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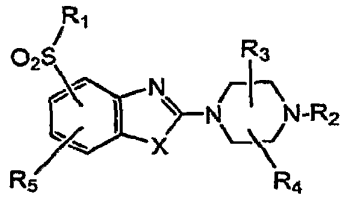
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(54) Title: BENZOXAZOLE AND BENZOTHIAZOLE DERIVATIVES AS 5-HYDROXYTRYTAMINE-6 LIGANDS



(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.

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BENZOXAZOLE AND BENZOTHIAZOLE DERIVATIVES AS 5-HYDROXYTRYPTAMINE-6 LIGANDS

FIELD OF THE INVENTION

This invention relates to benzoxazole and benzothiazole derivatives as 5-hydroxytryptamine-6 ligands, to processes for preparing them, methods of using them and pharmaceutical compositions containing them.

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).

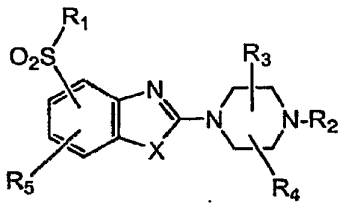
Therefore, it is an object of this invention to provide compounds which are useful as therapeutic agents in the treatment of a variety of central nervous system disorders related to or affected by the 5-HT6 receptor.

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 benzoxazole or benzothiazole compound of formula I



(I)

wherein

X is O or SO_n;

n is 0 or an integer of 1 or 2;

R_1 is an 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_2 is H or an alkyl, cycloalkyl or aryl group each group optionally substituted;

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

R_5 is H, halogen, NR_6R_7 or an alkyl, alkoxy, alkenyl, alkynyl or cycloalkyl, group each group optionally substituted;

R_6 is an alkyl or cycloalkyl group each group optionally substituted; and

R_7 is H or an alkyl or cycloalkyl group each group optionally substituted; or

a stereoisomer thereof or a pharmaceutically acceptable salt thereof.

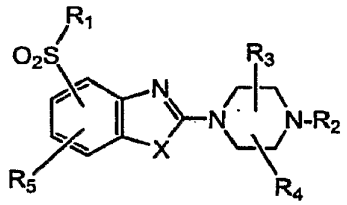
The present invention also provides methods and compositions useful for the therapeutic treatment of central nervous system disorders related to or affected by the 5-HT6 receptor.

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 benzoxazole and benzothiazole 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 benzoxazole or benzothiazole compound of formula I



(I)

wherein

X is O or SO_n;

n is 0 or an integer of 1 or 2;

R_1 is an 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_2 is H or an alkyl, cycloalkyl or aryl group each group optionally substituted;

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

R_5 is H, halogen, NR_6R_7 or an alkyl, alkoxy, alkenyl, alkynyl or cycloalkyl, group each group optionally substituted;

R_6 is an alkyl or cycloalkyl group each group optionally substituted; and

R_7 is H or an alkyl or cycloalkyl group each group optionally substituted; or

a stereoisomer thereof or a pharmaceutically acceptable salt thereof.

Preferred compounds of the invention are those compounds of formula I wherein X is O. Another group of preferred compounds is those formula I compounds wherein R_2 is H or an optionally substituted alkyl group. Also preferred

are those formula I compounds wherein R_1 is an optionally substituted phenyl or naphthyl group. Preferred substituents include halo, alkyl, haloalkyl and alkoxy.

More preferred compounds of the invention are those compounds of formula I wherein X is O and the SO_2-R_1 moiety is attached to the benzoxazole ring in the 4- or 7-position. Another group of more preferred compounds is those compounds of formula I wherein X is O and R_2 is H or C_1-C_4alkyl. A further group of more preferred compounds are those compounds of formula I wherein X is O; R_1 is an optionally substituted phenyl or naphthyl group; and R_2 is H or C_1-C_4alkyl.

Among the preferred compounds of the invention are:

4-(1-naphthylsulfonyl)-2-piperazin-1-yl-1,3-benzoxazole;
7-(1-naphthylsulfonyl)-2-piperazin-1-yl-1,3-benzoxazole;
5-(1-naphthylsulfonyl)-2-piperazin-1-yl-1,3-benzoxazole;
6-(1-naphthylsulfonyl)-2-piperazin-1-yl-1,3-benzoxazole;
6-(1-naphthylsulfonyl)-2-piperazin-1-ylbenzothiazole
4-(1-naphthylsulfonyl)-2-piperazin-1-ylbenzothiazole ;
7-(1-naphthylsulfonyl)-2-piperazin-1-ylbenzothiazole
4-(2,5-dichlorophenylsulfonyl)-2-piperazin-1-yl-1,3-benzoxazole;
7-(2,5-dichlorophenylsulfonyl)-2-piperazin-1-yl-1,3-benzoxazole;
5-(2,5-dichlorophenylsulfonyl)-2-piperazin-1-yl-1,3-benzoxazole;
2-(4-isopropylpiperazin-1-yl)-4-(1-naphthylsulfonyl)-1,3-benzoxazole;
2-(4-methylpiperazin-1-yl)-4-(1-naphthylsulfonyl)-1,3-benzoxazole;
2-(4-ethylpiperazin-1-yl)-4-(1-naphthylsulfonyl)-1,3-benzoxazole;
2-(4-isopropylpiperazin-1-yl)-7-(1-naphthylsulfonyl)-1,3-benzoxazole;
2-(4-methylpiperazin-1-yl)-7-(1-naphthylsulfonyl)-1,3-benzoxazole;
2-(4-ethylpiperazin-1-yl)-7-(1-naphthylsulfonyl)-1,3-benzoxazole;
2-(4-isopropylpiperazin-1-yl)-5-(1-naphthylsulfonyl)-1,3-benzoxazole;
2-(4-methylpiperazin-1-yl)-5-(1-naphthylsulfonyl)-1,3-benzoxazole;
2-(4-ethylpiperazin-1-yl)-5-(1-naphthylsulfonyl)-1,3-benzoxazole;
4-(phenylsulfonyl)-2-piperazin-1-yl-1,3-benzoxazole;
7-(phenylsulfonyl)-2-piperazin-1-yl-1,3-benzoxazole;
5-(phenylsulfonyl)-2-piperazin-1-yl-1,3-benzoxazole;
4-(3-fluorophenylsulfonyl)-2-piperazin-1-yl-1,3-benzoxazole;
7-(3-fluorophenylsulfonyl)-2-piperazin-1-yl-1,3-benzoxazole;

4-(4-fluorophenylsulfonyl)-2-piperazin-1-yl-1,3-benzoxazole;
7-(4-fluorophenylsulfonyl)-2-piperazin-1-yl-1,3-benzoxazole;
4-(3-chlorophenylsulfonyl)-2-piperazin-1-yl-1,3-benzoxazole;
7-(3-chlorophenylsulfonyl)-2-piperazin-1-yl-1,3-benzoxazole;
4-(4-isopropylphenylsulfonyl)-2-piperazin-1-yl-1,3-benzoxazole;
7-(4-isopropylphenylsulfonyl)-2-piperazin-1-yl-1,3-benzoxazole;
2-(piperazin-1-yl)-4-{3-(trifluoromethyl)phenylsulfonyl}-1,3-benzoxazole;
2-(piperazin-1-yl)-7 -{3-(trifluoromethyl)phenylsulfonyl}-1,3-benzoxazole;
4-(3-methoxyphenylsulfonyl)-2-piperazin-1-yl-1,3-benzoxazole;
7-(3-methoxyphenylsulfonyl)-2-piperazin-1-yl-1,3-benzoxazole;
4-(1-naphthylsulfonyl)-2-(4-propyl-piperazin-1-yl)-1,3-benzoxazole
2-(4-*n*-butylpiperazin-1-yl)-4-(1-naphthylsulfonyl)-1,3-benzoxazole;
2-(4-*t*-butylpiperazin-1-yl)-4-(1-naphthylsulfonyl)-1,3-benzoxazole;
2-(4-cyclobutylpiperazin-1-yl)-4-(1-naphthylsulfonyl)-1,3-benzoxazole;
2-(4-cyclobutylpiperazin-1-yl)-7-(1-naphthylsulfonyl)-1,3-benzoxazole;
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 or cycloalkyl groups, preferably halogen atoms or lower alkyl, or lowerhaloalkyl groups. Unless otherwise specified, typically, 1-3 substituents may be present. In certain embodiments, substituents may be for example halogen, CN, OH, phenyl, carbamoyl, carbonyl, alkoxy or aryloxy.

The term "halo" or "halogen", as used herein, whether used alone or as part of another group, designates fluorine, chlorine, bromine, and iodine.

As used herein, the term "alkyl", includes both (C_1-C_{10}) straight chain and (C_3-C_{12}) branched-chain monovalent saturated hydrocarbon moiety. An example of

alkyl is lower alkyl, i.e., C_1-C_6 straight-chain alkyl or C_3-C_6 branched-chain alkyl, for example C_1-C_4 straight-chain alkyl or C_3-C_4 branched-chain alkyl. Examples of saturated hydrocarbon alkyl moieties include, but are not limited to, chemical groups 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, halogen, CN, OH, phenyl, carbamoyl, carbonyl, alkoxy or aryloxy.

The term "alkoxy" as used herein, whether used alone or as part of another group, refers to the group R-O- where R is an alkyl group as defined herein. 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.

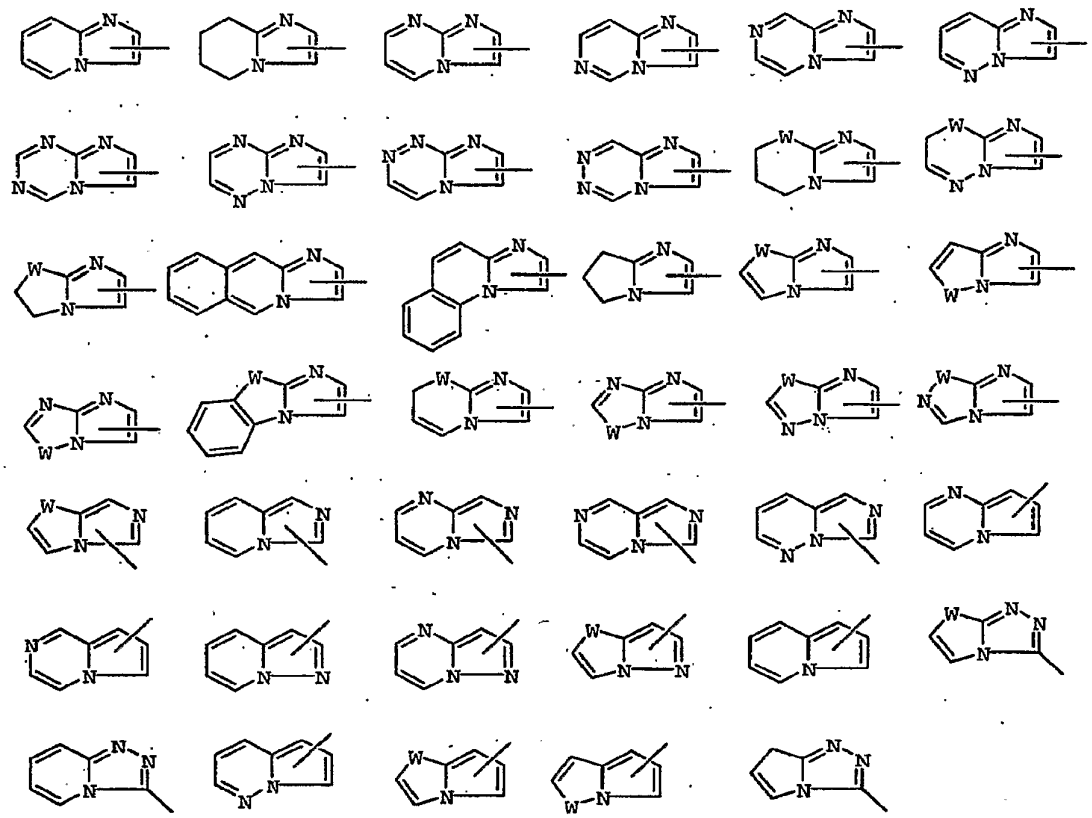
The term "alkenyl", as used herein, refers to either a (C_2-C_8) straight chain or (C_3-C_{10}) branched-chain monovalent hydrocarbon moiety containing at least one double bond. Such hydrocarbon alkenyl moieties may be mono or polyunsaturated, and may exist in the E or Z configurations. The compounds 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, 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 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 "aryl", as used herein, refers to an aromatic carbocyclic moiety of up to 20 carbon atoms, 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. A preferred aryl group is phenyl. Another preferred aryl group is naphthyl. The term "heteroaryl" as used herein designates an aromatic heterocyclic ring system, which may be a single ring (monocyclic) or multiple rings (bicyclic, up to three rings) fused together or linked covalently and having for example 5 to 20 ring members. 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 quarternized. Preferred heteroaryl groups are mono- or bi- cyclic aromatic rings having 5 to 10 ring members and from 1 to 3 heteroatoms the same or different selected from N, O and S. 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 hereinbelow:



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.

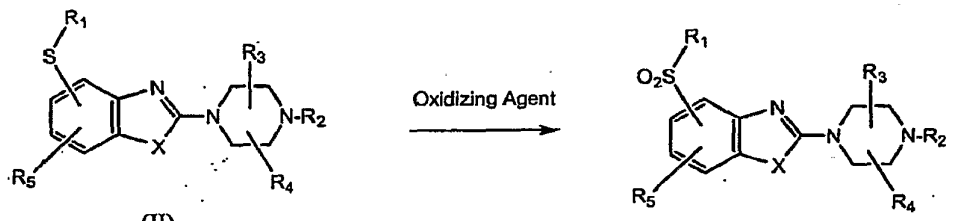
The compounds of the present invention may be converted to salts, in particular pharmaceutically acceptable salts using art recognized procedures. Suitable salts with bases are, for example, metal salts, such as alkali metal or alkaline earth metal salts, for example sodium, potassium or magnesium salts, 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. 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, napthalenesulfonic, 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 wherein R_2 is other than H (Ia) which comprises reacting a compound of formula II with at least two molar

equivalents of an oxidizing agent, optionally in the presence of a solvent, to give the compound of formula Ia. The process is shown hereinbelow in flow diagram I wherein R_2 is other than H.

FLOW DIAGRAM I



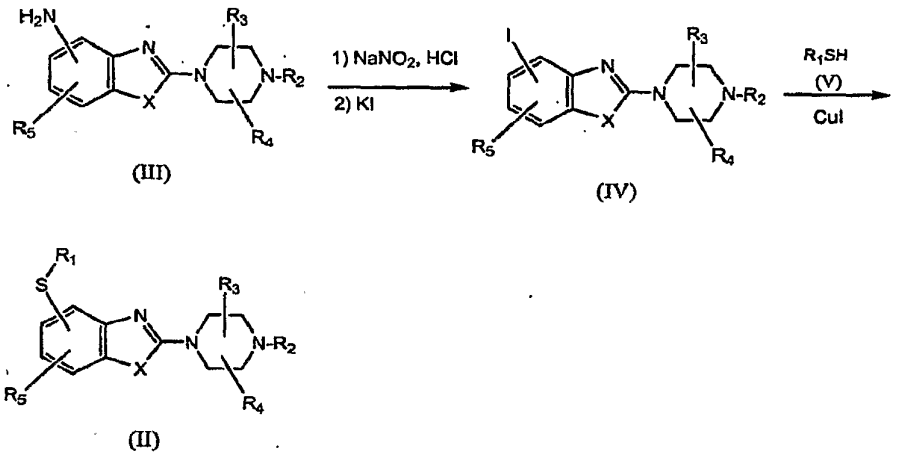
(II) (Ia)

Oxidizing agents suitable for use in the process of the invention include potassium peroxymonosulfate, peracetic acid, *m*-chloroperbenzoic acid, chromium trioxide, t-butylperoxide, preferably *m*-chloroperbenzoic acid, or the like, or a mixture thereof.

Solvents suitable for use in the process of the invention include solvents such as alkanols, i.e., methanol, ethanol, propanol or the like, water, acetone, chloroform, methylene chloride or the like, or a mixture thereof, preferably chloroform or methylene chloride.

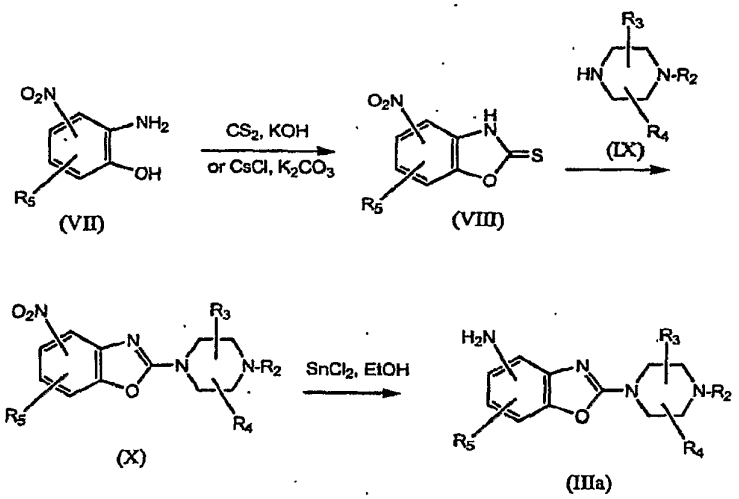
Compounds of formula II may be prepared using conventional synthetic methods and, if required, standard isolation or separation techniques. For example, compounds of formula II may be prepared by sequentially diazotizing an aminobenzoxazole or -benzothiazole of formula III with $NaNO_2$ and reacting the diazotized product with potassium iodide to give the iodo compound of formula IV; coupling the formula IV compound with a thiol of formula V in the presence of a coupling agent, such as CuI, to give the desired compound of formula II. The reaction is shown in flow diagram II.

FLOW DIAGRAM II



Compounds of formula III wherein X is O (IIIa) may be prepared by reacting a 2-aminophenol of formula VII with CS_2 in the presence of a base, such as KOH, or with $CsCl_2$ in the presence of K_2CO_3 to give the mercaptobenzoxazole or -benzothiazole compound of formula VIII; reacting the formula VIII compound with a piperazine of formula IX to give the compound of formula X; and reducing the formula X compound to give the desired compound of formula IIIa. The reaction is shown in flow diagram III.

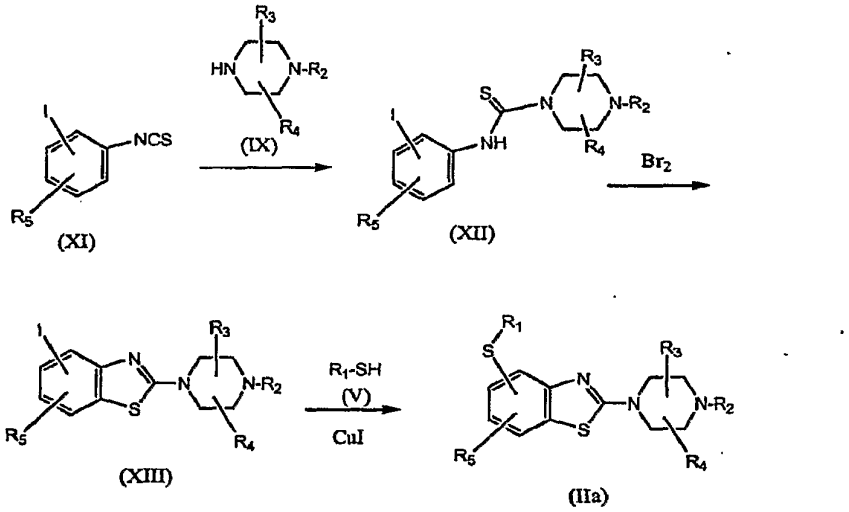
FLOW DIAGRAM III



Compounds of formula II wherein X is S (IIa) may be prepared by reacting an isothiocyanate of formula XI with a piperazine of formula IX to give the thiourea of

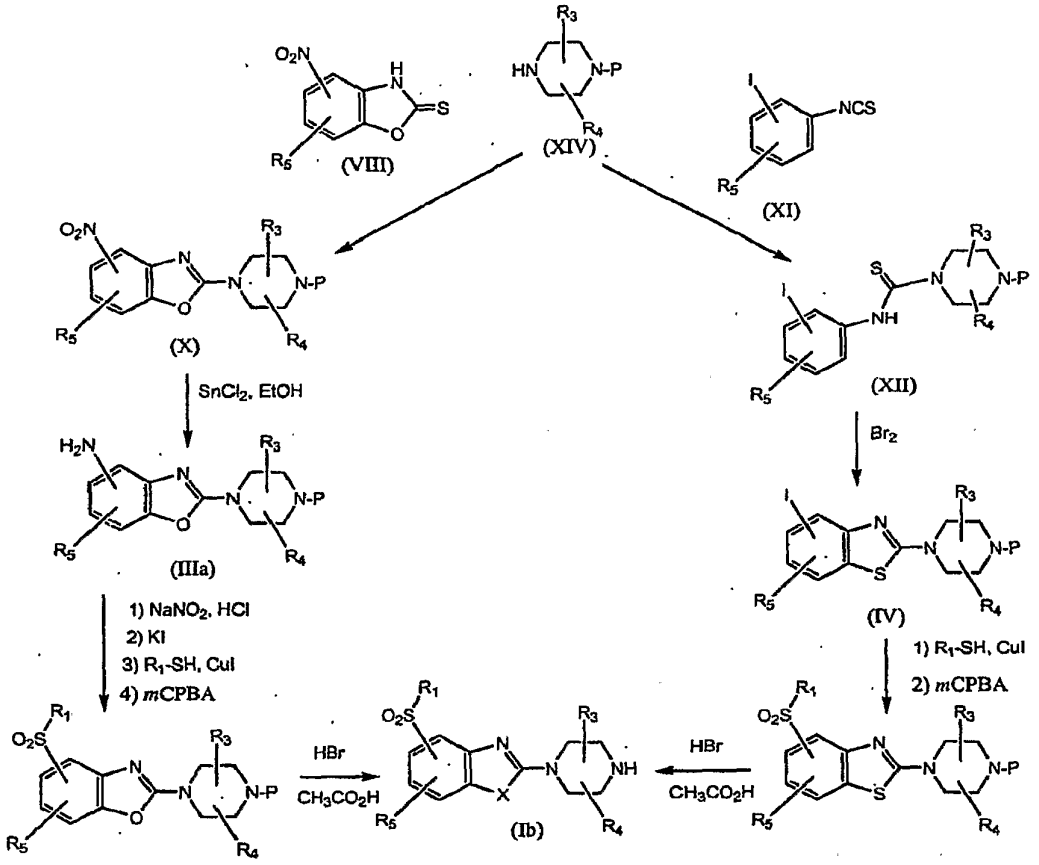
formula XII; reacting the formula XII thiourea with bromine to give the iodobenzothiazole compound of formula XIII; and coupling said compound XIII with a thiol of formula V in the presence of a coupling agent, such as CuI, to give the desired compound of formula IIa. The reaction is shown in flow diagram IV.

FLOW DIAGRAM IV



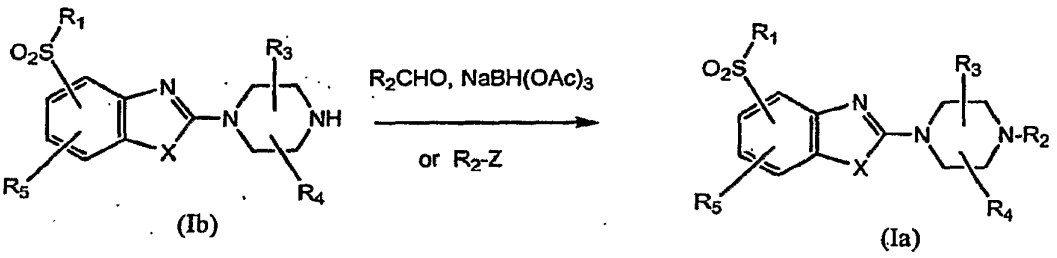
Compounds of formula I wherein R_2 is H (Ib) may be prepared by employing a protected piperazine compound of formula XIV in the reactions shown hereinabove in flow diagrams III or IV to give the protected formula II compound; oxidizing said formula II compound, as shown in flow diagram I; and deprotecting the oxidized compound using standard deprotection procedures, such as HBr and acetic acid, to give the desired compound of formula Ia. The reaction is shown in flow diagram V wherein P represents a protecting group such as benzyloxycarbonyl, *t*-butoxy-carbonyl, benzyl, acetyl, or any conventional group known to protect a basic nitrogen in standard synthetic procedures (i. e. T. W. Greene and P. G. M. Wuts, Protective Groups in Organic Synthesis, 3rd ed, John Wiley & Sons, publisher).

FLOW DIAGRAM V



The compound of formula Ib may be alkylated using conventional alkylation techniques, such as reductive amination or simple alkylation with an alkylating agent, to give compounds of formula I wherein R_2 is other than H (Ia). The reaction is shown in flow diagram VI wherein Z represents Cl, Br or I and Ac represents acetyl.

FLOW DIAGRAM VI



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.

The present invention also provides the use of a compound of formula I as described herein in the manufacture of a medicament for treating a central nervous system disorder related to or affected by the 5-HT6 receptor 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.

The inventive use includes: the use of a compound of formula I as described herein in the manufacture of a medicament for treating schizophrenia; 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 developmental disorder such as schizophrenia; Down's syndrome, Fragile X syndrome, autism or the like; a behavioral disorder, e.g., anxiety, depression, or obsessive compulsive disorder; a motion or motor disorder such as Parkinson's disease or epilepsy; 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.

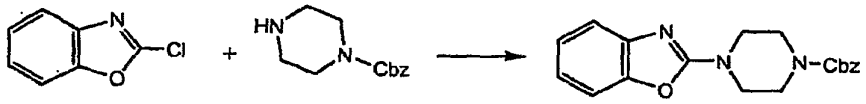
In one embodiment, the present invention provides the use of a compound of formula I as described herein in the manufacture of a medicament for treating attention deficit disorders (ADD, also known as Attention Deficit Hyperactivity Disorder or ADHD) in both children and adults.

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 and DMSO designate tetrahydrofuran, ethyl acetate and dimethylsulfoxide, respectively. All chromatography is performed using SiO_2 as support. Unless otherwise noted, all parts are parts by weight. In the chemical drawings, the term Cbz represents benzyloxycarbonyl.

EXAMPLE 1

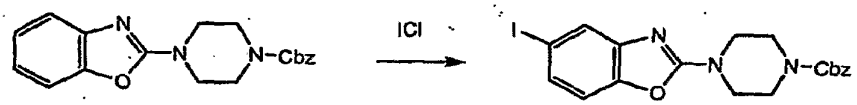
Preparation of 4-Benzoxazol-2-yl-piperazine-1-carboxylic acid benzyl ester



A mixture of 2-chlorobenzoxazole (1.00 g, 6.51 mmol), benzyl 1-piperazinecarboxylate (1.43 g, 6.51 mmol), and K_2CO_3 (1.80 g, 13.0 mmol) in DMF (13 mL) was stirred at 100 °C overnight, cooled, diluted with water, and extracted with EtOAc. The extracts were combined, washed with water and brine, dried over Na_2SO_4 and concentrated *in vacuo* to provide the title compound (1.70 g, 77%), characterized by NMR and mass spectral analyses.

EXAMPLE 2

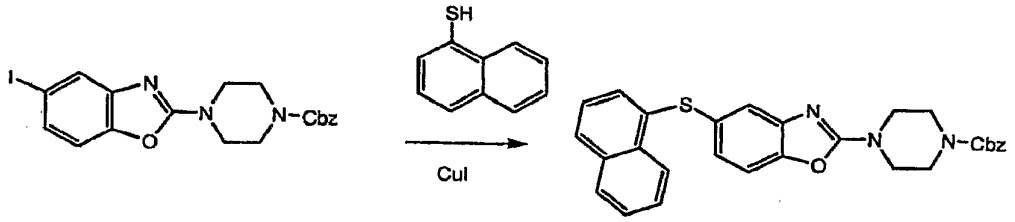
Preparation of 4-(5-Iodobenzoxazol-2-yl)piperazine-1-carboxylic acid benzyl ester



A mixture of 4-benzoxazol-2-yl-piperazine-1-carboxylic acid benzyl ester (0.50 g, 1.48 mmol) and iodine monochloride (0.265 g, 1.63 mmol) in acetic acid (4.94 mL) was stirred at 60 °C overnight, cooled, and concentrated *in vacuo* to provide the title compound, which was used without further purification, in Example 3.

EXAMPLE 3

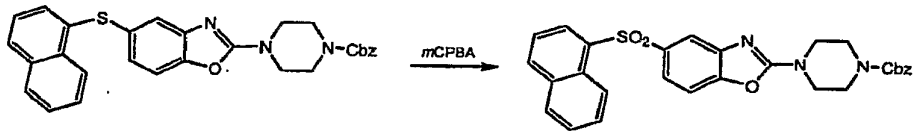
Preparation of 4-[5-(1-naphthylsulfanyl)benzoxazol-2-yl]piperazine-1-carboxylic acid benzyl ester



A mixture of 4-(5-iodobenzoxazol-2-yl)piperazine-1-carboxylic acid benzyl ester, prepared in Example 2 (1.48 mmol theory), 1-napthalenethiol (0.237 g, 1.48 mmol), CuI (0.042 g, 0.22 mmol), and K_2CO_3 (0.409 g, 2.96 mmol) in isopropanol was heated at 90 °C overnight, diluted with 20% MeOH in CH_2Cl_2, and filtered through a pad of silica gel. The filtrate was concentrated to dryness. The resultant residue was purified by chromatography with 5% MeOH in CH_2Cl_2 to provide the title compound (230 mg, 31% overall yield from 4-benzoxazol-2-yl-piperazine-1-carboxylic acid benzyl ester), characterized by NMR and mass spectral analyses.

EXAMPLE 4

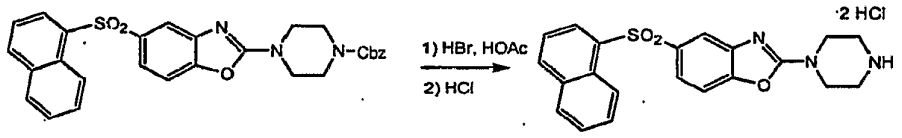
Preparation of 4-[5-(1-Naphthylsulfonyl)benzoxazol-2-yl]piperazine-1-carboxylic acid benzyl ester



A mixture of 4-[5-(1-naphthylsulfanyl)benzoxazol-2-yl]piperazine-1-carboxylic acid benzyl ester (0.110 g, 0.22 mmol) and meta-chloroperbenzoic acid (*m*CPBA) (0.096 g, 0.55 mmol) in $CHCl_3$ was stirred at room temperature for 3 h and concentrated *in vacuo*. The resultant residue was purified by chromatography with CH_2Cl_2 to provide the title compound (120 mg, 100%), characterized by NMR and mass spectral analyses.

EXAMPLE 5

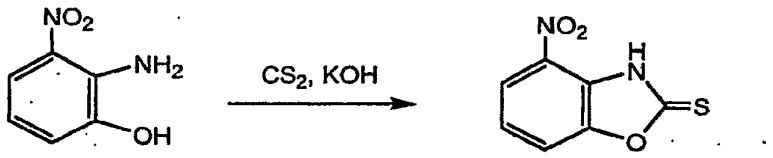
Preparation of 5-(1-Naphthylsulfonyl)-2-piperazin-1-ylbenzoxazole Dihydrochloride



A solution of 4-[5-(1-naphthylsulfonyl)benzoxazol-2-yl]piperazine-1-carboxylic acid benzyl ester (0.110 g, 0.19 mmol) in 33 wt.% of HBr in HOAc (1.3 mL) was stirred at rt for 40 min and diluted with Et_2O. The precipitate was filtered, washed with Et_2O, and purified with Gilson reverse phase HPLC. The purified material was treated with a solution of HCl in ether, stirred at room temperature for 5 minutes and concentrated to dryness to give the title compound (60 mg, 68%), characterized by NMR and mass spectral analyses. MS (ES^+) *m/e* 394 (MH^+).

EXAMPLE 6

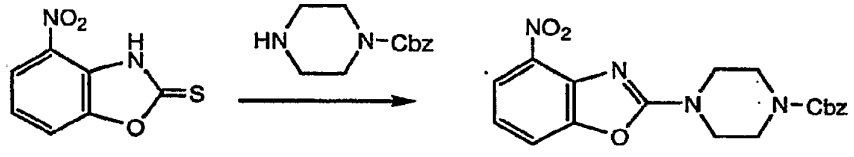
Preparation of 4-Nitro-3H-benzoxazole-2-thione



A solution of KOH (3.31 g, 59.0 mmol) in EtOH and water was treated with carbon disulfide (10.4 g, 136.3 mmol) followed by 2-amino-3-nitrophenol (7.00 g, 45.4 mmol). The mixture was heated at reflux temperature overnight, cooled, concentrated, acidified with 1M HCl and filtered. The filtercake was washed with water and dried *in vacuo* to provide the title compound (7.0 g, 79%), characterized by NMR and mass spectral analyses.

EXAMPLE 7

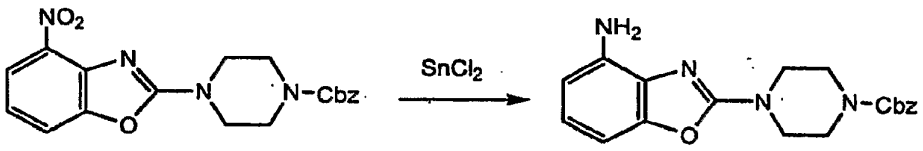
Preparation of 4-(4-Nitrobenzoxazol-2-yl)piperazine-1-carboxylic acid benzyl ester



A mixture of 4-nitro-3H-benzoxazole-2-thione (7.00 g, 35.7 mmol) and benzyl 1-piperazinecarboxylate (15.72 g, 71.36 mmol) in xylenes was heated at reflux temperature overnight, cooled and concentrated *in vacuo* to provide the title compound which was used, without further purification, in Example 8.

EXAMPLE 8

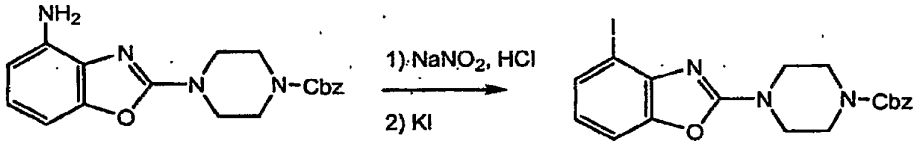
Preparation of 4-(4-Aminobenzoxazol-2-yl)piperazine-1-carboxylic acid benzyl ester



A mixture of 4-(4-nitrobenzoxazol-2-yl)piperazine-1-carboxylic acid benzyl ester, from Example 7 (35.7 mmol theory), $SnCl_2$ (40.25 g, 178.4 mmol), and concentrated HCl solution (4.46 mL) in EtOH was heated at 70 °C overnight, cooled, diluted with 20% MeOH in CH_2Cl_2, neutralized with NaOH to pH 8-10 and extracted with $CHCl_3$. The extracts were combined, dried over Na_2SO_4, concentrated, and purified by chromatography with 1-5% MeOH in CH_2Cl_2 to provide the title compound (3.0 g, 24% overall yield from 4-nitro-3H-benzoxazole-2-thione), characterized by NMR and mass spectral analyses.

EXAMPLE 9

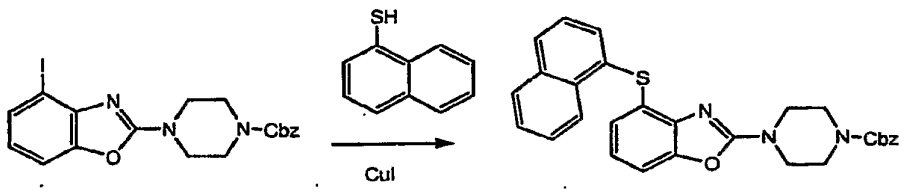
Preparation of 4-(4-Iodobenzoxazol-2-yl)piperazine-1-carboxylic acid benzyl ester



A mixture of $NaNO_2$ (0.881 g, 12.8 mmol) in 1N HCl (31 mL) and MeOH (62 mL) at 0 °C was treated dropwise with a solution of 4-(4-aminobenzoxazol-2-yl)piperazine-1-carboxylic acid benzyl ester (3.00 g, 8.51 mmol) in MeOH, stirred for 30 min, treated slowly with a solution of KI (3.53 g, 21.3 mmol) in water, stirred at room temperature for an additional 30 min, concentrated and extracted with EtOAc. The extracts were combined, dried over Na_2SO_4, concentrated and purified by chromatoraphy with 1-3% MeOH in CH_2Cl_2 to provide the title compound (2.05 g, 52%), characterized by NMR and mass spectral analyses.

EXAMPLE 10

Preparation of 4-[4-(1-Naphthylsulfanyl)benzoxazol-2-yl]piperazine-1-carboxylic acid benzyl ester



A mixture of 4-(4-iodobenzoxazol-2-yl)piperazine-1-carboxylic acid benzyl ester (0.80 g, 1.73 mmol), 1-naphthylthiol (0.276 g, 1.73 mmol), CuI (0.066 g, 0.35 mmol), ethylene glycol (0.214 g, 3.45 mmol), and K_2CO_3 (0.477 g, 3.45 mmol) in

isopropanol was heated at 90 °C overnight, cooled, diluted with 20% MeOH in CH_2Cl_2 and filtered through a pad of silica gel. The filtrated was concentrated and purified by chromatography with 1-3% MeOH in CH_2Cl_2 to provide the title compound (0.856 g, 93%), characterized by NMR and mass spectral analyses.

EXAMPLE 11

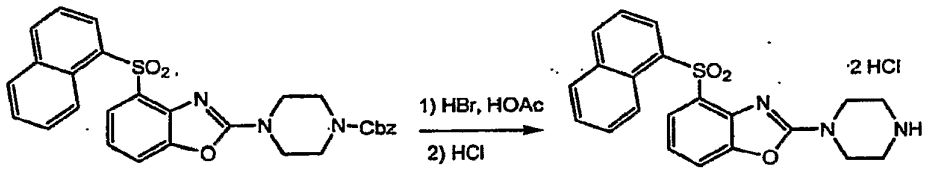
Preparation of 4-[4-(1-Naphthylsulfonyl)benzoxazol-2-yl]piperazine-1-carboxylic acid benzyl ester



A mixture of 4-[4-(1-naphthylsulfanyl)benzoxazol-2-yl]piperazine-1-carboxylic acid benzyl ester (0.297 g, 0.60 mmol) and meta-chloroperbenzoic acid (mCPBA) (0.311 g, 1.80 mmol) in $CHCl_3$ was stirred at room temperature for 30 min and concentrated *in vacuo* to provide the title compound which was used, without further purification, in Example 12.

EXAMPLE 12

Preparation of 4-(1-Naphthylsulfonyl)-2-piperazin-1-ylbenzoxazole Dihydrochloride

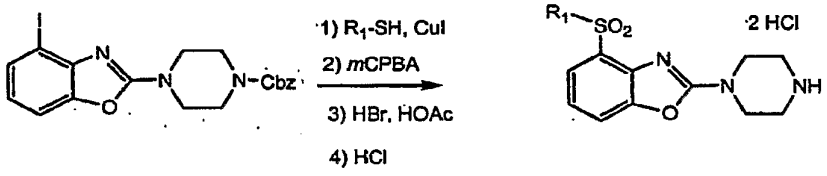


A solution of 4-[4-(1-naphthylsulfonyl)benzoxazol-2-yl]piperazine-1-carboxylic acid benzyl ester obtained in Example 11 (0.60 mmol theory) in 33 wt.% of HBr in

HOAc (1.3 mL) was stirred at room temperature for 40 min, diluted with Et_2O and filtered. The filtercake was washed with Et_2O and purified by Gilson reverse phase HPLC. The purified material was treated with a solution of HCl in ether, stirred at room temperature for 5 minutes and concentrated to dryness to afford the title compound (58 mg, 21% overall yield from 4-[4-(1-naphthylsulfanyl)benzoxazol-2-yl]piperazine-1-carboxylic acid benzyl ester), characterized by NMR and mass spectral analyses. MS (ES^+) *m/e* 394 (MH^+).

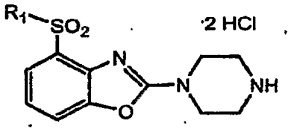
EXAMPLES 13-21

Preparation of 4-(Arylsulfonyl)-2-piperazin-1-ylbenzoxazole Dihydrochloride Compounds



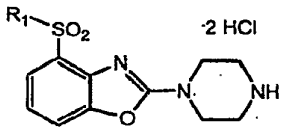
Using essentially the same procedures described in Examples 10, 11 and 12 and employing the desired thiol, R_1SH, in step 1, the compounds shown in Table I were obtained and identified by HNMR and mass spectral analyses.

Table I



Ex. No.	R1	$[M+H]^+$ *m/e*
13	phenyl	344
14	3-fluorophenyl	362
15	4-fluorophenyl	362
16	3-chlorophenyl	378

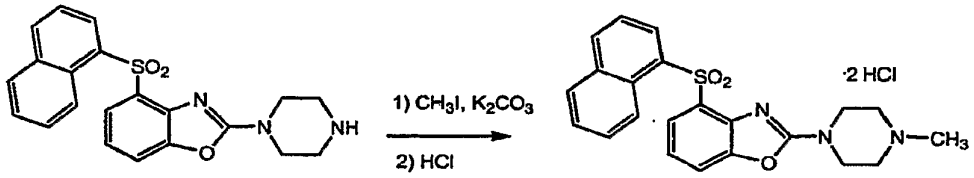
Table I, cont.



Ex. No.	R1	[M+H]$^+$ *m/e*
17	4-isopropylphenyl	386
18	3-(trifluoromethyl)phenyl	412
19	4-(trifluoromethyl)phenyl	412
20	3-methoxyphenyl	374
21	2,5-dichlorophenyl	412

EXAMPLE 22

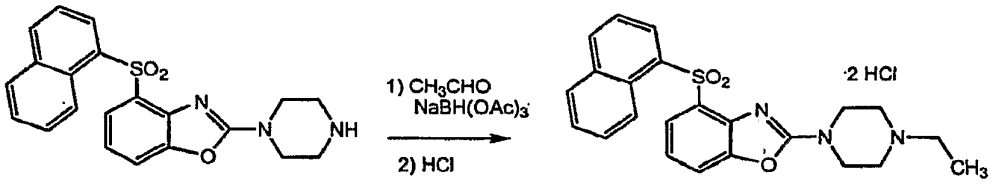
Preparation of 2-(4-Methylpiperazin-1-yl)-4-(1-naphthylsulfonyl)benzoxazole Dihydrochloride



A mixture of 4-(1-naphthylsulfonyl)-2-piperazin-1-ylbenzoxazole (0.050 g, 0.127 mmol), methyl iodide (0.018 g, 0.127 mmol) and K_2CO_3 (0.017 g, 0.127 mmol) in DMF was stirred at room temperature overnight, concentrated and purified by Gilson reverse phase HPLC. The purified material was treated with a solution of HCl in ether, stirred at room temperature for 5 minutes and concentrated to dryness to afford the title compound (20 mg, 33%), characterized by NMR and mass spectral analyses. MS (ES$^+$) *m/e* 408 (MH$^+$).

EXAMPLE 23

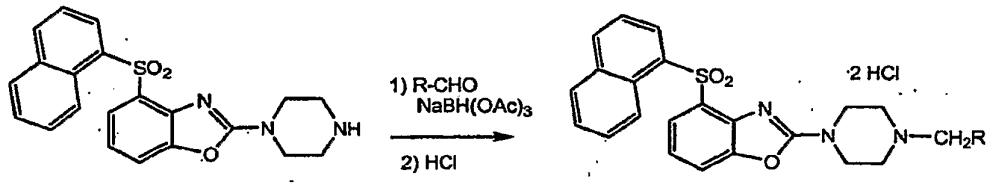
Preparation of 2-(4-Ethylpiperazin-1-yl)-4-(1-naphthylsulfonyl)benzoxazole Dihydrochloride



A mixture of 4-(1-naphthylsulfonyl)-2-piperazin-1-ylbenzoxazole (0.070 g, 0.18 mmol), acetaldehyde (0.016 g, 0.36 mmol), $NaBH(OAc)_3$ (0.075 g, 0.36 mmol), and acetic acid (0.021 g, 0.36 mmol) in 1,2-dichloroethane was stirred at room temperature overnight, diluted with 20% MeOH in CH_2Cl_2 (with 0.5% NH_4OH) and filtered through a pad of silica gel. The filtrate was concentrated and purified by Gilson reverse phase HPLC. The purified material was treated with a solution of HCl in ether, stirred at room temperature for 5 minutes and concentrated to dryness to five the title compound (17 mg, 19%), characterized by NMR and mass spectral analyses. MS (ES^+) *m/e* 422 (MH^+).

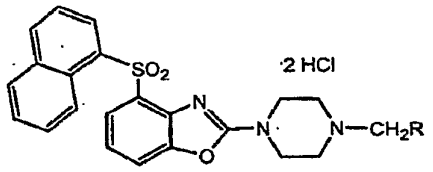
EXAMPLES 24-31

Preparation of 2-(4-Alkylpiperazin-1-yl)-4-(1-naphthylsulfonyl)benzoxazole Dihydrochloride Compounds



Using essentially the same procedure described in Example 23 and employing the appropriate aldehyde, R-CHO, or cyloalkyl ketone, the compounds shown in Table II were obtained and identified by NMR and mass spectral analyses.

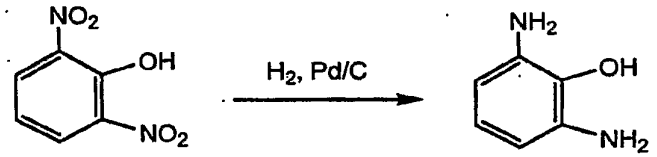
Table II



Ex. No.	CH2R	[M+H]+ m/e
24	propyl	436
25	isopropyl	436
26	butyl	450
27	isobutyl	450
28	phenylpropyl	512
29	cyclobutyl	448
30	cyclopentyl	462
31	cyclohexyl	476

EXAMPLE 32

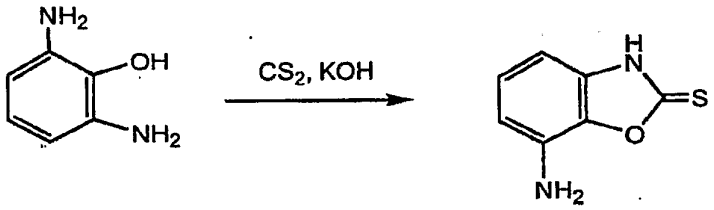
Preparation of 2,6-Diaminophenol



A mixture of 2,6-dinitrophenol (2.50 g, 13.6 mmol) and 10% Pd/C (300 mg) in MeOH was shaken under H_2 (40 psi) overnight and filtered. The filtrate was concentrated *in vacuo* to provide the title compound (1.50 g, 89%), characterized by NMR and mass spectral analyses.

EXAMPLE 33

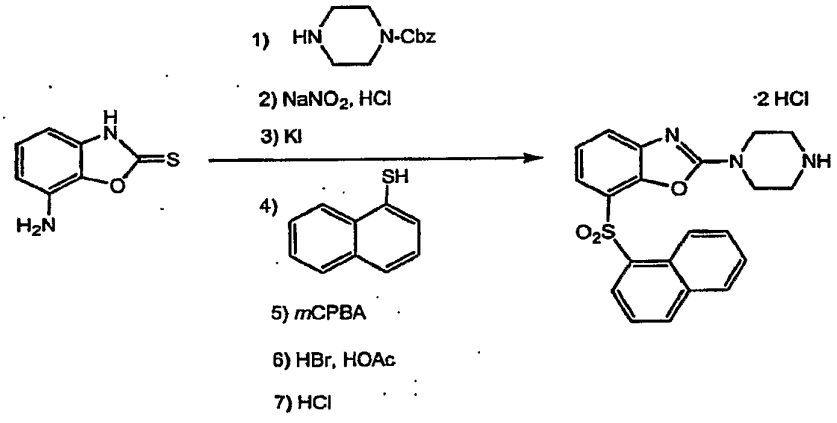
Preparation of 7-Amino-3H-benzoxazole-2-thione



A solution of KOH (0.875 g, 15.6 mmol) in EtOH (14.3 mL) and water (2.6 mL) was treated with carbon disulfide (0.828 g, 10.9 mmol), followed by of 2, 6-diaminophenol (1.50 g, 12.1 mmol). The mixture was heated at reflux temperature for 3 h, concentrated, neutralized with 1M HCl to pH 7, and extracted with EtOAc. The extracts were combined, dried over Na_2SO_4 and concentrated *in vacuo* to afford the title compound (0.90 g, 45%), characterized by NMR and mass spectral analyses.

EXAMPLE 34

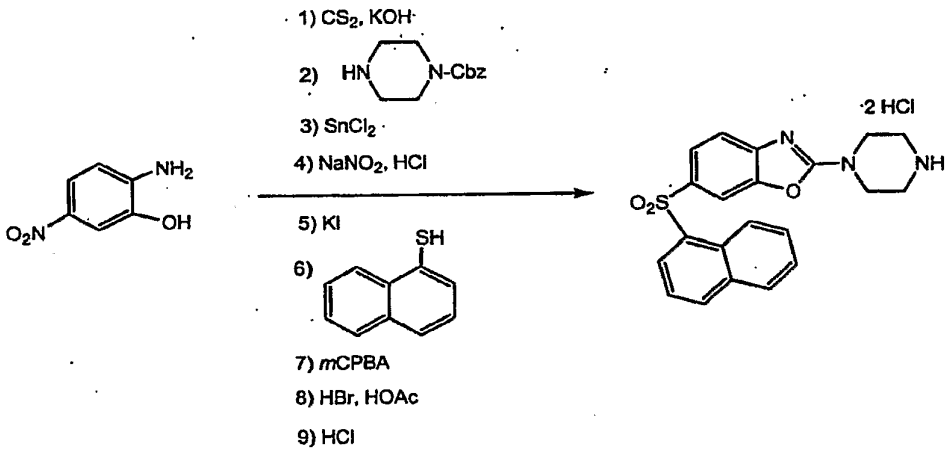
Preparation of 7-(1-naphthylsulfonyl)-2-piperazin-1-ylbenzoxazole Dihydrochloride



Using essentially the same procedures described in Examples 7, 9, 10, 11 and 12 and employing 7-amino-3H-benzoxazole-2-thione as starting material, the title compound was obtained and identified by HNMR and mass spectral analyses. MS (ES^+) *m/e* 394 (MH^+)

EXAMPLE 35

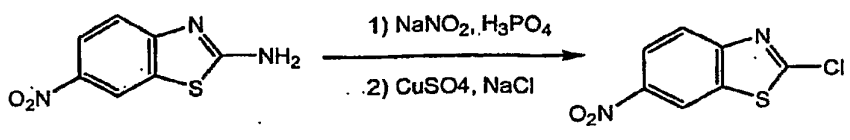
Preparation of 6-(1-naphthylsulfonyl)-2-piperazin-1-ylbenzoxazole Dihydrochloride



Using essentially the same procedures described in Examples 6, 7, 8, 9, 10, 11 and 12 and employing 2-amino-5-nitrophenol as starting material, the title compound was obtained and identified by HNMR and mass spectral analyses. MS (ES^+) *m/e* 394 (MH^+)

EXAMPLE 36

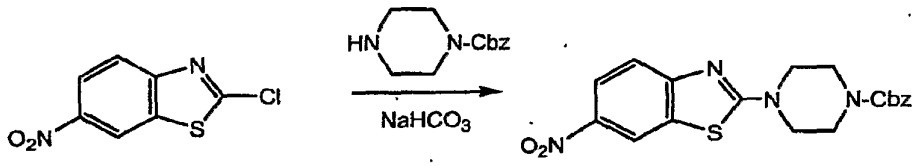
Preparation of 2-Chloro-6-nitrobenzothiazole



A solution of $NaNO_2$ (3.18 g, 46.1 mmol) in water was slowly added to a solution of 2-amino-6-nitro-benzothiazole (3.00 g, 15.4 mmol) in 85% H_3PO_4 over a period of 30 min at 0 °C. The reaction solution was stirred for 1 hour and was gradually added to a solution of $CuSO_4$ (7.61 g, 76.8 mmol) and NaCl (13.5 g, 230 mmol) in water over a 30 min period at 0 °C. The resultant suspension was allowed to warm to room temperature, stirred until gas evolution ceased, diluted with water and extracted with CH_2Cl_2. The extracts were combined, dried over Na_2SO_4 and concentrated *in vacuo* to provide the title compound (3.15 g, 95%), characterized by NMR and mass spectral analyses.

EXAMPLE 37

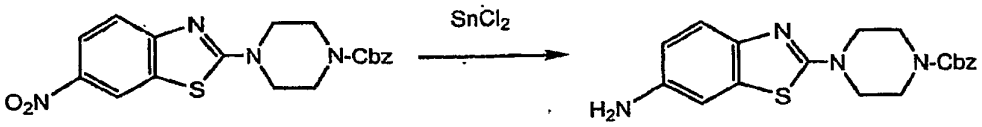
Preparation of 4-(6-Nitrobenzothiazol-2-yl)piperazine-1-carboxylic acid benzyl ester



A mixture of 2-chloro-6-nitrobenzothiazole (1.00g, 4.66 mmol), benzyl 1-piperazinecarboxylate (1.03g, 4.66 mmol), and $NaHCO_3$ (0.783 g, 9.32 mmol) in EtOH was heated at reflux temperature for 2 h, concentrated, and extracted with EtOAc. The combined extracts were dried over Na_2SO_4 and concentrated *in vacuo* to provide the title compound (1.13 g, 61%), characterized by NMR and mass spectral analyses.

EXAMPLE 38

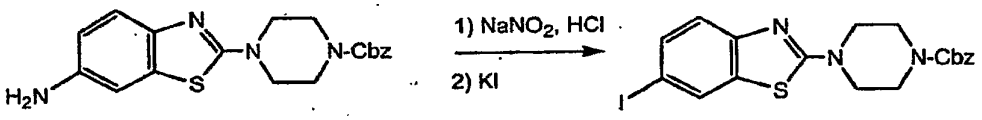
Preparation of 4-(6-Aminobenzothiazol-2-yl)piperazine-1-carboxylic acid benzyl ester



A mixture of 4-(6-nitrobenzothiazol-2-yl)piperazine-1-carboxylic acid benzyl ester (1.13 g, 2.84 mmol), $SnCl_2$ (2.56 g, 11.3 mmol), and conc. HCl (0.35 mL, 4.25 mmol) in EtOH was heated at 70 °C overnight, diluted with water, neutralized with 1 N NaOH to pH 10, and extracted with CH_2Cl_2. The combined extracts were filtered through a pad of silica gel. The filtrate was concentrated *in vacuo* to provide the title compound (0.80 g, 77%), characterized by NMR and mass spectral analyses.

EXAMPLE 39

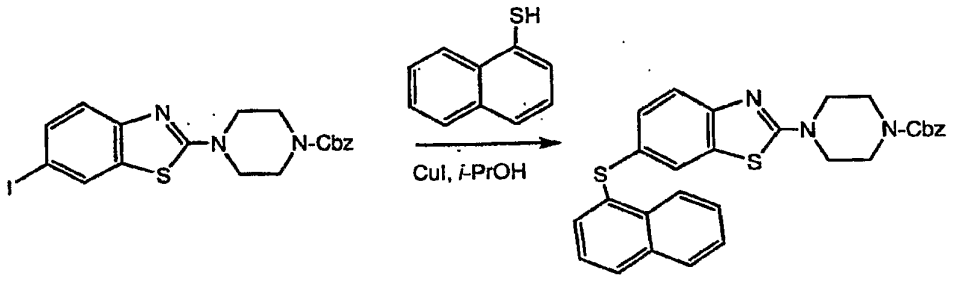
Preparation of 4-(6-Iodobenzothiazol-2-yl)piperazine-1-carboxylic acid benzyl ester



A solution of 1 N HCl (8 mL) and MeOH (16 mL) was treated with $NaNO_2$ (0.224 g, 3.26 mmol) at 0 °C followed by slow addition of a solution of 4-(6-amino-benzothiazol-2-yl)piperazine-1-carboxylic acid benzyl ester (8.00g, 2.17 mmol) in MeOH. The reaction mixture was stirred for 30 min, treated with a solution of KI (0.901 g, 5.43 mmol) in water, stirred for an additional 30 min, concentrated and extracted with CH_2Cl_2. The extracts were combined, dried over Na_2SO_4 and concentrated *in vacuo* to provide the title compound (0.74 g, 71%), characterized by NMR and mass spectral analyses.

EXAMPLE 40

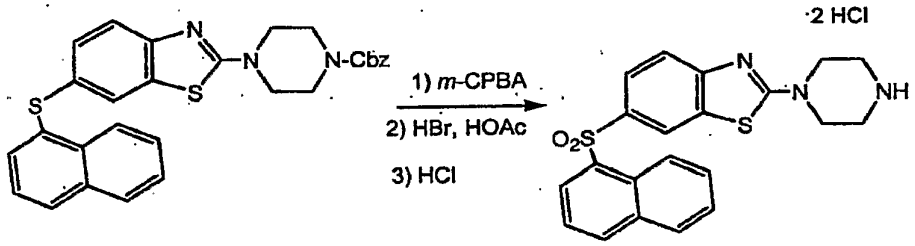
Preparation of 4-[6-(1-naphthylsulfanyl)benzothiazol-2-yl]piperazine-1-carboxylic acid benzyl ester



A mixture of 4-(6-iodobenzothiazol-2-yl)piperazine-1-carboxylic acid benzyl ester (0.370 g, 0.77 mmol), 1-napthalenethiol (0.124 g, 0.77 mmol), CuI (0.015 g, 0.08 mmol), and K_2CO_3 (0.213 g, 0.77 mmol) in isopropanol was heated at 90 °C overnight, cooled to 25° C, diluted with 20% MeOH in CH_2Cl_2, and filtered through a pad of silica gel. The filtrate was concentrated *in vacuo* to provide the title compound which used in Example 41 without further purification.

EXAMPLE 41

Preparation of 6-(1-Naphthylsulfonyl)-2-piperazin-1-ylbenzothiazole Dihydrochloride



A mixture of 4-[6-(1-naphthylsulfanyl)benzothiazol-2-yl]piperazine-1-carboxylic acid benzyl ester obtained in Example 40 (0.77 mmol theory) and meta-chloroperbenzoic acid (*m*CPBA) (0.399 g, 2.31 mmol) in $CHCl_3$ was stirred at room temperature for 2 h and concentrated *in vacuo*. The resultant residue was dissolved in 33 wt.% of HBr in HOAc (3.9 mL), stirred at room temperature for 40 min, diluted with Et_2O and filtered. The filtercake was washed with Et_2O and purified with Gilson reverse phase HPLC. The purified material was treated with a solution of HCL in

ether, stirred for 5 minutes and concentrated to dryness to afford the title compound (315 mg, 85% overall yield from 4-(6-iodobenzothiazol-2-yl)piperazine-1-carboxylic acid benzyl ester), characterized by NMR and mass spectral analyses. MS (ES^+) *m/e* 410 (MH^+).

Example 42

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 III, below.

TABLE III

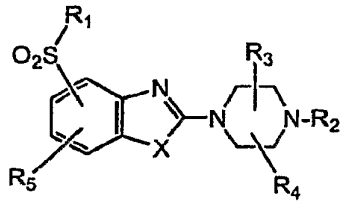
Test Compound (Example No.)	5-HT_6 Binding Ki (nM)
5	52
12	3.1
13	67
14	54
15	64

TABLE III.cont.

Test Compound (Example No.)	5-HT_6 Binding Ki (nM)
16	31
17	22
18	22
19	33
20	25
21	13
22	10
23	12
24	36
25	13
26	88
27	176
28	127
29	72
30	78
31	91
34	7
35	196
41	500

What is claimed is:

1. A compound of formula I



(I)

wherein

X is O or SO_n;

n is 0 or an integer of 1 or 2;

R_1 is an 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_2 is H or an alkyl, cycloalkyl or aryl group each group optionally substituted;

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

R_5 is H, halogen, NR_6R_7 or an alkyl, alkoxy, alkenyl, alkynyl or cycloalkyl, group each group optionally substituted;

R_6 is an alkyl or cycloalkyl group each group optionally substituted; and

R_7 is H or an alkyl or cycloalkyl group each group optionally substituted; or

a stereoisomer thereof or a pharmaceutically acceptable salt thereof.

2. A compound as claimed in claim 1 wherein X is O.

3. A compound as claimed in claim 1 or claim 2 wherein R_2 is H or an optionally substituted alkyl group.

4. A compound as claimed in any one of claims 1-3 wherein R_1 is an optionally substituted phenyl or naphthyl group.

5. A compound as claimed in any one of claims 2-4 wherein the SO_2-R_1 moiety is attached to the benzoxazole ring in the 4- or 7-position.

6. A compound as claimed in any one of claims 2-5 wherein R_2 is H or C_1-C_4alkyl.

7. A compound as claimed in any one of claims 1-6 wherein R_3, R_4 and R_5 are H.

8. The compound according to claim 1 selected from the group consisting essentially of:
4-(1-naphthylsulfonyl)-2-piperazin-1-yl-1,3-benzoxazole;
7-(1-naphthylsulfonyl)-2-piperazin-1-yl-1,3-benzoxazole;
5-(1-naphthylsulfonyl)-2-piperazin-1-yl-1,3-benzoxazole;
6-(1-naphthylsulfonyl)-2-piperazin-1-yl-1,3-benzoxazole;
6-(1-naphthylsulfonyl)-2-piperazin-1-ylbenzothiazole
4-(1-naphthylsulfonyl)-2-piperazin-1-ylbenzothiazole ;
7-(1-naphthylsulfonyl)-2-piperazin-1-ylbenzothiazole
4-(2,5-dichlorophenylsulfonyl)-2-piperazin-1-yl-1,3-benzoxazole;
7-(2,5-dichlorophenylsulfonyl)-2-piperazin-1-yl-1,3-benzoxazole;
5-(2,5-dichlorophenylsulfonyl)-2-piperazin-1-yl-1,3-benzoxazole;
2-(4-isopropylpiperazin-1-yl)-4-(1-naphthylsulfonyl)-1,3-benzoxazole;
2-(4-methylpiperazin-1-yl)-4-(1-naphthylsulfonyl)-1,3-benzoxazole;
2-(4-ethylpiperazin-1-yl)-4-(1-naphthylsulfonyl)-1,3-benzoxazole;
2-(4-isopropylpiperazin-1-yl)-7-(1-naphthylsulfonyl)-1,3-benzoxazole;
2-(4-methylpiperazin-1-yl)-7-(1-naphthylsulfonyl)-1,3-benzoxazole;
2-(4-ethylpiperazin-1-yl)-7-(1-naphthylsulfonyl)-1,3-benzoxazole;
2-(4-isopropylpiperazin-1-yl)-5-(1-naphthylsulfonyl)-1,3-benzoxazole;
2-(4-methylpiperazin-1-yl)-5-(1-naphthylsulfonyl)-1,3-benzoxazole;
2-(4-ethylpiperazin-1-yl)-5-(1-naphthylsulfonyl)-1,3-benzoxazole;
4-(phenylsulfonyl)-2-piperazin-1-yl-1,3-benzoxazole;
7-(phenylsulfonyl)-2-piperazin-1-yl-1,3-benzoxazole;
5-(phenylsulfonyl)-2-piperazin-1-yl-1,3-benzoxazole;

4-(3-fluorophenylsulfonyl)-2-piperazin-1-yl-1,3-benzoxazole;
7-(3-fluorophenylsulfonyl)-2-piperazin-1-yl-1,3-benzoxazole;
4-(4-fluorophenylsulfonyl)-2-piperazin-1-yl-1,3-benzoxazole;
7-(4-fluorophenylsulfonyl)-2-piperazin-1-yl-1,3-benzoxazole;
4-(3-chlorophenylsulfonyl)-2-piperazin-1-yl-1,3-benzoxazole;
7-(3-chlorophenylsulfonyl)-2-piperazin-1-yl-1,3-benzoxazole;
4-(4-isopropylphenylsulfonyl)-2-piperazin-1-yl-1,3-benzoxazole;
7-(4-isopropylphenylsulfonyl)-2-piperazin-1-yl-1,3-benzoxazole;
2-(piperazin-1-yl)-4-{3-(trifluoromethyl)phenylsulfonyl}-1,3-benzoxazole;
2-(piperazin-1-yl)-7 -{3-(trifluoromethyl)phenylsulfonyl}-1,3-benzoxazole;
4-(3-methoxyphenylsulfonyl)-2-piperazin-1-yl-1,3-benzoxazole;
7-(3-methoxyphenylsulfonyl)-2-piperazin-1-yl-1,3-benzoxazole;
4-(1-naphthylsulfonyl)-2-(4-propyl-piperazin-1-yl)-1,3-benzoxazole
2-(4-*n*-butylpiperazin-1-yl)-4-(1-naphthylsulfonyl)-1,3-benzoxazole;
2-(4-*t*-butylpiperazin-1-yl)-4-(1-naphthylsulfonyl)-1,3-benzoxazole;
2-(4-cyclobutylpiperazin-1-yl)-4-(1-naphthylsulfonyl)-1,3-benzoxazole;
2-(4-cyclobutylpiperazin-1-yl)-7-(1-naphthylsulfonyl)-1,3-benzoxazole;
a stereoisomer thereof; and
a pharmaceutically acceptable salt thereof.

9. 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 described in any one of claims 1-8.

10. A method as claimed in claim 9 wherein said disorder is a cognitive disorder, a developmental disorder or a neurodegenerative disorder.

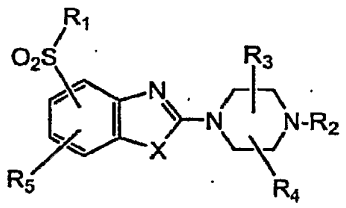
11. A method as claimed in claim 10 wherein said disorder is a cognitive disorder.

12. A method as claimed in claim 10 wherein said disorder is selected from the group consisting of: a learning disorder; attention deficit disorder; Down's syndrome; Fragile X syndrome; and autism.

13. A method as claimed in claim 10 wherein said disorder is stroke or head trauma.

14. A pharmaceutical composition which comprises a pharmaceutically acceptable carrier and an effective amount of a compound of formula I as described in any one of claims 1-8.

15. A process for the preparation of a compound of formula Ia



(Ia)

wherein

X is O or SO_n;

n is 0 or an integer of 1 or 2;

R_1 is an 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_2 is H or an alkyl, cycloalkyl or aryl group each group optionally substituted;

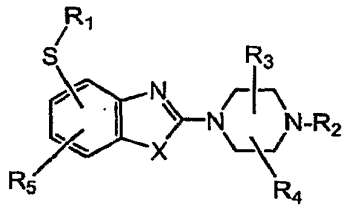
R_3 and R_4 are each independently H or an optionally substituted alkyl group; and

R_5 is H, halogen, NR_6R_7 or an alkyl, alkoxy, alkenyl, alkynyl or cycloalkyl, group each group optionally substituted;

R_6 is an alkyl or cycloalkyl group each group optionally substituted; and

R_7 is H or an alkyl or cycloalkyl group each group optionally substituted

which process comprises reacting a compound of formula II



(II)

wherein R_1, R_2, R_3, R_4 and R_5 are as described for formula I with at least two molar equivalents of an oxidizing agent optionally in the presence of a solvent.

16. The use of a compound of formula I as described in any one of claims 1-8 in the manufacture of a medicament for treating a central nervous system disorder related to or affected by the 5-HT6 receptor.