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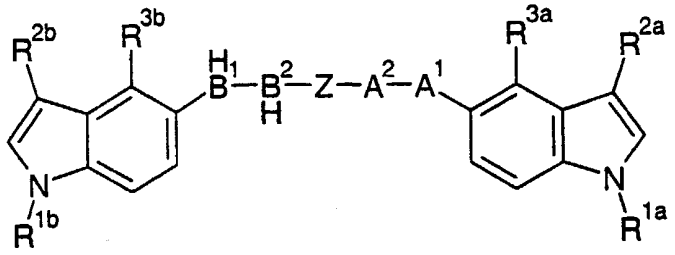

(I)

(57) Abstract: A compound of formula (I) wherein R^{1a}, R^{1b}, R^{3a} and R^{3b} independently represent hydrogen or C_1-C_4 alkyl; R^{2a} and R^{2b} independently represents hydrogen, C_1-C_4 alkyl or CH_2CN; A^1 represents O, S or NR^{4a}; B^1 represents O, S or NR^{4b}; R^{4a} represents hydrogen, C_1-C_4 alkyl, C_2-C_4 alkenyl; or together R^{3a} and R^{4a} form a ring; R^{4b} represents hydrogen, C_1-C_4 alkyl, C_2-C_4 alkenyl; or together R^{3b} and R^{4b} form a ring; A^2 and B^2 independently represent C(O), C(NH), OC(O), NHC(O), NHC(S), SO_2, or a bond; Z represents $(CH_2)_n$ $Y(CH_2)_m$; n and m are independently 0-4; Y represents O, S, NR^5, CHR^6, Ar, or Ccy; Ccy represents a 5-10 membered carbocycle including cyclopentane and adamantane; Ar represents phenyl, naphthyl; or a 5- or 6- membered heterocyclic ring containing zero to four nitrogens, zero to one sulfurs and zero to one oxygens; Ar is optionally substituted with one or more substituents selected from: hydrogen, halogen, C_1-C_4 alkyl, C_2-C_4 alkenyl, C_2-C_4 alkynyl, CN, NO_2, CF_3, OR^7, NR^8R^9, and $COOR^{10}$; R^7, R^8 and R^9 are independently hydrogen, C_1-C_4 alkyl, aryl, heteroaryl, $C(O)R^{11}$, $C(O)R^{12}$, SO_2R^{13}, or; R^8 and R^9 together may be $(CH_2)_j$ $Q(CH_2)_k$, where Q is O, S, NR^{14} or a bond; j is 2-4; k is 0-2; R^5, R^6, R^{10}, R^{11}, R^{12}, R^{13} and R^{14} are independently hydrogen, C_{1-4} alkyl, aryl or heteroaryl; or an enantiomer thereof, and pharmaceutically acceptable salts thereof, processes for preparing them, pharmaceutical compositions containing them and their use in therapy, especially for treatment of conditions associated with reductions in nicotinic transmission. The compounds of the invention enhance the efficacy of agonists at nicotinic receptors.

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POSITIVE MODULATORS OF NICOTINIC RECEPTOR AGONISTS

The present invention relates to novel compounds or pharmaceutically acceptable salts thereof, processes for preparing them, pharmaceutical compositions containing them and their use in therapy. The novel compounds referred to are positive modulators of nicotinic receptor agonists, said positive modulator having the capability to increase the efficacy of the said nicotinic receptor agonists.

Background

Cholinergic receptors normally bind the endogenous neurotransmitter acetylcholine (ACh), thereby triggering the opening of ion channels. ACh receptors in the mammalian central nervous system can be divided into muscarinic (mAChR) and nicotinic (nAChR) subtypes based on the agonist activities of muscarine and nicotine, respectively. The nicotinic acetylcholine receptors are ligand-gated ion-channels containing five subunits (for reviews, see Colquhon et al. (1997) Advances in Pharmacology 39, 191-220; Williams et al. (1994) Drug News & Perspectives 7, 205-223; Doherty et al. (1995) Annual reports in Medicinal Chemistry 30, 41-50). Members of the nAChR gene family have been divided into two groups based on their sequences; members of one group are considered β subunits, while a second group are classified as α subunits (for reviews, see Karlin & Akabas (1995) Neuron 15, 1231-1244; Sargent (1993) Annu. Rev. Neurosci. 16, 403-443). Three of the α subunits, α7, α8 and α9, form functional receptors when expressed alone and thus presumably form homooligomeric receptors.

An allosteric transition state model of the nAChR involves at least a resting state, an activated state and a "desensitized" closed channel state (Williams et al., *supra*; Karlin & Akabas, *supra*). Different nAChR ligands can thus differentially stabilize the conformational state to which they preferentially bind. For example, the agonists ACh and (–)-nicotine stabilize the active and desensitized states.

Changes of the activity of nicotinic receptors has been implicated in a number of diseases. Some of these, e.g. myasthenia gravis and ADNFLE (autosomal dominant nocturnal front lobe epilepsy) (Kuryatov et al. (1997) J. Neurosci. 17(23):9035-47), are associated with reductions in the activity of nicotinic transmission either through a decrease in receptor number or increased desensitization, a process by which receptors become insensitive to the agonist. Reductions in nicotinic receptors have also been hypothesized to mediate cognitive deficits seen in diseases such as Alzheimer's disease and schizophrenia

(Williams et al., *supra*). The effects of nicotine from tobacco are also mediated by nicotinic receptors. Increased activity of nicotinic receptors may reduce the desire to smoke.

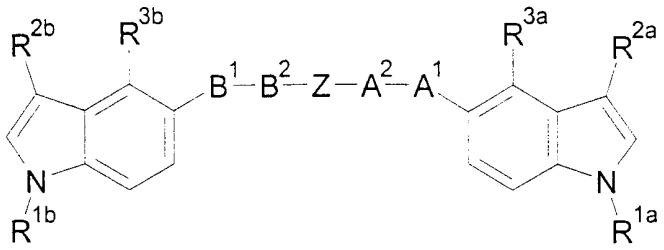
The use of compounds which bind nicotinic acetylcholine receptors in the treatment of a range of disorders involving reduced cholinergic function such as Alzheimer's disease, cognitive or attention disorders, attention deficit hyperactivity disorders, anxiety, depression, smoking cessation, neuroprotection, schizophrenia, analgesia, Tourette's syndrome, and Parkinson's disease has been discussed in McDonald et al. (1995) "Nicotinic Acetylcholine Receptors: Molecular Biology, Chemistry and Pharmacology", Chapter 5 in Annual Reports in Medicinal Chemistry, vol. 30, pp. 41-50, Academic Press Inc., San Diego, CA; and in Williams et al., *supra*.

However, treatment with nicotinic receptor agonists which act at the same site as ACh is problematic because ACh not only activates, but also blocks receptor activity through processes which include desensitization (for a review, see Ochoa et al. (1989) Cellular and Molecular Neurobiology 9, 141-178) and uncompetitive blockade (open-channel block); Forman & Miller (1988) Biophysical Journal 54(1):149-58. Furthermore, prolonged activation appears to induce a long-lasting inactivation. Therefore agonists of ACh can be expected to reduce activity as well as enhance it. At nicotinic receptors in general, and, of particular note, at the α7-nicotinic receptor, desensitization limits the duration of current during agonist application.

Disclosure of the Invention

It has surprisingly been found that certain compounds can enhance the efficacy of agonists at nicotinic receptors. It is believed that compounds having this type of action (hereinafter referred to as "positive modulators") will be particularly useful for treatment of conditions associated with reductions in nicotinic transmission. In a therapeutic setting such compounds could restore normal interneuronal communication without affecting the temporal profile of activation. In addition, they would not produce long-term inactivation as prolonged application of agonist may.

According to the invention it has been found that compounds of Formula I:



I

wherein,

R^{1a}, R^{1b}, R^{3a} and R^{3b} independently represent hydrogen, or C_1- C_4 alkyl;

R^{2a} and R^{2b} independently represents hydrogen, C_1- C_4 alkyl, or CH_2CN;

A^1 represents oxygen, sulfur, or NR^{4a};

B^1 represents oxygen, sulfur, or NR^{4b};

R^{4a} represents hydrogen, C_1- C_4 alkyl, C_2- C_4 alkenyl; or together R^{3a} and R^{4a} form a ring;

R^{4b} represents hydrogen, C_1- C_4 alkyl, C_2 - C_4 alkenyl; or together R^{3b} and R^{4b} form a ring;

A^2 and B^2 independently represent C(O), C(NH), OC(O), NHC(O), NHC(S), SO_2 , or a bond;

Z represents $(CH_2)_n Y(CH_2)_m$;

n and m are independently 0-4;

Y represents oxygen, sulfur, NR^5, CHR^6, Ar, or Ccy;

Ccy represents a 5-10 membered carbocycle including cyclopentane and adamantane;

Ar represents phenyl, naphthyl; or a 5- or 6-membered heterocyclic ring containing zero to four nitrogens, zero to one sulfurs and zero to one oxygens;

Ar is optionally substituted with one or more substituents selected from: hydrogen, halogen, C_1- C_4 alkyl, C_2 - C_4 alkenyl, C_2- C_4 alkynyl, CN, NO_2, CF_3, OR^7, NR^8R^9, and $COOR^{10}$;

R^7, R^8 and R^9 are independently hydrogen, C_1- C_4 alkyl, aryl, heteroaryl, $C(O)R^{11}$, $C(O)R^{12}$, SO_2R^{13}, or; R^8 and R^9 together may be $(CH_2)_j Q(CH_2)_k$, where

Q is oxygen, sulfur, NR^{14}, or a bond;

j is 2-4;

k is 0-2;

R^5, R^6, R^{10}, R^{11}, R^{12}, R^{13} and R^{14} are independently hydrogen, C_1- C_4 alkyl, aryl, or heteroaryl;

or an enantiomer thereof, and pharmaceutically acceptable salts thereof, enhance the efficacy of agonists at nicotinic receptors.

Preferred compounds of the invention include the following:

1,3-Bis(indolyl-5-oxymethyl)benzene;

N,N'-Di(5-indolyl)-1,3-adamantanedicarboxamide;

or an enantiomer thereof, and pharmaceutically acceptable salts thereof.

Unless otherwise indicated, the C_1–C_4 alkyl groups referred to herein, e.g., methyl, ethyl, n-propyl, n-butyl, i-propyl, i-butyl, t-butyl, s-butyl, may be straight-chained or branched, and the C_3–C_4 alkyl groups may also be cyclic, e.g., cyclopropyl, cyclobutyl.

Unless otherwise indicated, the C_2–C_4 alkenyl groups referred to herein may contain one or two double bonds, e.g., ethenyl, i-propenyl, n-butenyl, i-butenyl, allyl, 1,3-butadienyl. Unless otherwise indicated, the C_2–C_4 alkynyl groups referred to herein contain one triple bond, e.g., ethynyl, propynyl, 1- or 2-butynyl.

Halogen referred to herein may be fluoride, chloride, bromide, or iodide.

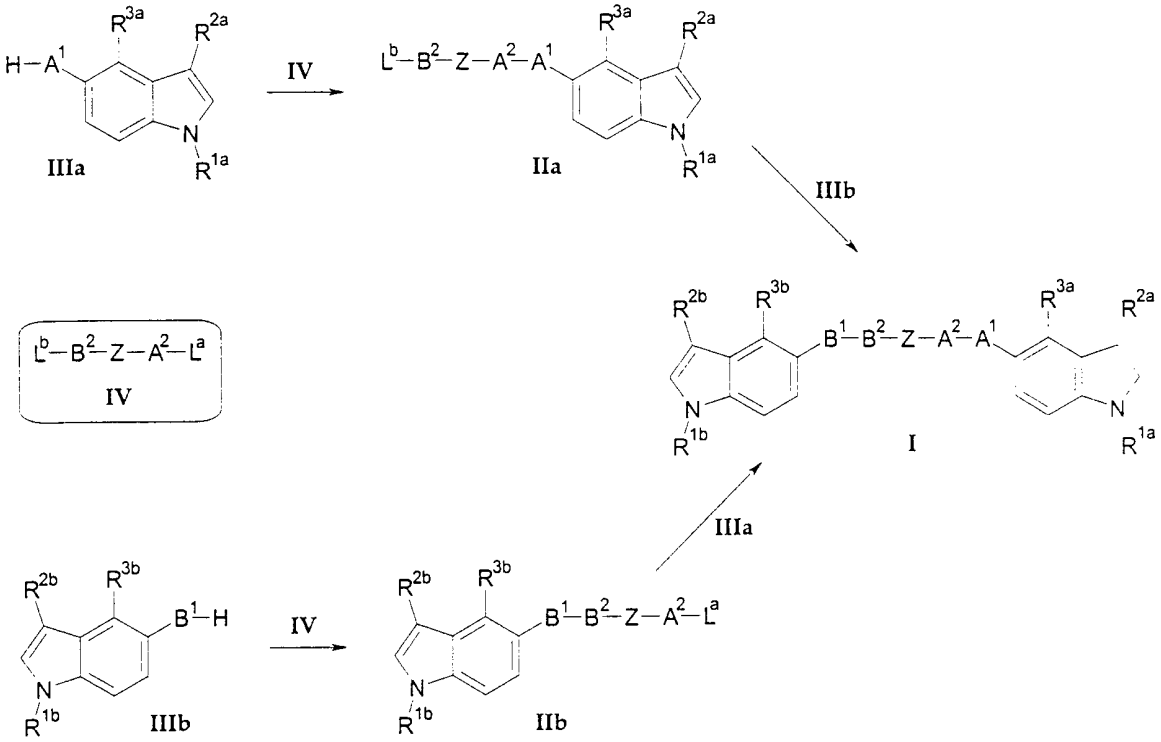
The compounds of the invention have the advantage that they may be less toxic, be more efficaous, be longer acting, have a broader range of activity, be more potent, produce fewer side effects, are more easily absorbed or have other useful pharmacological properties.

Methods of Preparation

In the reaction schemes and text that follow, R^{1a}, R^{1b}, R^{2a}, R^{2b}, R^{3a}, R^{3b}, A^1, A^2, B^1, B^2, and Z, unless otherwise indicated, are as defined above for formula I. The compounds of formula I may be prepared according to the methods outlined in Schemes I and II.

Compounds of formula I may be prepared from compounds of formula IIIa or IIIb, wherein R^{1a}, R^{1b}, R^{2a}, R^{2b}, R^{3a}, R^{3b}, A^1, A^2, B^1 and B^2 are as defined in formula I, by reaction with an intermediate of formula IIa or IIb, wherein L^a or L^b is a suitable leaving group representing halogen, triflate (TfO), methanesulfonate (MsO), or *p*-toluenesulfonate (pTsO) and R^{1a}, R^{1b}, R^{2a}, R^{2b}, R^{3a}, R^{3b}, A^1, A^2, B^1 , B^2, and Z are as defined in formula I, in the presence of a suitable base and solvent. Intermediates of formula IIa or IIb may be prepared from compounds of formula IIIa or IIIb, wherein R^{1a}, R^{1b}, R^{2a}, R^{2b}, R^{3a}, R^{3b}, A^1, and B^1 are as defined in formula I, by selective reaction of one of the leaving groups of a compound of

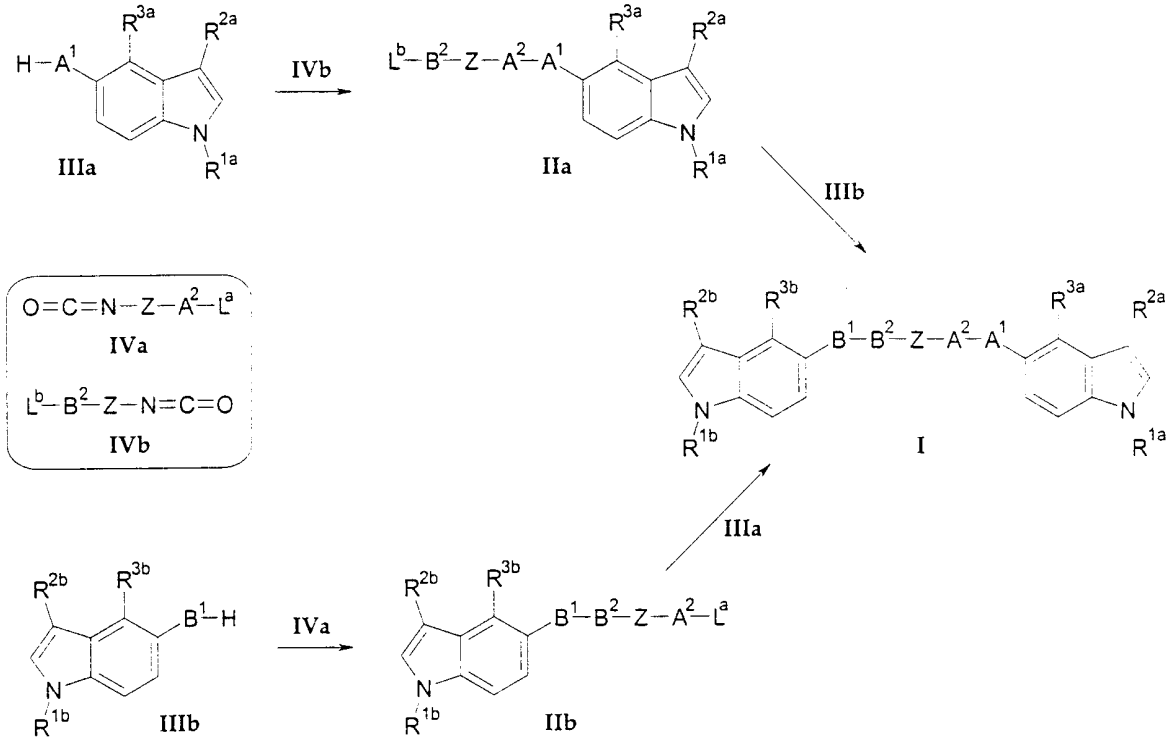
formula IV, wherein L^a and L^b are suitable leaving groups independently representing halogen, triflate (TfO), methanesulfonate (MsO), or *p*-toluenesulfonate (pTsO) and A^2, B^2 and Z are as defined in formula I, in the presence of a suitable base and solvent. Suitable bases include sodium carbonate (Na_2CO_3), cesium carbonate (Cs_2CO_3), potassium carbonate (K_2CO_3), triethylamine (TEA) or *N,N*-diisopropylethylamine (DIPEA). Suitable solvents for the reaction include *N,N*-dimethylformamide (DMF), *N*-methylpyrrolidone (NMP), acetonitrile (ACN), dimethylsulfoxide (DMSO) or tetrahydrofuran (THF). The reaction is preferably performed at a temperature of 0-100 °C and most preferably at ambient temperature.



Scheme I

Intermediates of formula IIa or IIb may be prepared from compounds of formula IIIa or IIIb, wherein R^{1a}, R^{1b}, R^{2a}, R^{2b}, R^{3a}, R^{3b}, A^1 and B^1 are as defined in formula I, by condensation with a compound of formula IVa or IVb, wherein N=C=O is an isocyanate group and L^a or L^b are suitable leaving groups (or synthetic precursors) representing halogen, triflate (TfO), methanesulfonate (MsO), or *p*-toluenesulfonate (pTsO) and A^2, B^2, and Z are as defined in formula I, in the presence of a suitable solvent. Suitable solvents for the

reaction include *N,N*-dimethylformamide (DMF), *N*-methylpyrrolidone (NMP), acetonitrile (ACN), dimethylsulfoxide (DMSO), tetrahydrofuran (THF), chloroform, ethyl acetate (EtOAc), ethanol (EtOH) or methanol (MeOH). The reaction is preferably performed at a temperature of 0-100 °C and most preferably at ambient temperature.



Scheme II

Compounds of formula IIIa and IIIb are either commercially available or may be prepared by methods known to one skilled in the art (see, for example, 'Indoles: Reactions and Synthesis' in 'Heterocyclic Chemistry', 3rd Edition, J. A. Joule, K. Mills, and G F. Smith, (Pub.) Stanley Thornes Ltd. (1998) and references therein).

Compounds of formula IIIa and IIIb, wherein A^1 represents NR^{4a} where together R^{3a} and R^{4a} form a ring and/or wherein B^1 represents NR^{4b} where together R^{3b} and R^{4b} form a ring, may be prepared by methods known to one skilled in the art (see, for example, J. E. Macor, J. T. Froman, R. J Post, K. Ryan, Tetrahedron Lett., 38, 1673-1676, 1997).

Compounds of formula IV, IVa and IVb are commercially available or may be prepared by methods known to one skilled in the art.

Where necessary, hydroxy, amino or other reactive groups may be protected using a protecting group as described in the standard text, 'Protecting Groups in Organic Synthesis', 3rd Edition, T. W. Greene and P. G. M. Wuts, 1999, J Wiley & Sons, Inc.

The above described reactions, unless otherwise noted, are usually conducted at a pressure of about one to about three atmospheres, preferably at ambient pressure (about one atmosphere). Unless otherwise stated, the above described reactions are conducted under an inert atmosphere, preferably under a nitrogen atmosphere.

The compounds of the invention and intermediates may be isolated from their reaction mixtures by standard techniques.

Acid addition salts of the compounds of formula I which may be mentioned include salts of mineral acids, for example the hydrochloride and hydrobromide salts; and salts formed with organic acids such as formate, acetate, maleate, benzoate, tartrate, and fumarate salts. Acid addition salts of compounds of formula I may be formed by reacting the free base or a salt, enantiomer or protected derivative thereof, with one or more equivalents of the appropriate acid. The reaction may be carried out in a solvent or medium in which the salt is insoluble or in a solvent in which the salt is soluble, e.g., water, dioxane, ethanol, tetrahydrofuran or diethyl ether, or a mixture of solvents, which may be removed in vacuum or by freeze drying. The reaction may be a metathetical process or it may be carried out on an ion exchange resin.

The compounds of formula I exist in tautomeric or enantiomeric forms, all of which are included within the scope of the invention. The various optical isomers may be isolated by separation of a racemic mixture of the compounds using conventional techniques, e.g. fractional crystallization, or chiral HPLC. Alternatively the individual enantiomers may be made by reaction of the appropriate optically active starting materials under reaction conditions which will not cause racemization.

The compounds of formula I, or an enantiomer thereof, and pharmaceutically acceptable salts thereof, may be used on their own or in the form of appropriate medicinal preparations for enteral or parenteral administration. According to a further aspect of the invention, there is provided a pharmaceutical composition including preferably less than 80% and more preferably less than 50% by weight of a compound of the invention in admixture with an inert pharmaceutically acceptable diluent or carrier.

Examples of diluents and carriers are:

– for tablets and dragees: lactose, starch, talc, stearic acid; for capsules: tartaric acid or lactose;

– for injectable solutions: water, alcohols, glycerin, vegetable oils; for suppositories: natural or hardened oils or waxes.

There is also provided a process for the preparation of such a pharmaceutical composition, which comprises mixing the ingredients.

It will be understood that a pharmaceutical composition comprising a positive modulator of a nicotinic receptor agonist together with a pharmaceutically acceptable carrier said positive modulator having the capability to increase the efficacy of the said receptor agonist. For the purposes of the present invention, the term "positive modulator" or "positive modulator of a nicotinic receptor agonist" shall be understood as a compound having the capability to increase the maximum efficacy of a nicotinic receptor agonist.

It will be understood that the invention includes compositions comprising either a positive modulator as the only active substance, thus modulating the activity of endogenous nicotinic receptor agonists such as acetylcholine or choline, or a positive modulator in combination with a nicotinic receptor agonist. Thus, the said pharmaceutical compositions containing a positive modulator of a nicotinic receptor agonist may, in addition comprise a nicotinic receptor agonist.

In a preferred form of the invention, the said nicotinic receptor agonist is an α7-nicotinic receptor agonist. Example of an α7-nicotinic receptor agonist is (-)-Spiro[1-Azabicyclo[2.2.2.]Octane-3,5*-Oxazolidine]-2*-One. Several α7-nicotinic receptor agonists are known in the art, e.g. from WO 96/06098, WO 97/30998 and WO 99/03859.

A further aspect of the invention provides a method for the treatment of a condition associated with reduced nicotine transmission, by administering to a patient in need of such treatment, a medically effective amount of a positive modulator of a nicotinic receptor agonist, said positive modulator having the capability to increase the efficacy of the said nicotinic receptor agonist.

It will be understood that the methods of treatment of this invention includes either a positive modulator as the only active substance, thus modulating the activity of endogenous nicotinic receptor agonists such as acetylcholine or choline, or a positive modulator administered together with a nicotinic receptor agonist.

In another preferred form of the invention, the said method of treatment includes a nicotinic receptor agonist, which is an α7-nicotinic receptor agonist. Example of an α7-nicotinic receptor agonist is (-)-Spiro[1-Azabicyclo[2.2.2.]Octane-3,5*-Oxazolidine]-2*-One.

Several α7-nicotinic receptor agonists are known in the art, e.g. from WO 96/06098, WO 97/30998 and WO 99/03859.

Utility

A further aspect of the invention is the use of compound according to the invention in the manufacture of a medicament for the treatment or prophylaxis of a condition associated with reduced nicotinic receptor transmission or a condition associated with reduced nicotinic density which could be one of the below mentioned diseases or conditions which comprises administering a therapeutically effective amount of compounds according to the invention to a patient.

It will be understood that the use includes compositions comprising either a positive modulator as the only active substance, thus modulating the activity of endogenous nicotinic receptor agonists such as acetylcholine or choline, or a positive modulator in combination with a nicotinic receptor agonist. Thus, the said use of pharmaceutical compositions containing a positive modulator of a nicotinic receptor agonist may, in addition comprise a nicotinic receptor agonist.

In a preferred form of the invention, the use of the said nicotinic receptor agonist is represented by an α7-nicotinic receptor agonist. Example of an α7-nicotinic receptor agonist is (-)-Spiro[1-Azabicyclo[2.2.2.]Octane-3,5*-Oxazolidine]-2*-One. Several α7-nicotinic receptor agonists are known in the art, e.g. from WO 96/06098, WO 97/30998 and WO 99/03859.

Examples of diseases or conditions include schizophrenia, mania and manic depression, anxiety, Alzheimer's disease, learning deficit, cognition deficit, attention deficit, memory loss, Lewy Body Dementia, Attention Deficit Hyperactivity Disorder, Parkinson's disease, Huntington's disease, Tourette's syndrome, jetlag, and nicotine addiction (including that resulting from exposure to products containing nicotine).

It will be understood that the said positive modulator can be administered either with the purpose of acting on endogenous nicotine receptor agonists such as acetylcholine or choline, or in combination with an exogenous nicotinic receptor agonist.

A further aspect of the invention relates to a compound for treating or preventing a condition or disorder as exemplified above arising from dysfunction of nicotinic acetylcholine receptor neurotransmission in a mammal, preferably a human, compositions comprising either a positive modulator as the only active substance, thus modulating the activity of endogenous nicotinic receptor agonists, or a positive modulator in combination with a nicotinic receptor

agonist. Thus, the said use of pharmaceutical compositions containing a positive modulator of a nicotinic receptor agonist may, in addition comprise a nicotinic receptor agonist, effective in treating or preventing such disorder or condition and an inert pharmaceutically acceptable carrier.

Experimental Methods

The activity of the compounds of the invention may be measured in the tests set out below:

(a) *Xenopus* oocyte current recording

The *Xenopus* oocyte has provided a powerful means of assessing the function of proteins thought to be subunits of ligand-gated ion-channels. Injection of RNA transcribed from cDNA clones encoding the appropriate receptor subunits, or injection of cDNA in which the coding sequence is placed downstream of a promoter, results in the appearance of functional ligand-gated ion-channels on the surface of the oocyte (see e.g. Boulter et al. (1987) Proc. Natl. Acad. Sci. U.S.A. 84, 7763-7767).

Consequently, one convenient technique to assess the enhancement of nicotinic efficacy is two-electrode voltage-clamp recording from *Xenopus* oocytes expressing α7-nicotinic receptors from cRNA.

Xenopus laevis frogs (Xenopus I, Kalamazoo, MI) were anesthetized using 0.15% tricaine. Oocytes were removed to OR2 solution (82 mM NaCl, 2.5 mM KCl, 5 mM HEPES, 1.5 mM NaH_2PO_4, 1 mM $MgCl_2$, 0.1 mM EDTA; pH 7.4). The oocytes were defolliculated by incubation in 25 ml OR2 containing 0.2% collagenase 1A (Sigma) two times for 60 min on a platform vibrating at 1 Hz and stored in Leibovitz's L-15 medium (50 μg/ml gentomycin, 10 Units/ml penicillin, and 10 μg/ml streptomycin). Approximately 50 ng of cRNA was injected in each oocyte the following day. cRNA was synthesised from cDNA using Message Machine (purchased from Abion).

The external recording solution consisted of 90 mM NaCl, 1 mM KCl, 1 mM $MgCl_2$, 1 mM $BaCl_2$, 5 mM HEPES; pH 7.4. Two-electrode voltage-clamp recording was carried out using an Oocyte Clamp amplifier (OC 725C; Warner Instrument, Hamden, CT). Oocytes were impaled with two electrodes of 1-2 MΩ tip resistance when filled with 3M KCl. Recordings were begun when membrane potential became stable at potentials negative to -20mV (resting membrane potentials are less negative when Ba^{++} replaces Ca^{++} in bathing

solutions). Membrane potential was clamped at -80 mV. ACh was purchased from Sigma. Oocytes were continuously perfused (5 ml/min) with recording solution with or without ACh.

Current amplitude was measured from baseline to peak. EC_{50} values, maximal effect, and Hill slopes were estimated by fitting the data to the logistic equation using GraphPad Prism (GraphPad Software, Inc., San Diego, CA).

Increases in agonist efficacy elicited by a positive modulator can be calculated in two ways:

(1) As percent potentiation of current amplitude which is defined as $100(I_m-I_c)/I_c$ where I_m is current amplitude in the presence of modulator and I_c is current in the absence of modulator.

(2) As percent potentiation of "area under curve" of an agonist trace, which is the integration of net current over time. Area under the curve is a common representation of the total ion flux through the channel.

(b) Ca^{2+} flux imaging

Imaging of Ca^{2+} flux through nAChR α7 receptors transiently expressed in a cell line is another means of assaying modulator activity.

Cells expressing α7 receptors (for example HEK-293 cells or cell cultured neurons) are grown to confluence in 96 well plates and loaded with fluo-3, a fluorescent calcium indicator. To screen for α7 modulatory activity, the 96 well plate is placed in a fluorescence imaging plate reader (FLIPR) and test compounds along with an α7 agonist are applied simultaneously to all wells. Receptor activation is measured by calcium influx into cells which is quantified by the increase in fluorescence intensity of each well, recorded simultaneously by the FLIPR. A modulatory effect is determined by the increase in fluorescence over that of agonist alone. Similarly, to test for nAChR α7 agonist activity, test compounds along with an α7 modulator are applied simultaneously to all wells. Receptor activation is measured by calcium influx into cells which is quantified by the increase in fluorescence intensity of each well, recorded simultaneously by the FLIPR. An agonist effect is determined by the increase in fluorescence over that of modulator alone.

Cell-cultured neurons are prepared according to the following method: Eighteen day old Sprague-Dawley rat fetuses (E-18) were asceptically removed from the pregnant male, sacrificed, the frontal cortices of the brains removed, the menniges stripped, and the cleaned cortex placed into cold HBSS. If hippocampus was desired, the hippocampus was dissected

away from the cortex and then placed into cold HBSS. The tissues were mechanically dispersed, washed once in HBSS (200 g for 30 minutes in 4 °C) resuspended in a modification of Sato's medium supplemented with glutamine, antibiotics, potassium chloride, insulin, transferrin, selenium, and 5% heat-inactivated fetal bovine serum (FBS; endotoxin free) and plated into each of a 24-well plate (coated with poly-L-lysine). The wells could contain glass coverslips which were also coated with PLL. The plates were incubated at 37 °C in a CO_2 incubator. After 24 hours the medium was removed, fresh medium added, and the cells allowed to grow for at least another 11 days, feeding when necessary.

The compounds of the invention are compounds, which causes a 100% potentiation (2-fold increase) of baseline current (as described above), as measured baseline to peak at low concentration of Acetylcholine (30 μM), indicating that they are expected to have useful therapeutic activity. The compounds of the invention are also compounds, which increase the flux of Ca^{2+} when applied in the Ca^{2+} flux-imaging assay, as described above. Any increase of Ca^{2+} flux, caused by a compound of the invention, compared to the Ca^{2+} flux caused by an agonist alone (as measured in Fluorescence Intensity Units) indicates that they are expected to have useful therapeutic activity.

The use of compounds of the invention have the advantage that they may be less toxic, be more efficacious, be longer acting, have a broader range of activity, be more potent, produce fewer side effects, are more easily absorbed or have other useful pharmacological properties.

General Experimental Procedures

Commercial reagents were used without further purification. Mass spectra were recorded following either chemical ionization (MS CI) or electrospray (MS ES) ionization methods and are reported as *m/z* for the protonated parent molecular ion (MH^+). Room temperature refers to 20–25 °C.

Examples

The following examples are preferred non-limiting examples embodying preferred aspects of the invention.

Example 1

1,3-Bis(indolyl-5-oxymethyl)benzene

To a solution of 5-hydroxyindole (0.133 g) in *N,N*-dimethylformamide (20 ml) was added cesium carbonate (0.652 g) and α,α'-dibromo-*m*-xylene (0.132 g). The suspension was stirred under nitrogen at ambient temperature overnight. Cesium salts were removed by

filtration and washed with acetone. The residue left on concentrating the combined filtrate and washings was chromatographed over silica gel with a mixture of ethyl acetate and hexanes and precipitated from ether with hexanes to give 0.1 g of the title compound. MS CI (MH^+) = 369.

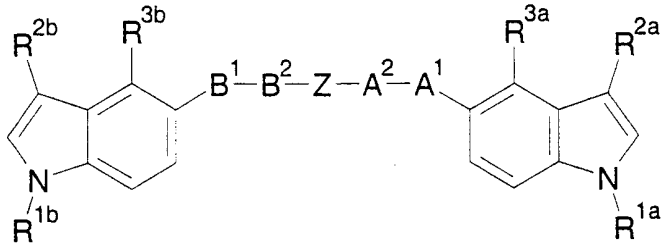
Example 2

N,N'-Di(5-indolyl)-1,3-adamantanedicarboxamide

To a solution of 1,3-adamantanedicarboxylic acid (0.112 g) in chloroform (10 ml) at 0 °C was added thionyl chloride (0.18 g). The solution was allowed to warm to room temperature overnight and reduced to a residue at reduced pressure. The residue was dissolved in dry tetrahydrofuran and concentrated twice more to remove excess thionyl chloride. To a solution of the resulting acid chloride in tetrahydrofuran (20 ml) at 0 °C was added 5-aminoindole (0.13 g) and triethylamine (0.1 g) and the resulting suspension was allowed to warm to room temperature overnight. The precipitated triethylamine hydrochloride was removed by filtration and washed with tetrahydrofuran. The residue left on concentrating the combined filtrate and washings was chromatographed over silica gel with a mixture of ethyl acetate and hexanes to give 0.16 g of the title compound. MS ES (MH^+) = 453.

CLAIMS

1. A compound of Formula I:



I

wherein:

R^{1a}, R^{1b}, R^{3a} and R^{3b} independently represent hydrogen, or C_1- C_4 alkyl;

R^{2a} and R^{2b} independently represents hydrogen, C_1- C_4 alkyl, or CH_2CN;

A^1 represents oxygen, sulfur, or NR^{4a};

B^1 represents oxygen, sulfur, or NR^{4b};

R^{4a} represents hydrogen, C_1- C_4 alkyl, C_2- C_4 alkenyl; or together R^{3a} and R^{4a} form a ring;

R^{4b} represents hydrogen, C_1- C_4 alkyl, C_2 - C_4 alkenyl; or together R^{3b} and R^{4b} form a ring;

A^2 and B^2 independently represent C(O), C(NH), OC(O), NHC(O), NHC(S), SO_2 , or a bond;

Z represents $(CH_2)_n Y(CH_2)_m$;

n and m are independently 0-4;

Y represents oxygen, sulfur, NR^5, CHR^6, Ar, or Ccy;

Ccy represents a 5-10 membered carbocycle including cyclopentane and adamantane;

Ar represents phenyl, naphthyl; or a 5- or 6-membered heterocyclic ring containing zero to four nitrogens, zero to one sulfurs and zero to one oxygens;

Ar is optionally substituted with one or more substituents selected from: hydrogen, halogen, C_1- C_4 alkyl, C_2 - C_4 alkenyl, C_2- C_4 alkynyl, CN, NO_2, CF_3, OR^7, NR^8R^9, and $COOR^{10}$;

R^7, R^8 and R^9 are independently hydrogen, C_1- C_4 alkyl, aryl, heteroaryl, $C(O)R^{11}$, $C(O)R^{12}$, SO_2R^{13}, or; R^8 and R^9 together may be $(CH_2)_j Q(CH_2)_k$, where Q is oxygen, sulfur, NR^{14}, or a bond;

j is 2-4;

k is 0-2;

R^5, R^6, R^{10}, R^{11}, R^{12}, R^{13} and R^{14} are independently hydrogen, C_1- C_4 alkyl, aryl or heteroaryl;

or an enantiomer thereof, and pharmaceutically acceptable salts thereof.

2. A compound according to claim 1, said compound being:

1,3-Bis(indolyl-5-oxymethyl)benzene;

N,N'-Di(5-indolyl)-1,3-adamantanedicarboxamide;

or an enantiomer thereof, and pharmaceutically acceptable salts thereof.

3. A compound according to claim 1 or claim 2, for use in therapy.

4. A pharmaceutical composition including a compound as defined in claim 1 or claim 2, in admixture with an inert pharmaceutically acceptable diluent or carrier.

5. The pharmaceutical composition according to claim 4, in addition comprising a nicotinic receptor agonist.

6. The pharmaceutical composition according to claim 4 or claim 5, for the use in the treatment or prophylaxis of human diseases or conditions in which the compound is having the capability to increase the efficacy of a nicotinic receptor agonist.

7. The pharmaceutical composition according to claim 4 or claim 5, for use in the treatment or prophylaxis of psycotic disorders or intellectual impairment disorders.

8. The pharmaceutical composition according to claim 4 or claim 5, for use in the treatment or prophylaxis of human diseases or conditions in which activation of the $\alpha 7$ nicotinic receptor is beneficial.

9. The pharmaceutical composition according to claim 7, for use in the treatment or prophylaxis of Alzheimer's disease, learning deficit, cognition deficit, attention deficit, memory loss, Attention Deficit Hyperactivity Disorder, Lewy Body Dementia, anxiety, schizophrenia, or mania or manic depression, Parkinson's disease, Huntington's disease, Tourette's syndrome, neurodegenerative disorders in which there is loss of cholinergic

synapse, jetlag, cessation of smoking, nicotine addiction including that resulting from exposure to products containing nicotine, pain, or ulcerative colitis.

10. The pharmaceutical composition according to claim 7, for use in the treatment or prophylaxis of Alzheimer's disease, learning deficit, cognition deficit, attention deficit, Lewy Body Dementia, memory loss or Attention Deficit Hyperactivity Disorder.

11. The pharmaceutical composition according to claim 7, for use in the treatment or prophylaxis of anxiety, schizophrenia, or mania or manic depression.

12. The pharmaceutical composition according to claim 7, for use in the treatment or prophylaxis of Parkinson's disease, Huntington's disease, Tourette's syndrome, or neurodegenerative disorders in which there is loss of cholinergic synapses.

13. The pharmaceutical composition according to claim 7, for use in the treatment or prophylaxis of jetlag, nicotine addiction including that resulting from exposure to products containing nicotine, pain, or ulcerative colitis.

14. The pharmaceutical composition according to claim 7, for use in the treatment or prophylaxis of Alzheimer's disease.

15. Use of a compound as defined in claim 1 or claim 2, in the manufacture of a medicament for the treatment or prophylaxis of psychotic disorders or intellectual impairment disorders.

16. The use of a compound as defined in claim 1 or claim 2, in the manufacture of a medicament for the treatment or prophylaxis of human diseases or conditions in which activation of the $\alpha 7$ nicotinic receptor is beneficial.

17. The use of a compound as defined in claim 1 or claim 2, in the manufacture of a medicament for the treatment or prophylaxis of Alzheimer's disease, learning deficit, cognition deficit, attention deficit, memory loss, Attention Deficit Hyperactivity Disorder, Lewy Body Dementia, anxiety, schizophrenia, mania or manic depression, Parkinson's disease, Huntington's disease, Tourette's syndrome, neurodegenerative disorders in which there is loss of cholinergic synapse, jetlag, cessation of smoking, nicotine addiction including that resulting from exposure to products containing nicotine, pain, or ulcerative colitis.

18. The use according to claim 17, wherein the condition or disorder is Alzheimer's disease, learning deficit, cognition deficit, attention deficit, memory loss, Lewy Body Dementia, or Attention Deficit Hyperactivity Disorder.

19. The use according to claim 17, wherein the disorder is anxiety, schizophrenia, mania or manic depression.

20. The use according to claim 17, wherein the disorder is Parkinson's disease, Huntington's disease, Tourette's syndrome, or neurodegenerative disorders in which there is loss of cholinergic synapses.

21. The use according to claim 17, wherein the condition or disorder is Alzheimer's disease.

22. The use according to claim 17, wherein the condition or disorder is jetlag, nicotine addiction including that resulting from exposure to products containing nicotine, pain, and for ulcerative colitis.

23. A method for the treatment of a condition associated with reduced nicotine transmission, by administering to a patient in need of such treatment, a medically effective amount of a compound according to claim 1 or claim 2, said compound having the capability to increase the efficacy of a nicotinic receptor agonist

24. The method according to claim 23, wherein the said compound is administered together with a nicotinic receptor agonist.

25. The method according to claim 23 or claim 24, wherein the said agonist is an α7-nicotinic receptor agonist.

26. A method of treatment or prophylaxis of psychotic disorders or intellectual impairment disorders, which comprises administering a therapeutically effective amount of a compound, as defined in claim 1 or claim 2.

27. A method of treatment or prophylaxis of human diseases or conditions in which activation of the α7 nicotinic receptor is beneficial which comprises administering a therapeutically effective amount of a compound, as defined in claim 1 or claim 2.

28. The method according to any one of claims 23 to 27, wherein the disorder is Alzheimer's disease, learning deficit, cognition deficit, attention deficit, memory loss, Attention Deficit Hyperactivity Disorder, Lewy Body Dementia, anxiety, schizophrenia, mania or manic depression, Parkinson's disease, Huntington's disease, Tourette's syndrome, neurodegenerative disorders in which there is loss of cholinergic synapse, jetlag, cessation of smoking, nicotine addiction including that resulting from exposure to products containing nicotine, pain, or ulcerative colitis.

29. The method according to claim 28, wherein the disorder is Alzheimer's disease, learning deficit, cognition deficit, attention deficit, memory loss, Lewy Body Dementia, or Attention Deficit Hyperactivity Disorder.

30. The method according to claim 28, wherein the disorder is Parkinson's disease, Huntington's disease, Tourette's syndrome, or neurodegenerative disorders in which there is loss of cholinergic synapses.

31. The method according to claim 28, wherein the disorder is anxiety, schizophrenia, mania or manic depression.

32. The method according to claim 28, wherein the disorder is jetlag, nicotine addiction, pain, and for ulcerative colitis.

33. The method according to claim 28, wherein the disorder is Alzheimer's disease.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 00/02149

A. CLASSIFICATION OF SUBJECT MATTER

IPC7: C07D 209/08, A61K 31/404, A61P 25/00
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)

IPC7: C07D, A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 9626923 A1 (PIERRE FABRE MEDICAMENT), 6 Sept 1996 (06.09.96), see particularly page 38, line 1 - line 5 and examples --	1-33
X	WO 9964044 A1 (ADVANCED MEDICINE, INC.), 16 December 1999 (16.12.99), see claims --	1-33
X	J.Med.Chem., Volume 39, 1996, Serge Halazy et al, "Serotonin Dimers: Application of the Bivalent Ligand Approach to the Design of New Potent and Selective 5-HT1B/1D Agonists" page 4920 - page 4927 --	1-33

[X] Further documents are listed in the continuation of Box C. [X] See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
22 February 2001	28-02-2001
Name and mailing address of the ISA/ Swedish Patent Office Box 5055, S-102 42 STOCKHOLM Facsimile No. +46 8 666 02 86	Authorized officer Nebil Gecer/ELY Telephone No. +46 8 782 25 00

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 00/02149

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	STN International, File CAPLUS, CAPLUS accession no. 1975:601816, Document no. 83:201816, Il'ina, G.N. et al: "Synthesis and pharmacological activity of 5,5'-acyldioxytryptamine"; Khim.-Farm. Zh. (1975), 9(7), 17-21 -- --------	1-33

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE00/02149

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: **23-33**
because they relate to subject matter not required to be searched by this Authority, namely:

See extra sheet*

2. ☒ Claims Nos.: **1**
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

See extra sheet**

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

*Claims 23-33 relate to methods of treatment of the human or animal body by surgery or by therapy/diagnostic methods practised on the human or animal body/ Rule. 39.1.(iv). Nevertheless, a search has been executed for these claims. The search has been based on the alleged effects of the compound(s)/composition(s).

**Claim 1 is formulated in such a manner that it relates to a large number of possible compounds. It is not reasonable to make a meaningful search over the whole of the claimed scope. Consequently, the search has mainly been carried out for those parts of the claims which appear to be supported and disclosed, namely those parts related to the compounds prepared in the examples and closely related homologous compounds.

INTERNATIONAL SEARCH REPORT

Information on patent family members

05/02/01

International application No.
PCT/SE 00/02149

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9964044 A1	16/12/99	AU 3233899 A	09/12/99
		AU 4335299 A	30/12/99
		AU 4336899 A	30/12/99
		AU 4337699 A	30/12/99
		AU 4423499 A	30/12/99
		AU 4425399 A	30/12/99
		AU 4426599 A	30/12/99
		AU 4543599 A	30/12/99
		AU 4543799 A	30/12/99
		AU 4543999 A	30/12/99
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		AU 4550899 A	30/12/99
		AU 4551499 A	30/12/99
		AU 4551599 A	30/12/99
		AU 4552099 A	30/12/99
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		BR 9901760 A	30/05/00
		CN 1243870 A	09/02/00
		EP 0964047 A	15/12/99
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		EP 1019360 A	19/07/00
		NO 20006220 D	00/00/00
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		WO 9964039 A	16/12/99
		WO 9964041 A	16/12/99
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		WO 9964046 A	16/12/99
		WO 9964052 A	16/12/99
		WO 9964053 A	16/12/99
		WO 9964055 A	16/12/99
		WO 9966944 A	29/12/99

INTERNATIONAL SEARCH REPORT

Information on patent family members

05/02/01

International application No.
PCT/SE 00/02149

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9626923 A1	06/09/96	AU 4946896 A	18/09/96
		FR 2731223 A	06/09/96