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HETEROCYCLYLALKYLINDOLE OR -AZAINDOLE COMPOUNDS AS 5-HYDROXYTRYPTAMINE-6 LIGANDS

This invention relates to heterocyclylalkylindole or -azaindole compounds useful as 5-hydroxytryptamine-6 ligands, to processes for preparing them, to pharmaceutical compositions containing them and to methods of treatment using them.

BACKGROUND OF THE INVENTION

A number of central nervous system disorders such as anxiety, depression, motor disorders, etc., are believed to involve a disturbance of the neurotransmitter 5-hydroxytryptamine (5-HT) or serotonin. Serotonin is localized in the central and peripheral nervous systems and is known to affect many types of conditions including psychiatric disorders, motor activity, feeding behavior, sexual activity, and neuroendocrine regulation among others. The effects of serotonin are regulated by the various 5-HT receptor subtypes. Known 5-HT receptors include various 5-HT1, 5-HT2, 5-HT3, 5-HT4, 5-HT5, 5-HT6 and 5-HT7 subtypes.

The recently identified human 5-hydroxytryptamine-6 (5-HT6) receptor subtype has been cloned, and the extensive distribution of its mRNA has been reported. Highest levels of 5-HT6 receptor mRNA have been observed in the olfactory tubercle, the striatum, nucleus accumbens, dentate gyrus and CA1, CA2 and CA3 regions of the hippocampus. Northern blot analyses have revealed that 5-HT6 receptor mRNA appears to be exclusively

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present in the brain, with little evidence for its presence in peripheral tissues.

The high affinity of a number of antipsychotic agents for the 5-HT6 receptor, in addition to its mRNA localization in striatum, olfactory tubercle and nucleus accumbens suggests that some of the clinical actions of these compounds may be mediated through this receptor. Compounds which interact with, stimulate or inhibit the 5-HT6 receptor are commonly referred to as 5-HT6 ligands. These 5-HT6 receptor ligands are believed to be of potential use in the treatment of a variety of central nervous system disorders such as anxiety, depression, epilepsy, obsessive-compulsive disorders, migraine, cognitive disorders, sleep disorders, feeding disorders, attention deficit disorders, panic attacks, disorders relating to withdrawl from drug abuse, schizophrenia, or the like or in the treatment of certain gastrointestinal disorders such as irritable bowel syndrome.

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.

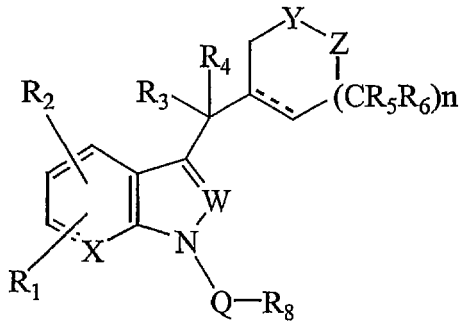
It is another object of this invention to provide therapeutic methods and pharmaceutical compositions useful for the treatment of central nervous system disorders related to or affected by the 5-HT6 receptor.

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

These and other objects and features of the invention will become more apparent by the detailed description set forth hereinbelow.

SUMMARY OF THE INVENTION

The present invention provides a compound of formula I



(I)

wherein

Q is SO_2, CO, $CONR_{24}$, $CSNR_{25}$ or CH_2;

W is N or CR_7;

X is N or CR_9;

Y is NR or $CR_{10}R_{29}$;

Z is NR_{21} or $CR_{11}R_{30}$ with the proviso that when Y is NR then Z must be $CR_{11}R_{30}$ and with the further proviso that at least one of Y and Z must be NR or NR_{21};

n is 0 or an integer of 1 or 2;

R and R_{21} are each independently H, $CNR_{26}NR_{27}R_{28}$, or a C_1-C_6alkyl, C_3-C_6cycloalkyl, cycloheteroalkyl, aryl or heteroaryl group each optionally substituted;

R_1, R_2 and R_9 are each independently H, halogen, CN, OCO_2R_{12}, CO_2R_{13}, $CONR_{22}R_{23}$, $CNR_{14}NR_{15}R_{16}$, SO_mR_{17},

$NR_{18}R_{19}$, OR_{20}, or a C_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_3-C_6- cycloalkyl, cycloheteroalkyl, C_1-C_6alkanoyl, aryl or heteroaryl group each optionally substituted;

m is 0 or an integer of 1 or 2;

R_3 and R_4 are each independently H, halogen, C_1-C_4alkyl or C_1-C_4haloalkyl or R_3 and R_4 may be taken together with the atom to which they are attached to form a carbonyl group;

R_5 and R_6 are each independently H or an optionally substituted C_1-C_6alkyl group;

R_7 is H, halogen, or a C_1-C_6alkyl, C_1-C_6alkoxy, aryl or heteroaryl group each optionally substituted;

R_8 is an optionally substituted C_1-C_6alkyl, aryl or heteroaryl group;

R_{10}, R_{11}, R_{29} and R_{30} are each independently H or an optionally substituted C_1-C_6alkyl group;

R_{12}, R_{13} and R_{17} are each independently H or an optionally substituted C_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_3-C_6cycloalkyl, cycloheteroalkyl, aryl or heteroaryl group;

R_{14}, R_{15}, R_{16}, R_{18}, R_{19}, R_{26}, R_{27} and R_{28} are each independently H or C_1-C_4alkyl;

R_{20}, R_{22} and R_{23} are each independently H or an optionally substituted C_1-C_6alkyl group;

R_{24} and R_{25} are each independently H or an alkyl, aryl or heteroaryl group each optionally substituted; and

---- represents a single bond or a double bond; or

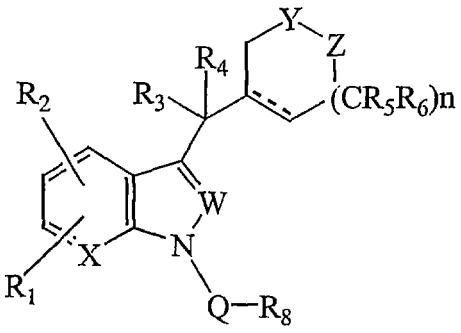
a pharmaceutically acceptable salt thereof.

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

DETAILED DESCRIPTION OF THE INVENTION

The 5-hydroxytryptamine-6 (5-HT6) receptor is one of the most recent receptors to be 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. At present, there are no known fully selective agonists. Significant efforts are being made to understand the possible 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.

Surprisingly, it has now been found that heterocyclylalkylindole or-azaindole compounds of formula I demonstrate affinity for the 5-HT6 receptor along with significant receptor 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 heterocyclylalkylindole or -azaindole compounds of formula I



(I)

wherein

Q is SO_2, CO, $CONR_{24}$, $CSNR_{25}$ or CH_2;

W is N or CR_7;

X is N or CR_9;

Y is NR or $CR_{10}R_{29}$;

Z is NR_{21} or $CR_{11}R_{30}$ with the proviso that when Y is NR then Z must be $CR_{11}R_{30}$ and with the further proviso that at least one of Y and Z must be NR or NR_{21};

n is 0 or an integer of 1 or 2;

R and R_{21} are each independently H, $CNR_{26}NR_{27}R_{28}$, or a C_1-C_6alkyl, C_3-C_6cycloalkyl, cycloheteroalkyl, aryl or heteroaryl group each optionally substituted;

R_1, R_2 and R_9 are each independently H, halogen, CN, OCO_2R_{12}, CO_2R_{13}, $CONR_{22}R_{23}$, $CNR_{14}NR_{15}R_{16}$, SO_mR_{17}, $NR_{18}R_{19}$, OR_{20}, or a C_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_3-C_6- cycloalkyl, cycloheteroalkyl, C_1-C_6alkanoyl, aryl or heteroaryl group each optionally substituted;

m is 0 or an integer of 1 or 2;

R_3 and R_4 are each independently H, halogen, C_1-C_4alkyl or C_1-C_4haloalkyl or R_3 and R_4 may be taken together with the atom to which they are attached to form a carbonyl group;

R_5 and R_6 are each independently H or an optionally substituted C_1-C_6alkyl group;

R_7 is H, halogen, or a C_1-C_6alkyl, C_1-C_6alkoxy, aryl or heteroaryl group each optionally substituted;

R_8 is an optionally substituted C_1-C_6alkyl, aryl or heteroaryl group;

R_{10}, R_{11}, R_{29} and R_{30} are each independently H or an optionally substituted C_1-C_6alkyl group;

R_{12}, R_{13} and R_{17} are each independently H or an optionally substituted C_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_3-C_6cycloalkyl, cycloheteroalkyl, aryl or heteroaryl group;

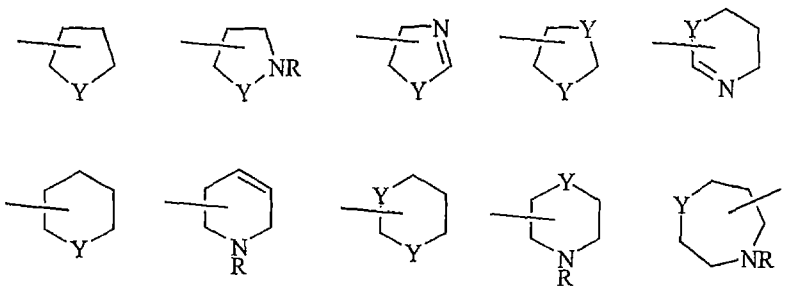
R_{14}, R_{15}, R_{16}, R_{18}, R_{19}, R_{26}, R_{27} and R_{28} are each independently H or C_1-C_4alkyl;

R_{20}, R_{22} and R_{23} are each independently H or an optionally substituted C_1-C_6alkyl group;

R_{24} and R_{25} are each independently H or an alkyl, aryl or heteroaryl group each optionally substituted; and

---- represents a single bond or a double bond; or a pharmaceutically acceptable salt thereof.

As used in the specification and claims, the term halogen designates Br, Cl, I or F; the term aryl designates phenyl or naphthyl; and the term cycloheteroalkyl designates a 5- to 7-membered monocyclic ring system containing 1 or 2 heteroatoms, which may be the same or different, selected from N, NR, O or S and optionally containing one double bond wherein R is hydrogen or an optional substituent as described herein. Exemplary of the cycloheteroalkyl ring systems included in the term as designated herein are the following rings wherein Y is NR, O or S.



For example cycloheteroalkyl includes radicals derived from rings such as piperidine, morpholine, piperazine and pyrrolidine.

Similarly, as used in the specification and claims, the term heteroaryl designates a 5- to 10-membered monocyclic or bicyclic aromatic ring system containing 1 or 2 heteroatoms, which may be the same or different, selected from nitrogen, oxygen and sulphur. Such heteroaryl ring systems include pyrrolyl, azolyl, oxazolyl, thiazolyl, imidazolyl, furyl, thienyl, quinolinyl, isoquinolinyl, indolinyl, benzothienyl, benzofuranyl, benzisoxazolyl and the like. 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; and the term haloalkoxy designates an OC_nH_{2n+1} group having from one to 2n+1 halogen atoms which may be the same or different.

In the specification and claims, when the terms C_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_3-C_7cycloalkyl, cycloheteroalkyl, C_1-C_6alkanoyl, aryl or heteroaryl are designated as being optionally substituted, 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 (eg heteroaryl and cycloheteroalkyl) or cycloalkyl groups, preferably halogen atoms or lower alkyl groups. Typically, up to 3 substituents may be present. When any of the foregoing substituents represents or contains an alkyl substituent group, this may be linear or branched and may contain up to 12, preferably up to 6, more preferably up to 4 carbon atoms, such as methyl, ethyl, propyl, isopropyl and n- or t- butyl.

Pharmaceutically acceptable salts may be any acid addition salt formed by a compound of formula I and a pharmaceutically acceptable acid such as phosphoric, sulfuric, hydrochloric, hydrobromic, citric, maleic, mandelic, malonic, succinic, fumaric, acetic, lactic, nitric, sulfonic, p-toluenesulfonic, methanesulfonic acid or the like.

Examples of R_1 and R_2 are independently hydrogen, halogen (such as fluorine, chlorine) C_1-C_6alkyl, C_1-C_6alkoxy, hydroxy, and cyano; for example where substitution is in the 5- and/or 6- position.

Examples of n are 0 or 1. Examples of R_5 and R_6 are independently hydrogen and (C_1-C_6)alkyl.

Examples of R_3 and R_4 are independently hydrogen and (C_1-C_6)alkyl.

Q may be for example SO_2, C=O or CH_2.

Examples of R_8 are aryl e.g., phenyl or naphthyl, or heteroaryl e.g., thienyl (such as thien-2-yl) or quinolyl (such as quinolin-8-yl); said aryl and heteroaryl groups being unsubstituted or optionally substituted by one or more (e.g., 1 to 3) substituents the same or different as described herein. Such substituents include nitro, cyano, thiocyanato, cyanato, hydroxyl, alkyl of 1-6 carbon atoms, halo(C_1-C_6)alkyl, (C_1-C_6)alkoxy, halo(C_1-C_6)alkoxy, amino, (C_1-C_6)alkylamino, di-$(C_1-C_6$alkyl)amino, formyl, $(C_1-C_6$alkoxy)carbonyl, carboxyl, (C_1-C_6)alkanoyl, (C_1-C_6)alkylthio, (C_1-C_6)alkylsulphinyl, (C_1-C_6)alkylsulphonyl, carbamoyl, (C_1-C_6)alkylamido, phenyl, phenoxy, benzyl, benzyloxy, heteroaryl and cycloheteroalkyl or (C_3-C_8)cycloalkyl groups. Such optionally substituted groups for R_8 are also examples of aryl or heteroaryl for each of R, R_1, R_2, R_7, R_9, R_{12}, R_{13}, R_{17}, R_{21}, R_{24} and R_{25}.

Examples of W are CR_7 wherein R_7 is for example hydrogen or (C_1-C_6)alkyl.

Examples of Y are NR and $CR_{10}R_{29}$ where R, R_{10} and R_{29} are each selected from hydrogen and C_1-C_6alkyl.

Examples of Z are NR_{21} and $CR_{11}R_{30}$ where R, R_{11} and R_{30} are each selected from hydrogen and C_1-C_6alkyl.

Preferred compounds of the invention are those compounds of formula I wherein n is 1. Also preferred are those compounds of formula I wherein R_3 and R_4 are H. Further preferred compounds of the invention are those compounds of formula I wherein Q is SO_2 or CO. Also preferred are compounds of formula I where R_8 is an optionally substituted aryl group. Another preferred group of formula I compounds are those compounds wherein ---- represents a single bond.

More preferred compounds of the invention are those compounds of formula I wherein Q is SO_2; X is CR_9; Y is $CR_{10}R_{29}$; Z is NR_{21}; and R_3 and R_4 are H. Another group of more preferred inventive compounds are those formula I compounds wherein Q is SO_2; X is CR_9; Y is $CR_{10}R_{29}$; Z is NH; R_3 and R_4 are H; R_8 is an optionally substituted aryl group; and ---- represents a single bond.

Among the preferred compounds of the invention, which each illustrate values for the variables in formula I, are:

5-fluoro-1-(phenylsulfonyl)-3-(piperidin-4-ylmethyl)-1H-indole;

5-fluoro-1-(phenylsulfonyl)-3-(1,2,5,6-tetrahydro-3-pyridinylmethyl)-1H-indole;

4-{[5-fluoro-3-(4-piperidinylmethyl)-1H-indol-1-yl]-sulfonyl}aniline;

1-[(2,6-dichlorophenyl)sulfonyl]-5-fluoro-3-(4-piperidinylmethyl)-1H-indole;

1-[(3,4-dichloro-2-thienyl)sulfonyl]-5-fluoro-3-(4-piperidinylmethyl)-1H-indole;

5-fluoro-1-(1-naphthylsulfonyl)-3-(4-piperidinylmethyl)-1H-indole;

1-[(3,4-dimethoxyphenyl)sulfonyl]-5-fluoro-3-(piperidin-4-ylmethyl)-1H-indole;

4-{[5-fluoro-3-(piperidin-4-ylmethyl)-1H-indol-1-yl]sulfonyl}benzonitrile;

8-{[5-fluoro-3-(piperidin-4-ylmethyl)-1H-indol-1-yl]sulfonyl}quinoline;

1-(phenylsulfonyl)-3-(piperidin-4-ylmethyl)-1H-indole;

1-(1-naphthylsulfonyl)-3-(piperidin-4-ylmethyl)-1H-indole;

4-{[3-(piperidin-4-ylmethyl)-1H-indol-1-yl]sulfonyl}-phenylamine;

1-[(3,4-dichlorothien-2-yl)sulfonyl]-3-(piperidin-4-ylmethyl)-1H-indole;

1-(phenylsulfonyl)-3-(piperidin-4-ylmethyl)-1H-pyrrolo-[2,3-b]pyridine;

1-(1-naphthylsulfonyl)-3-(piperidin-4-ylmethyl)-1H-pyrrolo[2,3-b]pyridine;

4-{[3-(piperidin-4-ylmethyl)-1H-pyrrolo[2,3-b]pyridin-1-yl]sulfonyl}phenylamine;

1-[(3,4-dichlorothien-2-yl)sulfonyl]-3-(piperidin-4-ylmethyl)-1H-pyrrolo[2,3-b]pyridine;

6-fluoro-1-(phenylsulfonyl)-3-(4-piperidinylmethyl)-1H-indole;

6-fluoro-1-(1-naphthylsulfonyl)-3-(4-piperidinylmethyl)-1H-indole;

6-fluoro-1-(3,4-dimethoxyphenylsulfonyl)-3-(4-piperidinylmethyl)-1H-indole;

6-fluoro-1-(2-chlorophenylsulfonyl)-3-(4-piperidinyl-methyl)-1H-indole;

6-fluoro-1-(5-chlorothien-2-ylsulfonyl)-3-(4-piperidinyl-methyl)-1H-indole;

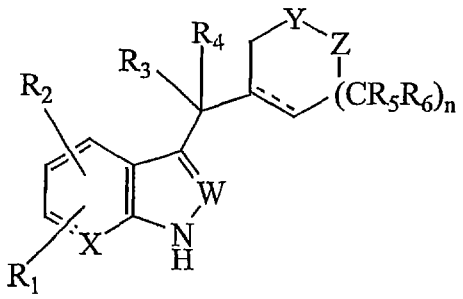
6-fluoro-1-(2-fluorophenylsulfonyl)-3-(4-piperidinyl-methyl)-1H-indole;

6-fluoro-1-(3-fluorophenylsulfonyl)-3-(4-piperidinyl-methyl)-1H-indole; and

the pharmaceutically acceptable salts thereof.

This invention also provides processes for preparing compounds of formula (I) which processes comprise one of the following:

a) reacting a compound of formula



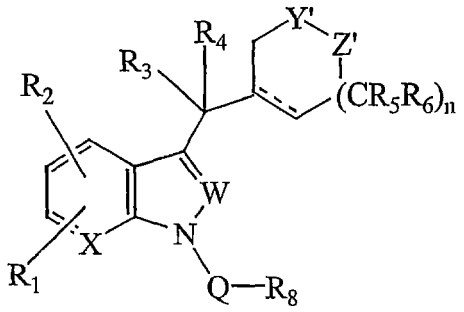
wherein n, W, X, Y, Z, R_1, R_2, R_3, R_4, R_5 and R_6 are as defined herein, with an appropriate sulphonylating, acylating, carbamoylating, thiocarbamoylating or alkylating agent containing the group:

R_8-Q-

where R_8 is as defined above and Q is SO_2, CO, $CONR_{24}$, $CSNR_{25}$ or CH_2 ; said reactants protected on reactive sites and/or on reactive substituent groups as required, and removing any protecting groups to give a corresponding compound of formula (I);

or

b) removing a protecting group from a compound of formula



wherein n, Q, W, X, R_1, R_2, R_3, R_4, R_5, R_6 and R_8 are as defined herein and one of Y' and Z' is N-G where G is a protecting group to give a compound of formula (I) wherein Y or Z is NH;

or

c) alkylating a compound of formula (I) as defined in claim 1 wherein R or R_{21} is hydrogen with an alkylating agent of formula R-L or R_{21}-L wherein L is a leaving group, such as halogen, and R and R_{21} are each as defined in herein excepting hydrogen, to give a corresponding compound of formula (I);

or

d) converting a compound of formula (I) having a reactive substituent group to a different compound of formula I;

or

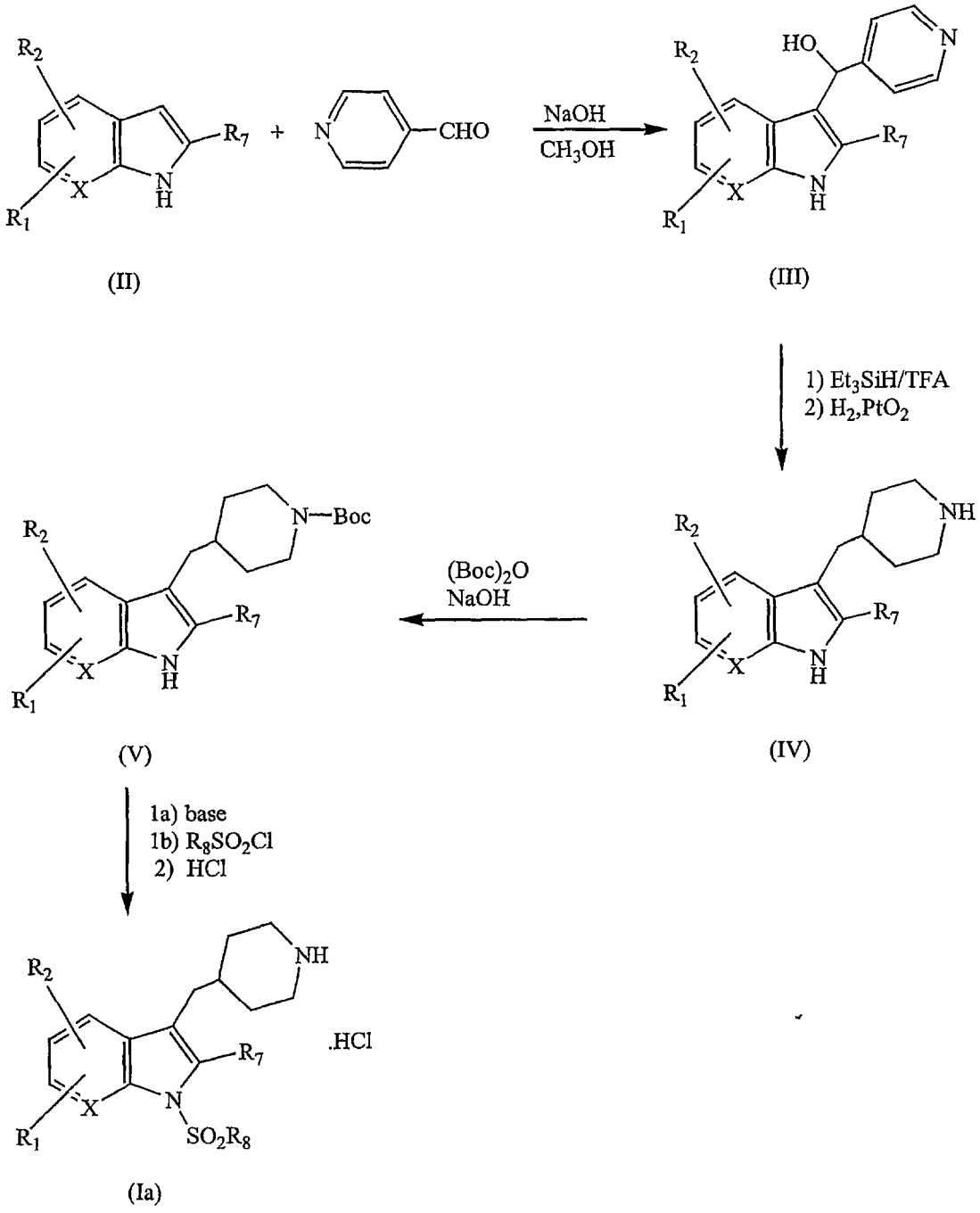
e) converting a basic compound of formula (I) to an acid addition salt or vice versa.

Methods for carrying out the reactions described above are well known to those skilled in the art and/or are illustrated herein. In any of the reactions described herein reactive substituent groups or sites in the molecule may be protected prior to reaction by use of appropriate protecting groups inert to the reaction conditions and removed after the reaction.

In detail, compounds of the invention may conveniently be prepared using conventional synthetic methods and, if required, standard separation or isolation techniques. For example, compounds of formula I wherein Q is SO_2; W is CR_7; Y is CH_2; Z is NH; n is 1; - --- represents a single bond; and R_3 and R_4 are H (Ia) may be prepared by reacting a compound of formula II with 4-pyridinecarboxaldehyde to give the corresponding hydroxymethylpyridine of formula III. Said formula III compound may be fully reduced to give the piperidinyl-methyl compound of formula IV. Said formula IV compound may be protected with a group such as t-butyl carbonate (Boc) to give the protected compound of formula V and the protected compound may then be sulfonated using the appropriate sulfonyl halide reagent and deprotected to

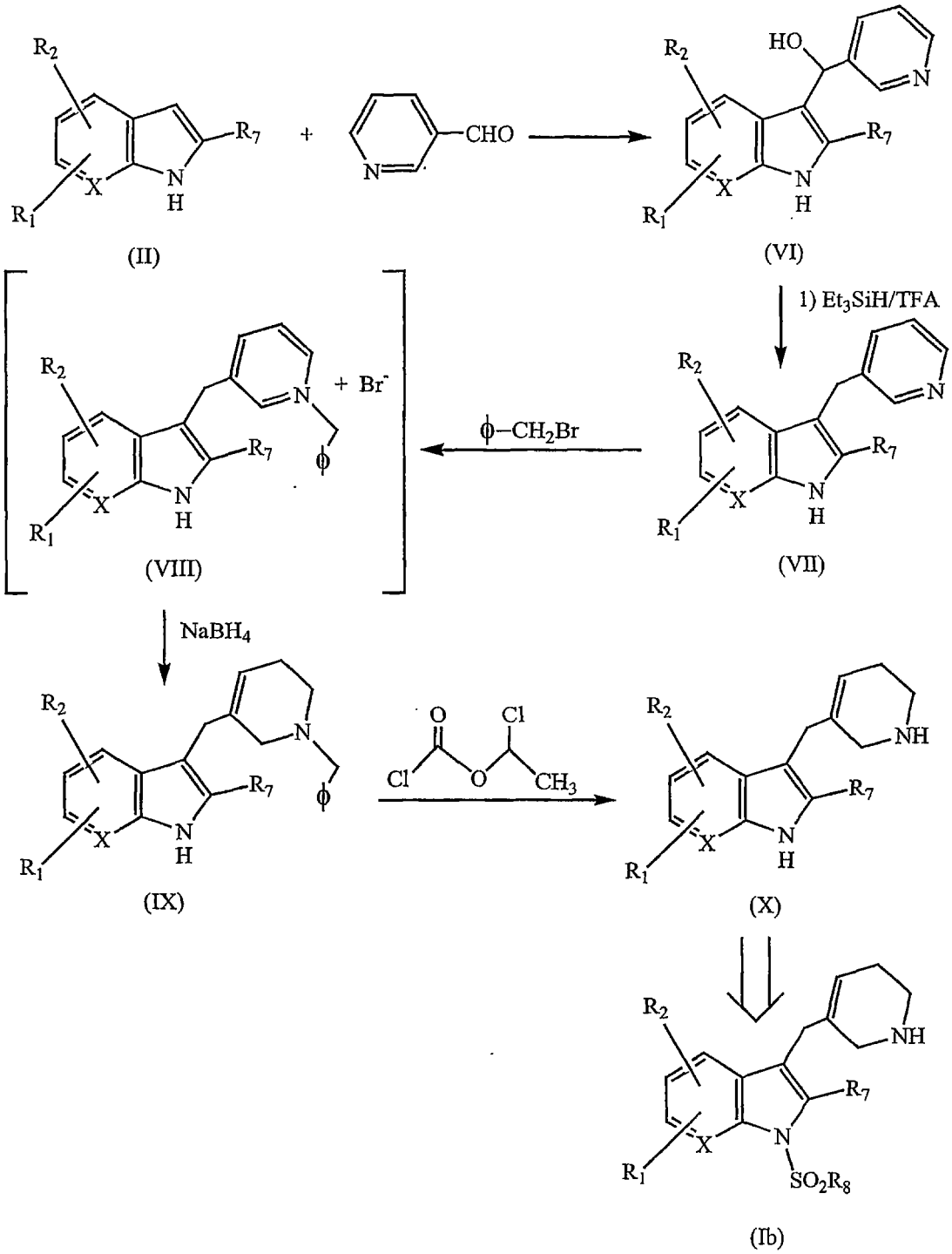
give the desired formula Ia compound. The reaction sequence is shown in flow diagram I.

FLOW DIAGRAM I



Compounds of formula I wherein ---- represents a double bond; Q is SO_2; Y is NH; Z is CH_2; n is 1; and R_3 and R_4 are H(Ib) may be prepared by reacting the formula II substrate with 3-pyridine carboxaldehyde to form the corresponding hydroxymethylpyridine compound of formula VI; partially reducing said formula VI compound to give the indolyl- or azaindolylmethylpyridine of formula VII; reacting said formula VII pyridine with benzylbromide to form the pyridinium bromide of formula VIII, reacting the formula VIII pyridinium salt with $NaBH_4$ to give the tetrahydro-3-pyridinylmethyl compound of formula IX; debenzylating said formula IX compound with chloroethylchloroformate to give the compound of formula X; and then sequentially protecting, sulfonating and deprotecting said formula X compound as described hereinabove to give the desired formula Ib compound. The reaction sequence is shown in flow diagram II, wherein G represents a protecting group and ϕ represents a phenyl group.

Flow Diagram II



Compounds of formula I wherein R and R_{21} are other than hydrogen may be prepared by alkylating a compound of

formula Ia or Ib with an appropriate alkylating agent such as an alkyl halide. Compounds of formula I wherein Q is CO, $CONR_{24}$ $CSNR_{25}$ or CH_2 may be prepared by reacting a protected compound of formula V or formula IX with an appropriate carbonyl halide, carbamoyl halide, thiocarbamoyl acid halide or alkyl halide respectively. Employing these and other literature procedures, the formula I compounds of the invention may be prepared.

Advantageously, the inventive compound of formula I may be utilized in the treatment of central nervous system disorders relating to or affected by the 5-HT6 receptor such as motor, mood, psychiatric, cognitive, neurodegenerative, or the like disorders. In particular, CNS disorders such as anxiety, depression, schizophrenia, Alzheimer's disease, Parkinson's disease, eating disorders, disorders related to alcohol or drug withdrawl, sexual dysfunction, attention deficit disorder, memory loss or the like. Accordingly, the present invention provides a method for the treatment of a disorder of the central nervous system (CNS) related to or affected by the 5-HT6 receptor in a patient in need thereof which comprises providing said patient with a therapeutically effective amount of a compound of formula I as described hereinabove. The compounds may be provided via 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 administered 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.

Solid carriers suitable for use in the composition of the invention include one or more substances which may also act as flavoring agents, lubricants, solubilizers, suspending agents, fillers, glidants, compression aides, binders, tablet-disintegrating agents or encapsulating materials. In powders, the carrier may be a finely divided solid which is in admixture with a finely divided compound of formula I. In tablets, the formula I compound may be mixed with a carrier having the necessary compression properties in suitable proportions and compacted in the shape and size desired. Said powders and tablets may contain up to 99% by weight of the formula I compound. Solid carriers suitable for use in the composition of the invention include calcium phosphate, magnesium stearate, talc, sugars, lactose, dextrin, starch, gelatin, cellulose, methyl cellulose, sodium carboxymethyl cellulose, polyvinylpyrrolidine, low melting waxes and ion exchange resins.

Any pharmaceutically acceptable liquid carrier suitable for preparing solutions, suspensions, emulsions, syrups and elixirs may be employed in the composition of the invention. Compounds of formula I may be dissolved or suspended in a pharmaceutically acceptable liquid carrier such as water, an organic solvent, or a

pharmaceutically acceptable oil or fat, or a mixture thereof. Said liquid composition may contain other suitable pharmaceutical additives such as solubilizers, emulsifiers, buffers, preservatives, sweeteners, flavoring agents, suspending agents, thickening agents, coloring agents, viscosity regulators, stabilizers, osmo-regulators, or the like. Examples of liquid carriers suitable 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) or their derivatives, or oils (e.g., fractionated coconut oil and arachis oil). For parenteral administration the carrier may also be an oily ester such as ethyl oleate or isopropyl myristate.

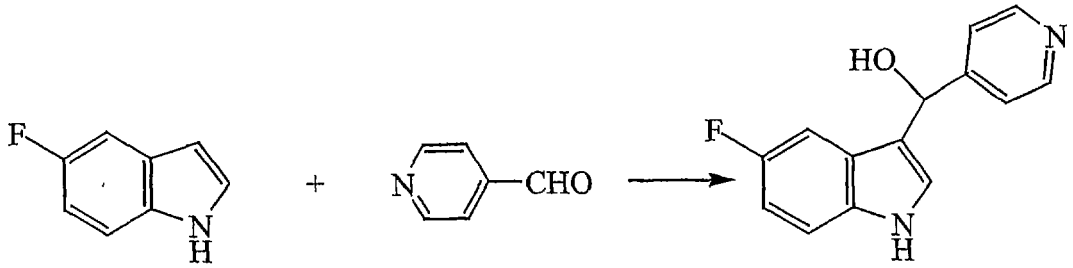
Compositions of the invention which are sterile solutions or suspensions are suitable for intramuscular, intraperitoneal or subcutaneous injection. Sterile solutions may also be administered intravenously. Inventive compositions suitable for oral administration may be in either liquid or solid composition form.

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.

Unless otherwise stated, all parts are parts by weight. The terms HPLC and NMR designate high performance liquid chromatography and nuclear magnetic resonance, respectively.

EXAMPLE 1

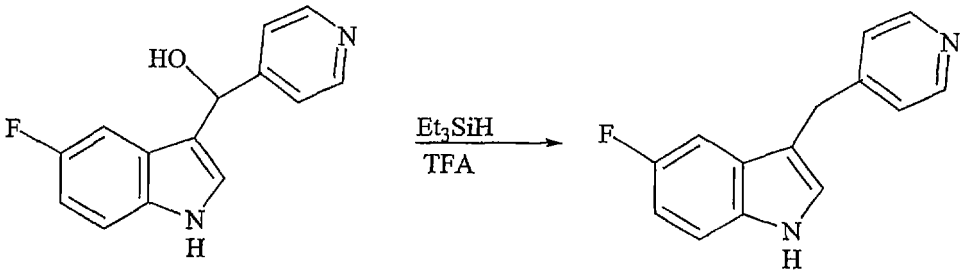
Preparation of (5-Fluoro-1*H*-indol-3-yl)(4-pyridinyl)-methanol



A stirred solution of 5-fluoroindole (3.10 g, 23.0 mmol) in methanol is treated with 4-pyridinecarboxaldehyde (2.20 ml, 23.0 mmol), then treated with aqueous NaOH (2.5 ml, 50%) at 0°C, stirred for 1 hr at 0°C, warmed to room temperature, stirred for 3 hr, and diluted with water. The resultant mixture is filtered. The filtercake is dried under vacuum to afford the title product as a light yellow solid, 5.2 g (93%) mp 171-173°C, identified by mass spectral and NMR analyses.

EXAMPLE 2

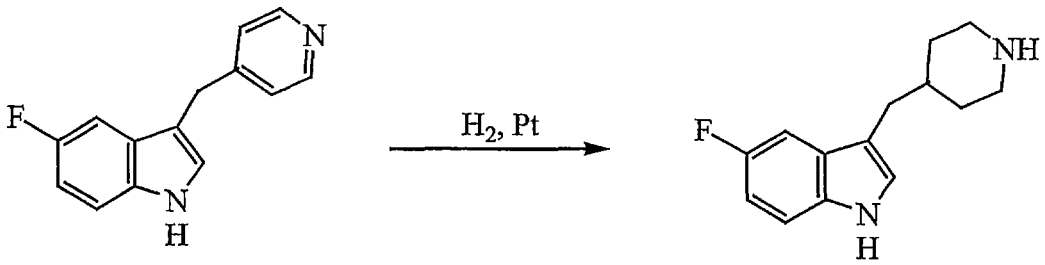
Preparation of 5-Fluoro-3-(4-pyridinylmethyl)-1*H*-indole



A suspension of (5-fluoro-1*H*-indol-3-yl)-pyridin-4-yl-methanol (3.36 g, 13.9 mmol) in methylene chloride is treated with triethylsilane (2.48 ml, 15.5 mmol) followed by trifluoroacetic acid (11.9 ml, 155 mmol) at room temperature, stirred overnight and concentrated *in vacuo*. The resultant residue is treated with saturated Na_2CO_3 to pH>9 and extracted with methylene chloride. The combined extracts are washed sequentially with water and brine, dried over Na_2SO_4 and concentrated *in vacuo*. This residue is purified by flash chromatography (silica gel, CH_2Cl_2/MeOH: 95/5) to give the title product as a white solid, 2.5 g (80%) mp 141-142 °C (lit. mp 149 °C, Malleron *et al*, J. Med. Chem. 1993, 36, 1194).

EXAMPLE 3

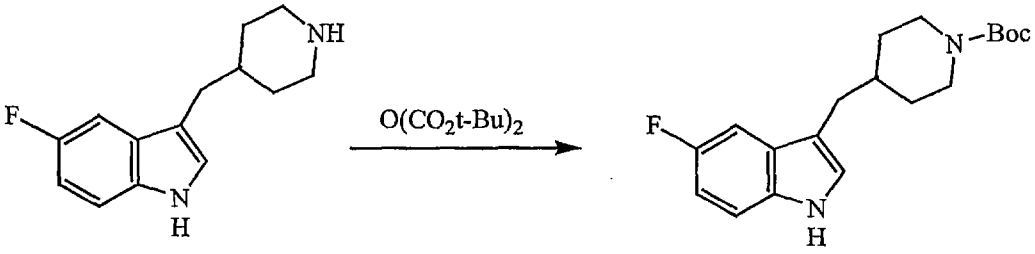
Preparation of 5-Fluoro-3-(4-piperidinylmethyl)-1*H*-indole



A mixture of 5-fluoro-3-(4-pyridinylmethyl)-1*H*-indole (4.50 g, 20 mmol) and PtO_2 (0.50 g, 2.2 mmol) in ethanol and acetic acid is hydrogenated under 45 psi at room temperature for 48 hr. After filtration of the catalyst and concentration of the filtrate, the residue is taken up with water, basified to pH 11 with 1N NaOH and extracted with CH_2Cl_2/iPrOH (3/1). The combined extracts are dried over Na_2SO_4 and concentrated *in vacuo* to give a pink solid. The solid is crystallized from EtOAc to afford the title compound as a white solid, 4.0 g (86%) mp 155-157°C (Lit. mp 163°C, Malleron et al, J Med. Chem. 1193,36,1194).

EXAMPLE 4

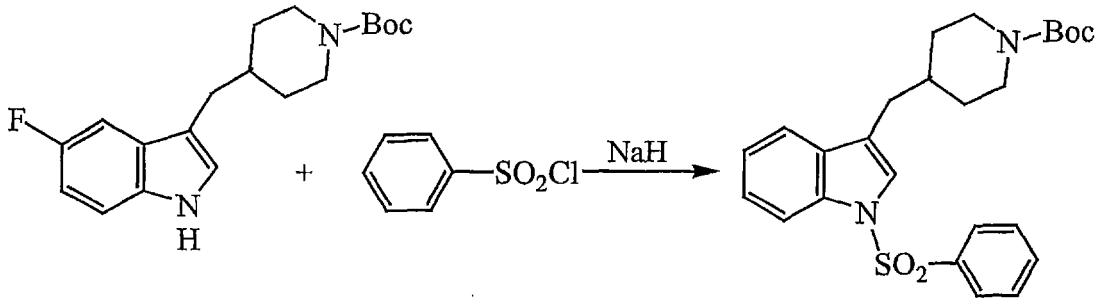
Preparation of *tert*-Butyl 4-[(5-fluoro-1*H*-indol-3-yl)methyl]-1-piperidinecarboxylate



A solution of 5-fluoro-3-(4-piperidinylmethyl)-1*H*-indole (1.0 g, 4.3 mmol) and di-tert-butyl dicarbonate (0.94 g, 4.3 mmol) in 1N NaOH and dioxane is stirred under nitrogen at room temperature for 24 hr, quenched with water and diluted with ethyl acetate. The organic phase is separated, washed with H_2O and saturated NaCl, dried over $MgSO_4$, and concentrated *in vacuo*. The resultant residue is purified by flash chromatography (silica gel, EtOAc/hexane: 2/8) to afford the title compound as a white solid, 1.4 g, mp 144-145 °C, identified by NMR and mass spectral analyses.

EXAMPLE 5

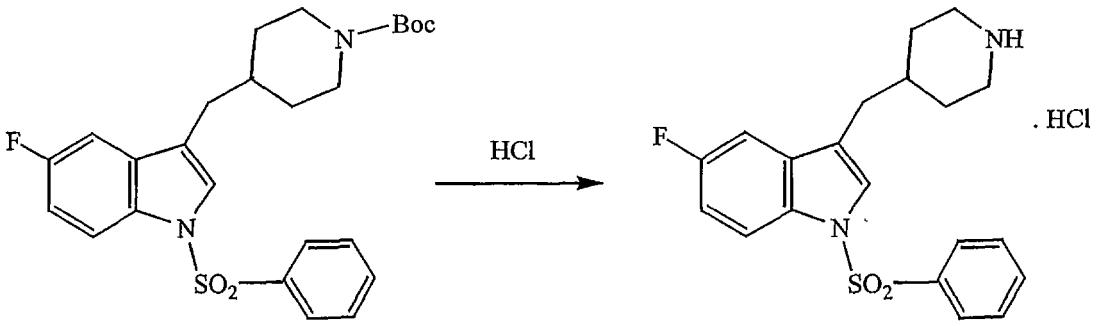
Preparation of *tert*-Butyl 4-{[5-fluoro-1-(phenylsulfonyl)-1*H*-indol-3-yl)methyl]-1-piperidinecarboxylate



A stirred solution of *tert*-butyl 4-[(5-fluoro-1*H*-indol-3-yl)methyl]-1-piperidinecarboxylate (665 mg, 2.0 mmol) in tetrahydrofuran is treated with NaH (60 % in mineral oil, 120 mg, 3.0 mmol) portion-wise, under nitrogen, at room temperature, stirred for 0.5 hr, treated with benzenesulfonyl chloride (0.38 ml, 3.0 mmol), stirred for 18 hr under nitrogen at room temperature, quenched with water and diluted with ethyl acetate. The resultant phases are separated and the organic phase is washed with water and saturated NaCl, dried over $MgSO_4$ and concentrated *in vacuo*. The resultant residue is purified by flash chromatography (silica gel, EtOAc/hexane, 2/8) to afford the title compound as a white solid, 740 mg, mp 155-157°C, identified by NMR and mass spectral analyses.

EXAMPLE 6

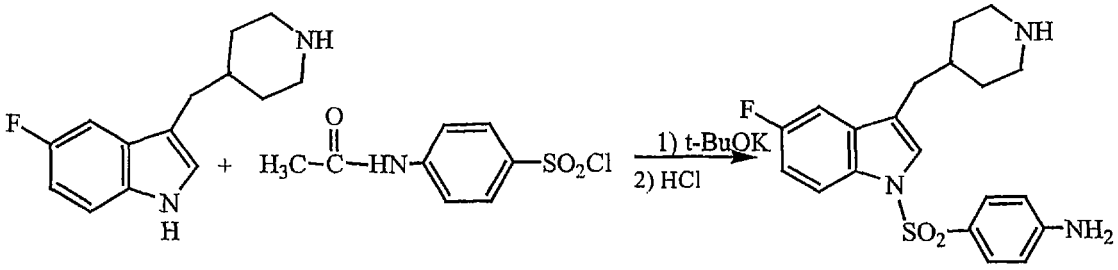
Preparation of 5-Fluoro-1-phenylsulfonyl)-3-(4-piperidinylmethyl)-1*H*-indole hydrochloride



A solution of *tert*-butyl 4-{[5-fluoro-1-(phenylsulfonyl)-1*H*-indol-3-yl)methyl]-1-piperidine carboxylate (637 mg, 1.35 mmol) in methanol and HCl (1M in Et_2O, 7.0 ml) is heated at reflux temperature under N_2 for 18 hr and concentrated *in vacuo*. The resultant residue is diluted with ether and filtered. The filtercake is dried under vacuum to give the title product as an off-white solid, 500 mg, mp 233-235°C, (dec.), identified by NMR and mass spectral analyses.

EXAMPLE 7

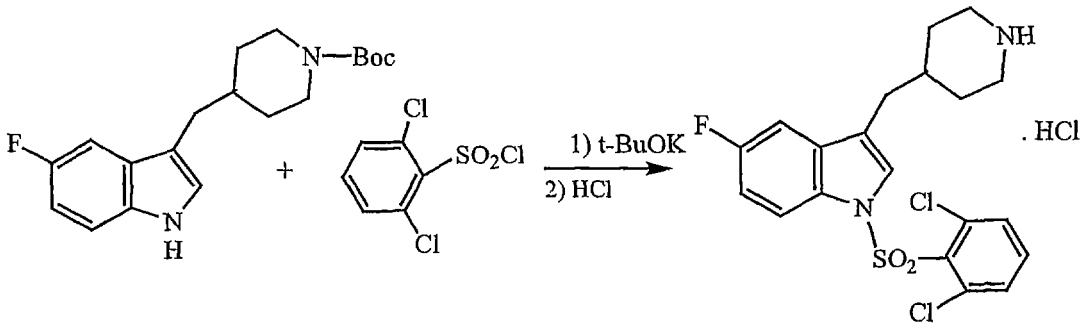
Preparation of 4-{[5-Fluoro-3-(4-piperidinylmethyl)-1H-indole-1-yl]sulfonyl}aniline



A stirred solution of *tert*-butyl 4-[(5-fluoro-1*H*-indol-3-yl)methyl]-1-piperidinecarboxylate (332 mg, 1.0 mmol) in tetrahydofuran (THF) is treated with tBuOK (1.1 ml, 1.1 mmol, 1M in THF solution) under nitrogen at room temperature, stirred for 0.5 hr, treated with N-acetylsulfonilyl chloride (234 mg, 1.0 mmol), stirred for 18 hr and concentrated *in vacuo*. The resultant residue is treated with methanol, followed by 1N HCl (2 ml) heated at reflux temperature for 3 hr, cooled and concentrated *in vacuo*. This residue is dissolved in isopropanol, treated with 1N NaOH to pH>9 and filtered. The filtercake is washed with water and dried under vaccum to afford the title compound as an off-white solid, 170 mg, mp 162-164°C, identified by NMR and mass spectral analyses.

EXAMPLE 8

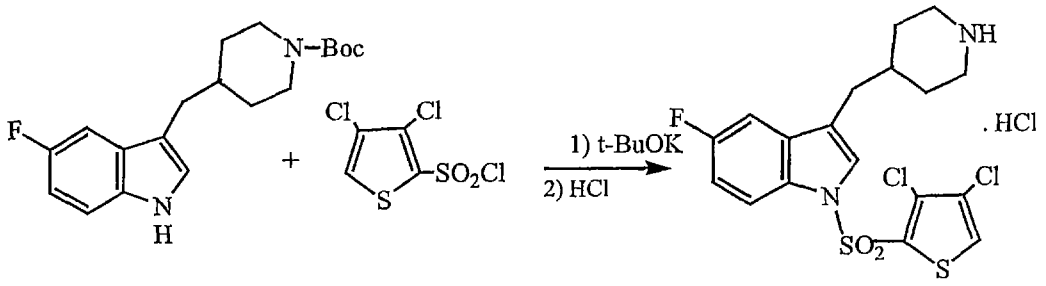
Preparation of 1-[2,6-Dichlorophenyl)sulfonyl]-5-fluoro-3-(4-piperidinylmethyl)-1H-indole hydrochloride



A stirred solution of *tert*-butyl 4-[(5-fluoro-1*H*-indol-3-yl)methyl]-1-piperidinecarboxylate (332 mg, 1.0 mmol) in tetrahydrofuran (THF) is treated with tBuOK (1.1 ml, 1.1 mmol, 1M in THF solution) under nitrogen at room temperature, stirred for 0.5 hr, treated with 2,6-dichlorobenzenesulfonyl chloride (246 mg, 1.0 mmol), stirred for 18 hr at room temperature, quenched with water and diluted with ethyl acetate. The phases are separated and the organic phase is dried over Na_2SO_4 and concentrated *in vacuo*. The resultant residue is treated with methanol and 1N HCl (2 ml), heated at reflux temperature for 3 hr, cooled, and filtered. The filtercake is washed with ethyl acetate and dried to afford the title compound as a white solid, 338 mg, mp 288-290°C, identified by NMR and mass spectral analyses.

EXAMPLE 9

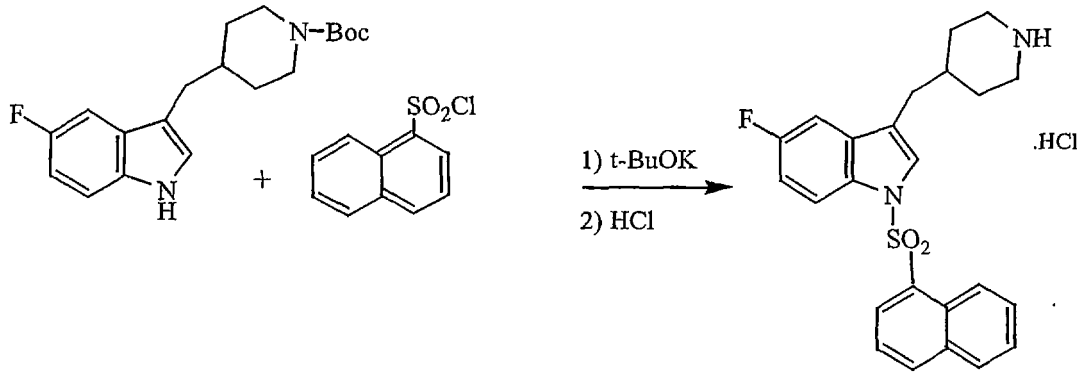
Preparation of 1-[3,4-Dichloro-2-thienyl)sulfonyl]-5-fluoro-3-(4-piperidinylmethyl)-1*H*-indole hydrochloride



A stirred solution of *tert*-butyl 4-[(5-fluoro-1*H*-indol-3-yl)methyl]-1-piperidinecarboxylate (332 mg, 1.0 mmol) in tetrahydrofuran (THF) is treated with tBuOK (1.1 ml, 1.1 mmol, 1M in THF solution) under nitrogen at room temperature, stirred for 0.5 hr, treated with (3,4-dichlorothien-2-yl)sulfonyl chloride (252 mg, 1.0 mmol), stirred for 18 hr at room temperature, quenched with water and diluted with ethyl acetate. The phases are separated and the organic phase is dried over Na_2SO_4 and concentrated *in vacuo*. The resultant residue is treated with methanol, followed by 1N HCl (2 ml), heated at reflux temperature for 3 hr, cooled and filtered. The filtercake is washed with ethyl acetate and dried to afford the title compound as an off-white solid, 327 mg, mp 205-207°C, identified by NMR and mass spectral analyses.

EXAMPLE 10

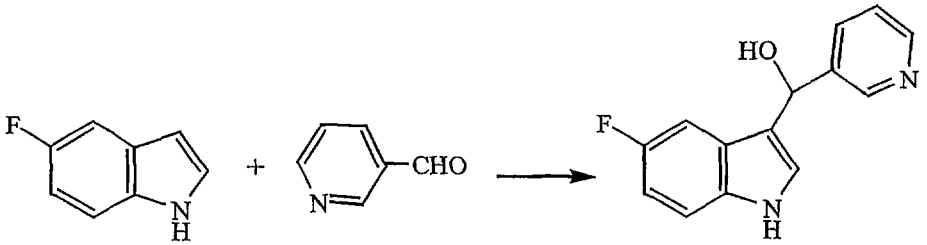
Preparation of 5-Fluoro-1-(1-naphthylsulfonyl)-3-(4-piperidinylmethyl)-1*H*-indole hydrochloride



Using essentially the same procedure described in Example 9 and substituting naphthalenesulfonyl chloride, the title product is obtained as a white solid, 346 mg, mp 295-297°C, identified by NMR and mass spectral analyses.

EXAMPLE 11

Preparation of (5-Fluoro-1*H*-indol-3-yl)(3-pyridinyl)methanol

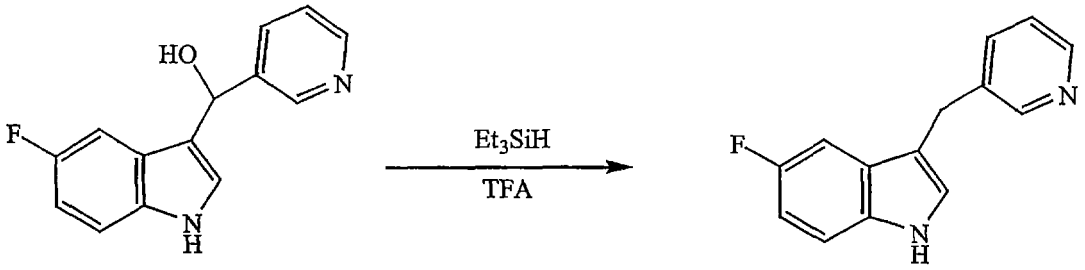


A stirred solution of 5-fluoroindole (4 g, 30 mmol) in methanol is treated with 3-pyridine carboxaldehyde (2.79 ml, 30 mmol), cooled to 0°C, treated with 50% NaOH

(3.25 ml), stirred at 0°C for 1 hr, warmed to room temperature, stirred for 3 hr, treated with water and extracted with ethyl acetate. The extracts are combined, dried over Na_2SO_4 and concentrated *in vacuo*. The residue is treated with ethyl acetate and filtered. The filtrate is further concentrated and filtered. The filtercakes are combined and dried to afford the title compound as a pale orange solid 5.2 g (73%) mp 131-133°C, identified by NMR and mass spectral analyses.

EXAMPLE 12

Preparation of 5-Fluoro-3-(3-pyridinylmethyl)-1*H*-indole

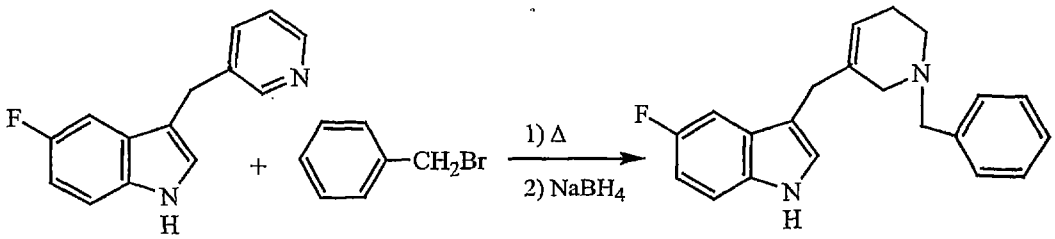


A suspension of (5-fluoro-1H-indole-3-yl)-pyridin-3-yl-methanol (5.00 g, 21 mmol) in methylene chloride is treated with triethylsilane (3.70 ml, 23 mmol) and trifluoroacetic acid (TFA), stirred at room temperature overnight, and concentrated *in vacuo*. The resultant residue is basified with 2.5 N NaOH and saturated $NaHCO_3$, and extracted with methylene chloride. The extracts are combined, dried over Na_2SO_4 and concentrated *in vacuo*. This residue is purified by column chromatography (50%EtOAc/CH_2Cl_2) to give the title compound as a pale

orange solid 3.24 g (68%) mp 109-112°C, identified by NMR and mass spectral analyses.

EXAMPLE 13

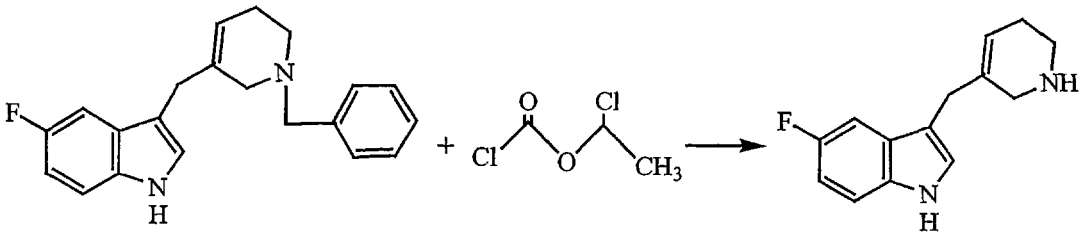
Preparation of 3-[(1-Benzyl-1,2,3,6-tetrahydro-3-pyridinyl)methyl]-5-fluoro-1*H*-indole



A solution of 5-fluoro-3-pyridin-3-yl-1H-indole (1.2 g, 5.3 mmol) in methyl ethyl ketone is treated with benzyl bromide (4.32 ml, 35.4 mmol), heated at reflux temperature for 3 hr, cooled and decanted. The resulting oil is stirred with ether to remove residual benzyl bromide and decanted. The remaining residue is dissolved in methanol, cooled to 0°C, treated with crushed $NaBH_4$ (670 mg) pellets, stirred at 0°C for 1 hr, quenched with saturated $NaHCO_3$ and concentrated *in vacuo*. The resultant aqueous solution is extracted with methylene chloride. The extracts are combined, dried over Na_2SO_4 and concentrated *in vacuo*. The resulting yellow foam residue is purified by column chromatography (40% EtOAc/hexanes) to give the title compound as a pale yellow solid, 730 mg (43%) mp 133-136°C, identified by NMR and mass spectral analyses.

EXAMPLE 14

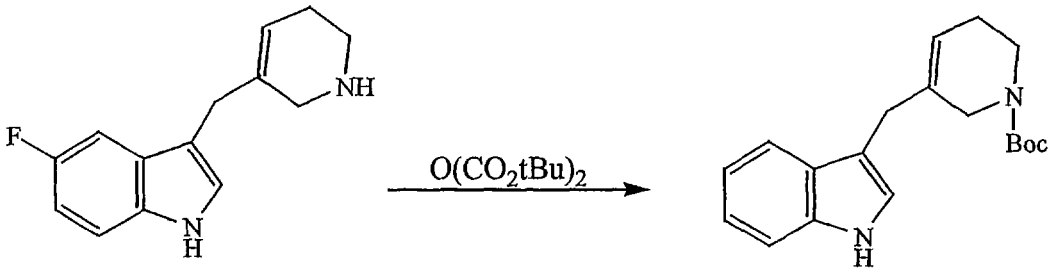
Preparation of 5-Fluoro-3-(1,2,3,6-tetrahydro-3-pyridinylmethyl)-1*H*-indole



A solution of 3-[(1-benzyl-1,2,3,6-tetrahydro-3-pyridinyl)methyl]-5-fluoro-1*H*-indole (500 mg, 1.57 mmol) in dichloroethane is treated with chloroethylchloroformate (0.51 mL, 4.7 mmol), stirred at 80°C for 4.5 hr, cooled and concentrated in vacuo to give a residue. The residue is treated with methanol, heated at reflux temperature overnight, cooled and concentrated *in vacuo*. The resultant residue is purified by column chromatography (10% MeOH/CH_2Cl_2+NH_4OH) to give the title compound as a pale yellow solid, 240 mg (66%) mp 145°C (dec.), identified by NMR and mass spectral analyses.

EXAMPLE 15

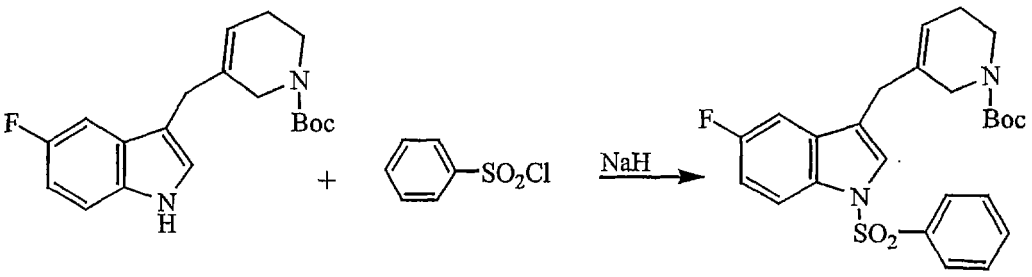
Preparation of *tert*-Butyl 5-[(5-fluoro-1*H*-indol-3-yl)methyl]-3,6-dihydro-1(2*H*)-pyridinecarboxylate



A mixture of 5-fluoro-3-(1,2,3,6-tetrahydro-3-pyridinylmethyl)-1*H*-indole (0.53 g, 2.3 mmol) and di-tert-butyl dicarbonate (0.55 g, 2.5 mmol) in 1N NaOH(2.5 ml) and dioxane is stirred under nitrogen at room temperature for 18 hr, quenched with water and diluted with ethyl acetate. The organic phase is separated, washed with water and saturated NaCl, dried over $MgSO_4$ and concentrated *in vacuo*. The resultant residue is purified by flash chromatography (silica gel, EtOAc/hexane: 3/7) to afford the title compound as a yellow foam, 0.46 g, mp 78-80°C, identified by NMR and mass spectral analyses.

EXAMPLE 16

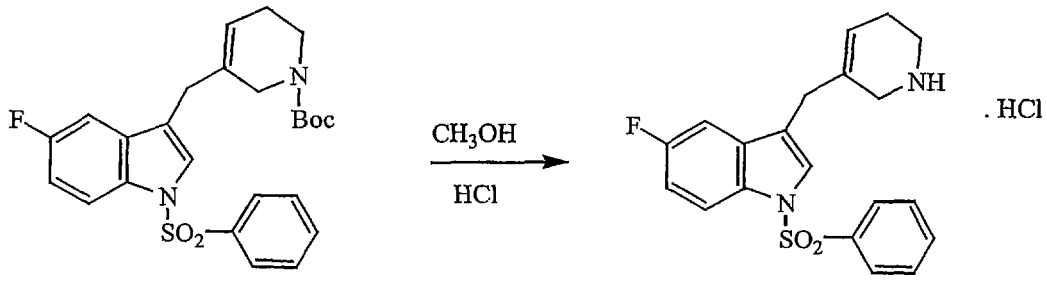
Preparation of *tert*-Butyl 5-{[5-fluoro-1-(phenylsulfonyl)-1*H*-indol-3-yl]methyl}-3,6-dihydro-1(2*H*)-pyridinecarboxylate



A stirred solution of *tert*-butyl 5-[(5-fluoro-1*H*-indol-3-yl)methyl]-3,6-dihydro-1(2*H*)-pyridinecarboxylate (430 mg, 1.30 mmol) in tetrahydrofuran is treated with NaH (60% in mineral oil, 78 mg, 1.95 mmol) portion-wise under nitrogen at room temperature, stirred for 0.5 hr, treated with benzenesulfonyl chloride (0.25 ml, 1.95 mmol), stirred for 17 hr under nitrogen at room temperature, quenched with ice-water and diluted with ethyl acetate. The phases are separated and the aqueous phase is extracted with ethyl acetate. The combined extracts and organic phase are washed with water and saturated NaCl, dried over $MgSO_4$ and concentrated *in vacuo*. The resultant residue is purified by flash chromatography (silica gel, EtOAc/hexane, 1/9) to afford the title compound as a yellow solid, 350 mg, mp 63-65 °C, identified by NMR and mass spectral analyses.

EXAMPLE 17

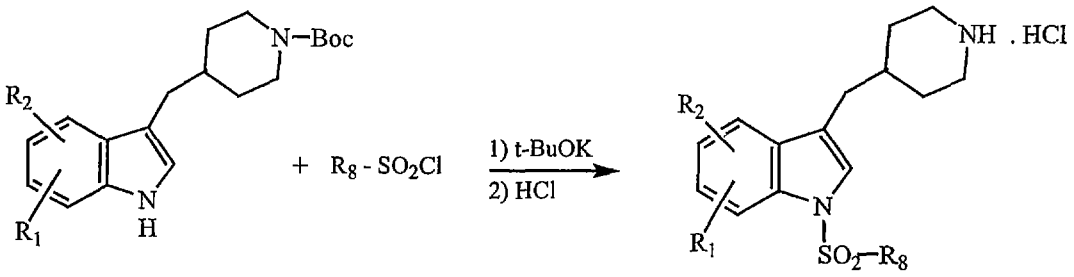
Preparation of 5-Fluoro-1-(phenylsulfonyl)-3-(1,2,5,6-tetrahydro-3-pyridinylmethyl)-1*H*-indole hydrochloride



A solution of *tert*-butyl 5-{[5-fluoro-1-(phenylsulfonyl)-1*H*-indol-3-yl]methyl}-3,6-dihydro-1(2*H*)-pyridinecarboxylate (320 mg, 0.68 mmol) in methanol and HCl (1M in Et_2O, 1.0 ml) is heated at reflux temperature under nitrogen for 18 hr, cooled and concentrated *in vacuo*. The resultant residue is treated with ether and filtered. The filtercake is dried *in vacuo* to afford the title compound as a brown solid, 211 mg, mp 96°C (dec.), identified by NMR and mass spectral analyses.

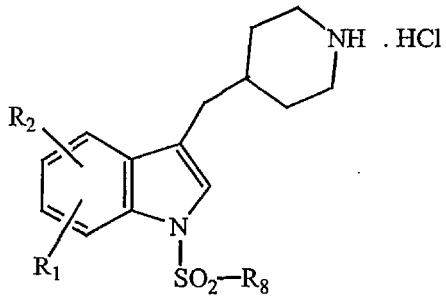
EXAMPLES 18-28

Preparation of 1-Arylsulfonyl-substituted-3[(4-piperidinyl)methyl]indole hydrochloride



Using essentially the same procedures described hereinabove and employing the appropriate indole substrate and arylsulfonyl chloride, the compounds shown in Table I are obtained and identified by mass spectral and NMR analyses.

Table I



Ex. No.	R_1	R_2	R_8	mp °C
18	H	5-F	3,4-dimethoxyphenyl	246 dec
19	H	5-F	4-benzonitrile	249 dec
20	H	5-F	quinolin-8-yl	245 dec
21	6-F	H	phenyl	>250 dec
22	6-F	H	1-naphthyl	265 dec
23	6-F	H	3,4-dimethoxyphenyl	218-220 dec
24	6-F	H	2-chlorophenyl	249-251 dec
25	6-F	H	5-chlorothien-2-yl	227-229 dec
26	6-F	H	2-fluorophenyl	206-208 dec
27	6-F	H	3-fluorophenyl	240 dec
28	6-F	H	4-aminophenyl	198-200

EXAMPLE 21

Comparative Evaluation of 5-HT6 Binding Affinity of Test Compounds

The affinity of test compounds for the serotonin 5-HT6 receptor is evaluated in the following manner. Cultured Hela cells expressing human cloned 5-HT6 receptors are harvested and centrifuged at low speed (1,000 x g) for 10.0 min to remove the culture media. The harvested cells are suspended in half volume of fresh physiological phosphate buffered saline solution and recentrifuged at the same speed. This operation is repeated. The collected cells are then homogenized in ten volumes of 50 mM Tris.HCl (pH 7.4) and 0.5 mM EDTA. The homogenate is centrifuged at 40,000 x g for 30.0 min and the precipitate is collected. The obtained pellet is resuspended in 10 volumes of Tris.HCl buffer and recentrifuged at the same speed. The final pellet is suspended in a small volume of Tris.HCl buffer and the tissue protein content is determined in aliquots of 10-25 µl volumes. Bovine Serum Albumin is 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 is adjusted to give a tissue protein concentration of 1.0 mg/ml of suspension. The prepared membrane suspension (10 times concentrated) is aliquoted in 1.0 ml volumes and stored at -70° C until used in subsequent binding experiments.

Binding experiments are performed in a 96 well microtiter plate format, in a total volume of 200 µl. To each well is 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-HT6 receptor is 2.9 nM, as determined by saturation binding with increasing concentrations of [^{3}H]LSD. The reaction is initiated by the final addition of 100.0 µl of tissue suspension. Nonspecific binding is measured in the presence of 10.0 µM methiothepin. The test compounds are added in 20.0 µl volume.

The reaction is allowed to proceed in the dark for 120 min at room temperature, at which time, the bound ligand-receptor complex is filtered off on a 96 well unifilter with a Packard Filtermate® 196 Harvester. The bound complex caught on the filter disk is 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 is heat-sealed and counted in a PackardTopCount® with a tritium efficiency of 31.0%.

Specific binding to the 5-HT6 receptor is 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 is expressed as a percentage of specific binding

in the absence of test compound. The results are 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 is 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 is 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 are determined and compared to those values obtained by representative compounds known to demonstrate binding to the 5-HT6 receptor. The data are shown in Table II, below.

Table II

Test Compound (Ex. No.)	5-HT6 Binding Ki (nM)
6	12.0
7	1.0
10	13.0
18	8.0
19	162.0
20	2.0

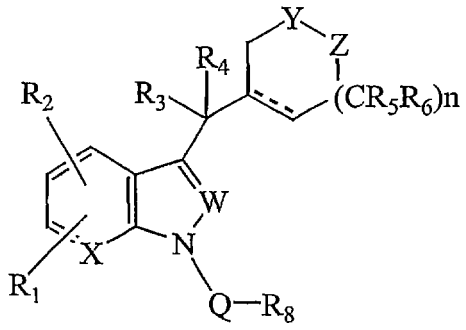
Table II cont'd

Test Compound (Ex. No.)	5-HT6 Binding Ki (nM)
21	13.0
22	24.0
23	19.0
24	13.0
25	18.0
26	17.0
27	29.0
28	3.0
Comparative Examples	**5-HT6 Binding Ki**
Clozapine	6.0
Loxapine	41.4
Bromocriptine	23.0
Methiothepin	8.3
Mianserin	44.2
Olanzepine	19.5

As can be seen from the results set forth above, the compounds of the invention demonstrate a high degree of affinity for the 5-HT6 receptor.

WHAT IS CLAIMED IS:

1. A compound of formula I



(I)

wherein

Q is SO_2, CO, $CONR_{24}$, $CSNR_{25}$ or CH_2;

W is N or CR_7;

X is N or CR_9;

Y is NR or $CR_{10}R_{29}$;

Z is NR_{21} or $CR_{11}R_{30}$ with the proviso that when Y is NR then Z must be $CR_{11}R_{30}$ and with the further proviso that at least one of Y and Z must be NR or NR_{21};

n is 0 or an integer of 1 or 2;

R and R_{21} are each independently H, $CNR_{26}NR_{27}R_{28}$, or a C_1-C_6alkyl, C_3-C_6cycloalkyl, cycloheteroalkyl, aryl or heteroaryl group each optionally substituted;

R_1, R_2 and R_9 are each independently H, halogen, CN, OCO_2R_{12}, CO_2R_{13}, $CONR_{22}R_{23}$, $CNR_{14}NR_{15}R_{16}$, SO_mR_{17}, $NR_{18}R_{19}$, OR_{20}, or a C_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_3-C_6- cycloalkyl, cycloheteroalkyl, C_1-C_6alkanoyl, aryl or heteroaryl group each optionally substituted;

m is 0 or an integer of 1 or 2;

R_3 and R_4 are each independently H, halogen, C_1-C_4alkyl or C_1-C_4haloalkyl or R_3 and R_4 may be taken together with the atom to which they are attached to form a carbonyl group;

R_5 and R_6 are each independently H or an optionally substituted C_1-C_6alkyl group;

R_7 is H, halogen, or a C_1-C_6alkyl, C_1-C_6alkoxy, aryl or heteroaryl group each optionally substituted;

R_8 is an optionally substituted C_1-C_6alkyl, aryl or heteroaryl group;

R_{10}, R_{11}, R_{29} and R_{30} are each independently H or an optionally substituted C_1-C_6alkyl group;

R_{12}, R_{13} and R_{17} are each independently H or an optionally substituted C_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_3-C_6cycloalkyl, cycloheteroalkyl, aryl or heteroaryl group;

R_{14}, R_{15}, R_{16}, R_{18}, R_{19}, R_{26}, R_{27} and R_{28} are each independently H or C_1-C_4alkyl;

R_{20}, R_{22} and R_{23} are each independently H or an optionally substituted C_1-C_6alkyl group;

R_{24} and R_{25} are each independently H or an alkyl, aryl or heteroaryl group each optionally substituted; and

---- represents a single bond or a double bond; or

a pharmaceutically acceptable salt thereof.

2. A compound according to claim 1 wherein n is 1.

3. A compound according to claim 1 or claim 2 wherein R_3 and R_4 are H.

4. A compound according to any one of claims 1 to 3 wherein Q is SO_2 or CO.

5. A compound according to any one of claims 1 to 4 wherein ---- represents a single bond.

6. A compound according to any one of claims 1 to 5 wherein X is CR_9

7. A compound according to claim 6 wherein R_9 is hydrogen.

8. A compound according to any one of claims 1 to 7 wherein Y is $CR_{10}R_{29}$.

9. A compound according to any one of claims 1 to 8 wherein Z is NR_{21}.

10. A compound according to claim 9 wherein R_{21} is hydrogen.

11. A compound according to any one of claims 1 to 7 wherein Y is NR and Z is CH_2.

12. A compound according to any one of claims 1 to 11 wherein R_8 is aryl or heteroaryl; said aryl and heteroaryl groups being optionally substituted by one to 3 substituents the same or different selected from nitro, cyano, thiocyanato, cyanato, hydroxyl, alkyl of 1-6 carbon atoms, halo(C_1-C_6)alkyl, (C_1-C_6)alkoxy, halo(C_1-C_6)alkoxy, amino, (C_1-C_6)alkylamino, di-(C_1-C_6alkyl)amino, formyl, (C_1-C_6alkoxy)carbonyl, carboxyl, (C_1-C_6)alkanoyl, (C_1-C_6)alkylthio, (C_1-C_6)alkylsuphinyl, (C_1-C_6)alkyl-sulphonyl, carbamoyl, (C_1-C_6)alkylamido, phenyl, phenoxy,

benzyl, benzyloxy, heteroaryl, cycloheteroalkyl and (C_3-C_8)cycloalkyl groups.

13. A compound according to claim 2 wherein X is CR_9; Y is $CR_{10}R_{29}$; Z is NR_{21}; R_3 and R_4 are H; and ---- represents a single bond.

14. A compound according to claim 12 wherein Q is SO_2; R_{21} is H; R_8 is an optionally substituted aryl group; and ---- represents a single bond.

15. A compound according to claim 6 wherein Q is SO_2; R_{21} is H; R_8 is an optionally substituted aryl group; and ---- represents a single bond.

16. A compound according to claim 1 selected from the group consisting of:

5-fluoro-1-(phenylsulfonyl)-3-(piperidin-4-ylmethyl)-1H-indole;

5-fluoro-1-(phenylsulfonyl)-3-(1,2,5,6-tetrahydro-3-pyridinylmethyl)-1H-indole;

4-{[5-fluoro-3-(4-piperidinylmethyl)-1H-indol-1yl]sulfonyl}aniline;

1-[(2,6-dichlorophenyl)sulfonyl]-5-fluoro-3-(4-piperidinylmethyl)-1H-indole;

1-[(3,4-dichloro-2-thienyl)sulfonyl]-5-fluoro-3-(4-piperidinylmethyl)-1H-indole;

5-fluoro-1-(1-naphthylsulfonyl)-3-(4-piperidinylmethyl)-1H-indole;

1-[(3,4-dimethoxyphenyl)sulfonyl]-5-fluoro-3-(piperidin-4-ylmethyl)-1H-indole;

4-{[5-fluoro-3-(piperidin-4-ylmethyl)-1H-indol-1-yl]sulfonyl}benzonitrile;

8-{[5-fluoro-3-(piperidin-4-ylmethyl)-1H-indol-1-yl]sulfonyl}quinoline;

1-(phenylsulfonyl)-3-(piperidin-4-ylmethyl)-1H-indole;

1-(1-naphthylsulfonyl)-3-(piperidin-4-ylmethyl)-1H-indole;

4-{[3-(piperidin-4-ylmethyl)-1H-indol-1-yl]sulfonyl}phenylamine;

1-[(3,4-dichlorothien-2-yl)sulfonyl]-3-(piperidin-4-ylmethyl)-1H-indole;

1-(phenylsulfonyl)-3-(piperidin-4-ylmethyl)-1H-pyrrolo[2,3-b]pyridine;

1-(1-naphthylsulfonyl)-3-(piperidin-4-ylmethyl)-1H-pyrrolo[2,3-b]pyridine;

4-{[3-(piperidin-4-ylmethyl)-1H-pyrrolo[2,3-b]pyridin-1-yl]sulfonyl}phenylamine;

1-[(3,4-dichlorothien-2-yl)sulfonyl]-3-(piperidin-4-ylmethyl)-1H-pyrrolo[2,3-b]pyridine;

6-fluoro-1-(phenylsulfonyl)-3-(4-piperidinylmethyl)-1H-indole;

6-fluoro-1-(1-naphthylsulfonyl)-3-(4-piperidinylmethyl)-1H-indole;

6-fluoro-1-(3,4-dimethoxyphenylsulfonyl)-3-(4-piperidinylmethyl)-1H-indole;

6-fluoro-1-(2-chlorophenylsulfonyl)-3-(4-piperidinylmethyl)-1H-indole;

6-fluoro-1-(5-chlorothien-2-ylsulfonyl)-3-(4-piperidinylmethyl)-1H-indole;

6-fluoro-1-(2-fluorophenylsulfonyl)-3-(4-piperidinylmethyl)-1H-indole;

6-fluoro-1-(3-fluorophenylsulfonyl)-3-(4-piperidinylmethyl)-1H-indole; and
a pharmaceutically acceptable salt thereof.

17. 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 with a therapeutically effective amount of a compound of formula I a pharmaceutically acceptable salt thereof as claimed in any one of claims 1 to 16.

18. The method according to claim 17 wherein said disorder is a mood disorder, a cognitive disorder or a motor disorder.

19. The method according to claim 17 wherein said disorder is anxiety or depression.

20. The method according to claim 17 wherein said disorder is schizophrenia.

21. The method according to claim 17 wherein said disorder is attention deficit disorder or memory loss.

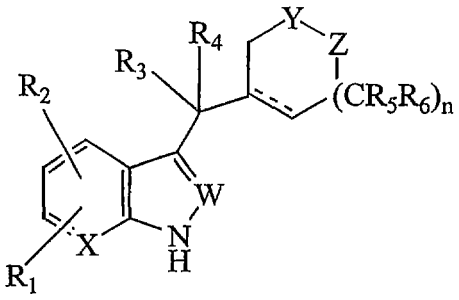
22. The method according to claim 17 wherein said disorder is caused by alcohol or drug withdrawl.

23. A pharmaceutical composition which comprises a pharmaceutically acceptable carrier and a compound of

formula I or a pharmaceutically acceptable salt thereof as claimed in any one of claims 1 to 16.

24. A process for the preparation of a compound of formula I which comprises one of the following:

a) reacting a compound of formula



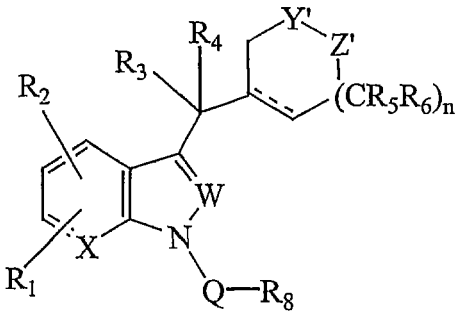
wherein n, W, X, Y, Z, R_1, R_2, R_3, R_4, R_5 and R_6 are as defined herein, with an appropriate sulphonylating, acylating, carbamoylating, thiocarbamoylating or alkylating agent containing the group:

R_8-Q-

where R_8 is as defined above and Q is SO_2, CO, $CONR_{24}$, $CSNR_{25}$ or CH_2 ; said reactants protected on reactive sites and/or on reactive substituent groups as required, and removing any protecting groups, to give a corresponding compound of formula (I);

or

b) removing a protecting group from a compound of formula



wherein n, Q, W, X, R_1, R_2, R_3, R_4, R_5 R_6, and R_8 are as defined herein and at of Y' and Z' is N-G where G is a protecting group to give a compound of formula (I) wherein Y or Z is NH;

or

c) alkylating a compound of formula (I) as defined in claim 1 wherein R or R_{21} is hydrogen with an alkylating agent of formula R-L or R_{21}-L wherein L is a leaving group, such as halogen, and R and R_{21} are as defined in claim 1 excepting hydrogen to give a corresponding compound of formula (I);

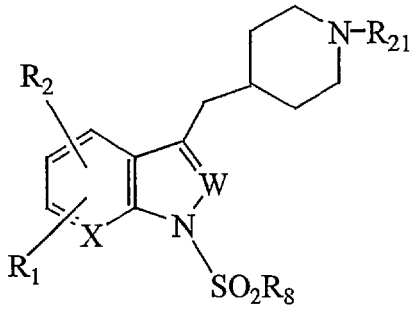
or

d) converting a compound of formula (I) having a reactive substituent group to a different compound of formula I;

or

e) converting a basic compound of formula (I) to an acid addition salt or vice versa.

25. A process for the preparation of a compound of formula Ia'



(Ia')

wherein

W is N or CR_7;

X is N or CR_9;

R_1, R_2 and R_9 are each independently H, halogen, CN, OC_2R_{12}, CO_2R_{13}, $CONR_{22}R_{23}$, $CNR_{14}NR_{15}R_{16}$, SO_mR_{17}, $NR_{18}R_{19}$, OR_{20}, or a C_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_3-C_6cycloalkyl, cycloheteroalkyl, C_1-C_6alkanoyl, aryl or heteroaryl group each optionally substituted;

m is 0 or an integer of 1 or 2;

R_7 is H, halogen, or a C_1-C_6alkyl, C_1-C_6alkoxy, aryl or heteroaryl group each optionally substituted;

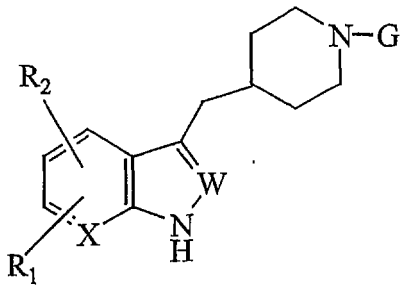
R_8 is an optionally substituted C_1-C_6alkyl, aryl or heteroaryl group;

R_{12}, R_{13} and R_{17} are each independently H or an optionally substituted C_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_3-C_6cycloalkyl, cycloheteroalkyl, aryl or heteroaryl group;

R_{14}, R_{15}, R_{16}, R_{18}, R_{19}, R_{26}, R_{27} and R_{28} are each independently H or C_1-C_4 alkyl; and

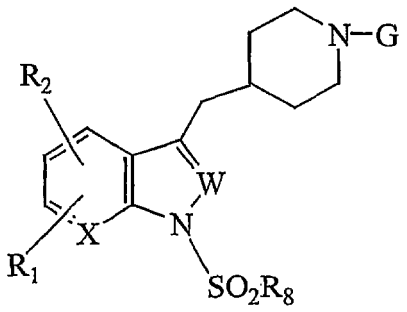
R_{21} is H, $CNR_{26}NR_{27}R_{28}$, or a C_1-C_6alkyl, C_3-C_6cycloalkyl, cycloheteroalkyl, aryl or heteroaryl group each optionally substituted

which process comprises reacting a compound of formula IVa



(IVa)

wherein G represents a protecting group and W, X, R_1 and R_2 are as defined hereinabove with an arylsulfonyl chloride, R_8SO_2Cl, wherein R_8 is as defined hereinabove in the presence of a base to form the intermediate of formula Va;



(Va)

deprotecting the formula Va compound in the presence of an acid to give the compound of formula Ia' wherein R_{21} is

H; and optionally reacting said formula Va compound with an alkylating agent, R_{21}-Hal, wherein Hal is Cl, I or Br and R_{21} is other than H.