(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
25 October 2007 (25.10.2007)

PCT

(10) International Publication Number
WO 2007/120594 A1

(51) International Patent Classification:
C07D 498/06 (2006.01) *A61P 25/00* (2006.01)
A61K 31/5383 (2006.01)

(21) International Application Number:
PCT/US2007/008710

(22) International Filing Date: 9 April 2007 (09.04.2007)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/791,479 12 April 2006 (12.04.2006) US

(71) Applicant *(for all designated States except US)*: **WYETH** [US/US]; Five Giralda Farms, Madison, New Jersey 07940 (US).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: **ELOKDAH, Hassan, Mahmoud** [US/US]; 1319 Katie Lane, North Wales, Pennsylvania 19454 (US). **GREENFIELD, Alexander, Alexei** [US/US]; 122 Harris Road, West Windsor, New Jersey 08550 (US). **GROSANU, Cristina** [US/US]; 89 Wood Street, Keansburg, New Jersey 07734 (US). **ROBICHAUD, Albert Jean** [US/US]; 3 Riverview Court, Ringoes, New Jersey 08551 (US).

(74) Agent: **LENCES, Barbara, L.**; Wyeth, Patent Law Department, Five Giralda Farms, Madison, New Jersey 07940, (US).

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

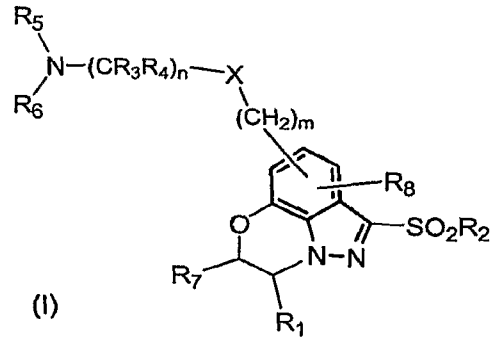
(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, MT, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:
— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))*
— *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))*

Published:
— *with international search report*
— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: SUBSTITUTED-DIHYDRO[1,4]OXAZINO[2,3,4-HI]INDAZOLE DERIVATIVES AS 5-HYDROXYTRYPTAMINE-6 LIGANDS



(I)

(57) Abstract: The present invention provides a compound of formula I and the use thereof for the treatment of a central nervous system disorder related to or affected by the 5-HT6 receptor (I) .

WO 2007/120594 A1

SUBSTITUTED-DIHYDRO[1,4]OXAZINO[2,3,4-hi]INDAZOLE DERIVATIVES AS 5-HYDROXYTRYPTAMINE-6 LIGANDS

BACKGROUND OF THE INVENTION

Serotonin (5-hydroxytryptamine) (5-HT) receptors play a critical role in many physiological and behavioral functions in humans and animals. These functions are mediated through various 5-HT receptors distributed throughout the body. There are now approximately fifteen different human 5-HT receptor subtypes that have been cloned, many with well-defined roles in humans. One of the most recently identified 5-HT receptor subtypes is the 5-HT6 receptor, first cloned from rat tissue in 1993 (Monsma, F. J.; Shen, Y.; Ward, R. P.; Hamblin, M. W. *Molecular Pharmacology* 1993, *43*, 320-327) and subsequently from human tissue (Kohen, R.; Metcalf, M. A.; Khan, N.; Druck, T.; Huebner, K.; Sibley, D. R. *Journal of Neurochemistry* 1996, *66*, 47-56). The receptor is a G-protein coupled receptor (GPCR) positively coupled to adenylate cyclase (Ruat, M.; Traiffort, E.; Arrang, J-M.; Tardivel-Lacombe, L.; Diaz, L.; Leurs, R.; Schwartz, J-C. *Biochemical Biophysical Research Communications* 1993, *193*, 268-276). The receptor is found almost exclusively in the central nervous system (CNS) areas both in rat and in human. *In situ* hybridization studies of the 5-HT6 receptor in rat brain using mRNA indicate principal localization in the areas of 5-HT projection including striatum, nucleus accumbens, olfactory tubercle, and hippocampal formation (Ward, R. P.; Hamblin, M. W.; Lachowicz, J. E.; Hoffman, B. J.; Sibley, D. R.; Dorsa, D. M. *Neuroscience* 1995, *64*, 1105-1111).

There are many potential therapeutic uses for 5-HT6 ligands in humans based on direct effects and on indications from available scientific studies. These studies provided information including the localization of the receptor, the affinity of ligands with known *in vivo* activity, and results obtained from various animal studies conducted so far (Woolley, M. L.; Marsden, C. A.; Fone, K. C. F. *Current Drug Targets: CNS & Neurological Disorders* 2004, *3(1)*, 59-79).

One therapeutic use of modulators of 5-HT6 receptor function is in the enhancement of cognition and memory in human diseases such as Alzheimer's. The high levels of receptor found in important structures in the forebrain, including the caudate/putamen, hippocampus, nucleus accumbens, and cortex indicate a role for the receptor in memory and cognition since these areas are known to play a vital role in memory (Gerard, C.; Martres, M.-P.; Lefevre, K.; Miquel, M.C.; Verge, D.; Lanfumey, R.; Doucet, E.; Hamon, M.; El Mestikawy, S. *Brain Research*, 1997, *746*, 207-219). The ability of known 5-HT_6 receptor ligands to enhance cholinergic transmission also supported the cognition use (Bentley, J. C.; Boursson, A.; Boess, F. G.; Kone, F. C.; Marsden, C. A.; Petit, N.; Sleight, A. J. *British Journal of Pharmacology*, 1999, *126(7)*, 1537-1542). Studies have demonstrated that a known 5-HT_6 selective antagonist significantly increased glutamate and aspartate levels in the frontal cortex without elevating levels of noradrenaline, dopamine, or 5-HT. This selective elevation of neurochemicals known to be involved in memory and cognition indicates the role 5-HT_6 ligands play in cognition (Dawson, L. A.; Nguyen, H. Q.; Li, P. *British Journal of Pharmacology*, 2000, *130(1)*, 23-26). Animal studies of memory and learning with a known selective 5-HT_6 antagonist found positive effects (Rogers, D. C.; Hatcher, P. D.; Hagan, J. J. *Society of Neuroscience, Abstracts* 2000, *26*, 680). More recent studies have supported this finding in several additional animal models of cognition and memory including in a novel object discrimination model (King, M. V.; Sleight, A. J.; Wooley, M. L.; Topham, I. A.; Marsden, C. A.; Fone, K. C. F. *Neuropharmacology* 2004, *47(2)*, 195-204 and Wooley, M. L.; Marsden, C. A.; Sleight, A. J.; Fone, K. C. F. *Psychopharmacology*, 2003, *170(4)*, 358-367) and in a water maze model (Rogers, D. C.; Hagan, J. J. *Psychopharmacology*, 2001, *158(2)*, 114-119 and Foley, A. G.; Murphy, K. J.; Hirst, W. D.; Gallagher, H. C.; Hagan, J. J.; Upton, N.; Walsh, F. S.; Regan, C. M. *Neuropsychopharmacology* 2004, *29(1)*, 93-100).

A related therapeutic use for 5-HT_6 ligands is the treatment of attention deficit disorders (ADD, also known as Attention Deficit Hyperactivity Disorder or ADHD) in both children and adults. Because 5-HT_6 antagonists enhance the activity of the nigrostriatal dopamine pathway and because ADHD has been linked to abnormalities in the caudate (Ernst, M; Zametkin, A. J.; Matochik, J. H.; Jons, P. A.; Cohen, R. M.

Journal of Neuroscience 1998, *18(15)*, 5901-5907), 5-HT_6 antagonists attenuate attention deficit disorders.

Early studies examining the affinity of various CNS ligands with known therapeutic utility or a strong structural resemblance to known drugs implicates 5-HT_6 ligands in the treatment of schizophrenia and depression. For example, clozapine (an effective clinical antipsychotic) has high affinity for the 5-HT_6 receptor subtype. Also, several clinical antidepressants have high affinity for the receptor as well and act as antagonists at this site (Branchek, T. A.; Blackburn, T. P. *Annual Reviews in Pharmacology and Toxicology* 2000, *40*, 319-334).

Further, recent *in vivo* studies in rats indicate that 5-HT_6 modulators are useful in the treatment of movement disorders including epilepsy (Stean, T.; Routledge, C.; Upton, N. *British Journal of Pharmacology* 1999, *127* Proc. Supplement 131P and Routledge, C.; Bromidge, S. M.; Moss, S. F.; Price, G. W.; Hirst, W.; Newman, H.; Riley, G.; Gager, T.; Stean, T.; Upton, N.; Clarke, S. E.; Brown, A. M. *British Journal of Pharmacology* 2000, *130(7)*, 1606-1612).

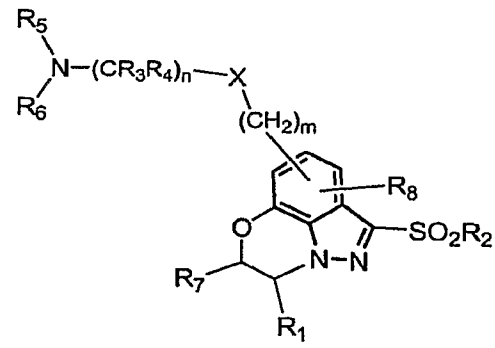
Therefore, it is an object of this invention to provide compounds which are useful as therapeutic agents in the treatment of a variety of central nervous system disorders related to or affected by the 5-HT6 receptor.

It is another object of this invention to provide therapeutic methods and pharmaceutical compositions useful for the treatment of central nervous system disorders related to or affected by the 5-HT6 receptor.

It is a feature of this invention that the compounds provided may also be used to further study and elucidate the 5-HT6 receptor.

SUMMARY OF THE INVENTION

The present invention provides a substituted-dihydro[1,4]oxazino[2,3,4-hi]indazole compound of formula I



(I)

wherein

X is a bond, O, S, NR or CONR;

m is 0 or an integer of 1;

R is H or an optionally substituted alkyl group;

R_1 and R_7 are each independently H or an optionally substituted alkyl group;

R_2 is an alkyl, cycloalkyl, aryl or heteroaryl group each group optionally substituted or an optionally substituted 8- to 13-membered bicyclic or tricyclic ring system having a N atom at the bridgehead and optionally containing 1, 2 or 3 additional heteroatoms selected from N, O or S;

R_3 and R_4 are each independently H, or an optionally substituted alkyl group;

n is 0 or an integer of 2, 3, 4, 5, or 6;

R_5 and R_6 are each independently H or an alkyl, alkenyl, alkynyl or cycloalkyl, group each group optionally substituted or R_5 and R_6 may be taken together with the atom to which they are attached to form an optionally substituted 3- to 7-membered ring optionally containing an additional heteroatom selected from NR, O or S;

R_8 is H, halogen, OR_9, or an optionally substituted alkyl group; and

R_9 is H, alkyl or haloalkyl; or

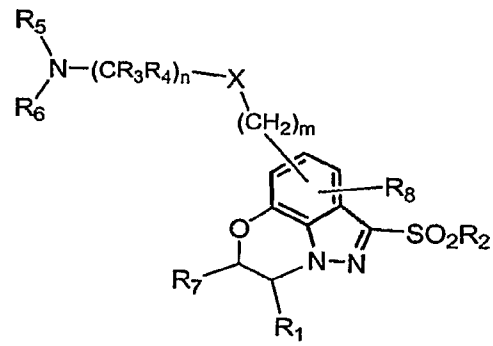
a stereoisomer thereof or a pharmaceutically acceptable salt thereof.

The present invention also provides methods and compositions useful for the therapeutic treatment of central nervous system disorders related to or affected by the 5-HT6 receptor.

DETAILED DESCRIPTION OF THE INVENTION

The 5-hydroxytryptamine-6 (5-HT6) receptor has been identified by molecular cloning. Its ability to bind a wide range of therapeutic compounds used in psychiatry, coupled with its intriguing distribution in the brain has stimulated significant interest in new compounds which are capable of interacting with or affecting said receptor. Significant efforts are being made to understand the role of the 5-HT6 receptor in psychiatry, cognitive dysfunction, motor function and control, memory, mood and the like. To that end, compounds which demonstrate a binding affinity for the 5-HT6 receptor are earnestly sought both as an aid in the study of the 5-HT6 receptor and as potential therapeutic agents in the treatment of central nervous system disorders, for example see C. Reavill and D. C. Rogers, Current Opinion in Investigational Drugs, 2001, 2(1):104-109, Pharma Press Ltd and Woolley, M. L.; Marsden, C. A.; Fone, K. C. F. *Current Drug Targets: CNS & Neurological Disorders* 2004, *3(1)*, 59-79.

Surprisingly, it has now been found that dihydro[1,4]oxazino[2,3,4-hi]indazole compounds of formula I demonstrate 5-HT6 affinity along with significant sub-type selectivity. Advantageously, said formula I compounds are effective therapeutic agents for the treatment of central nervous system (CNS) disorders associated with or affected by the 5-HT6 receptor. Accordingly, the present invention provides a dihydro[1,4]oxazino[2,3,4-hi]indazole compound of formula I



(I)

wherein

X is a bond, O, S, NR or CONR;

m is 0 or an integer of 1;

R is H or an optionally substituted alkyl group;

R_1 and R_7 are each independently H or an optionally substituted alkyl group;

R_2 is an alkyl, cycloalkyl, aryl or heteroaryl group each group optionally substituted or an optionally substituted 8- to 13-membered bicyclic or tricyclic ring system having a N atom at the bridgehead and optionally containing 1, 2 or 3 additional heteroatoms selected from N, O or S;

R_3 and R_4 are each independently H, or an optionally substituted alkyl group;

n is 0 or an integer of 2, 3, 4, 5, or 6;

R_5 and R_6 are each independently H or an alkyl, alkenyl, alkynyl or cycloalkyl, group each group optionally substituted or R_5 and R_6 may be taken together with the atom to which they are attached to form an optionally substituted 3- to 7-membered ring optionally containing an additional heteroatom selected from NR, O or S;

R_8 is H, halogen, OR_9, or an optionally substituted alkyl group; and

R_9 is H, alkyl or haloalkyl; or

a stereoisomer thereof or a pharmaceutically acceptable salt thereof.

An example of R_2 is optionally substituted naphthyl, e.g., naphth-1-yl. R_5 and R_6 together with the nitrogen may for example form a 5 or 6 membered ring (e.g., pyrrolidine, piperidine or piperazine). NR in the piperazine ring may be for example NH or Nalkyl, e.g., N-methyl.

R_3 and R_4 when present may each be hydrogen. R_1, R7 and R_8 may each be hydrogen.

Preferred compounds of the invention are those compounds of formula I wherein X is a bond or O. Another group of preferred compounds is those formula I compounds wherein R_2 is an optionally substituted aryl or heteroaryl group or an optionally subtituted 8- to 13-membered bicyclic or tricyclic ring system having a N atom at the bridgehead and optionally containing 1, 2 or 3 additional heteroatoms selected from N, O or S. Also preferred are those formula I compounds wherein R_5 and R_6 are each independently H or alkyl or R_5 and R_6 are taken together with the atom to which they are attached to form an optionally substituted 3- to 7-membered ring optionally containing an additional heteroatom NR.

More preferred compounds of the invention are those compounds of formula I wherein X is a bond and m and n are 0. Another group of more preferred compounds is those compounds of formula I wherein X is O; m is 0; and n is 2. A further group of more preferred compounds are those compounds of formula I

wherein R_2 is an optionally substituted aryl or heteroaryl group and R_5 and R_6 are each independently H or alkyl or R_5 and R_6 are taken together with the atom to which they are attached to form an optionally substituted 3- to 7-membered ring optionally containing an additional heteroatom NR.

Among the preferred compounds of the invention are:

8-(4-Methylpiperazin-1-yl)-6-(1-naphthylsulfonyl)-2,3-dihydro[1,4]oxazino[2,3,4-hi]-indazole;

N-Methyl-2-{[6-(1-naphthylsulfonyl)-2,3-dihydro[1,4]oxazino[2,3,4-hi]indazol-8-yl]oxy}-ethanamine;

N, N-Dimethyl-2-{[6-(1-naphthylsulfonyl)-2,3-dihydro[1,4]oxazino[2,3,4-hi]indazol-8-yl]oxy}ethanamine;

6-(1-Naphthylsulfonyl)-8-(2-piperidin-1-ylethoxy)-2,3-dihydro[1,4]oxazino[2,3,4-hi]-indazole;

6-(1-Naphthylsulfonyl)-8-(2-pyrrolidin-1-ylethoxy)-2,3-dihydro[1,4]oxazino[2,3,4-hi]-indazole;

2-{[6-(1-Naphthylsulfonyl)-2,3-dihydro[1,4]oxazino[2,3,4-hi]indazol-8-yl]oxy}-ethanamine;

a stereoisomer thereof; or a pharmaceutically acceptable salt thereof.

An optionally substituted moiety may be substituted with one or more substituents. The substituent groups, which are optionally present, may be one or more of those customarily employed in the development of pharmaceutical compounds or the modification of such compounds to influence their structure/activity, persistence, absorption, stability or other beneficial property. Specific examples of such substituents include halogen atoms, nitro, cyano, thiocyanato, cyanato, hydroxyl, alkyl, haloalkyl, alkoxy, haloalkoxy, amino, alkylamino, dialkylamino, formyl, alkoxycarbonyl, carboxyl, alkanoyl, alkylthio, alkylsuphinyl, alkylsulphonyl, carbamoyl, alkylamido, phenyl, phenoxy, benzyl, benzyloxy, heterocyclyl (e.g., heteroaryl, cycloheteroalkyl) or cycloalkyl groups, preferably halogen atoms or lower alkyl, lower alkoxy, lower haloalkyl or lower haloalkoxy groups. Unless otherwise specified, typically, 1-3 substituents may be present.

The term "halogen", as used herein, designates fluorine, chlorine, bromine, and iodine.

As used herein, the term "alkyl" as used herein as a group or when it forms part of a group, e.g., alkoxy, alkylamido, alkanoyl, includes both (C_1-C_{10}) straight chain and (C_3-C_{12}) branched-chain monovalent saturated hydrocarbon moiety. Examples of saturated hydrocarbon alkyl moieties include, but are not limited to, chemical groups of 1-6 carbon atoms such as methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl, *tert*-butyl, isobutyl, *sec*-butyl; higher homologs such as *n*-pentyl, *n*-hexyl, and the like. Specifically included within the definition of "alkyl" are those alkyl groups that are optionally substituted. Suitable alkyl substitutions include, but are not limited to, CN, OH, halogen, phenyl, carbamoyl, carbonyl, alkoxy or aryloxy.

As used herein, the term "haloalkyl" designates a C_nH_{2n+1} group having from one to 2n+1 halogen atoms which may be the same or different. Examples of haloalkyl groups include CF_3, CH_2Cl, C_2H_3BrCl, $C_3H_5F_2$, or the like.

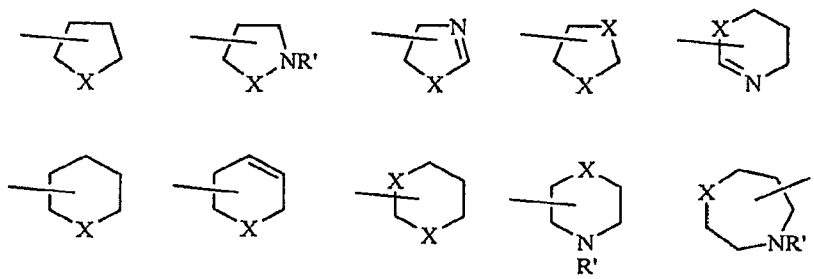
The term "alkenyl", as used herein, refers to either a (C_2-C_8) straight chain or (C_3-C_{10}) branched-chain monovalent hydrocarbon moiety containing at least one double bond. Such hydrocarbon alkenyl moieties may be mono or polyunsaturated, and may exist in the E or Z configurations. The compounds of this invention are meant to include all possible E and Z configurations. Examples of mono or polyunsaturated hydrocarbon alkenyl moieties include, but are not limited to, chemical groups such as vinyl, 2-propenyl, isopropenyl, crotyl, 2-isopentenyl, butadienyl, 2-(butadienyl), 2,4-pentadienyl, 3-(1,4-pentadienyl), or the like.

Similarly, the term "alkynyl", as used herein, refers to either a (C_2-C_8) straight chain or (C_3-C_{10}) branched-chain monovalent hydrocarbon moiety containing at least one triple bond. Such hydrocarbon alkenyl moieties may be mono or polyunsaturated. Examples of mono or polyunsaturated hydrocarbon alkynyl moieties include, but are not limited to, chemical groups such as 2-propynyl, 3-pentynyl, or the like.

The term "cycloalkyl", as used herein, refers to a monocyclic, bicyclic, tricyclic, fused, bridged, or spiro monovalent saturated hydrocarbon moiety of 3-10 carbon atoms. Examples of cycloalkyl moieties include, but are not limited to, chemical groups such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, norbornyl, adamantyl, spiro[4.5]decanyl, or the like.

The term "cycloheteroalkyl" as used herein designates a five- to seven-membered cycloalkyl ring system containing 1, 2 or 3 heteroatoms, which may be the

same or different, selected from N, O or S and optionally containing one double bond. Exemplary of the cycloheteroalkyl ring systems included in the term as designated herein are the following rings wherein X is NR', O or S and R' is H or an optional substituent as defined hereinabove.

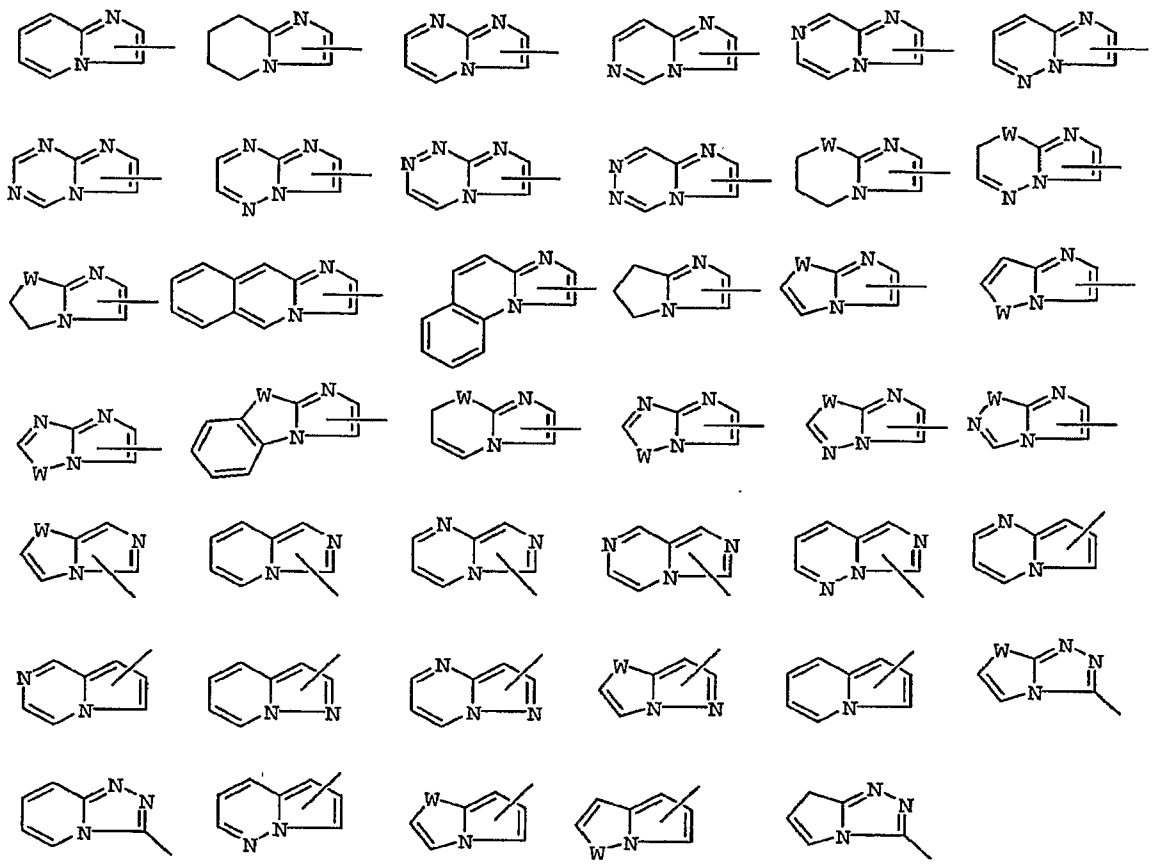


The term "aryl", as used herein, refers to an aromatic carbocyclic moiety of up to 20 carbon atoms, e.g., 6-20 carbons, which may be a single ring (monocyclic) or multiple rings (bicyclic, up to three rings) fused together or linked covalently. Examples of aryl moieties include, but are not limited to, phenyl, 1-naphthyl, 2-naphthyl, biphenyl, anthryl, phenanthryl, fluorenyl, indanyl, biphenylenyl, acenaphthenyl, acenaphthylenyl, and the like.

The term "heteroaryl" as used herein designates an aromatic heterocyclic ring system, e.g., of 5 – 20 ring atoms, which may be a single ring (monocyclic) or multiple rings (bicyclic, up to three rings) fused together or linked covalently. Preferably, heteroaryl is a 5- to 6-membered ring. The rings may contain from one to four hetero atoms selected from N, O or S, wherein the nitrogen or sulfur atom is optionally oxidized, or the nitrogen atom is optionally quaternized. Examples of heteroaryl moieties include, but are not limited to, furan, thiophene, pyrrole, pyrazole, imidazole, oxazole, isoxazole, thiazole, isothiazole, oxadiazole, triazole, pyridine, pyrimidine, pyrazine, pyridazine, benzimidazole, benzoxazole, benzisoxazole, benzothiazole, benzofuran, benzothiophene, thianthrene, dibenzofuran, dibenzothiophene, indole, indazole, quinoline, isoquinoline, quinazoline, quinoxaline, purine, or the like.

Exemplary of the 8- to 13-membered bicyclic or tricyclic ring systems having a N atom at the bridgehead and optionally containing 1, 2 or 3 additional heteroatoms selected from N, O or S included in the term as designated herein are the following

ring systems wherein W is NR', O or S; and R' is H or an optional substituent as described herein:



While shown without respect to stereochemistry, compounds of formula I include all stereochemical forms of the structure; i.e., the R and S configurations for each asymmetric center. Therefore, single stereochemical isomers as well as enantiomeric and diastereomeric mixtures of the present compounds are within the scope of the invention. The compounds of this invention may contain one or more asymmetric centers and may thus give rise to optical isomers and diastereomers. The present invention includes such optical isomers and diastereomers; as well as the racemic and resolved, enantiomerically pure R and S stereoisomers; as well as other mixtures of the R and S stereoisomers and pharmaceutically acceptable salts thereof. Where a stereoisomer is preferred, it may in some embodiments be provided substantially free of the corresponding enantiomer. Thus, an enantiomer substantially free of the corresponding enantiomer refers to a compound that is

isolated or separated via separation techniques or prepared free of the corresponding enantiomer. "Substantially free", as used herein, means that the compound is made up of a significantly greater proportion of one steriosomer, preferably less than about 50%, more preferably less than about 75%, and even more preferably less than about 90%.

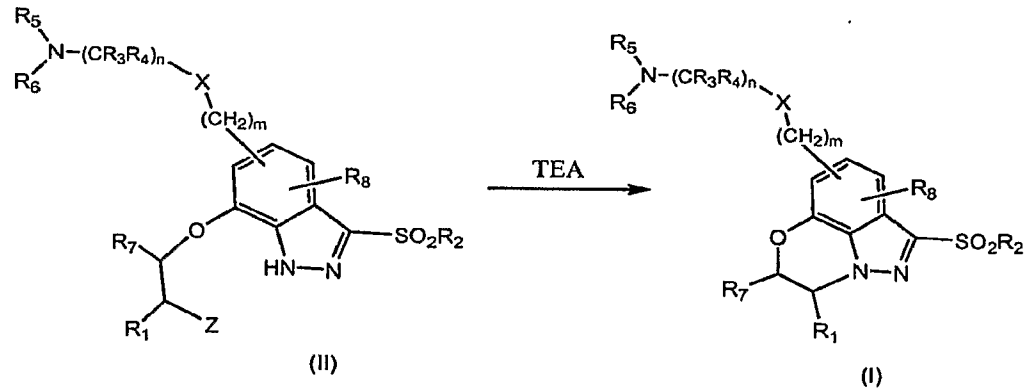
Formula I structures depicted herein are also meant to include compounds which differ only in the presence of one or more isotopically enriched atoms. For example, compounds having the present structure except for the replacement of a hydrogen by a deuterium or tritium, or the replacement of a carbon by a ^{13}C- or ^{14}C-enriched carbon are within the scope of this invention.

The compounds of the present invention may be converted to salts, in particular pharmaceutically acceptable salts using art recognized procedures. Suitable salts with bases are, for example, metal salts, such as alkali metal or alkaline earth metal salts, for example sodium, potassium or magnesium salts, or salts with ammonia or an organic amine, such as morpholine, thiomorpholine, piperidine, pyrrolidine, a mono-, di- or tri-lower alkylamine, for example ethyl-tert-butyl-, diethyl-, diisopropyl-, triethyl-, tributyl- or dimethylpropylamine, or a mono-, di-, or trihydroxy lower alkylamine, for example mono-, di- or triethanolamine. The term 'lower' as used herein denotes 1-6 carbon atoms. Internal salts may furthermore be formed. The term "pharmaceutically acceptable salt", as used herein, refers to salts derived from organic and inorganic acids such as, for example, acetic, propionic, lactic, citric, tartaric, succinic, fumaric, maleic, malonic, mandelic, malic, phthalic, hydrochloric, hydrobromic, phosphoric, nitric, sulfuric, methanesulfonic, naphthalenesulfonic, benzenesulfonic, toluenesulfonic, camphorsulfonic, and similarly known acceptable acids when a compound of this invention contains a basic moiety.

Compounds of the invention include esters, carbamates or other conventional prodrug forms, which in general, are functional derivatives of the compounds of the invention and which are readily converted to the inventive active moiety *in vivo*. Correspondingly, the method of the invention embraces the treatment of the various conditions described hereinabove with a compound of formula I or with a compound which is not specifically disclosed but which, upon administration, converts to a compound of formula I *in vivo*.

Advantageously, the present invention also provides a convenient and effective process for the preparation of a compound of formula I which comprises reacting a compound of formula II with triethylamine, optionally in the presence of a solvent, to give the compound of formula I. The process is shown hereinbelow in flow diagram I wherein Z is Cl, Br or I and TEA designates triethylamine.

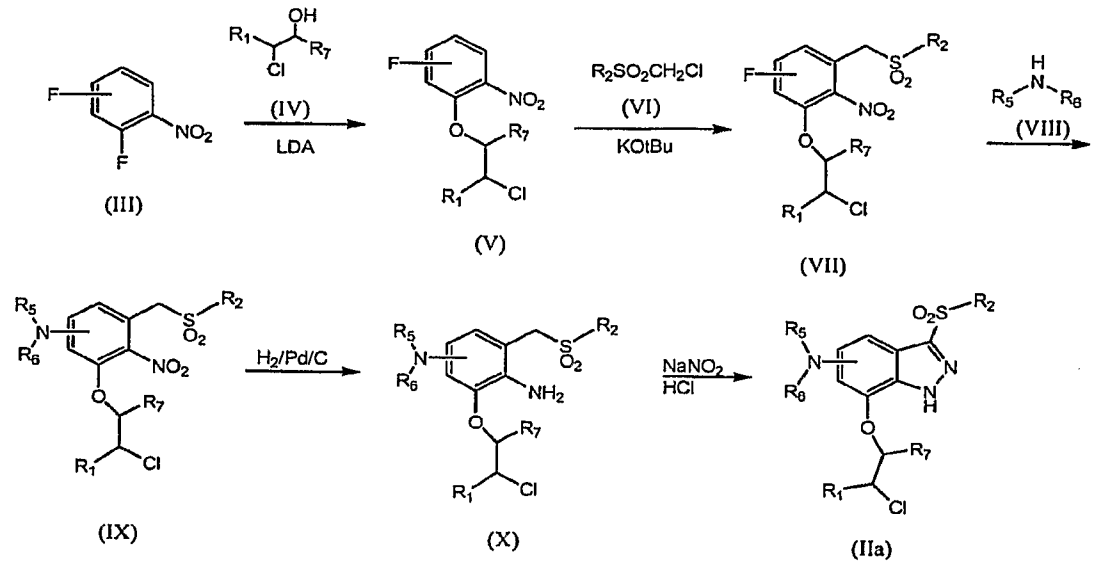
FLOW DIAGRAM I



Solvents suitable for use in the process of the invention include aprotic solvents such as dimethyl formamide, dimethylsulfoxide, dioxane, or the like, or mixtures thereof.

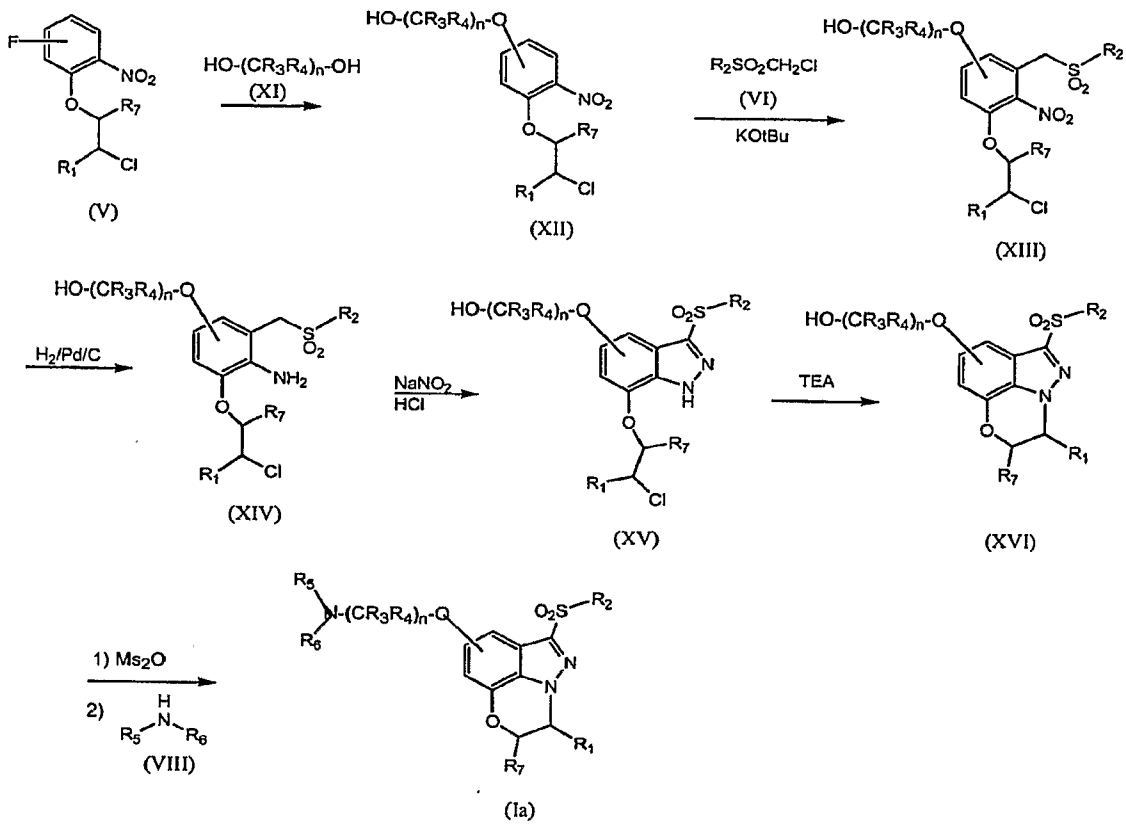
Compounds of formula II may be prepared using conventional synthetic methods and, if required, standard isolation or separation techniques. For example, compounds of formula II wherein X is a bond; Z is Cl; and m and n are 0 (IIa) may be prepared by reacting a difluoronitrobenzene compound of formula III with a 1-chloro-2-hydroxy compound of formula IV in the presence of a base such as lithium diisopropylamide (LDA) to form the compound of formula V; reacting the formula V compound with a chloromethanesulfonyl compound of formula VI in the presence of a base such as potassium t-butoxide to give the compound of formula VII; reacting the formula VII compound with an amine of formula VIII to give the compound of formula IX; reducing the formula IX compound with a conventional reducing agent such as H_2 and a Palladium on Carbon catalyst to form the amino compound of formula X; cyclizing the formula X amine in the presence of $NaNO_2$ and HCl to give the desired compound of formula IIa. The reaction is shown in flow diagram II.

FLOW DIAGRAM II



Compounds of formula I may also be prepared by alternative methods. For example, compounds of formula I wherein X is O and m is 0 (Ia) may be prepared by reacting the formula V compound with a dihydroxy compound of formula XI in the presence of $CsCO_3$ to give the nitrobenzene compound of formula XII; reacting the formula XII compound with a chloromethanesulfonyl compound of formula VI in the presence of a base such as potassium t-butoxide to give the compound of formula XIII; reducing the formula XIII compound with a conventional reducing agent such as H_2 and a Palladium on Carbon catalyst to form the amino compound of formula XIV; cyclizing the formula XIV amine in the presence of $NaNO_2$ and HCl to give the indazole compound of formula XV; reacting the formula XV indazole with triethylamine to give the compound of formula XVI; and reacting the formula XVI with methane sulfonic anhydride (Me_2O) to form the mesylate intermediate and reacting said intermediate with an amine of formula VIII to give the desired compound of formula Ia. The reaction is shown in flow diagram III.

FLOW DIAGRAM III



Advantageously, the formula I compounds of the invention are useful for the treatment of CNS disorders related to or affected by the 5-HT6 receptor including motor, mood, personality, behavioral, psychiatric, cognitive, neurodegenerative, or the like disorders, for example Alzheimer's disease, Parkinson's disease, attention deficit disorder, anxiety, epilepsy, depression, obsessive compulsive disorder, sleep disorders, neurodegenerative disorders (such as head trauma or stroke), feeding disorders (such as anorexia or bulimia), schizophrenia, memory loss, disorders associated with withdrawal from drug or nicotine abuse, or the like or certain gastrointestinal disorders such as irritable bowel syndrome. Accordingly, the present invention provides a method for the treatment of a disorder of the central nervous system related to or affected by the 5-HT6 receptor in a patient in need thereof which comprises providing said patient a therapeutically effective amount of a compound of formula I as described hereinabove. The compounds may be provided by oral or

parenteral administration or in any common manner known to be an effective administration of a therapeutic agent to a patient in need thereof.

The term "providing" as used herein with respect to providing a compound or substance embraced by the invention, designates either directly administering such a compound or substance, or administering a prodrug, derivative or analog which forms an equivalent amount of the compound or substance within the body.

The inventive method includes: a method for the treatment of schizophrenia; a method for the treatment of a disease associated with a deficit in memory, cognition, and/or learning or a cognitive disorder such as Alzheimer's disease or attention deficit disorder; a method for the treatment of developmental disorders such as schizophrenia; Down's syndrome, Fragile X syndrome, autism or the like; a method for the treatment of behavioral disorders, e.g., anxiety, depression, or obsessive compulsive disorder; a method for the treatment of motion or motor disorders such as Parkinson's disease or epilepsy; a method for the treatment of a neurodegenerative disorder such as stroke or head trauma or withdrawal from drug addiction including addiction to nicotine, alcohol, or other substances of abuse, or any other CNS disease or disorder associated with or related to the 5-HT6 receptor.

In one embodiment, the present invention provides a method for treating attention deficit disorders (ADD, also known as Attention Deficit Hyperactivity Disorder or ADHD) in both children and adults. Accordingly, in this embodiment, the present invention provides a method for treating attention deficit disorders in a pediatric patient.

The present invention therefore provides a method for the treatment of each of the conditions listed above in a patient, preferably in a human, said method comprises providing said patient a therapeutically effective amount of a compound of formula I as described hereinabove. The compounds may be provided by oral or parenteral administration or in any common manner known to be an effective administration of a therapeutic agent to a patient in need thereof.

The therapeutically effective amount provided in the treatment of a specific CNS disorder may vary according to the specific condition(s) being treated, the size, age and response pattern of the patient, the severity of the disorder, the judgment of the attending physician and the like. In general, effective amounts for daily oral administration may be about 0.01 to 1,000 mg/kg, preferably about 0.5 to 500 mg/kg

and effective amounts for parenteral administration may be about 0.1 to 100 mg/kg, preferably about 0.5 to 50 mg/kg.

In actual practice, the compounds of the invention are provided by administering the compound or a precursor thereof in a solid or liquid form, either neat or in combination with one or more conventional pharmaceutical carriers or excipients. Accordingly, the present invention provides a pharmaceutical composition which comprises a pharmaceutically acceptable carrier and an effective amount of a compound of formula I as described hereinabove.

In one embodiment, the invention relates to compositions comprising at least one compound of formula I, or a pharmaceutically acceptable salt thereof, and one or more pharmaceutically acceptable carriers, excipients, or diluents. Such compositions include pharmaceutical compositions for treating or controlling disease states or conditions of the central nervous system. In certain embodiments, the compositions comprise mixtures of one or more compounds of formula I.

In certain embodiments, the invention relates to compositions comprising at least one compound of formula I, or a pharmaceutically acceptable salt thereof, and one or more pharmaceutically acceptable carriers, excipients, or diluents. Such compositions are prepared in accordance with acceptable pharmaceutical procedures. Pharmaceutically acceptable carriers are those carriers that are compatible with the other ingredients in the formulation and are biologically acceptable.

The compounds of formula I may be administered orally or parenterally, neat, or in combination with conventional pharmaceutical carriers. Applicable solid carriers can include one or more substances that can also act as flavoring agents, lubricants, solubilizers, suspending agents, fillers, glidants, compression aids, binders, tablet-disintegrating agents, or encapsulating materials. In powders, the carrier is a finely divided solid that is in admixture with the finely divided active ingredient. In tablets, the active ingredient is mixed with a carrier having the necessary compression properties in suitable proportions and compacted in the shape and size desired. The powders and tablets preferably contain up to 99% of the active ingredient. Suitable solid carriers include, for example, calcium phosphate, magnesium stearate, talc, sugars, lactose, dextrin, starch, gelatin, cellulose, methyl cellulose, sodium

carboxymethyl cellulose, polyvinylpyrrolidine, low melting waxes and ion exchange resins.

In certain embodiments, a compound of formula I is provided in a disintegrating tablet formulation suitable for pediatric administration.

Liquid carriers can be used in preparing solutions, suspensions, emulsions, syrups and elixirs. The active ingredient can be dissolved or suspended in a pharmaceutically acceptable liquid carrier such as water, an organic solvent, a mixture of both, or a pharmaceutically acceptable oil or fat. The liquid carrier can contain other suitable pharmaceutical additives such as, for example, solubilizers, emulsifiers, buffers, preservatives, sweeteners, flavoring agents, suspending agents, thickening agents, colors, viscosity regulators, stabilizers or osmo-regulators. Suitable examples of liquid carriers for oral and parenteral administration include water (particularly containing additives as above, e.g. cellulose derivatives, preferably sodium carboxymethyl cellulose solution), alcohols (including monohydric alcohols and polyhydric alcohols e.g. glycols) and their derivatives, and oils (e.g. fractionated coconut oil and arachis oil). For parenteral administration, the carrier can also be an oily ester such as ethyl oleate and isopropyl myristate. Sterile liquid carriers are used in sterile liquid form compositions for parenteral administration. The liquid carrier for pressurized compositions can be halogenated hydrocarbon or other pharmaceutically acceptable propellant.

In certain embodiments, a liquid pharmaceutical composition is provided wherein said composition is suitable for pediatric administration. In other embodiments, the liquid composition is a syrup or suspension.

Liquid pharmaceutical compositions that are sterile solutions or suspensions can be administered by, for example, intramuscular, intraperitoneal or subcutaneous injection. Sterile solutions can also be administered intravenously. Compositions for oral administration can be in either liquid or solid form.

The compounds of formula I may be administered rectally or vaginally in the form of a conventional suppository. For administration by intranasal or intrabronchial inhalation or insufflation, the compounds of formula I can be formulated into an aqueous or partially aqueous solution, which can then be utilized in the form of an aerosol. The compounds of formula I can also be administered transdermally through the use of a transdermal patch containing the active compound and a carrier

that is inert to the active compound, is non-toxic to the skin, and allows delivery of the agent for systemic absorption into the blood stream via the skin. The carrier can take any number of forms such as creams and ointments, pastes, gels, and occlusive devices. The creams and ointments can be viscous liquid or semisolid emulsions of either the oil-in-water or water-in-oil type. Pastes comprised of absorptive powders dispersed in petroleum or hydrophilic petroleum containing the active ingredient can also be suitable. A variety of occlusive devices can be used to release the active ingredient into the blood stream such as a semipermeable membrane covering a reservoir containing the active ingredient with or without a carrier, or a matrix containing the active ingredient. Other occlusive devices are known in the literature.

Preferably the pharmaceutical composition is in unit dosage form, e.g. as tablets, capsules, powders, solutions, suspensions, emulsions, granules, or suppositories. In such form, the composition is sub-divided in unit dose containing appropriate quantities of the active ingredient; the unit dosage forms can be packaged compositions, for example, packeted powders, vials, ampoules, prefilled syringes or sachets containing liquids. The unit dosage form can be, for example, a capsule or tablet itself, or it can be the appropriate number of any such compositions in package form.

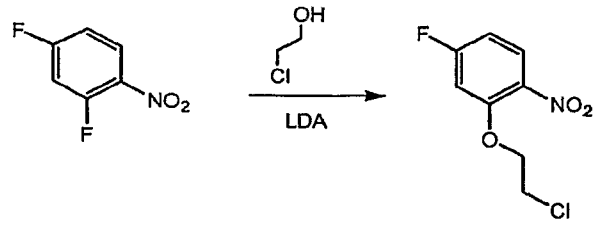
The therapeutically effective amount of a compound of formula I provided to a patient will vary depending upon what is being administered, the purpose of the administration, such as prophylaxis or therapy, the state of the patient, the manner of administration, and the like. In therapeutic applications, compounds of formula I are provided to a patient suffering from a condition in an amount sufficient to treat or at least partially treat the symptoms of the condition and its complications. An amount adequate to accomplish this is a "therapeutically effective amount" as described previously herein. The dosage to be used in the treatment of a specific case must be subjectively determined by the attending physician. The variables involved include the specific condition and the size, age, and response pattern of the patient. The treatment of substance abuse follows the same method of subjective drug administration under the guidance of the attending physician. Generally, a starting dose is about 5 mg per day with gradual increase in the daily dose to about 150 mg per day, to provide the desired dosage level in the patient.

In certain embodiments, the present invention is directed to prodrugs of compounds of formula I. The term "prodrug," as used herein, means a compound that is convertible *in vivo* by metabolic means (e.g. by hydrolysis) to a compound of formula I. Various forms of prodrugs are known in the art such as those discussed in, for example, Bundgaard, (ed.), Design of Prodrugs, Elsevier (1985); Widder, et al. (ed.), Methods in Enzymology, vol. 4, Academic Press (1985); Krogsgaard-Larsen, et al., (ed). "Design and Application of Prodrugs, Textbook of Drug Design and Development, Chapter 5, 113-191 (1991), Bundgaard, et al., Journal of Drug Delivery Reviews, 8:1-38(1992), Bundgaard, J. of Pharmaceutical Sciences, 77:285 et seq. (1988); and Higuchi and Stella (eds.) Prodrugs as Novel Drug Delivery Systems, American Chemical Society (1975).

For a more clear understanding, and in order to illustrate the invention more clearly, specific examples thereof are set forth hereinbelow. The following examples are merely illustrative and are not to be understood as limiting the scope and underlying principles of the invention in any way. The term HNMR designates proton nuclear magnetic resonance. The term MS desigates mass spectrum. The terms THF, EtOAc, DMF and DMSO designate tetrahydrofuran, ethyl acetate, dimethyl formamide and dimethylsulfoxide, respectively. All chromatography is performed using SiO_2 as support. Unless otherwise noted, all parts are parts by weight.

EXAMPLE 1

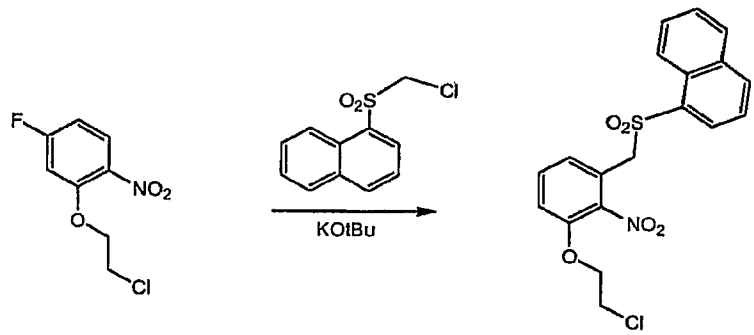
Preparation of 1-(2-Chloroethoxy)-4-fluoro-1-nitro-benzene



A solution of 2-chloro-ethanol (1) (8.3 ml, 120 mmoles) in THF, under nitrogen, was cooled to 0°C, treated dropwise with lithium diisopropylamide (LDA) (60 ml, 120 mmoles, while maintaining the temperature constant at 0°C. The mixture was stirred at 0°C for 15 minutes, treated with 2,4-difluoro-1-nitro-benzene (1) (11 ml, 100 mmoles), stirred at room temperature overnight, diluted with water and extracted with EtOAc. The extracts were combined, washed with brine, dried over Na_2SO_4, and concentrated under vacuum to afford the title compound as an off-white solid (20.0 g, 91 mmoles), identified by HNMR and mass spectral analyses.

EXAMPLE 2

Preparation of 1-[3-(2-Chloroethoxy)-5-fluoro-2-nitrophenylmethanesulfonyl]-naphthalene

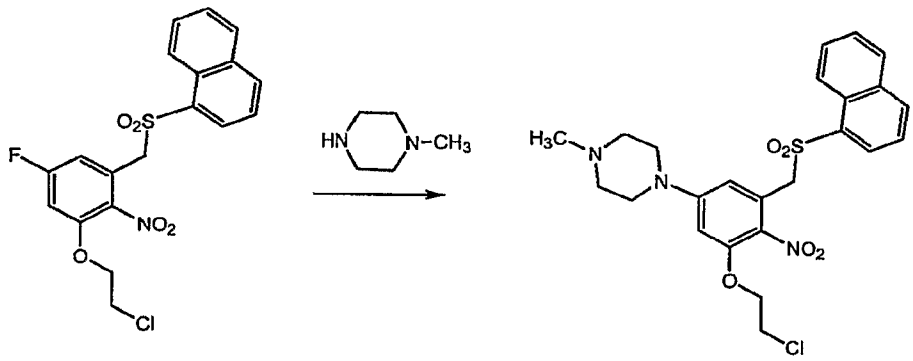


A mixture of 2-(2-chloroethoxy)-4-fluoro-1-nitro-benzene (1.3 g, 6 mmoles) and 1-chloromethane-sulfonyl-naphthalene (2.16g, 9mmoles) in THF, under nitrogen,

was stirred at –78°C, treated dropwise with a solution of 1M potassium t-butoxide (18 ml, 18 mmoles) over a 30 min. period, allowed to warm to –40°C, stirred at –40°C for 5 hours, poured into cold 2N HCl and extracted with EtOAc. The extracts were combined, dried over Na_2SO_4, and concentrated under vacuum. The resultant residue was recrystallized from CH_2Cl_2/hexane to afford the title compound as an off-white solid (2.25 g, 5.3 mmoles), identfied by HNMR and mass spectral analyses.

EXAMPLE 3

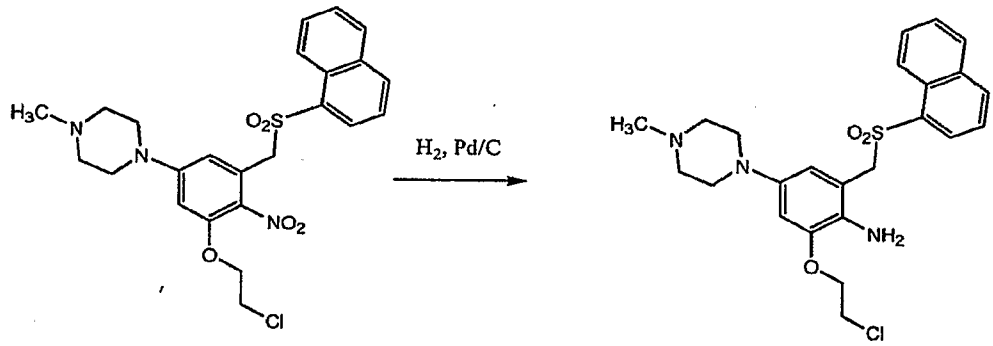
Preparation of 1-[3-(2-Chloroethoxy)-5-(naphthalene-1-sulfonylmethyl)-4-nitro-phenyl]-4-methylpiperazine



A mixture of 1-[3-(2-chloroethoxy)-5-fluoro-2-nitrophenylmethanesulfonyl]-naphthalene (0.42 g, 0.1 mmoles) and N-methylpiperazine (0.168 g, 1.1 mmoles) in DMF was stirred under nitrogen at 40°C for 10 hours. The reaction mixture was cooled to room temperature, diluted with water and extracted with EtOAc. The extracts were combined, washed sequentially with water and brine, dried over Na_2SO_4, and concentrated under vacuum to afford the title compound (0.45 g, 0.85 mmoles), identified by HNMR and mass spectral analysis.

EXAMPLE 4

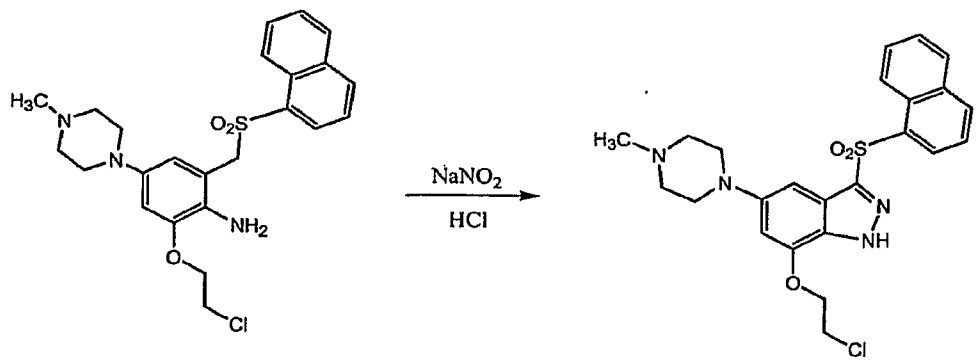
Preparation of 2-(2-Chloroethoxy)-4-(4-methylpiperazin-1-yl)-6-(naphthalene-1-sulfonylmethyl)phenylamine



A mixture of 1-[3-(2-chloroethoxy)-5-(naphthalene-1-sulfonylmethyl)-4-nitro-phenyl]-4-methylpiperazine (0.45 g, 0.85 mmoles) and 10%Pd/C in a 1:1 mixture of THF and methanol was hydrogenated on a Parr hydrogenator at 40lb/in^2 for 20 hours. The reaction mixture was filtered through Celite. The filtrate was diluted with EtOAc, washed with water, dried over Na_2SO_4, and concentrated under vacuum to afford the title compound as an off white solid (0.4 g, 0.82 mmoles), identified by HNMR and mass spectral analyses.

EXAMPLE 5

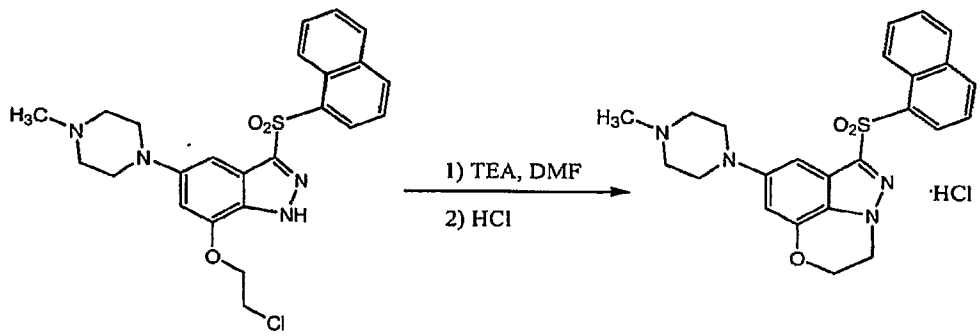
Preparation of 7-(2-Chloroethoxy)-5-(4-methylpiperazin-1-yl)-3-naphthalene-1-sulfonyl)-1*H*-indazole



A mixture of 2-(2-chloroethoxy)-4-(4-methylpiperazin-1-yl)-6-(naphthalene-1-sulfonylmethyl)phenylamine (0.47 g, 1.0 mmoles) in THF and 4M HCl (15 ml) was stirred, under nitrogen, at 3°C and treated dropwise with a solution of sodium nitrite (0.076 g, 1.1 mmoles) in H_2O. The reaction mixture was poured into a cold solution of saturated sodium bicarbonate and extracted with EtOAc. The extracts were combined, dried over Na_2SO_4, and concentrated under vacuum to afford the title compound as an off white solid (0.39g, 0.8 mmoles), identified by HNMR and mass spectral analyses.

EXAMPLE 6

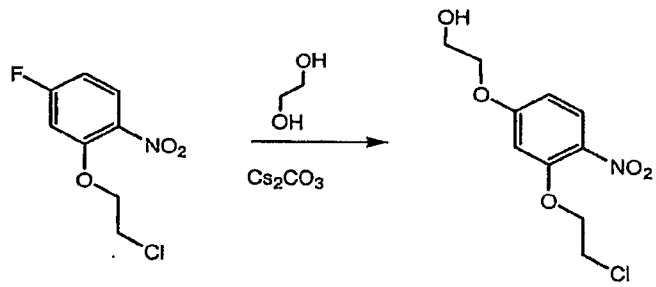
Preparation of 8-(4-Methylpiperazin-1-yl)-6-(1-naphthylsulfonyl)-2,3-dihydro [1,4] oxazino [2,3,4-hi] indazole Hydrochloride



A mixture of 7-(2-chloroethoxy)-5-(4-methylpiperazin-1-yl)-3-naphthalene-1-sulfonyl)-1*H*-indazole (0.06 g, 0.12 mmoles) and triethylamine (0.2 ml, 0.12 mmoles) in DMF was stirred overnight at 70°C, cooled to room temperature, diluted with water and extracted with EtOAc. The extracts were combined, washed sequentially with water and brine, dried over Na_2SO_4 and concentrated under vacuum. The resultant residue was purified by flash chromatography using as eluent 5%CH_3OH/EtOAc. The purified compound was dissolved in methanol, treated with1M HCl in ether (0.2 ml, 0.2 mmoles) and evaporated to dryness to afford the title compound as a grey solid, mp >225° C, identified by HNMR and mass spectral analyses, MS: (ES) *m/z* 448.

EXAMPLE 7

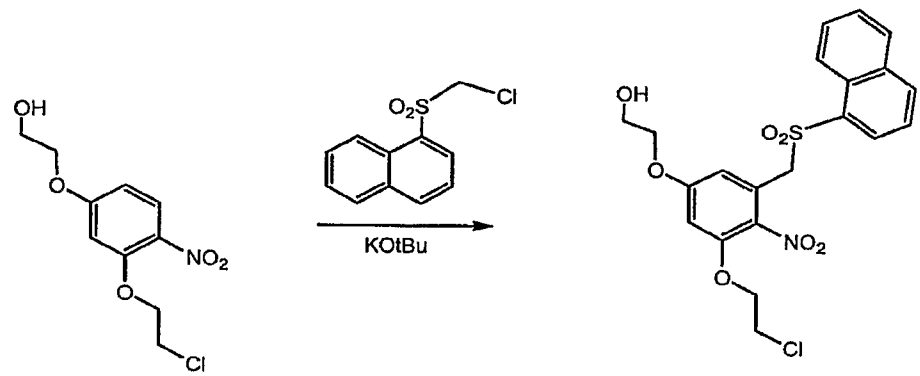
Preparation of 2-[3-(2-Chloroethoxy)-4-nitrophenoxy]ethanol



A mixture of 2-(2-chloroethoxy)-4-fluoro-1-nitro-benzene (91.3 g, 6 mmoles), 2-hydroxyethanol (0.57 g, 7.2 mmoles), and cesium carbonate (2.34 g, 7.2 mmoles) in DMF were stirred together at room temperature for 1 hour, diluted with water and extracted with EtOAc. The extracts were combined, washed sequentially with water and brine, dried over Na_2SO_4 and concentrated under vacuum to afford the title compound (0.63 g, 2.4 mmoles), identified by HNMR and mass spectral analyses.

EXAMPLE 8

Preparation 2-[3-Chloroethoxy)-5-(naphthalene-1-sulfonylmethyl)-4-nitro-phenoxy]ethanol

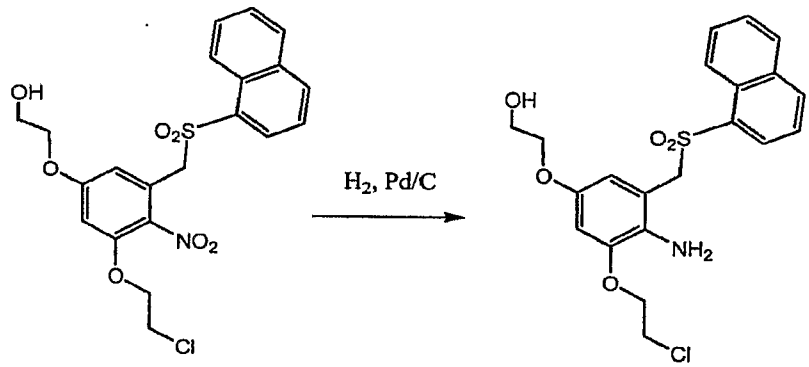


A mixture of 2-[3-(2-chloroethoxy)-4-nitrophenoxy]ethanol (0.63 g, 2.4 mmoles) and 1-chloromethane-sulfonyl-naphthalene (0.87 g, 3.6 mmoles) in THF

was stirred at –78°C, under nitrogen, treated dropwise with a solution of 1M potassium t-butoxide (7.2 ml, 7.2 mmoles) over a 30 min. period, allowed to warm to –40°C, stirred at –40°C for 5 hours, poured into cold 2N HCl and extracted with EtOAc. The extracts were combined, dried over Na_2SO_4 and concentrated under vacuum. The resultant residue was recrystallized from CH_2Cl_2/hexane to afford the title compound as an off-white solid (1.34 g, 2.88 mmoles), identified by HNMR and mass spectral analyses.

EXAMPLE 9

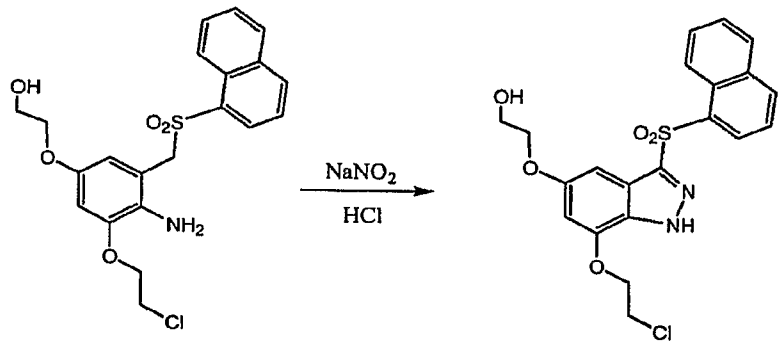
Preparation 2-[4-Amino-3-(2-chloroethoxy)-5-(naphthalene-1-sulfonylmethyl)-phenoxy]ethanol



A mixture of 2-[3-chloroethoxy)-5-(naphthalene-1-sulfonylmethyl)-4-nitro-phenoxy]ethanol (1.34 g, 2.88 mmoles) and 10%Pd/C in a 1:1 mixture of THF and methanol was hydrogenated on a Parr hydrogenator at 40lb/in^2 for 20 hours. The reaction mixture was filtered through Celite. The filtrate was diluted with EtOAc, washed with water, dried over Na_2SO_4, and concentrated under vacuum to afford the title compound (1.22 g, 2.8 mmoles), identified by HNMR and mass spectral analyses.

EXAMPLE 10

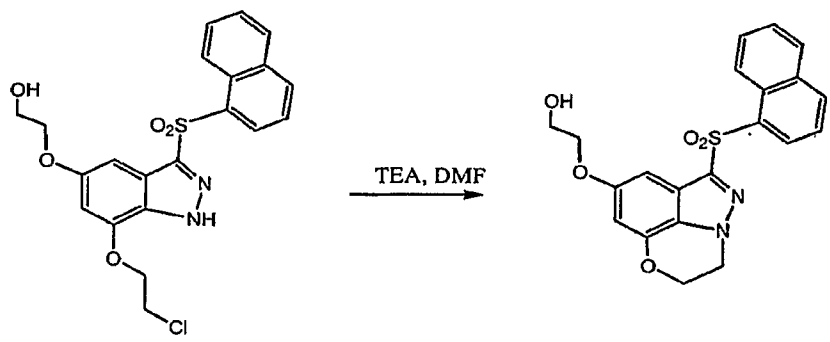
Preparation of 2-[7-(2-Chloroethoxy)-3-(naphthalene-1-sulfonyl)-1*H*-indazol-5-yloxy]ethanol



A mixture of 2-[4-amino-3- (2-chloroethoxy)-5-(naphthalene-1-sulfonylmethyl)-phenoxy]ethanol (1.22 g, 2.8 mmoles) in THF and 4M HCl was stirred, under nitrogen, at 3°C, treated dropwise with a solution of sodium nitrite (0.20 g, 2.94 mmoles) in H_2O, poured into a cold solution of saturated sodium bicarbonate and extracted with EtOAc. The extracts were combined, dried over Na_2SO_4 and concentrated under vacuum to afford the title compound (1.18 g, 2.65 mmoles), identified by HNMR and mass spectral analyses.

EXAMPLE 11

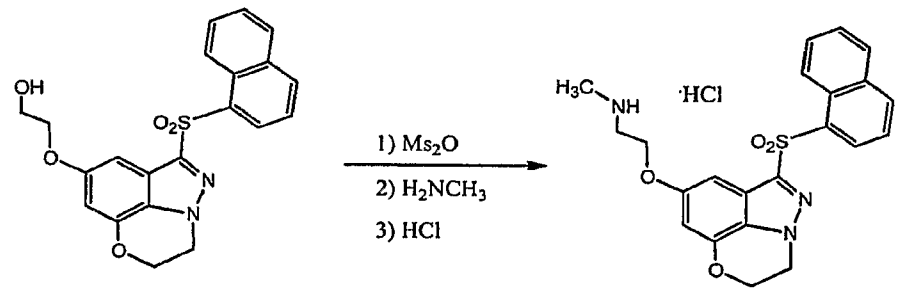
Preparation of 2-[2-(Naphthalene-1-sulfonyl)-7,8-dihydro-6-oxa-1, 8a-diaza-acenaphthylen-4-yloxy]ethanol



A mixture of 2-[7-(2-chloroethoxy)-3-(naphthalene-1-sulfonyl)-1*H*-indazol-5-yloxy]ethanol (1.18 g, 2.65 mmoles) and triethylamine (0.4 ml, 2.65 mmoles) in DMF was stirred overnight at 70°C, cooled to room temperature, diluted with water and extracted with EtOAc. The extracts were combined, washed sequentially with water and brine, dried over Na_2SO_4 and concentrated under vacuum. The resultant residue was purified by flash chromatography using as eluent 5%CH_3OH/EtOAc to afford the title compound (1.03 g, 2.5 mmoles), identified by HNMR and mass spectral analyses.

EXAMPLE 12

Preparation of N-methyl-2-{[6-(1-naphthylsulfonyl)-2,3-dihydro[1,4]oxazino [2,3,4-hi]indazol-8-yl]oxy}ethanamine Hydrochloride

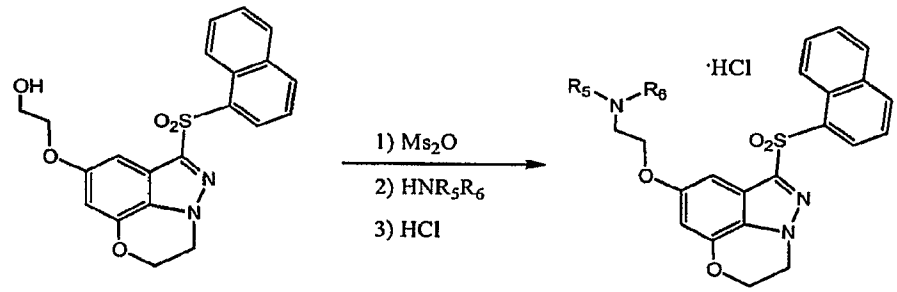


A mixture of 2-[2-(naphthalene-1-sulfonyl)-7,8-dihydro-6-oxa-1, 8a-diaza-acenaphthylen-4-yloxy]ethanol (0.41 g, 1.0 mmoles), methane sulfonic anhydride (Ms_2O)(0.176 g, 1.05 mmoles) and triethylamine (0.143 ml, 1.05 mmole) in CH_2Cl_2 was stirred at 0°C to room temperature for 5 hours and concentrated *in vacuo* to give a residue. A mixture of the residue and methylamine (0.5 ml of 1M solution in THF, 0.5 mmoles) in DMSO was stirred overnight at 70°C, cooled to room temperature, diluted with water and extracted with EtOAc. The extracts were combined, washed sequentially with water and brine, dried over Na_2SO_4 and concentrated under vacuum. The resultant residue was purified by flash chromatography using as eluent 5%CH_3OH/EtOAc. The purified compound was dissolved in methanol, treated with 1M HCl in ether (0.2 ml, 0.2 mmoles) and evaporated to dryness to afford the title

product as a dark pale solid, identified by HNMR and mass spectral analyses, MS: (ES) *m/z* 423.

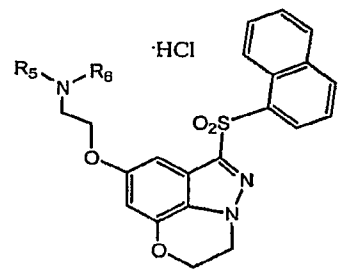
EXAMPLES 13-15

Preparation of 8-Aminoethoxy-6-(1-naphthylsulfonyl)-2,3-dihydro[1,4]oxazino-[2,3,4-hi]indazole Compounds



Using essentially the same procedure described in Example 12 and employing the desired amine, the compounds shown in Table I were obtained and identified by HNMR and mass spectral analyses.

Table I



Ex. No.	R5	R6	mp °C	[M+H]+
13	CH_3	CH_3	--	437.5
14	$CH_2CH_2CH_2CH_2CH_2$		90-92	477
15	$CH_2CH_2CH_2CH_2$		127-129	463

Example 16

Comparative Evaluation of 5-HT_6 Binding Affinity of Test Compounds

The affinity of test compounds for the serotonin 5-HT_6 receptor was evaluated in the following manner. Cultured Hela cells expressing human cloned 5-HT_6 receptors were harvested and centrifuged at low speed (1,000 x g) for 10.0 minutes to remove the culture media. The harvested cells were suspended in half volume of fresh physiological phosphate buffered saline solution and recentrifuged at the same speed. This operation was repeated. The collected cells were then homogenized in ten volumes of 50 mM Tris.HCl (pH 7.4) and 0.5 mM EDTA. The homogenate was centrifuged at 40,000 x g for 30.0 min and the precipitate was collected. The obtained pellet was resuspended in 10 volumes of Tris.HCl buffer and recentrifuged at the same speed. The final pellet was suspended in a small volume of Tris.HCl buffer and the tissue protein content was determined in aliquots of 10-25 µl volumes. Bovine Serum Albumin was used as the standard in the protein determination according to the method described in Lowry et al., J. Biol. Chem., 193: 265 (1951). The volume of the suspended cell membranes was adjusted to give a tissue protein concentration of 1.0 mg/ml of suspension. The prepared membrane suspension (10 times concentrated) was aliquoted in 1.0 ml volumes and stored at -70° C until used in subsequent binding experiments.

Binding experiments were performed in a 96 well microtiter plate format, in a total volume of 200 µl. To each well was added the following mixture: 80.0 µl of incubation buffer made in 50 mM Tris.HCl buffer (pH 7.4) containing 10.0 mM $MgCl_2$ and 0.5 mM EDTA and 20 µl of [^{3}H]-LSD (S.A., 86.0 Ci/mmol, available from Amersham Life Science), 3.0 nM. The dissociation constant, K_D of the [^{3}H]LSD at the human serotonin 5-HT_6 receptor was 2.9 nM, as determined by saturation binding with increasing concentrations of [^{3}H]LSD. The reaction was initiated by the final addition of 100.0 µl of tissue suspension. Nonspecific binding was measured in the presence of 10.0 µM methiothepin. The test compounds were added in 20.0 µl volume.

The reaction was allowed to proceed in the dark for 120 minutes at room temperature, at which time, the bound ligand-receptor complex was filtered off on a 96 well unifilter with a Packard Filtermate® 196 Harvester. The bound complex

caught on the filter disk was allowed to air dry and the radioactivity is measured in a Packard TopCount® equipped with six photomultiplier detectors, after the addition of 40.0µl Microscint®-20 scintillant to each shallow well. The unifilter plate was heat-sealed and counted in a PackardTopCount® with a tritium efficiency of 31.0%.

Specific binding to the 5-HT_6 receptor was defined as the total radioactivity bound less the amount bound in the presence of 10.0µM unlabeled methiothepin. Binding in the presence of varying concentrations of test compound was expressed as a percentage of specific binding in the absence of test compound. The results were plotted as log % bound versus log concentration of test compound. Nonlinear regression analysis of data points with a computer assisted program Prism® yielded both the IC_{50} and the K_i values of test compounds with 95% confidence limits. A linear regression line of data points was plotted, from which the IC_{50} value is determined and the K_i value is determined based upon the following equation:

$$K_i = IC_{50} / (1 + L/K_D)$$

where L was the concentration of the radioactive ligand used and K_D is the dissociation constant of the ligand for the receptor, both expressed in nM.

Using this assay, the following Ki values were determined. The data are shown in Table II, below.

TABLE II

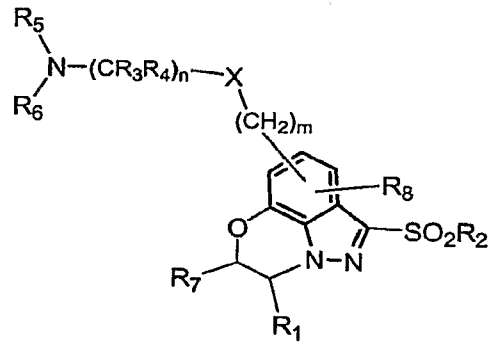
Test Compound (Example No.)	5-HT$_6$ Binding Ki (nM)
6	1.0
12	5.1
13	7.9
14	26
15	14

Comparative Examples	5-HT6 Binding Ki (nM)
Clozapine	6.0
Loxapine	41.4
Bromocriptine	23.0
Methiothepin	8.3
Mianserin	44.2
Olanzepine	19.5

As can be seen by the data shown in Table II, the compounds of the invention demonstrate significant binding to the 5-HT6 receptor.

What is claimed is:

1. A compound of formula I



(I)

wherein

X is a bond, O, S, NR or CONR;

m is 0 or an integer of 1;

R is H or an optionally substituted alkyl group;

R_1 and R_7 are each independently H or an optionally substituted alkyl group;

R_2 is an alkyl, cycloalkyl, aryl or heteroaryl group each group optionally substituted or an optionally substituted 8- to 13-membered bicyclic or tricyclic ring system having a N atom at the bridgehead and optionally containing 1, 2 or 3 additional heteroatoms selected from N, O or S;

R_3 and R_4 are each independently H, or an optionally substituted alkyl group;

n is 0 or an integer of 2, 3, 4, 5, or 6;

R_5 and R_6 are each independently H or an alkyl, alkenyl, alkynyl or cycloalkyl, group each group optionally substituted or R_5 and R_6 may be taken together with the atom to which they are attached to form an optionally substituted 3- to 7-membered ring optionally containing an additional heteroatom selected from NR, O or S;

R_8 is H, halogen, OR_9, or an optionally substituted alkyl group; and

R_9 is H, alkyl or haloalkyl; or

a stereoisomer thereof or a pharmaceutically acceptable salt thereof.

2. A compound according to claim 1 wherein X is a bond or O.

3. The compound according to claim 2 wherein X is a bond and m and n are 0.

4. The compound according to claim 2 wherein X is O; m is 0; and n is 2.

5. A compound according to any one of claims 1 to 4 wherein R_2 is an optionally substituted aryl or heteroaryl group or an optionally subtituted 8- to 13-membered bicyclic or tricyclic ring system having a N atom at the bridgehead and optionally containing 1, 2 or 3 additional heteroatoms selected from N, O or S.

6. A compound according to claim 5 wherein R_2 is an optionally substituted aryl or heteroaryl group.

7. A compound according to claim 6 wherein R_2 is optionally substituted naphthyl.

8. A compound according to any one of claims 1 to 7 wherein R_5 and R_6 are each independently H or alkyl or R_5 and R_6 are taken together with the atom to which they are attached to form an optionally substituted 3- to 7-membered ring optionally containing an additional heteroatom NR.

9. A compound according to claim 8 wherein NR is Nalkyl.

10. A compound according to any one of claims 1 to 9 wherein R_1, R_7 and R_8, and R_3 and R_4 when present, are hydrogen.

11. A compound according to claim 1 which is one of the following:
8-(4-Methylpiperazin-1-yl)-6-(1-naphthylsulfonyl)-2,3-dihydro[1,4]oxazino[2,3,4-hi]- indazole;
N-Methyl-2-{[6-(1-naphthylsulfonyl)-2,3-dihydro[1,4]oxazino[2,3,4-hi]indazol-8-yl]oxy}-ethanamine;

N, N-Dimethyl-2-{[6-(1-naphthylsulfonyl)-2,3-dihydro[1,4]oxazino[2,3,4-hi]indazol-8-yl]oxy}ethanamine;
6-(1-Naphthylsulfonyl)-8-(2-piperidin-1-ylethoxy)-2,3-dihydro[1,4]oxazino[2,3,4-hi]-indazole;
6-(1-Naphthylsulfonyl)-8-(2-pyrrolidin-1-ylethoxy)-2,3-dihydro[1,4]oxazino[2,3,4-hi]-indazole;
2-{[6-(1-Naphthylsulfonyl)-2,3-dihydro[1,4]oxazino[2,3,4-hi]indazol-8-yl]oxy}-ethanamine;
or a stereoisomer thereof; or a pharmaceutically acceptable salt thereof.

12 A method for the treatment of a central nervous system disorder related to or affected by the 5-HT6 receptor in a patient in need thereof which comprises providing to said patient a therapeutically effective amount of a compound of formula I as claimed in any one of claims 1 to 11 or a stereoisomer thereof; or a pharmaceutically acceptable salt thereof.

13. The method according to claim 12 wherein said disorder is a cognitive disorder, a developmental disorder or a neurodegenerative disorder.

14. The method according to claim 12 wherein said disorder is a cognitive disorder.

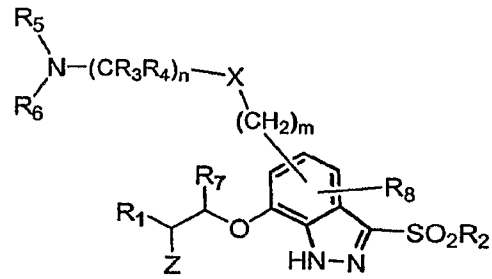
15. The method according to claim 12 wherein said disorder is selected from the group consisting of: a learning disorder; attention deficit disorder; Down's syndrome, Fragile X syndrome or autism.

16. The method according to claim 12 wherein said disorder is stroke or head trauma.

17. A pharmaceutical composition which comprises a pharmaceutically acceptable carrier and a compound of formula I as claimed in any one of claims 1 to 11 or a stereoisomer thereof or a pharmaceutically acceptable salt thereof.

18. A process for the preparation of a compound of formula I as defined in claim 1

which process comprises reacting a compound of formula II



(II)

wherein X, m, n, R_1, R_2, R_3, R_4, R_5, R_6, R_7 and R_8 are as defined for formula I in claim 1and Z is Cl, Br or I, with triethylamine, optionally in the presence of a solvent.

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2007/008710

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D498/06 A61K31/5383 A61P25/00

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)
C07D A61K A61P

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

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, CHEM ABS Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2004/050085 A (HOFFMANN LA ROCHE [CH]) 17 June 2004 (2004-06-17) example 26	1-18
A	WO 01/09142 A (UPJOHN CO [US]; TENBRINK RUTH E [US]) 8 February 2001 (2001-02-08) the whole document	1-18
A	FR 2 769 914 A1 (SYNTHELABO [FR]) 23 April 1999 (1999-04-23) the whole document	1-18

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

☒ See patent family annex.

* Special categories of cited documents :

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

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

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

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

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

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

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

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

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
19 September 2007	27/09/2007

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Diederen, Jeroen

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2007/008710

Box II Observations where certain claims were found unsearchable (Continuation of item 2 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. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 12-16 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
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:

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 III Observations where unity of invention is lacking (Continuation of item 3 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.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2007/008710

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2004050085 A	17-06-2004	AU 2003289903 A1	23-06-2004
		BR 0316962 A	25-10-2005
		CA 2508315 A1	17-06-2004
		CN 1713908 A	28-12-2005
		EP 1569638 A1	07-09-2005
		HR 20050457 A2	31-10-2005
		JP 2006509777 T	23-03-2006
		KR 20050084155 A	26-08-2005
		MX PA05005790 A	18-10-2005
		NZ 539950 A	31-05-2007
		ZA 200504412 A	26-04-2006
WO 0109142 A	08-02-2001	AT 251167 T	15-10-2003
		AU 767282 B2	06-11-2003
		AU 6219700 A	19-02-2001
		BR 0012791 A	18-06-2002
		CA 2376927 A1	08-02-2001
		CN 1361781 A	31-07-2002
		DE 60005685 D1	06-11-2003
		DE 60005685 T2	12-08-2004
		DK 1200447 T3	02-02-2004
		EP 1200447 A1	02-05-2002
		ES 2208371 T3	16-06-2004
		JP 2003506328 T	18-02-2003
		MX PA02000984 A	30-07-2002
		PT 1200447 T	27-02-2004
		TW 222450 B	21-10-2004
		ZA 200110539 A	24-03-2003
FR 2769914 A1	23-04-1999	NONE	