclo[2.2.2]oct-3-yl)-amine.

(2,4-Dimethoxy-benzyl)-(2-methyl-1-aza-bicyclo[2.2.2]oct-3-yl)-amine (70 mg, 0.24 mmol) and 5-bromo chloropyrimidine (93 mg, 0.48 mmol) were dissolved in 1,4-dioxane (1 ml). Glacial acetic acid (42 □L, 0.72 mmol) was added and the reaction mixture was stirred under microwave radiation at 150°C for 30 minutes. The reaction mixture was concentrated in vacuo, redissolved in EtOAc and washed with 1M aqueous sodium carbonate. The organic phase was dried (Na_2SO_4), filtered and concentrated in vacuo. The crude reaction mixture was purified by chromatography [eluent gradient: 10-30% MeOH/Et_3N (9:1) in EtOAc) to give pure (5-bromo-pyrimidin-2-yl)-(2,4-dimethoxy-benzyl)-(2-methyl-1-aza-bicyclo[2.2.2]oct-3-yl)-amine.

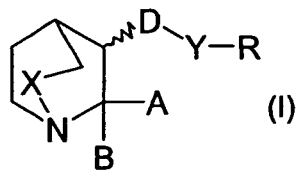
(5-Bromo-pyrimidin-2-yl)-(2,4-dimethoxy-benzyl)-(2-methyl-1-aza-bicyclo[2.2.2]oct-3-yl)-amine (30 mg, 66 □mol), palladium(II) acetate (1 mg, 3.2 □mol), potassium fluoride (12 mg, 198 □mol) and 2-(di-t-butylphosphino)biphenyl (1.6 mg, 6.4 □mol) were combined and purged three times with argon and vacuum. Anhydrous THF (1 ml) was added and the reaction mixture stirred stirred under microwave radiation at 110°C for 40 minutes. The crude reaction mixture was applied directly to a silica gel column and chromatographed [eluent gradient: 5-20% MeOH/Et_3N (9:1) in EtOAc) to give pure (2,4-dimethoxy-benzyl)-(2-methyl-1-aza-bicyclo[2.2.2]oct-3-yl)-(5-phenyl-pyrimidin-2-yl)-amine. MS (ES^+): m/e = 445.3 (MH^+).

Example 5: Soft Capsules

5000 soft gelatin capsules, each comprising as active ingredient 0.05 g of one of the compounds of formula (I) mentioned in the preceding Examples, are prepared as follows:
Composition: Active ingredient: 250 g, Lauroglycol : 2 litres
Preparation process: The pulverized active ingredient is suspended in Lauroglykol® (propylene glycol laurate, Gattefossé S.A., Saint Priest, France) and ground in a wet pulverizer to produce a particle size of about 1 to 3 µm. 0.419 g portions of the mixture are then introduced into soft gelatin capsules using a capsule-filling machine.

Claims:

1. A compound of formula (I)



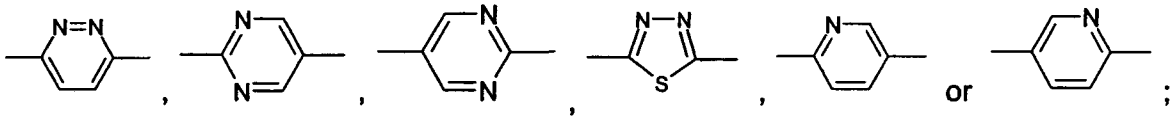
(I)

wherein

X represents CH_2 or a single bond ;

R represents a substituted or unsubstituted C_5-C_{10}aryl or a substituted or unsubstituted C_5-C_{10}heteroaryl, or a group $N(R^1)(R^5)$, or a group $N(R^2)(CHR^3R^4)$;

Y represents a group of formula



or ;

D represents NH,NR^6, S, S(O), SO_2

A and B represent, independently of each other, hydrogen or C_1-C_7alkyl under the proviso that not both A and B can represent hydrogen at the same time, or

A and B represent together with the carbon atom to which they are attached form a C_3-C_7cycloalkyl group,

R^1 represents hydrogen, C_1-C_4alkyl, or CF_3;

R^2 represents hydrogen, C_1-C_4alkyl, or CF_3;

R^3 represents hydrogen, C_1-C_4alkyl, or CF_3;

R^4 represents a substituted or unsubstituted C_5-C_{10}aryl or substituted or unsubstituted C_5-C_{10}heteroaryl;

R^5 represents a substituted or unsubstituted C_5-C_{10}aryl or substituted or unsubstituted C_5-C_{10}heteroaryl;

R^6 represents C_1-C_4alkyl, benzyl or benzyl substituted by one or more substituents selected from the group consisting of halogen, C_1-C_4alkyl, C_1-C_4alkoxy;

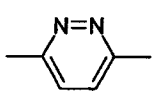
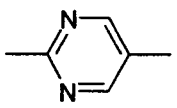
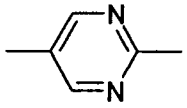
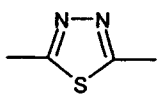
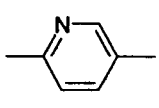
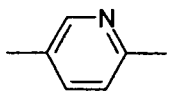
in free base or acid addition salt form.

2. A compound of formula (I) according to claim 1 wherein

X represent CH_2,

R represents C_5-C_{10}aryl, which is substituted by one or more substituents selected from halogen, NO_2, CN, C_1-C_4alkoxy which is unsubstituted or substituted by halogen, or C_1-C_4alkyl which is unsubstituted or substituted by halogen, C_1-C_4alkylsulfonyl, C_1-C_4alkylcarbonylamino;

Y represents a group of formula






or

;

D represents NH;

A represents hydrogen or C_1-C_7alkyl and B represents hydrogen, C_1-C_7alkyl or

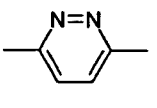
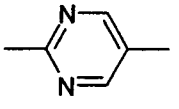
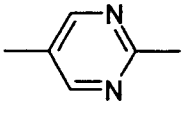
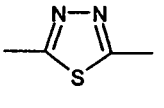
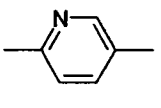
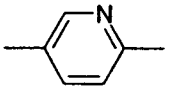
A and B represent together with the carbon atom to which they are attached form a cyclopropyl, cyclopentyl or cyclohexyl group,

3. A compound of formula (I) according to claim 1 wherein

X represents CH_2,

R represents hetero-C_5-C_{10}aryl, which which is unsubstituted or substituted by one or more substituents selected from halogen, C_1-C_4alkoxy, CN or C_1-C_4alkyl which is unsubstituted or substituted by halogen, phenyl which is unsubstituted or substituted by phenyl, C_1-C_4alkoxy or benzyl;

Y represents a group of formula






or

;

D represents NH;

A represents hydrogen or C_1-C_7alkyl and B represents hydrogen, C_1-C_7alkyl or

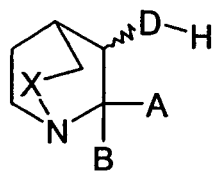
A and B represent together with the carbon atom to which they are attached form a cyclopropyl, cyclopentyl or cyclohexyl group.

4. Processes for the preparation of a compound of formula (I) as defined in claim 1, or a salt thereof,

which comprises in a first process the step of reacting a compound of formula (II)

Z-Y-R (II)

wherein Y and R are as defined above for a compound of formula (I) and Z is a leaving group, e.g. F, Cl, Br, I or OSO_2CF_3, with a compound of formula (III)

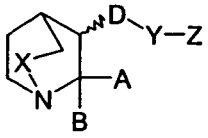


(III)

wherein A, B, D, X have the meanings as defined for a compound of formula (I), and recovering the so obtained compound of formula (I) in free base or acid addition salt form and optionally oxidizing the so obtained compound

and

which comprises in a second process the step of reacting a compound of formula (IV)



(IV)

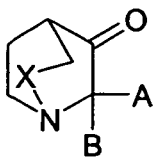
wherein A, B,D and Y are as defined above for a compound of formula (I) and Z represents a leaving group, e.g. F, Cl, Br, I or OSO_2CF_3, with a compound of formula (V)

$R\text{-}B(OH)_2$ (V)

wherein R is as defined above for a compound of formula (I), and recovering the so obtained compound of formula (I) in free base or acid addition salt form.

and

which comprises in a third process, wherein D represents NH or NR^6, the step of reacting a compound of formula (VI)



(VI)

wherein A, B and X are as defined above for compounds of formula (I) with a compound of formula (VII)

H_2N-Y-R (VII)

wherein Y and R are as defined above for compounds of formula (I) and recovering the so obtained compound of formula (I) in free base or acid addition salt form.

5. A compound of any one of claims 1 to 3 in free base or pharmaceutically acceptable acid addition salt form, for use as a pharmaceutical.

6. A compound of any one of claims 1 to 3 in free base or pharmaceutically acceptable acid addition salt form, for use in the prevention, treatment and delay of progression of psychotic and neurodegenerative disorders on its own or in combination with already existing drugs..

7. A pharmaceutical composition comprising a compound of any one of claims 1 to 3 in free base or pharmaceutically acceptable acid addition salt form, in association with a pharmaceutical carrier or diluent.

8. The use of a compound of any one of claims 1 to 3 in free base or pharmaceutically acceptable acid addition salt form, as a pharmaceutical for the prevention and the treatment of psychotic and neurodegenerative disorders.

9. The use of a compound of any one of claims 1 to 3 in free base or pharmaceutically acceptable acid addition salt form, for the manufacture of a medicament for the prevention, treatment and delay of progressionof psychotic and neurodegenerative disorders.

10. A method for the prevention, treatment and delay of progression of psychotic and neurodegenerative disorders, in a subject in need of such treatment, which comprises administering to such subject a therapeutically effective amount of a compound of any one of claims 1 to 3 in free base or pharmaceutically acceptable acid addition salt form.

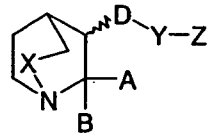
11. A compound of any one of claims 1 to 3 in free base or pharmaceutically acceptable acid addition salt form, for use in the prevention, treatment and / or delay of progression of a disease or condition in which α7 nAChR activation plays a role or is implicated.

12. The use of a compound of any one of claims 1 to 3 in free base or pharmaceutically acceptable acid addition salt form, as a pharmaceutical for the prevention, treatment and / or delay of progression of of a disease or condition in which α7 nAChR activation plays a role or is implicated.

13. A method for prevention, treatment and / or delay of progression of a disease or condition in which α7 nAChR activation plays a role or is implicated, in a subject in need of such treatment, which comprises administering to such subject a therapeutically effective amount of a compound of any one of claims 1 to 3 in free base or pharmaceutically acceptable acid addition salt form.

14. A compound of formula (IV)

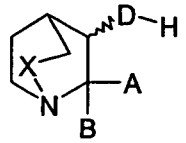
(IV)



wherein
A, B, D and Y are as defined in claim 1 for a compound of formula (I) and
Z represents F, Cl, Br, I or OSO_2CF_3.

15. A process for the preparation of a compound of formula (IV) as defined in claim 14, or a salt thereof, which comprises the step of reacting a compound of formula (III)

(III)



wherein A, B, D, X are as defined in claim 1 for a compound of formula (I), with a compound of formula (IIX)

Z-Y-Z (IIX)

wherein Y are as defined in claim 1 for a compound of formula (I) and Z is a leaving group, e.g. F, Cl, Br, I or OSO_2CF_3, optionally in the presence of one or more reaction auxiliaries such as a arylboronic acid.

16. A pharmaceutical combination, which comprises at least one nicotinic-alpha 7 receptor agonist and at least one compound selected from the group consisting of

(a) conventional antipsychotics; and

(b) atypical antipsychotics,

and wherein the active ingredients are present in each case in free form or in the form of a pharmaceutically acceptable salt.