HETEROCYCLYLOXY-, -THIOXY- AND -AMINOBENZAZOLE DERIVATIVES AS 5-HYDROXYTRYPTAMINE-6 LIGANDS

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

BACKGROUND OF THE INVENTION

Various 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 the 5-*HT1 family* (e.g. 5-*HT1A*), the 5-*HT2 family* (e.g. 5-HT2A), 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. Lower levels of 5-HT6 receptor mRNA were seen in the granular layer of the cerebellum,

several diencephalic nuclei, amygdala and in the cortex. Northern blots have revealed that 5-HT6 receptor mRNA appears to be exclusively 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. Therefore, 5-HT6 receptor ligands are believed to be of potential use in the treatment of certain CNS disorders such as anxiety, depression, epilepsy, obsessive compulsive disorders, attention deficit disorder, migraine, cognitive memory enhancement (e.g. for the treatment of Alzheimer's disease), sleep disorders, feeding disorders (e.g. anorexia and bulimia), panic attacks, withdrawal from drug abuse (e.g. cocaine, ethanol, nicotine and benzodiazepines), 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.

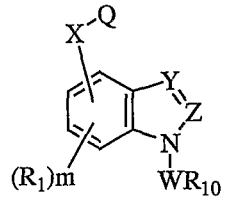
It is another object of this invention to provide therapeutic methods and pharmaceutical compositions useful for the treatment of central nervous system disorders related to or affected by the 5-HT6 receptor.

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 compounds of formula I



(I)

wherein

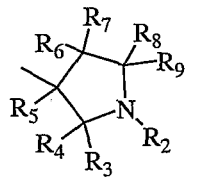
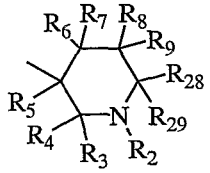
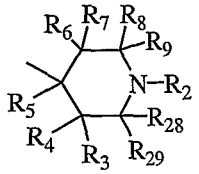
W is SO_2, CO, CONH, CSNH or $(CH_2)_x$;

X is O, SO_n or NR_{11};

Y is CR_{12} or N;

Z is CR_{13} or N with the proviso that when Y is N then Z must be CR_{13};

m and x are each independently 0 or an integer of 1, 2 or 3;

Q is  ,  or  ;

R_1 is halogen, CN, OR_{14}, CO_2R_{15}, $CONR_{16}R_{17}$, $CNR_{18}NR_{19}R_{20}$, $SO_2NR_{21}R_{22}$, SO_pR_{23} or a C_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_3-C_6cycloalkyl, cycloheteroalkyl, phenyl or heteroaryl group each optionally substituted;

R_2 is H, $CNR_{24}NR_{25}R_{26}$ or a C_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_3-C_6cycloalkyl, cycloheteroalkyl, aryl or heteroaryl group each optionally substituted;

R_3, R_4, R_5, R_6, R_7, R_8, R_9, R_{28} and R_{29} are each independently H or an optionally substituted C_1-C_6alkyl group;

R_{10} is an optionally substituted C_1-C_6alkyl, aryl or heteroaryl group;

n and p are each independently 0 or an integer of 1 or 2;

R_{11} is H or a C_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_3-C_6cycloalkyl or cycloheteroalkyl group each optionally substituted;

R_{12} and R_{13} are each independently H, halogen or a C_1-C_6alkyl, aryl, heteroaryl or C_1-C_6alkoxy group each optionally substituted;

R_{14} is H, COR_{27} or a C_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, aryl or heteroaryl group each optionally substituted;

R_{15} and R_{27} are each independently H or a C_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_3-C_6cycloalkyl, cycloheteroalkyl, aryl or heteroaryl group each optionally substituted;

R_{16}, R_{17}, R_{18}, R_{19}, R_{20}, R_{24}, R_{25} and R_{26} are each independently H or an optionally substituted C_1-C_6alkyl group;

R_{21} and R_{22} are each independently H or a C_1-C_6alkyl, aryl or heteroaryl group each optionally substituted; and

R_{23} is an optionally substituted C_1-C_6alkyl, aryl, or heteroaryl group; or

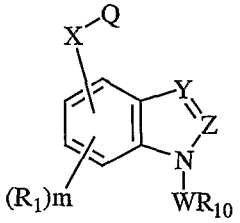
the stereoisomers thereof or the pharmaceutically acceptable salts thereof.

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 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 heterocyclyloxy-, -thioxy- or -aminobenzazole derivatives of formula I demonstrate 5-HT6 affinity. Advantageously, said benzazole derivatives may be used as 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 heterocyclyloxy-, -thioxy- or -aminobenzazole derivatives of formula I



(I)

wherein

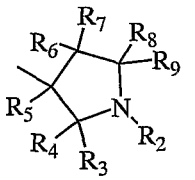
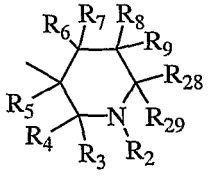
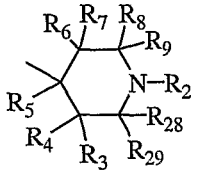
W is SO_2, CO, CONH, CSNH or $(CH_2)_x$;

X is O, SO_n or NR_{11};

Y is CR_{12} or N;

Z is CR_{13} or N with the proviso that when Y is N then Z must be CR_{13};

m and x are each independently 0 or an integer of 1, 2 or 3;

Q is  ,  or  ;

R_1 is halogen, CN, OR_{14}, CO_2R_{15}, $CONR_{16}R_{17}$, $CNR_{18}NR_{19}R_{20}$, $SO_2NR_{21}R_{22}$, SO_pR_{23} or a C_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_3-C_6cycloalkyl, cycloheteroalkyl, phenyl or heteroaryl group each optionally substituted;

R_2 is H, $CNR_{24}NR_{25}R_{26}$ or a C_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_3-C_6cycloalkyl, cycloheteroalkyl, aryl or heteroaryl group each optionally substituted;

R_3, R_4, R_5, R_6, R_7, R_8, R_9, R_{28} and R_{29} are each independently H or an optionally substituted C_1-C_6alkyl group;

R_{10} is an optionally substituted C_1-C_6alkyl, aryl or heteroaryl group;

n and p are each independently 0 or an integer of 1 or 2;

R_{11} is H or a C_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_3-C_6cycloalkyl, cycloheteroalkyl, aryl or heteroaryl group each optionally substituted;

R_{12} and R_{13} are each independently H, halogen or a C_1-C_6alkyl, aryl, heteroaryl or C_1-C_6alkoxy group each optionally substituted;

R_{14} is H, COR_{27} or a C_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, aryl or heteroaryl group each optionally substituted;

R_{15} and R_{27} are each independently H or a C_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_3-C_6cycloalkyl, cycloheteroalkyl, aryl or heteroaryl group each optionally substituted;

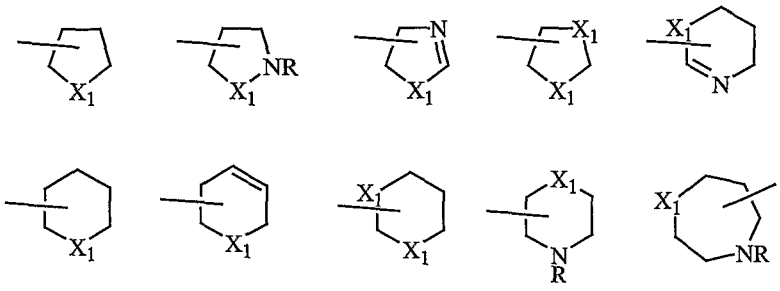
R_{16}, R_{17}, R_{18}, R_{19}, R_{20}, R_{24}, R_{25} and R_{26} are each independently H or an optionally substituted C_1-C_6alkyl group;

R_{21} and R_{22} are each independently H or a C_1-C_6alkyl, aryl or heteroaryl group each optionally substituted; and

R_{23} is an optionally substituted C_1-C_6alkyl, aryl, or heteroaryl group; or

the stereoisomers thereof or the pharmaceutically acceptable salts thereof.

As used in the specification and claims, the term halogen designates Br, Cl, I or F and the term cycloheteroalkyl designates a C_5-C_7cycloalkyl ring system containing 1, 2 or 3 heteroatoms, which may be the same or different, selected from N, O or S and optionally containing one double bond. Exemplary of the cycloheteroalkyl ring systems included in the term as designated herein are the following rings wherein X_1 is NR, O or S and R is H or an optional substituent as defined hereinbelow.



Similarly, as used in the specification and claims, the term heteroaryl designates a 5- to 10-membered aromatic ring system containing 1, 2 or 3 heteroatoms, which may be the same or different, selected from N, O or S. Such heteroaryl ring systems include pyrrolyl, azolyl, oxazolyl, thiazolyl, imidazolyl, furyl, thienyl, quinolinyl, isoquinolinyl, indolinyl, benzothienyl, benzofuranyl, benzisoxazolyl or the like. The term haloalkyl as used herein 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 as used herein 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, phenyl 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 (e.g. heteroaryl and cycloheteroalkyl) or cycloalkyl groups, preferably halogen atoms or lower alkyl groups. Typically, 0-3 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.

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, malonic, mandelic, succinic, fumaric, acetic, lactic, nitric, sulfonic, p-toluene sulfonic, methane sulfonic acid or the like.

Compounds of the invention may exist as one or more stereoisomers. The various stereoisomers include enantiomers, diastereomers, atropisomers and geometric isomers. One skilled in the art will appreciate that one stereoisomer may be more active or may exhibit beneficial effects when enriched relative to the other steroisomer(s) or when separated from the other stereoisomer(s). Additionally, the skilled artisan knows how to separate, enrich, or selectively prepare said stereoisomers. Accordingly, the present invention comprises compounds of Formula I, the stereoisomers thereof and the pharmaceutically acceptable salts thereof. The compounds of the invention may be present as a mixture of stereoisomers, individual stereoisomers, or as an optically active or enantiomerically pure form.

Preferred compounds of the invention are those compounds of formula I wherein W is SO_2 or CO. Also preferred are those compounds of formula I wherein X is O. Another group of preferred compounds of the invention are those compounds of formula I wherein Y is CR_{12}. Further preferred compounds of the invention are those compounds of formula I wherein R_{10} is an aryl or heteroaryl group each optionally substituted. Preferably Q is an optionally substituted 3-pyrrolidinyl group. Z may be for example N.

Examples of R_{10} are aryl e.g. phenyl or naphthyl, or heteroaryl e.g.,pyrazolyl (such as pyrazol-4-yl) 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 halo, 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 and cycloheteroalkyl or (C_3-C_8)cycloalkyl groups.

More preferred compounds of the invention are those compounds of formula I wherein W is SO_2; X is O; and R_{10} is an aryl or heteroaryl group each optionally substituted. Another group of more preferred compounds of the invention are those compounds of formula I wherein W is SO_2; X is O; Y is CR_{12}; and Q is a 3-pyrrolidinyl group.

Among the preferred compounds of the invention are:

1-(phenylsulfonyl)-4-(3-pyrrolidinyloxy)-1H-indole;

4-(3-pyrrolidinyloxy)1-(thien-2-ylsulfonyl)-1H-indole;

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

1-(1-naphthylsulfonyl)-4-(3-pyrrolidinyloxy)-1H-indole;

1-[(5-chloro-1,3-dimethyl-1H-pyrazol-4-yl)sulfonyl]-4-(3-pyrrolidinyloxy)-1H-indole;

1-(phenylsulfonyl)-4-(3-pyrrolidinyloxy)-1H-indazole;

1-(1-naphthylsulfonyl)-4-(3-pyrrolidinyloxy)-1H-indazole;

1-[(2-chlorophenyl)sulfonyl]-4-(3-pyrrolidinyloxy)-1H-indazole;

1-[(2-fluorophenyl)sulfonyl]-4-(3-pyrrolidinyloxy)-1H-indazole;

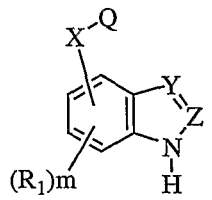
1-[3,4-dimethoxyphenyl)sulfonyl]-4-(3-pyrrolidinyloxy)-1H-indazole;

1-[(5-chlorothien-2-yl)sulfonyl]-4-(3-pyrrolidinyloxy)-1H-indazole;

N-(2-chloro-4-{[4-(3-pyrrolidinyloxy)-1H-indazol-1-yl]sulfonyl}phenyl)acetamide;
N-(4-{[4-(3-pyrrolidinyloxy)-1H-indazol-1y}(sulfonyl]phenyl)acetamide;
8-{[4-(3-pyrrolidinyloxy)-1H-indazol-1-yl]sulfonyl}quinoline;
1-(1-naphthylsulfonyl)-4-(piperidin-4-yloxy)-1H-indazole;
1-(1-naphthylsulfonyl)-4-(piperidin-3-yloxy)-1H-indazole;
1-[(5-chlorothien-2-yl)sulfonyl]-4-(piperidin-4-yloxy)-1H-indazole;
1-[(5-chlorothien-2-yl)sulfonyl]-4-(piperidin-3-yloxy)-1H-indazole;
1-(phenylsulfonyl)-4-(piperidin-3-yloxy)-1H-indole;
4-{[4-(piperidin-3-yloxy)-1H-indol-1-yl]sulfonyl}aniline;
1-(1-naphthylsulfonyl)-4-(piperidin-3-yloxy)-1H-indole;
1-(phenylsulfonyl)-4-(piperidin-4-yloxy)-1H-indole;
4-{[4-(piperidin-4-yloxy)-1H-indol-1-yl]sulfonyl}aniline;
1-(1-naphthylsulfonyl)-4-(piperidin-4-yloxy)-1H-indole;
1-(phenylsulfonyl)-5-(pyrrolidin-3-yloxy)-1H-indole;
1-(phenylsulfonyl)-6-(pyrrolidin-3-yloxy)-1H-indole;
1-(phenylsulfonyl)-6-(pyrrolidin-3-yloxy)-1H-indazole;
1-(phenylsulfonyl)-5-(pyrrolidin-3-yloxy)-1H-indazole; or the stereoisomers thereof or pharmaceutically acceptable salts thereof.

This invention also provides a process for the preparation of a compound of formula I which comprises one of the following:

a) reacting a compound of formula (B)



(B)

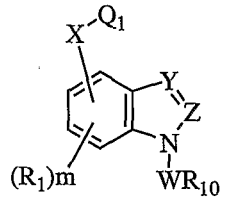
wherein m, Q, X, Y, Z and R_1 are as defined herein, with an appropriate sulphonylating, acylating, carbamoylating, thiocarbamoylating, arylating or alkylating agent containing the group:

$$R_{10}\text{-}W\text{-}$$

where R_{10} is as defined above and W is SO_2, CO, CONH, CSNH or $(CH_2)_x$; 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);

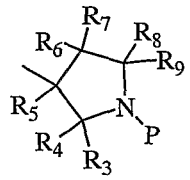
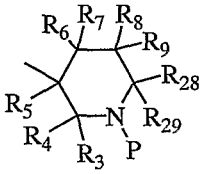
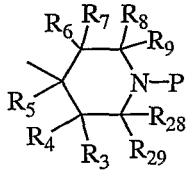
or

b) removing a protecting group from a compound of formula (C):



(C)

wherein m, W, X, Y, Z, R_1 and R_{10} are as defined herein and

Q_1 is  ,  or  ;

where P is a protecting group to give a corresponding compound of formula (I) wherein R_2 is H;

or

c) alkylating a compound of formula (I) as defined herein wherein R_2 is hydrogen with an alkylating agent of formula R_2-L wherein L is a leaving group, such as

halogen, and R_2 is as defined herein excepting hydrogen to give a corresponding compound of formula (I);

or

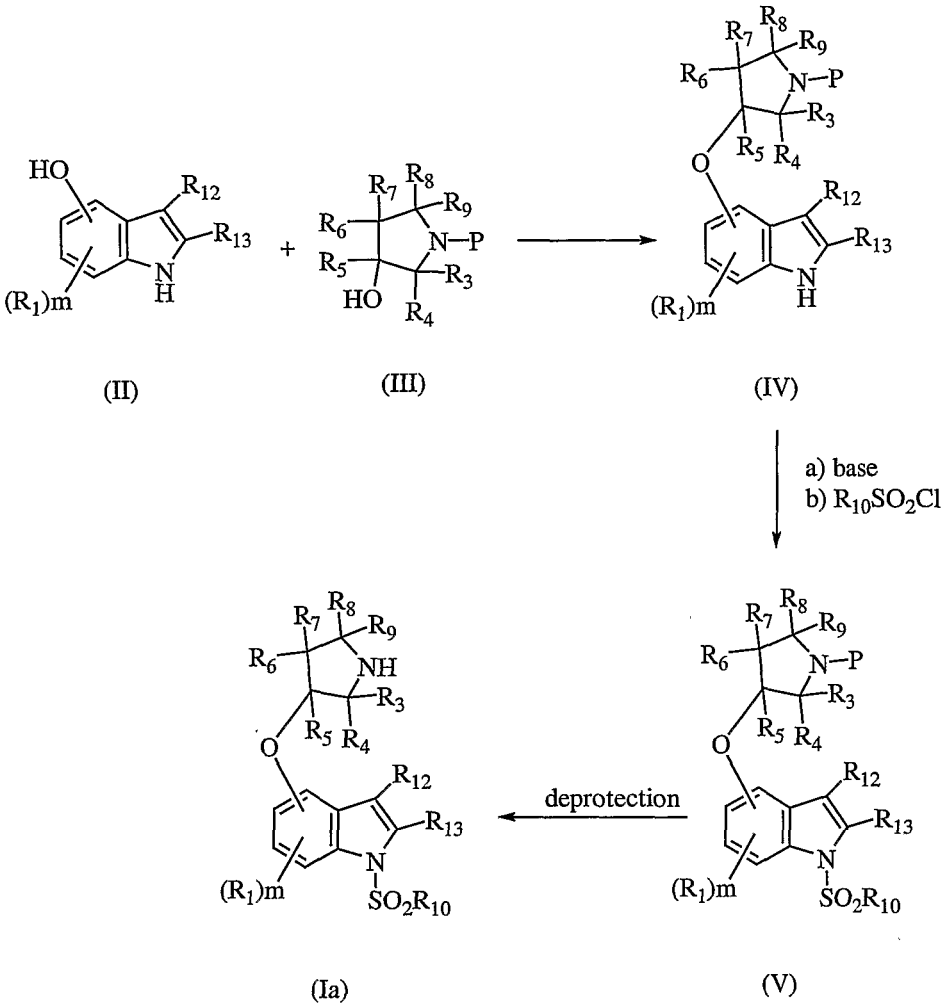
d) converting a compound of formula (I) having a reactive substituent group to a different compound of formula I;

or

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

Compounds of the invention may be conveniently prepared using conventional synthetic methods and, if required, standard separation and isolation techniques. For example, compounds of formula I wherein W is SO_2; X is O; Y is CR_{12}; Z is CR_{13}; Q is an optionally substituted 3-pyrrolidinyl group; and R_2 is H (Ia) may be prepared by reacting an hydroxyindole of formula II with a protected 3-hydroxypyrrolidine of formula III in the presence of triphenylphosphine and diethyl azodicarboxylate to give the pyrrolidinyloxyindole of formula IV. Sulfonylation followed by deprotection gives the desired compound of formula Ia. The reaction is shown in flow diagram I wherein P is a protecting group.

Flow Diagram I

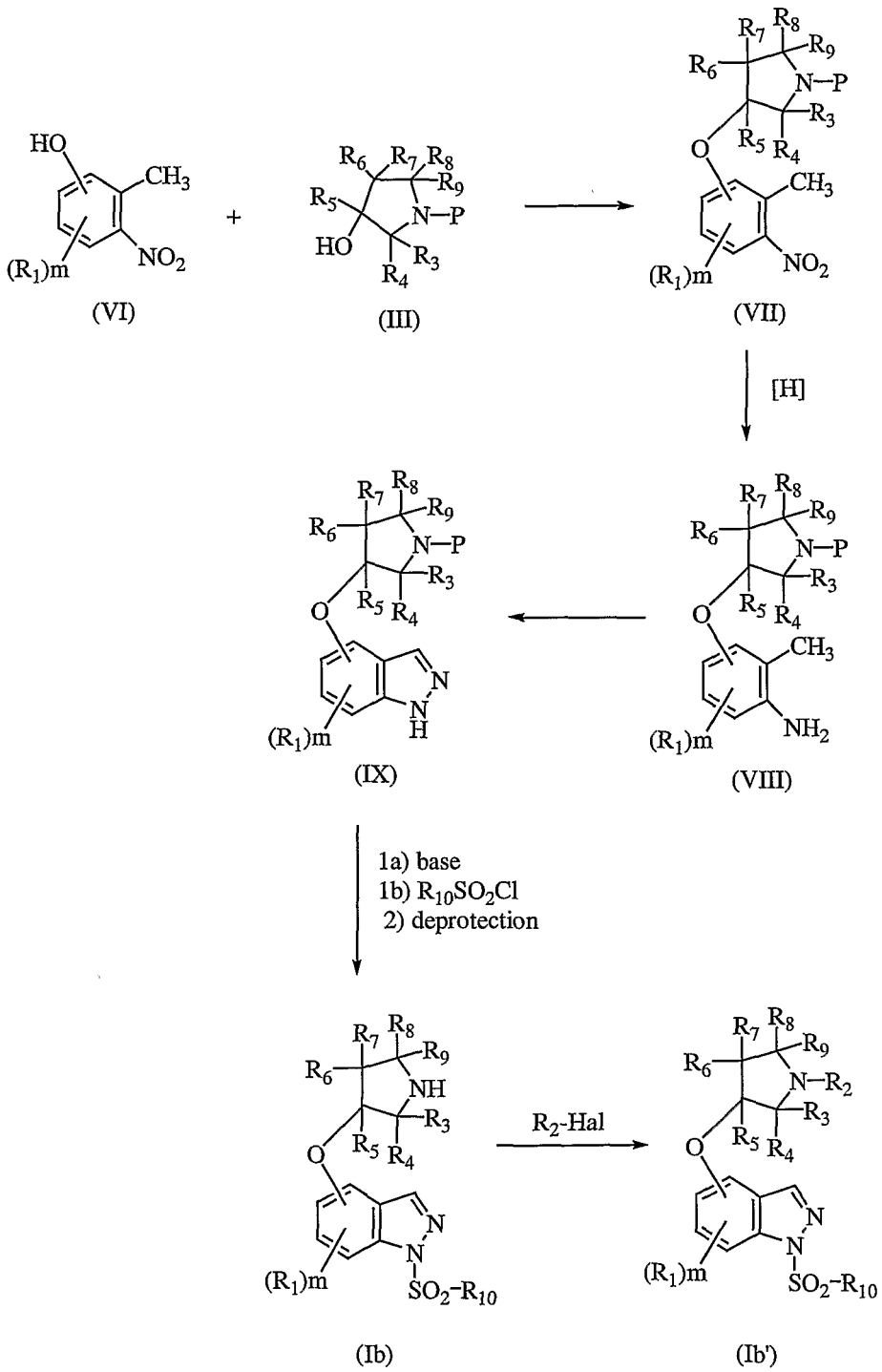


Commonly used protecting groups include t-butyl-carboxylate, benzyl, acetyl, benzyloxycarbonyl, or any conventional group known to protect a basic nitrogen in standard synthetic procedures.

Compounds of formula I wherein W is SO_2; X is O; Y is CH; Z is N; and Q is optionally substituted 3-pyrrolidinyl group (Ib) may be prepared by reacting a nitromethylphenol of formula VI with a protected 3-hydroxypyrrolidine of formula III in the presence of

triphenylphosphine and diethyl azodicarboxylate to give the corresponding pyrrolidinyloxybenzene of formula VII, reducing the nitro group, for example via catalytic hydrogenation, to give the amine of formula VIII, reacting the formula VIII amine with isoamylnitrite in the presence of potassium acetate and acetic anhydride to give the pyrrolidinyl-oxyindazole of formula IX. Sulfonylation and deprotection of said formula IX compound gives the desired compound of formula Ib. Subsequent reaction of the formula Ib compound with a suitable alkylating reagent such as an alkyl or aryl halide, R_2-Hal, gives those compounds of formula Ib' wherein R_2 is other than H. The reaction sequence is shown in flow diagram II wherein P is a protecting group and Hal is Cl, Br or I.

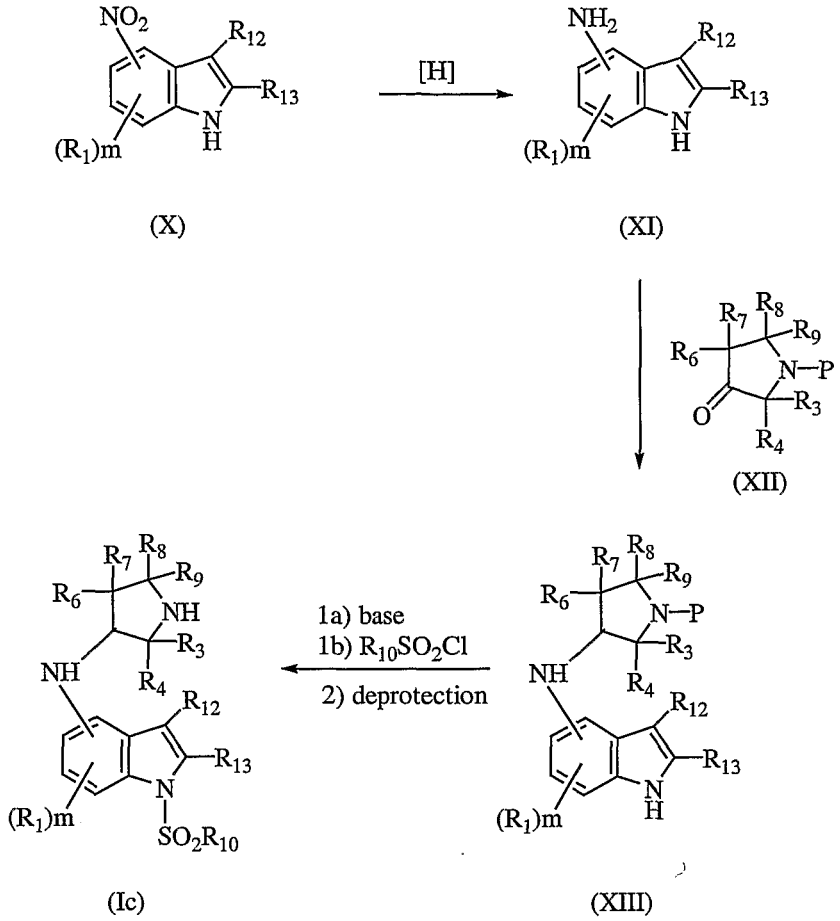
Flow Diagram II



Similarly, compounds of formula I wherein X is S and W is SO_2 may be prepared by employing the appropriate indolylthiol or thiophenol and utilizing the reactions shown in flow diagrams I and II, respectively. Oxidation of the thus-formed heterocyclylthiobenzazole derivatives of formula I gives those compounds of formula I wherein X is SO_n and n is 1 or 2.

Compounds of formula I wherein W is SO_2; X is NH; Y is CR_{12}; Z is CR_{13}; Q is an optionally substituted 3-pyrrolidinyl group; and R_2 and R_5 are H(Ic) may be prepared by hydrogenating a nitroindole of formula X to give the corresponding aminoindole of formula XI and reacting the formula XI aminoindole with a protected 3-pyrrolidinone of formula XII to give the protected pyrrolidinylaminoindole of formula XIII. Subsequent sulfonylation and deprotection afford the desired compound of formula Ic. The reaction sequence is shown in flow diagram III.

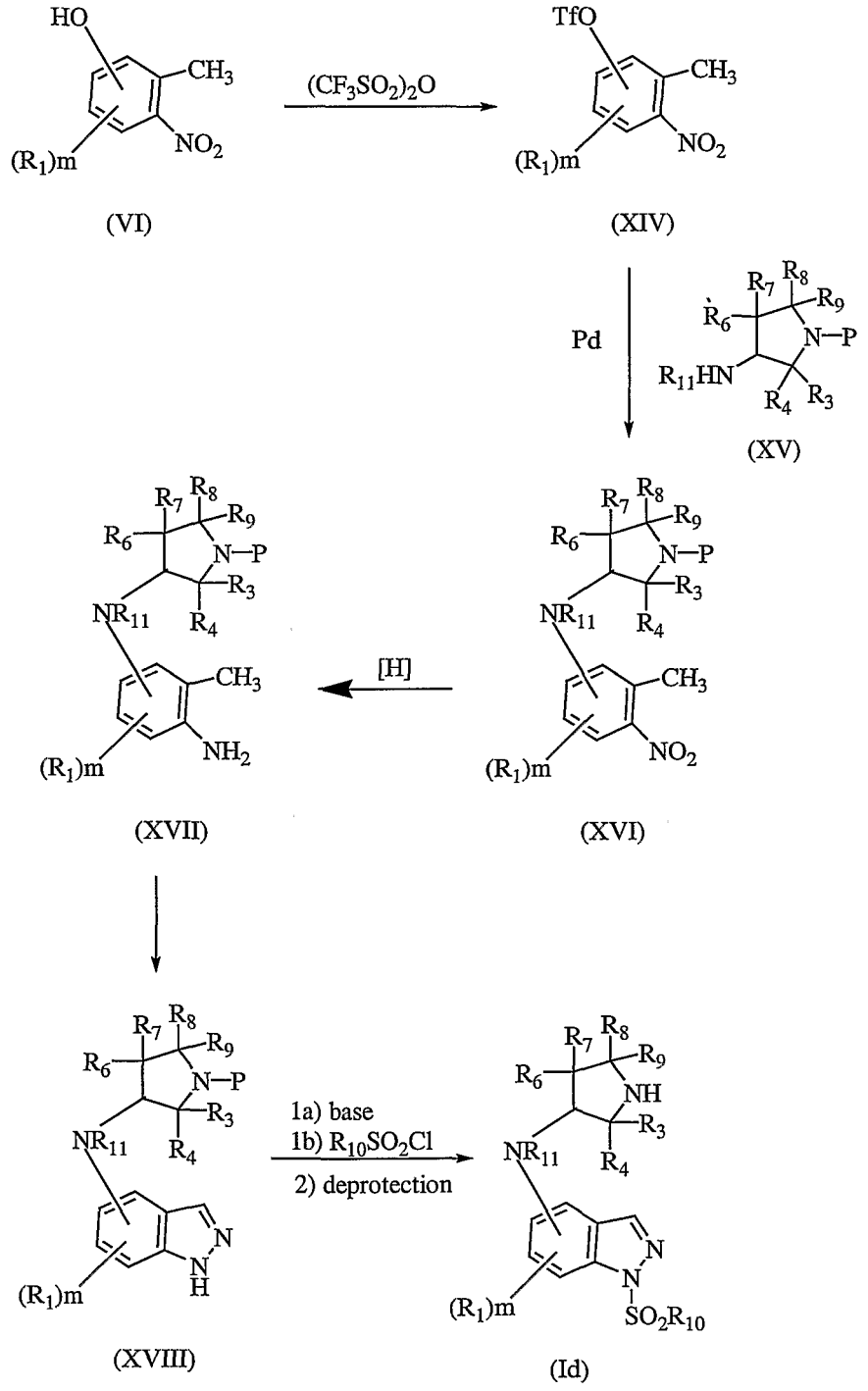
Flow Diagram III



Compounds of formula I wherein W is SO_2; X is NR_{11}; Y is CH; Z is N; and Q is an optionally substituted 3-pyrrolidinyl group (Id) may be prepared by reacting the nitromethylphenol compound of formula VI with trifluoromethanesulfonic anhydride in the presence of a base to give the compound of formula XIV, coupling the formula XIV compound with a protected 3-aminopyrrolidine compound of formula XV in the presence of a palladium catalyst to give the pyrrolidinylaminobenzene of formula XVI, reducing the nitro group to give the amine of formula XVII and reacting the formula XVII amine with isoamylnitrite in the presence of potassium acetate and acetic anhydride to give the pyrrolidinylaminoindazole of formula XVIII. Subsequent sulfonylation and deprotection

as described hereinabove give the desired compound of formula Id. The reaction sequence is shown in flow diagram IV wherein Tf designates a trifluoromethanesulfonyl group.

Flow Diagram IV



Corresponding compounds of formula I wherein Q is an optionally substituted 3- or 4-piperidinyl group may be prepared by utilizing the reaction sequences described hereinabove and illustrated in flow diagrams I, II, III and IV and by employing the appropriate protected piperidinylhydroxy, piperidinone or piperidinylamine, respectively, in place of the corresponding pyrrolidinyl starting materials of formulas III, XII or XV.

Compounds of formula I wherein W is CO may be prepared by reacting the benzazole precursor, for example a compound of formula IV, IX, XIII or XVIII, with the appropriate isocyanate, carbonyl halide or carbamoyl halide in the presence of a base. Similarly, compounds of formula I wherein W is $(CH_2)_x$ and x is an integer of 1, 2 or 3 may be prepared by reacting the appropriately substituted alkylhalide with a compound of formula IV, IX, XIII or XVIII in the presence of a base. Compounds of formula I wherein W is $(CH_2)_x$ and x is 0 may be prepared via a palladium-catalyzed N-arylation such as that described by D. W. Old *et al.*, Organic Letters, 2000 (2), pp 1403-1406. Using these and other conventional methods, compounds of formula I may be prepared from readily available starting materials.

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, for example, Alzheimer's disease, Parkinson's disease, attention deficit disorder, anxiety, epilepsy, depression, obsessive compulsive disorder, migraine, sleep disorders, feeding disorders (such as anorexia or bulimia), schizophrenia, memory loss, disorders associated with withdrawl from drug 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 (CNS) 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.

"Providing" as used herein with respect to providing a compound or substance covered by the invention, means 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 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.

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.

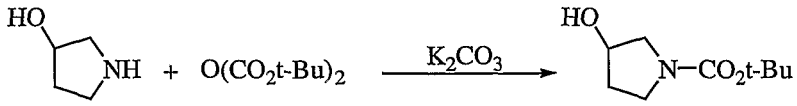
Compositions of the invention which are sterile solutions or suspensions are suitable for intramuscular, intraperitoneal or subcutaneous injection. Sterile solutions may also be administered intravenously. Inventive compositions suitable for oral administration may be in either liquid or solid composition 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. The terms THF and EtOAc designate tetrahydrofuran and ethyl acetate, respectively.

EXAMPLE 1

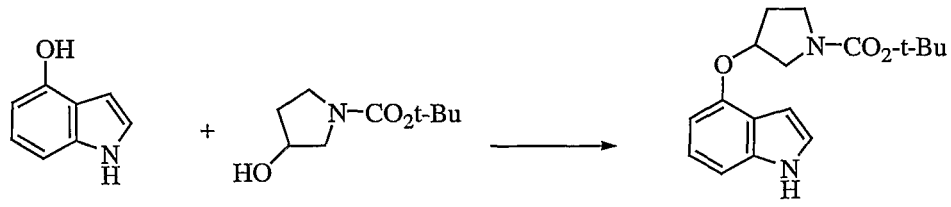
Preparation of *t*-Butyl 3-Hydroxy-1-pyrrolidine-carboxylate



A stirred solution of 3-pyrrolidinol (5.0 g 57 mmol) and potassium carbonate (8.23 g, 60 mmol) in a mixture of THF/H_2O is treated with a solution of di-*t*-butyl dicarbonate (12.5 g, 57 mmol) in THF over a 15 minute period at room temperature, stirred for 20 h at room temperature and diluted with EtOAc. The organic phase is separated, washed with H_2O, dried over Na_2SO_4 and concentrated *in vacuo*. The resultant residue is dissolved in EtOAc/hexane and filtered through a thin layer of silica gel. The silica gel layer is washed with EtOAc. The combined filtrates are concentrated *in vacuo* to give the title product as a white solid, 8.5 g, mp 52-54°C, identified by NMR and mass spectral analyses.

EXAMPLE 2

Preparation of *t*-Butyl 3-(1H-Indol-4-yloxy)-1-pyrrolidinecarboxylate

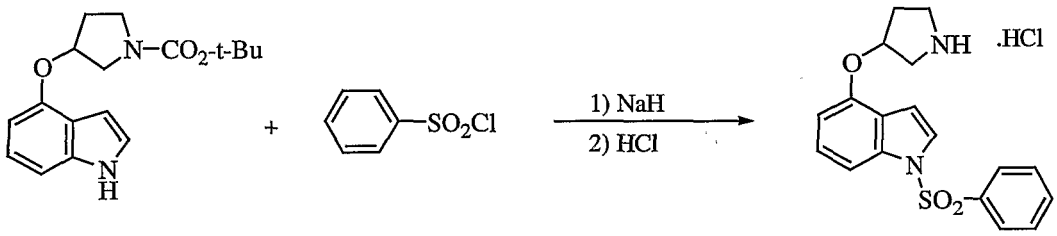


A solution of 4-hydroxyindole (2.66 g, 20.0 mmol), *t*-butyl 3-hydroxy-1-pyrrolidinecarboxylate (7.5 g, 40.0

mmol) and triphenylphosphine (ϕ_3P)(10.5 g 40.0 mmol) in THF is treated with diethyl azodicarboxylate (DEAC)(6.3 ml, 40.0 mmol) under nitrogen at room temperature, stirred for 2 h at room temperature and concentrated *in vacuo*. The resultant residue is stirred under ether, cooled and filtered. The filtercake is washed with cold ether. The filtrates are combined and concentrated *in vacuo*. The residue is purified by flash chromatography (silica gel, EtOAc/hexane: 2/80) to give the title compound as a white solid, 3.98 g, mp 164-165°C, identified by NMR and mass spectral analyses.

EXAMPLE 3

Preparation of 1-(Phenylsulfonyl)-4-(3-pyrrolidinyloxy)-1H-indole Hydrochloride



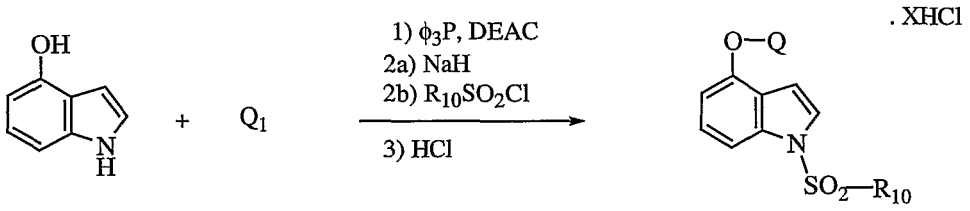
A stirred solution of *t*-butyl 3-(1H-indol-4-yloxy)-1-pyrrolidinecarboxylate (0.605 g 2.0 mmol) in THF is treated with sodium hydride (0.12 g, 60% in mineral oil, 3.0 mmol) under nitrogen at room temperature. After 30 minutes, benzenesulfonyl chloride (0.38 ml, 3.0 mmol) is added and the reaction mixture is stirred at room temperature for 48 h, quenched with ice-water and diluted with EtOAc. The organic phase is separated, washed sequentially with H_2O and brine, dried over $MgSO_4$ and concentrated *in vacuo*. The resultant residue is purified by flash chromatography (silica gel, EtOAc/hexane 2/8 to give the protected pyrrolidinyloxy intermediate as an

off-white foam, 0.50 g, mp 48-50°C, identified by NMR and mass spectral analyses.

A solution of thus-obtained *t*-butyl 3-{[1-(phenylsulfonyl)-1H-indol-4-yl]oxy}-1-pyrrolidinecarboxylate (0.41 g, 0.93 mmol) in methanol and HCl (5.0 ml, 1M in ether) is heated at 60°C under nitrogen for 2 h and concentrated *in vacuo*. The residue is treated with ethyl acetate and filtered. The filtercake is dried under vacuum to give the title product as an off white solid, 0.301 g, mp 200-201°C, identified by NMR and mass spectral analyses.

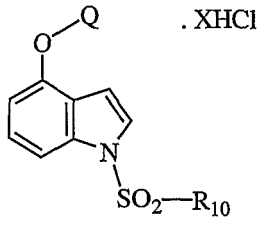
EXAMPLES 4-9

Preparation of 1-(Arylsulfonyl)-4-(3-pyrrolidinyloxy)-1H-indole Hydrochloride



Using essentially the same procedures described hereinabove for Examples 2 and 3 and employing the appropriate protected pyrrolidinol or piperidinol (Q_1) and arylsulfonyl chloride, the compounds shown in Table I are obtained and identified by NMR and mass spectral analyses.

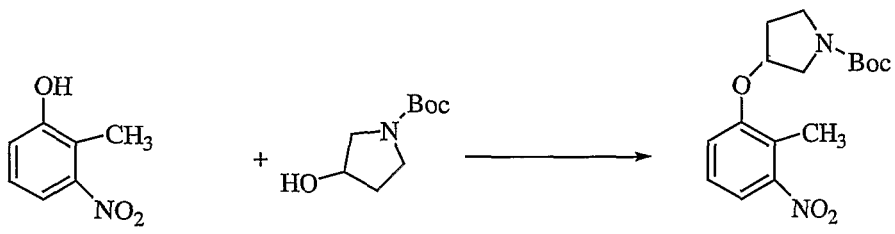
Table I



Ex. No.	Q	R10	X	mp °C	M+H
4	3-pyrrolidinyl	thiophene-2-yl	1	158-160	342
5	3-pyrrolidinyl	4-aminophenyl	2	140(dec)	359
6	3-pyrrolidinyl	1-naphthyl	1	179(dec)	393
7	3-pyrrolidinyl	5-chloro-1,3-dimethyl-1H-pyrazol-4-yl	1	100(dec)	395
8	4-piperidinyl	4-aminophenyl	2	117-119	372
9	3-piperidinyl	4-aminophenyl	2	160(dec)	372

EXAMPLE 10

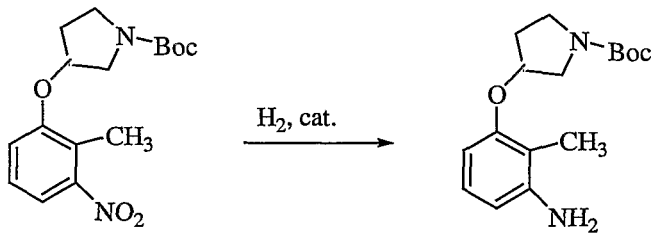
Preparation of t-Butyl 3-(2-Methyl-3-nitrophenoxy)-pyrrolidin-1-carboxylate



A stirred solution of 3-nitro-2-methylphenol (7.6 g, 49.7 mmol), *t*-butyl 3-hydroxypyrrolidin-1-carboxylate (9.3 g, 49.7 mmol) and triphenylphosphine (13.0 g, 49.7 mmol) in THF is treated with diethyl azodicarboxylate (8.7 g, 49.7 mmol), stirred at room temperature for 3 h and concentrated *in vacuo*. The resultant residue is mixed with ethyl acetate and filtered. The filtrate is concentrated *in vacuo* to give a residue, which is purified by chromatography (SiO_2, 25% EtOAc in hexanes) to afford the title compound as an off-white solid, 11.7 g (73%) identified by NMR and mass spectral analyses.

EXAMPLE 11

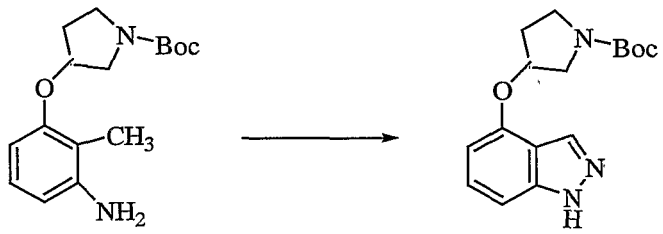
Preparation of *t*-Butyl 3-(3-Amino-2-methylphenoxy)-pyrrolidin-1-carboxylate



A mixture of *t*-butyl 3-(2-methyl-3-nitrophenoxy)pyrrolidin-1-carboxylate (11.0 g, 34.2 mmol) and 10% Pd/C (0.55 g) in ethanol is hydrogenated (45 psi) at room temperature overnight. After filtering off the catalyst, the filtrate is concentrated to afford the title compound as an off-white solid, 9.98 g, mp 137°C, identified by NMR and mass spectral analyses.

EXAMPLE 12

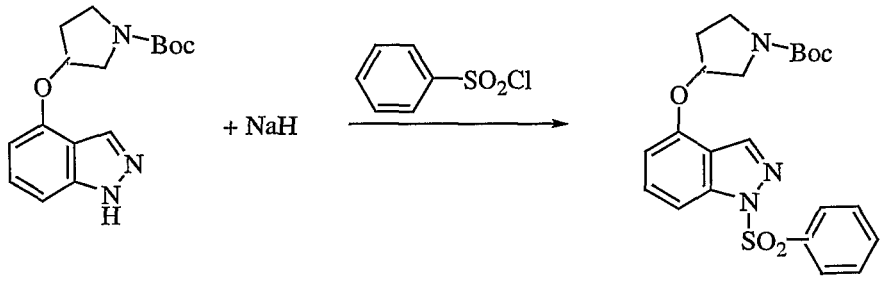
Preparation of *t*-Butyl 3-(1H-Indazol-4-yloxy)pyrrolidin-1-carboxylate



A solution of *t*-butyl 3-(3-amino-2-methylphenoxy)pyrrolidin-1-carboxylate (4.6 g, 15.4 mmol), potassium acetate (1.81 g, 18.5 mmol) and acetic anhydride (5.02 g, 49.2 mmol) in benzene is treated dropwise with isoamylnitrite (4.13 ml, 30.8 mmol), heated at reflux temperature overnight, cooled to room temperature and filtered. The filtercake is washed with benzene. The combined filtrates are concentrated to give a yellow oil residue. The residue is purified by chromatography (SiO_2, 25% EtOAc in hexanes). The resultant oil is dissolved in ethanol, treated with 40% aqueous NaOH, heated at reflux temperature for 45 min, cooled with an ice-water bath, neutralized to pH 9 with concentrated HCl and concentrated *in vacuo*. The resulting aqueous mixture is extracted with EtOAc. The combined extracts are washed with water and brine, dried over $MgSO_4$ and concentrated *in vacuo* to give the title compound as a tan solid, 2.6 g, mp 196-198°C, identified by NMR and mass spectral analyses.

EXAMPLE 13

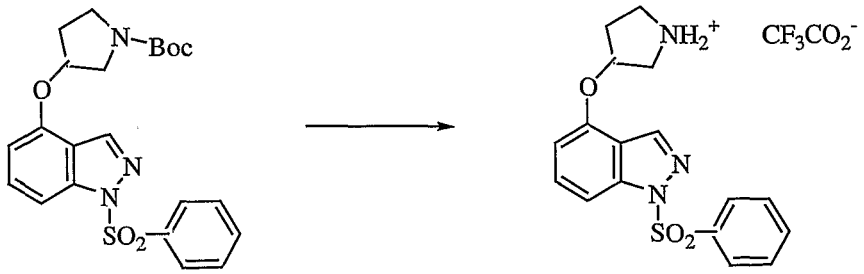
Preparation of *t*-Butyl 3-{[(1-Phenylsulfonyl)-1H-indazol-4-yl]oxyl}-pyrrolidin-1-carboxylate



A solution of *t*-butyl 3-(1H-indazol-4-yloxy)pyrrolidin-1-carboxylate (0.303 g, 1.00 mmol) in dimethyl formamide is treated with sodium hydride (80 mg, 2.0 mmol, 60% in mineral oil) at room temperature under nitrogen, stirred for 10 min, treated with benzenesulfonyl chloride (0.21 g, 1.20 mmol), stirred for 18 h, quenched with H_2O and diluted with ether. The organic phase is washed with H_2O and brine, dried over $MgSO_4$ and concentrated *in vacuo*. The residue is purified by chromatography (SiO_2, 20% EtOAc in hexanes) to afford the title compound as a white solid, 0.42 g, mp 134-135°C, identified by NMR and mass spectral analyses.

EXAMPLE 14

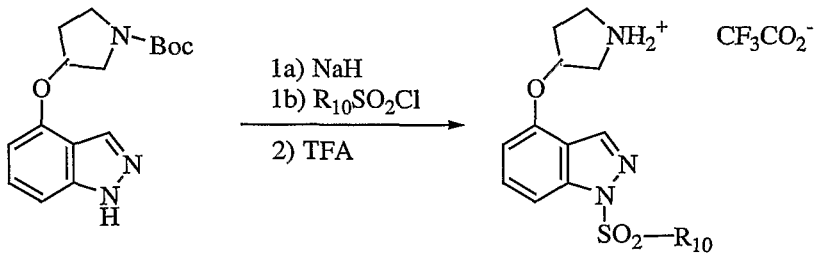
Preparation of 1-(Phenylsulfonyl)-4-(pyrrolidin-3-yloxy)-1H-indazole, trifluoroacetic acid salt



A mixture of *t*-butyl 3-{[(1-phenylsulfonyl)-1H-indazol-4-yl]oxy}-pyrrolidin-1-carboxylate (354 mg, 0.80 mmol) and trifluoroacetic acid (3 mL) is prepared at 0°C, stirred at room temperature for 90 min. and concentrated *in vacuo*. The residue is triturated with ether to afford the title compound as a white solid, 260 mg, mp 168-169°C, identified by NMR and mass spectral analyses.

EXAMPLES 15-22

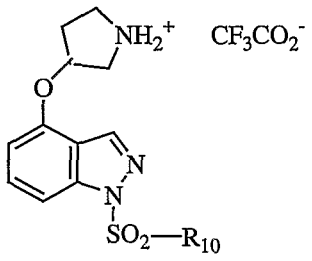
Preparation of 1-(Arylsulfonyl)-4-(3-pyrrolidinyloxy)-1H-indazole trifluoroacetic acid salt



Using essentially the same procedures described hereinabove for Examples 8-12, and employing the appropriate arylsulfonyl chloride, the compounds shown in

Table II are obtained and identified by NMR and mass spectral analyses.

Table II



Ex. No.	R_{10}	mp °C
15	1-naphthyl	200-201
16	2-chlorophenyl	161-163
17	2-fluorophenyl	162-163
18	3,4-dimethoxyphenyl	64-70
19	5-chlorothiophene-2-yl	102-103
20	4-acetamido-3-chlorophenyl	68-72
21	4-acetamidophenyl	110-112
22	8-quinolinyl	79

EXAMPLE 23

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 III, below.

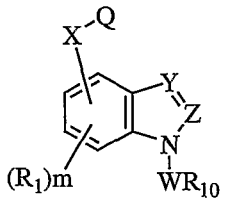
Table III

Test Compound (Ex. No.)	5-HT6 Binding Ki (nM)
3	8.0
4	25.0
5	5.0
6	13.0
7	--
8	3.0
9	11.0
14	19.0
15	3.0
16	19.0
17	25.0
18	75.0
19	9.0
20	12.0
21	124.0
22	22.0
Comparative Examples	**5-HT6 Binding Ki (nM)**
Clozapine	6.0
Loxapine	41.4
Bromocriptine	23.0
Methiothepin	8.3
Mianserin	44.2
Olanzepine	19.5

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

WHAT IS CLAIMED IS:

1. A compound of formula I



(I)

wherein

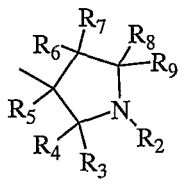
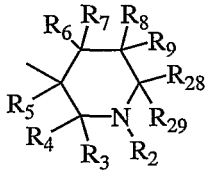
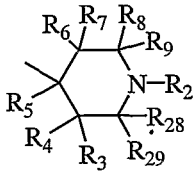
W is SO_2, CO, CONH, CSNH or $(CH_2)_x$;

X is O, SO_n or NR_{11};

Y is CR_{12} or N;

Z is CR_{13} or N with the proviso that when Y is N then Z must be CR_{13};

m and x are each independently 0 or an integer of 1, 2 or 3;

Q is  ,  or  ;

R_1 is halogen, CN, OR_{14}, CO_2R_{15}, $CONR_{16}R_{17}$, $CNR_{18}NR_{19}R_{20}$, $SO_2NR_{21}R_{22}$, SO_pR_{23} or a C_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_3-C_6cycloalkyl, cycloheteroalkyl, phenyl or heteroaryl group each optionally substituted;

R_2 is H, $CNR_{24}NR_{25}R_{26}$ or a C_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_3-C_6cycloalkyl, cycloheteroalkyl, aryl or heteroaryl group each optionally substituted;

R_3, R_4, R_5, R_6, R_7, R_8, R_9, R_{28} and R_{29} are each independently H or an optionally substituted C_1-C_6alkyl group;

R_{10} is an optionally substituted C_1-C_6alkyl, aryl or heteroaryl group;

n and p are each independently 0 or an integer of 1 or 2;

R_{11} is H or a C_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_3-C_6cycloalkyl, cycloheteroalkyl, aryl or heteroaryl group each optionally substituted;

R_{12} and R_{13} are each independently H, halogen or a C_1-C_6alkyl, aryl, heteroaryl or C_1-C_6alkoxy group each optionally substituted;

R_{14} is H, COR_{27} or a C_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, aryl or heteroaryl group each optionally substituted;

R_{15} and R_{27} are each independently H or a C_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_3-C_6cycloalkyl, cycloheteroalkyl, aryl or heteroaryl group each optionally substituted;

R_{16}, R_{17}, R_{18}, R_{19}, R_{20}, R_{24}, R_{25} and R_{26} are each independently H or an optionally substituted C_1-C_6alkyl group;

R_{21} and R_{22} are each independently H or a C_1-C_6alkyl, aryl or heteroaryl group each optionally substituted; and

R_{23} is an optionally substituted C_1-C_6alkyl, aryl, or heteroaryl group; or

the stereoisomers thereof or the pharmaceutically acceptable salts thereof.

2. The compound according to claim 1 wherein W is SO_2.

3. The compound according to claim 1 or claim 2 wherein X is O.

4. The compound according to any one of claims 1 to 3 wherein Q is an optionally substituted 3-pyrrolidinyl group.

5. The compound according to any one of claims 1 to 3 wherein R_{10} is an optionally substituted aryl or heteroaryl group.

6. The compound according to any one of claims 1 to 5 wherein Y is CR_{12}.

7. The compound according to any one of claims 1 to 6 wherein Z is N.

8. The compound according to claim 1 selected from the group consisting of:
1-(phenylsulfonyl)-4-(3-pyrrolidinyloxy)-1H-indole;
4-(3-pyrrolidinyloxy)1-(thien-2-ylsulfonyl)-1H-indole;
4-{[4-(3-pyrrolidinyloxy)-1H-indol-1-yl]sulfonyl}aniline;
1-(1-naphthylsulfonyl)-4-(3-pyrrolidinyloxy)-1H-indole;
1-[(5-chloro-1,3-dimethyl-1H-pyrazol-4-yl)sulfonyl]-4-(3-pyrrolidinyloxy)-1H-indole;
1-(phenylsulfonyl)-4-(3-pyrrolidinyloxy)-1H-indazole;
1-(1-naphthylsulfonyl)-4-(3-pyrrolidinyloxy)-1H-indazole;
1-[(2-chlorophenyl)sulfonyl]-4-(3-pyrrolidinyloxy)-1H-indazole;
1-[(2-fluorophenyl)sulfonyl]-4-(3-pyrrolidinyloxy)-1H-indazole;
1-[3,4-dimethoxyphenyl)sulfonyl]-4-(3-pyrrolidinyloxy)-1H-indazole;
1-[(5-chlorothien-2-yl)sulfonyl]-4-(3-pyrrolidinyloxy)-1H-indazole;

N-(2-chloro-4-{[4-(3-pyrrolidinyloxy)-1H-indazol-1-yl]sulfonyl}phenyl)acetamide;
N-(4-{[4-(3-pyrrolidinyloxy)-1H-indazol-1y}]sulfonyl)-phenyl)acetamide;
8-{[4-(3-pyrrolidinyloxy)-1H-indazol-1-yl]sulfonyl}-quinoline;
1-(1-naphthylsulfonyl)-4-(piperidin-4-yloxy)-1H-indazole;
1-(1-naphthylsulfonyl)-4-(piperidin-3-yloxy)-1H-indazole;
1-[(5-chlorothien-2-yl)sulfonyl]-4-(piperidin-4-yloxy)-1H-indazole;
1-[(5-chlorothien-2-yl)sulfonyl]-4-(piperidin-3-yloxy)-1H-indazole; 1-(phenylsulfonyl)-4-(piperidin-3-yloxy)-1H-indole;
4-{[4-(piperidin-3-yloxy)-1H-indol-1-yl]sulfonyl}aniline;
1-(1-naphthylsulfonyl)-4-(piperidin-3-yloxy)-1H-indole;
1-(phenylsulfonyl)-4-(piperidin-4-yloxy)-1H-indole;
4-{[4-(piperidin-4-yloxy)-1H-indol-1-yl]sulfonyl}aniline;
1-(1-naphthylsulfonyl)-4-(piperidin-4-yloxy)-1H-indole;
1-(phenylsulfonyl)-5-(pyrrolidin-3-yloxy)-1H-indole;
1-(phenylsulfonyl)-6-(pyrrolidin-3-yloxy)-1H-indole;
1-(phenylsulfonyl)-6-(pyrrolidin-3-yloxy)-1H-indazole;
1-(phenylsulfonyl)-5-(pyrrolidin-3-yloxy)-1H-indazole;
the stereoisomers thereof; and
the pharmaceutically acceptable salts thereof.

9. 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 to said patient a therapeutically effective amount of a compound of formula I as claimed in any one of Claims 1 to 8; or a stereoisomer thereof or the pharmaceutically acceptable salts thereof.

10. The method according to claim 9 wherein said disorder is a motor disorder, anxiety disorder or cognitive disorder.

11. The method according to claim 9 wherein said disorder is schizophrenia or depression.

12. The method according to claim 10 wherein said disorder is Alzheimer's disease or Parkinson's disease.

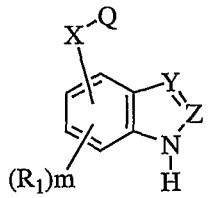
13. The method according to claim 10 wherein said disorder is attention deficit disorder.

14. A pharmaceutical composition which comprises a pharmaceutically acceptable carrier and a compound of formula I as claimed in any one of Claims 1 to 8; or a stereoisomer thereof or the pharmaceutically acceptable salts thereof.

15. The composition according to claim 14 having a formula I compound wherein X is O; Q is an optionally substituted 3-pyrrolidinyl group and R_{10} is an optionally substituted aryl or heteroaryl group.

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

a) reacting a compound of formula (B)



(B)

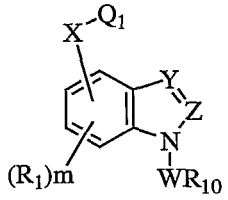
wherein m, Q, X, Y, Z and R_1 are as defined in claim 1, with an appropriate sulphonylating, acylating, carbamoylating, thiocarbamoylating, arylating or alkylating agent containing the group:

$$R_{10}\text{-}W\text{-}$$

where R_{10} is as defined above and W is SO_2, CO, CONH, CSNH or $(CH_2)_x$; 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);

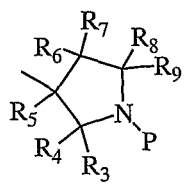
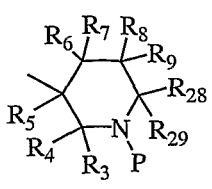
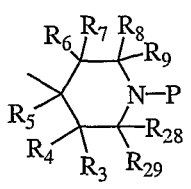
or

b) removing a protecting group from a compound of formula (C):



(C)

wherein m, W, X, Y, Z, R_1 and R_{10} are as defined in claim 1, and

Q_1 is  ,  or  ;

where P is a protecting group to give a corresponding compound of formula (I) wherein R_2 is H;

or

c) alkylating a compound of formula (I) as defined in claim 1 wherein R_2 is hydrogen with an alkylating agent of formula R_2-L wherein L is a leaving group, such as halogen, and R_2 is as defined in claim 1 excepting hydrogen to give a corresponding compound of formula (I);

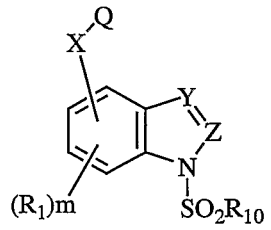
or

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.

17. A method for the preparation of a compound of formula Ie



(Ie)

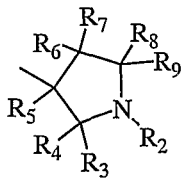
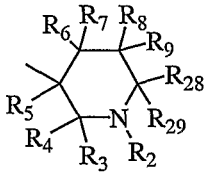
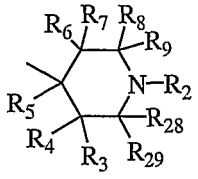
wherein

X is O, SO_n or NR_{11};

Y is CR_{12} or N;

Z is CR_{13} or N with the proviso that when Y is N then Z must be CR_{13};

m is 0 or an integer of 1, 2 or 3;

Q is  ,  or  ;

R_1 is halogen, CN, OR_{14}, CO_2R_{15}, $CONR_{16}R_{17}$, $CNR_{18}NR_{19}R_{20}$, $SO_2NR_{21}R_{22}$, SO_pR_{23} or a C_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_3-C_6cycloalkyl, cycloheteroalkyl, phenyl or heteroaryl group each optionally substituted;

R_2 is H, $CNR_{24}NR_{25}R_{26}$ or a C_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_3-C_6cycloalkyl, cycloheteroalkyl, aryl or heteroaryl group each optionally substituted;

R_3, R_4, R_5, R_6, R_7, R_8, R_9, R_{28} and R_{29} are each independently H or an optionally substituted C_1-C_6alkyl group;

R_{10} is an optionally substituted C_1-C_6alkyl, aryl or heteroaryl group;

n and p are each independently 0 or an integer of 1 or 2;

R_{11} is H or a C_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_3-C_6cycloalkyl, cycloheteroalkyl, aryl or heteroaryl group each optionally substituted;

R_{12} and R_{13} are each independently H, halogen or a C_1-C_6alkyl, aryl, heteroaryl or C_1-C_6alkoxy group each optionally substituted;

R_{14} is H, COR_{27} or a C_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, aryl or heteroaryl group each optionally substituted;

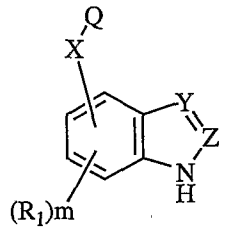
R_{15} and R_{27} are each independently H or a C_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_3-C_6cycloalkyl, cycloheteroalkyl, aryl or heteroaryl group each optionally substituted;

R_{16}, R_{17}, R_{18}, R_{19}, R_{20}, R_{24}, R_{25} and R_{26} are each independently H or an optionally substituted C_1-C_6alkyl group;

R_{21} and R_{22} are each independently H or a C_1-C_6alkyl, aryl or heteroaryl group each optionally substituted; and

R_{23} is an optionally substituted C_1-C_6alkyl, aryl, or heteroaryl group

which process comprises reacting a compound of formula XIX



(XIX)

wherein X, Y, Z, m and Q are as described hereinabove with a sulfonyl chloride, $R_{10}SO_2Cl$, wherein R_{10} is as described hereinabove in the presence of a base to give the desired compound of formula Ie.