Title

Selective β_3 Adrenergic Agonists

Field of Invention

The present invention is in the field of medicine, particularly in the treatment of Type II diabetes and obesity. More specifically, the present invention relates to selective β_3 adrenergic receptor agonists useful in the treatment of Type II diabetes and obesity.

Background of the Invention

The current preferred treatment for Type II, non-insulin dependent diabetes as well as obesity is diet and exercise, with a view toward weight reduction and improved insulin sensitivity. Patient compliance, however, is usually poor. The problem is compounded by the fact that there are currently no approved medications that adequately treat either Type II diabetes or obesity. The invention described herein is directed toward an effective and timely treatment for these serious diseases.

One therapeutic opportunity that has recently been recognized involves the relationship between adrenergic receptor stimulation and anti-hyperglycemic effects. Compounds that act as β_3 receptor agonists have been shown to exhibit a marked effect on lipolysis, thermogenesis and serum glucose levels in animal models of Type II (non-insulin dependent) diabetes.

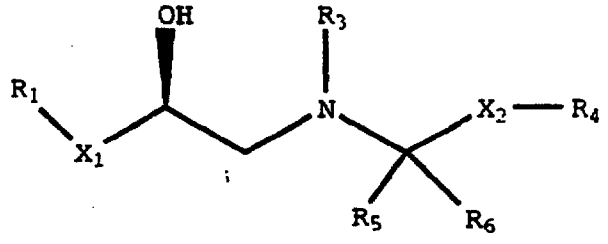
The β_3 receptor, which is found in several types of human tissue including human fat tissue, has roughly 50% homology to the β_1 and β_2 receptor subtypes yet is

considerably less abundant. The importance of the β_3 receptor is a relatively recent discovery since the amino-acid sequence of the human receptor was only elucidated in the late 1980's. A large number of publications have appeared in recent years reporting success in discovery of agents that stimulate the β_3 receptor. Despite these recent developments, there remains a need to develop a selective β_3 receptor agonist which has minimal agonist activity against the β_1 and β_2 receptors. In addition, indolylpropanolamines have been disclosed by Beedle et. al. U.S. patent 5,013,761.

The present invention provides compounds which are selective β_3 receptor agonists. As such, the compounds effectively lead to an increase in insulin sensitivity and are useful in treating Type II diabetes and other ailments implicated by the β_3 receptor, without cardiac or tremor-related side effects.

Summary of Invention

The present invention encompasses novel compounds described by Formula I below.

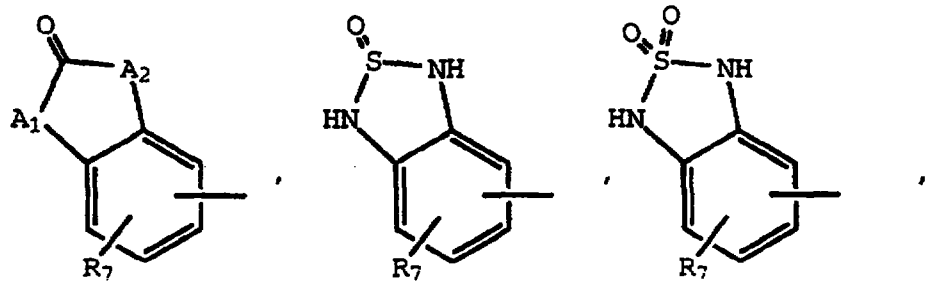


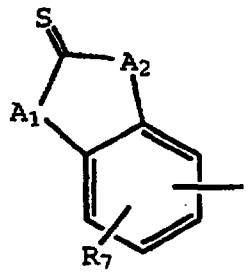
(I)

wherein:

X_1 is $-OCH_2-$, $-SCH_2-$, or a bond;

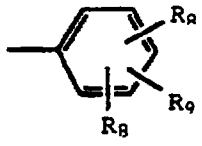
R_1 is a fused heterocycle of the formula:

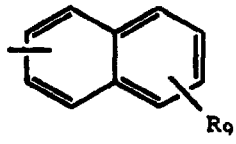


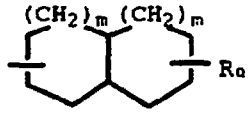


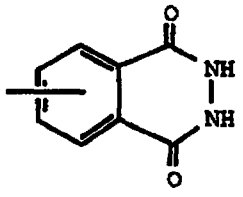
R_2 and R_3 are independently H, C_1-C_4 alkyl, or aryl;

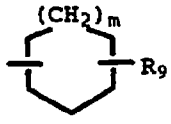
R_4 is an optionally substituted heterocycle or a moiety selected from the group consisting of:

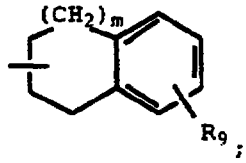












X_2 is a bond, or a 1 to 5 carbon straight or branched alkylene;

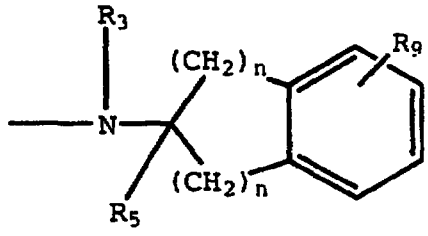
R_5 is H, or C_1-C_4 alkyl;

R_6 is H, or C_1-C_4 alkyl;

or R_5 and R_6 combine with the carbon to which each is attached to form a C_3-C_6 cycloalkyl;

or R_6 combines with to X_2 and the carbon to which X_2 is attached to form a C_3-C_8 cycloalkyl;

or R_6 combines with X_2, the carbon to which X_2 is attached, and R_4 to form:



provided that R_5 is H;

R_7 is H, halo, hydroxy, C_1-C_4 alkyl, C_1-C_4 haloalkyl, aryl, CN, $COOR_2$, $CONHR_2$, $NHCOR_2$, OR_2, NHR_2, SR_2, SO_2R_2, SO_2NHR_2, or SOR_2;

R_8 is independently H, halo or C_1-C_4 alkyl;

R_9 is halo, CN, OR_{10}, C_1-C_4 alkyl, C_1-C_4 haloalkyl, CO_2R_2, $CONR_{11}R_{12}$, CONH(C_1-C_4 alkyl or C_1-C_4 alkoxy), SR_2, $CSNR_2$, $CSNR_{11}R_{12}$, SO_2R_2, $SO_2NR_{11}R_{12}$, SOR_2, $NR_{11}R_{12}$, optionally substituted aryl, optionally substituted heterocycle, or C_2-C_4 alkenyl substituted with CN, CO_2R_2 or $CONR_{11}R_{12}$;

R_{10} is C_1-C_4 alkyl, C_1-C_4 haloalkyl, $(CH_2)_nC_3$-C_8 cycloalkyl, $(CH_2)_n$aryl, $(CH_2)_n$heterocycle, $(CH_2)_nC_3$-C_8 optionally substituted cycloalkyl, $(CH_2)_n$ optionally substituted aryl, $(CH_2)_n$ optionally substituted heterocycle;

R_{11} and R_{12} are independently H, C_1-C_4 alkyl, aryl, $(CH_2)_n$aryl, or combine with the nitrogen to which each is bound to form morpholinyl, piperidinyl, pyrrolidinyl, or piperazinyl;

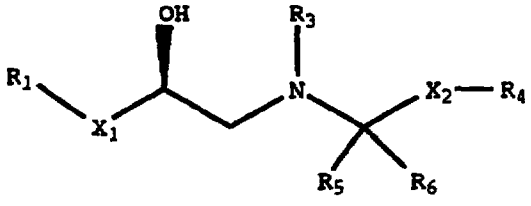
A_1 and A_2 are independently O, S, NH, CH_2, NCH_3, or NCH_2CH_3;

m is 0 or 1;

n is 0, 1, 2, or 3;

or a pharmaceutically acceptable salt thereof.

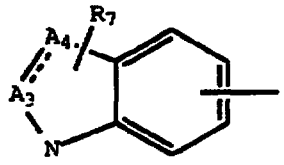
The present invention also encompasses novel compounds described by Formula II below.



(II)

wherein:

R_1 is



(II)

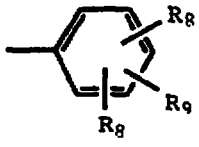
X_1 is $-OCH_2-$, $-SCH_2-$, or a bond;

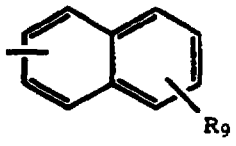
The bond between A_3 and A_4 is either a single or double bond;

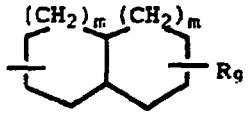
A_3 and A_4 are independently carbon or nitrogen;

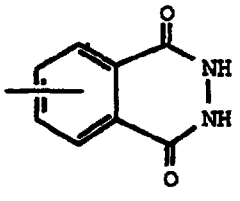
R_2 and R_3 are independently H, C_1-C_4 alkyl, or aryl;

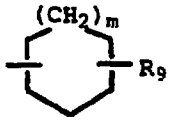
R_4 is an optionally substituted heterocycle or a moiety selected from the group consisting of:

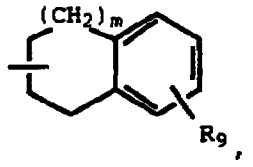












X_2 is a bond, or a 1 to 5 carbon straight or branched alkylene;

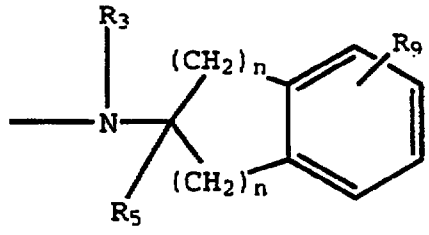
R_5 is H, or C_1-C_4 alkyl;

R_6 is H, or C_1-C_4 alkyl;

or R_5 and R_6 combine with the carbon to which each is attached to form a C_3-C_6 cycloalkyl;

or R_6 combines with to X_2 and the carbon to which X_2 is attached to form a C_3-C_8 cycloalkyl;

or R_6 combines with X_2, the carbon to which X_2 is attached, and R_4 to form:



provided that R_5 is H;

R_7 is H, halo, hydroxy, C_1-C_4 alkyl, C_1-C_4 haloalkyl, aryl, CN, $COOR_2$, $CONHR_2$, $NHCOR_2$, OR_2, NHR_2, SR_2, SO_2R_2, SO_2NHR_2, or SOR_2;

R_8 is independently H, halo or C_1-C_4 alkyl;

R_9 is halo, CN, OR_{10}, C_1-C_4 alkyl, C_1-C_4 haloalkyl, CO_2R_2, $CONR_{11}R_{12}$, CONH(C_1-C_4 alkyl or C_1-C_4 alkoxy), SR_2, $CSNR_2$, $CSNR_{11}R_{12}$, SO_2R_2, $SO_2NR_{11}R_{12}$, SOR_2, $NR_{11}R_{12}$, optionally substituted aryl, optionally substituted heterocycle, or C_2-C_4 alkenyl substituted with CN, CO_2R_2 or $CONR_{11}R_{12}$;

R_{10} is C_1-C_4 alkyl, C_1-C_4 haloalkyl, $(CH_2)_nC_3$-C_8 cycloalkyl, $(CH_2)_n$aryl, $(CH_2)_n$heterocycle, $(CH_2)_nC_3$-C_8 optionally substituted cycloalkyl, $(CH_2)_n$ optionally substituted aryl, or $(CH_2)_n$ optionally substituted heterocycle;

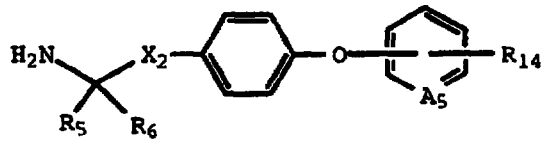
R_{11} and R_{12} are independently H, C_1-C_4 alkyl, aryl, $(CH_2)_n$aryl or combine with the nitrogen to which each is bound to form morpholinyl, piperidinyl, pyrrolidinyl, or piperazinyl;

m is 0 or 1;

n is 0, 1, 2, or 3;

or a pharmaceutically acceptable salt thereof.

The present invention also provides for novel intermediates, useful in the preparation of compounds of Formulas I and II, described by Formula III below.



(III)

wherein:

A_5 is CH or N;

X_2 is a bond or a 1 to 5 carbon straight or branched alkylene.

R_5 is H, C_1-C_4 alkyl;

R_6 is H, C_1-C_4 alkyl;

or R_5 and R_6 combine with the carbon to which each is attached to form a C_3-C_6 cycloalkyl;

or R_6 combines with X_2 and the carbon to which X_2 is attached to form a C_3-C_8 cycloalkyl;

R_{14} is C_1-C_4 alkyl, C_1-C_4 haloalkyl, hydroxy, carboxy, tetrazolyl, acyl, $COOR_2$, $CONR_{11}R_{12}$, $CONH(C_1$-C_4 alkoxy), cyano, C_1-C_4 alkoxy, C_1-C_4 alkyl, phenyl, nitro, $NR_{11}R_{12}$, $NHCO(C_1$-C_4 alkyl), NHCO(benzyl), NHCO(phenyl), SR_2, $S(C_1$-C_4 alkyl), $OCO(C_1$-C_4 alkyl), $SO_2(NR_{11}R_{12})$, $SO_2(C_1$-C_4 alkyl), or SO_2(phenyl);

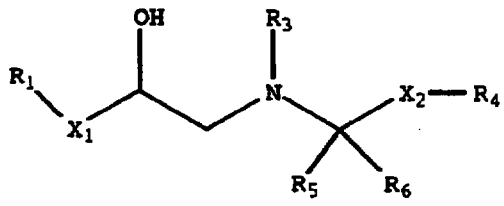
or pharmaceutically acceptable salts thereof.

The present invention also provides novel processes for making, as well as novel pharmaceutical formulations of, compounds of Formulas I and II.

The compounds of the present invention are selective β_3 receptor agonists and as such are useful for treating Type II diabetes and obesity, as well as useful for agonizing the β_3 receptor. Therefore, the present invention also provides for methods of treating Type II diabetes and obesity, as well as a method of agonizing the β_3 receptor.

In addition, the present invention provides the use of compounds of Formulas I and II for treating Type II diabetes and obesity as well the use of compounds of Formulas I and II for agonizing the β_3 receptor.

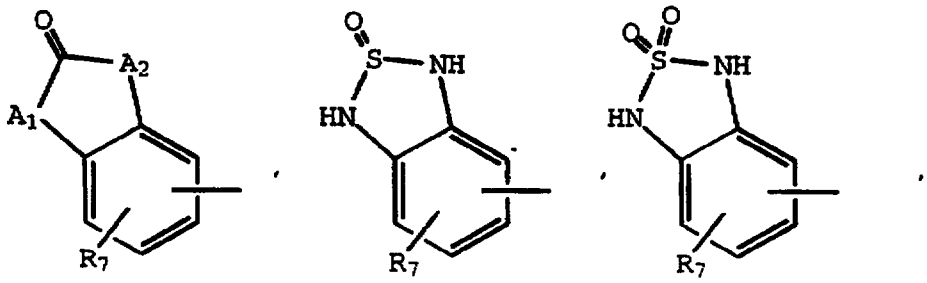
Another representation of the compounds of the present invention is given by Formula IV below.



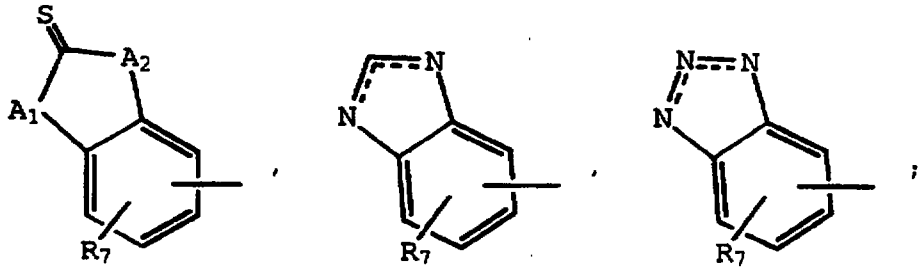
(IV)

wherein:

R_1 is a fused heterocycle of the formula:



(a) (b) (c)

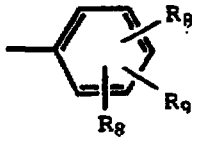


(d) (e) (f)

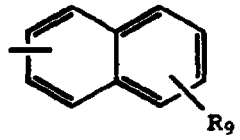
R_2 is H, C_1-C_4 alkyl, or aryl;

R_3 is H, C_1-C_4 alkyl, aryl, or heterocycle;

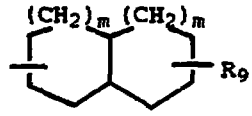
R_4 is an optionally substituted heterocycle or a moiety selected from the group consisting of:



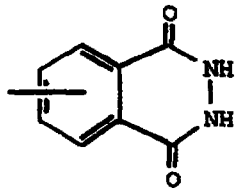
(g)



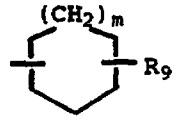
(h)



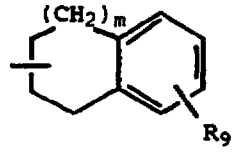
(i)



(j)



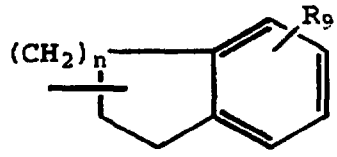
(k)



(l) ;

R_5 is H, or C_1-C_4 alkyl;

R_6 is H, C_1-C_4 alkyl, bonds to X_2 to form a C_3-C_8 cycloalkyl, or combines with X_2 and R_4 to form:



(m) ;

R_7 is H, halo, hydroxy, C_1-C_4 alkyl, C_1-C_4 alkoxy, NH_2, SR_2, SO_2R_2, or SOR_2;

R_8 is independently H, halo or C_1-C_4 alkyl;

R_9 is halo, CN, OR_{10}, C_1-C_4 alkyl, C_1-C_4 haloalkyl, CO_2R_2, $CONR_{11}R_{12}$, CONH(C_1-C_4 alkyl or C_1-C_4 alkoxy), SR_2, $CSNR_2$, $CSNR_{11}R_{12}$, SO_2R_2, $SO_2NR_{11}R_{12}$, SOR_2, $NR_{11}R_{12}$, optionally substituted aryl, optionally substituted aryloxy, optionally substituted heterocycle, or C_2-C_4 alkenyl optionally substituted with CN, CO_2R_2 or $CONR_{11}R_{12}$;

R_{10} is independently C_1-C_4 alkyl, C_1-C_4 haloalkyl, $(CH_2)_nC_3$-C_8 cycloalkyl, $(CH_2)_n$aryl, $(CH_2)_n$heterocycle, said aryl, C_3-C_8 cycloalkyl, or heterocycle being optionally substituted;

R_{11} and R_{12} are independently H, C_1-C_4 alkyl, or combine with the nitrogen to which each are bound to form a morpholinyl, piperdinyl, pyrrolyl, or piperazine;

A_1 and A_2 are independently O, S, NH, or NCH_3;

X_1 is $-OCH_2-$, $-SCH_2-$, or absent;

X_2 is absent or a 1 to 5 carbon straight or branched alkylene;

m is 0 or 1;

n is 0, 1, 2, or 3;

or a pharmaceutically acceptable salt or solvate thereof.

Detailed Description

For the purposes of the present invention, as disclosed and claimed herein, the following terms are defined below. As they relate to the present invention, the terms below may not be interpreted, individually or collectively, to describe chemical structures that are unstable or impossible to construct.

The term "halo" represents fluorine, chlorine, bromine, or iodine.

The term "C_1-C_4 alkyl" represents a cyclo, straight or branched chain alkyl group having from one to four carbon atoms such as methyl, ethyl, n-propyl, isopropyl, cyclopropyl, n-butyl, isobutyl, sec-butyl, t-butyl and the like. A "haloalkyl" is one such alkyl substituted with one or more halo atoms, preferably one to three halo atoms. An example of a haloalkyl is trifluoromethyl. An "alkoxy" is a alkyl group covalently bonded by an -O- linkage.

The term "1 to 5 carbon straight or branched alkylene" represents a one to five carbon, straight or branched, alkylene moiety. A branched alkylene may have one or more points of branching. A 1 to 5 carbon straight or branched alkylene may optionally be unsaturated at one or more carbons. Thus, a 1 to 5 carbon straight or branched alkylene includes 1 to 5 carbon alkylene, alkenylene and alkylidene moieties. Examples include methylene, ethylene, propylene, butylene, $-CH(CH_3)CH_2-$ $CH(C_2H_5)CH_2-$, $-CH(CH_3)CH(CH_3)-$, $-CH_2C(CH_3)_2-$,

$-CH_2CH(CH_3)CH_2-$, $-C(CH_3)_2CH=$, $-CH=CHCH_2-$, $-CH=CH-$, and the like.

The "acyl" moiety, alone or in combination, is derived from an alkanoic acid containing from one to seven carbon atoms. The term "acyl" also includes moieties derived from an aryl carboxylic acid.

The term "aryl" represents an optionally substituted or unsubstituted phenyl or naphthyl. The term $(CH_2)_n$aryl is preferably benzyl or phenyl.

The notation "---" when used in conjunction with a bond indicates that bond may either be a double bond or a single bond.

The term "optionally substituted" as used herein means an optional substitution of one to three, preferably one or two groups independently selected from halo, C_1-C_4 haloalkyl, hydroxy, carboxy, tetrazolyl, acyl, $COOR_2$, $CONR_{11}R_{12}$, CONH(C_1-C_4 alkoxy), cyano, C_1-C_4 alkoxy, C_1-C_4 alkyl, phenyl, benzyl, nitro, $NR_{11}R_{12}$, NHCO(C_1-C_4 alkyl), NHCO(benzyl), NHCO(phenyl), SR_2, S(C_1-C_4 alkyl), OCO(C_1-C_4 alkyl), $SO_2(NR_{11}R_{12})$, SO_2(C_1-C_4 alkyl), or SO_2(phenyl); provided that such substitution does not entirely destroy biological activity, as defined in this specification.

R_{11} and R_{12} are independently H, C_1-C_4 alkyl, or combine with the nitrogen to which each is bound to form morpholinyl, piperidinyl, pyrrolidinyl, or piperazinyl.

The term "heterocycle" represents a stable, optionally substituted or unsubstituted, saturated or unsaturated 5 or 6 membered ring, said ring having from one to four heteroatoms that are the same or different and that are selected from the group consisting of sulfur, oxygen, and nitrogen; and when heterocycle contains two adjacent carbon atoms, the adjacent carbon atoms may be structured to form a group of the formula -CH=CH-; provided that (1) when the heterocyclic ring contains 5 members, the heteroatoms comprise not more than two sulfur or two oxygen atoms but not both; and (2) when the heterocyclic ring contains 6 members and is aromatic, sulfur and oxygen are

not present. The heterocycle may be attached at any carbon or nitrogen which affords a stable structure. The heterocycle may be optionally substituted. Examples of an heterocycle include pyrazole, pyrazoline, imidazole, isoxazole, triazole, tetrazole, oxazole, 1,3-dioxolone, thiazole, oxadiazole, thiadiazole, pyridine, pyrimidine, piperazine, morpholine, pyrazine, pyrrolidine, piperidine, oxazolidone, oxazolidinedione, imidazolidinone.

The term "leaving group" as used in the specification is understood by those skilled in the art. Generally, a leaving group is any group or atom that enhances the electrophilicity of the atom to which it is attached for displacement. Preferred leaving groups are p-nitrobenzene sulfonate, triflate, mesylate, tosylate, imidate, chloride, bromide, and iodide.

The term "pharmaceutically effective amount", as used herein, represents an amount of a compound of the invention that is capable of agonizing the β_3 receptor in mammals. The particular dose of the compound administered according to this invention will, of course, be determined by the particular circumstances surrounding the patient, including the compound administered, the route of administration, the particular condition being treated, and similar considerations.

The term "unit dosage form" refers to physically discrete units suitable as unitary dosages for human subjects and other mammals, each unit containing a predetermined quantity of active material calculated to produce the desired therapeutic effect, in association with a suitable pharmaceutical carrier.

The term "treating," as used herein, describes the management and care of a patient for the purpose of combating the disease, condition, or disorder and includes the administration of a compound of present invention to prevent the onset of the symptoms or complications, to alleviate symptoms or complications, or to eliminate the disease, condition, or disorder.

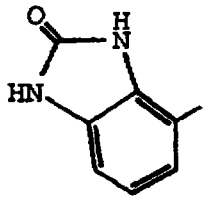
The term "agonizing," as used herein, means stimulating or affecting a receptor to elicit a pharmacological response.

The term "selective" means preferential agonism of the β_3 receptor over agonism of the β_1 or β_2 receptor. In general, the compounds of the present invention demonstrate at a minimum a twenty fold differential (preferably over a 50x differential) in the dosage required to behave as an agonist to the β_3 receptor and the dosage required for equal agonism of the β_1 and β_2 as measured in the Functional Agonist Assay. The compounds demonstrate this differential across the range of doses. Thus, β_3 selective compounds behave as agonists for the β_3 receptor at much lower concentrations with lower toxicity by virtue of their minimal agonism of the other receptors.

As previously noted, the present invention provides a method of treating type II diabetes and obesity, comprising administering to a mammal in need thereof compounds of the Formulas I and II. Preferred embodiments of the present invention are set out in paragraphs below.

Preferred compounds are those of Formulas I and II, wherein:

(a) R_1 is



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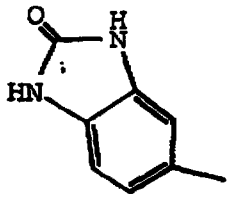

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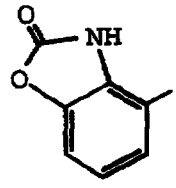

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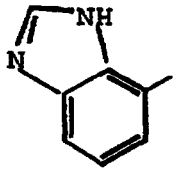

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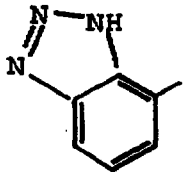

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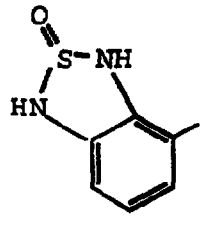

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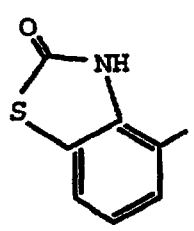
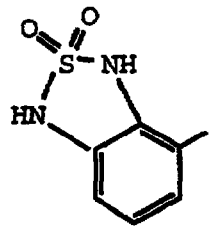
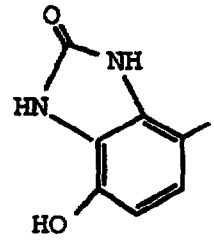
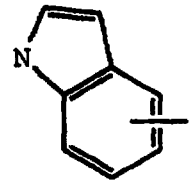




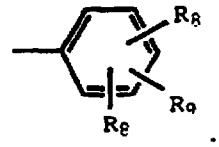
or 

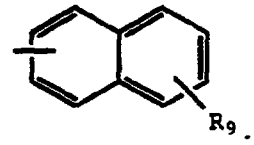
(b) X_1 is $-OCH_2-$, the oxygen of which is attached to R_1.

(c) X_1 is a bond.

(d) R_5 and R_6 are independently C_1-C_4 alkyl.

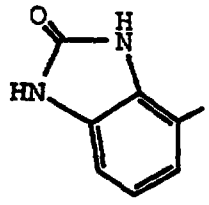
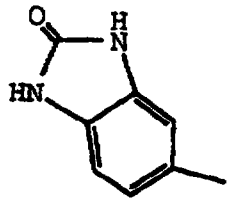
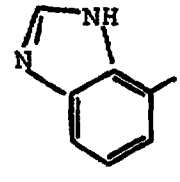
(e) X_2 is isopropylene, ethylene, methylene, or a bond.

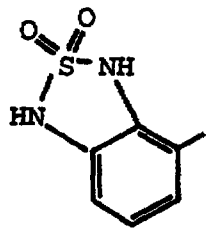
(f) R_4 is 

(g) R_4 is 

Other preferred compounds are those of Formulas I and II, wherein:

(aa) R_1 is



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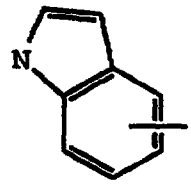


(bb) R_5 and R_6 are methyl or ethyl.

(cc) X_2 is methylene or ethylene.

(dd) R_8 is hydrogen.

(ee) R_8 is halo.

(ff) R_9 is OR_{10}.

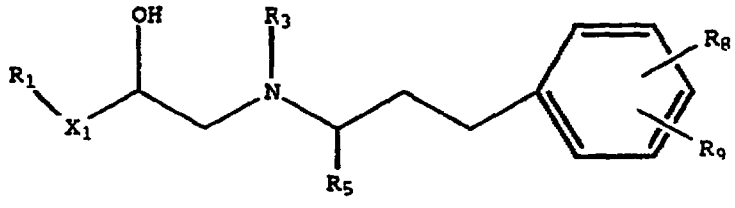
(gg) R_9 is $CONR_{11}R_{12}$.

(hh) R_9 is CN.

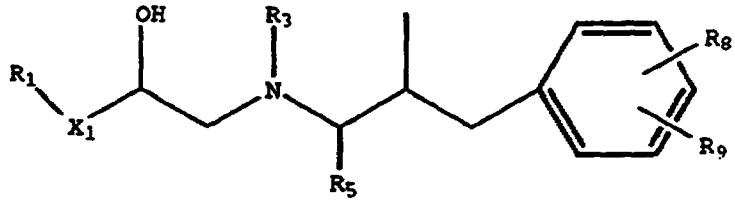
(ii) R_9 is optionally substituted aryl.

(jj) R_{10} is $(CH_2)_n$aryl, $(CH_2)_n$heterocycle, $(CH_2)_n$ optionally substituted aryl, or $(CH_2)_n$ optionally substituted heterocycle.

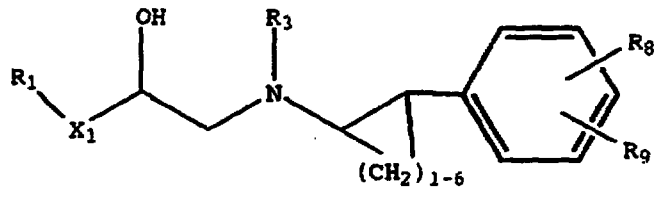
More preferred compounds are those of Formula Ia, Ib, Ic, and Id:



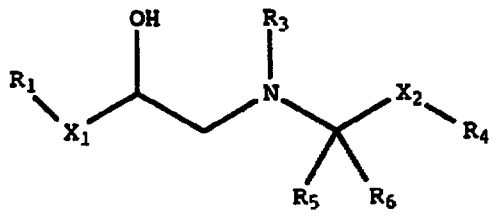
(Ia)



(Ib)

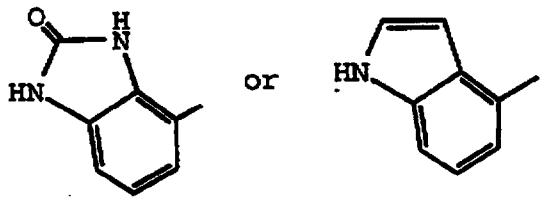


(Ic)



(Id)

Especially preferred compounds are those of Formulas Ia, Ib, Ic, or Id wherein: R_1 is



X_1 is $-OCH_2-$ the oxygen of which is attached to R_1, R_3 is H, and R_9 is $CONH_2$ or OR_{10}, wherein R_{10} is a optionally substituted aryl, particularly phenyl, or optionally substituted heterocycle, particularly pyridine.

Other especially preferred compounds include the following:

(S, R and S, S) 4-(3-[N-(2-[4-(5-carbamoyl-2-pyridyloxy)phenyl]-1-methylethyl)amino]-2-hydroxypropoxy)-1,3-dihydro-2H-benzimidazol-2-one

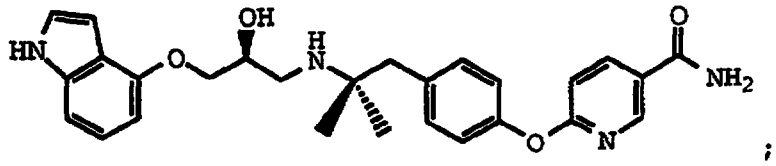
(S, R and S, S) 5-(3-[N-(3-[2-oxo-1,3-dihydro-2H-benzimidazole-4-yloxy]-2-hydroxypropyl)amino]butyl)-2-thiophenesulfonamide

(S, R and S, S) 4-(3-[N-(3-[4-(4-carbamoylphenoxy)phenyl]-1-methylpropyl)amino]-2-hydroxypropoxy)-1,3-dihydro-2H-benzimidazol-2-one

(All isomers of:) 5-(4-[3-(N-[3-(2-oxo-1,3-dihydro-2H-benzimidazole-4-yloxy)-2-hydroxypropyl]amino)-2-methylbutyl]-3-fluorophenyl)-1H-tetrazole

(All isomers of:) 4-(3-[N-(2-[(4-carbamoylphenyl)methyl]-1-methylpropyl)amino]-2-hydroxypropoxy)-1,3-dihydro-2H-benzimidazol-2-one

Most preferred comounds include the following structures:



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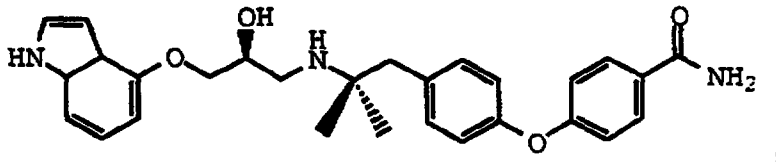

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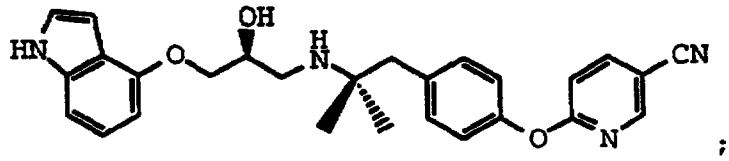

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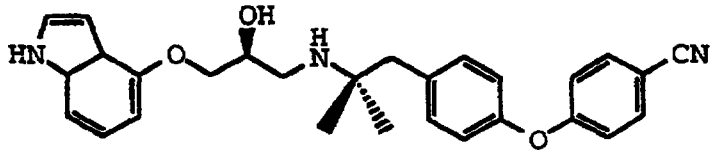


By virtue of their acidic moieties, the compounds of Formulas I and II include the pharmaceutical acceptable base addition salts thereof. Such salts include those derived from inorganic bases such as ammonium and alkali and alkaline earth metal hydroxides, carbonates, bicarbonates, and the like, as well as salts derived from basic organic amines such as aliphatic and aromatic amines, aliphatic diamines, hydroxy alkamines, and the like. Such bases useful in preparing the salts of this invention thus include ammonium hydroxide, potassium carbonate, sodium bicarbonate, calcium hydroxide, methylamine, diethylamine, ethylenediamine, cyclohexylamine, ethanolamine and the like.

Because of the basic moiety, the compounds of Formulas I and II can also exist as pharmaceutically acceptable acid addition salts. Acids commonly employed to form such salts include inorganic acids such as hydrochloric, hydrobromic, hydroiodic, sulfuric and phosphoric acid, as well as organic acids such as para-toluenesulfonic, methanesulfonic, oxalic, para-bromophenylsulfonic, carbonic, succinic, citric, benzoic, acetic acid, and related inorganic and organic acids. Such pharmaceutically acceptable salts thus include sulfate, pyrosulfate, bisulfate, sulfite, bisulfite, phosphate, mono-hydrogenphosphate, dihydrogenphosphate, metaphosphate, pyrophosphate, chloride, bromide, iodide, acetate, propionate, decanoate, caprylate, acrylate, formate, isobutyrate, heptanoate, propiolate, oxalate, malonate, succinate, suberate, sebacate, fumarate, maleate, 2-butyne-1,4 dioate, 3-hexyne-2, 5-dioate, benzoate, chlorobenzoate, hydroxybenzoate, methoxybenzoate, phthalate, xylenesulfonate, phenylacetate, phenylpropionate, phenylbutyrate, citrate, lactate, hippurate, β-hydroxybutyrate, glycollate, maleate, tartrate, methanesulfonate, propanesulfonate, naphthalene-1-sulfonate, naphthalene-2-sulfonate, mandelate and the like salts.

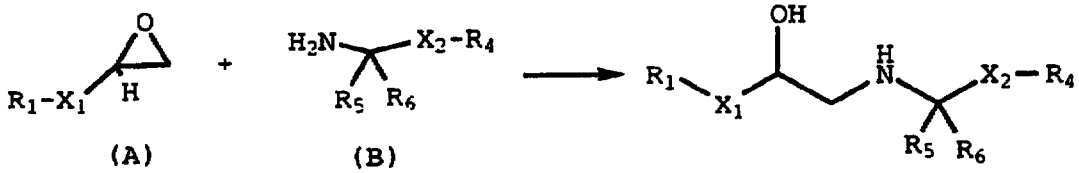
It is recognized that various stereoisomic forms of the compounds of Formulas I and II may exist. The compounds may be prepared as racemates and can be conveniently used as such. Therefore, the racemates, individual enantiomers, diastereomers, or mixtures thereof form part of the present invention. Unless otherwise specified, whenever a compound is described or referenced in this specification all the racemates, individual enantiomers, diastereomers, or mixtures thereof are included in said reference or description.

It is also recognized that various tautomeric forms of the compounds of Formulas I and II may exist, and all tautomeric forms are part of the present invention.

Unless otherwise specified, whenever a compound is described or referenced in this specification all tautomeric forms, or mixtures thereof, are included in said reference or description.

The compounds of Formulas I and II are prepared as described in the following Schemes and Examples. Schemes 1 and 2 describe methodology for the preparation of final embodiments of the present invention. Schemes 3-5 describe methodology for the preparation of intermediates required for the construction of the final embodiments of the invention.

Scheme I

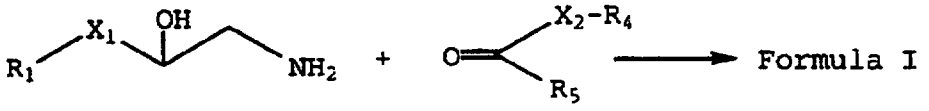


(A) (B)

In Scheme I, X_1, X_2, R_1, R_2, R_4, R_5, and R_6 have the same meaning as previously described. The reaction of Scheme I is carried out under conditions appreciated in the art for the amination of epoxides. For example, the epoxide (A) may be combined with the amine (B) in an alcohol, preferably, ethanol at room temperature to the reflux temperature of the reaction mixture. Preferably, the reaction is carried under conditions generally described in Atkins et al., Tetrahedron Lett. 27:2451 (1986). These conditions include mixing the reagents in the presence of trimethylsilyl acetamide in a polar aprotic solvent such as acetonitrile, dimethylformamide (DMF), acetone, dimethylsulfoxide (DMSO), dioxane, diethylene glycol dimethyl ether (diglyme), tetrahydrofuran (THF), or other polar aprotic solvents in which the reagents are soluble. Preferably, the solvent is DMSO. The reaction is carried out at temperatures ranging from about 0°C to reflux.

Some of the compounds of the present invention are prepared by a novel combinatorial/parallel synthesis. This synthesis is described in Scheme II.

Scheme II



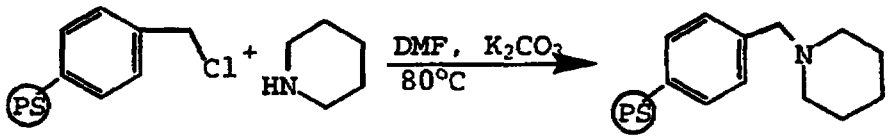
(IV) (V)

In Scheme II, X_1, X_2, R_1, R_2, R_4, and R_5 have the same meaning as previously described. R_6 is H. The reaction of Scheme II is preferably carried out by adding to a glass vial: a non-reactive solvent such as methanol, DMF, methylene chloride or acetonitrile, amine (IV), and ketone (V). The solution is shaken to allow for imine formation and treated with Amberlite IRA400 borohydride resin (Aldrich). The slurry is then shaken an additional 24 hours to effect reduction to the secondary amine. Methylene chloride and polystyrene-linked benzaldehyde resin (Frechet, J.M. et al., J. Am Chem. Soc. 93:492 (1971)) is added to the vial, in order to scavenge excess primary amine starting material. The slurry is shaken, preferably overnight. The slurry is then filtered through a cotton plug, and the residual solids rinsed with methanol. Evaporation under a flow of air, followed by drying for several hours at room temperature in a vacuum oven yields the desired product of sufficient purity.

A modification of Scheme II is necessary when the amine hydrochloride salt is used. Addition of resin-bound base to the initial reaction mixture prior to reduction or scavenging allows the desired reaction to proceed. Imine formation using amine hydrochloride salts, an aldehyde or ketone, and a resin bound amine base may be carried out using two different resins: poly(4-vinylpyridine), commercially available from Aldrich, and

resin (VIII), synthesized by the reaction of Merrifield resin with piperidine (Scheme IIa):

Scheme IIa



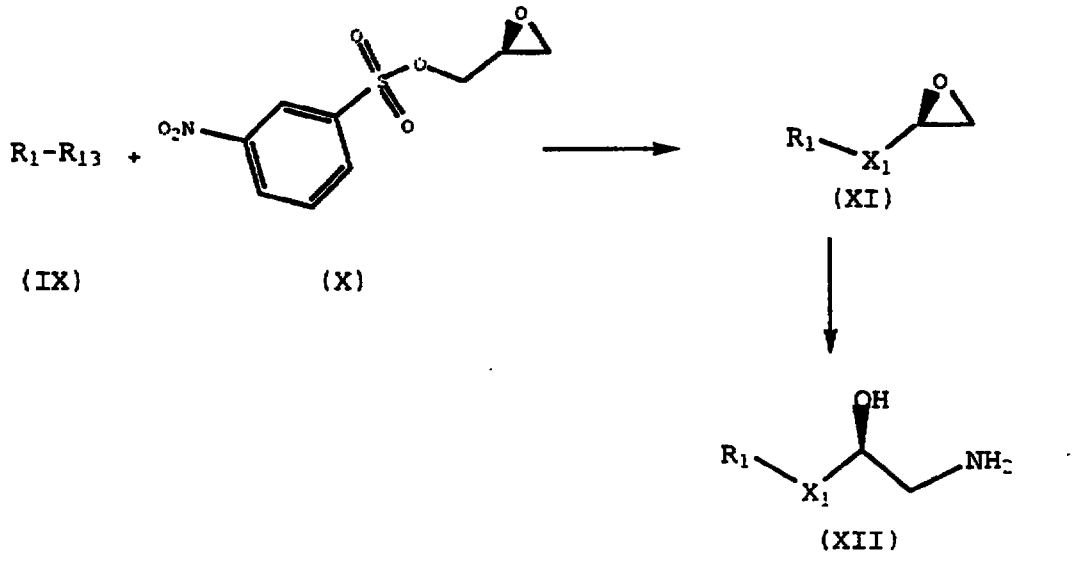
(VI) (VII) (VIII)

In Scheme IIa, PS is polysytrene. Both the poly(4-vinylpyridine) and resin (VIII) promote imine formation.

Scheme II can also be carried out by utilization of traditional fashion. Reductive aminations described in scheme II are well known in the art. They are typically performed by mixing the amine and ketone starting materials in a solvent and adding a reducing agent. Solvents typically include lower alcohols, DMF, and the like. A wide variety of reducing agents can be utilized, most commonly utilized are sodium borohydride and sodium cyanoborohydride. The reaction is typically performed at room temperature to the reflux temperature of the solvent. Products are isolated by techniques well known in the art.

The ketone and amino starting materials of Scheme II can be prepared by techniques recognized and appreciated by one skilled in the art. The synthesis of the starting materials is generally described in Schemes III and IV.

Scheme III



In Scheme III, R_1 is the same as previously defined. R_{13} is OH or SH. Equimolar amounts of the aromatic compound (Compound IX) and (2S)-(+)-glycidyl 3-nitrobenzenesulfonate (Compound X) are dissolved in an inert solvent such as acetone and treated with 1.1 equivalents of a non-reactive acid scavenger, such as K_2CO_3. The suspension is then heated at reflux for 16-20 hours with stirring. The solvent is removed *in vacuo*. The residue is partitioned between chloroform or other organic solvent and water. The organic layer is dried over Na_2SO_4 and concentrated *in vacuo* to give the epoxide (XI) in sufficient purity (>95%) and yield (85-100%).

The epoxide (XI) is dissolved in an alcohol, preferably methanol, and treated with one equivalent of dibenzylamine. The solution is preferably stirred at reflux for three to four hours and then cooled to ambient temperature. Approximately 10 equivalents of ammonium formate are added to the flask, followed by 10% palladium on carbon, and the suspension stirred vigorously at reflux for 30-45 minutes. The reaction mixture is then filtered through Celite, concentrated *in vacuo* to a minimum volume and treated with 1.1 equivalents of a 1.0 M anhydrous

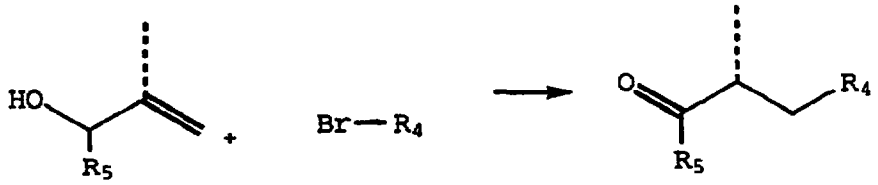
solution of HCl in ether. The solution is concentrated to dryness. The solid residue is triturated with pentane to yield products of sufficient purity (>97%) and yield (60-100%). If desired, further purification may be carried out by passing over a short plug of silica, eluting with $CHCl_3$, then 95:5 $CHCl_3$/MeOH, the 25:5:1 $CHCl_3$/MeOH/NH_4OH.

Alternatively, the epoxide (XI) is treated with a solution of methanol saturated with ammonia gas and stirred at room temperature in a sealed tube for 16 hours. This solution is then evaporated, and the residue subjected to standard purifications such as column chromatography or recrystallization. The HCl salt is then optionally produced by the addition of HCl gas in ether.

The reaction of Scheme III is further described in Beedle et al., U.S. patent 5,013,761 and reference cited therein. U.S. patent 5,013,761 is herein incorporated by reference.

The ketone moieties of Scheme II, that are either unknown in the art or not commercially available, are prepared in accordance with Scheme IV.

Scheme IV



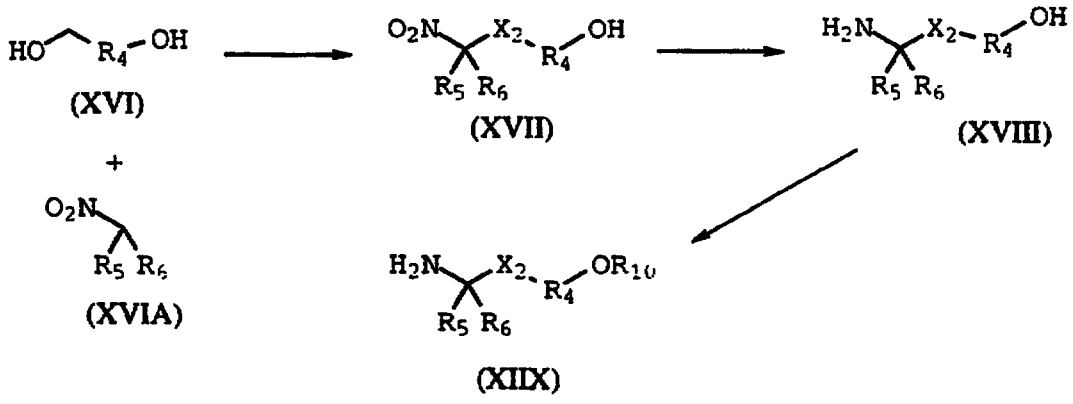
(XIII) (XIV) (XV)

In Scheme IV, R_4 and R_5 are the same as previously defined. The notation ---- indicates optional branching. Preferably, R_4 is a substituted phenyl. The reaction described in Scheme IV is referred to as a Heck reaction and is described in A.J. Chalk et al., J. Org. Chem. 41: 1206 (1976). The reaction is achieved by treating compound (XIII) with an arylpalladium reagent. The arylpalladium reagent is generated in situ by treating Compound (XIV) with a palladium-triarylphosphine complex.

The reaction is generally carried out in under conditions appreciated in the art.

Additional amines, of the type where X_2 is methylene, R_4 is aryl, and R_{10} is aryl, heterocycle, optionally substituted aryl, or optionally substituted heterocycle, that are reacted in a manner analogous to Scheme I are prepared in accordance with Scheme V.

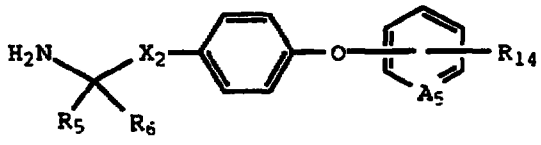
Scheme V



Compounds of formula (XVII) can be prepared by reacting arylalkyl alcohols of formula (XVI) with excess (5 mol/equiv) of a compound of formula (XVIA) by methods well known in the art. (see Sh. Prikl. Kin., *Vol 45*, 1573-77 (1972); Russ). The reaction can also be carried out by mixing the reagents in an aprotic solvent, preferably diglyme, and adding potassium *t*-butoxide (0.5 mol/equiv.). The reaction is then heated to reflux and water removed. After removal of water is complete, generally 2-8 hours depending upon the scale of the reaction, the resulting solution is subjected to aqueous workup including acidic washes and the product is isolated by crystallization. Compounds of formula (XVIII) can be prepared by hydrogenation of the corresponding compounds of formula (XVII) over a precious metal catalyst. The hydrogenation can be affected at between 20 and 60 psi of hydrogen, and with a variety of solvents, temperatures, and catalysts well known in the art. The reaction is preferably carried

out at 50 psi of hydrogen over 5% palladium on carbon wetted with 2B3 ethanol. Compound (XVII) is charged to the reactor along with one equivalent of acetic acid, diluted with methanol, heated to 50 degrees °C, and subjected to hydrogen for 5-24 hours depending on the scale of the reaction. The product is isolated as the acetic acid salt upon work up by methods well known in the art.

A skilled artisan would appreciate that compounds of the formula (XVIII) could be coupled with a wide variety of aromatic halides to yield the claimed ethers. The coupling can be carried out according to procedures well known in the art and is preferably performed by mixing the starting materials in N,N-dimethylacetamide and toluene in the presence of potassium carbonate. The reaction is then heated to reflux for 5 to 24 hours and water removed. The product is typically isolated by aqueous work up after rotory evaporation of the reaction solvent. The crude product can be purified by methods well know in the art. A skilled artisan would appreciate that the amines prepared by Scheme V can be utilized in Scheme I to prepare compounds of the present invention. Scheme V also describes preparation of novel intermediates of the Formula III.



(III)

wherein:

A_5 is CH or N;

X_2 is a bond or a 1 to 5 carbon straight or branched alkylene.

R_5 is H, C_1-C_4 alkyl;

R_6 is H, C_1-C_4 alkyl;

or R_5 and R_6 combine with the carbon to which each is attached to form a C_3-C_6 cycloalkyl;

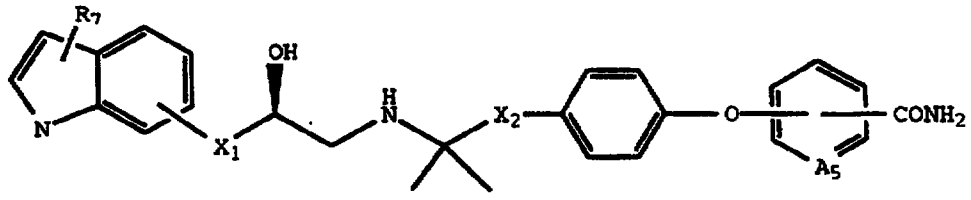
or R_6 combines with X_2 and the carbon to which X_2 is attached to form a C_3-C_8 cycloalkyl;

R_{14} is C_1-C_4 alkyl, C_1-C_4 haloalkyl, hydroxy, carboxy, tetrazolyl, acyl, $COOR_2$, $CONR_{11}R_{12}$, $CONH(C_1$-C_4 alkoxy), cyano, C_1-C_4 alkoxy, C_1-C_4 alkyl, phenyl, nitro, $NR_{11}R_{12}$, $NHCO(C_1$-C_4 alkyl), NHCO(benzyl), NHCO(phenyl), SR_2, $S(C_1$-C_4 alkyl), $OCO(C_1$-C_4 alkyl), $SO_2(NR_{11}R_{12})$, $SO_2(C_1$-C_4 alkyl), or SO_2(phenyl);

or pharmaceutically acceptable salts thereof.

Compounds of Formula III are useful in the preparation of compounds of Formulas I and II, and as such represent an additional embodiment of the present invention.

Another embodiment of the present invention is a process of preparing novel compounds of the formula IA



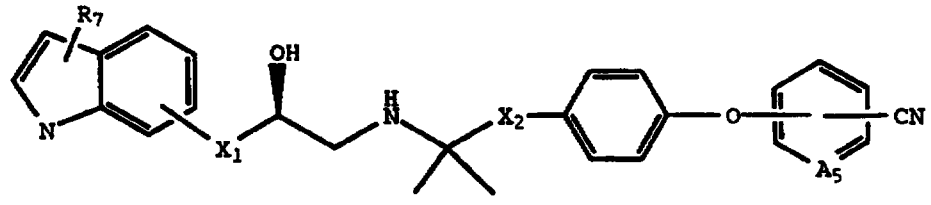
(IA)

wherein:

A_5 is CH or N;

which comprises:

in step 1, hydrolysis of a compound of the formula IB:



(IB),

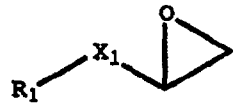
and in step 2, reacting the product of step 1 to form an acid addition salt.

Step one of the process can be carried out by a variety of agents known in the art, it is however preferably affected by utilization of one of the following

agents: polyphosphoric acid, H_2O_2 and K_2CO_3 in dimethylsulfoxide, H_2O_2 and ammonium hydroxide, H_2O_2 and sodium hydroxide, potassium hydroxide and *t*-butanol, or water and HCl. Step 2 of the process involves the addition of an agent capable of forming an acid addition salt with the product of step 1. Step 2 can be carried out by numerous methods known in the art involving the addition of a mineral acid, or other acid, to a solution of the product of step 1.

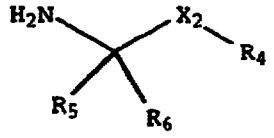
Another embodiment of the present invention is a process of preparing a compound of Formulas I and II which comprises:

In step 1, reacting an epoxide of the formula (XI):



(XI)

with an amine of formula:



(B);

and in step 2, reacting the product of step 1 to form an acid addition salt.

The process can be carried out by a variety of agents known in the art, it is however preferably affected by reacting the amine and epoxide in a solvent at elevated temperature. Preferred solvents include: lower alcohols, dimethylformamide, dimethylsulfoxide, acetone and the like. The reaction is generally performed at a temperature ranging from ambient to the reflux temperature of the solvent. Most preferably, it is done in ethanol at 40 - 60 °C. Step 2 can be carried out by numerous methods known in the art involving the addition of a mineral acid, or other acid, to a solution of the product of step 1.

Starting materials for the compounds described in Schemes I, II, III, IV or V are either commercially available, known in the art, or can be prepared by methods known in the art or described herein.

Preparations and Examples

The following examples and preparations are provided merely to further illustrate the invention. The scope of the invention is not construed as merely consisting of the following examples. In the following examples and preparations, melting point, nuclear magnetic resonance spectra, mass spectra, high pressure liquid chromatography over silica gel, gas chromatography, N,N-dimethylformamide, palladium on charcoal, tetrahydrofuran, ethyl acetate, thin layer chromatography and elemental analysis are abbreviated M.Pt., NMR, MS, HPLC, GC, DMF, Pd/C, THF, EtOAc, TLC and EA respectively. The terms "EA", "TLC", "NMR", and "MS", when being utilized in the preparations, indicate that the data indicated was consistent with the desired structure.

Preparations 1 through 18 encompass the methodology required to prepare the heterocyclic ethanol amines used in Scheme II to prepare final embodiments of the invention.

Preparation 1

(S)-3-(2-Amino-3-nitrophenoxy)-1,2-epoxypropane

A solution of 2-amino-3-nitrophenol (5.95 g, 38.6 mmol) and (2S)-(+)-glycidyl 3-nitrobenzenesulfonate (10.0 g, 38.6 mmol) in 150 mL of acetone was treated with 1.1 equivalents of K_2CO_3 (5.86 g, 42.4 mmol) and stirred at reflux for 18 hours. The suspension was cooled to ambient temperature; the solids were filtered; and the filtrate concentrated *in vacuo* to dryness. The resulting solids were partitioned between chloroform and water, and the aqueous layer extracted once with chloroform. The organic

layers were combined and dried over Na_2SO_4 and concentrated *in vacuo* to 8.0 g (99%) of an orange solid. TLC (R_f = 0.5, $CHCl_3$) and NMR indicated >95% purity, so the material was used without further purification. NMR.

Preparation 2

(S)-[3-(N,N-Dibenzylamino)-2-hydroxypropoxy]-2-amino-3-nitrobenzene

(S)-3-(2-Amino-3-nitrophenoxy)-1,2-epoxypropane (8.0 g, 38.1 mmol) was dissolved in 250 mL of methanol and treated with dibenzylamine (8.05 mL, 42.0 mmol, d=1.026). The mixture was stirred at reflux for 10 hours and then cooled to 0°C. The resulting orange precipitate was filtered and washed with cold methanol, then dried to yield 12.1 g (78%) of a pale orange solid that was pure by NMR and TLC analysis. The material was used without further purification. NMR.

Preparation 3

(S)-[3-(N,N-Dibenzylamino)-2-hydroxypropoxy]-2,3-diamino benzene

(S)-[3-(N,N-Dibenzylamino)-2-hydroxypropoxy]-2-amino-3-nitrobenzene (10.6 g, 26.0 mmol) was suspended in 1 L of 2:1 ethanol/water at ambient temperature and treated with excesses of sodium bicarbonate (26.22 g, 0.31 mol) and sodium hydrosulfite (54.34 g, 0.31 mol). The orange reaction mixture slowly became colorless over 1 hour, and the mixture was left to stir at ambient temperature for 16 hours. The suspension was filtered, and the filtrate concentrated *in vacuo* to a leave a white solid. This residue was partitioned between chloroform and water, and the organic layer washed twice with brine. The combined organic extracts were concentrated *in vacuo* to give 8.8 g of a brown oil. The compound was recrystallized rapidly from toluene to give 7.96 g (81%) of pale brown needles. NMR.

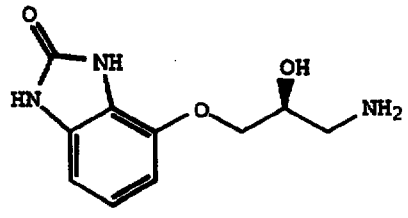
Preparation 4

(S)-4-[2-Hydroxy-3-(N,N-dibenzylamino)propoxy]-1,3-dihydro-2H-benzimidazol-2-one

(S)-[3-(N,N-Dibenzylamino)-2-hydroxypropoxy]-2,3-diaminobenzene (4.4 g, 11.6 mmol) was suspended in a mixture of toluene (60 mL) and 2N HCl (100 mL) at ambient temperature with vigorous stirring. An excess of triphosgene (17.3 g, 58.3 mmol) was added, and the stirring continued for 14 hours. The biphasic mixture was cautiously quenched and neutralized with sodium bicarbonate, causing an off-white precipitate to form at the interface. The precipitate was filtered and dried *in vacuo* to yield 4.35 g (93%) of a pale solid that was used without further purification. TLC, NMR and MS all indicated high purity of the intermediate.

Preparation 5

(S)-4-[2-Hydroxy-3-aminopropoxy]-1,3-dihydro-2H-benzimidazol-2-one



(S) 4-[2-Hydroxy-3-(N,N dibenzylamino)propoxy]-1,3-dihydro-2H-benzimidazol-2-one (4.35 g, 10.8 mmol) was dissolved in methanol (200 mL) and treated with a vast excess of ammonium formate (13.0 g, 0.21 mol), followed by 10% palladium on carbon (1.5 g). The suspension was stirred at reflux for 3 hours. After cooling the suspension, the reaction mixture was filtered through Celite. The filtrate concentrated *in vacuo* to a pale brown oil which slowly crystallized upon standing. The resulting solid was triturated using chloroform containing methanol and filtered to give 1.56 g (65%) as the desired product of a pale grey solid. NMR. MS.

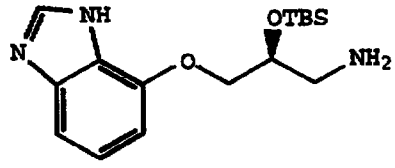
Preparation 6

(S)-4-[2-(Dimethyl-*tert*-butylsilyl)oxy-3-(dibenzylamino) propoxy]benzimidazole

(S)-[3-(N,N-Dibenzylamino)-2-hydroxypropoxy]-2,3-diaminobenzene (1g, 2.7mmol) was dissolved in N,N Dimethylformamide (10 mL) and imidazole (0.27g, 4.0 mmol) and *tert*-butyldimethylsilyl chloride (0.6g, 4.0 mmol) were added. The solution was stirred at ambient temperature for 18 hours and then was partitioned between chloroform and water. The combined organic extracts were dried over sodium sulfate and concentrated *in vacuo* to give the desired benzimidazole 1.3g (96%). NMR.

Preparation 7

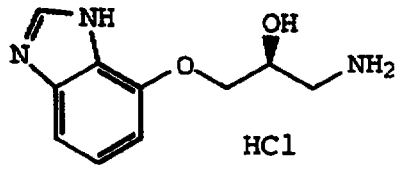
(S)-4-[2-(Dimethyl-*tert*-butylsilyl)oxy-3-aminopropoxy]-benzimidazole



(S)-4-[2-(Dimethyl-*tert*-butylsilyl)oxy-3-(dibenzylamino)propoxy]benzimidazole (1.27g. 2.5mmol) was dissolved in methanol (140 mL) and treated with an excess of ammonium formate (1.64g, 25.0 mmol) followed by 10% palladium on carbon (410 mg). The resulting suspension was stirred at reflux for 1 hour. After cooling, the reaction mixture was filtered through a pad of celite. The filtrate was concentrated *in vacuo* to a brown oil (780 mg, 97%). NMR.

Preparation 8

(S)-4-[2-Hydroxy-3-aminopropoxy]benzimidazole



(S)-4-[2-(Dimethyl *tert*-butylsilyl)oxy-3-aminopropoxy]benzimidazole (10 mg, 31 mmol) was dissolved in THF (1 mL) and the mixture cooled to 0 °C. Tetrabutylammonium fluoride (1 mL, 1.0 M solution in THF) was added. The reaction stirred at this temperature for 4 hours. The reaction was quenched by addition of water. Evaporation of the aqueous layer provided the desired alcohol. NMR. MS.

Preparation 9

(S)-3-(4-Amino-3-nitrophenoxy)-1,2-epoxypropane

A solution of 4-amino-3-nitrophenol (2.54 g, 16.5 mmol) and (2S)-(+)-glycidyl 3-nitrobenzenesulfonate (4.27 g, 16.5 mmol) in 50 mL of acetone was treated with 1.1 equivalents of K_2CO_3 (2.50 g, 18.1 mmol) and stirred at reflux for 20 hours. The suspension was cooled to ambient temperature, concentrated *in vacuo* to dryness. The resulting solids were partitioned between chloroform and water, and the aqueous layer extracted with chloroform. The organic layers were combined and dried over $MgSO_4$ and concentrated *in vacuo* to provide 3.0 g (87%) of an orange solid. TLC and NMR indicated >95% purity, so the material was used without further purification. NMR.

Preparation 10

(S)-[3-(N,N-Dibenzylamino)-2-hydroxypropoxy]-4-amino-3-nitrobenzene

The epoxide from preparation 9 (3.0 g, 14.3 mmol) was dissolved in 100 mL of methanol and treated with

dibenzylamine (3.02 mL, 15.7 mmol). The mixture was stirred at reflux for 6 hours and, after cooling, the solvent was removed *in vacuo*. The resulting orange solid (5.8 g, 100%) was used without further purification. NMR.

Preparation 11

(S)-[3-(N,N-Dibenzylamino)-2-hydroxypropoxy]-3,4-diamino benzene

The nitroaniline from preparation 10 (4.89 g, 12.0 mmol) was suspended in a mixture of ethanol (400 mL) and water (300 mL) at ambient temperature and treated with sodium bicarbonate (12.1 g, 144 mmol, 12 equiv.) and sodium hydrosulfite (25.1 g, 144 mmol, 12 equiv.) The reaction mixture slowly became colorless over three hours. The reaction mixture was partitioned between chloroform and brine. The organic layer was washed several times with brine, dried over magnesium sulfate and concentrated *in vacuo* to give a brown oil. NMR.

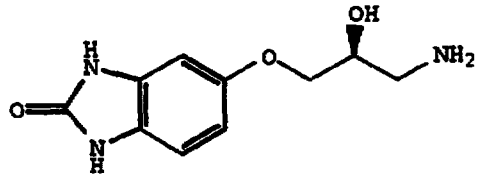
Preparation 12

(S)-5-[2-Hydroxy-3-(N,N dibenzylamino)propoxy]-1,3-dihydro-2H-benzimidazol-2-one

The diamine from Preparation 11 (2.1 g, 5.6 mmol) was suspended in a mixture of toluene (40 mL) and 2N HCl (70 mL) at ambient temperature with vigorous stirring. An excess of triphosgene (17.3 g, 58.3 mmol) was added. The stirring continued for 14 hours. The biphasic mixture was cautiously quenched and neutralized with sodium bicarbonate, which caused an off-white precipitate to form at the interface. The precipitate was filtered and dried *in vacuo* to yield 1.06 g (47%) of a grey solid that was used without further purification. TLC, NMR and MS all indicated high purity of the intermediate.

Preparation 13

(S)-5-[2-Hydroxy-3-amino)propoxy]-1,3-dihydro-2H-benzimidazol-2-one



The compound from preparation 12 (0.75 g, 1.9 mmol) was dissolved in methanol (100 mL) and treated with an excess of ammonium formate (0.7 g, 11.2 mmol), followed by 10% palladium on carbon (400 mg). The suspension was stirred at reflux for 3 hours. After cooling the suspension, the reaction mixture was filtered through celite and the filtrate concentrated *in vacuo* to a greyish black solid (0.25 g, 60%). NMR. MS.

Preparation 14

(S)-5-[2-(Dimethyl *tert*-butylsilyl)oxy-3-(dibenzylamino) propoxy]benzimidazole

This compound was prepared in a manner analogous to Preparation 6. NMR. MS.

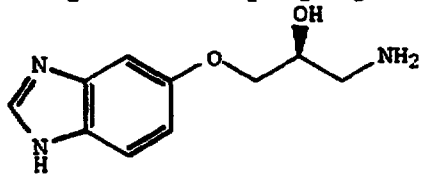
Preparation 15

(S)-5-[2-(Dimethyl-*tert*-butylsilyl)oxy-3-amino propoxy]-benzimidazole

This compound was prepared in a manner analogous to Preparation 7. NMR. MS.

Preparation 16

(S)-4-[2-Hydroxy-3-amino propoxy]benzimidazole



The desired aminoalcohol was prepared in a manner similar to Preparation 8.
NMR. MS.

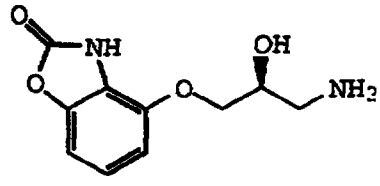
Preparation 17

4-[(2S)-2,-3-oxo-propoxy]-2(3H)benzoxazolone

A solution of 4-Hydroxy-2(3H)benzoxazolone (1.00 g, 6.6 mmol) and (2S)-(+)-glycidyl 3-nitrobenzenesulfonate (1.72 g, 6.6 mmol) in 50 mL of acetone was treated with 1.1 equivalents of K_2CO_3 (1.01 g, 7.3 mmol) and stirred at reflux for 4 hours. The suspension was cooled to ambient temperature, the solvent concentrated *in vacuo* to dryness. The resulting solids were partitioned between chloroform and water, and the aqueous layer extracted once with chloroform. The organic layers were combined and dried over Na_2SO_4 and concentrated *in vacuo* to give a white solid. Flash chromatography (chloroform/methanol 9/1) provided the monoalkylated product (0.55 g, 40%). NMR. MS.

Preparation 18

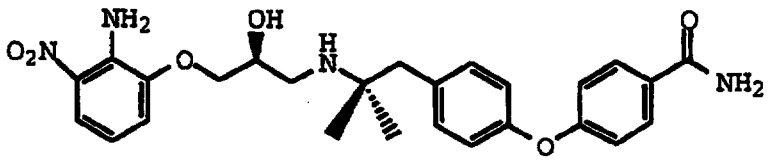
(S)-4-[2-Hydroxy-3-aminopropoxy]-2(3H)benzoxazolone



A solution of 4-[(2S)-2, 3-oxo-propoxy]-2(3H)benzoxazolone (0.15 g, 0.72 mmol) in methanol (2 mL) was cooled to -78 °C using a dry ice/acetone bath. Ammonia gas (2 mL) was condensed into the reaction mixture. The reaction vessel was capped and allowed to warm slowly to room temperature overnight. The reaction was quenched by uncapping the reaction vessel and allowing the ammonia gas to evaporate. NMR. MS.

Preparation 19

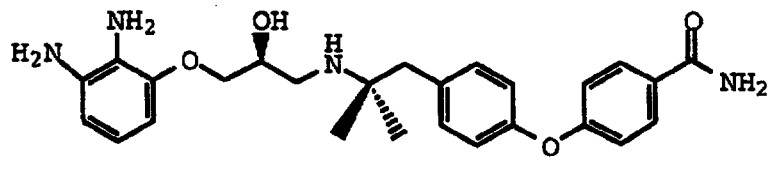
(S)-4-(4-[2-(N-[3-(2-amino-3-nitrophenoxy)-2-hydroxypropyl]amino)-2-methylpropyl]phenoxy)benzamide



A suspension of (S)-3-(2-amino-3-nitrophenoxy)-1,2-epoxypropane (5 g, 23.8 mmol) and 4-(4-(2-amino-2-methylpropyl)phenoxy)benzamide (20.3 g 71.1 mmol) in absolute ethanol (200 mL) was heated to 55°C for 12 h. All solids went into solution at 50°C. Upon completion of the reaction, the solvent was evaporated to dryness. The residue was redissolved in ethyl acetate and washed with a saturated solution of sodium bicarbonate. The layers were separated and the aqueous phase was extracted with ethyl acetate. The two organic layers were combined and washed with brine. The phases were separated and the organic layer was dried over sodium sulfate, filtered, and the solvent evaporated. Column chromatography eluting with 20% MeOH/$CHCl_3$ gave 7.26 g (62%) of product. NMR. MS.

Preparation 20

(S)-4-(4-[2-(N-[3-(2,3-diaminophenoxy)-2-hydroxypropyl]amino)-2-methylpropyl]phenoxy)benzamide



The nitroaniline from preparation 19 (0.484 g, 0.98 mmol) was dissolved in absolute ethanol (40 mL) and treated with a solution of sodium bicarbonate (0.50 g, 5.95 mmol) in water (10 mL) followed by a solution of sodium hydrosulfite (1.41 g, 8.1 mmol) in water (15 mL). Once the color had completely diminished, the solvents were evaporated. The residue was washed with water to remove excess salts. The

leftover amorphous material was dissolved in methanol and gravity filtered. The solvent was evaporated to give 0.454 g (100%) of product. NMR. MS.

Preparation 21

4-t-butyldimethylsilyloxyindole

A solution of 4-hydroxyindole (3.0 g, 22.5 mmol), *t*-butyldimethylsilyl chloride (5.09 g, 33.8 mmol) and imidazole (3.83 g, 56.3 mmol) in dimethylformamide (60 mL) was stirred at room temperature for 24 hours. Aqueous ammonium chloride was added (100 ml) and extracted several times with ethyl acetate. The organic layers were combined, dried over magnesium sulfate, and evaporated to give a crude oil. Flash chromatography (10% ethyl acetate/hexanes) yielded the desired product (5.55 g, 100%) as a white solid. NMR.

Prepartion 22

4-t-butyldimethylsilyloxy-2-phenylindole

4-t-Butyldimethylsilyoxyindole (4.67g, 18.9 mmol) was dissolved in THF (100 ml) at -78°C under a nitrogen atmosphere and treated with butyllithium (13.0 ml, 1.6 M in hexanes, 20.8 mmol) dropwise over 10 minutes. After stirring for 30 minutes, carbon dioxide gas was passed through the solution for 20 minutes. The clear solution was allowed to warm to room temperature and vigorous effervescence was observed. The excess carbon dioxide was removed under vacuum on a rotary evaporator at room temperature while the solvent was concentrated to an approximately 50 ml volume. Additional THF (60 mL) was added and the solution was cooled to -78°C. To this mixture, *t*-butyllithium (12.2 ml, 20.8 mmol) was added dropwise over 10 minutes, and the mixture stirred for 2h at -78°C. Tributyltin chloride (5.4 ml, 19.8 mmol) was added

dropwise. After stirring for 1.5 h, the cold solution was poured over crushed ice-water (100g), and saturated ammonium chloride was added until solution became acidic. The aqueous solution was extracted with ether (3 x 100 ml), dried over magnesium sulfate, and concentrated to give 12.68 g of a yellow oil.

To a solution of this 1-carboxy-2-(tributylstannyl)indole (12.68g) in ethanol (100 ml) was added iodobenzene (2.1 ml, 18.9 mmol) and bis(triphenylphosphine)palladium(II) chloride (0.60 g, 0.85 mmol). The mixture was maintained at reflux for 48 h. The mixture was cooled to room temperature, filtered through a pad of celite, and concentrated at reduced pressure. Flash chromatography (5% ethyl acetate/hexanes) provided the 4-*t*-butyldimethylsilyloxy-2-phenylindole as a white solid. NMR. MS.

Preparation 23

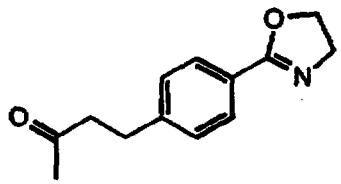
4-hydroxy-2-phenylindole

4-t-Butyldimethylsilyoxy-2-phenylindole (55 mg, 0.17 mmol) was dissolved in THF (10 ml) at 0°C and treated with tetrabutylammonium flouride (0.5 ml, 1.0 M in THF, excess). After stirring at this temperature for 10 minutes, the reaction was quenched by addition of saturated ammonium chloride. The mixture was extracted several time with ethyl acetate, dried over magnesium sulfate, and evaporated to give a crude oil. Flash chromatography (5% ethyl acetate/hexanes) provided the desired phenol (30 mg, 84.8%) as a white solid. NMR. MS.

Preparations 24 through 37 describe syntheses of compounds utilized in combinatorial/parallel scheme II.

Preparation 24

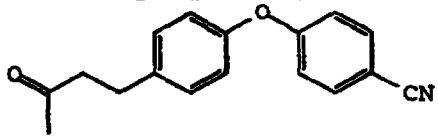
4-(3-oxobutyl)-1-(2-oxazolidine)benzene



4-bromo-1-(2-oxazolidine)benzene (3.0 g, 13.3 mmol), 3-buten-2-ol (1.4 g, 20 mmol), $Pd(OAc)_2$ (60 mg, 0.26 mmol), (*o*-tolyl)$_3$P (158 mg, 0.52 mmol), sodium bicarbonate (1.34 g, 15.9 mmol) in 30 mL of N-methylpyrrolidinone was heated under nitrogen at 130°C for 1 hour. The reaction mixture was then cooled and was partitioned between ethyl acetate and water. The combined organic layers were washed with water and then dried (Na_2SO_4), filtered and concentrated *in vacuo* to yield 2.6 g of a tan oil. Purification by flash chromatography (silica gel, 1:1 ethyl acetate/hexane) yielded 1.9 g of a pale yellow oil which crystallized upon drying under vacuum. Recrystallization from hexane gave 1.47 g (49%) of white needles, m.p. 62-64°C. NMR. MS.

Preparation 24

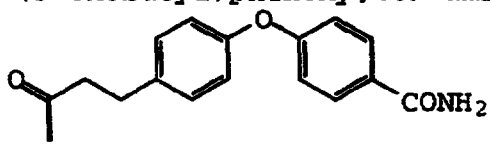
4-[4-(3-oxobutyl)phenoxy]benzonitrile



4-fluorobenzonitrile (6.05 g, 50mmol), 4-(4-hydroxyphenyl)-2-butanone (8.21 g, 50mmol) and potassium carbonate (8.3 g, 60mmol) were dissolved in N,N-dimethylacetamide (50 mL) and heated at 150°C for 4 hours under nitrogen. The reaction mixture was then poured into 800 mL of ice water. A slowly crystallizing solid was filtered to give 13 g of crude product. This material was recrystallized from ethanol/water (3:1) to give 10.48 g (79%) of pale brown crystals, m.p. 64-66°C. EA. NMR. MS.

Preparation 25

[4-(3-oxobutyl)phenoxy]benzamide



4-[4-(3-oxobutyl)phenoxy]benzonitrile (6.0 g, 22.6mmol) and potassium carbonate (1.0 g, 7.2mmol) were slurried in DMSO (50mL) and cooled to 0°C in an ice bath. Aqueous 30% hydrogen peroxide (6 mL) was added slowly, and the mixture stirred at 0°C for 1 hour. The reaction was quenched by pouring into 500 mL water, and the subsequent white precipitate was collected and washed with water. This material was recrystallized from 300 mL ethanol to give 5.35 g (84%) white crystals, m.p. 169-172°C. NMR. MS. EA.

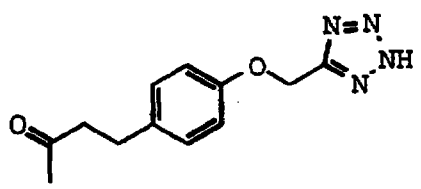
Preparation 26

2-triphenylmethyl-5-chloromethyltetrazole

5-Chloromethyltetrazole (1.19 g, 10 mmol) in CH_2Cl_2 (10 mL) was treated with triphenylmethyl chloride (2.79 g, 10 mmol) and diisopropylethylamine (2.0 mL, 11.5 mmol) and stirred for 40 minutes at room temperature. The reaction mixture was concentrated *in vacuo* and partitioned between ethyl acetate/water. The organic layer was washed with saturated $NaHCO_3$ solution, then brine, dried (Na_2SO_4) and concentrated *in vacuo* to yield 3.48 g of an off-white solid. Trituration of this residue in diethyl ether yielded 3.04 g (84%) of a white solid, m.p.162-165°C. NMR. MS. EA.

Preparation 27

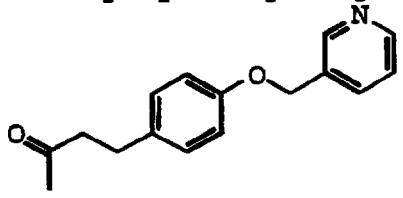
5-[4-(2-oxobutyl)phenoxymethyl]tetrazole



4-(4-hydroxyphenyl)-2-butanone (493 mg, 3 mmol) was cooled to 5°C and treated with NaH (180 mg, 4.5 mmol, 60% in mineral oil) under nitrogen. After 15 minutes the ice bath was removed and the solution allowed to warm to room temperature over 45 minutes. The reaction was cooled to 5°C and treated with 2-triphenylmethyl-5-chloromethyltetrazole (1.08 g, 3 mmol) and stirred at room temperature for 3 hours. The reaction mixture was poured into EtOAc (300 mL), and washed with water then brine. The organic layer was dried ($MgSO_4$) and concentrated *in vacuo* to provide a yellow solid. This material was suspended in a mixture of MeOH (100 mL) and THF (50 mL) and treated with 4N HCl in dioxane (7.5 mL, 30 mmol). The resulting mixture was stirred for 1.5 hr. and then concentrated *in vacuo* to provide a tan solid. The residue was applied to a silica chromatography column and eluted with 33-100% ethyl acetate in hexane to provide 235 mg (32%) of a white solid, m.p.148-150°C. NMR. MS. EA.

Preparation 28

3-[4-(2-oxobutyl)phenoxymethyl]pyridine

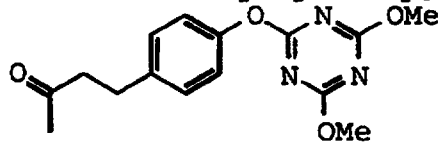


4-(4-hydroxyphenyl)-2-butanone (4.11 g, 25 mmol) and potassium carbonate (10.37 g, 75 mmol) in acetone (30 mL) was treated with 3-picolyl chloride hydrochloride (4.27 g, 26 mmol) under nitrogen. The mixture was stirred at reflux for 21 hours, proceeding about 50% towards completion. Potassium iodide (2.0 g, 13 mmol, 0.5 eq) was added and after 3 hours no picolyl chloride was observed on TLC. The volatiles were removed *in vacuo* and the resulting residue partitioned between EtOAc/water. The combined organic layers were washed with water, saturated $NaHCO_3$ solution, 10% Na_2SO_3, and then brine. The organic layer was dried

($MgSO_4$) and concentrated *in vacuo* to provide 4.8 g of a yellow oil. The material was purified on a Waters Prep 2000LC by elution with 10-80% ethyl acetate in hexanes over 45 minutes to yield 2.20 g (34%) of an oil which solidified on standing, m.p. 35-37°C. NMR. MS. EA.

Preparation 29

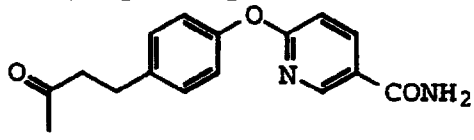
2,6-dimethoxy-4-[4-(2-oxobutyl)phenoxy]-1,3,5-triazine



4-(4-hydroxyphenyl)-2-butanone (4.93 g, 30 mmol) was added to a solution of sodium methoxide (1.62 g, 30 mmol) in methanol (150 mL) under nitrogen. After stirring for 1 hour the methanol was removed *in vacuo* and the residue suspended in acetone (200 mL). The suspension was treated with 4,6-dimethoxy-2-chlorotriazine and refluxed for 3 hours. The volatiles were removed *in vacuo* and the residue partitioned between ethyl acetate/water. The organic layers were dried ($MgSO_4$) and concentrated *in vacuo* to provide 10.28 g of a white semi-solid. The material was purified on a Waters Prep 2000LC by elution with a gradient of 20-60% ethyl acetate in hexanes over 55 minutes to yield 4.43 g (49%) of a colorless oil. NMR. MS. EA.

Preparation 30

2-[4-(2-oxobutyl)phenoxy]-5-carboxamidopyridine

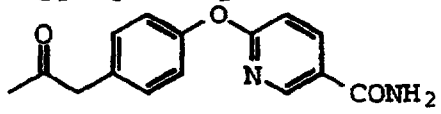


4-(4-hydroxyphenyl)-2-butanone (3.28 g, 20 mmol) in anhydrous DMF (150 mL) was treated with NaH (1.2 g, 30 mmol, 60% in mineral oil) under nitrogen. The solution was stirred for 30 minutes at ambient temperature and then treated with 6-chloronicotinamide (3.13 g, 20 mmol). The reaction was stirred at 60°C for 1.5 hours and then 90°C

for five hours. The reaction was allowed to cool, poured into 50% saturated ammonium chloride solution, and extracted with EtOAc. The organic layer was dried ($MgSO_4$) and concentrated *in vacuo* with a xylene azeotrope to yield 11.4 g of a brown oil. The material was purified on a Waters Prep 2000LC by elution with 75-100% EtOAc over 60 minutes. The resulting material was triturated in cold EtOAc and collected by filtration to provide 2.73 g (48%) white solid m.p. 137-139°C. EA. NMR. MS.

Preparation 31

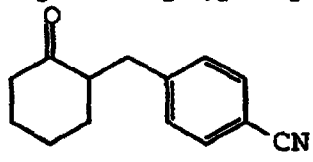
2-[4-(2-oxopropyl)phenoxy]-5-carboxamidopyridine



In a manner similar to the above examples, 3-(4-hydroxyphenyl)-2-propanone (2.25 g, 15 mmol) was treated with NaH (0.9 g, 22.5 mmol, 60% in mineral oil) followed by reaction with 6-chloronicotinamide (2.34 g, 15 mmol). Following workup the material was purified on a Waters Prep 2000LC to provide 1.28 g (32%) of a light yellow solid. m.p. 172-174°C. NMR. MS. EA.

Preparation 32

{4-[(2-oxocyclohexyl)methyl]phenyl}methanenitrile



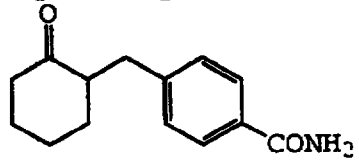
A mixture of methyl cyclohexanone-2-carboxylate (11.0 g, 70 mmol, from Fluka), α-bromo-p-tolunitrile (12.3 g, 63 mmol), potassium carbonate (10.5 g, 76 mmol) in THF (200 mL) was refluxed for 24 hours. The progress of the reaction was followed by GC. The reaction was diluted with water and the THF was removed under reduced pressure. The aqueous portion was extracted with EtOAc, dried ($MgSO_4$) to give 19.3 g of a white solid that was 74% pure by gas chromatrophy. The solid was recrystallized from

hexane/EtOAc to give 7.75 g white crystals that were 100% pure by glc. A second crop of 3.65 g was obtained by adding more hexane to the filtrate. Overall, 11.4 g (67%) of 1-[(4-cyanophenyl)methyl]-1-methoxycarbonyl-2-oxocyclohexane carboxylate, was obtained; mp 82-84°C. NMR. MS.

Under a blanket of nitrogen, a mixture of 1-[(4-cyanophenyl)methyl]-1-methoxycarbonyl-2-oxocyclohexane carboxylate (7.6 g, 28 mmol), sodium cyanide (2.1 g, 42 mmol) and DMSO (100 mL) was heated at 115°C for 1.5 hours. The progress of the reaction was monitored by gc. The reaction was cooled and partitioned between water, EtOAc and brine. The organic layer was washed with water and dried ($MgSO_4$). After concentration, crude product was obtained as a tan oil. Purification by plug filtration (200 g silica gel, 15% EtOAc/hexane) gave 3.3 g (55%) product as colorless oil. NMR. MS.

Preparation 33

4-[(2-oxocyclohexyl)methyl]benzamide



A DMSO (20 mL) solution of the compound of Preparation 28 (2.5 g, 11.7 mmol) was cooled in an ice bath. Solid K_2CO_3 (500 mg) was added followed immediately by 30% H_2O_2 (3 mL). After 20 minutes, TLC (3/7 EtOAc/hexane) showed a trace of starting material remained. The ice bath was removed and the reaction was stirred and room temperature for 1 hour. The reaction was diluted with 500 mL water and the white solid collected and dried to give 2.44 g (90%) desired amide. The product was recrystallized from 1/9 EtOAc/hexane to give 2.02 g of the titled product as white crystals, mp 167-170°C. NMR. MS.

Preparation 34

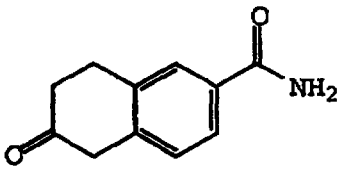
2-Tetralone-6-carboxylic acid, ethylene ketal

6-bromo-2-tetralone (2.0 g, 8.89 mmol) was dissolved in toluene (50 mL) and treated with excess ethylene glycol (4.88 mL, 88.9 mmol) and catalytic *p*-toluenesulfonic acid (15 mg). The solution was stirred at reflux 16 hours, and water was removed from the reaction mixture using a Dean-Stark condenser. After cooling to ambient temperature, the toluene solution was washed 2 x 1N NaOH, 1 x water, 1 x brine, dried over Na_2SO_4 and concentrated *in vacuo* to give 2.23 g (93%) of 6-bromo-2-tetralone ethylene ketal as a brown oil which was used without further purification.

6-Bromo-2-tetralone ethylene ketal (2.2 g, 8.15 mmol) was dissolved in anhydrous THF (30 mL), cooled to -78°C and treated with *tert*-butyllithium (12.05 mL, 20.4 mmol, 1.7M in pentane) under an atmosphere of nitrogen. After stirring for 30 minutes, anhydrous carbon dioxide gas was passed through the reaction mixture for 20 minutes at -78°C. The suspension was then allowed to warm to ambient temperature. The solution was quenched with water and acidified with 1N HCl, then extracted 2 x EtOAc. The organic extracts were washed with brine, dried over Na_2SO_4 and concentrated *in vacuo* to a pale brown oil. The oily residue was applied to a silica flash chromatography column and eluted with 30%-50% EtOAC in hexanes to yield tetralone-6-carboxylic acid, ethylene ketal 1.06 g (55%) of a slowly crystallizing solid. NMR. MS.

Preparation 35

2-Tetralone-6-carboxamide



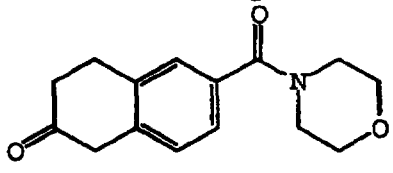
Tetralone-6-carboxylic acid, ethylene ketal (395 mg, 2.07 mmol) was co-dissolved in CH_2Cl_2 (50 mL) with

N-hydroxysuccinimide (260 mg, 2.76 mmol) at 0°C and treated with a slight excess of 1,3-dicyclohexylcarbodiimide (502 mg, 2.50 mmol). The mixture was allowed to warm to ambient temperature over 30 minutes, during which time a fine white precipitate formed. Ammonium chloride (333 mg, 6.23 mmol) and triethylamine (1.58 mL, 12.5 mmol, d=0.797) were added. The solution was stirred at ambient temperature for 16 hours. The suspended urea and salts were filtered away and the solution concentrated *in vacuo* to a colorless oil. The oil was applied to a silica flash chromatography column and eluted with 50-100% EtOAc in hexanes to yield 250 mg (64%) of 2-tetralone-6-carboxamide, ethylene ketal as a white solid, clean by NMR, TLC.

2-Tetralone-6-carboxamide ethylene ketal (250 mg, 1.07 mmol) and catalytic *p*-toluenesulfonic acid were stirred in acetone (50 mL) at ambient temperature for 48 hours. The volatiles were removed *in vacuo* and the residue triturated in ethyl acetate. The solids were filtered, washed and dried to yield 77.5 mg (38%) of 2-Tetralone-6-carboxamide as a white powder, pure by NMR, TLC. MS.

Preparation 36

2-Tetralone-6-morpholinamide



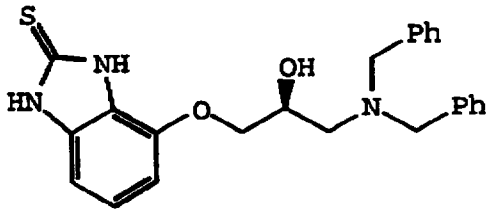
2-Tetralone-6-carboxylic acid, ethylene ketal (395 mg, 2.07 mmol) was codissolved in CH_2Cl_2 (50 mL) with N-hydroxysuccinimide (260 mg, 2.76 mmol) at 0°C and treated with a slight excess of 1,3-dicyclohexylcarbodiimide (502 mg, 2.50 mmol). The mixture was allowed to warm to ambient temperature over 30 minutes, during which time a fine white precipitate formed. Morpholine (0.91 mL, 10.4 mmol, d=0.998) was added and the solution stirred at ambient temperature for 16 hours. The suspended urea was filtered away and the solution concentrated *in vacuo* to a colorless

oil. The oil was applied to a silica flash chromatography column and eluted with 50-100% EtOAc in hexanes to yield 323 mg (51%) of 2-tetralone-6-morpholinamide, ethylene ketal as a slowly crystallizing solid, clean by NMR, TLC.

2-Tetralone-6-morpholinamide, ethylene ketal (323 mg, 1.06 mmol) and catalytic *p*-toluenesulfonic acid were stirred in acetone (50 mL) at ambient temperature for 48 hours. TLC indicated a mixture of 2-tetralone-6-morpholinamide, ethylene ketal and desired product, so the solution was heated to reflux for 16 hours. The volatiles were removed *in vacuo* and the residue applied to a silica flash chromatography column and eluted with 50-100% EtOAc in hexanes to yield 27 mg (10%) of 2-tetralone-6-morpholinamide a slowly crystallizing solid, pure by NMR, TLC. MS.

Preparation 37

(R) 4-[2-Hydroxy-3-(N,N-dibenzylamino)propoxy]-1,3-dihydro-2H-benzimidazol-2-thione

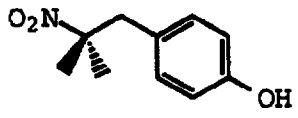


[3-(N,N-Dibenzylamino)-2hydroxypropoxy]-2,3-diamino benzene (400 mg, 1.1 mmol) was dissolved in a mixture of methylene chloride (70mL) and pyridine (35mL) and cooled to 0°C. Dimethylamino pyridine (DMAP; 311mg, 2.5mmol) was added and thiophosgene (179mg, 0.119mL, 1.6mmol) was introduced in a dropwise fashion. After 30 minutes, another equivalent of thiophosgene was added and the mixture was stirred for 5 hours. Water was carefully added and the resulting biphasic mixture extracted with methylene chloride. The organic solution was dried over MgSO4 and, filtered and evaporated to leave a brown oil (445mg, ca. 100%). MS, NMR.

The above titled compound is converted to the amine for reaction in accordance with Scheme 1 by techniques appreciated in the art.

Preparation 38

4-(2-Methyl-2-nitropropyl)phenol

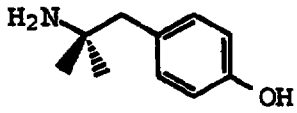


A mixture of 4-hydroxybenzyl alcohol (100.08 g, 806 mmol), 2-nitropropane (400 mL, 4.45 mol) and diglyme (800 mL) was heated to 38 °C. Potassium *t*-butoxide (45.29 g, 403.6 mmol) was added, and the mixture was heated to reflux at 132 °C with a Dean-Stark trap. Water began collecting in the trap, and continued at a high rate for approximately 1.5 h. When water collection slowed (around 2.5 h) then portions of solvent (30-40 mL each) were removed every thirty minutes. During the water collection and solvent removal the temperature rose from 132 °C to 149 °C. After 4 h less than 1% of the 4-hydroxybenzyl alcohol remained by HPLC analysis. The heating mantle was removed, and the reaction mixture was allowed to cool. When the temperature was 100°C water (200 mL) was added, and the solution was allowed to cool to room temperature. Solvent was removed on a rotary evaporator under vacuum until 593 g of solution remained. Water (500 mL) and EtOAc (500 mL) were added and the layers were separated (layer separation was poor, but addition of 20% aqueous NaCl was ineffectual). The aqueous layer was extracted with EtOAc (200 mL), and the combined organic layers were extracted with 1*N* HCl (500 mL) and water (300 mL). The organic layer was distilled *in vacuo* to 261 g of oil to which EtOAc was added (160 mL). Heptane (3.4 L) was added rapidly with vigorous stirring for 30 min, and the product crystallized to yield a beige solid (112.36 g, 71% yield, >98% purity by HPLC analysis). Another crop of crystals may be obtained from the filtrate

by concentrating and filtering the solids, or by concentrating more fully to a solution and adding heptane to crystallize. NMR. E.A.

Preparation 39

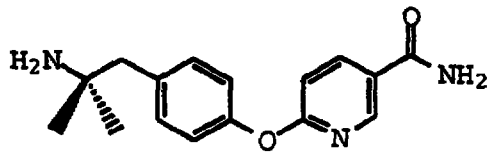
4-(2-amino-2-methylpropyl)phenol acetic acid salt



A one-gallon high-pressure reactor was charged with 4(2-methyl-2-nitropropyl)phenol (120 g, 614 mmol), HOAc (35.2 mL, 614 mmol), 5% Palladium on carbon (24 g) wetted with 2B3 EtOH (60 mL), and MeOH (1230 mL). The mixture was heated to 50°C with agitation (600 rpm), and the reactor was purged with N_2 and pressurized to 50 psi with H_2. After 15.5 h the reactor was purged with N_2, and the cooled mixture was filtered. The filter cake was washed with MeOH and the filtrate was concentrated to 514 g of slurry on a rotary evaporator. To this slurry was added EtOAc (2 L) with vigorous agitation. After stirring for 1 h, the resulting crystals were filtered and washed with a small amount of EtOAc. The product was dried overnight in a 45°C vacuum oven to yield 118.83 g (86%) of product as small white needles (mp 211-216 °C dec). This material was 99% pure by HPLC analysis, and while another 9.00 g of material was obtained from the mother liquor it was found to be only 88 % pure.

Preparation 40

2-(4-(2-amino-2-methylpropyl)phenoxy)-5-carboxamidopyridine

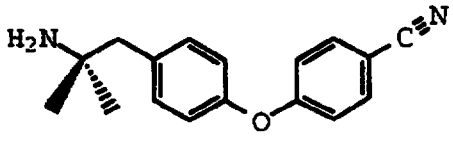


A mixture of 4-(2-amino-2-methylpropyl)phenol acetic acid salt (45.06 g, 200 mmol), powdered K_2CO_3 (69.1 g, 500 mmol), 6-chloronicotinamide (31.32 g, 200 mmol), DMAC (622 mL) and *iso*-octane (70 mL) was slowly heated to reflux at

140°C. A water trap filled with *iso*-octane was used to collect water formed in the reaction, and reflux was maintained for 5.5 h. The mixture was allowed to cool to room temperature, and the solids were filtered and washed with EtOAc. The filtrate was concentrated *in vacuo* to 88.6 g of solid which was dissolved in EtOAc (500 mL). To this solution was added water (800 mL), 1*N* HCl (200 mL) and MeOH (50 mL). The pH of this mixture was adjusted to 7.2 with con. HCl, and the aqueous layer was separated and washed with methyl *t*-butyl ether (500 mL). The product was crystallized by addition of 10*N* NaOH (20 mL) which raised the pH to 11. This pH was maintained by addition of 10*N* NaOH as needed during the course of the crystallization (90 min). The product was filtered, washed with water and dried *in vacuo* at 45 °C to 53.11 g (93%) of white solid which was >98% pure by HPLC analysis: ^{1}H NMR (300 MHz, DMSO-d_6) NMR was consistent with the desired product;

Preparation 41

4-(4-(2-amino-2-methylpropyl)phenoxy)benzonitrile

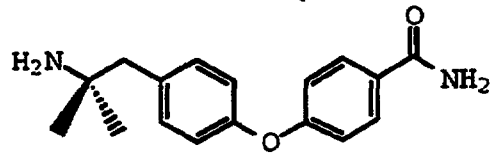


A mixture of 4-(2-amino-2-methylpropyl)phenol acetic acid salt (45.06 g, 200 mmol), powdered K_2CO_3 (69.1 g, 500 mmol), and DMAC (550 mL) was heated to 75-100°C. Toluene (166 mL) was added, and the mixture was slowly heated to reflux at 134°C. The reflux temperature was raised by distillation of toluene and water into a water trap until the temperature reached 141°C. The mixture was then allowed to cool to below 100°C at which point 4-fluorobenzonitrile (24.46 g, 202 mmol) was added along with 50 mL of toluene. The mixture was again heated to reflux at 140°C with water being collected in a toluene-filled water trap for 4 h. The mixture was allowed to cool to room temperature, and the solids were filtered and rinsed with

toluene. The filtrate was concentrated on a rotary evaporator to 77 g of syrup which was dissolved in EtOAc (400 mL). This solution was extracted with water (400 mL), and the aqueous layer was back-extracted with EtOAc (100 mL). The combined organic layers were washed with water (3x400 mL) and concentrated *in vacuo* to 53.4 g (100%) of oil which was >98% pure by HPLC analysis: ^{1}H NMR (300 MHz, DMSO-d_6) NMR was consistent with the desired product;

Preparation 42

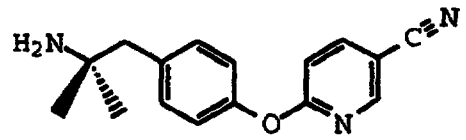
4-(4-(2-amino-2-methylpropyl)phenoxy)benzamide



Aqueous 30% H_2O_2 (62.1 mL, 548 mmol) was added dropwise to a mixture of 4-(4-(2-amino-2-methylpropyl)phenoxy)-benzonitrile (53.2 g, 200 mmol), K_2CO_3 (15.78 g, 114 mmol) and DMSO (270 mL) over 20 min while the temperature was held at 20°C with a cooling bath. The mixture was stirred at this temperature for 1 h after the addition was complete, and then water (209 mL) was added slowly. The slurry was cooled in an ice bath with stirring for 1 h, and the product was then filtered, washed with water and dried *in vacuo* at 50°C to yield 55.0 g (97%) of white solid. Analysis by HPLC indicated purity of >99%: ^{1}H NMR (300 MHz, DMSO-d_6) NMR was consistent with the desired product;

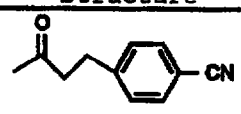
Preparation 43

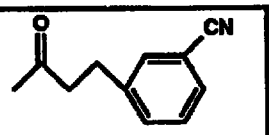
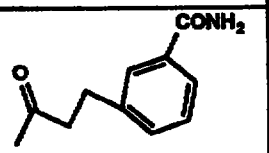
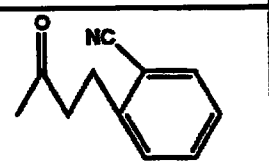
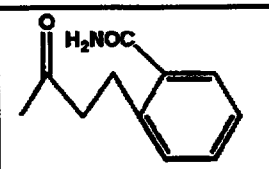
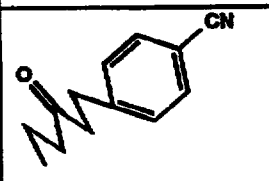
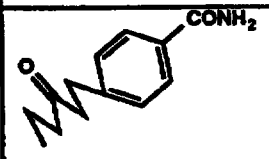
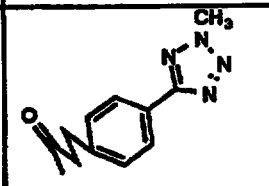
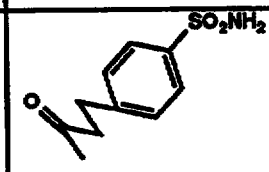
2-(4-(2-amino-2-methylpropyl)phenoxy)-5-carbonitrilepyridine

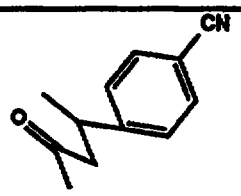
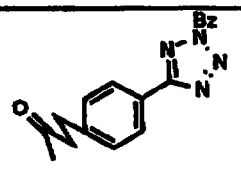
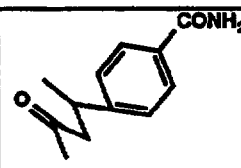
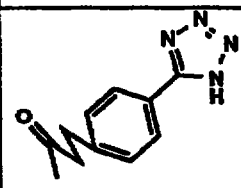
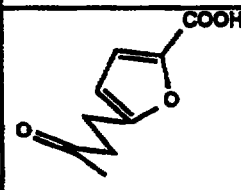
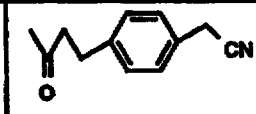
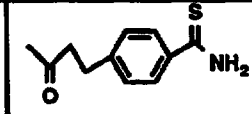
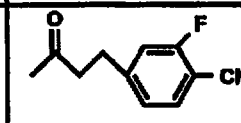


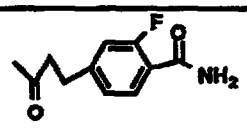
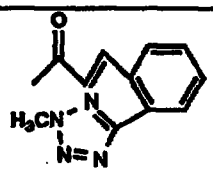
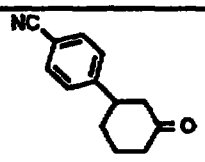
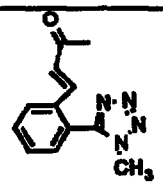
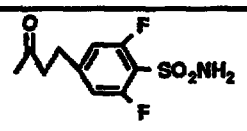
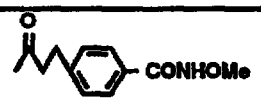
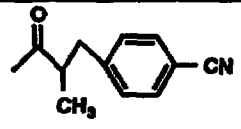
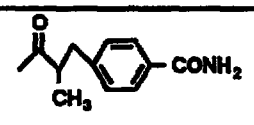
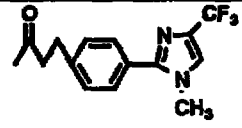
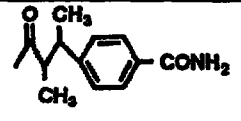
A mixture of 4-(2-amino-2-methylpropyl)phenol acetic acid salt (22.53g, 100 mmol), powdered K_2CO_3 (34.55 g, 250 mmol) and DMAC (275 ml) was heated to 100°C. Toluene (94 ml) was added and the mixture slowly heated to reflux. The reflux temperature was raised by distillation of toluene and water until it reached 140°C. The mixture was then cooled to below 100°C and 2-chloronicotinonitrile (13.86g, 100 mmol) added with a toluene rinse (50 ml). The mixture was again heated to reflux and the reflux temperature raised to 140°C as before. Then the water trap was filled with toluene and the reflux continued for 40 min., at which point an HPLC showed no 2-chloronicotinonitrile remained but the reaction was not complete. After cooling the reaction below reflux, additional 2-chloronicotinonitrile (0.63 g, 4.5 mmol) was added and reflux continued for 90 min. The reaction was cooled to room temperature and the solids filtered with a toluene wash. The filtrate was concentrated on a rotary evaporator to 41 g of syrup which was dissolved in EtOAc (200 ml). This solution was washed with water (200 ml) and the aqueous layer back-extracted with EtOAc (50 ml). The combined organic layers were washed with water (3x200 ml) and concentrated *in vacuo* to 26.93 g of solid, ~100% of theory. HPLC indicated 94.3% purity. ^{1}H NMR (300 MHz, DMSO-d_6) was consistent with the desired product;

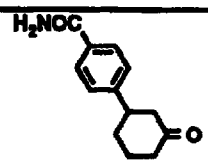
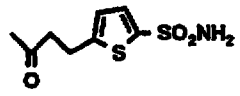
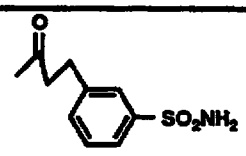
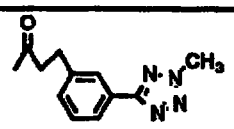
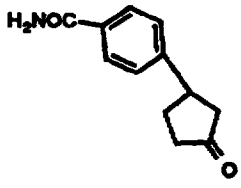
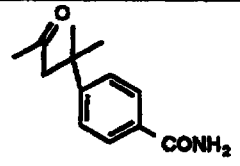
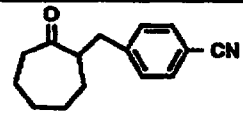
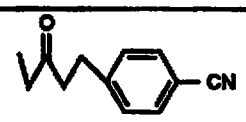
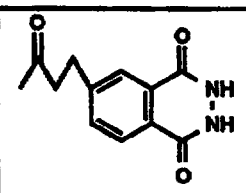
The following compounds were prepared in a manner analogous to schemes IV and/or preparations 24 through 33 described herein or by techniques appreciated in the art:

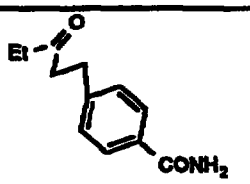
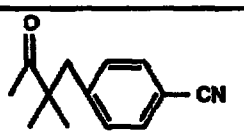
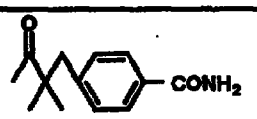
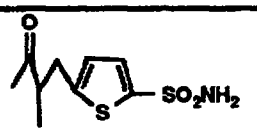
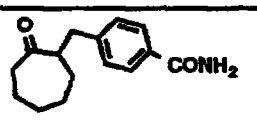
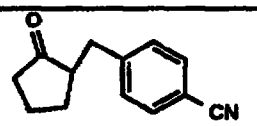
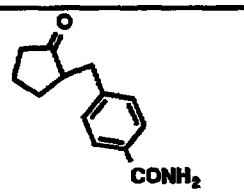
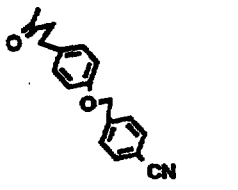
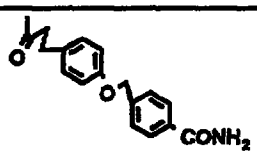
Name	Structure	m.p.	Yield	Confirmed	
				NMR	M.S.
(4-(3-oxobutyl) phenyl)methanenitrile Preparation 44		oil	33%	x	x

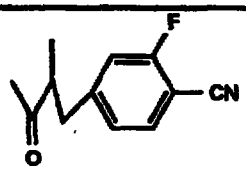
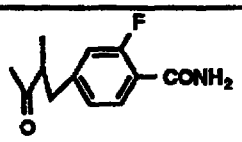
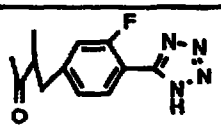
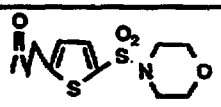
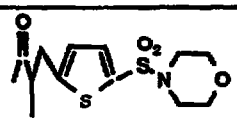
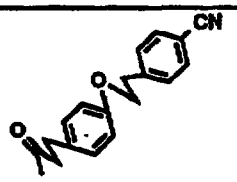
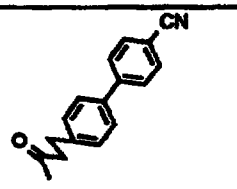
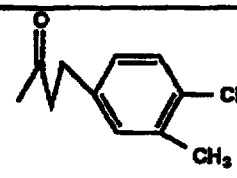
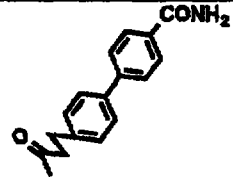
(3-(3-oxobutyl) phenyl)methanenitrile Preparation 45		oil	44%	x	x
3-(3-oxobutyl) benzamide Preparation 46		104-6	45%	x	x
(2-(3-oxobutyl) phenyl)methanenitrile Preparation 47		oil	43%	x	x
(2-(3-oxobutyl) benzamide Preparation 48		113-114	91%	x	x
(4-(3-oxohexyl)phenyl) methanenitrile Preparation 49		oil	85%	x	x
4-(3-oxohexyl) benzamide Preparation 50		90-93	67%	x	x
3-methyl-5-(4-(3-oxobutyl)phenyl)-1H-tetrazole Preparation 51		90-93	67%	x	x
(4-(3-oxobutyl)phenyl) sulfonamide Preparation 52		132-4	36%	x	x

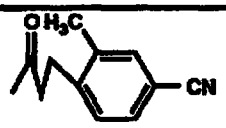
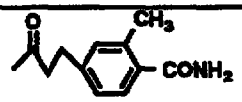
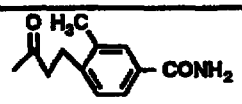
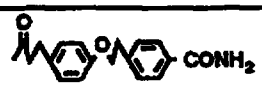
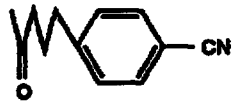
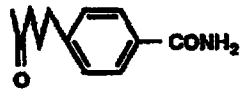
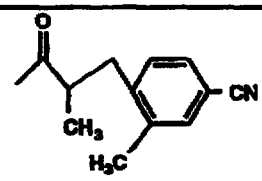
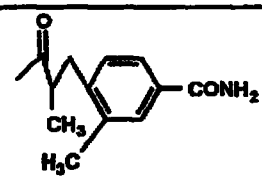
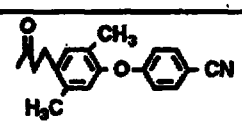
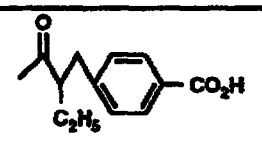
(4-(1-methyl-3-oxobutyl)phenyl) methanenitrile Preparation 53		oil	44%	x	x
3-benzyl-5-(4-(3-oxobutyl)phenyl)-1H-tetrazole Preparation 54		66-9	41%	x	x
4-(1-methyl-3-oxobutyl)benzamide Preparation 55		127-9	95%	x	x
5-(4-(3-oxobutyl) phenyl)-1H-tetrazole Preparation 56		197-9	94%	x	x
5-(3-oxobutyl)-2-furanoic acid Preparation 57		129-32	86%	x	x
3-(2-fluoro-4-(3-oxobutyl)phenyl) propenoic acid Preparation 58		143-6	95%	x	x
(4-(3-oxobutyl)phenyl) ethanenitrile Preparation 59		oil	100%	x	x
(4-(3-oxobutyl)phenyl) thioamide Preparation 60		96-8	low*	x	x
(2-fluoro-4-(3-oxobutyl)phenyl) methanenitrile Preparation 61		oil	78%	x	x

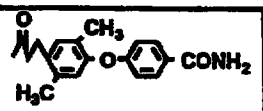
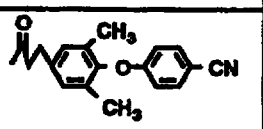
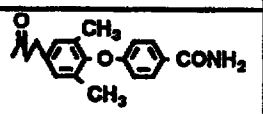
2-fluoro-4-(3-oxobutyl)benzamide Preparation 62		150-3	85%	x	x
3-methyl-5-(2-(3-oxobutenyl)phenyl-1N-tetrazole Preparation 63		64-5	45%	x	x
(4-(3-oxocyclohexyl)-phenyl)methanenitrile Preparation 64		66-69	36%	x	x
1-methyl-5-(2-(3-oxo-butenyl)phenyl)-1H-tetrazole Preparation 65		100-102	18%	x	x
(2,6-difluoro-(4-(3-oxobutyl)phenyl)) sulfonamide Preparation 66		oil	41%	x	x
N-methoxyl-4-(3-oxobutyl)benzamide Preparation 67			low	x	x
(4-(2-methyl-3-oxobutyl)phenylmethane nitrile Preparation 68		oil	66%	x	x
4-(2-methyl-3-oxobutyl)benzamide Preparation 69		112-115	87%	x	x
(1-methyl-2-(4-(3-oxobutyl)phenyl)-4-trifluoromethyl) imidazole Preparation 70		62-3	68%	x	x
4-(1,2-dimethyl-3-oxobutyl)benzamide Preparation 71		100-102	90%	x	x

4-(3-oxocyclohexyl) benzamide Preparation 72		188-91	42%	x	x
5-(3-oxobutyl)-2-thiophene sulfonamide Preparation 73		96-98	66%	x	x
(3-(3-oxobutyl)phenyl) sulfonamide Preparation 74		87-90	35%	x	x
2-methyl-5-(3-(3-oxobutyl)phenoxy) phenyl)tetrazole Preparation 75		98	65%	x	x
4-(3-oxocyclopentyl) benzamide Preparation 76		203-4	43%	x	x
4-(1,1-dimethyl-3-oxobutyl)benzamide Preparation 77		106-8	61%	x	x
(4-(3-oxocycloheptyl) phenyl)methanenitrile Preparation 78		oil	54%	x	x
(4-(3-oxohexyl)phenyl) methanenitrile Preparation 79		oil	77%	x	x
4-(3-oxobutyl)-phthalhydrazide Preparation 80		161-4	13%	x	x

4-(3-oxohexyl) benzamide Preparation 81		158-61	82%	x	x
(4-(2,2-dimethyl-3-oxobutyl)phenyl) methanenitrile Preparation 82		oil	72%	x	x
4-(2,2-dimethyl-3-oxobutyl)benzamide Preparation 83		127-131	62%	x	x
5-(2-methyl-3-oxobutyl)-2-thiophene sulfonamide Preparation 84		oil	low	x	x
4-((2-oxocycloheptyl) methyl)benzamide Preparation 85		132-4	88%	x	x
(4-((2-oxocyclopentyl) methyl)phenyl) methanenitrile Preparation 86		oil	62%	x	x
4-((2-oxocyclopentyl) methyl)benzamide Preparation 87		138-142	81%	x	x
(4-(4-(3-oxobutyl) phenoxy)methylphenyl) methanenitrile Preparation 88		94-7	84%	x	x
4-(4-(3-oxobutyl) phenoxy)methyl benzamide Preparation 89		215-17	95%	x	x

(2-fluoro-4-(2-methyl-3-oxobutyl)phenyl) methanenitrile Preparation 90		oil	42%	x	x
2-fluoro-4-(2-methyl-3-oxobutyl)benzamide Preparation 91		112-15	93%	x	x
5-(2-fluoro-4-(2-methyl-3-oxobutyl) phenyl)-1H-tetrazole Preparation 92		175-8	32%	x	x
5-(3-oxobutyl)-2-(morpholinosulfonyl)-thiophene Preparation 93		80-83	69%	x	x
5-(2-methyl-3-oxobutyl)-2-(morpholinosulfonyl)-thiophene Preparation 94		oil	15%	x	x
(4-(2-(4-(3-oxobutyl)phenoxy) ethyl)phenyl) methanenitrile Preparation 95		oil	41%	x	
(4-(4-(3-oxobutyl) phenyl)phenyl) methanenitrile Preparation 96		133-5	62%	x	x
(2-methyl-4-(3-oxobutyl)phenyl) methanenitrile Preparation 97		oil	55%	x	x
4-(4-(3-oxobutyl) phenyl)benzamide Preparation 98		229-31	94%	x	x

(3-methyl-4-(3-oxobutyl)phenyl) methanenitrile Preparation 99		34-6	75%	x	x
2-methyl-4-(3-oxobutyl)benzamide Preparation 100		147-50	39%	x	x
3-methyl-4-(3-oxobutyl)benzamide Preparation 101		103-5	46%	x	x
4-(2-(4-(3-oxobutyl) phenoxy)ethyl) benzamide Preparation 102		semi-solid	17%	x	x
(4-(4-oxopentyl) phenyl)methanenitrile Preparation 103		oil	quant	x	x
4-(4-oxopentyl) benzamide Preparation 104		111-13	87%	x	x
(3-methyl-4-(2-methyl-3-oxobutyl)phenyl) methanenitrile Preparation 105		oil	64%	x	x
(3-methyl-4-(2-methyl-3-oxobutyl)benzamide Preparation 106		105-7	71%	x	x
(4-(2,5-dimethyl-4-(3-oxobutyl)phenoxy) phenyl)methanenitrile Preparation 107		57-9	low	x	x
4-(2-ethyl-3-oxobutyl)benzoic acid Preparation 108		126-9	24%	x	x

4-(2,5-dimethyl-(3-oxobutyl)phenoxy) benzamide Preparation 109		191-3	76%	x	x
(4-2,6-dimethyl-(3-oxobutyl)phenoxy) phenyl)methanenitrile Preparation 110		yello w oil	72%	x	x
4-(2,6-dimethyl-(3-oxobutyl)phenoxy) benzamide Preparation 111		238-41	63%	x	x

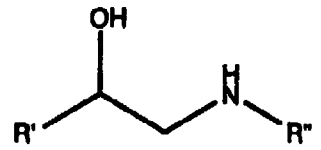
Example 1 is a combinatorial/parallel method for preparing compounds of the present invention in matrix fashion.

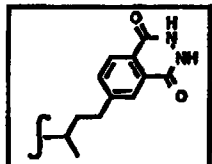
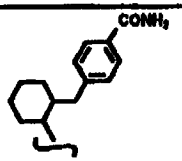
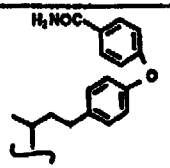
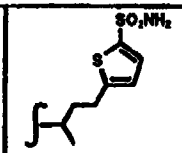
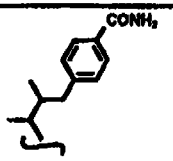
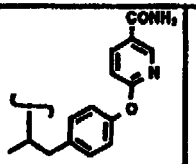
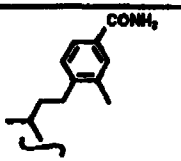
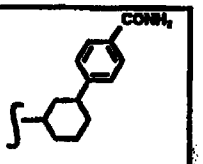
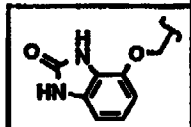
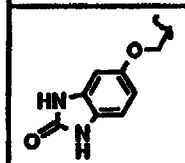
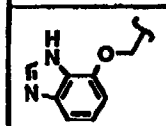
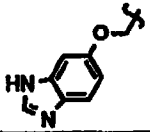
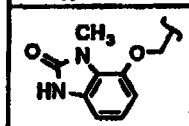
Example 1

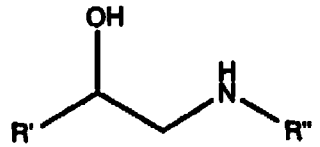
A 5x8 grid of 4 mL screw cap vials was arranged. To each of the eight rows of vials in the grid was added 33 µmol of ketone (from preparations 24-37, 44-111, or commercially available), one ketone per row, as a stock solution in methanol (0.5M, 65 µl). If solubility was a problem, acetonitrile/methanol or DMF was used. To each column of vials in the grid was added 50 µmol of amine hydrochloride, one amine hydrochloride (or amine) (from preparations 1 through 16, or commercially available) per column, as a stock solution in methanol (0.5M, 100 µl). To each vial was then added resin VIII (18-20 mg), 1.01 meq/g, 70-90µeq base). Teflon lined caps were then placed on each vial. The slurries were then shaken for 24 hours, at which time each vial was treated with approximately 30 mg (2.5 mmol BH_4-/g resin, 75 µmol) of Amberlite IRA400 borohydride resin (Aldrich Chemical). The caps were replaced, and the vials were shaken for an additional 24 hours, then 150 µl methylene chloride and 40 mg (1 mmol/g resin, 0.4 mmol) polystyrene-linked benzaldehyde resin (Frechet, J.M.; Schuerch, C.J. Am. Chem. Soc. 1971, 93, 492.) in order to scavenge excess primary amine starting material were added to the vial, and the slurry was shaken for 1 day. Each

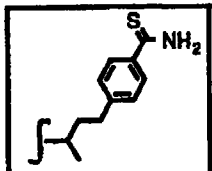
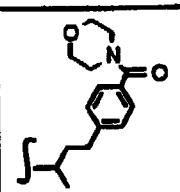
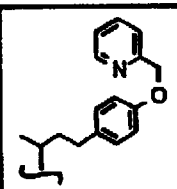
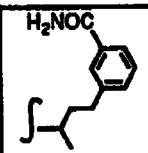
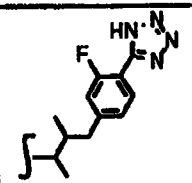
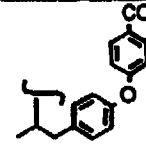
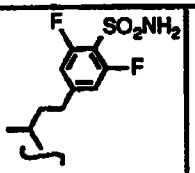
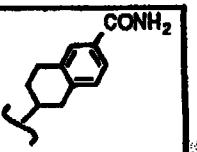
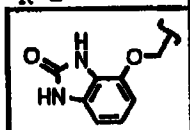
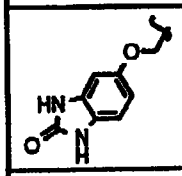
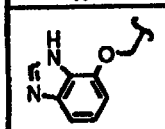
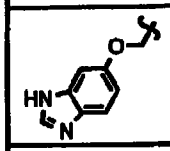
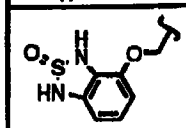
mmol BH_4-/g resin, 75 µmol) of Amberlite IRA400 borohydride resin (Aldrich Chemical). The caps were replaced, and the vials were shaken for an additional 24 hours, then 150 µl methylene chloride and 40 mg (1 mmol/g resin, 0.4 mmol) polystyrene-linked benzaldehyde resin (Frechet, J.M.; Schuerch, C.J. Am. Chem. Soc. 1971, 93, 492.) in order to scavenge excess primary amine starting material were added to the vial, and the slurry was shaken for 1 day. Each vial was then filtered through a cotton plug. The residual resin was rinsed with three small portions of methanol (approximately 200 µl). The resulting solutions were then treated with 20µl of conc. HCl (120 µmol) to ensure formation of the HCl salt of the product amine, then each vial was diluted to a volume of approximately 4 mL, and 1 mL of each solution was transferred to a tared 4 mL screw cap vial. This solution was allowed to evaporate in a fume hood under an air stream until dry, then placed in a vacuum oven for 24 hours at room temperature. The resulting residues were then weighed and submitted directly for testing with no further purification. The bulk of the material (75%) was similarly evaporated.

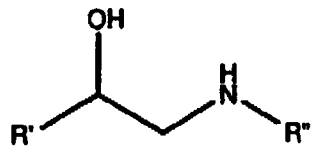
The following matrices list additional examples 2-201. These compounds were prepared using combinatorial/parallel techniques in accordance with the present invention. All reaction conditions were the same from plate to plate and in substantial accordance with Scheme 2 and Example 1. The scaffold for each plate was the same and is depicted at the top corner of the 5x8 matrix. The variable functional groups are illustrated in the rows and columns. The ketones and the amines depicted on each plate were prepared in accordance with the schemes and preparations described herein or by techniques known in the art.

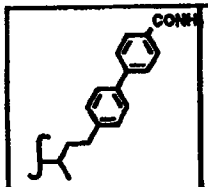
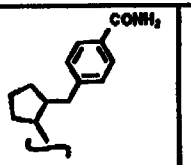
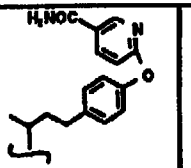
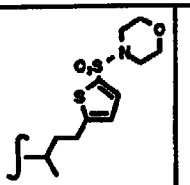
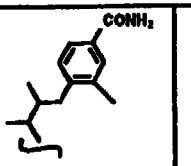
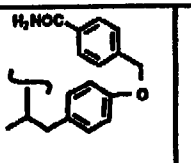
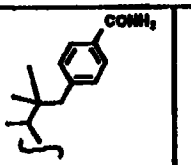
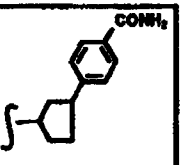
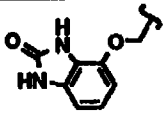
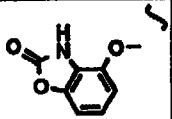
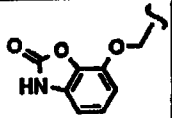
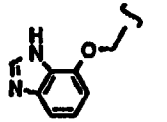
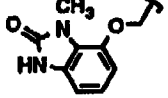


R'= \ R''=								
	Example 2	Example 3	Example 4	Example 5	Example 6	Example 7	Example 8	Example 9
	Example 10	Example 11	Example 12	Example 13	Example 14	Example 15	Example 16	Example 17
	Example 18	Example 19	Example 20	Example 21	Example 22	Example 23	Example 24	Example 25
	Example 26	Example 27	Example 28	Example 29	Example 30	Example 31	Example 32	Example 33
	Example 34	Example 35	Example 36	Example 37	Example 38	Example 39	Example 40	Example 41

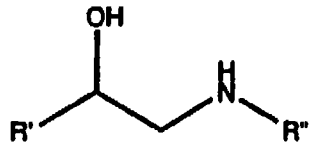


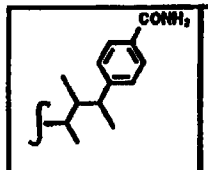
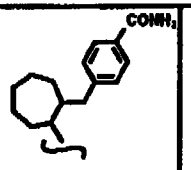
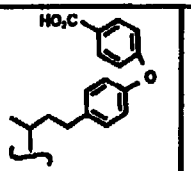
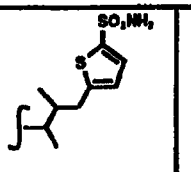
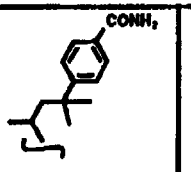
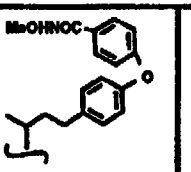
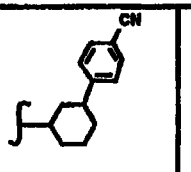
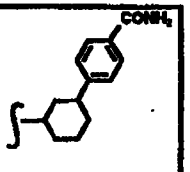
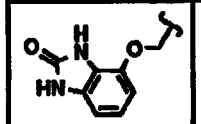
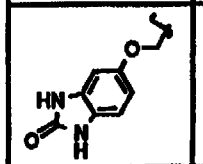
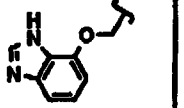
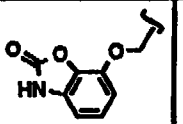
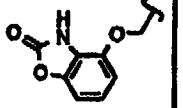
R'= \ R''=								
	Example 42	Example 43	Example 44	Example 45	Example 46	Example 47	Example 48	Example 49
	Example 50	Example 51	Example 52	Example 53	Example 54	Example 55	Example 56	Example 57
	Example 58	Example 59	Example 60	Example 61	Example 62	Example 63	Example 64	Example 65
	Example 66	Example 67	Example 68	Example 69	Example 70	Example 71	Example 72	Example 73
	Example 74	Example 75	Example 76	Example 77	Example 78	Example 79	Example 80	Example 81



R'= \ R''=								
	Example 82	Example 83	Example 84	Example 85	Example 86	Example 87	Example 88	Example 89
	Example 90	Example 91	Example 92	Example 93	Example 94	Example 95	Example 96	Example 97
	Example 98	Example 99	Example 100	Example 101	Example 102	Example 103	Example 104	Example 105
	Example 106	Example 107	Example 108	Example 109	Example 100	Example 111	Example 112	Example 113
	Example 114	Example 115	Example 116	Example 117	Example 118	Example 119	Example 120	Example 121

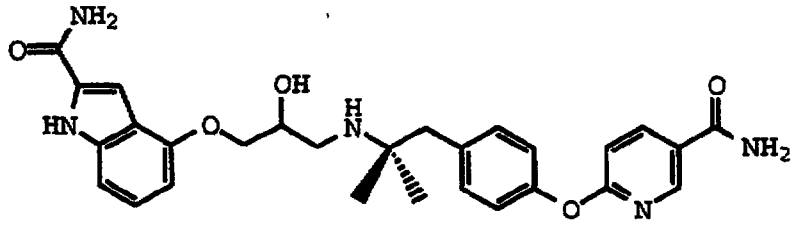
R'= \ R''=								
	Example 122	Example 123	Example 124	Example 125	Example 126	Example 127	Example 128	Example 129
	Example 130	Example 131	Example 132	Example 133	Example 134	Example 135	Example 136	Example 137
	Example 138	Example 139	Example 140	Example 141	Example 142	Example 143	Example 144	Example 145
	Example 146	Example 147	Example 148	Example 149	Example 150	Example 151	Example 152	Example 153
	Example 154	Example 155	Example 156	Example 157	Example 158	Example 159	Example 160	Example 161



R' = \ R'' =								
	Example 162	Example 163	Example 164	Example 165	Example 166	Example 167	Example 168	Example 169
	Example 170	Example 171	Example 172	Example 173	Example 174	Example 175	Example 176	Example 177
	Example 178	Example 179	Example 180	Example 181	Example 182	Example 183	Example 184	Example 185
	Example 186	Example 187	Example 188	Example 189	Example 190	Example 191	Example 192	Example 193
	Example 194	Example 195	Example 196	Example 197	Example 198	Example 199	Example 200	Example 201

Example 202

4-(3-[N-(2-[4-(5-carbamoyl-2-pyridyloxy)phenyl]-1,1-dimethylethyl)amino]-2-hydroxypropoxy)-2-indolecarboxamide



4-(oxiranylmethoxy)-1H-indole-2-carboxamide, (2:1 with dioxane) (0.304 g, 0.36 mmol, 1 eq) and the product of Preparation 40 (0.312 g, 1.09 mmol, 3 eq) were suspended in absolute ethanol (15 mL). The suspension was heated to 50°C at which time all of the reagents went into solution and heating was continued for 12 hours. Upon completion of the reaction, the mixture was cooled to room temperature and crystals slowly formed. The white solid was filtered and dried under reduced pressure to provide 0.190 g (100% yield) of product.

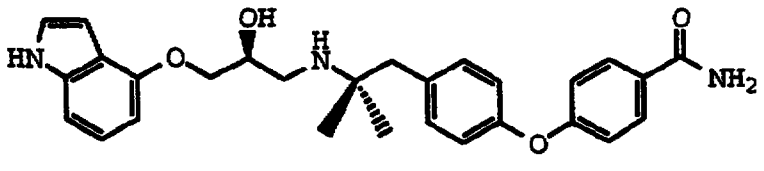
Anal calcd for $C_{28}H_{31}N_5O_5$; C, 64.97; H, 6.04; N, 13.53.

Found; C, 64.79; H, 6.08; N, 13.27.

MS: m/z (%) = 517.9 (100%), 290.1 (73%), 227.0 (38%).

Example 203

(S)-4-(3-[N-(2-[4-(4-carbamoylphenoxy)phenyl]-1,1-dimethylethyl)amino]-2-hydroxypropoxy)indole

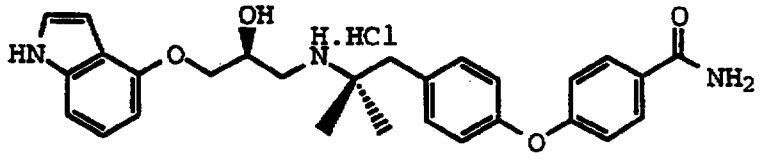


A stirred mixture of (S)-(+)-(oxiranylmethoxy)-1H-indole (7.00 g, 37.0 mmol) and 4-(4-(2-amino-2-methylpropyl)-phenoxy)benzamide (21.0 g, 73.8 mmol) in methanol (260 mL) was heated to 45°C for 22 hours. The mixture was then heated an additional 4 hours at 60°C. The reaction mixture was concentrated *in vacuo* to an oily residue. The residue

was partitioned with ethyl acetate (200 mL), water (35 mL), and 1N HCl (33 mL). The organic solution was washed two times with a solution of 1N HCl (2 mL) in water (33 mL). The ethyl acetate solution was dried with Na_2SO_4, filtered, and the filtrate was concentrated *in vacuo* to a foamy pale yellow residue. The crude product was purified by flash chromatography with 400 g 230-400 mesh silica gel and ethyl acetate:ethanol (5:1 to 4:1 gradient). Concentration of the appropriate fractions afforded 14.8 g (84.5%) of the desired product as a white foamy solid. ^{1}H NMR (DMSO-d_6) was consistent with the desired product.

Example 204

(S)-4-(3-[N-(2-[4-(4-carbamoylphenoxy)phenyl]-1,1-dimethylethyl)amino]-2-hydroxypropoxy)indole hydrochloride salt



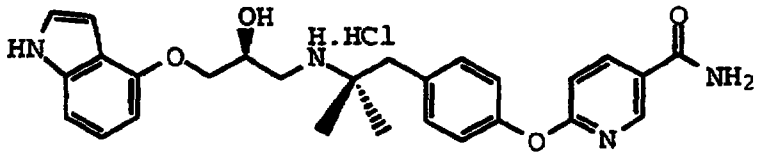
A stirred solution of the product of Example 203 (11.48 g, 24.24 mmol) in ethyl acetate (150 mL) was treated by slow addition with of a 1M HCl/ethyl acetate (24 mL, 24 mmol) solution at ambient temperature. An additional EtOAc (50 mL) was added to the resulting white precipitate, and the slurry was stirred approximately 1 hour at ambient temperature. The product slurry was pressure filtered through a stainless steel filter under nitrogen. The collected product was kept under a steady nitrogen purge for approx. 2 hrs. The filter was then placed in a vacuum oven overnight at 60°C. The product was dried to constant weight in a drying oven at 75°C to afford 10.38 g (84.1%) as a white solid.

^{1}H NMR (DMSO-d_6): δ1.22 (s, 6H), δ2.8-3.5 (m, 5H), δ4.05-4.35 (m, 3H), δ6.45-6.55 (m, 2H), δ6.95-7.40 (m, 6H), δ7.15-7.40 (m, 4H), δ7.85-8.05 (m, 3H), δ11.10 (br. s, 1H).

EA: Calculated for $C_{28}H_{32}ClN_3O_4$: C 65.94, H 6.32, N 8.24. Found: C 65.72, H 6.25, N 7.97.

Example 205

(S)-4-(3-[N-(2-[4-(5-carbamoyl-2-pyridyloxy)phenyl]-1,1-dimethylethyl)amino]-2-hydroxypropoxy)indole hydrochloride salt

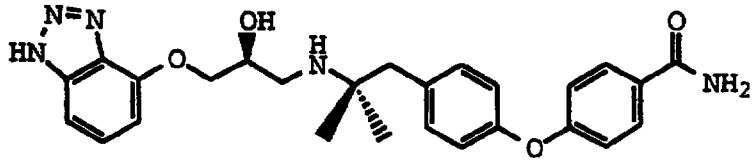


A mixture of 4-(2-amino-2-methylpropyl)phenoxy)-5-carboxamidepyridine (21.11 g, 74.00 mmol), (S)-(+)-4-(oxiranylmethoxy)-1H-indole (7.00 g, 37.00 mmol), HOAc (90.4 mg, 1.48 mmol), and water (12 mL) in MeOH (260 mL) was stirred at 60 °C for 19.25 hours. The mixture was cooled and concentrated in vacuo to an oil. The residue was dissolved in EtOAc (185 ml) and water (75 mL) and the resulting layers were separated. The organic layer was extracted with solutions of 1N HCl (34 mL), 1N HCl/MeOH (30 mL/5 mL), 1N HCl/water/MeOH (15 mL/20 mL/10 mL), and 1N HCl (10 mL). The combined acidic aqueous extracts (containing excess starting amine and product) were washed with EtOAc (40 mL). The organic layers were combined and discarded. The pH of the aqueous layer was made slightly basic (pH 7.0-7.5) with the addition of 5N NaOH (10 mL) and 1N HCl (1 mL). The aqueous layer was then extracted with EtOAc (100 mL, 2 x 50 mL). The pH of the aqueous layer was raised slightly with the addition of 5N NaOH (0.25 mL). The aqueous layer was diluted with water (5 mL) and MeOH (5 mL) and then was extracted with EtOAc (2 x 50 mL). The pH of the aqueous layer was raised with 5N NaOH (1 mL) and the layer was extracted with more EtOAc (2 x 50 mL). The pH of the aqueous layer was again raised with the addition of 5N NaOH (1 mL) and the layer was again extracted with EtOAc (2 x 50 mL). The combined organic extracts of the basic

aqueous layer were concentrated in vacuo to approximately 300 mL. The organic layer was washed with water (50 mL) and then was concentrated in vacuo to 16.64 g of an oil. Purification of 16.31 g of the oil by flash chromatography over 230-400 mesh silica gel using 25:4:0.1 chloroform/methanol/~28% ammonia as an eluent yielded 13.35 g (76.02%) of the free base as product. ^{1}H NMR (DMSO-d_6) was consistent with the desired product.
A stirred solution of the free base (11.86 g, 25.00 mmol) in EtOAc (280 mL) and isopropanol (20 mL) was made acidic with the dropwise addition of 34 mL (approx. 25 mmol HCl) of an approximately 0.725M HCl(g) in EtOAc solution. The resulting slurry was stirred for 2 hours at ambient temperature. The mixture was filtered (nitrogen pressure). The filter cake was washed twice with EtOAc (2 x 20 mL) and dried in vacuo at 50 °C to yield 12.48 g (97.65%) of a white powder. ^{1}H NMR was consistent with the desired product and showed small amounts of EtOAc, IPA, and water): ^{1}H NMR (500 MHz, DMSO-d_6): δ11.14 (s, 1H), 9.1 (br s, 1H), 8.7 (br s, 1H), 8.64 (d, 1H), 8.29-8.27 (m, 1H), 8.08 (s, 1H), 7.50 (s, 1H), 7.30-7.29 (d, 2H), 7.24-7.23 (m, 1H), 7.14-6.99 (m, 5H), 6.54-6.49 (m, 2H), 5.93 (br s, 1H), 4.33 (m, 1H), 4.19-4.11 (m, 2H), 3.35 (m, 1H), 3.14 (m, 1H), 3.04 (m, 2H), 1.27 (s, 6H); MS (FD+) m/z 949 (31%), 475 (100%).

Example 206

(S)-4-(3-[N-(2-[4-(4-carbamoylphenoxy)phenyl]-1,1-dimethylethyl)amino]-2-hydroxypropoxy)benzotriazole



The diamino product from preparation 20 (0.304 g, 0.65 mmol) was dissolved in glacial acetic acid (10 mL) and treated with a solution of sodium nitrite (0.047 g, 0.68

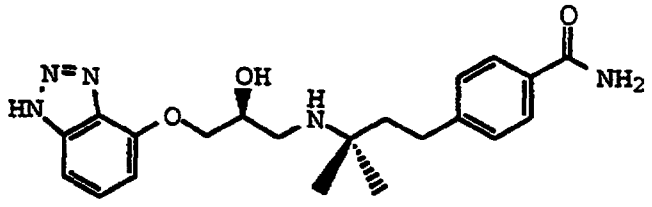
mmol) in water (5 mL) all at once. The reaction was stirred for 5 min and then evaporated to dryness. The resulting residue was purified using column chromatography eluting with 20% MeOH/$CHCl_3$ to provide 0.27 g (87%) as a solid.

MS: m/z (%) = 475.9 (100%), 249.0 (5%), 950.7 (5%)

^{1}H NMR (300 MHz, d-MeOH): δ 1.35 (6H, s); 3.03 (2H, s); 3.40 (2H, m); 4.35 (3H, m); 6.95 (1H, d); 7.02 (4H, m); 7.31 (2H, d); 7.38 (2H, d); 7.87 (3H, d).

Example 207

(S)-4-(3-[N-(3-[4-carbamoylphenyl]-1,1-dimethylpropyl)amino]-2-hydroxypropoxy)benzotriazole



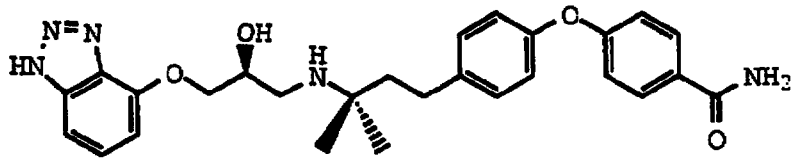
The above titled compound, 0.086 g (63%) was obtained by a procedure described in Example 206 starting from 0.113 g of the appropriate diamine.

MS: m/z (%): 398.3 (100%); 796.1 (20%)

^{1}H NMR (300 MHz, d-MeOH): d 1.3 (6H, s); 1.85 (2H, m); 2.65 (2H, m); 3.02 (2H, m); 4.2 (3H, m); 6.72 (1H, d); 7.20 (1H, d); 7.25 (2H, d); 7.35 (1H, d); 7.75 (2H, d).

Example 208

(S)-4-(3-[N-(3-[4-(4-carbamoylphenoxy)phenyl]-1,1-dimethylpropyl)amino]-2-hydroxypropoxy)benzotriazole



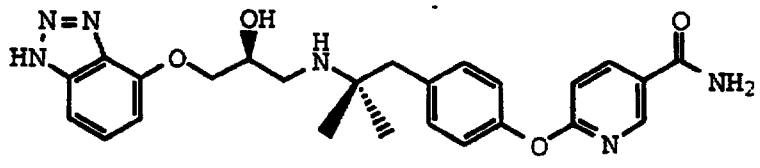
The above titled compound, 0.163 g (69%) was obtained by a procedure described in Example 206 starting from 0.231 g of the appropriate diamine.

MS: m/z (%): 490.0 (100%, m^++1)

^{1}H NMR (300 MHz, d-MeOH): d 1.42 (6H, s); 1.98 (2H, m); 2.70 (2H, m); 3.20 (2H, m); 4.30 (3H, s); 6.80 (1H, m); 6.98 (4H, m); 7.25 (2H, d); 7.35 (2H, d); 7.85 (2H, d).

Example 209

(S)-4-(3-[N-(2-[4-(5-carbamoyl-2-pyridyloxy)phenyl]-1,1-dimethylethyl)amino]-2-hydroxypropoxy)benzotriazole



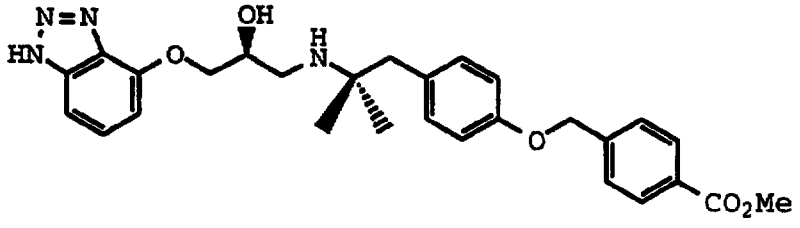
The above titled compound, 0.156 g (65%) was obtained by a procedure described in Example 206 starting from 0.235 g of the appropriate diamine.

MS: m/z (%): 477.0 (100%, m^++1)

^{1}H NMR (300 MHz, d-MeOH): d 1.21 (6H, s); 2.90 (2H, s); 3.15 (2H, m); 4.25 (3H, m); 6.79 (1H, d); 7.0 (3H, m); 7.3 (4H, m); 8.25 (1H, d); 8.6 (1H, s).

Example 210

(S)-4-(3-[N-(2-[4-([4-methoxycarbonylphenyl]methoxy)phenyl]-1,1-dimethylethyl)amino]-2-hydroxypropoxy)benzotriazole



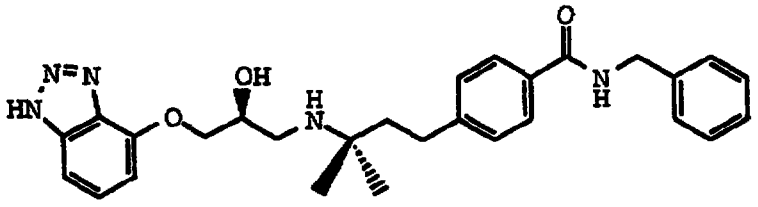
The above titled compound, 0.093 g (65%) was obtained by a procedure described in Example 206 starting from 0.109 g of the appropriate diamine.

MS: m/z (%): 505.1 (100%, m^++1)

^{1}H NMR (300 MHz, d-MeOH): 1.3 (6H, s); 2.95 (2H, s); 3.25 (2H, m); 3.95 (3H, s); 4.30 (3H, m); 5.16 (2H, s); 6.85 (1H, d); 6.90 (2H, d); 7.20 (2H, d); 7.40 (2H, m); 7.60 (2H, d); 8.15 (2H, d).

Example 211

(S)-4-(3-[N-(3-[4-(N-benzylcarbamoyl)phenyl]-1,1-dimethylpropyl)amino]-2-hydroxypropoxy)benzotriazole



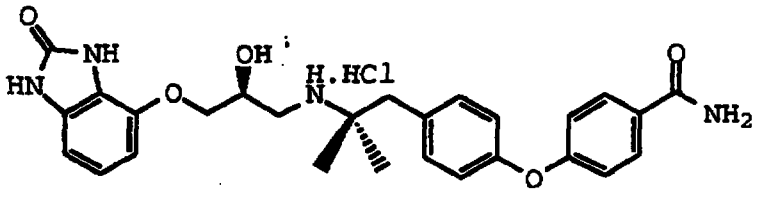
The above titled compound, 0.160 g (63%) was obtained by a procedure described in Example 206 starting from 0.211 g of the appropriate diamine.

MS: m/z (%): 488 (100%, m^++1)

^{1}H NMR (300 MHz, d-MeOH): 1.45 (6H, s); 2.0 (2H, m); 2.8 (2H, m); 3.25 (2H, m); 4.35 (3H, s); 4.6 (2H, s); 6.85 (1H, m); 7.25 (1H, m); 7.35 (8H, m); 7.80 (2H, d).

Example 212

(S)-4-(3-[N-(2-[4-(4-carbamoylphenoxy)phenyl]-1,1-dimethylethyl)amino]-2-hydroxypropoxy)-2-oxo-2,3-1H-benzoimidazole hydrochloride salt



Crude 4-(4-(2-(N-((2S)-3-(2,3-diaminophenoxy)-2-hydroxy propyl)amino)-2-methylpropyl)phenoxy)benzamide (1.49 g, 3.2 mmol) from Preparation 20 was dissolved in 1N HCl (100 mL). Toluene (100 mL) was added and the biphasic mixture treated with triphosgene (4.7 g, 16 mmol) and stirred vigorously for 18 h. A gum precipitated on the sides of the reaction vessel during the course of the reaction. The liquid was

decanted off and the gum dissolved in MeOH. The solution was absorbed on silica and chromatographed on 200 g of silica eluting with EtOAc/water/n-propanol (80 vol/15 vol/5 vol, shake and use top layer) to remove the starting material. The column was then eluted with $CHCl_3$/MeOH/NH_4OH (25 vol/5 vol/1 vol) to obtain the product. After concentrating and azeotroping with EtOH there was obtained 715 mg (46%) of a white foam.
MS. ^1H NMR (DMSO-d_6) consistent with desired product.

The free base (528 mg, 1.08 mmol) prepared above was dissolved in EtOH and treated with 4N HCl in dioxane (0.75 mL, 3.0 mmol). The solution was concentrated *in vacuo* to provide 595 mg of a white foam as the hydrochloride salt.
MS. ^1H NMR (DMSO-d_6) consistent with desired product.

As previously noted, the compounds of the present invention are potent, selective β3 adrenergic receptor agonists. This pharmacological activity was determined in the functional agonist β3 assay.

Functional Agonists
β_3 Assay

Cell Lines

The $h\beta_2$ DNA was expressed from a plasmid 57537 obtained from American Type Culture Collection. $h\beta_1$ and $h\beta_3$ adrenergic receptors were cloned from human genomic libraries using the polymerase chain reaction method with degenerate probes. Full length receptors were cloned, expressed and sequenced to verify identity according to published sequences ($h\beta_1$: T. Frielle et. al. (1993) Molecular Pharmacology 44: 264-270). These receptors were then expressed in the DXB-11 variant of CHO cells using a vector restoring tetrahydrofolate reductase and hygromycin resistance. Rat β_3 receptor expressing CHO cell line is known in the art. Mol. Pharm., Vol 40, pp. 895-99 (1991). CHO cells were grown in 10% dialyzed FBS./high glucose DMEM/0.1% proline.

cAMP Assay

Cell membranes were harvested from the above cell line using hypotonic 25 mM Hepes (pH 7.4), 1 mM EDTA, 20 µg/mL leupeptin, 1 mM PMSF buffer with scraping followed by differential centrifugation. Membranes were incubated in 25 mM Tris (pH 7.6), 0.2% BSA, 2.6 mM Mg, 0.8 mM ATP, 0.1 mM GTP, 5 mM creatine phosphate, creatine kinase 50 U/mL, 0.2 mM IBMX at 32°C. Agonists were added and incubation continued for 15 m. cAMP produced was assayed using a fluorescent tracer-immuno assay method.

Intact cell assays were performed using suspended cells removed from culture flasks by trypsin treatment. Cells were preincubated with 0.5 mM IBMX at 37°C. Agonists were added and incubation continued for 15 m. Incubation was stopped by heating suspension in boiling water. cAMP or cGMP in these and the soleus incubations were assayed by RIA (Amersham).

The compounds of the invention are agonists of the β_3 receptor. Isoproterenol is accepted in the art as a non-selective β_3 agonist and is widely used as a comparator in evaluating the activity of compounds. See Trends in Pharm. Sci. 15: 3 (1994). In the Functional Agonist β_3 assay, the compounds demonstrated at least 30%, preferably 50% and most preferably over 85% of isoproterenol's response at a single dose of 50µmol. Dose response titrations on the agonists described reveal EC_{50} values of < 10 µM, preferably < 1mmol. In the functional assay, dose titration furnishes an EC_{50} for isoproterenol of 1.1±0.5 µM.

When screened against the β_1 and β_2 receptors in the functional assay, dose titration experiments indicate that greatly reduced or no receptor stimulation is observed with the compounds of the invention. This is defined by measuring the intrinsic activity (maximal response achieved) as compared to isoproterenol. The claimed

compounds of Formula I are selective β_3 receptor agonists and have an intrinsic activity of < 3% of isoproterenol's response.

Thus, the compounds of the invention are selective β_3 adrenergic receptor agonists.

As agonists of β_3, the compounds are useful in treating conditions in a mammal in which the β_3 receptor has been demonstrated to play a role. The prefered mammal of treatment is a human. The relationship between modulating the β_3 receptor and treatment of diseases, such Type II diabetes and obesity, is well established in the art. Other conditions recognized in the art include: gastrointestinal disorders such as gastrointestinal motility, asthma, and depression. Thus, the present compounds are useful in the treatment of inflammatory bowel disease (Crohn's disease or ulcerative colitis), irritable bowel syndrome, non-specific diarrhoea dumping syndrome, asthma, and depression.

In treating non-human mammals, the compounds of the present invention are useful for increasing weight gain and/or improving the feed utilization efficiency and/or increasing lean body mass and/or decreasing birth mortality rate and increasing post/natal survival rate.

The compounds of Formulas I and II are preferably formulated prior to administration. Therefore, yet another embodiment of the present invention is a pharmaceutical formulation comprising a compound of Formula I or II and one or more pharmaceutically acceptable carriers, diluents or excipients.

The present pharmaceutical formulations are prepared by known procedures using well-known and readily available ingredients. In making the compositions of the present invention, the active ingredient will usually be mixed with a carrier, or diluted by a carrier, or enclosed within a carrier which may be in the form of a capsule, sachet, paper or other container. When the carrier serves

as a diluent, it may be a solid, semisolid or liquid material which acts as a vehicle, excipient or medium for the active ingredient. Thus, the compositions can be in the form of tablets, pills, powders, lozenges, sachets, cachets, elixirs, suspensions, emulsions, solutions, syrups, aerosol (as a solid or in a liquid medium), soft and hard gelatin capsules, suppositories, sterile injectable solutions and sterile packaged powders.

Some examples of suitable carriers, excipients, and diluents include lactose, dextrose, sucrose, sorbitol, mannitol, starches, gum acacia, calcium phosphate, alginates, tragacanth, gelatin, calcium silicate, microcrystalline cellulose, polyvinylpyrrolidone, cellulose, water syrup, methyl cellulose, methyl and propylhydroxybenzoates, talc, magnesium stearate and mineral oil. The formulations can additionally include lubricating agents, wetting agents, emulsifying and suspending agents, preserving agents, sweetening agents or flavoring agents. The compositions of the invention may be formulated so as to provide quick, sustained or delayed release of the active ingredient after administration to the patient.

The compositions are preferably formulated in a unit dosage form, each dosage containing from about 0.1 to about 500 mg, preferably about 5 to about 200 mg, of the active ingredient. However, it will be understood that the therapeutic dosage administered will be determined by the physician in the light of the relevant circumstances including the condition to be treated, the choice of compound to be administered and the chosen route of administration, and therefore, the above dosage ranges are not intended to limit the scope of the invention in any way. The compounds can be administered by a variety of routes including the oral, rectal, transdermal, subcutaneous, topical, intravenous, intramuscular or intranasal routes. For all indications, a typical daily dose will contain from about 0.05 mg/kg to about 20 mg/kg

of the active compound of this invention. Preferred daily doses will be about 0.1 to about 10 mg/kg, ideally about 0.1 to about 5 mg/kg. However, for topical administration a typical dosage is about 1 to about 500 µg compound per cm^2 of an affected tissue. Preferably, the applied amount of compound will range from about 30 to about 300 $\mu g/cm^2$, more preferably, from about 50 to about 200 $\mu g/cm^2$, and, most preferably, from about 60 to about 100 $\mu g/cm^2$.

The following formulation examples are illustrative only and are not intended to limit the scope of the invention in any way.

Formulation 1

Hard gelatin capsules are prepared using the following ingredients:

	Quantity (mg/capsule)
(S)-4-(3-[N-(2-[4-(4-carbamoylphenoxy)phenyl]-1,1-dimethylethyl)amino]-2-hydroxypropoxy)indole hydrochloride salt	25
starch, dried	425
magnesium stearate	10
Total	460 mg

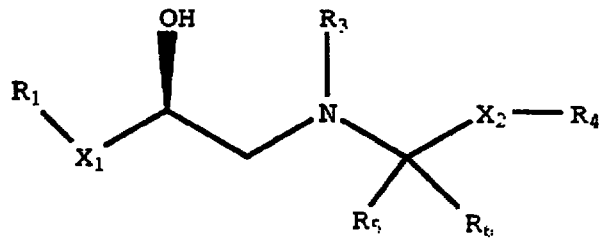
The above ingredients are mixed and filled into hard gelatin capsules in 460 mg quantities.

The principles, preferred embodiments and modes of operation of the present invention have been described in the foregoing specification. The invention which is intended to be protected herein, however, is not to be construed as limited to the particular forms disclosed, since they are to be regarded as illustrative rather than restrictive. Variations and changes may be made by those

skilled in the art without departing from the spirit of the invention.

We claim:

1. A compound of the Formula I:

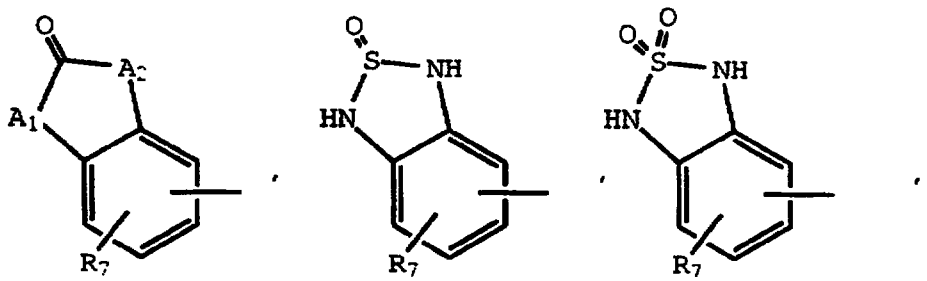


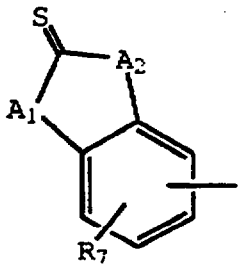
(I)

wherein:

X_1 is $-OCH_2-$, $-SCH_2-$, or a bond;

R_1 is a fused heterocycle of the formula:





R_2 and R_3 are independently H, C_1-C_4 alkyl, or aryl;

R_4 is an optionally substituted heterocycle or a moiety selected from the group consisting of:

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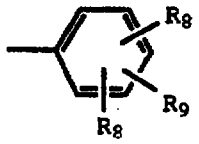
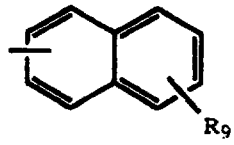
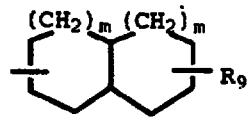
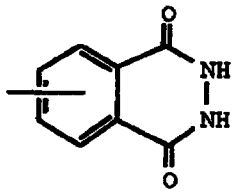
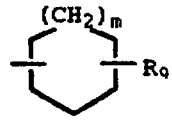
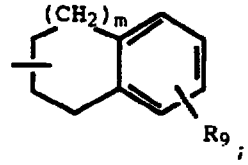







X_2 is a bond, or a 1 to 5 carbon straight or branched alkylene;

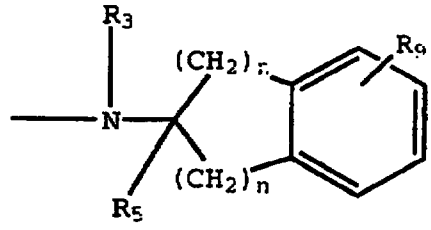
R_5 is H, or C_1-C_4 alkyl;

R_6 is H, or C_1-C_4 alkyl;

or R_5 and R_6 combine with the carbon to which each is attached to form a C_3-C_6 cycloalkyl;

or R_6 combines with to X_2 and the carbon to which X_2 is attached to form a C_3-C_8 cycloalkyl;

or R_6 combines with X_2, the carbon to which X_2 is attached, and R_4 to form:



provided that R_5 is H;

R_7 is H, halo, hydroxy, C_1-C_4 alkyl, C_1-C_4 haloalkyl, aryl, CN, $COOR_2$, $CONHR_2$, $NHCOR_2$, OR_2, NHR_2, SR_2, SO_2R_2, SO_2NHR_2, or SOR_2;

R_8 is independently H, halo or C_1-C_4 alkyl;

R_9 is halo, CN, OR_{10}, C_1-C_4 alkyl, C_1-C_4 haloalkyl, CO_2R_2, $CONR_{11}R_{12}$, CONH(C_1-C_4 alkyl or C_1-C_4 alkoxy), SR_2, $CSNR_2$, $CSNR_{11}R_{12}$, SO_2R_2, $SO_2NR_{11}R_{12}$, SOR_2, $NR_{11}R_{12}$, optionally substituted aryl, optionally

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substituted heterocycle, or C_2-C_4 alkenyl substituted with CN, CO_2R_2 or $CONR_{11}R_{12}$;

R_{10} is C_1-C_4 alkyl, C_1-C_4 haloalkyl, $(CH_2)_nC_3$-C_8 cycloalkyl, $(CH_2)_n$aryl, $(CH_2)_n$heterocycle, $(CH_2)_nC_3$-C_8 optionally substituted cycloalkyl, $(CH_2)_n$ optionally substituted aryl, $(CH_2)_n$ optionally substituted heterocycle;

R_{11} and R_{12} are independently H, C_1-C_4 alkyl, aryl, $(CH_2)_n$aryl, or combine with the nitrogen to which each is bound to form morpholinyl, piperidinyl, pyrrolidinyl, or piperazinyl;

A_1 and A_2 are independently O, S, NH, CH_2, NCH_3, or NCH_2CH_3;

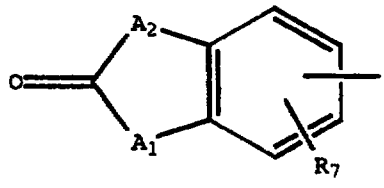
m is 0 or 1;

n is 0, 1, 2, or 3;

or a pharmaceutically acceptable salt thereof.

2. A compound of Claim 1, wherein R_7 is H, halo, hydroxy, C_1-C_4 alkyl, C_1-C_4 alkoxy, NH_2, SR_2, SO_2R_2, or SOR_2.

3. A compound of Claim 2 wherein: R_1 is



4. A compound of Claim 3 wherein R_5 and R_6 are methyl; and A_1 and A_2 are NH.

5. A compound of Claim 4 wherein R_4 is

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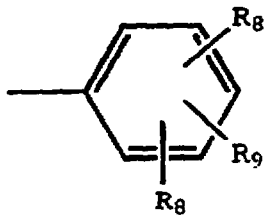
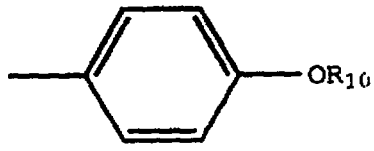
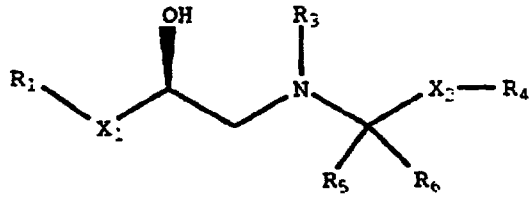


6. A compound of Claim 5 wherein R_4 is



7. A compound of Claim 6 wherein R_{10} is phenyl or pyridyl; said phenyl or pyridyl being substituted with $-CONR_{11}R_{12}$, $-CO_2R_2$, $-SO_2R_2$, or $-SO_2NR_{11}R_{12}$.

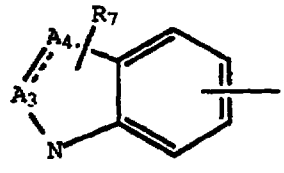
8. A compound of the Formula II:



(II)

wherein:

R_1 is



(II)

X_1 is $-OCH_2-$, $-SCH_2-$, or a bond;

The bond between A_3 and A_4 is either a single or double bond;

A_3 and A_4 are independently carbon or nitrogen;

R_2 and R_3 are independently H, C_1-C_4 alkyl, or aryl;

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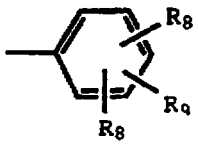
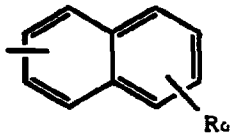
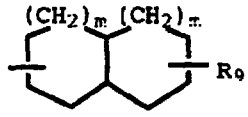
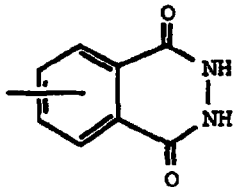
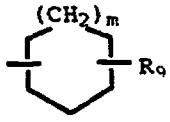
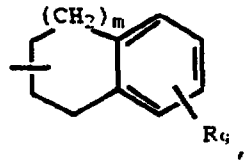
R_4 is an optionally substituted heterocycle or a moiety selected from the group consisting of:

X_2 is a bond, or a 1 to 5 carbon straight or branched alkylene;

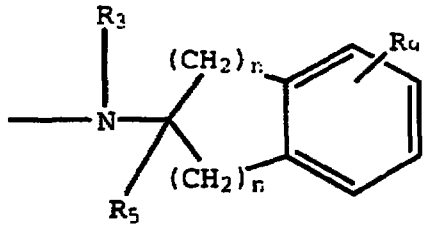
R_5 is H, or C_1-C_4 alkyl;

R_6 is H, or C_1-C_4 alkyl;

or R_5 and R_6 combine with the carbon to which each is attached to form a C_3-C_6 cycloalkyl;

or R_6 combines with to X_2 and the carbon to which X_2 is attached to form a C_3-C_8 cycloalkyl;

or R_6 combines with X_2, the carbon to which X_2 is attached, and R_4 to form:



provided that R_5 is H;

R_7 is H, halo, hydroxy, C_1-C_4 alkyl, C_1-C_4 haloalkyl, aryl, CN, $COOR_2$, $CONHR_2$, $NHCOR_2$, OR_2, NHR_2, SR_2, SO_2R_2, SO_2NHR_2, or SOR_2;

R_8 is independently H, halo or C_1-C_4 alkyl;

R_9 is halo, CN, OR_{10}, C_1-C_4 alkyl, C_1-C_4 haloalkyl, CO_2R_2, $CONR_{11}R_{12}$, CONH(C_1-C_4 alkyl or C_1-C_4 alkoxy), SR_2, $CSNR_2$, $CSNR_{11}R_{12}$, SO_2R_2, $SO_2NR_{11}R_{12}$, SOR_2,

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$NR_{11}R_{12}$, optionally substituted aryl, optionally substituted heterocycle, or C_2-C_4 alkenyl substituted with CN, CO_2R_2 or $CONR_{11}R_{12}$;

R_{10} is C_1-C_4 alkyl, C_1-C_4 haloalkyl, $(CH_2)_nC_3$-C_8 cycloalkyl, $(CH_2)_n$aryl, $(CH_2)_n$heterocycle, $(CH_2)_nC_3$-C_8 optionally substituted cycloalkyl, $(CH_2)_n$ optionally substituted aryl, or $(CH_2)_n$ optionally substituted heterocycle;

R_{11} and R_{12} are independently H, C_1-C_4 alkyl, aryl, $(CH_2)_n$aryl or combine with the nitrogen to which each is bound to form morpholinyl, piperidinyl, pyrrolidinyl, or piperazinyl;

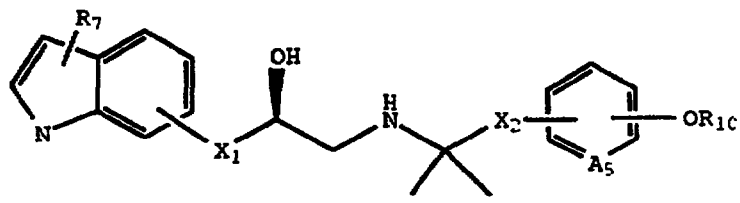
m is 0 or 1;

n is 0, 1, 2, or 3;

or a pharmaceutically acceptable salt thereof.

9. A compound of Claim 8 wherein A_3 and A_4 are CH.

10. A compound of Claim 9 of the formula:



wherein:

A_5 is CH or N.

11. A compound of Claim 10 wherein R_7 is H; X_1 is $-OCH_2-$; and X_2 is methylene or ethylene.

12. A compound of Claim 11 wherein R_{10} is phenyl or pyridyl said phenyl or pyridyl being substituted with $CONR_{11}R_{12}$, CN, CO_2R_2, SO_2R_2, or $SO_2NR_{11}R_{12}$.

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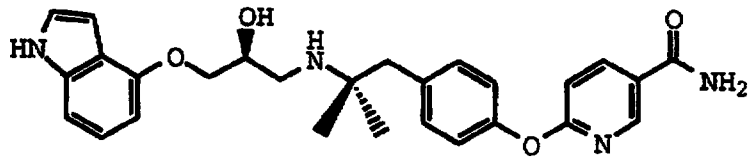
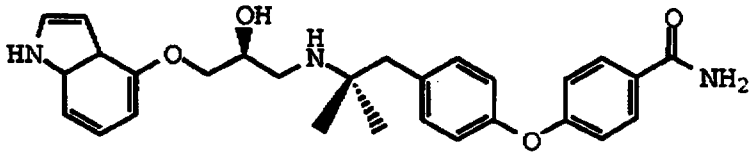
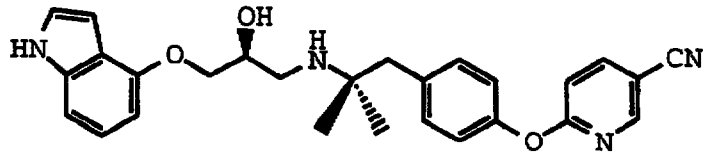
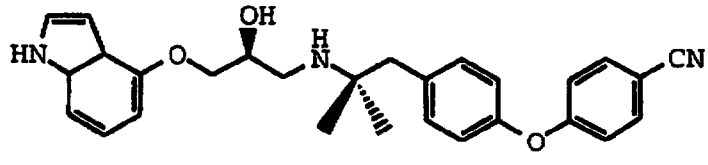
13. A compound of Claim 12 selected from the group consisting of:

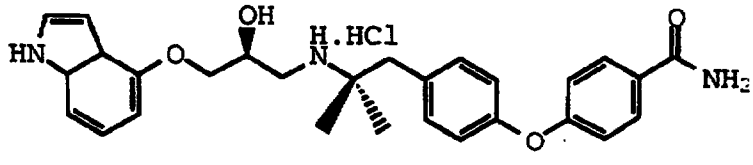

;

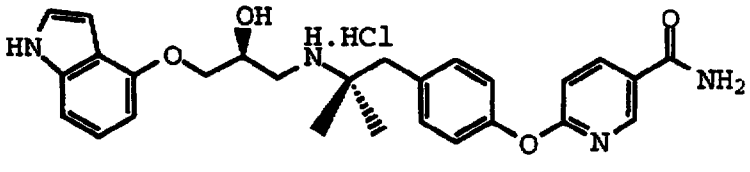

;


;


;

or pharmaceutically acceptable salts thereof; or


; or


.

14. A compound of Claim 8 wherein:
A_4 is N; and
A_3 is CH or N.

15. A compound of Claim 14 of the formula:

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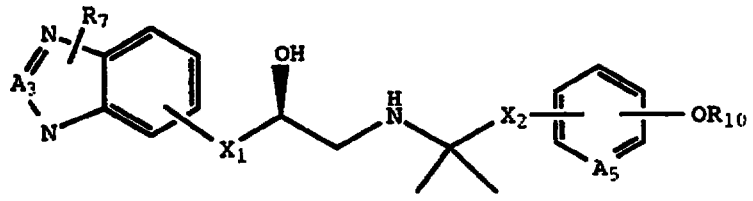


wherein:

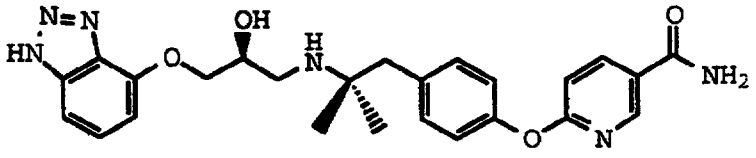
A_5 is CH or N.

16. A compound of Claim 15 wherein R_7 is H, halo, hydroxy, C_1-C_4 alkyl, C_1-C_4 alkoxy, NH_2, SR_2, SO_2R_2, or SOR_2.

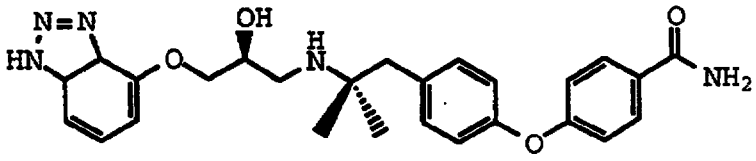
17. A compound of Claim 16 wherein R_7 is H; X_1 is $-OCH_2-$; and X_2 is methylene or ethylene.

18. A compound of Claim 17 wherein R_{10} is phenyl or pyridyl said phenyl or pyridyl being substituted with $CONR_{11}R_{12}$, CO_2R_2, CN, SO_2R_2, or $SO_2NR_{11}R_{12}$.

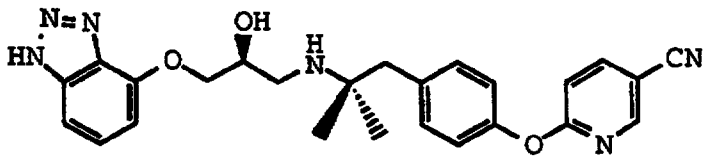
19. A compound of Claim 18 selected from the group consisting of:



;



;



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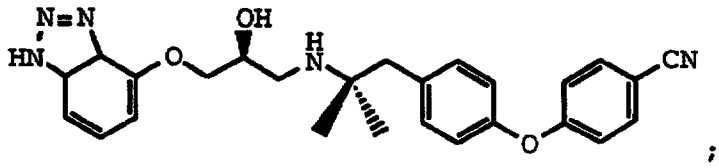

;

or pharmaceutically acceptable salts thereof.

20. A method of treating Type II Diabetes comprising administering to a mammal in need thereof a compound of Claim 1.

21. A method of treating Type II Diabetes comprising administering to a mammal in need thereof a compound of Claim 7.

22. A method of treating Type II Diabetes comprising administering to a mammal in need thereof a compound of Claim 8.

23. A method of treating Type II Diabetes comprising administering to a mammal in need thereof a compound of Claim 10.

24. A method of treating Type II Diabetes comprising administering to a mammal in need thereof a compound of Claim 13.

25. A method of treating Type II Diabetes comprising administering to a mammal in need thereof a compound of Claim 14.

26. A method of treating Type II Diabetes comprising administering to a mammal in need thereof a compound of Claim 19.

27. A method of treating obesity comprising administering to a mammal in need thereof a compound of Claim 1.

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28. A method of treating obesity comprising administering to a mammal in need thereof a compound of Claim 7.

29. A method of treating obesity comprising administering to a mammal in need thereof a compound of Claim 8.

30. A method of treating obesity comprising administering to a mammal in need thereof a compound of Claim 10.

31. A method of treating obesity comprising administering to a mammal in need thereof a compound of Claim 13.

32. A method of treating obesity comprising administering to a mammal in need thereof a compound of Claim 14.

33. A method of treating obesity comprising administering to a mammal in need thereof a compound of Claim 19.

34. A method of agonizing the β_3 receptor comprising administering to a mammal in need thereof a compound of Claim 1.

35. A method of agonizing the β_3 receptor comprising administering to a mammal in need thereof a compound of Claim 7.

36. A method of agonizing the β_3 receptor comprising administering to a mammal in need thereof a compound of Claim 8.

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37. A method of agonizing the β_3 receptor comprising administering to a mammal in need thereof a compound of Claim 9.

38. A method of agonizing the β_3 receptor comprising administering to a mammal in need thereof a compound of Claim 13.

39. A method of agonizing the β_3 receptor comprising administering to a mammal in need thereof a compound of Claim 14.

40. A method of agonizing the β_3 receptor comprising administering to a mammal in need thereof a compound of Claim 19.

41. A pharmaceutical formulation comprising as an active ingredient a compound of Claim 1, associated with one or more pharmaceutically acceptable carriers, excipients or diluents.

42. A pharmaceutical formulation comprising as an active ingredient a compound of Claim 7, associated with one or more pharmaceutically acceptable carriers, excipients or diluents.

43. A pharmaceutical formulation comprising as an active ingredient a compound of Claim 8, associated with one or more pharmaceutically acceptable carriers, excipients or diluents.

44. A pharmaceutical formulation comprising as an active ingredient a compound of Claim 9, associated with one or more pharmaceutically acceptable carriers, excipients or diluents.

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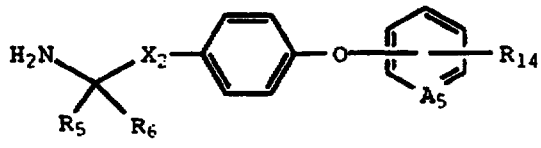
45. A pharmaceutical formulation comprising as an active ingredient a compound of Claim 13, associated with one or more pharmaceutically acceptable carriers, excipients or diluents.

46. A pharmaceutical formulation comprising as an active ingredient a compound of Claim 14, associated with one or more pharmaceutically acceptable carriers, excipients or diluents.

47. A pharmaceutical formulation comprising as an active ingredient a compound of Claim 19, associated with one or more pharmaceutically acceptable carriers, excipients or diluents.

48. A compound of the Formula III:



(III)

wherein:

A_5 is CH or N;

X_2 is a bond or a 1 to 5 carbon straight or branched alkylene.

R_5 is H, C_1-C_4 alkyl;

R_6 is H, C_1-C_4 alkyl;

or R_5 and R_6 combine with the carbon to which each is attached to form a C_3-C_6 cycloalkyl;

or R_6 combines with X_2 and the carbon to which X_2 is attached to form a C_3-C_8 cycloalkyl;

R_{14} is C_1-C_4 alkyl, C_1-C_4 haloalkyl, hydroxy, carboxy, tetrazolyl, acyl, $COOR_2$, $CONR_{11}R_{12}$, $CONH(C_1$-C_4 alkoxy), cyano, C_1-C_4 alkoxy, C_1-C_4 alkyl, phenyl, nitro, $NR_{11}R_{12}$, $NHCO(C_1$-C_4 alkyl), NHCO(benzyl), NHCO(phenyl), SR_2, $S(C_1$-C_4 alkyl), $OCO(C_1$-C_4 alkyl), $SO_2(NR_{11}R_{12})$, $SO_2(C_1$-C_4 alkyl), or SO_2(phenyl);

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or pharmaceutically acceptable salts thereof.

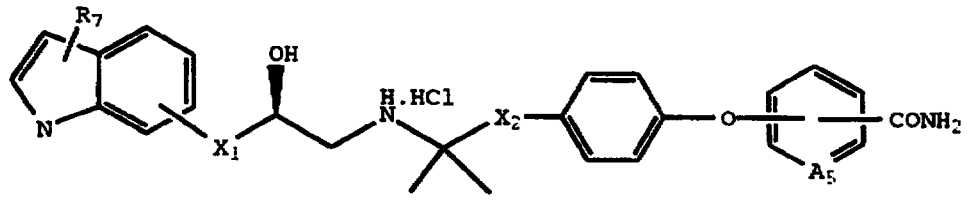
49. A compound of claim 48, wherein:

R_5 and R_6 are methyl; and

X_2 is methylene or ethylene.

50. A compound of Claim 49, wherein R_{14} is $CONH_2$.

51. A process of preparing a compound of claim 1 of the formula IA



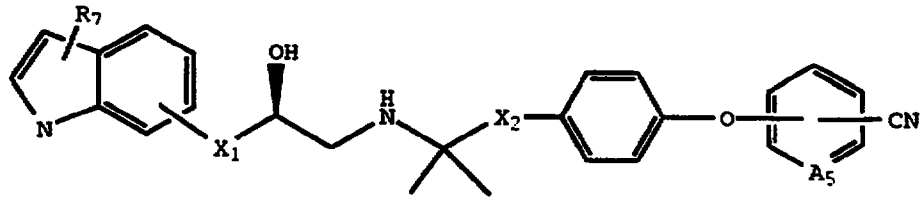
(IA)

wherein:

A_5 is CH or N;

which comprises:

in step 1, hydrolysis of a compound of the formula IB:



(IB);

and in step 2, reacting the product of step 1 to form an acid addition salt.

52. A process of preparing a compound of Claim 1, which comprises:

in step 1 reacting an epoxide of the formula (XI):

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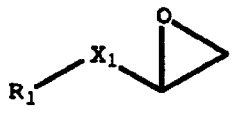
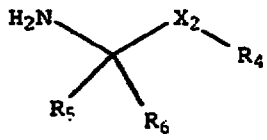
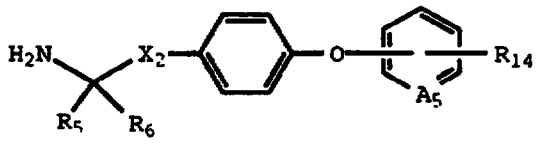

(XI)

with an amine of formula (B):


(B);

and in step 2 reacting the product of step 1 to form an acid addition salt..

53. A process of Claim 52, wherein the amine is of the formula (IIIA):


(IIIA)

wherein:

A_5 is CH or N;

R_{14} is C_1-C_4 alkyl, C_1-C_4 haloalkyl, hydroxy, carboxy, tetrazolyl, acyl, $COOR_2$, $CONR_{11}R_{12}$, $CONH(C_1$-C_4 alkoxy), cyano, C_1-C_4 alkoxy, C_1-C_4 alkyl, phenyl, nitro, $NR_{11}R_{12}$, $NHCO(C_1$-C_4 alkyl), NHCO(benzyl), NHCO(phenyl), SR_2, $S(C_1$-C_4 alkyl), $OCO(C_1$-C_4 alkyl), $SO_2(NR_{11}R_{12})$, $SO_2(C_1$-C_4 alkyl), or SO_2(phenyl).

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