DESCRIPTION

FIELD OF INVENTION

[0001] The present invention provides a compound that is a 5-HT3 receptor antagonist and is therefore useful for the treatment of diseases treatable by inhibition of the 5-HT3 receptor such as emesis, pain, drug addiction, neurodegenerative and psychiatric disorders, and GI disorders. Also provided are pharmaceutical compositions containing the compound and a process for preparing the compound.

BACKGROUND

[0002] Serotonin type 3 (5-HT3) receptors are part of the serotonergic system. Unlike other receptors of this system, which are all G-protein coupled receptors, the 5-HT3 receptors are ligand-gated ion channels and belong to the superfamily of Cys-loop receptors that include nicotinic acetylcholine, γ-aminobutyric acid (GABA)A and glycine receptors and a Zn+2 activated cation channel (*see* Davies et al., 2003, .J. Biol. Chem., 278, 712-717; Connolly et al., 2004, Biochem Soc Trans 32, 529-534). The *5*-HT_3 receptors are made up of 5 subunits arranged around a central ion conducting pore, which is permeable to sodium, potassium, and calcium ions (*see* Boess et al., 1995, J. Neurochem. 64, 1401-1405; Connolly et al., 2004, Biochem Soc Trans 32, 529-534). Binding of serotonin to the *5*-HT_3 receptors opens the channel, which, in turn, leads to an excitatory response in neurons. Functional data reported for 5-HT3 receptors refer to 5-HT3A or 5-HT3AB receptors since the properties of these receptor subtypes have been most extensively studied to date.

[0003] 5-HT3 receptors are known to be expressed in the central nervous system in regions involving vomiting reflex, processing of pain, cognition and anxiety control and play a role in the pathogenesis of diseases such as emesis, migraine, drug addiction, and neurodegenerative and psychiatric disorders such as anxiety and depression (see Hewlett et al., 2003 J. Clin. Psychiatry 64, 1025-1030; Kelley et al., 2003a, Eur J. Pharmacol., 461, 19-25; Haus et al., 2000 Scand J Rheumatol Suppl 113, 55-58; and Faris et al., 2006 Jaffect Disorder 92, 79-90), eating disorders (Hammer et al., 1990 Am J Physiol 259, R627-R636, and Jiang & Gietzen 1994 Pharmacol Biochem Behav 47, 59-63), schizophrenia (see Hermann et al. 1996 Biochem Biophys Res Commun 225, 957-960; Sirota et al., 2000 Am J Psychiatry 157, 287-289; Adler et al., 2005 Am J Psychiatry 162, 386-388; Koike et al., Levkovitz et al, 2005 Schizophr Res 76, 67-72), cognitive dysfunction associated with schizophrenia (see Zhang et al., 2006 Schizophr Res 88, 102-110; Akhondzadeh et al., 2009 Schizophr Res 107, 206-212), cognitive dysfunction associated with Parkinson's disease, Huntington's Chorea, presenile dementias and Alzheimer's disease (see Costall and Naylor 2004 CNS Neurol Discord 3, 27-37) substance abuse and addiction (see Johnson et al., 2002 Psycho-pharmacology (Berl) 160, 408-413; Johnson, 2004 CNS Drags 18, 1105-1118; Dawes et al., 2005 Addict Behav 30,

1630-1637, Johnson 2006 Drug Alcohol Depend 84, 256-263), autism spectrum disorders (see Anderson et al Neurogenetics 10, 209-216) and pain (see Kayser et al, 2007 Pain 130, 235; Glaum et al., 1998 Neurosci Lett 95, 313-317; Schworer & Ramadori 1993 Clin Investig 71, 659; Thompson and Lummis 2007 Exp Opin Ther Targets, 11, 527-540). In addition, 5-HT3 receptors are expessed in the GI tract and hence may play a role in GI disorders such as dyspepsia, gastroesophagal reflux disease and irritable bowel syndrome (see Graeff 1997 Psychiatr Clin North Am 20, 723; Thompson and Lummis 2007 Exp Opin Ther Targets, 11, 527-540; Barnes et al. 2009 Neuropharmacology 56, 273). Expression of the 5-HT3A subunit has also been discovered extraneuronally in immune cells such as monocytes, chondrocytes, T-cells, synovial tissue and platelets (Fiebich et al., 2004 Scan JRheumatol Suppl, 9-11, Stratz et al., 2008 Thromb Haemost 99, 784) and of 5-HT3A, C-E within the lamina propia in the epithelium of the gut mucosa (Kapeller et al., J Comp Neuro., 2008; 509: 356-371) thus suggesting they may be involved in immunological and inflammatory diseases like atherosclerosis, tendomyopathies and fibromyalgia.

[0004] The 5-HT3 antagonists currently on the market are approved only for the treatment of emesis or irritable bowel syndrome. It is desirable to discover 5-HT3 antagonists that can be used to treat other diseases amenable to alleviation by 5-HT3 receptors such as schizophrenia and cognitive disorder associated with schizophrenia. The present invention can fulfill this and related needs. It is desirable to discover 5-HT3 antagonists that have desirable pharmacokinetic and pharmacodynamic properties, such as selectivity over nicotinic-α7 receptors.

[0005] Certain antagonists of the 5-HT3 receptor containing an azabicyclic moiety are described in US 4,803,199; US 4,886,808; US 4,910,193; EP 0 469 449; and EP 0 491 664. Certain inhibitors of TGF-β containing an azabicyclic moiety are described in EP 1 156 045 and certain treatment of nephritis containing an azabicyclic moiety is described in EP1 243 268. Certain antagonists of 5-HT4 containing an azabicyclic moiety are described in EP 0 708 105. Certain ligands of nicotinic-α7 receptors are described in WO 2007/038367. Certain P2X7 antagonists are disclosed in WO 2009/023623.

SUMMARY

[0006] In a first aspect, this invention is directed to the compound 1-(1-methyl-1*H*-pyrazol-4-yl)-N-((1*R*, 5*S*, 7*S*)-9-methyl-3-oxa-9-azabicyclo[3.3.1]-nonan-7-yl)-1H-indole-3-carboxamide (I) or a pharmaceutically acceptable salt thereof.

[0007] In a second aspect, this present invention is directed to a pharmaceutical composition comprising the compound (I) or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable excipient.

[0008] Further described herein is the combination of compound (I) or a pharmaceutically acceptable salt thereof with an antipsychotic drug. As further described herein, the

antipsychotic drug may be AMG 747, bitopertin (RG1678), RG1578, AMG579, GSK1018921, aripiprazole, risperidone, olanzapine, quetiapine, ziprasidone, or clozapine.

[0009] In a third aspect, the invention is directed to use of compound (1) (or any embodiments thereof disclosed herein) or a pharmaceutically acceptable salt thereof as a medicament.

[0010] Further described herein is the compound (I) or a pharmaceutically acceptable salt thereof for use to treat a disease treatable by administration of a 5-HT3 receptor antagonist, wherein the disease treatable by administration of a 5-HT3 receptor antagonist is emesis, migraine, substance abuse and addiction, neurodegenerative and psychiatric disorders such as anxiety and depression, eating disorders, schizophrenia, cognitive dysfunction associated with schizophrenia, Parkinson's disease, Huntington's Chorea, presenile dementias and Alzheimer's disease, and pain; GI disorders such as dyspepsia, gastroesophagal reflux disease, and irritable bowel syndrome; and immunological disorders and inflammation such as atherosclerosis, tendomyopathies and fibromyalgia. Further described herein is the compound (I) or a pharmaceutically acceptable salt therefore for use in the treatment of schizophrenia or cognitive dysfunction associated with schizophrenia also known as cognitive impairment associated with schizophrenia. Further described herein is the combination the compound (I) in with an antipsychotic drug. As further described herein, the antipsychotic drug may be AMG 747, bitopertin (RG1678), RG1578, AMG579, GSK1018921, aripiprazole, risperidone, olanzapine, olanzapine, quetiapine, ziprasidone, or clozapine.

DETAILED DESCRIPTION OF THE INVENTION

[0011] Further described herein are protected derivatives of compound (I). For example, when compound (I) contains groups such as hydroxy, carboxy, thiol or any group containing a nitrogen atom(s), these groups can be protected with a suitable protecting groups. A comprehensive list of suitable protective groups can be found in T.W. Greene, Protective Groups in Organic Synthesis, John Wiley & Sons, Inc. (1999). The protected derivatives of compound (I) can be prepared by methods well known in the art.

[0012] A "pharmaceutically acceptable salt" of a compound means a salt that is pharmaceutically acceptable and that possesses the desired pharmacological activity of the parent compound. Such salts include: acid addition salts, formed with inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid or phosphoric acid, or formed with organic acids such as formic acid, acetic acid, propionic acid, hexanoic acid, cyclopentanepropionic acid, glycolic acid, pyruvic acid, lactic acid, malonic acid, succinic acid, malic acid, maleic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, 3-(4-hydroxybenzoyl)benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, 1,2-ethanedisulfonic acid, 2-hydroxyethanesulfonic acid, benzenesulfonic acid, 4-chlorobenzenesulfonic acid, 2-naphthalenesulfonic acid, 4-toluenesulfonic acid, camphorsulfonic acid, glucoheptonic acid, 4,4'-methylenebis-(3-hydroxy-2-ene-1-carboxylic acid), 3-phenylpropionic acid, trimethylacetic acid, tertiary butylacetic acid, lauryl sulfuric acid,

gluconic acid, glutamic acid, hydroxynaphthoic acid, salicylic acid, stearic acid or muconic acid, or salts formed when an acidic proton present in the parent compound either is replaced by a metal ion, e.g., an alkali metal ion, an alkaline earth ion, or an aluminum ion; or coordinates with an organic base such as ethanolamine, diethanolamine, triethanolamine, tromethamine or *N*-methylglucamine. It is understood that the phannaceutically acceptable salts are non-toxic. Additional information on suitable pharmaceutically acceptable salts can be found in Remington's Pharmaceutical Sciences, 17th ed., Mack Publishing Company, Easton, PA, 1985.

[0013] The compounds of the present invention may have asymmetric centers. Compounds of the present invention containing an asymmetrically substituted atom may be isolated in optically active or racemic forms. It is well known in the art how to prepare optically active forms, such as by resolution of materials. All chiral, diastereomeric, meso, racemic forms are within the scope of this invention, unless the specific stereochemistry or isomeric form is specifically indicated.

[0014] Furthermore, all polymorphic forms and hydrates of the compound (I) are within the scope of this invention.

[0015] The terms "compound" and "a compound of the invention" and "compound of the present invention" and their plural forms include the embodiment of compound (I) or a pharmaceutically acceptable salt of this embodiment. All references to compounds, include all isotopes of the atoms contained therein, including isotopically-labeled compounds.

[0016] The compounds of the present invention exist as tautomers. All tautomeric forms of the compounds of the invention are contemplated to be within the scope of the present invention.

[0017] "Optional" or "optionally" means that the subsequently described event or circumstance may but need not occur, and that the description includes instances where the event or circumstance occurs and instances in which it does not.

[0018] A "phannaceutically acceptable carrier or excipient" means a carrier or an excipient that is useful in preparing a pharmaceutical composition that is generally safe, non-toxic and neither biologically nor otherwise undesirable, and includes a carrier or an excipient that is acceptable for veterinary use as well as human pharmaceutical use. "A pharmaceutically acceptable carrier/excipient" as used in the specification and claims includes both one and more than one such excipient. Pharmaceutically acceptable excipients are well known in the art, such as those in Remington's Pharmaceutical Sciences, 17th ed., Mack Publishing Company, Easton, PA, 1985.

[0019] The terms "condition," "disorder," and "disease" relate to any unhealthy or abnormal state.

[0020] "Treat," "treating," or "treatment" of a disease includes:

1. (1) preventing the disease, i.e. causing the clinical symptoms of the disease not to develop in a mammal that may be exposed to or predisposed to the disease but does not yet experience or display symptoms of the disease;
2. (2) inhibiting the disease, i.e., arresting, controlling, slowing, stopping, or reducing the development of the disease or its clinical symptoms; or
3. (3) relieving the disease, i.e., causing regression of the disease or its clinical symptoms or improvement of the disease or its clinical symptoms

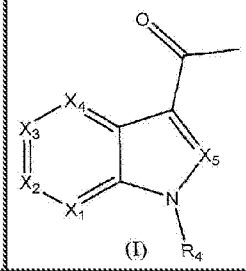
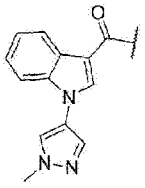
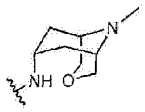
[0021] The terms "treat," "treating," and "treatment," do not necessarily indicate a total elimination of any or all symptoms or a cure of the disease.

[0022] As used herein the terms "patient" and "subject" includes humans and non-human animals, for example, mammals, such as mice, rats, guinea pigs, dogs, cats, rabbits, cows, horses, sheep, goats, and pigs. The term also includes birds, fish, reptiles, amphibians. It is understood that a more particular patient is a human. Also, more particular patients and subjects are non-human mammals, such as mice, rats, and dogs.

[0023] A "therapeutically effective amount" means the amount of the compound (I) or a pharmaceutically acceptable salt thereof that, when administered in single or multiple doses, to a mammal for treating a disease, is sufficient to effect such treatment for the disease. The "therapeutically effective amount" will vary depending on the compound, the disease and its severity and the age, weight, etc., of the mammal to be treated, the degree of or involvement or the severity of the condition, disorder, or disease, the response of the individual patient; the particular compound administered; the mode of administration; the bioavailability characteristics of the preparation administered; the dose regimen selected; the use of concomitant medication; and other relevant circumstances.

[0024] The term "disease treatable by administration of a 5-HT3 receptor antagonist" includes emesis, migraine, substance abuse and addiction, neurodegenerative and psychiatric disorders such as anxiety and depression, eating disorders, schizophrenia, cognitive dysfunction associated with schizophrenia, Parkinson's disease, Huntington's Chorea, presenile dementias and Alzheimer's disease, and pain; GI disorders such as dyspepsia, gastroesophagal reflux disease, and irritable bowel syndrome; and immunological disorders and inflammation such as atherosclerosis, tendomyopathies and fibromyalgia. In a particular embodiment the disease is cognitive dysfunction associated with schizophrenia also known as cognitive impairment associated with schizophrenia.

[0025] The compound of the Invention is shown in Table I below:

Cpd. No.		-Z-R^1	Salt	Name	MW Calcd.	MS Obs. $(M+1)^+$
15			TFA	1-(1-methyl-1H-pyrazol-4-yl)-N-((1R,5S,7S)-9-methyl-3-oxa-9-azabicyclo[3.3.1]nonan-7-yl)-1H-indole-3-carboxamide, 2,2,2-trifluoroacetic acid salt	379.456	380.30

Embodiments

[0026] In one embodiment, the compound is 1-(1-methyl-1H-pyrazol-4-yl)-N-((1*R*, 5*S*, 7*S*)-9-methyl-3-oxa-9-azabicyclo[3.3.1]-nonan-7-yl)-1H-indole-3-carboxamide (I) or pharmaceutical salt thereof.

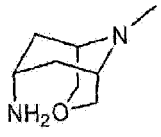
General Synthetic Scheme

[0027] Compounds of this invention can be made by the methods depicted in the reaction schemes shown below and other methods known in the art.

[0028] The starting materials and reagents used in preparing these compounds are either available from commercial suppliers such as Aldrich Chemical Co., (Milwaukee, Wis.), Bachem (Torrance, Calif.), or Sigma (St. Louis, Mo.) or are prepared by methods known to those skilled in the art following procedures set forth in references such as Fieser and Fieser's Reagents for Organic Synthesis, Volumes 1-17 (John Wiley and Sons, 1991); Rodd's Chemistry of Carbon Compounds, Volumes 1-5 and Supplementals (Elsevier Science Publishers, 1989); Organic Reactions, Volumes 1-40 (John Wiley and Sons, 1991), March's Advanced Organic Chemistry, (John Wiley and Sons, 4th Edition) and Larock's Comprehensive Organic Transformations (VCH Publishers Inc., 1989). These schemes are merely illustrative of some methods by which the compounds of this invention can be synthesized, and various modifications to these schemes can be made and will be suggested to one skilled in the art having referred to this disclosure. The starting materials and the intermediates, and the final products of the reaction may be isolated and purified if desired using conventional techniques, including but not limited to filtration, distillation, crystallization, chromatography. Such materials may be characterized using conventional means, including physical constants and spectral data.

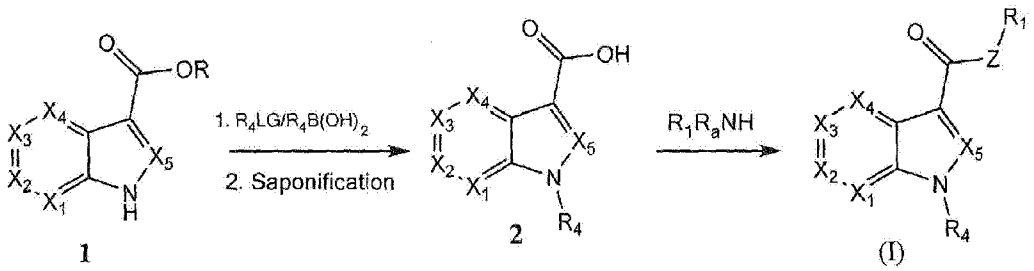
[0029] Unless specified to the contrary, the reactions described herein take place at atmospheric pressure over a temperature range from -78°C to 150°C, more preferably from 0°C to 12°C and most preferably at room (or ambient) temperature, e.g., 20°C.

[0030] Compounds of Formula (I) can be prepared as illustrated and described in Scheme A below, wherein Z is NR_a, where R_a is hydrogen, R is a ring of formula



X_1-X_5 are CR^6, where R^6 is hydrogen, and R_4 is pyrazolyl.

Scheme A



[0031] Step 1 involves formation of the C-N bond between R_4 and N-1 nitrogen of the compound of formula 1 where R is an acid protecting group such as C_{1-6} alkyl. Compounds of formula 1, R_4LG, wherein LG is a leaving group such as sulfonate or halo, and $R_4B(OH)_2$, or ester thereof, are either commercially available or they can be prepared by methods well known in the art.

[0032] Hydrolysis of the ester group under basic aqueous conditions provides the corresponding compound of formula 2. Compound 2 is then converted to a compound of Formula (I) where Z is NR_a, by forming an activated acid derivative of compound 2, followed by reaction with R_1R_aNH where R_1 is as defined above. For example, the activated acid derivative can be mixed anhydride such as with a mixture of TFAA and TFA in toluene or CDI or Boc_2O; or acid halide such as with oxalyl chloride, thionyl chloride; or under standard using standard peptide coupling reagents such as HATU in the presence of a base such as *N,N*-diisopropylethylamine, and a solvent, such as DMF and the like. Amines of formula R_1R_aNH or nitrogen protected derivative thereof are either commercially available or they can be prepared by methods known in the art e.g (1S,5R,6S)-4-oxa-1-azabicyclo[3.3.1]nonan-6-ol can be prepared as described in Journal of Medicinal Chemistry, 1993, 36, 683-689.

[0033] Alternatively, compound of Formula I can be synthesized by first coupling the acid derivative of compound 1 (R is H) with R_1R_aNH as described above, followed by formation of N-C bond as described in Step 1 of Scheme A above.

[0034] Detailed description of the synthesis of compound (I) is provided in Working Examples below.

Utility

[0035] 5-HT3 receptors are known to be expressed in the central nervous system in regions involving vomiting reflex, processing of pain, cognition and anxiety control and play a role in the pathogenesis of diseases such as emesis, migraine, drug addiction, and neurodegenerative and psychiatric disorders such as anxiety and depression (see Hewlett et al., 2003 J. Clin. Psychiatry 64, 1025-1030; Kelley et al., 2003a, Eur J. Pharmacol., 461, 19-25; Haus et al., 2000 Scand J Rheumatol Suppl 113, 55-58; and Faris et al., 2006 J affect Disorder 92, 79-90), eating disorders (Hammer et al., 1990 Am J Physiol 259, R627-R636, and Jiang & Gietzen 1994 Pharmacol Biochem Behav 47, 59-63), schizophrenia (see Hermann et al. 1996 Biochem Biophys Res Commun 225, 957-960; Sirota et al., 2000 Am J Psychiatry 157, 287-289; Adler et al., 2005 Am J Psychiatry 162, 386-388; Koike et al., Levkovitz et al, 2005 Schizophr Res 76, 67-72), cognitive dysfunction associated with schizophrenia (see Zhang et al., 2006 Schizophr Res 88, 102-110; Akhondzadeh et al., 2009 Schizophr Res 107, 206-212), congnitive dysfuntion associated with Parkinson's disease, Huntington's Chorea, presenile dementias and Alzheimer's disease (see Costall and Naylor 2004 CNS Neurol Disord 3, 27-37) substance abuse and addiction (see Johnson et al., 2002 Psycho-pharmacology (Berl) 160, 408-413; Johnson, 2004 CNS Drugs 18, 1105-1118; Dawes et al., 2005 Addict Behav 30, 1630-1637, Johnson 2006 Drug Alcohol Depend 84, 256-263), and pain (see Kayser et al, 2007 Pain 130, 235; Glaum et al., 1998 Neurosci Lett 95, 313-317; Schworer & Ramadori 1993 Clin Investig 71, 659; Thompson and Lummis 2007 Exp Opin Ther Targets, 11, 527-540). In addition, 5-HT3 receptors are expessed in the GI tract and hence may play a role in GI disorders such as dyspepsia, gastroesophagal reflux disease and irritable bowel syndrome (see Graeff 1997 Psychiatr Clin North Am 20, 723; Thompson and Lummis 2007 Exp Opin Ther Targets, 11, 527-540; Barnes et al. 2009 Neuropharmacology 56, 273). Expression of the 5-HT3A subunit has also been discovered extraneuronally in immune cells such as monocytes, chondrocytes, T-cells, synovial tissue and platelets (Fiebich et al., 2004 Scan J Rheumatol Suppl, 9-11, Stratz et al., 2008 Thromb Haemost 99, 784) and of 5-HT3A, C-E within the lamina propia in the epithelium of the gut mucosa (Kapeller et al., J Comp Neuro., 2008; 509: 356-371) thus suggesting they may be involved in immunological and inflammatory diseases like atherosclerosis, tendomyopathies and fibromyalgia.

Testing

[0036] The 5-HT3 inhibitory activity of the compound of the present invention can be tested using the *in vitro* assay and *in vivo* assay described in Biological Example 1, 2, and 3 below.

Administration and Pharmaceutical Composition

[0037] In general, the compounds of this invention will be administered in a therapeutically effective amount by any of the accepted modes of administration for agents that serve similar utilities. Therapeutically effective amounts of compound (I) may range from 0.01 to 75 mg per kg patient body weight per day, which can be administered in single or multiple doses. Preferably, the dosage level will be 0.01 to 10 mg/kg per day; more preferably 0.5 to 5 mg/kg per day or 0.1-2 mg/kg/day. For oral administration, the compositions are preferably provided in the form of tablets containing about 0.5 to 200 milligrams of the active ingredient, from 0.5, 1.0, 5.0, 10, 15, 20, 25, 50, 75, 100, 150, or 200 milligrams of the active ingredient. The actual amount of the compound of this invention, i.e., the active ingredient, will depend upon numerous factors such as the severity of the disease to be treated, the age and relative health of the subject, the potency of the compound utilized, the route and form of administration, and other factors. Although these dosages are based on an average human subject having a mass of 60 kg to 70 kg, the physician will be able to determine the appropriate dose for a patient (e.g., an infant) whose mass falls outside of this weight range.

[0038] In general, the compound of this invention will be administered as a pharmaceutical composition by any one of the following routes: oral, systemic (e.g., transdermal, intranasal or by suppository), or parenteral (e.g., intramuscular, intravenous or subcutaneous) administration. The preferred manner of administration is oral using a convenient daily dosage regimen, which can be adjusted according to the degree of affliction. Compositions can take the form of tablets, pills, capsules, semisolids, powders, sustained release formulations, solutions, suspensions, elixirs, aerosols, or any other appropriate compositions.

[0039] The choice of formulation depends on various factors such as the mode of drug administration (e.g., for oral administration, formulations in the form of tablets, pills or capsules are preferred) and the bioavailability of the drug substance. Recently, pharmaceutical formulations have been developed especially for drugs that show poor bioavailability based upon the principle that bioavailability can be increased by increasing the surface area i.e., decreasing particle size. For example, U.S. Pat. No. 4,107,288 describes a pharmaceutical formulation having particles in the size range from 10 to 1,000 nm in which the active material is supported on a crosslinked matrix of macromolecules. U.S. Pat. No. 5,145,684 describes the production of a pharmaceutical formulation in which the drug substance is pulverized to nanoparticles (average particle size of 400 nm) in the presence of a surface modifier and then dispersed in a liquid medium to give a pharmaceutical formulation that exhibits remarkably high bioavailability.

[0040] The compositions are comprised of in general, the compound (I) in combination with at least one pharmaceutically acceptable excipient. Acceptable excipients are non-toxic, aid administration, and do not adversely affect the therapeutic benefit of the compound of formula (I). Such excipient may be any solid, liquid, semi-solid or, in the case of an aerosol composition, gaseous excipient that is generally available to one of skill in the art.

[0041] Solid pharmaceutical excipients include starch, cellulose, talc, glucose, lactose, sucrose, gelatin, malt, rice, flour, chalk, silica gel, magnesium stearate, sodium stearate, glycerol monostearate, sodium chloride or dried skim milk. Liquid and semisolid excipients may be selected from glycerol, propylene glycol, water, ethanol and various oils, including those of petroleum, animal, vegetable or synthetic origin, e.g., peanut oil, soybean oil, mineral oil, sesame oil, etc. Preferred liquid carriers, particularly for injectable solutions, include water, saline, aqueous dextrose, and glycols.

[0042] Compressed gases may be used to disperse a compound of this invention in aerosol form. Inert gases suitable for this purpose are nitrogen, carbon dioxide, etc.

[0043] Other suitable pharmaceutical excipients and their formulations are described in Remington's Pharmaceutical Sciences, edited by E. W. Martin (Mack Publishing Company, 18th ed., 1990).

[0044] The level of the compound in a formulation can vary within the full range employed by those skilled in the art. Typically, the formulation will contain, on a weight percent (wt %) basis, from 0.01-99.99 wt % of the compound (I) based on the total formulation, with the balance being one or more suitable pharmaceutical excipients. Preferably, the compound is present at a level of 1-80 wt %.

[0045] The compounds of the present invention may be used in combination with one or more other drugs in the treatment of diseases or conditions for which the compound of the present invention or the other drugs may have utility, where the combination of the drugs together are safer or more effective than either drug alone. Such other drug(s) may be administered, by a route and in an amount commonly used therefore, contemporaneously or sequentially with the compound of the present invention. When the compound of the present invention is used contemporaneously with one or more other drugs, a pharmaceutical composition in unit dosage form containing such other drugs and the compound of the present invention can be used. However, the combination therapy may also include therapies in which the compound of the present invention and one or more other drugs are administered on different overlapping schedules. It is also contemplated that when used in combination with one or more other active ingredients, the compounds of the present invention and the other active ingredients may be used in lower doses than when each is used singly.

[0046] Accordingly, the pharmaceutical compositions of the present invention also include those that contain one or more other active ingredients, in addition to the compound of the present invention.

[0047] The above combinations include combinations of the compound of the present invention not only with one other active compound, but also with two or more other active compounds. Likewise, the compound of the present invention may be used in combination with other drugs that are used in the prevention, treatment, control, amelioration, or reduction of risk of the diseases or conditions for which the compound of the present invention is useful.

Such other drugs may be administered, by a route and in an amount commonly used therefore, contemporaneously or sequentially with a compound of the present invention. Accordingly, the pharmaceutical compositions of the present invention also include those that also contain one or more other active ingredients, in addition to the compound of the present invention. The weight ratio of the compound of the present invention to the second active ingredient may be varied and will depend upon the effective dose of each ingredient. Generally, an effective dose of each will be used.

[0048] In one embodiment, the compound of the present invention may be administered in combination with anti-Alzheimer's agents, beta-secretase inhibitors, gamma-secretase inhibitors, HMG-CoA reductase inhibitors, NSAID's including ibuprofen, vitamin E, and anti-amyloid antibodies. In another embodiment, the compound of the present invention may be administered in combination with sedatives, hypnotics, anxiolytics, antipsychotics, antianxiety agents, cyclopyrrolones, imidazopyridines, pyrazolopyrimidines, minor tranquilizers, melatonin agonists and antagonists, melatonergic agents, benzodiazepines, barbiturates, mGlu2/3 agonists, 5HT-2 antagonists, PDE10 antagonists, GlyT1 inhibitors, such as: adinazolam, allobarbital, alonimid, alprazolam, amisulpride, amitriptyline, amobarbital, amoxapine, aripiprazole, bentazepam, benzoctamine, brotizolam, bupropion, buspirone, butabarbital, butalbital, capuride, carbocloral, chloral betaine, chloral hydrate, clomipramine, clonazepam, cloperidone, clorazepate, chlordiazepoxide, clorethate, chlorpromazine, clozapine, cyprazepam, desipramine, dexclamol, diazepam, dichloralphenazone, divalproex, diphenhydramine, doxepin, estazolam, ethchlorvynol, etomidate, fenobam, flunitrazepam, flupentixol, fluphenazine, flurazepam, fluvoxamine, fluoxetine, fosazepam, glutethimide, halazepam, haloperidol, hydroxyzine, imipramine, lithium, lorazopam, lormetazepam, maprotiline, mecloqualone, melatonin, mephobarbital, meprobamate, methaqualone, midaflur, midazolam, nefazodone, nisobamate, nitrazopam, nortriptyline, olanzapine, oxazepam, paraldehyde, paroxetine, pentobarbital, perlapine, perphenazine, phenelzine, phenobarbital, prazepam, promethazine, propofol, protriptyline, quazepam, quetiapine, reclazepam, risperidone, roletamide, secobarbital, sertraline, suproclone, temazopam, thioridazine, thiothixene, tracazolate, kanylcypromaine, trazodone, triazolam, trepipam, tricetamide, triclofos, trifluoperazine, trimetozine, trimipramine, uldazepam, venlafaxine, zaleplon, ziprasidone, zolazepam, zolpidem, [4-(3-fluoro-5-trifluoromethylpyridin-2-yl)piperazin-1-yl][5-methanesulfonyl-2-((S)-2,2,2-trifluoro-1-methylethoxy)phenyl]methanone (RG1678), glytl inhibitors disclosed in US patent 7538114, Table 1 in column 14, and salts thereof, and combinations thereof.

[0049] In another embodiment, the compound of the present invention may be administered in combination with levodopa (with or without a selective extracerebral decarboxylase inhibitor such as carbidopa or benserazide), anticholinergics such as biperiden (optionally as its hydrochloride or lactate salt) and trihexyphenidyl (benzhexol) hydrochloride, COMT inhibitors such as entacapone, MOA-B inhibitors, antioxidants, A2a adenosine receptor antagonists, cholinergic agonists, NMDA receptor antagonists, serotonin receptor antagonists and dopamine receptor agonists such as alentemol, bromocriptine, fenoldopam, lisuride, naxagolide, pergolide and pramipexole. It will be appreciated that the dopamine agonist may

be in the form of a pharmaceutically acceptable salt, for example, alentemol hydrobromide, bromocriptine mesylate, fenoldopam mesylate, naxagolide hydrochloride and pergolide mesylate. Lisuride and pramipexole are commonly used in a non-salt form.

[0050] In another embodiment, the compound of the present invention may be administered in combination with a compound from the phenothiazine, thioxanthene, heterocyclic dibenzazepine, butyrophenone, diphenylbutylpiperidine and indolone classes of neuroleptic agent. Suitable examples of phenothiazines include chlorpromazine, mesoridazine, thioridazine, acetophenazine, fluphenazine, perphenazine and trifluoperazine. Suitable examples of thioxanthenes include chlorprothixene and thiothixene. An example of a dibenzazepine is clozapine. An example of a butyrophenone is haloperidol. An example of a diphenylbutylpiperidine is pimozide. An example of an indolone is molindolone. Other neuroleptic agents include loxapine, sulpiride and risperidone. It will be appreciated that the neuroleptic agents when used in combination with the subject compound may be in the form of a pharmaceutically acceptable salt, for example, chlorpromazine hydrochloride, mesoridazine besylate, thioridazine hydrochloride, acetophenazine maleate, fluphenazine hydrochloride, flurphenazine enathate, fluphenazine decanoate, trifluoperazine hydrochloride, thiothixene hydrochloride, haloperidol decanoate, loxapine succinate and molindone hydrochloride. Perphenazine, chlorprothixene, clozapine, haloperidol, pimozide and risperidone are commonly used in a non-salt form. Thus, the compound of the present invention may be administered in combination with acetophenazine, alentemol, aripiprazole, amisulpride, benzhexol, bromocriptine, biperiden, chlorpromazine, chlorprothixene, clozapine, diazepam, fenoldopam, fluphenazine, haloperidol, levodopa, levodopa with benserazide, levodopa with carbidopa, lisuride, loxapine, mesoridazine, molindolone, naxagolide, olanzapine, pergolide, perphenazine, pimozide, pramipexole, quetiapine, risperidone, sulpiride, tetrabenazine, trihexyphenidyl, thioridazine, thiothixene, trifluoperazine or ziprasidone.

[0051] In another embodiment, the compound of the present invention may be administered in combination with an anti-depressant or anti-anxiety agent, including norepinephrine reuptake inhibitors (including tertiary amine tricyclics and secondary amine tricyclics), selective serotonin reuptake inhibitors (SSRIs), monoamine oxidase inhibitors (MAOIs), reversible inhibitors of monoamine oxidase (RIMAs), serotonin and noradrenaline reuptake inhibitors (SNRIs), corticotropin releasing factor (CRF) antagonists, adrenoreceptor antagonists, neurokinin-1 receptor antagonists, atypical anti-depressants, benzodiazopines, 5-HTA agonists or antagonists, especially 5-HTA partial agonists, and corticotropin releasing factor (CRF) antagonists. Specific agents include: amitriptyline, clomipramine, doxepin, imipramine and trimipramine; amoxapine, desipramine, maprotiline, nortriptyline and protriptyline; fluoxetine, fluvoxamine, paroxetine and sertraline; isocarboxazid, phenelzine, tranylcypromine and selegiline; moclobemide, venlafaxine; duloxetine; aprepitant; bupropion, lithium, nefazodone, trazodone and viloxazine; alprazolam, chlordiazepoxide, clonazopam, chlorazepate, diazopam, halazepam, lorazepam, oxazopam and prazepam; buspirone, flesinoxan, gepirone and ipsapirone, and pharmaceutically acceptable salts thereof.

EXAMPLES

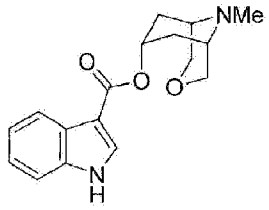
[0052] The following preparation of compound (I) is given to enable those skilled in the art to more clearly understand and to practice the present invention.

Synthetic Procedures

Reference 7

Synthesis of (1*R*,5*S*,7*S*)-9-methyl-3-oxa-9-azabicyclo[3.3.1]nonan-7-yl 1H-indole-3-carboxylate

[0053]

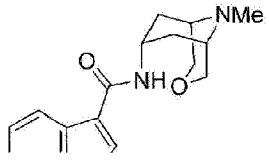


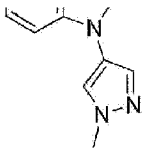
[0054] To a solution of 1H-indole-3-carboxylic acid (250 mg, 1.551 mmol) in PhMe (5171 µl) was added TFAA (219 µl, 1.551 mmol) then TFA (1293 µl). The mixture was stirred for 30 min then commercially available (1*R*,5*S*,7S)-9-methyl-3-oxa-9-azabicyclo[3.3.1]nonan-7-ol (203 mg, 1.293 mmol) was added. The reaction mixture stirred at RT for 1 h then was poured into aq $NaHCO_3$ and stirred until pH=7 and bubbling stopped. The reaction mixture was extracted with EtOAc and dried over $MgSO_4$. Purification by ISCO (0-20% MeOH/DCM) yielded the title compound as a pink solid.

Example 5

Synthesis of 1-(1-methyl-1H-pyrazol-4-yl)-*N*-((1*R*,5*S*,7S)-9-methyl-3-oxa-9-azabicyclo[3.3.1]nonan-7-y1)-1H-indole-3-carboxamide,2,2,2-trifluoroacetic acid salt

[0055]





Step 1: methyl 1-(1-methyl-1H-pyrazol-4-yl)-1H-indole-3-carboxylate, TFA

[0056] To a sealed tube was added copper(I) iodide (65.2 mg, 0.342 mmol), methyl 1H-indole-3-carboxylate (200 mg, 1.142 mmol) and potassium phosphate (509 mg, 2.397 mmol), then the reaction vessel was evacuated and purged with nitrogen (3x). Next, 4-bromo-1-methyl-1H-pyrazole (184 mg, 1.142 mmol) and (1*R*,2*R*)-*N*1,*N*2-dimethylcyclohexane-1,2-diamine (109 µl, 0.685 mmol) were added, followed by toluene (1142 µl). The reaction tube was evacuated and purged with nitrogen, then sealed and heated at 110 °C for 24 h. HPLC purification provided the title compound as a colorless oil.

Step 2: 1-(1-methyl-1H-pyrazol-4-yl)-1H-indole-3-carboxylic acid hydrochloride

[0057] To a solution of methyl 1-(1-methyl-1H-pyrazol-4-yl)-1H-indole-3-carboxylate, TFA (3.5 mg, 9.48 µmol) in MeOH (95 µl) was added a solution of aq. KOH (33.2 µl, 0.066 mmol, 2 M). The reaction mixture was stirred at RT overnight, then acidified with 1N HCl. The solvent was evaporated under reduced pressure and the residue was dried under vacuum overnight. The title compound was used without further purification.

Step 3: 1-(1-methyl-1H-pyrazol-4-yl)-*N*-((1*R*,5*S*,7S)-9-methyl-3-oxa-9-azabicyclo[3.3.1]nonan-7-yl)-1H-indole-3-carboxamide, 2,2,2-trifluoroacetic acid salt

[0058] To a mixture of 1-(1-methyl-1H-pyrazol-4-yl)-1H-indole-3-carboxylic acid hydrochloride (2.6 mg, 9.36 µmol) in DMF (187 µl) was added HATU (4.27 mg, 0.011 mmol) and DIPEA (8.18 µl, 0.047 mmol). After the reaction mixture was stirred at RT for 15 min, (1*R*,5*S*,7S)-9-methyl-3-oxa-9-azabicyclo[3.3.1]nonan-7-amine, TFA (3.04 mg, 0.011 mmol) was added and stirring was continued for 2 h. HPLC purification afforded the title compound as a white solid. MS (ESI, pos. ion) m/z: 380.30 (M+1).

Biological Examples

Biological Example 1

Inhibition of Ca flux Activity of 5-HT_3 *in vitro* assay

[0059] The 5-HT3 antagonist activity of the compound of the invention was determined by measuring the ability of the compounds to inhibit the calcium flux activity of 3HT3a receptor expressed in HEK-293T cells. HEK-293T cells were transfected with the 5-HT3a expression construct using Xtreme Gene 9 (Roche) in 150 mm tissue culture treated plates and incubated for 24 hours at 37°C. Cells were then split and plated at a density of 60K cells/well in poly-lysine coated, black 96-well plates with clear bottoms (BD BioSciences) and incubated overnight at 37° C. Growth media was removed and cells loaded with 200µL calcium indicator dye in HBSS containing 20 mM HEPES (Calcium 5 Assay kit, Molecular Devices) and incubated at 37° C for 1 hour. While cells were incubating, the 10X antagonist and agonist/antagonist addition plates were made. For 10X antagonist plate: half log serial dilutions (final concentrations range from 10^{-7} through 10^{-10} with the bottom well a negative, no ligand control) were made from test compounds in DMSO at a 1000X concentration and then diluted to 10X in HBSS/20mM HEPES. For addition plate: 5HT was diluted to 100X in HBSS/20mM HEPES (final concentration in the assay- 216nM) and 15 µL was added to each well of the addition plate, 15µL of 10X compound was also added to the addition plate, and finally 120 µL of HBSS/20mM HEPES (for a total of 150 uL). Cells were then removed from the incubator and equilibrated to room temperature for 10 minutes, then 22.5µL of 10X test compounds were added in triplicate to the plates and incubated at room temperature for 10 minutes (Tropisetron was used as a positive control in every assay). Test plate and addition plate were loaded into the FlexStation III (Molecular Devices), and using the fluidics, 22.5µL compound additions were made (at t = ~17 seconds), and fluorescence was measured for 90 seconds, reading every 2.2 seconds. Data sets were analyzed as max minus min using Software Max Pro (Molecular Devices). IC_{50} curves were generated using non-linear regression in GraphPad Prism.

[0060] Approximate IC_{50} value of a representative compound (I) in this assay are provided in the Table 2 below.

Table 2

Cpd. No. from Table 1 above	IC50 [nM]
15	0.662

[0061] In a head-to-head comparative study, Compound 15 of Table 1, Example 5, had an IC50 of 3.48 nM in this assay, while the compound of example Reference 7 above had an IC50 in this assay of 89.1 nM.

Biological Example 2

Rodent Novel Object Recognition (NOR) Assay in phencyclidine-induced cognitive

deficits modelling chizophrenia

[0062] The aim of this study is to investigate the ability of the compound of the invention to improve subchronic PCP-induced impairment in cognition memory using the NOR task in the rat, a paradigm of relevance to cognition in schizophrenia. Adult male Sprague-Dawley rats (250 - 350 g; Harlan, USA) are used for the experiments. Animal are acclimated to the facility for 7 days prior to experimentation. Seven groups of 14 animals per group are used for the experiment. One group of animals receive vehicle (0.9% saline twice daily) and the remaining six groups receive PCP (2.5 mg/kg, s.c. twice daily) for 7 days, followed by 5-days drug free. On the test day, the animals are allowed to acclimate to the testing room for 30 min prior to initiation of experiments. Experiments are carried out in a white plexiglass chamber, designated as the experimental arena. The arena is placed in a dark experimental room that is illuminated by a halogen lamp, providing a dim light to the arena.

[0063] Animals are placed in the arena for a 5 minute period to freely explore the test chamber in the absence of objects (habituation). Animals are then returned to their home cage immediately upon completion of habituation for a 120 min period. The test compound (0.1, 1, 10 mg/kg s.c.), or vehicle (veh, saline) is administered 120 min prior to T1 and galantamine (5 mg/kg, i.p.) is administered 30 min prior to T1 Animals are returned to the arena which contained two identical objects (plastic balls) placed at one end of the arena (acquisition, T1), and allowed to explore for a 5 min period. The time spent exploring the two objects is recorded. Animals are once again returned to the home cage for a period of 120 min (ITI).

[0064] ITI is followed by the retention phase (T2) where one of the objects presented in the first trial is replaced by a novel object and animals are allowed to explore for an additional 5 min period. Again, the time spent exploring the two objects is recorded.

[0065] For the retention phase, the differences between the time spent exploring the familiar object and the novel object are examined. All sessions are recorded and scored blindly for the time exploring objects. Exploration is defined as touching the object or directing nose towards object at a distance less that 2 cm. A minimal exploration criterion is used such that only animals with exploration time of greater than 5 seconds per object are included.

[0066] Comparisons of all treatment groups are conducted using a one-way ANOVA followed by a Bonferroni's post hoc test for multiple comparisons.

Biological Example 3

Nicotinic α-7 Receptor binding assay

[0067] The evaluation of binding at the nicotinic α-7 receptor was carried out at Eurofins Pharma Services. Compound 15 of Table 1, Example 5, had an IC50 in this assay of >10 μM while the compound of Reference 7 above had an IC50 in this assay of 1.66 μM.

Formulation Examples

[0068] The following are representative pharmaceutical formulations containing a compound of Formula (I).

Tablet Formulation

[0069] The following ingredients are mixed intimately and pressed into single scored tablets.

Ingredient	Quantity per tablet
compound of this invention	0.5-150 mg
cornstarch	50 mg
croscarmellose sodium	25 mg
lactose	120 mg
magnesium stearate	5 mg

Capsule Formulation

[0070] The following ingredients are mixed intimately and loaded into a hard-shell gelatin capsule.

Ingredient	Quantity per capsule
compound of this invention	0.5-150 mg
lactose spray dried	148 mg
magnesium stearate	2 mg

Injectable Formulation

[0071] Compound of the invention in 2% HPMC, 1% Tween 80 in DI water, pH 2.2 with MSA, q.s. to at least 20 mg/mL.

REFERENCES CITED IN THE DESCRIPTION

This list of references cited by the applicant is for the reader's convenience only. It does not form part of the European patent document. Even though great care has been taken in compiling the references, errors or omissions cannot be excluded and the EPO disclaims all liability in this regard.

Patent documents cited in the description

- US4803199A [0005]
- US4886808A [0005]
- US4910193A [0005]
- EP0469449A [0005]
- EP0491664A [0005]
- EP1156045A [0005]
- EP1243268A [0005]
- EP0708105A [0005]
- WO2007038367A [0005]
- WO2009023623A [0005]
- US4107288A [0039]
- US5145684A [0039]
- US7538114B [0048]

Non-patent literature cited in the description

- **DAVIES et al.**J. Biol. Chem., 2003, vol. 278, 712-717 [0002]
- **CONNOLLY et al.**Biochem Soc Trans, 2004, vol. 32, 529-534 [0002] [0002]
- **BOESS et al.**J. Neurochem., 1995, vol. 64, 1401-1405 [0002]
- **HEWLETT et al.**J. Clin. Psychiatry, 2003, vol. 64, 1025-1030 [0003] [0035]
- **KELLEY et al.**Eur J. Pharmacol., 2003, vol. 461, 19-25 [0003] [0035]
- **HAUS et al.**Scand J Rheumatol Suppl, 2000, vol. 113, 55-58 [0003] [0035]
- **FARIS et al.**Jaffect Disorder, 2006, vol. 92, 79-90 [0003]
- **HAMMER et al.**Am J Physiol, 1990, vol. 259, R627-R636 [0003] [0035]
- **JIANGGIETZEN**Pharmacol Biochem Behav, 1994, vol. 47, 59-63 [0003] [0035]
- **HERMANN et al.**Biochem Biophys Res Commun, 1996, vol. 225, 957-960 [0003] [0035]
- **SIROTA et al.**Am J Psychiatry, 2000, vol. 157, 287-289 [0003] [0035]
- **ADLER et al.**Am J Psychiatry, 2005, vol. 162, 386-388 [0003] [0035]
- **LEVKOVITZ et al.**Schizophr Res, 2005, vol. 76, 67-72 [0003] [0035]

- **ZHANG et al.**Schizophr Res, 2006, vol. 88, 102-110 [0003] [0035]
- **AKHONDZADEH et al.**Schizophr Res, 2009, vol. 107, 206-212 [0003] [0035]
- **COSTALLNAYLOR**CNS Neurol Discord, 2004, vol. 3, 27-37 [0003]
- **JOHNSON et al.**Psycho-pharmacology (Berl), 2002, vol. 160, 408-413 [0003] [0035]
- **JOHNSON**CNS Drags, 2004, vol. 18, 1105-1118 [0003]
- **DAWES et al.**Addict Behav, 2005, vol. 30, 1630-1637 [0003] [0035]
- **JOHNSON**Drug Alcohol Depend, 2006, vol. 84, 256-263 [0003] [0035]
- **ANDERSON et al.**Neurogenetics, vol. 10, 209-216 [0003]
- **KAYSER et al.**Pain, 2007, vol. 130, 235- [0003] [0035]
- **GLAUM et al.**Neurosci Lett, 1998, vol. 95, 313-317 [0003] [0035]
- **SCHWORERRAMADORI**Clin Investig, 1993, vol. 71, 659- [0003] [0035]
- **THOMPSONLUMMIS**Exp Opin Ther Targets, 2007, vol. 11, 527-540 [0003] [0003] [0035] [0035]
- **GRAEFF**Psychiatr Clin North Am, 1997, vol. 20, 723- [0003] [0035]
- **BARNES et al.**Neuropharmacology, 2009, vol. 56, 273- [0003] [0035]
- **FIEBICH et al.**Scan JRheumatol Suppl, 2004, 9-11 [0003]
- **STRATZ et al.**Thromb Haemost, 2008, vol. 99, 784- [0003] [0035]
- **KAPELLER et al.**J Comp Neuro., 2008, vol. 509, 356-371 [0003] [0035]
- **T.W. GREENE**Protective Groups in Organic SynthesisJohn Wiley & Sons, Inc.19990000 [0011]
- Remington's Pharmaceutical SciencesMack Publishing Company19850000 [0012] [0018]
- **FIESERFIESER'S**Reagents for Organic SynthesisJohn Wiley and Sons19910000vol. 1-17, [0028]
- Rodd's Chemistry of Carbon Compoundsvol. 1-5, [0028]
- SupplementalsElsevier Science Publishers19890000 [0028]
- Organic ReactionsJohn Wiley and Sons19910000vol. 1-40, [0028]
- March's Advanced Organic ChemistryJohn Wiley and Sons [0028]
- Larock's Comprehensive Organic TransformationsVCH Publishers Inc.19890000 [0028]
- Journal of Medicinal Chemistry, 1993, vol. 36, 683-689 [0032]
- **FARIS et al.**J affect Disorder, 2006, vol. 92, 79-90 [0035]
- **COSTALLNAYLOR**CNS Neurol Disord, 2004, vol. 3, 27-37 [0035]
- **JOHNSON**CNS Drugs, 2004, vol. 18, 1105-1118 [0035]
- **FIEBICH et al.**Scan J Rheumatol Suppl, 2004, 9-11 [0035]
- Remington's Pharmaceutical SciencesMack Publishing Company19900000 [0043]

Patentkrav

1. Forbindelse 1-(1-methyl-1H-pyrazol-4-yl)-N-((1R,5S,7S)-9-methyl-3-oxa-9-azabicyclo[3.3.1]-nonan-7-yl)-1H-indol-3-carboxamid eller et farmaceutisk acceptabelt salt deraf.

2. Farmaceutisk sammensætning, der omfatter en forbindelse ifølge krav 1 og et farmaceutisk acceptabelt excipiens.

3. Forbindelse ifølge krav 1 til anvendelse som et medikament.