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.

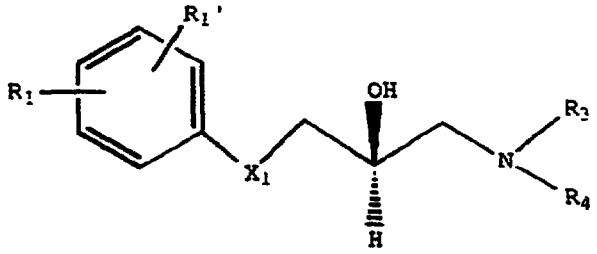
The β_3 receptor, which is found in several types of human tissue including human fat tissue, has roughly 50% homology to the β_1 and β_2 receptor subtypes yet is considerably less abundant. The importance of the β_3 receptor is a relatively recent discovery since the amino-acid sequence of the human 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.

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 provides compounds of the Formula I:



(I)

wherein:

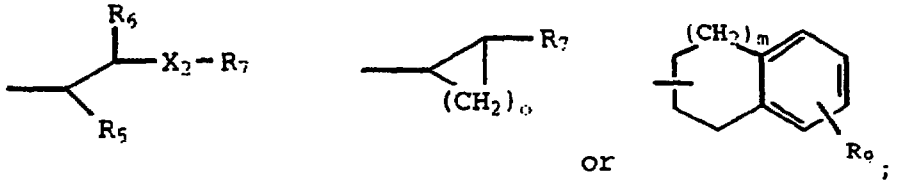
R_1 is OH, halo, SO_2NHR_2, CO_2R_2, $CONHR_2$, $NHCOR_2$, -NH(optionally substituted aryl), CF_3, or CF_2H;

R_1' is H, halo, C_1-C_4 alkyl, OH, SO_2NHR_2, CO_2R_2, $CONHR_2$, $NHCOR_2$, CF_3 or CF_2H;

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

R_3 is H or C_1-C_4 alkyl;

R_4 is a moiety selected from the group consisting of:

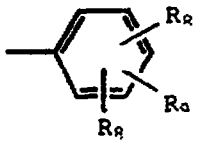
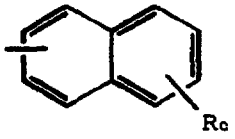
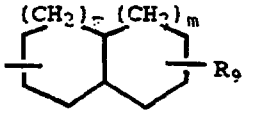
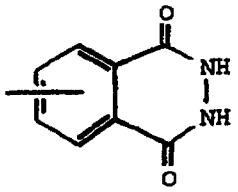
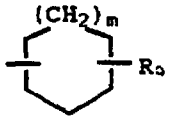
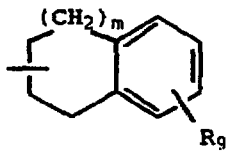


or

;

R_5 and R_6 are independently C_1-C_4 alkyl;

R_7 is an optionally substituted heterocycle or a group selected from the group consisting of:

;

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, $NR_{11}R_{12}$, aryl, heterocycle, optionally substituted aryl, optionally substituted heterocycle, or C_1-C_4 alkyl or C_2-C_4 alkenyl optionally substituted with CN;

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, $(CH_2)_n$ optionally substituted C_3-C_8 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, or combine with the nitrogen to which each are bound to form morpholinyl, piperidinyl, pyrrolidinyl, or piperazinyl;

X_1 is O or S;

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;

o is 1, 2, 3, 4, 5, or 6;

or a pharmaceutically acceptable salt or solvate thereof.

The present invention also provides a novel process for making compounds of Formula I.

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 stimulating 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 stimulating the β_3 receptor.

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

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 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 stimulating 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.

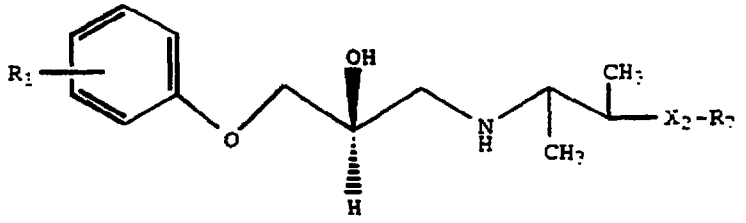
The term "treating," as used herein, describes the management and care of a patient for the purpose of combating the disease, condition, or disorder and includes the administration of a compound of present invention to prevent the onset of the symptoms or complications, to alleviate symptoms or complications,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

The term "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 compounds of the Formula I.

Preferred compounds are those of Formula Ia:

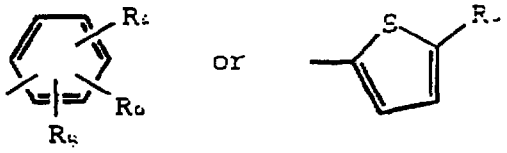


(Ia)

wherein:

R_1 is F, OH, $-SO_2NR_2$, $-NHCOR_2$, or CF_2H;

R_7 is



;

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

R_9 is OR_{10}, tetrazolyl, $CONR_{11}R_{12}$, or $SO_2NR_{11}R_{12}$;

R_{10} is $(CH_2)_n$aryl, $(CH_2)_n$heterocycle, said aryl or heterocycle being optionally substituted with tetrazolyl, CN, CO_2R_2, $CONR_{11}R_{12}$, or $SO_2NR_{11}R_{12}$;

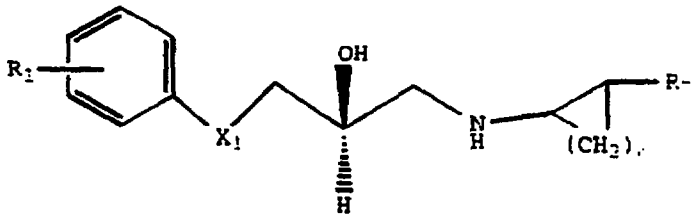
R_{11} and R_{12} are independently H, C_1-C_4 alkyl, or combine with the nitrogen to which each is bound to form morpholinyl, piperidinyl, pyrrolidinyl or piperazinyl;

X_2 is 1 to 2 carbon alkylene;

n is 0, 1, 2, or 3;

or a pharmaceutically acceptable salt.

Other preferred compounds are those of Formula Ib:

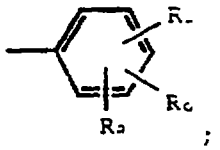


(Ib)

wherein:

R_1 is F, $-SO_2NR_2$, $-NHCOR_2$, or CF_2H;

R_7 is an optionally substituted heterocycle or



;

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

R_9 is OR_{10}, $CONR_{11}R_{12}$, or $SO_2NR_{11}R_{12}$;

R_{10} is independently $(CH_2)_n$aryl, $(CH_2)_n$heterocycle, said aryl or heterocycle being optionally substituted with tetrazolyl, CN, CO_2R_2, $CONR_{11}R_{12}$, or $SO_2NR_{11}R_{12}$;

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, piperdinyl, pyrrolidinyl or piperazinyl;

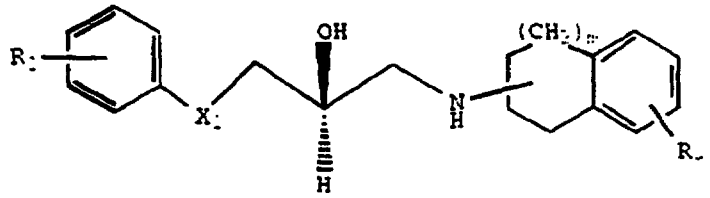
X_1 is O or S;

n is 0, 1, 2, or 3;

o is 1, 2, 3, 4, 5, or 6;

or a pharmaceutically acceptable salt or solvate thereof.

Additional preferred compounds are those of the Formula Ic:



(Ic)

wherein:

R_1 is F, $-SO_2NR_2$, $-NHCOR_2$, or CF_2H;

R_9 is OR_{10}, $CONR_{11}R_{12}$, $SO_2NR_{11}R_{12}$, SOR_2, $NR_{11}R_{12}$, optionally substituted aryl, optionally substituted aryloxy, or optionally substituted heterocycle;

R_{10} is $(CH_2)_n$aryl, $(CH_2)_n$heterocycle, said aryl or heterocycle being optionally substituted with tetrazolyl, $CONR_{11}R_{12}$, or $SO_2NR_{11}R_{12}$;

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;

X_1 is O or S;

m is 0 or 1;

n is 0, 1, 2, or 3;

or a pharmaceutically acceptable salt or solvate thereof.

Particularly preferred compounds are those of Formula Ia, Ib or Ic, wherein R_9 is $CONH_2$ and OR_{10}, wherein R_{10} is a optionally substituted aryl, particularly phenyl, or optionally substutituted heterocycle, particularly pyridine.

Additional preferred compounds include the following:

(All isomers of:) 5-{3-[2-hydroxy-3-(2-fluorophenyloxy)-propylamino]-2-methylbutyl}-thiophene-2-sulfonamide

(All isomers of:) 5-(2-fluoro-4-{3-[2-hydroxy-3-(2-fluorophenyloxy)-propylamino]-2-methylbutyl}-phenyl)-1H-tetrazole

(All isomers of:) 4-{3-[2-hydroxy-3-(3-hydroxyphenyloxy)-propylamino]-2-methylbutyl}benzamide

(All isomers of:) 4-{3-[2-hydroxy-3-(2-fluorophenyloxy)-propylamino]-2-methylbutyl}-3-methylbenzamide

(All isomers of:) 4-{3-[2-hydroxy-3-(3-acetylamino-phenyloxy)-propylamino]-2-methylbutyl}benzamide

By virtue of their acidic moieties, some of the compounds of Formula I include the pharmaceutically 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.

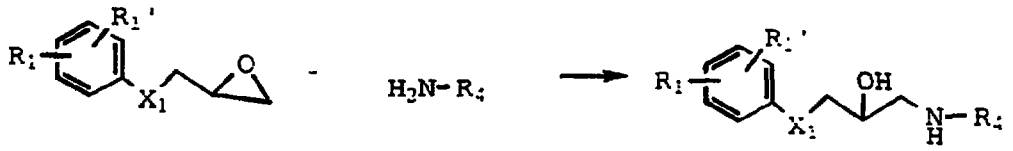
Because of the basic moiety, some of the compounds of Formula I can also exist as pharmaceutically acceptable acid addition salts. Acids commonly employed to form such salts include inorganic acids such as hydrochloric, hydrobromic, hydroiodic, sulfuric and phosphoric acid, as well as organic acids such 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 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.

The compounds of Formula I are prepared as described in the following Schemes and examples.

Scheme I



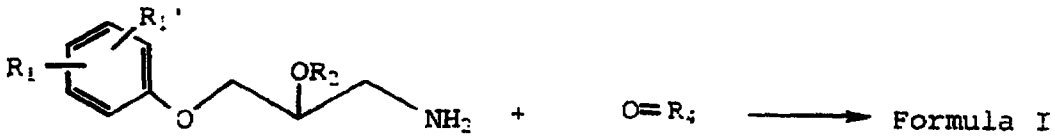
(II) (III)

In Scheme I, R_1, R_1' and R_4 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 (II) may be combined with the amine (III) in an alcohol, preferably, ethanol at room temperature to the reflux temperature of the reaction mixture. Preferably, the reaction is carried out under conditions generally described in Atkins et al., Tetrahedron Lett. 27:2451 (1986). These conditions include mixing the reagents in the presence of trimethylsilylacetamide in a polar aprotic solvent such as acetonitrile, dimethylformamide (DMF), acetone, dimethylsulfoxide (DMSO), dioxane, diethylene glycol methyl 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.

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

Scheme II



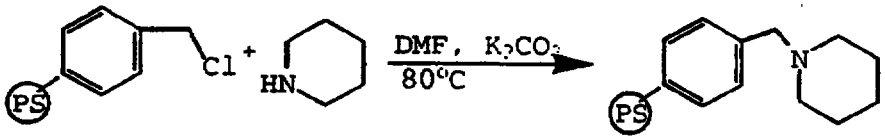
(IV) (V)

In Scheme II, R_1, R_1', R_2, and R_4 have the same meaning as previously described. 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



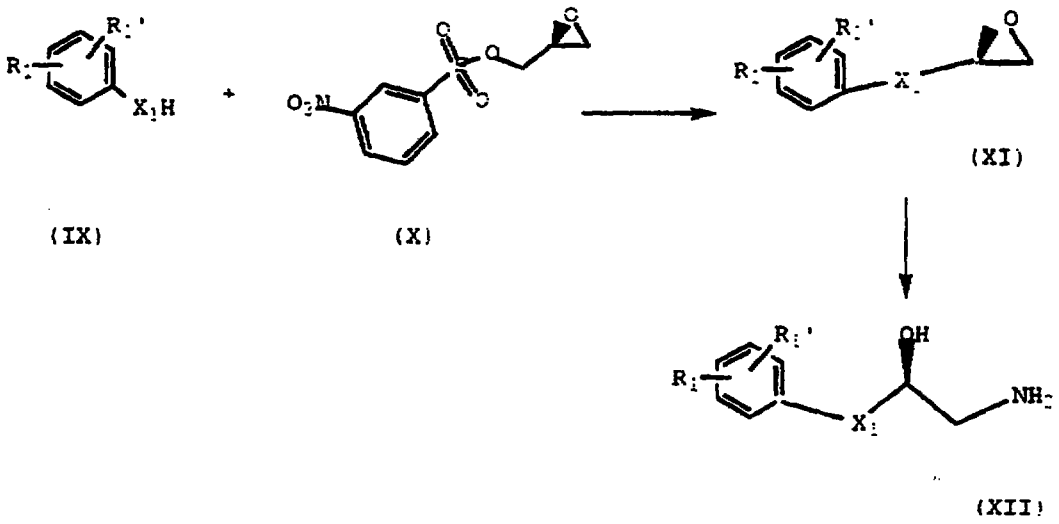
(VI) (VII) (VIII)

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 techniques. 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.

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

Scheme III



(IX) (X) (XI) (XII)

In Scheme III, X_1, R_1' and R_1 are the same as previously defined. 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

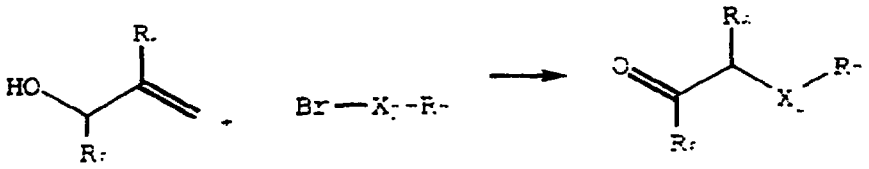
yield products of sufficient purity (>97%) and yield (60-100%). If desired, further purification may be carried out by passing over a short plug of silica, eluting with $CHCl_3$, then 95:5 $CHCl_3$/MeOH, then 25:5:1 $CHCl_3$/MeOH/NH_4OH.

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 utilized in Scheme II that are either unknown in the art or not commercially available are prepared in accordance with Scheme IV.

Scheme IV

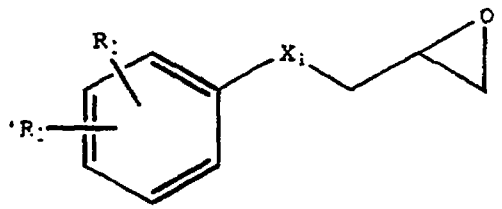


(XIII) (XIV) (XV)

In Scheme IV, X_2, R_4, R_5, R_6, and R_7 are the same as previously defined. 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.

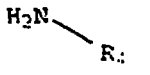
Another embodiment of the current invention is a process of preparing a compound of Formula I which comprises:

In step 1, reacting an epoxide of the formula:



(II)

with an amine of formula (B):



(III);

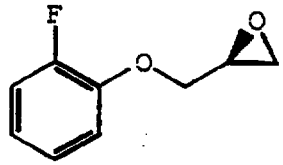
and in step 2, reacting the product of step 1 to form an acid addition salt.

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

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", "NMR", and "MS" indicate that the data was consistent with the desired structure.

Preparation 1

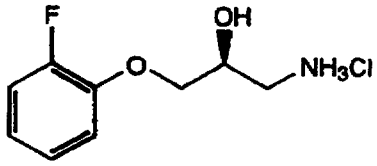
(S)-3-(2-fluorophenyl)-1,2-epoxypropane



A solution of 2-fluorophenol (865 mg, 7.72mol) and (2S)-(+)-glycidyl-3-nitrobenzenesulfonate (2.0 g, 7.72 mmol) in 50 mL of acetone was treated with 1.1 equivalents of K_2CO_3 (1.17 g, 8.5 mmol) and stirred at reflux for 18 hours. The suspension was cooled to ambient temperature, the solids 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 a colorless oil which slowly crystallized at 0°C to 1.11 g (86%) white needles. TLC (R_f = 0.5, $CHCl_3$) and NMR indicated >95% purity, so the material was used without further purification.

Preparation 2

(S)-3-(2-fluorophenyloxy)-2-hydroxypropylammonium chloride

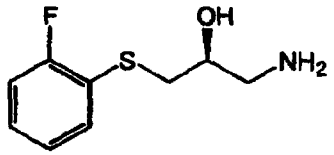


S-3-(2-fluorophenyl)-1,2-epoxypropane (1.08 g, 6.4 mmol) was dissolved in 50 mL of methanol and treated with dibenzylamine (1.23 mL, 6.4 mmol, d=1.026). The mixture was stirred at reflux for 3 hours and then cooled to ambient temperature. A vast excess

of ammonium formate (3.0 g, 47.6 mmol) was added followed by 10% palladium on carbon (350 mg), and the suspension was stirred at reflux for 45 minutes. After cooling the suspension, the reaction mixture was filtered through Celite and the filtrate concentrated *in vacuo* to a colorless oil. The oil was redissolved in 10 mL of methanol and treated with a 1.0 M anhydrous solution of HCl in ether (7.0 mL, 7 mmol) and reduced *in vacuo* to dryness. The residue was triturated in pentane and the solids filtered to yield 1.4 g (99%) of a dry white powder. NMR. EA.

Preparation 2

(S)-3-(2-fluorophenylthio)-2-hydroxypropylamine



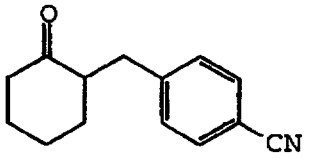
(2*S*)-(+)-glycidyl-3-nitrobenzenesulfonate (3.0 g, 11.6 mmol) and potassium carbonate (1.8 g, 13 mmol) in acetone (50 mL) was sparged with nitrogen for 5 minutes. 2-fluorothiophenol (1.5 g, 11.6 mmol) was added and the mixture stirred at ambient temperature under a blanket of nitrogen for 4 hours. The acetone was removed *in vacuo* and the residue partitioned between water/ethyl acetate. The organic layer was dried ($MgSO_4$) and concentrated to give 1.6 g (75%) of the intermediate epoxide as a colorless oil and was used without further purification.

The intermediate epoxide (1.2 g, 6.5 mmol) was dissolved in methanol (10 mL) and cooled to 0°C using an ice bath. The solution was saturated with ammonia gas and the reaction vessel was sealed and allowed to stir at ambient temperature for 16 hours. The reaction was opened at 0°C and the ammonia allowed to evaporate before the

mixture was concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel using 25:5:1 $CHCl_3$:MeOH:NH_4OH to give 980 mg of a colorless oil (75%) which rapidly crystallized under vacuum to give a white solid, mp 50-53 °C. NMR. MS. EA.

Preparation 4

4-[(2-oxocyclohexyl)methyl]benzonitrile



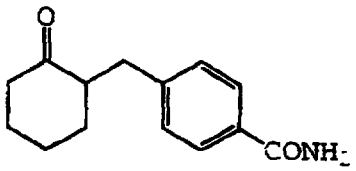
A mixture of methyl cyclohexanone-2-carboxylate (11.0 g, 70 mmol, from Fluka), α-bromo-p-tolunitrile (12.3 g, 63 mmol), potassium carbonate (10.5 g, 76 mmol) in THF (200 mL) was refluxed for 24 hours. The progress of the reaction was followed by GC. The reaction was diluted with water and the THF was 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 glc. 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 5

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 6

2-Tetralone-6-carboxylic acid, ethylene ketal

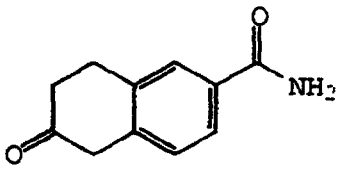
6-bromo-2-tetralone (2.0 g, 8.89 mmol) was dissolved in toluene (50 mL) and treated with excess ethylene glycol (4.88 mL, 88.9 mmol) and catalytic *p*-toluenesulfonic acid (15 mg). The solution was stirred at reflux 16 hours, and water was removed from the reaction mixture using a Dean-Stark condenser. 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 2-tetralone-6-carboxylic acid, ethylene ketal 1.06 g (55%) a slowly crystallizing solid. NMR, MS.

Preparation 7

2-Tetralone-6-carboxamide



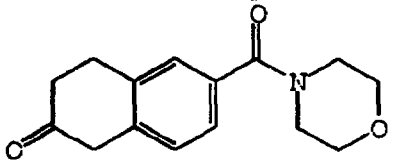
2-tetralone-6-carboxylic acid, ethylene ketal (395 mg, 2.07 mmol) was co-dissolved in CH_2Cl_2 (50 mL) with N-hydroxysuccinimide (260 mg, 2.76 mmol) at 0°C and treated with a slight excess of 1,3-dicyclohexylcarbodiimide (502 mg, 2.50 mmol). The mixture was allowed to warm to ambient temperature over 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 and the solution 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 8

2-Tetralone-6-morpholinamide

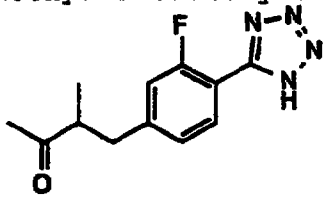


2-tetralone-6-carboxylic acid, ethylene ketal (395 mg, 2.07 mmol) was codissolved in CH_2Cl_2 (50 mL) with N-hydroxysuccinimide (260 mg, 2.76 mmol) at 0°C and treated with a slight excess of 1,3-dicyclohexylcarbodiimide (502 mg, 2.50 mmol). The mixture was allowed to warm to ambient temperature over 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 9

5-[2-fluoro-4-(2-methyl-3-oxobutyl)-phenyl]-tetrazole

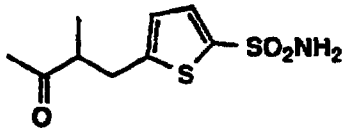


4-bromo-2-fluorobenzonitrile (5.3 g, 26.5 mmol) and 3-methyl-3-buten-2-ol (3.5 g, 40 mmol) were dissolved in N-methylpyrrolidinone (30 mL) and treated with catalytic palladium diacetate (115 mg, 0.5 mmol), tris-(o-tolyl)-phosphine (300 mg, 1.0 mmol), and $NaHCO_3$ (2.7 g, 32 mmol). The mixture was stirred at 120°C for one hour. The solution was cooled to ambient temperature and partitioned between H_2O/ethyl acetate, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was applied to a silica chromatography column and eluted with 4:1 hexane/ethyl acetate to yield 2.3 g of a pale yellow oil (43%)

The oil (1.3 g, 6.3 mmol) was dissolved in DMF (30 mL) and treated with sodium azide (455 mg, 7 mmol) and ammonium chloride (375 mg, 7 mmol) and stirred at 90°C for 16 hours. The reaction mixture was concentrated *in vacuo* and partitioned between 3N NaOH/diethyl ether. The aqueous layer was acidified with conc. HCl and cooled, and then extracted with diethyl ether, dried ($MgSO_4$), and concentrated *in vacuo* to a pale brown oil. The residue was applied to a silica chromatography column and eluted with 25:5:1 $CHCl_3$/MeOH/NH_4OH to yield 140 mg of a white solid (9%).

Preparation 10

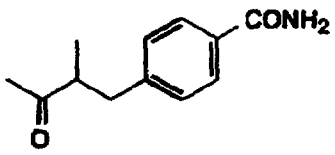
5-(2-methyl-3-oxobutyl)-thiophene-2-sulfonamide



5-bromothiophene-2-sulfonamide (5.2 g, 21.5 mmol) and 3-methyl-3-buten-2-ol (2.8 g, 32.2 mmol) were dissolved in N-methylpyrrolidinone (40 mL) and treated with catalytic palladium diacetate (96 mg, 0.43 mmol), tris-(*o*-tolyl)-phosphine (262 mg, 0.86 mmol), and $NaHCO_3$ (2.2 g, 25.8 mmol). The mixture was stirred at 160°C for 48 hours. TLC indicated the reaction was ca. 50% completed at that time. The solution was cooled to ambient temperature and partitioned between H_2O/ethyl acetate, dried ($MgSO_4$) and concentrated *in vacuo* to a dark brown oil. The residue was applied to a silica chromatography column and eluted with 2:3 hexane/ethyl acetate to yield 220 mg of a pale brown oil (4.1%).

Preparation 11

4-(2-methyl-3-oxobutyl)benzamide

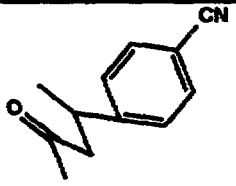
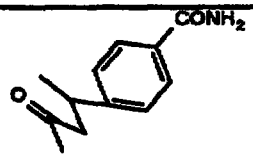
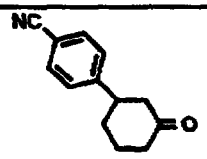
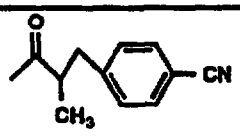


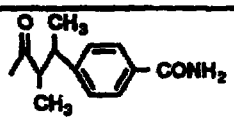
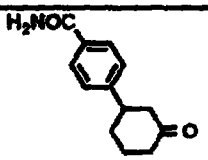
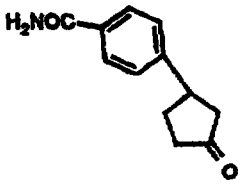
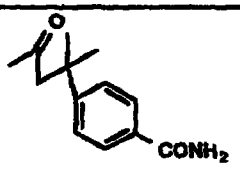
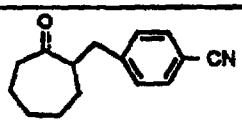
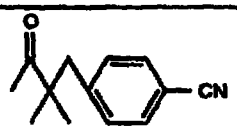
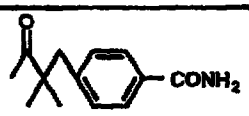
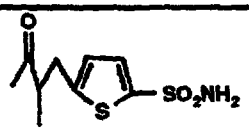
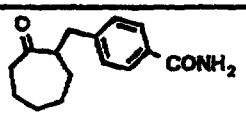
4-bromobenzonitrile (9.1 g, 50 mmol) and 3-methyl-3-buten-2-ol (6.5 g, 75 mmol) were dissolved in N-methylpyrrolidinone (40 mL) and treated with catalytic palladium diacetate (225 mg, 1.0 mmol), tris-(*o*-tolyl)-phosphine (610 mg, 2.0 mmol), and $NaHCO_3$ (5.0 g, 60 mmol). The mixture was stirred at 120°C for three hours. The solution was cooled to ambient temperature and partitioned between H_2O/ethyl acetate, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was applied to a silica

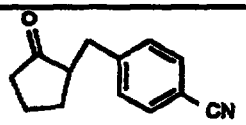
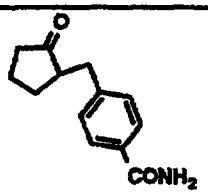
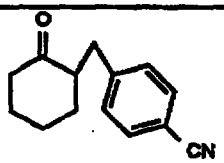
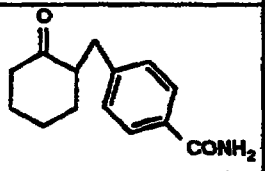
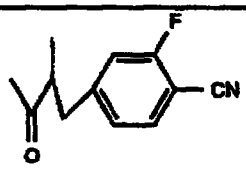
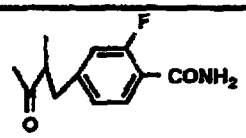
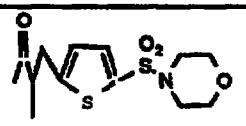
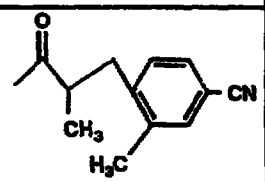
chromatography column and eluted with 3:1 hexane/ethyl acetate to yield 6.2 g of a pale yellow oil (66%)

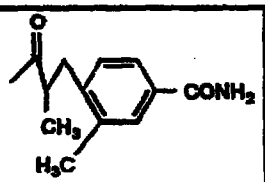
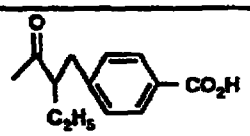
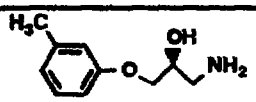
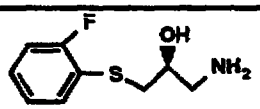
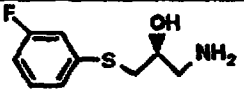
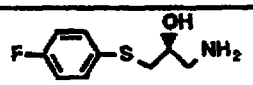
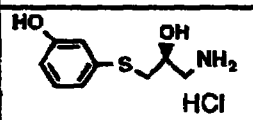
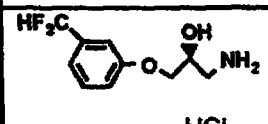
The oil (4.6 g, 24.6 mmol) was dissolved in DMSO (20 mL) and treated with K_2CO_3 (1.0 g) and H_2O_2 (6 mL, 30% w/w) and stirred at 0°C for 10 minutes. The reaction mixture was diluted with 500 mL water and saturated with NaCl, and then extracted with ethyl acetate. The organic extracts were dried ($MgSO_4$), and concentrated *in vacuo* to a white solid. The solid was recrystallized from 1:1 ethyl acetate/hexane to yield 3.22 g of a white solid (64%). M.P. 112-115.

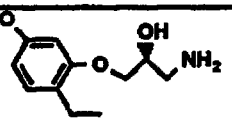
The following compounds were prepared in a manner analogous to the schemes and/or preparations described herein or by techniques appreciated in the art:

Name	Structure	m.p.	Yield	Confirmed by	
				NMR	M.S.
(4-(1-methyl-3-oxobutyl)phenyl) methanenitrile Preparation 12		oil	44%	x	x
4-(1-methyl-3-oxobutyl) benzamide Preparation 13		127-9	95%	x	x
4-(3-oxocyclohexyl) benzonitrile Preparation 14		66-69	36%	x	x
4-(2-methyl-3-oxobutyl) benzonitrile Preparation 15		oil	66%	x	x

4-(1,2-dimethyl-3-oxobutyl) benzamide Preparation 16		100-102	90%	x	x
4-(3-oxocyclohexyl) benzamide Preparation 17		188-91	42%	x	x
4-(3-oxocyclopentyl) benzamide Preparation 18		203-4	43%	x	x
4-(1,1-dimethyl-3-oxobutyl) benzamide Preparation 19		106-8	61%	x	x
4-(2-oxocycloheptyl-methyl) benzonitrile Preparation 20		oil	54%	x	x
4-(2,2-dimethyl-3-oxobutyl) benzonitrile Preparation 21		oil	72%	x	x
4-(2,2-dimethyl-3-oxobutyl) benzamide Preparation 22		127-131	62%	x	x
5-(2-methyl-3-oxobutyl)-2-thiophene sulfonamide Preparation 23		oil	low	x	x
4-((2-oxocycloheptyl) methyl)benzamide Preparation 24		132-4	88%	x	x

4-((2-oxocyclopentyl) methyl) benzonitrile Preparation 25		oil	62%	x	x
4-((2-oxocyclopentyl) methyl)benzamide Preparation 26		138-142	81%	x	x
4-((2-oxocyclohexyl) methyl) benzonitrile Preparation 27		oil	55%	x	x
4-((2-oxocyclohexyl) methyl)benzamide Preparation 28		167-70	90%	x	x
2-fluoro-4-(2-methyl-3-oxobutyl) benzonitrile Preparation 29		oil	42%	x	x
2-fluoro-4-(2-methyl-3-oxobutyl) benzamide Preparation 30		112-15	93%	x	x
5-(2-methyl-3-oxobutyl)-2-morpholinosulfonyl) -thiophene Preparation 31		oil	15%	x	x
3-methyl-4-(2-methyl-3-oxobutyl) benzonitrile Preparation 32		oil	64%	x	x

(3-methyl-4-(2-methyl-3-oxobutyl) benzamide Preparation 33		105-7	71%	x	x
4-(2-ethyl-3-oxobutyl)benzoic acid Preparation 34			24%	x	x
(2S)-3-amino-1-(3-methylphenoxy)-2-propanol Preparation 35		158-62	low	x	x
(2S)-3-amino-1-(2-fluoro-thiophenyl)-2-propanol Preparation 36		50-3	75%	x	x
(2S)-3-amino-1-(3-fluoro-thiophenol)-2-propanol Preparation 37		115-19	45%	x	x
(2S)-3-amino-1-(4-fluoro-thiophenol)-2-propanol Preparation 38		67-70	44%	x	x
(2S)-3-amino-1-(3-hydroxy-thiophenol)-2-propanol Preparation 39		oil	15%	x	x
(2S)-3-amino-1-(3-difluoro-methylphenoxy)-2-propanol Preparation 40		79-83	72%	x	x

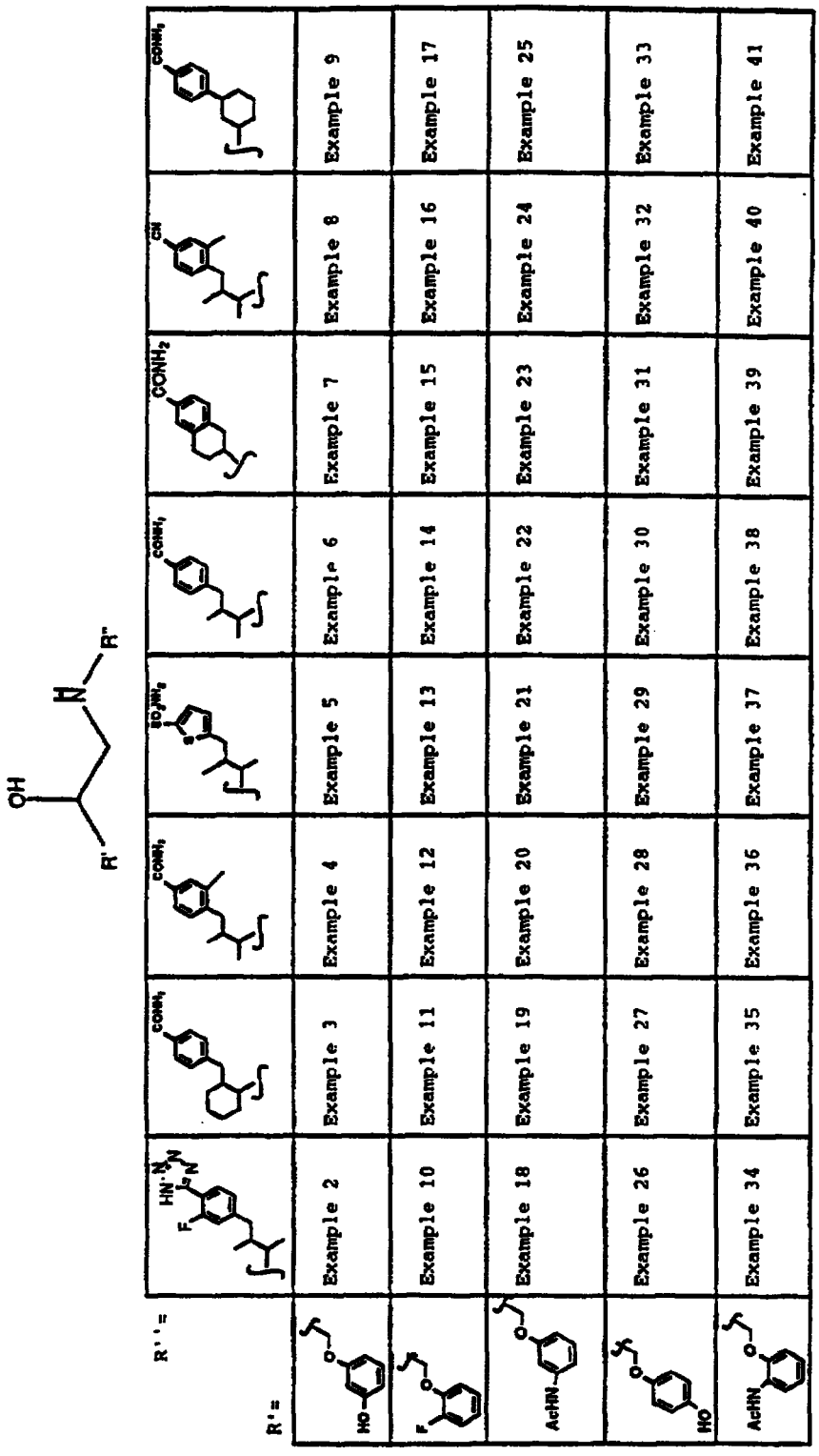
(2S)-3-amino-2-(3-hydroxy-6-ethylphenoxy)-2-propanol Preparation 41		hygro-scopic	60%	x	

Example 1

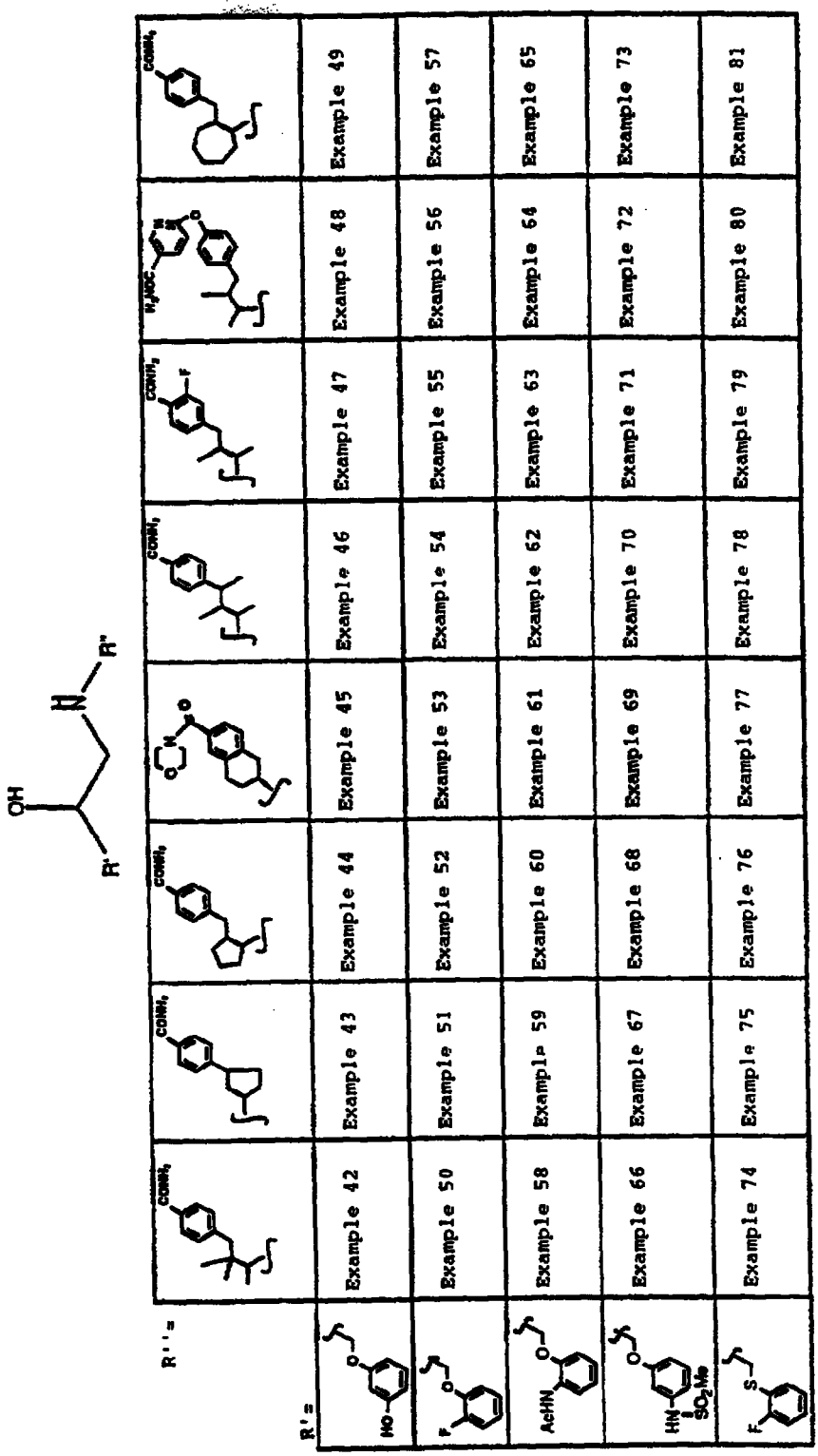
A 5x8 grid of 4 mL screw cap vials was arranged. To each of the eight rows of vials in the grid was added 33 µmol of ketone (from preparations 4-34, or commercially available), one ketone per row, as a stock solution in methanol (0.5M, 65 µl). If solubility was a problem, acetonitrile/methanol or DMF was used. To each column of vials in the grid was added 50 µmol of amine hydrochloride, one amine hydrochloride (or amine) (from preparations 2, 3, 36-41 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 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 2-81. 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

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 < 1mM. In the functional assay, dose titration furnishes an EC_{50} for isoproterenol of 1.1±0.5 mM.

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: asthma, depression, and gastrointestinal disorders such as gastrointestinal motility. 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 Formula I are preferably formulated prior to administration. Therefore, yet another embodiment of the present invention is a pharmaceutical formulation comprising a compound of Formula I 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 example is illustrative only and is not intended to limit the scope of the invention in any way.

Formulation 1

Hard gelatin capsules are prepared using the following ingredients:

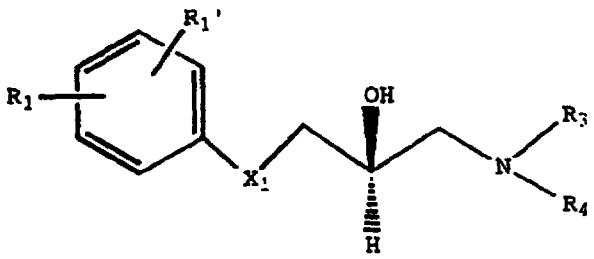
	Quantity (mg/capsule)
4-{3-[2-hydroxy-3-(3-hydroxyphenyloxy)-propylamino]-2-methylbutyl}benzamide	25
starch, dried	425
magnesium stearate	10
Total	460 mg

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 Formula:



(I)

wherein:

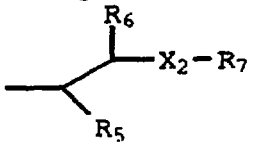
R_1 is OH, halo, SO_2NHR_2, CO_2R_2, $CONHR_2$, $NHCOR_2$, -NH(optionally substituted aryl), CF_3, or CF_2H;

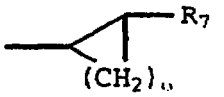
R_1' is H, halo, C_1-C_4 alkyl, OH, SO_2NHR_2, CO_2R_2, $CONHR_2$, $NHCOR_2$, CF_3 or CF_2H;

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

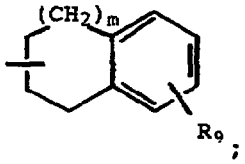
R_3 is H or C_1-C_4 alkyl;

R_4 is a moiety selected from the group consisting of:





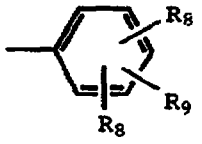
or



;

R_5 and R_6 are independently C_1-C_4 alkyl;

R_7 is an optionally substituted heterocycle or a group selected from the group consisting of:



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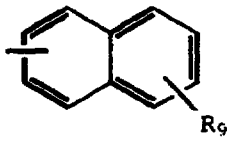

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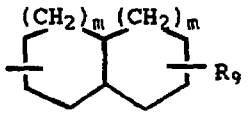

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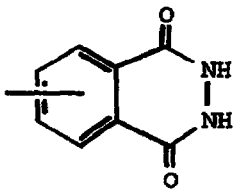

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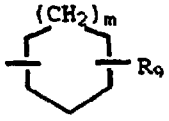

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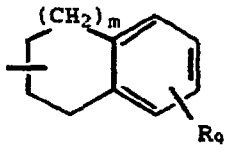

;

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

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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, $NR_{11}R_{12}$, aryl, heterocycle, optionally substituted aryl, optionally substituted heterocycle, or C_1-C_4 alkyl or C_2-C_4 alkenyl optionally substituted with CN;

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, $(CH_2)_n$ optionally substituted C_3-C_8 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, or combine with the nitrogen to which each are bound to form morpholinyl, piperidinyl, pyrrolidinyl, or piperazinyl;

X_1 is O or S;

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

m is 0 or 1;

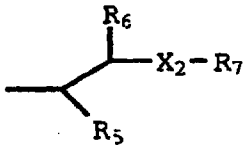
n is 0, 1, 2, or 3;

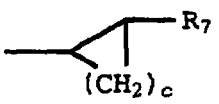
o is 1, 2, 3, 4, 5, or 6;

or a pharmaceutically acceptable salt or solvate thereof.

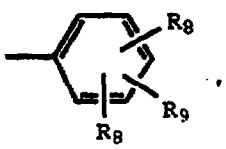
2. A compound of Claim 1 wherein R_1 is halo, CF_3, $CONHR_2$, or NH(optionally substituted aryl).

3. A compound of Claim 2 wherein R_4 is



, or


4. A compound of Claim 3 wherein R_7 is



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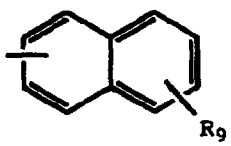

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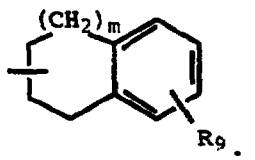

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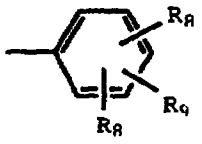
5. A compound of Claim 4 wherein R_9 is halo, CN, OR_{10}, CO_2R_2, $CONR_{11}R_{12}$, SR_2, SO_2R_2, $SO_2NR_{11}R_{12}$, SOR_2, or $NR_{11}R_{12}$.

6. A compound of Claim 5 wherein R_7 is



, and

R_9 is halo, CN, or OR_{10}.

7. A method of treating Type II diabetes comprising administering to a patient in need thereof a compound of Claim 1.

8. A method of treating Type II diabetes comprising administering to a patient in need thereof a compound of Claim 2.

9. A method of treating Type II diabetes comprising administering to a patient in need thereof a compound of Claim 3.

10. A method of treating Type II diabetes comprising administering to a patient in need thereof a compound of Claim 4.

11. A method of treating Type II diabetes comprising administering to a patient in need thereof a compound of Claim 5.

12. A method of treating Type II diabetes comprising administering to a patient in need thereof a compound of Claim 6.

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

14. A method of treating obesity comprising administering to a patient in need thereof a compound of Claim 2.

15. A method of treating obesity comprising administering to a patient in need thereof a compound of Claim 3.

16. A method of treating obesity comprising administering to a patient in need thereof a compound of Claim 4.

17. A method of treating obesity comprising administering to a patient in need thereof a compound of Claim 5.

18. A method of treating obesity comprising administering to a patient in need thereof a compound of Claim 6.

19. A method of stimulating the β3 receptor comprising administering to a patient in need thereof a compound of Claim 1.

20. A method of stimulating the β3 receptors comprising administering to a patient in need thereof a compound of Claim 2.

21. A method of stimulating the β3 receptor comprising administering to a patient in need thereof a compound of Claim 3.

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22. A method of stimulating the β3 receptor comprising administering to a patient in need thereof a compound of Claim 4.

23. A method of stimulating the β3 receptor comprising administering to a patient in need thereof a compound of Claim 5.

24. A method of stimulating the β3 receptor comprising administering to a patient in need thereof a compound of Claim 6.

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

26. A pharmaceutical formulation comprising as an active ingredient a compound of Claim 2, associated with one or more pharmaceutically acceptable carriers, excipients or diluents.

27. A pharmaceutical formulation comprising as an active ingredient a compound of Claim 3, associated with one or more pharmaceutically acceptable carriers, excipients or diluents.

28. A pharmaceutical formulation comprising as an active ingredient a compound of Claim 4, associated with one or more pharmaceutically acceptable carriers, excipients or diluents.

29. A pharmaceutical formulation comprising as an active ingredient a compound of Claim 5, associated with one or more pharmaceutically acceptable carriers, excipients or diluents.

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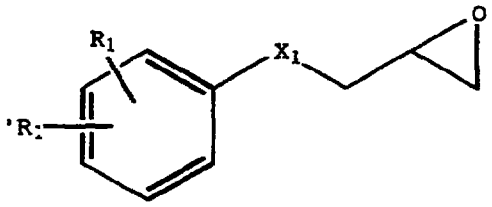
30. A pharmaceutical formulation comprising as an active ingredient a compound of Claim 6, associated with one or more pharmaceutically acceptable carriers, excipients or diluents.

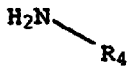
31. A process of preparing a compound of Formula I which comprises:

In step 1, reacting an epoxide of the formula:



(II)

with an amine of formula (B):



(III);

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

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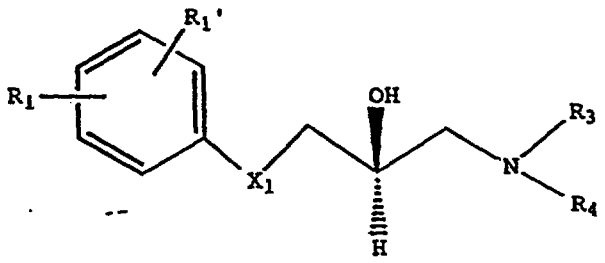
☑ Claim(s) : paged 38 to paged 41
☐ Drawing(s) : paged ..... to paged .....
☐ Abstract : paged ..... to paged .....
DATE OF RECEIPT 17.3.98

We claim:

1. A compound of Formula:



(I)

wherein:

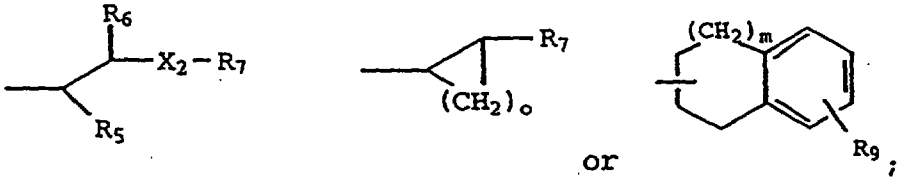
R_1 is OH, halo, SO_2NHR_2, CO_2R_2, $CONHR_2$, $NHCOR_2$, -NH(optionally substituted aryl), CF_3, or CF_2H;

R_1' is H, halo, C_1-C_4 alkyl, OH, SO_2NHR_2, CO_2R_2, $CONHR_2$, $NHCOR_2$, CF_3 or CF_2H;

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

R_3 is H or C_1-C_4 alkyl;

R_4 is a moiety selected from the group consisting of:

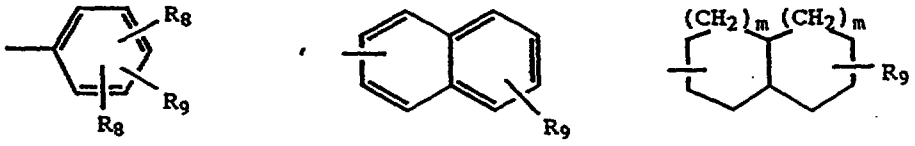


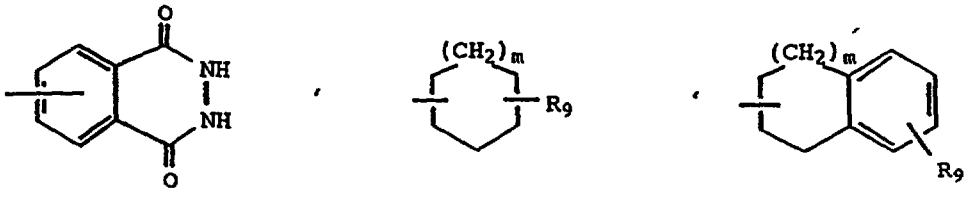
or

;

R_5 and R_6 are independently C_1-C_4 alkyl;

R_7 is an optionally substituted heterocycle or a group selected from the group consisting of:





;

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

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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, $NR_{11}R_{12}$, aryl, heterocycle, optionally substituted aryl, optionally substituted heterocycle, or C_1-C_4 alkyl or C_2-C_4 alkenyl optionally substituted with CN;

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, $(CH_2)_n$ optionally substituted C_3-C_8 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, or combine with the nitrogen to which each are bound to form morpholinyl, piperidinyl, pyrrolidinyl, or piperazinyl;

X_1 is O or S;

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

m is 0 or 1;

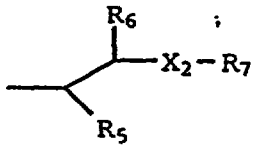
n is 0, 1, 2, or 3;

o is 1, 2, 3, 4, 5, or 6;

or a pharmaceutically acceptable salt or solvate thereof.

2. A compound of Claim 1 wherein R_1 is halo, CF_3, $CONHR_2$, or NH(optionally substituted aryl); and

R_4 is



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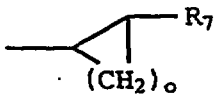
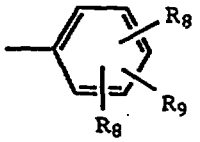


3. A compound of Claim 2 wherein R_7 is



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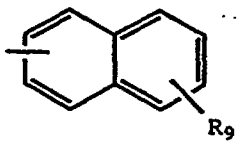
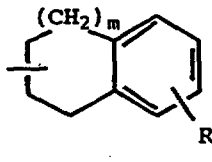


, or


; and

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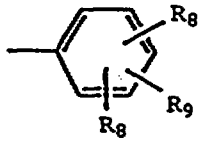
R_9 is halo, CN, OR_{10}, CO_2R_2, $CONR_{11}R_{12}$, SR_2, SO_2R_2, $SO_2NR_{11}R_{12}$, SOR_2, or $NR_{11}R_{12}$.

4. A compound of Claim 3 wherein R_7 is



, and

R_9 is halo, CN, CO_2R_2, or OR_{10}.

5. A compound of any of Claims 1 through 4 for use as a pharmaceutical.

6. A compound of any of Claims 1 through 4 for use in treating Type II diabetes.

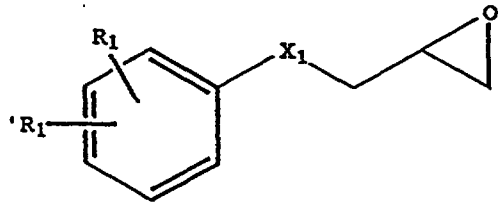
7. A compound of any of Claims 1 through 4 for use in treating obesity.

8. A compound of any of Claims 1 through 4 for use in agonizing the $ß_3$ receptor.

9. A pharmaceutical formulation comprising as an active ingredient a compound of any one of Claims 1 through 4, associated with one or more pharmaceutically acceptable carriers, excipients or diluents.

10. A process of preparing a compound of Formula I which comprises:

In step 1, reacting an epoxide of the formula:



(II)

with an amine of formula (B):

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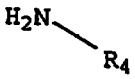

(III);

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

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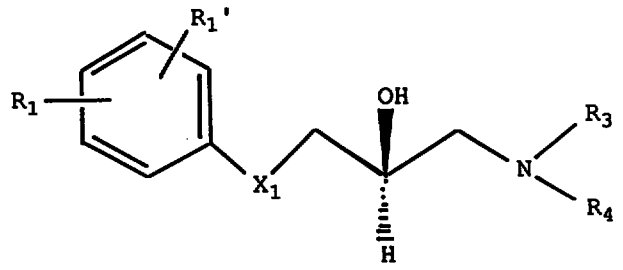
☐ Drawing(s) : paged ..... to paged .....
☐ Abstract : paged ..... to paged .....
DATE OF RECEIPT 16.4.99

We claim:

1. A compound of Formula:



(I)

wherein:

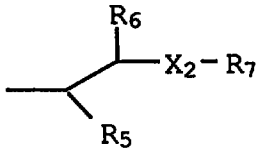
R_1 is OH, halo, SO_2NHR_2, CO_2R_2, $CONHR_2$, $NHCOR_2$, -NH(optionally substituted aryl), CF_3, or CF_2H;

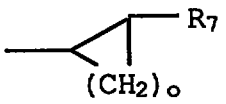
R_1' is H, halo, C_1-C_4 alkyl, OH, SO_2NHR_2, CO_2R_2, $CONHR_2$, $NHCOR_2$, CF_3 or CF_2H;

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

R_3 is H or C_1-C_4 alkyl;

R_4 is a moiety selected from the group consisting of:





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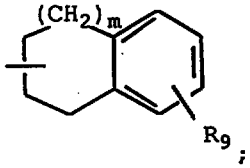
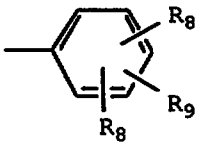


;

R_5 and R_6 are independently C_1-C_4 alkyl;

R_7 is an optionally substituted heterocycle or a group selected from the group consisting of:



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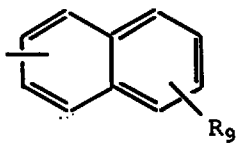

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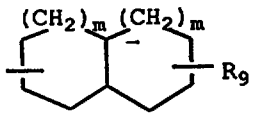

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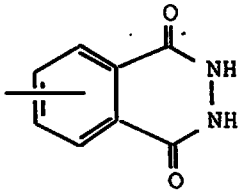

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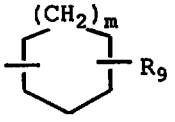

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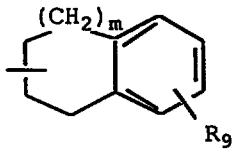


;

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, $NR_{11}R_{12}$, aryl, heterocycle, optionally substituted aryl,

optionally substituted heterocycle, or C_1-C_4 alkyl or C_2-C_4 alkenyl optionally substituted with CN;

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, $(CH_2)_n$ optionally substituted C_3-C_8 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, or combine with the nitrogen to which each are bound to form morpholinyl, piperidinyl, pyrrolidinyl, or piperazinyl;

X_1 is O or S;

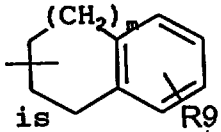
X_2 is absent or a 1 to 5 carbon straight or branched alkylene;

m is 0 or 1;

n is 0, 1, 2, or 3;

o is 1, 2, 3, 4, 5, or 6;

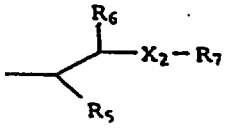
or a pharmaceutically acceptable salt or solvate thereof;

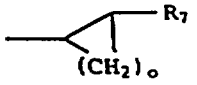
with the proviso that when R_4 is 

, then R_{10} is not C_1-C_4 alkyl.

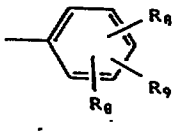
2. A compound of Claim 1 wherein R_1 is halo, CF_3, $CONHR_2$, or NH(optionally substituted aryl); and

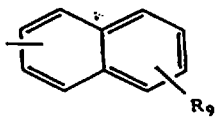
R_4 is

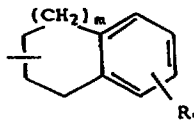


, or 

3. A compound of Claim 2 wherein R_7 is



, 

, or 

; and

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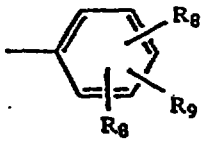
R_9 is halo, CN, OR_{10}, CO_2R_2, $CONR_{11}R_{12}$, SR_2, SO_2R_2, $SO_2NR_{11}R_{12}$, SOR_2, or $NR_{11}R_{12}$.

4. A compound of Claim 3 wherein R_7 is



, and

R_9 is halo, CN, CO_2R_2, or OR_{10}.

5. A compound of any of Claims 1 through 4 for use as a pharmaceutical.

6. A compound of any of Claims 1 through 4 for use in treating Type II diabetes.

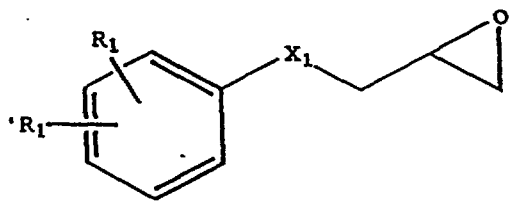
7. A compound of any of Claims 1 through 4 for use in treating obesity.

8. A compound of any of Claims 1 through 4 for use in agonizing the $ß_3$ receptor.

9. A pharmaceutical formulation comprising as an active ingredient a compound of any one of Claims 1 through 4, associated with one or more pharmaceutically acceptable carriers, excipients or diluents.

10. A process of preparing a compound of Formula I which comprises:

In step 1, reacting an epoxide of the formula:



(II)

with an amine of formula (B):

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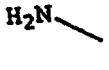

(III);

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

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*NO COVER LETTER

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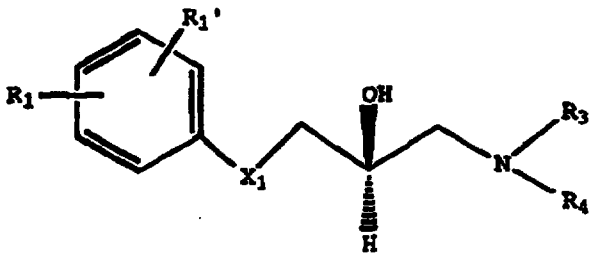
(54) Title: SELECTIVE β_3 ADRENERGIC AGONISTS

(57) Abstract

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 receptor agonists useful in the treatment of Type II diabetes and obesity. The invention provides compounds and method of treating Type II diabetes, comprising administering to a patient in need thereof compounds of formula (I).



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