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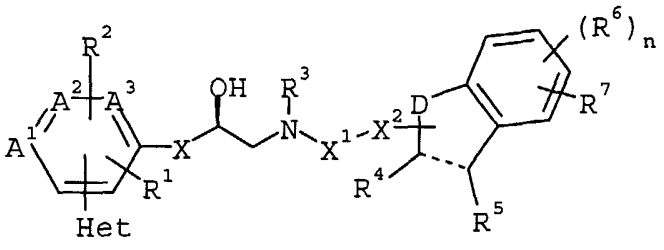
WO 03/016307 A1

(54) Title: β3 ADRENERGIC AGONISTS



(I)

(57) Abstract: The present invention relates to a β3 adrenergic receptor agonist of formula (I); or a pharmaceutical salt thereof; which is capable of increasing lipolysis and energy expenditure in cells and, therefore, is useful, *e.g.*, for treating Type 2 diabetes and/or obesity.

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For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

β_3 Adrenergic Agonists

The present invention is in the field of medicine, particularly in the treatment of Type 2 diabetes and obesity. More specifically, the present invention relates to β_3 adrenergic receptor agonists useful in the treatment of Type 2 diabetes and obesity.

The current preferred treatment for Type 2, 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 2 diabetes or obesity.

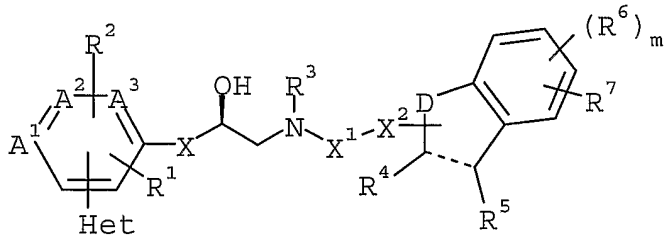
One therapeutic opportunity that has recently been recognized involves the relationship between adrenergic receptor stimulation and anti-hyperglycemic effects. Compounds that act as β_3 receptor agonists have been shown to exhibit a marked effect on lipolysis, thermogenesis and serum glucose levels in animal models of Type 2 (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. Stimulation of the β_1 and β_2 receptors can cause adverse effects such as tachycardia, arrhythmia, or tremors. An agonist that is selective for the β_3 receptor over the β_1 and β_2 receptors is, therefore, more desirable for treating Type 2 diabetes or obesity relative to a non-selective agonist.

However, recent studies have suggested the presence of an atypical β receptor associated with atrial tachycardia in rats (*Br. J. of Pharmacol.*,118:2085-2098, 1996). In other words, compounds that are not agonists of the β_1 and β_2 receptors can still modulate tachycardia through activation of a yet to be discovered β_4 or through some other unknown pathway.

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 relates to a compound of formula I:



I;

wherein:

the dashed line represents a single or double bond;

m is 0, 1 or 2;

A^1, A^2 and A^3 are carbon or nitrogen provided that only one of A^1, A^2 and A^3 can be nitrogen;

D is NR^8, O or S;

Het is an optionally substituted, optionally benzofused 5 or 6 membered heterocyclic ring;

R^1 and R^2 are independently H, halo, hydroxy, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_4 haloalkyl, or SO_2(C_1-C_6 alkyl);

R^3 is H or C_1-C_6 alkyl;

R^4 forms a bond with X^2 or is H, cyano, C_1-C_6 alkyl, $CONR^9R^9$ or CO_2R^9;

R^5 forms a bond with X^2 or is H or C_1-C_6 alkyl;

R^6 is independently at each occurrence halo, hydroxy, cyano, C_1-C_6 alkyl, C_1-C_4 haloalkyl or C_1-C_6 alkoxy;

R^7 is H, CO_2R^{10}, $CONR^{10}R^{10}$, $CH{=}CHR^{11}$, $CH_2CH_2R^{11}$, $NR^{10}R^{10}$, $NR^{10}SO_2R^{10}$, $O(CR^{12}R^{13})_nR^{14}$, $O(CR^{12}R^{13})_pR^{15}$, SO_2R^{10}, $SO_2NR^{10}R^{10}$, optionally substituted phenyl or optionally substituted heterocycle;

R^8 forms a bond with X^2 or is H or C_1-C_6 alkyl;

R^9 and R^{10} are independently at each occurrence H, C_1-C_6 alkyl or phenyl; or when two R^9 or two R^{10} moieties are connected to the same nitrogen atom, then said R^9 or R^{10} moieties may combine with the nitrogen to which they are attached to form a pyrollidinyl, piperidinyl or hexamethyleneimino ring;

R^{11} is cyano, CO_2R^{16}, $CONR^{16}R^{16}$, $CONR^{16}SO_2R^{16}$, SO_2R^{16}, heterocycle or optionally substituted phenyl;

R^{12} and R^{13} are independently at each occurrence H or C_1-C_6 alkyl;

R^{14} is hydrogen, CO_2R^{17}, $CONR^{17}R^{17}$, SO_2R^{17}, $SO_2NR^{17}R^{17}$, optionally substituted phenyl or optionally substituted heterocycle,

R^{15} is cyano, $NR^{18}R^{18}$, $NR^{18}SO_2R^{18}$ or OR^{18};

R^{16}, R^{17} and R^{18} are independently at each occurrence H, C_1-C_6 alkyl or phenyl; or when two R^{16} or two R^{17} or two R^{18} moieties are connected to the same nitrogen atom, then said R^{16} or R^{17} or R^{18} moieties may combine with the nitrogen to which they are attached to form a pyrollidinyl, piperidinyl or hexamethyleneimino ring;

n is 0, 1, 2 or 3;

p is 1, 2 or 3;

X is absent or is OCH_2 or SCH_2;

X^1 is absent or is $(CR^{19}R^{20})_q$;

X^2 is absent or is CO, $CONR^{21}$ or $NR^{21}CO$;

q is 1, 2, 3, 4 or 5;

R^{19} and R^{20} are independently at each occurrence H or C_1-C_6 alkyl; or R^{19} and R^{20} combine with the carbon to which they are both attached to form a C_3-C_7 carbocyclic ring; and

R^{21} is H or C_1-C_6 alkyl; or a pharmaceutical salt thereof.

The present invention also relates to processes for preparing, as well as novel pharmaceutical formulations containing, a compound of formula I. In another embodiment, the pharmaceutical formulations of the present invention may be adapted for use in treating Type 2 diabetes and obesity and for agonizing the β_3 receptor.

The present invention also relates to methods for treating Type 2 diabetes and obesity, as well as a method for agonizing the β_3 receptor employing a compound of formula I.

In addition, the present invention relates to a compound of formula I for use in treating Type 2 diabetes and obesity as well as a compound of formula I for use in agonizing the β_3 receptor. The present invention is further related to the use of a compound of formula I for the manufacture of a medicament for treating Type 2 diabetes and obesity as a well as for agonizing the β_3 receptor.

For the purposes of the present invention, as disclosed and claimed herein, the following terms are defined below.

The term "halo" represents fluoro, chloro, bromo, or iodo.

The term "C_1-C_6 alkyl" represents a straight, branched or cyclic hydrocarbon moiety having from one to six carbon atoms, *e.g.*, methyl, ethyl, n-propyl, isopropyl, cyclopropyl, n-butyl, isobutyl, sec-butyl, t-butyl, cyclobutyl, pentyl, cyclopentyl, hexyl, cyclohexyl and the like. The term "C_1-C_4 alkyl" refers specifically to methyl, ethyl, n-propyl, isopropyl, cyclopropyl, n-butyl, isobutyl, sec-butyl, t-butyl and cyclobutyl. A "C_1-C_4 haloalkyl" group is a C_1-C_4 alkyl moiety substituted with up to six halo atoms, preferably one to three halo atoms. An example of a haloalkyl group is trifluoromethyl. A "C_1-C_6 alkoxy" group is a C_1-C_6 alkyl moiety connected through an oxy linkage.

The term "optionally substituted" as used herein means an optional substitution of one to three, preferably one or two groups independently selected from halo, hydroxy, oxo, cyano, nitro, phenyl, benzyl, triazole, tetrazole, 4,5-dihydrothiazole, C_1-C_6 alkyl, C_1-C_4 haloalkyl, C_1-C_6 alkoxy, COR^{22}, $CONR^{22}R^{22}$, CO_2R^{22}, $NR^{22}R^{22}$, $NR^{22}COR^{23}$, $NR^{22}SO_2R^{23}$, $OCOR^{23}$, OCO_2R^{22}, $OCONR^{22}R^{22}$, SR^{22}, SOR^{23},

SO_2R^{23} and $SO_2(NR^{22}R^{22})$, where R^{22} is independently at each occurrence H, C_1-C_6 alkyl, phenyl or benzyl and R^{23} is independently at each occurrence C_1-C_6 alkyl, phenyl or benzyl.

The terms "heterocycle" and "heterocyclic" represent a stable, saturated, partially unsaturated, fully unsaturated or aromatic 5 or 6 membered ring, said ring having from one to four heteroatoms that are independently selected from the group consisting of sulfur, oxygen, and nitrogen. The heterocycle may be attached at any point which affords a stable structure. Representative heterocycles include 1,3-dioxolane, 4,5-dihydrooxazole, furan, imidazole, imidazolidine, isothiazole, isoxazole, morpholine, oxadiazole, oxazole, oxazolidinedione, oxazolidone, piperazine, piperidine, pyrazine, pyrazole, pyrazoline, pyridazine, pyridine, pyrimidine, pyrrole, pyrrolidine, tetrazole, thiadiazole, thiazole, thiophene and triazole. Representative "benzofused" heterocycles include benzoxazole, benzimidazole, benzofuran, benzothiophene, benzothiazole, azaindole, and indole. Further specific examples of benzofused and non-benzofused heterocycles are described below in the Preparations and Examples sections.

The term "suitable solvent" refers to any solvent, or mixture of solvents, inert to the ongoing reaction that sufficiently solubilizes the reactants to afford a medium within which to effect the desired reaction.

The term "patient" includes human and non-human animals such as companion animals (dogs and cats and the like) and livestock animals. Livestock animals are animals raised for food production. Ruminants or "cud-chewing" animals such as cows, bulls, heifers, steers, sheep, buffalo, bison, goats and antelopes are examples of livestock. Other examples of livestock include pigs and avians (poultry) such as chickens, ducks, turkeys and geese. Yet other examples of livestock include fish, shellfish and crustaceans raised in aquaculture. Also included are exotic animals used in food production such as alligators, water buffalo and ratites (e.g., emu, rheas or ostriches).

The preferred patient of treatment is a human.

The terms "treating" and "treat", as used herein, include their generally accepted meanings, *i.e.*, preventing, prohibiting, restraining, alleviating, ameliorating, slowing, stopping, or reversing the progression or severity of a pathological condition, or sequela thereof, described herein.

The terms "preventing", "prevention of", "prophylaxis", "prophylactic" and "prevent" are used herein interchangeably and refer to reducing the likelihood that the recipient of a compound of formula I will incur or develop any of the pathological conditions, or sequela thereof, described herein.

As used herein, the term "effective amount" means an amount of a compound of formula I that is capable of treating conditions, or detrimental effects thereof, described herein or that is capable of agonizing the β_3 receptor.

The term "selective β_3 receptor agonist" means a compound that displays preferential agonism of the β_3 receptor over agonism of the β_1 or β_2 receptor. Thus, β_3 selective compounds behave as agonists for the β_3 receptor at lower concentrations than that required for similar agonism at the β_1 and β_2 receptors. A β_3 selective compound also includes compounds that behave as agonists for the β_3 receptor and as antagonists for the β_1 and β_2 receptors.

The term "pharmaceutical" when used herein as an adjective means substantially non-deleterious to the recipient patient.

The term "formulation", as in pharmaceutical formulation, is intended to encompass a product comprising the active ingredient(s) (compound of formula I), and the inert ingredient(s) that make up the carrier, as well as any product which results, directly or indirectly, from combination, complexation or aggregation of any two or more of the ingredients, or from dissociation of one or more of the ingredients, or from other types of reactions or interactions of one or more of the ingredients. Accordingly, the pharmaceutical formulations of the present invention encompass any composition made by admixing a compound of the present invention and a pharmaceutical carrier.

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

Because certain compounds of the invention contain an acidic moiety (e.g., carboxy), the compound of formula I may exist as a pharmaceutical base addition salt 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.

Because certain compounds of the invention contain a basic moiety (e.g., amino), the compound of formula I can also exist as a pharmaceutical acid addition salt. Such salts include the salicylate, 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, glycolate, maleate, tartrate, methanesulfonate, propanesulfonate, naphthalene-l-sulfonate, naphthalene-2-sulfonate, mandelate and like salts. Preferred acid addition salts include the hydrochloride and glycolate salts.

Preferred Compounds of the Invention

Certain compounds of the invention are particularly interesting and are preferred. The following listing sets out several groups of preferred compounds. It will be understood that each of the listings may be combined with other listings to create additional groups of preferred compounds.

a) the bond represented by a dashed line is a double bond;

b) m is 0 or 1;

c) m is 0;

d) A^1, A^2 and A^3 are carbon;

e) D is NH;

f) Het is at the ortho-position relative to X;

g) Het is an optionally substituted 5-membered, non-benzofused ring;

h) Het is selected from benzothiophene; furan; isoxazole; oxazole; pyrrole; tetrazole and thiophene; wherein said Het moieties are optionally substituted once with methyl, cyano, SO_2NH_2 or $COCH_3$;

i) Het is pyrrol-1-yl;

j) Het is thien-2-yl optionally substituted once with methyl, cyano, SO_2NH_2 or $COCH_3$;

k) Het is thien-2-yl optionally substituted once with cyano, SO_2NH_2 or $COCH_3$;

l) Het is thien-2-yl;

m) R^1 is H, methyl, ethyl, CF_3, chloro or fluoro;

n) R^1 is H, methyl, chloro or fluoro;

o) R^1 is H or fluoro;

p) R^1 is H;

q) R^2 is H, methyl, ethyl, CF_3, chloro or fluoro;

r) R^2 is H, methyl, chloro or fluoro;

s) R^2 is H or fluoro;

t) R^2 is H;

u) R^3 is H;

v) R^4 is H;

w) R^5 forms a bond with X^2;

x) R^6 is cyano at each occurrence;

y) R^7 is at the 6- or 7-position of the indole, benzofuran or benzothiophene ring system to which it is attached;

z) R^7 is at the 7-position;

aa) R^7 is H or CO_2H;

bb) R^7 is $CH=CHR^{11}$; R^{11} is tetrazole, $CONR^{16}R^{16}$ or CO_2R^{16}; and R^{16} is independently H or C_1-C_4 alkyl at each occurrence;

cc) R^7 is $CH_2CH_2R^{11}$, R^{11} is CO_2R^{16} or $CONR^{16}R^{16}$, and R^{16} is independently H or C_1-C_4 alkyl at each ccurrence;

dd) R^7 is $CH_2CH_2R^{11}$, R^{11} is 1,2,3,4-tetrazole or phenyl substituted once with $SO_2NR^{22}R^{22}$, and R^{22} is independently H or C_1-C_4 alkyl at each occurrence;

ee) R^7 is thienyl substituted once with CO_2H or phenyl substituted once with CO_2H;

ff) R^7 is $OCH_2CONHSO_2(C_1$-C_4 alkyl); $OCH_2CH_2NHSO_2(C_1$-C_4 alkyl); OCH_2CN; $OCH_2CO_2R^{17}$; $OCH_2CONR^{18}R^{18}$; O(pyridine) wherein said pyridine moieity is substituted once with cyano or CO_2H; OCH_2(tetrazole) or OCH_2(4,5-dihydrothiazole), and R^{17} and R^{18} are independently H or C_1-C_4 alkyl at each occurrence;

gg) R^7 is $NHSO_2R^{10}$ and R^{10} is C_1-C_4 alkyl or phenyl;

hh) R^7 is $CH=CHR^{11}$; R^{11} is tetrazole or CO_2H;

ii) R^7 is $CH_2CH_2R^{11}$ and R^{11} is 1,2,3,4-tetrazole;

jj) R^7 is OCH_2CN; OCH_2CO_2H; or OCH_2(tetrazole);

kk) R^8 is H;

ll) X is OCH_2 and is connected through the 4-position of the indole ring (as shown in all of the exemplified compounds herein);

mm) X^1 is $(CR^{19}R^{20})_q$ where R^{19} and R^{20} are independently H or methyl at each occurrence and q is 2;

nn) X^1 is $C(CH_3)_2CH_2$;

oo) X^2 is absent;

pp) the compound of formula I is an acid addition salt;

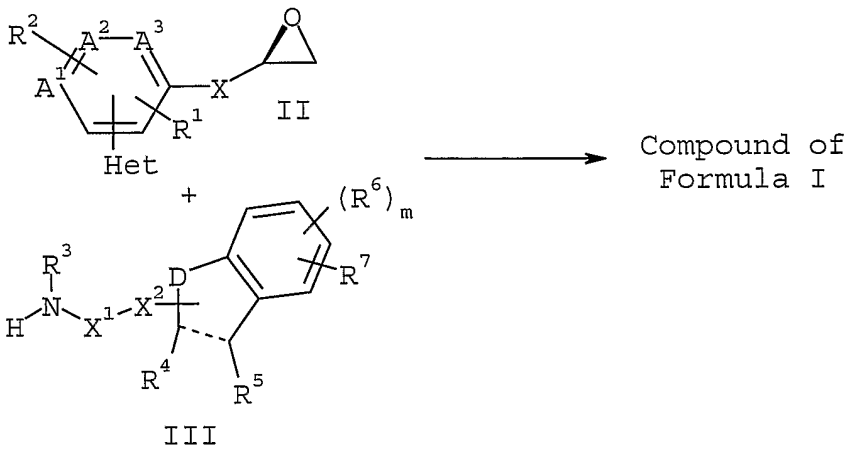
qq) the compound of formula I is the hydrochloride salt;

rr) the compound of formula I is the glycolate salt.

Synthesis

The compound of formula I may be prepared as described in the following Schemes and Examples.

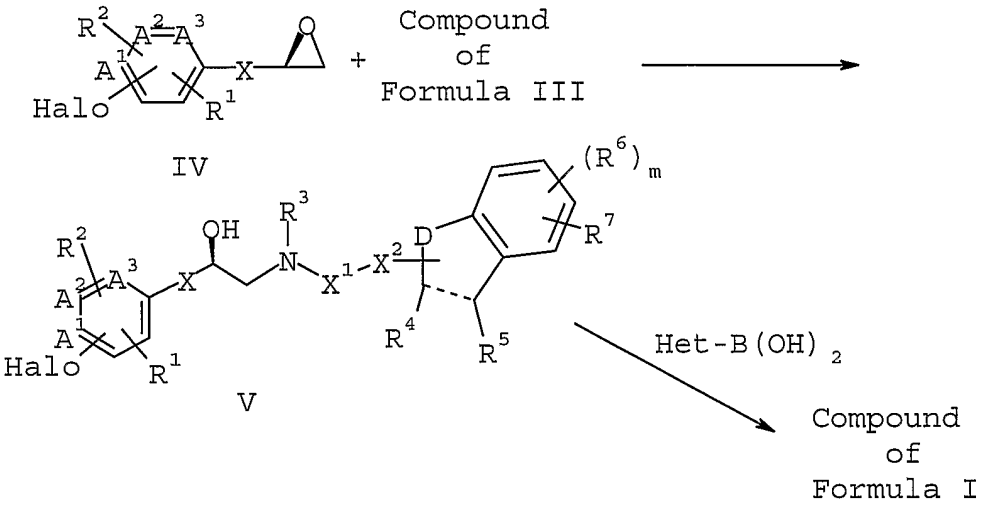
Scheme 1



The reaction of Scheme 1 may be carried out under conditions appreciated in the art for the amination of epoxides. For example, the epoxide of formula II may be combined with an amine of formula III in a lower alcohol, dimethylformamide, dimethylsulfoxide, or acetone, preferably ethanol, isopropanol, n-butanol or t-butanol, at room temperature to the reflux temperature of the reaction mixture, preferably between 40°C - 90°C. The reaction may also be carried out under conditions generally described in Atkins, *et al.*, *Tet. Let.*, 27:2451, 1986. These conditions include mixing the reagents in the presence of trimethylsilyl acetamide in a polar aprotic solvent such as acetonitrile, dimethylformamide, acetone, dimethylsulfoxide, dioxane, diethylene glycol dimethyl ether, tetrahydrofuran, or other polar aprotic solvents in which the reagents are soluble.

The compound of formula I may also be prepared via a Suzuki coupling reaction as shown in Scheme 2.

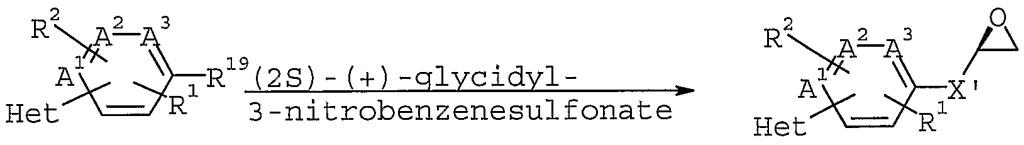
Scheme 2



A compound of formula IV may be reacted with a compound of formula III as described above in Scheme 1. The compound of formula V (an aryl halide) may then be reacted with a heteroaryl boronic acid, an aryl boronic ester, or an aryl boronic cyclic ester, preferably an aryl boronic acid, under conditions appreciated in the art for the coupling of aromatic halides with aryl boronic acids and their derivatives. This coupling is known in the art generally as a Suzuki coupling. The skilled artisan will recognize that an aryl triflate may also be employed in the present Suzuki coupling as an alternative to employing an aryl halide.

The epoxide starting materials employed in Schemes 1 and 2 may be prepared by techniques recognized and appreciated by one skilled in the art. See, *e.g.*, U.S. Patent No. 4,663,334; European Patent Application 171209; Korn, et al., *J. Pharm. Sci.*, 69(9):1010-13, 1980 and references cited below in the Preparations section for representative and/or analogous procedures for preparing the epoxides of formula II and IV. To illustrate, epoxides of formula II, where X is OCH_2 or SCH_2, may be prepared according to the procedure detailed in Scheme 3 wherein R^{19} is OH or SH and X' is OCH_2 or SCH_2.

Scheme 3



VI II(a)

Equimolar amounts of a compound of formula VI and (2S)-(+)-glycidyl 3-nitrobenzenesulfonate may be dissolved in an inert solvent such as acetone and treated with a slight excess of a weak base, such as potassium carbonate. The suspension may then be heated at reflux for 16-20 hours with stirring to provide a compound of formula II(a). Compounds of formula IV, where X is OCH_2 or SCH_2, may be prepared in an analogous fashion.

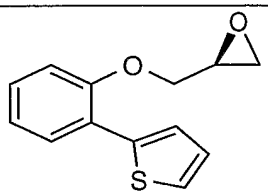
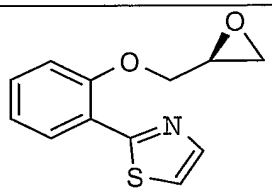
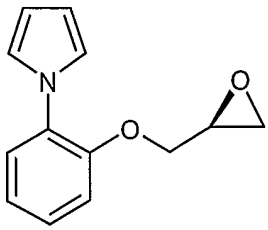
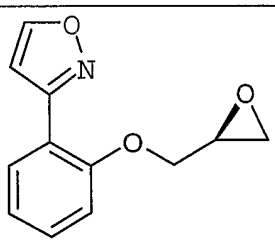
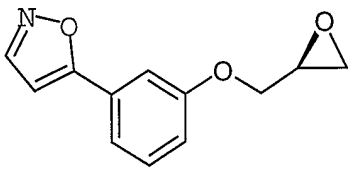
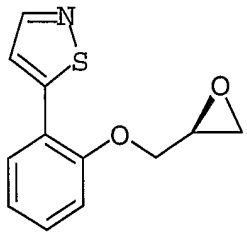
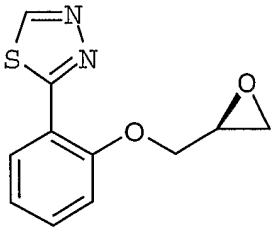
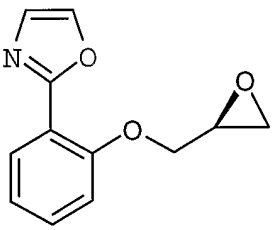
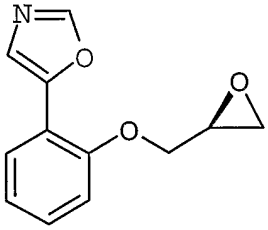
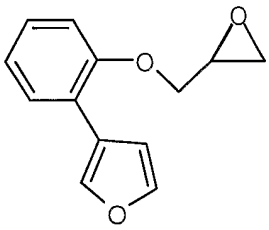
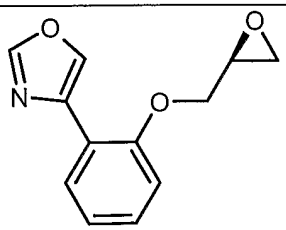
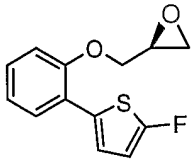
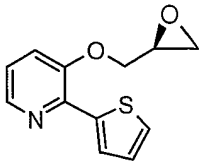
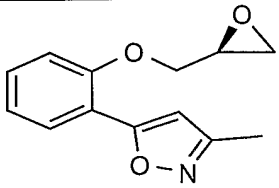
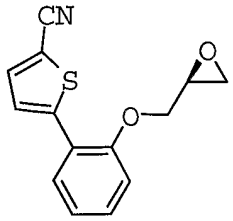
The amines of formula III employed in Scheme 1 may also be prepared by techniques recognized and appreciated by one skilled in the art. See, *e.g.*, the Preparations below or the references cited therein for representative and/or analogous procedures for preparing the amines of formula III.

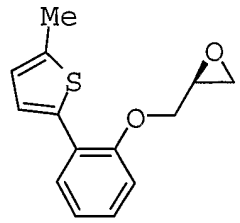
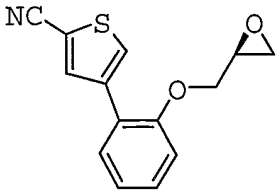
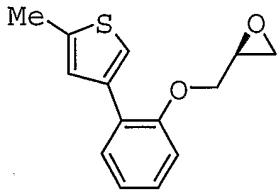
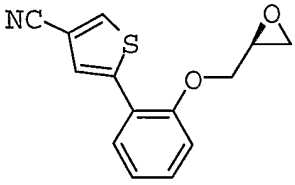
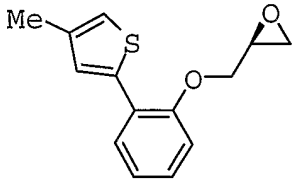
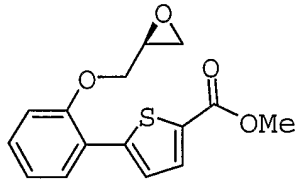
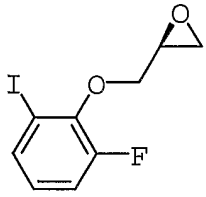
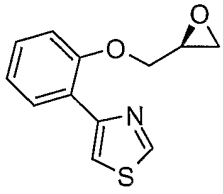
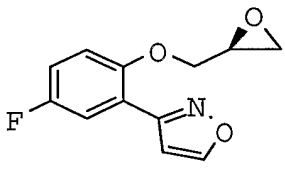
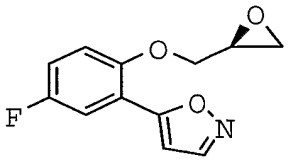
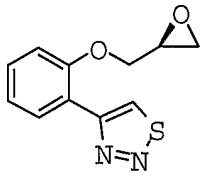
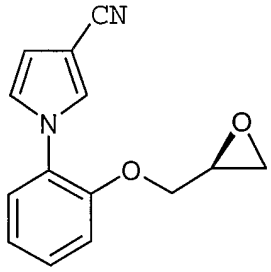
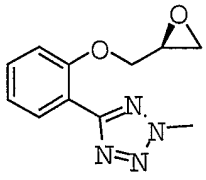
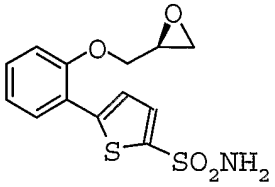
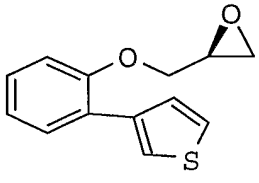
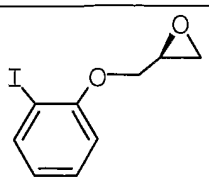
Compounds of formula VI and Het-$B(OH)_2$ are either commercially available, known in the art, or can be prepared by methods known in the art or described herein.

Epoxides of Formula II and IV

Epoxides 1-21 and 23-30 are prepared as described below for use as described in Scheme 1. Epoxide 22 and 31 are prepared as described below for use as described in Scheme 2. These epoxides are pictured below in Table 1.

Table 1

 1	 2	 3
 4	 5	 6
 7	 8	 9
 10	 11	 12
 13	 14	 15

 16	 17	 18
 19	 20	 21
 22	 23	 24
 25	 26	 27
 28	 29	 30
	 31	

Epoxide 1

A mixture of 2-(thien-2-yl)phenol (*J. Heterocycl. Chem.*, 22(6):1667-9, 1985; 1 equivalent), (2S)-glycidyl 3-nitrobenzenesulfonate (1.2 equivalents), potassium carbonate (1.2 equivalents) and acetone are refluxed for 16 hours, cooled to room temperature and the solids removed via filtration. The filtrate is concentrated and the crude product purified on silica gel (ethyl acetate/hexane) to give the title epoxide.

Epoxide 5

A solution of 3-(dimethylamino)-1-(3-hydroxyphenyl)-2-propen-1-one (2.2 g, 11.5 mmol) and hydroxylamine hydrochloride (1.17 g, 16.8 mmol) in 45 ml dioxane/water 1:1 is heated for 2 hours at 60°C. The reaction is poured into ice-water and the precipitate is collected by filtration, washed with water, and dried *in vacuo* to give 1.4 g of 3-(5-isoxazolyl)phenol (75.5%). This phenolic product is reacted with (2S)-glycidyl 3-nitrobenzenesulfonate substantially as described for Epoxide 1 to give 1.33 g of the title epoxide (70%).

Epoxide 9

A mixture of 2-methoxybenzaldehyde (10.0 g, 73.4 mmol), tosylmethylisocyanide (14.34 g, 73.4 mmol) and potassium carbonate (10.14 g, 73.4 mmol) in 220 ml methanol is heated at reflux for 6 hours. The solvent is removed under reduced pressure and the residue poured into ice-water (800 ml). The precipitate is collected by filtration, washed with water, and dried *in vacuo* to give 9.05 g of 5-(2-methoxyphenyl)oxazole (70 %). Boron tribromide (1M in dichloromethane, 36 ml) is added slowly to a cold solution (0°C) of the above oxazole (3.0 g, 17.1 mmol) in dichloromethane (215 ml). After stirring overnight at room temperature, ice-water (50 ml) is added carefully. The aqueous layer is extracted with dichloromethane (50 ml), and the combined organic layers are dried over sodium sulfate and concentrated under reduced pressure. The precipitate which formed after addition of dichloromethane (70 ml) is collected by filtration, heated

with dichloromethane (15 ml), and filtered again to give 3.16 g of 2-(5-oxazolyl)phenol. This phenolic product is reacted with (2S)-glycidyl 3-nitrobenzenesulfonate substantially as described for Epoxide 1 to give 400 mg of the title epoxide (9.5%).

Epoxide 11

A mixture of 2-bromo-1-(2-benzyloxyphenyl)ethanone (*J. Med. Chem.*, 35:3045, 1992; 10.0 g, 32.77 mmol) and sodium formate (4.46 g, 65.6 mmol) in dry dimethylformamide (100 ml) is stirred at room temperature overnight. The mixture is poured into water (400 ml) and extracted with dichloromethane (2 x 100 ml). The combined extracts are dried over sodium sulfate and concentrated under reduced pressure. The residue is dissolved in acetic acid (100 ml), treated with ammonium acetate (12.62 g, 163.7 mmol), and the mixture is heated for 3 hours. After cooling, the mixture is diluted with water (400 ml) and extracted with dichloromethane (2 x 100 ml). The combined organic layers are washed with saturated aqueous sodium bicarbonate solution (2 x 100 ml), dried over sodium sulfate, and concentrated *in vacuo*. 4-(2-Benzyloxyphenyl)oxazole (1.99 g, 24%) is obtained after chromatography (silica gel, dichloromethane).

To a solution of the oxazole from above (1.99 g, 7.92 mmol) in dichloromethane (20 ml) is added 10% palladium on carbon (1.99 g). The mixture is put under an atmosphere of hydrogen, stirred at room temperature overnight, then filtered through Celite. The solvent is removed under reduced pressure to give 1.15 g of 2-(oxazol-4-yl)phenol (90%).

The title epoxide (1.05 g, 72%) is prepared from the above phenol (1.08 g, 6.7 mmol) and (2S)-glycidyl 3-nitrobenzenesulfonate substantially as described for Epoxide 1.

Epoxide 12

Epoxide 12 is prepared from 2-methoxyphenylboronic acid and 2-bromo-5-fluorothiophene; by a procedure substantially similar to that described for Epoxide 30.

Epoxide 13

To dioxane is added 3-methoxypyridyl-2-boronic acid (1 equivalent), 2-bromothiophene (0.9 equivalents) and potassium carbonate. Palladium (0) tetrakistriphenylphoshine (0.03 equivalents) is then added and the resulting mixture is heated to 85°C for 3 hours. The reaction is cooled to room temperature and poured into ethyl acetate and water. The aqueous layer is extracted twice with ethyl acetate. The organic extracts are combined, and dried over sodium sulfate, concentrated and the resulting residue is flash chromatographed in toluene/hexanes to afford 3-methoxy-2-(thien-2-yl)pyridine (90%).

The protected product from above is demethylated with pyridine hydrochloride neat at 200 degrees for 3 hours. The reaction is poured into ice/water and ethyl acetate is added. The layers are separated and the organic layer is washed with water, dried over sodium sulfate and concentrated. The resulting residue is flash chromatographed with ethyl acetate/hexanes to afford 3-hydroxy-2-(thien-2-yl)pyridine (77%). 3-Hydroxy-2-(thien-2-yl)pyridine is reacted with (2S)-glycidyl 3-nitrobenzenesulfonate substantially as described for Epoxide 1 to yield the title epoxide.

Epoxide 14

Epoxide 14 is prepared from 2-(3-methylisoxazol-5-yl)phenol (J. Org. Chem. 49:4419, 1984) and (2S)-glycidyl 3-nitrobenzenesulfonate by a procedure substantially similar to that described for Epoxide 1.

Epoxide 15

A solution of 5-bromothiophene-2-carbonitrile (1.25 g, 6.647 mmol) in 50 ml of dioxane is degassed with argon. Tetrakis(triphenylphosphine)palladium(0) (768 mg, 0.665 mmol) is added and the mixture stirred for 5 minutes. 2-Methoxybenzene boronic acid (2.02 g, 13.3 mmol) and 13.3 ml of aqueous 2 N sodium carbonate are successively added and the mixture is stirred for 16 hours at 85°C. Extractive work-up (2 x 50ml dichloromethane and 2 x 30 ml water). Organic phase is dried over sodium sulfate,

filtered and evaporated. The residue (4.05 g) is purified via flash column on silica (eluent: 100% hexane>hexane/ethyl acetate 96:4 gradient to give 1.37 g of 2-(5-cyanothien-2-yl)anisole (96%). MS = 215 (M+).

An intimate mixture of 2-(5-cyanothien-2-yl)anisole (1.2 g, 5.9 mmol) and pyridinium hydrochloride (13.7 g, 119 mmol) is heated for 1 hour to 210°C under argon. The mixture is cooled to ambient temperature and a 1:1 mixture of water and ethyl acetate is added to break and dissolve the solid cake formed during the reaction. The slurry is then transferred to a separation funnel and dichloromethane is added until the organic phase had a higher density than the water phase (organic phase = lower phase). The organic phase contains the desired product and is separated. The remaining aqueous phase is additionally extracted twice with dichloromethane and the collected organic phases are dried over sodium sulfate and evaporated. The residue is purified via flash column on silica (eluent: 100% hexane>hexane/ethyl acetate 8:2 gradient) to give 973 mg of 2-(5-cyanothien-2-yl)phenol (87%). M+ = 201.

To a solution of 2-(5-cyanothien-2-yl)phenol (970 mg, 4.82 mmol) in 20 ml of dry 2-butanone is added (2S)-glycidyl 3-nitrobenzenesulfonate (1.25 g, 4.82 mmol) and potassium carbonate (732 mg, 5.301 mmol) successively. After stirring for 48 hours at 75°C, the mixture is diluted with ethyl acetate and extracted with 2N aqueous sodium hydroxide (2x30 ml) and water (1x30 ml). The title epoxide is directly used without additional purification (M+ = 257).

Epoxides 16-20

Epoxides 16-20 are prepared by a procedure substantially similar to that described for Epoxide 15. The starting halogeno thiophenes used to prepare Epoxides 15-20 are known from the literature, see e.g., *J. Mater. Chem.*, 5(4), 653-61, 1995; *J. Chem. Soc.*, Perkin Trans. 2, 5:625-30, 1982; *Chem. Scr.*, 5(5), 217-26, 1974; *Bull. Soc. Chim. Fr.*, 11:4115-20, 1967; *Bull. Soc. Chim. Fr.*, 11:4121-6, 1967; *Bull. Inst. Chem. Res.*, 52(3):561-5, 1974; *J. Med. Chem.*, 43(16):3168-3185, 2000; *Bioorg. Med. Chem. Lett.*, 10(5):415-418, 2000; and JP 08311060.

Epoxide 21

2-Thienyl-1-methoxybenzene (10 g, 53 mmol) is cooled to –78°C in dry tetrahydrofuran (265 ml) under nitrogen while stirring. n-Butyl lithium in hexanes (1.6M, 37 ml, 59 mmol, 1.1 eq.) is added slowly and the resulting mixture is stirred cold for an hour. Chloromethyl formate (4.1 ml, 53 mmol, 1.0 eq.) is added and the reaction is stirred cold for another hour. The mixture is allowed to warm to room temperature before quenching with saturated bicarbonate solution and ethyl acetate. The layers are separated and the organic phase is washed with brine, dried over sodium sulfate and concentrated. The residue is purified via flash chromatography in 5% ethyl acetate/ hexanes to afford 7.9 g of 2-(5-methoxycarbonylthien-2-yl)-1-methoxybenzene (61%).

2-(5-Methoxycarbonylthien-2-yl)-1-methoxybenzene is demethylated and the resulting phenol is reacted with (2S)-glycidyl 3-nitrobenzenesulfonate to prepare the title epoxide by the procedures described for Epoxide 1.

Epoxide 22

To a solution of 2-fluoro-6-iodoanisole (Justus Liebigs, *Ann. Chem.*, 746:134, 1971; 4.31 g, 17.1 mmol) in dichloromethane (35 ml) is added a 1M solution of borontribromide in dichloromethane (18.2 ml). The mixture is kept under argon and stirred for 4 hours at room temperature. The mixture is poured into a saturated aqueous sodium bicarbonate solution and the aqueous layer is extracted with ethyl acetate. The combined organic extracts are dried over sodium sulfate and concentrated under reduced pressure to give 2-fluoro-6-iodophenol (4.2 g).

The title epoxide (4.44 g, 86%) is prepared from 2-fluoro-6-iodophenol and (2S)-glycidyl 3-nitrobenzenesulfonate substantiallly as described for Epoxide 1 except using butanone as solvent.

Epoxides 24 and 25

To a solution of 6-fluorochroman-4-one (21.0 g, 126 mmol) in acetic acid (105 ml) is added bromine (6.5 ml, 126 mmol) at such a rate as to not raise the temperature

above 25°C. After the addition is complete, the reaction is allowed to stir for 2 hours before pouring into 1 liter of ice. The resulting mixture is stirred overnight. The precipitate which formed is filtered and placed in drying oven to produce 21 g of 3-bromo-6-fluorochroman-4-one.

The product from (14 g, 57 mmol) above is dissolved in triethylamine (100 ml) and is stirred at reflux for 2 hours. The reaction is cooled and concentrated, taken up in chloroform, washed with 2N aqueous hydrochloric acid and water. The organic layer is dried over sodium sulfate and concentrated. The product residue is crystallized from hot ethyl acetate.

The product from above (6-fluorochromen-4-one (5.25 g, 32.0 mmol) and hydroxylamine hydrochloride (4.65 g, 67.2 mmol) are dissolved in ethanol (180 ml) and the resulting mixture is heated to reflux. The reaction is allowed to stir for 18 hours before cooling and concentrating. The residue is taken up in toluene and filtered to give 690 mg of 4-fluoro-2-isoxazol-5-yl-phenol and from the filtrate 594 mg of 4-fluoro-2-isoxazol-3-yl-phenol.

4-Flouro-2-isoxazol-3-yl-phenol and 4-fluoro-2-isoxazol-5-yl-phenol are separately reacted with (2S)-glycidyl 3-nitrobenzenesulfonate substantially as described for Epoxide 1 to yield the title epoxides.

Epoxide 27

2-(3-Formyl-1-pyrrolyl)phenol (3 g, 16 mmol) and triethylamine (17.6 mmol) are added to a suspension of hydroxylamine hydrochloride (1.22 g, 17.6 mmol) in acetic anhydride (7.7 ml) and is allowed to stir overnight at ambient temperature. The mixture is refluxed for 5 hours, concentrated, dissolved in 50 ml ethanol and stirred for 10 minutes with 50 ml 2 M aqueous sodium hydroxide. After neutralisation with aqueous hydrochloric acid, and extraction with ethyl acetate, the organic layer is dried and concentrated. The residue is purified by chromatography (toluene/ethanol 9:1) to yield 2.4 g of 2-(3-cyano-1-pyrrolyl)phenol (92%). This phenolic product is reacted with (2S)-glycidyl 3-nitrobenzenesulfonate substantially as described for Epoxide 1 to yield the title epoxide.

Epoxide 28

A slurry of 2-cyano phenol (25 g, 209.87 mmol), triethylamine hydrochloride (43.3 g, 314.81 mmol), and sodium azide (20.5 g, 314.81 mmol) in toluene (200 mL) is heated to the reflux temperature of the mixture and then the mixture is allowed to stir at reflux for 15 hours. The mixture is cooled and washed with water (200 mL). The aqueous layer is washed with ether (100 mL), made acidic with concentrated HCl, and the resulting solid is collected by filtration. The solid is washed twice with water (200 mL) and dried under vacuum at 100°C for 15 hours to give 33.05 g of 2-(tetrazol-3-yl)phenol (97%).

2-(Tetrazol-3-yl)phenol (32.8 g, 202.3 mmol) is dissolved in dimethylformamide (100 mL) and water (25 mL) and cooled in ice. Sodium hydroxide (8.49 g, 212.3 mmol) in water (20 mL) is added and the solution is warmed to ambient temperature. After thirty minutes, iodomethane (31.58 g, 222.5 mmol) is added neat. The solution is stirred for 15 hours then diluted with ethyl acetate (300 mL) and water (500 mL). The aqueous layer is washed three times with ethyl acetate (300 mL) and the organic layers are combined, washed three times with water (1 L), once with brine (1.2 L), dried over magnesium sulfate, filtered and concentrated *in vacuo*. The solid is purified by flash column chromatography (80% hexane:20% ethyl acetate gradient to 50% hexane:50% ethyl acetate as an eluent) to give 23.5 g of 2-(1-methyltetrazol-3-yl)phenol (66%).

2-(1-Methyltetrazol-3-yl)phenol (0.25 g, 1.54 mmol), (S)-glycidyl nosylate (0.42 g, 1.62 mmol), and potassium carbonate (0.45 g, 3.23 mmol) is dissolved in methyl ethyl ketone (2 mL), the mixture is heated to the reflux temperature of the mixture, and then is allowed to stir at reflux for 15 hours. The slurry is cooled, filtered and concentrated *in vacuo*. The solid is purified by flash column chromatography (80% hexane:20% ethyl acetate gradient to 50% hexane:50% ethyl acetate as an eluent) to give 270 mg (75%) of the title epoxide. FDMS m/e = 233 (M^++1).

Epoxide 29

A 25 ml 1-propanol solution of 2-methoxyphenyl boronic acid (1.2 g, 7.5 mmol) and 5-bromothien-2-ylsulfonamide (1.2 g, 5 mmol) is stirred under N_2 at room

temperature. Palladium(II) acetate (56 mg, 0.25 mmol), triphenylphosphine (200 mg, 0.75 mmol), 2M aqueous Na_2CO_3 (3 ml, 6 mmol), and 7 ml H_2O are added and the resulting mixture is refluxed (~88°C) for 1 hour. The reaction is cooled, diluted with ethyl acetate, washed with brine, and the brine back extracted with ethyl acetate. The extracts are combined, washed with aqueous $NaHCO_3$, brine, dried (Na_2SO_4), filtered, and the filtrate is concentrated. The residue is purified by chromatography (SiO_2, ethyl acetate/hexane gradient) to give 943 mg (70%) of 5-(2-methoxyphenyl)thiophene-2-sulfonamide.

A 70 ml CH_2Cl_2 suspension of 5-(2-methoxyphenyl)thiophene-2-sulfonamide (1.0 g, 3.7 mmol) is stirred under N_2 at -75 °C as boron tribromide (1.1 ml, 12 mmol) is syringed into the reaction mixture. The amber solution is stirred for 30 minutes at -75°C, then at 0°C for 2-3 hours. The reaction is quenched with ice, extracted with CH_2Cl_2. The extracts are washed with brine, dried (Na_2SO_4), filtered, and the filtrate is concentrated. The residue is purified by chromatography (SiO_2, ethyl acetate/hexane gradient) to give 720 mg of 5-(2-hydroxyphenyl)thiophene-2-sulfonamide (76%).

5-(2-Hydroxyphenyl)thiophene-2-sulfonic acid amide (1.8 g, 7.1 mmol), K_2CO_3 (1.1 g, 8.5 mmol), and (2S)-glycidyl 3-nitrobenzenesulfonate (2.1 g, 7.8 mmol) are reacted as described for the preparation of Epoxide 1 to give 1.5 g of the title epoxide (70%).

Epoxide 30

A solution of 3-bromothiophene (978 mg, 6 mmol) in 50 ml of dioxane is degassed with argon. Tetrakis-(triphenylphosphine)-palladium(0) (700 mg, 0.6 mmol) is added and the mixture is stirred for 5 minutes. 2-Methoxybenzene boronic acid (1.824 g, 12 mmol) and 12 ml of aqueous 2 N sodium carbonate are successively added and the resulting mixture is stirred for 16 hours at 85°C. The mixture is allowed to cool to room temperature then is extracted with dichloromethane (2x50 ml). The organic extracts are washed with water (2x30 ml) then dried over sodium sulfate, filtrated and evaporated. The residue is purified via flash column on silica (eluent: hexane/ethyl acetate 99:1 gradient to give 2-(thien-3-yl)anisole.

An intimate mixture of 2-(thien-3-yl)anisole (1.2 g, 4 mmol) and 6.0 g (50 mmol) of pyridinium hydrochloride is heated for 20 minutes to 200°C (1000W MW, microwave). The mixture is allowed to cool to room temperature then is extracted with ethyl acetate and dichloromethane. The organic extracts are washed with water, dried over sodium sulfate and evaporated. The residue is purified via flash column on silica (eluent: 100% hexane>hexane/ethyl acetate 9:1 gradient) to give 700 mg of 2-(thien-3-yl)phenol (97%). M+ = 176.

To a solution of 2-(thien-3-yl)phenol (700 mg, 4 mmol) in 20 ml of dry 2-butanone is added s(-) glycidyl nosylate (1.03 g, 4 mmol) and potassium carbonate (605 mg, 4.4 mmol) successively. After stirring for 16 hours at 80°C the mixture is diluted with ethyl acetate and extracted with 2N aqueous sodium hydroxide (2 x 30 ml) and water (1 x 30 ml). The residue is purified via flash column on silica (eluent: DCM/hexane 8:2>1/1 gradient) to give 689 mg of the title epoxide (74.7%). M+ = 232.

Epoxide 31

A mixture of 2-iodophenol (5.00 g, 22.7 mmol), (2S)-glycidyl 3-nitrobenzenesulfonate (5.89 g, 22.7 mmol) and potassium carbonate (3.44 g, 24.9 mmol) in methylethylketone (150 ml) is refluxed for 18 hours. After cooling, the salts are removed by filtration. The filter cake is rinsed thoroughly with dichloromethane and the collected filtrates are evaporated. The residue is purified via flash chromatography on silica gel using a hexane-hexane/ethyl acetate gradient (100 to 90:10).

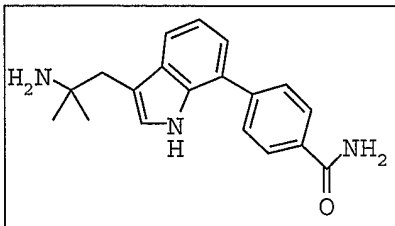
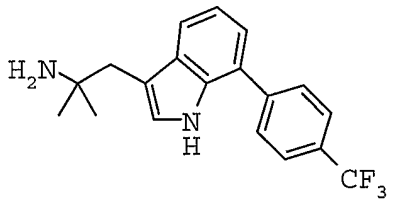
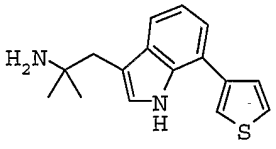
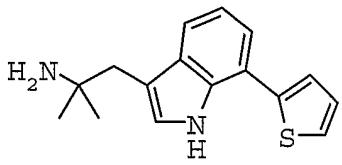
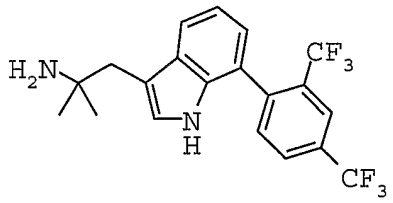
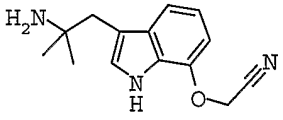
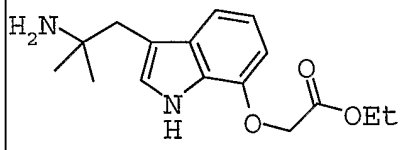
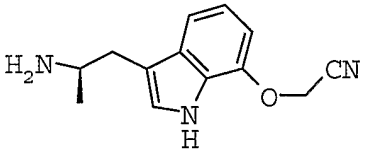
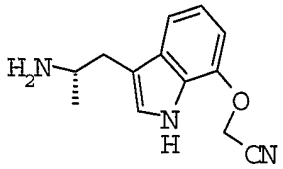
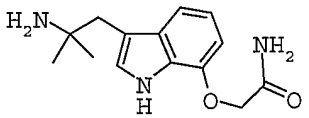
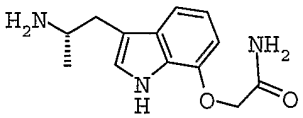
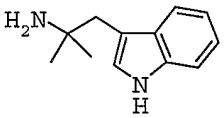
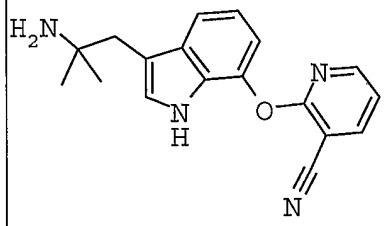
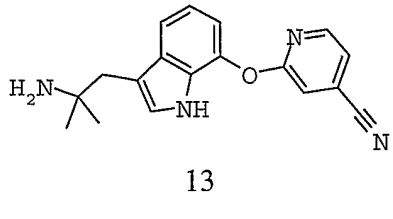
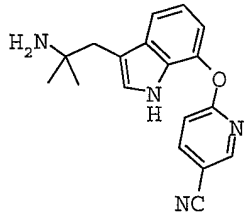
Epoxides 2-4, 6-8, 10, 23 and 26

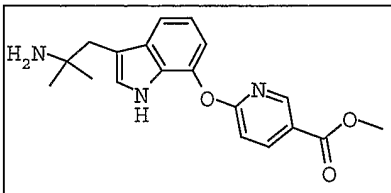
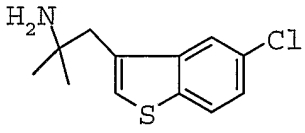
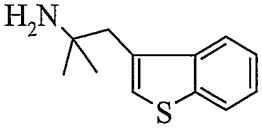
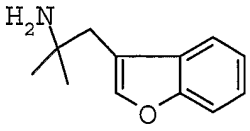
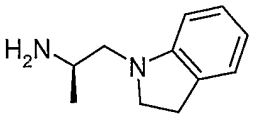
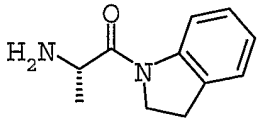
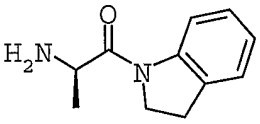
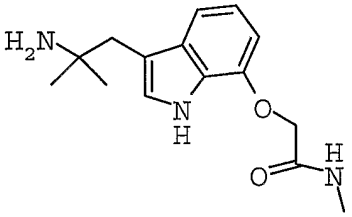
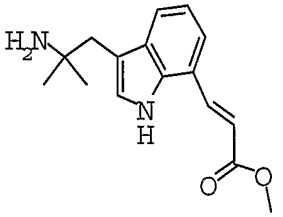
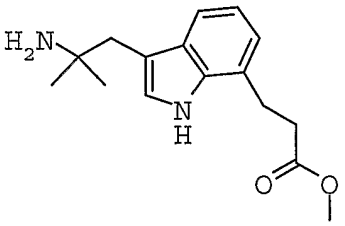
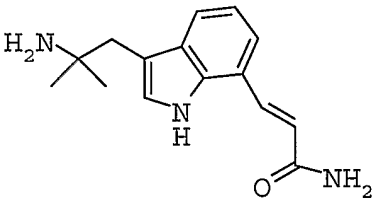
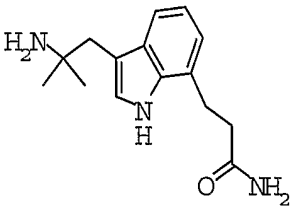
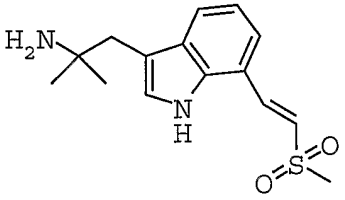
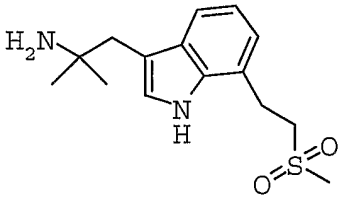
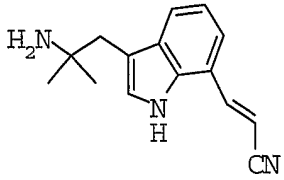
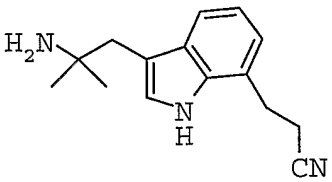
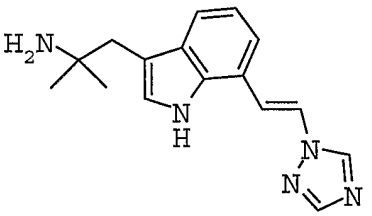
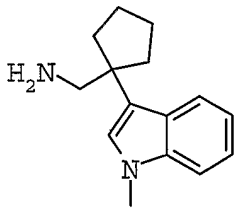
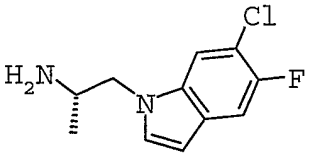
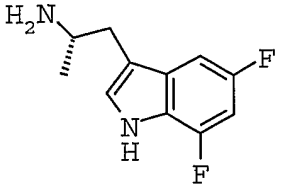
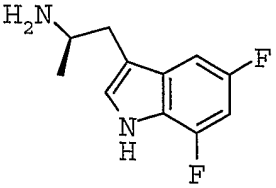
2-(Thiazol-2-yl)phenol (Arnold, *et al.*, WO 94/22846); 2-(pyrrol-1-yl)phenol (*J. Het. Chem.*, 8:283-287, 1971); 2-(isoxazol-3-yl)phenol (*J. Het. Chem.*, 8:283-287, 1971); 2-(isothiazol-5-yl)phenol (*J. Chem. Res. (S), 349, 1988; J. Chem. Res. (S), 163, 1992*); 2-(1,3,4-thiadiazol-2-yl)phenol (WO 94/22846); 2-(oxazol-2-yl)phenol (WO 94/22846); 2-(furan-3-yl)phenol (Ger. Offen. DE2914166); 2-thiazol-4-yl-phenol (WO 94/22846); and 2-(1,2,3-thiadiazol-2-yl)phenol (WO 94/22846); are reacted with (2S)-glycidyl 3-nitrobenzenesulfonate substantially as described for Epoxide 1 to yield the title epoxides.

Amines of Formula III

Amines 1-88 are prepared as described below or are obtained from commercial sources for use as described in Schemes 1 or 2. These amines are pictured below in Table 2.

Table 2

 1	 2	 3
 4	 5	 6
 7	 8a	 8b
 9	 10	 11
 12	 13	 14

 15	 16	 17
 18	 19	 20
 21	 22	 23
 24	 25	 26
 27	 28	 29
 30	 31	 32
 33		

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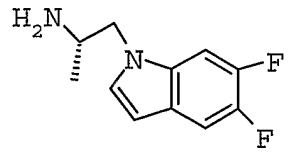
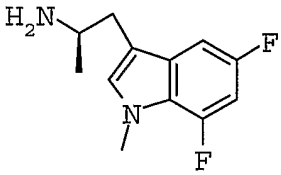
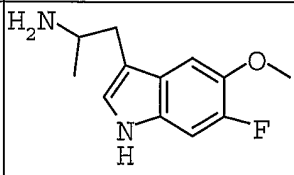
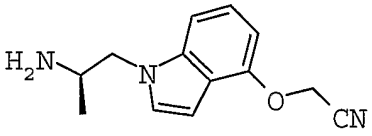
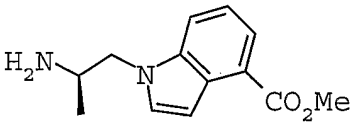
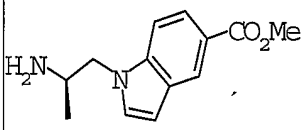
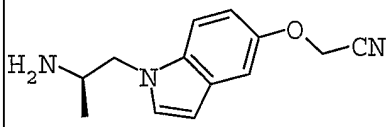
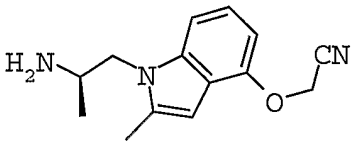
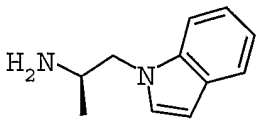
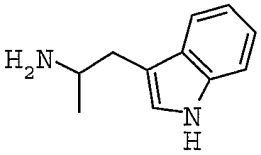
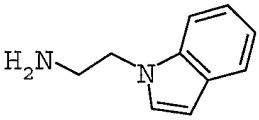
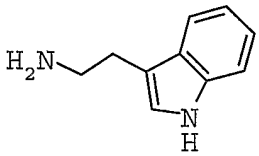
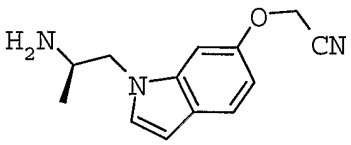
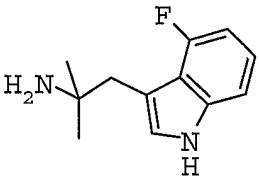
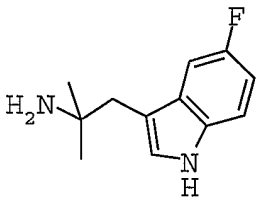
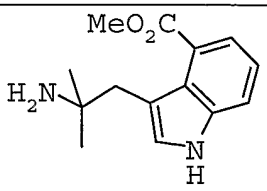
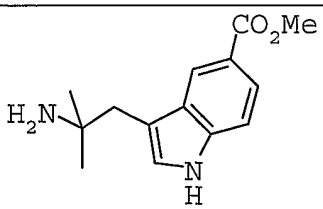
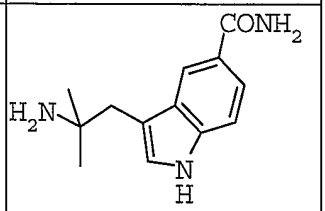
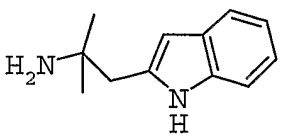
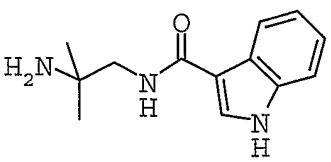
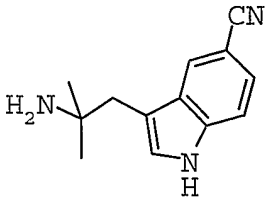
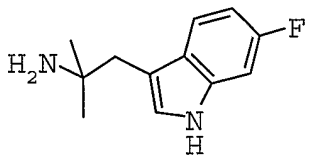
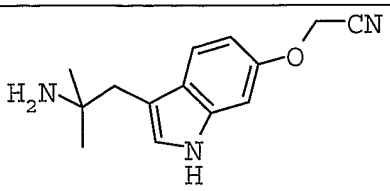
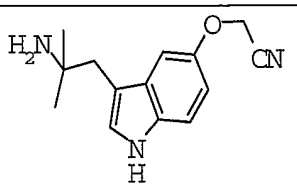
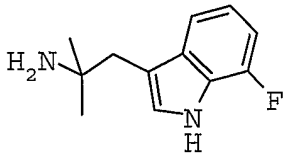
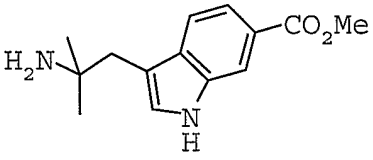
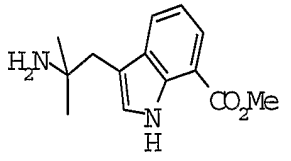
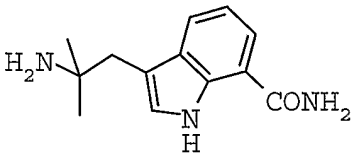
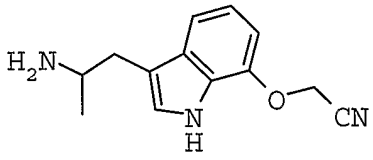
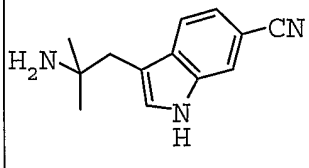
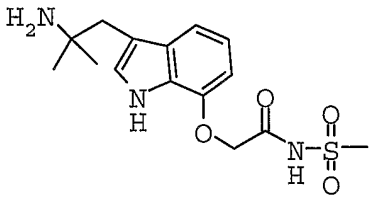
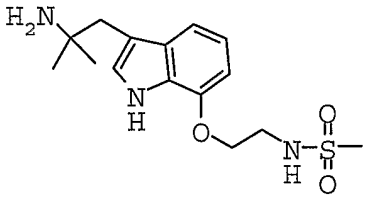
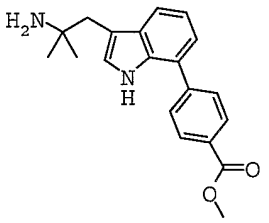
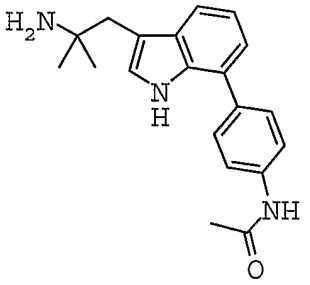
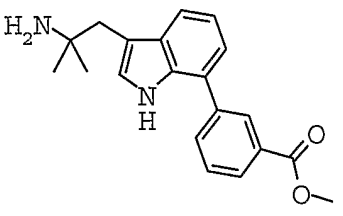
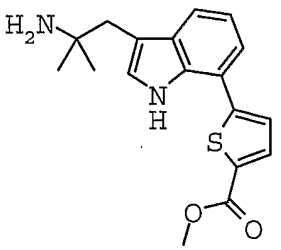
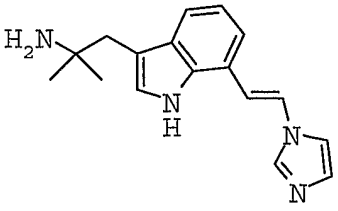
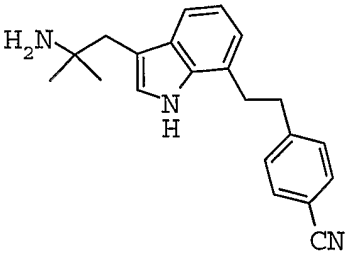
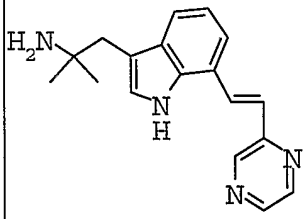
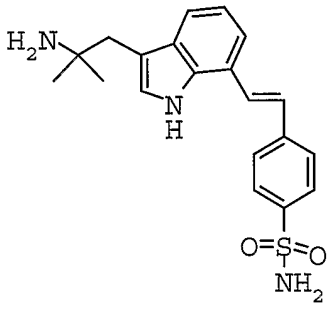
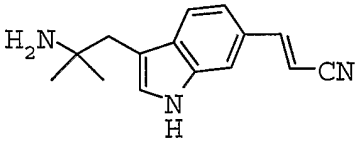
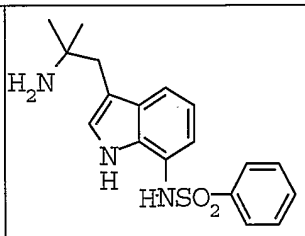
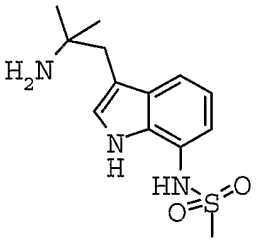
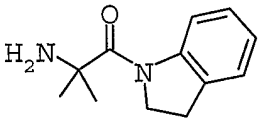
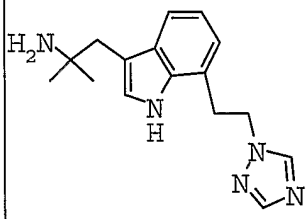
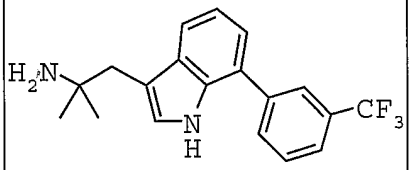
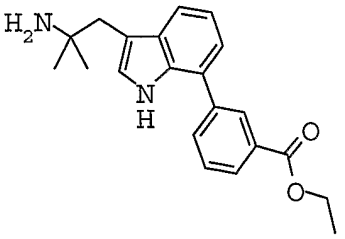
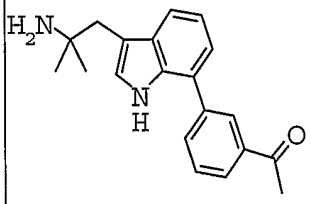
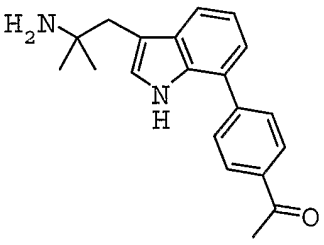
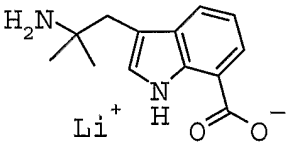
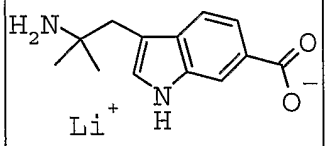
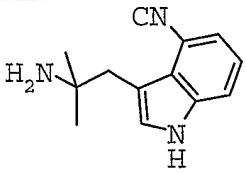
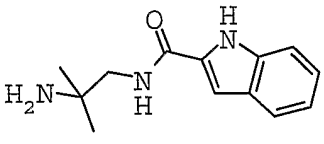
 36	 37	 38
 39	 40	 41
 42	 43	 44
 45	 46	 47
 48	 49	 50
 51	 52	 53
 54	 55	 56

 57	 58	 59
 60	 61	 62
 63	 64	 65
 66	 67	 68
 69	 70	 71
 72	 73	 74

 75	 76	 77
 78	 79	 80
 81	 82	 83
 84	 85	 86
 87	 88	

Amine 1

A mixture of 7-benzyloxy gramine (1.99 g, 7.10 mmol), solid NaOH (298 mg, 7.22 mmol) and 2-nitropropane (4.5 mL, 50 mmol) is heated to reflux. After 10 minutes

at reflux, a thick slurry developed which is difficult to stir. Gas evolution is observed, and an additional 1 mL of 2-nitropropane is added to loosen the mixture. After 29 hours, the mixture is allowed to cool to ambient temperature. Ether (30 mL) is added and the mixture is filtered. The filtrate is treated with 10% acetic acid (6 mL), the layers are separated and the organic layer is rinsed with water (2 x 25 mL). The organic layer is dried (Na_2SO_4) and concentrated to give 2.12 g of 3-(2-methyl-2-nitropropyl)-7-(benzyloxy)indole (92%). MS (ES+) *m/z* 325.

A mixture of 3-(2-methyl-2-nitropropyl)-7-(benzyloxy)indole (25.0 g, 77.1 mmol), Raney Nickel® (9.5 g wet lump), and 3A ethanol (250 mL) is pressurized to 50 psig with H_2 and is heated to 60°C. After 1 hour, the mixture is cooled to ambient temperature. The mixture is diluted with tetrahydrofuran (100 mL) and is warmed to 50°C. The catalyst is removed by filtration and the cake is rinsed with 50°C tetrahydrofuran (4 x 50 mL). The filtrate is concentrated to a solid which is dried in a 50°C vacuum oven to provide 22.41 (99%) of 2-methyl-1-[7-(benzyloxy)indol-3-yl]prop-2-ylamine. MS (ES+) *m/z* 295 (100%).

Solid di-*tert*-butyl dicarbonate (20 g, 92 mmol) is added to a slurry of 2-methyl-1-[7-(benzyloxy)indol-3-yl]prop-2-ylamine (31.54 g, 107.1 mmol), triethylamine (16.5 mL, 118 mmol) and CH_2Cl_2 (300 mL) at ambient temperature; within 2 hours the slurry became a homogeneous solution. After 23.5 hours, the solution is poured into water (200 mL), and the layers are separated. The organic layer is extracted with 0.5 *M* $NaHSO_4$ (200 mL), and the combined aqueous layers are rinsed with CH_2Cl_2 (125 mL). The combined organic layers are rinsed with 50% saturated NaCl/saturated $NaHCO_3$ (300 mL), dried (Na_2SO_4), filtered and concentrated. The resulting residue is purified by flash chromatography with CH_2Cl_2 followed by 5% ethyl acetate/CH_2Cl_2 to provide 25 g of [2-(7-benzyloxy-1H-indol-3-yl)-1,1-dimethyl-ethyl]-carbamic acid tert-butyl ester (70%). MS (ES-) *m/z* 393 (100 %).

A mixture of [2-(7-benzyloxy-1H-indol-3-yl)-1,1-dimethyl-ethyl]-carbamic acid tert-butyl ester (20.75 g, 52.6 mmol), 5 % Pd/C (1.00 g, 5 wt %), and 3A ethanol (200 mL) is pressurized to 55 psig with H_2, and is heated to 50°C. After 40 minutes, the slurry is filtered, and the filtrate is concentrated to give 15.41 g of [2-(7-hydroxy-1H-indol-3-yl)-1,1-dimethyl-ethyl]-carbamic acid tert-butyl ester (96%). FDMS m/e = 305 (M^++1).

To a solution of [2-(7-hydroxy-1H-indol-3-yl)-1,1-dimethyl-ethyl]-carbamic acid tert-butyl ester (6.04 g, 19.8 mmol) in dichloromethane (125 mL) is added triethylamine (14 mL, 99.2 mmol). The mixture is cooled to 0 °C and trifluoromethanesulfonyl anhydride (4.4 mL, 25.8 mmol) is added dropwise as a solution in dichloromethane (25 mL). The mixture is warmed to ambient and stirred overnight. The solution is diluted with brine and extracted three times with dichloromethane. The combined organics are dried over anhydrous sodium sulfate then filtered and evaporated. The residue is purified using silica gel chromatography (hexane/20% ethyl acetate in hexane gradient elution) to give 7.199 g of trifluoro-methanesulfonic acid 3-(2-tert-butoxycarbonylamino-2-methyl-propyl)-1H-indol-7-yl ester (83%). FDMS m/e = 437 (M^++1).

A solution of 4-bromobenzamide (150 mg, 0.75 mmol), bis(pinacolato)diboron (209 mg, 0.825 mmol), potassium acetate (0.221 g, 2.25 mmol) and {1,1'-bis(diphenylphosphino)-ferrocene}dichloropalladium dichloromethane complex (18 mg, 0.0225 mmol) in dimethylsulfoxide (5 mL) is heated to 80°C for two hours. The mixture is cooled to 20°C and trifluoro-methanesulfonic acid 3-(2-tert-butoxycarbonylamino-2-methyl-propyl)-1H-indol-7-yl ester (262 mg, 0.600 mmol), {1,1'-bis(diphenylphosphino)-ferrocene}dichloropalladium dichloromethane complex (18 mg, 0.0225 mmol) and sodium carbonate (1.9 mL, 2M, 3.75 mmol) are added. The mixture is heated to 80°C overnight. The mixture is diluted with brine and ethyl acetate. The organic fraction is washed seven times with brine, then dried over anhydrous sodium sulfate, filtered and evaporated. The residue is purified using silica gel chromatography (dichloromethane/10% methanol, 0.7M ammonia in dichloromethane gradient elution) to give 143 mg of {2-[7-(4-carbamoyl-phenyl)-1H-indol-3-yl]-1,1-dimethyl-ethyl}-carbamic acid tert-butyl ester (58%). FDMS m/e = 408 (M^++1).

To a solution of {2-[7-(4-carbamoyl-phenyl)-1H-indol-3-yl]-1,1-dimethyl-ethyl}-carbamic acid tert-butyl ester (333 mg, 0.817 mmol) in dioxane (5 mL) at 0°C is added hydrochloric acid (4 mL, 4M solution in dioxane, 16 mmol). The mixture is stirred at 0°C for three hours and then warmed to ambient for three hours. The mixture is diluted with saturated sodium bicarbonate and then extracted three times with ethyl acetate. The combined organics are dried over anhydrous sodium sulfate, filtered and then the solvent is removed in vacuo to give 208 mg of the title compound (83%). FDMS m/e = 308 (M^++1).

Amine 2

To a solution of trifluoro-methanesulfonic acid 3-(2-tert-butoxycarbonylamino-2-methyl-propyl)-1H-indol-7-yl ester (305 mg, 0.699 mmol) in tetrahydrofuran (4.5 mL) is added sodium carbonate (1 mL, 2M, 2 mmol), tetrakis(triphenylphosphine)-palladium (32 mg, 0.0280 mmol) and 4-trifluoromethylbenzeneboronic acid (0.199 g, 1.05 mmol). The mixture is refluxed for 22 hours, then cooled, diluted with brine and extracted three times with ethyl acetate. The combined organics are dried over anhydrous sodium sulfate, filtered and then evaporated in vacuo. The residue is purified using silica gel chromatography (hexane/20% ethyl acetate, hexane gradient elution) to give 282 mg of {1,1-dimethyl-2-[7-(4-trifluoromethyl-phenyl)-1H-indol-3-yl]-ethyl}-carbamic acid tert-butyl ester (93%). FDMS m/e = 433 (M^++1).

The title amine is prepared from {1,1-dimethyl-2-[7-(4-trifluoromethyl-phenyl)-1H-indol-3-yl]-ethyl}-carbamic acid tert-butyl ester as described above for Amine 1 (205 mg, 99%). FDMS m/e = 333 (M^++1).

Amine 3

To a solution of trifluoro-methanesulfonic acid 3-(2-tert-butoxycarbonylamino-2-methyl-propyl)-1H-indol-7-yl ester (340 mg, 0.779 mmol) in dimethylformamide (5 mL) is added triethylamine (0.14 mL, 1.01 mmol), tetrakis(triphenylphosphine)-palladium (36 mg, 0.0312 mmol) and 3-thiopheneboronic acid (130 mg, 1.01 mmol). The mixture is refluxed for 22 hours, then cooled and diluted with brine and ethyl acetate. The organic phase is washed 7 times with brine. The organics are dried over anhydrous sodium sulfate, filtered and then evaporated in vacuo. The residue is purified using silica gel chromatography (hexane/20% ethyl acetate, hexane gradient elution) to give 198 mg of [1,1-dimethyl-2-(7-thiophen-3-yl-1H-indol-3-yl)-ethyl]-carbamic acid tert-butyl ester (69%). FDMS m/e = 371 (M^++1).

The title amine is prepared from [1,1-dimethyl-2-(7-thiophen-3-yl-1H-indol-3-yl)-ethyl]-carbamic acid tert-butyl ester as described above for Amine 1 (132 mg, 95%). FDMS m/e = 271 (M^++1).

Amine 4

To a solution of trifluoro-methanesulfonic acid 3-(2-tert-butoxycarbonylamino-2-methyl-propyl)-1H-indol-7-yl ester (437 mg, 1.00 mmol) in dimethylformamide (6 mL) is added triethylamine (0.18 mL, 1.30 mmol), tetrakis(triphenylphosphine)-palladium (46 mg, 0.0401 mmol) and 2-thiopheneboronic acid (167 mg, 1.30 mmol). The mixture is refluxed for 22 hours, then cooled and diluted with brine and ethyl acetate. The organic phase is washed 7 times with brine. The organics are dried over anhydrous sodium sulfate, filtered and then evaporated in vacuo. The residue is purified using silica gel chromatography (hexane/20% ethyl acetate, hexane gradient elution) to give 116 mg of [1,1-Dimethyl-2-(7-thiophen-2-yl-1H-indol-3-yl)-ethyl]-carbamic acid tert-butyl ester (31%). FDMS m/e = 371 (M^++1).

The title amine is prepared from [1,1-Dimethyl-2-(7-thiophen-2-yl-1H-indol-3-yl)-ethyl]-carbamic acid tert-butyl ester as described above for Amine 1 (120 mg, 95%). FDMS m/e = 271 (M^++1).

Amine 5

To a solution of trifluoro-methanesulfonic acid 3-(2-tert-butoxycarbonylamino-2-methyl-propyl)-1H-indol-7-yl ester (262 mg, 0.600 mmol) in dimethylformamide (3.5 mL) is added triethylamine (0.11 mL, 0.780 mmol), tetrakis(triphenylphosphine)-palladium (28 mg, 0.0240 mmol) and 2,4-bistrifluoromethylbenzeneboronic acid (201 mg, 0.780 mmol). The mixture is heated to 100°C for 20 hours, then cooled, diluted with brine and ethyl acetate. The organics are washed seven times with brine then dried over anhydrous sodium sulfate, filtered and evaporated in vacuo. The residue is purified using silica gel chromatography (hexane/20% ethyl acetate, hexane gradient elution) to give 268

mg of {2-[7-(2,4-Bis-trifluoromethyl-phenyl)-1H-indol-3-yl]-1,1-dimethyl-ethyl}-carbamic acid tert-butyl ester (89%). FDMS m/e = 501 (M^++1).

The title amine is prepared from {2-[7-(2,4-Bis-trifluoromethyl-phenyl)-1H-indol-3-yl]-1,1-dimethyl-ethyl}-carbamic acid tert-butyl ester as described above for Amine 1 (208 mg, 100%). FDMS m/e = 401 (M^++1).

Amines 6 and 7

A mixture of [2-(7-hydroxy-1H-indol-3-yl)-1,1-dimethyl-ethyl]-carbamic acid tert-butyl ester (15.55 g, 51.1 mmol), bromoacetonitrile (10.7 mL, 153 mmol), K_2CO_3 (17.78 g, 128.6 mmol) and 2-butanone is heated to reflux. After 1 hour the mixture is allowed to cool and is filtered through celite. The filtrate is concentrated to an oil which is purified by flash chromatography with CH_2Cl_2 followed by 5 % ethyl acetate/CH_2Cl_2 to give 15.18 g of [2-(7-cyanomethoxy-1H-indol-3-yl)-1,1-dimethyl-ethyl]-carbamic acid tert-butyl ester (86%). MS (ES-) *m/z* 342.

To a solution of [2-(7-cyanomethoxy-1H-indol-3-yl)-1,1-dimethylethyl]-carbamic acid tert-butyl ester in 20 ml dry ethanol is added 2 ml 10% HCl in ethanol and the mixture is stirred at room temperature for 2 days. The solvent is evaporated, the residue re-dissolved in ethanol and loaded on a SCX column. After washing with ethanol the product is eluted with 10% NH_3 in ethanol, evaporated and purified on a silica column eluting with CH_2Cl_2/10% NH_3 in ethanol from 99/1 to 90/10, to yield 231 mg of Amine 6 (34%) and 213 mg of Amine 7 (26%).

Alternate Preparation for Amine 6

To solution of [2-(7-cyanomethoxy-1H-indol-3-yl)-1,1-dimethyl-ethyl]-carbamic acid tert-butyl ester (1.0 g, 2.85 mmol) in dioxane (5.0 mL) at 0° C is added 4 N HCl (3.0 mL). The reaction mixture is allowed to continue for 1 hour at 0°C and warmed to room temperature. The reaction mixture is evaporated to dryness, the resulting residue is taken up with water (25.0 mL), and saturated $NaHCO_3$ (5.0 mL) is added. This aqueous mixture is extracted with ethyl acetate (2 x 50 mL). The combined organic extracts are

washed with brine and dried (Na_2SO_4). Evaporated to dryness give 590 mg of the title amine (86%). FDMS m/e = 244.1 ($M^+ + 1$).

Amines 8a and 8b

Phosphorous oxychloride (252 mL, 2.7 mol) is added dropwise over 15 minutes to precooled dimethylformamide (-10°C) (1800 mL) while maintaining the temperature below –5°C and the resulting solution is stirred for 1 hour at –10 to 0°C. A solution of 7-benzyloxyindole (502 g, 2.25 mmol) in dimethylformamide (900 mL) is added dropwise while maintaining the temperature below 0°C. The cooling is removed and the resulting mixture is allowed to warm to room temperature and stir for 1 hour. After cooling to 0°C, 5 N NaOH (4.5 L) is added over 20 minutes at 0°C to 5°C. The resulting mixture is heated at reflux for 30 minutes. Upon cooling to 10°C, the product precipitates. After stirring for 20 minutes, the product is filtered, washed thoroughly with water (4 x 1.5 L) and vacuum dried at 40°C to give 574.5 g of 7-benzyloxy-3-carbanal-1H-indole (101.6%).

The crude aldehyde from above (570 g, 2.25 mol), ammonium acetate (173.4, 2.25 mol) and nitroethane (661.8 g, 8.8 mol) are added to xylenes (1.35 L). The heterogeneous mixture is heated at reflux under a Dean-Stark trap with 4A molecular sieves in the sleeve for 30 minutes without reflux return and 45 minutes with reflux return to remove water. When the reaction is complete the mixture is cooled to room temperature over 1 hour and is then cooled to 0°C for 30 minutes. The solid product is collected by filtration and is washed sequentially with xylenes (1 L), water (1 L), and xylenes (1 L). Vacuum drying overnight at 40°C affords 610 g (88%) of 7-benzyloxy-3-(2-nitroprop-1-enyl)-1H-indole (nitroolefin).

Lithium aluminum hydride (LAH, 24 g, 600 mmol) is added portionwise to dry tetrahydrofuran (1800 mL) at –5°C to 5°C. A solution of the nitroolefin from above (61.6 g, 200 mmol) in tetrahydrofuran (1200 mL) is added to the LAH solution over 30 minutes while maintaining the temperature at –5°C to 5°C. When the addition is complete, the reaction mixture is allowed to warm to 30°C over 1.5 hours and is stirred at 25°C to 35°C for 2 hours. To complete the reaction, the mixture is heated to 60°C for 30 minutes. After cooling to 0°C, the reaction is quenched by the sequential addition of water (30 mL), 5 N NaOH (30 mL), and water (100 mL) and the resulting mixture is stirred over the weekend.

The aluminum salts are removed by filtration and the cake rinsed with tetrahydrofuran (500 mL). The combined filtrates are concentrated to give 47.6 g (55% purity corrected yield, approx 65% pure) of 7-benzyloxy-3-(2-aminopropyl)-1H-indole.

To 7-benzyloxy-3-(2-aminopropyl)-1H-indole (45.6 g, 65% pure, 102 mmol) is added dichloromethane (450 mL) and triethylamine (18.1 g, 179 mmol) to give a slurry. t-Butyloxycarbonyl anhydride (35.5 g, 163 mmol) is added portionwise to the mixture over 5 minutes and is rinsed into the flask with dichloromethane (50 mL). Carbon dioxide gas is evolved and the temperature increases from 23°C to 31°C. Within 1 hour the reaction is complete and the solution is washed sequentially with 1 N HCl, water, and 10% saturated sodium chloride solution. The crude product is purified by silica gel chromatography (500 g silica gel) eluting with dichloromethane followed by 5% ethyl acetate/dichloromethane. Crystallization of the product containing fractions from ethyl acetate/hexanes affords 33.9 g (86% yield) of {1-methyl-2-[7-(benzyloxy)-1H-indol-3-yl]ethyl}-carbamic acid tert-butyl ester.

{1-Methyl-2-[7-(benzyloxy)-1H-indol-3-yl]ethyl}-carbamic acid tert-butyl ester (38.9 g, 102 mmol) is added to a slurry of 5% Pd/carbon (3.89 g of 50% water wet catalyst) in ethanol denatured with toluene (389 mL). The resulting mixture is pressurized with hydrogen (50 psig) and is heated to 50 °C while shaking in a Paar™ hydrogenation apparatus. The reaction is complete after 3 hours, the catalyst is removed by filtration and the solvent is removed by rotary evaporation to afford a nearly quantitative yield of the oxygen-sensitive {1-methyl-2-[7-hydroxy-1H-indol-3-yl]ethyl}-carbamic acid tert-butyl ester. The phenol is used immediately in the next step without purification.

The crude {1-methyl-2-[7-hydroxy-1H-indol-3-yl]ethyl}-carbamic acid tert-butyl ester from above (29.2 g, 102 mmol theory) is dissolved in methyl ethyl ketone (300 mL) and bromoacetonitrile (20.4 mL, 306 mmol) and potassium carbonate (33.8 g, 250 mmol) is added. The mixture is heated at 80°C for 2 hours. The solids are removed by filtration, the cake is washed with methyl ethyl ketone, and the combined filtrates are concentrated by rotary evaporation. The crude product is purified by flash chromatography (500 g silica gel, eluted with 8 x 500 mL dichloromethane, 4 x 500 mL 5% ethyl acetate/dichloromethane, 6 x 500 mL 10% ethyl acetate/dichloromethane). The fractions containing product are concentrated and hexane is added to the solution to precipitate out

the product affording 23.7 g (70.2% yield) of racemic {1-methyl-2-[7-cyanomethoxy-1H-indol-3-yl]ethyl}-carbamic acid tert-butyl ester.

The two enantiomeric compounds that make up racemic {1-methyl-2-[7-cyanomethoxy-1H-indol-3-yl]ethyl}-carbamic acid tert-butyl ester are separated by preparative chiral chromatography in quantitative yield. Analytical chromatographic conditions: ChiralPak AD (4.6 mm x 250 mm), 60% 3A ethanol, 40% heptane, 1 mL/min, 245 nm.

To a solution of (R)-{1-methyl-2-[7-cyanomethoxy-1H-indol-3-yl]ethyl}-carbamic acid tert-butyl ester (1.2 mmol) in 10 ml dry ethanol is added 1 ml 10% HCl in ethanol and the mixture is stirred at room temperature for 2 days. The solvent is evaporated, the residue re-dissolved in ethanol and loaded on a SCX column. After washing with ethanol the product is eluted with 10% NH_3 in ethanol and evaporated to yield 220 mg of Amine 8a (80 %) as a colourless oil. Amine 8b is prepared from (S)-{1-methyl-2-[7-cyanomethoxy-1H-indol-3-yl]ethyl}-carbamic acid tert-butyl ester by a procedure substantially similar to that described for amine 8a.

Amine 9

To a solution of [2-(7-cyanomethoxy-1H-indol-3-yl)-1,1-dimethyl-ethyl]-carbamic acid tert-butyl ester (2.8 mmol) in 10 ml dry dioxane is added 1 ml concentrated HCl and the mixture is stirred at room temperature overnight. The solvent is evaporated, the residue re-dissolved in ethanol and loaded on a SCX column. After washing with ethanol the product is eluted with 10% NH_3 in ethanol and evaporated to yield 667 mg of Amine 9 (91%).

Amine 10

To a solution of Amine 8b (1.4 mmol) in 5 ml dry dioxane is added 0.5 ml concentrated HCl and the mixture is stirred at room temperature overnight. The solvent is evaporated, the residue re-dissolved in ethanol and loaded on a SCX column. After washing with ethanol the product is eluted with 10% NH_3 in ethanol and evaporated to yield 320 mg of Amine 10 (92%).

Amine 11

Amine 11 is prepared according to the literature procedure detailed in *J. Med. Chem.*, 23:285-289, 1980.

Amine 12

To a solution of [2-(7-Hydroxy-1H-indol-3-yl)-1,1-dimethyl-ethyl]-carbamic acid tert-butyl ester (274 mg, 0.900 mmol) in dimethylformamide (15 mL) is added sodium hydride (26 mg, 1.07 mmol). The mixture is stirred at ambient temperature for 25 minutes under nitrogen. 2-Chloro-nicotinonitrile (187 mg, 1.35 mmol) is added and the mixture is heated in an oil bath to eighty degrees Celsius for 15 hours, under nitrogen. Water (50 ml) is added to quench the reaction and the mixture is extracted three times with 50 mL of ethyl acetate. The organic layers are combined and washed twice with 50 mL of 1.00 N sodium hydroxide. The organic layer is dried with sodium sulfate, filtered and the solvent evaporated. The residue is dissolved in dichloromethane and purified using silica gel chromatography (6% 2M ammonia in methanol, 94% dichloromethane used as mobile phase) to give 350 mg (96%) of {2-[7-(3-cyano-pyridin-2-yloxy)-1H-indol-3-yl]-1,1-dimethyl-ethyl}-carbamic acid tert-butyl ester. FDMS m/e = 407 (M^++1).

{2-[7-(3-Cyano-pyridin-2-yloxy)-1H-indol-3-yl]-1,1-dimethyl-ethyl}-carbamic acid tert-butyl ester (119 mg, 0.293 mmol) is dissolved in 10 mL of 1,4 dioxane. The mixture is cooled to zero degrees Celsius in an ice/water bath. To the mixture is added 10 mL of 4N hydrochloric acid in 1,4 dioxane, and the resulting mixture is stirred at zero degrees, under nitrogen, for five hours. The solvent is evaporated, and the residue is taken up in water. The pH of the water is adjusted to 9 using sodium bicarbonate, and is extracted three times with 50 mL of ethyl acetate. The organic layers are combined, dried with sodium sulfate, filtered, and the solvent removed in vacuo to give 218 mg of the title amine (83%). FDMS m/e = 307 (M^++1).

Amines 13 and 14

The title amines are prepared from [2-(7-hydroxy-1H-indol-3-yl)-1,1-dimethyl-ethyl]-carbamic acid tert-butyl ester and 2-chloro-isonicotinonitrile and [2-(7-hydroxy-1H-indol-3-yl)-1,1-dimethyl-ethyl]-carbamic acid tert-butyl ester and 6-chloro-nicotinonitrile, respectively, as described for the preparation of Amine 12.

Amine 15

To a solution of [2-(7-hydroxy-1H-indol-3-yl)-1,1-dimethyl-ethyl]-carbamic acid tert-butyl ester (104 mg, 0.342 mmol) in dimethylformamide (10 mL) is added sodium hydride (10 mg, 0.410 mmol). The mixture is stirred at ambient temperature for 30 minutes under nitrogen. 6-Chloro-nicotinic acid methyl ester (99 mg, 0.581 mmol) is added and the mixture is heated in an oil bath to eighty degrees Celsius for 15 hours, under nitrogen. The mixture is then heated an additional 5 hours at eighty-five degrees Celsius. Water (100 ml) is added to quench the reaction and the mixture is extracted three times with 50 mL of ethyl acetate. The organic layers are combined and washed twice with 50 mL of 1.00 N sodium hydroxide. The organic layer is dried with sodium sulfate, filtered and the solvent evaporated. The residue is dissolved in dichloromethane and purified using silica gel chromatography (6% 2M ammonia in methanol, 94% dichloromethane used as mobile phase) to give 87 mg (58%) of 6-[3-(2-tert-butoxycarbonylamino-2-methyl-propyl)-1H-indol-7-yloxy]-nicotinic acid methyl ester. FDMS m/e = 440 (M^++1).

6-[3-(2-tert-Butoxycarbonylamino-2-methyl-propyl)-1H-indol-7-yloxy]-nicotinic acid methyl ester (87 mg, 0.198 mmol) is dissolved in 5 mL of 1,4 dioxane. The mixture is cooled to zero degrees Celsius in an ice/water bath. To the mixture is added 15 mL of 4N hydrochloric acid in 1,4 dioxane, and the mixture is stirred at zero degrees, under nitrogen, for five hours. The solvent is evaporated, and the residue is taken up in water. The pH of the water is adjusted to 10 using sodium bicarbonate, and is extracted three times with 50 mL of ethyl acetate. The organic layers are combined, dried with sodium sulfate, filtered, and the solvent removed in vacuo to give 24 mg of the title amine (36%). FDMS m/e = 340 (M^++1).

Amine 16

The title amine is prepared from 3-(bromomethyl)-5-chlorobenzo[B]thiophene in a similar fashion as described in US Patent 4,321,398.

Amine 17

3-Methylbenzo[b]thiophene (9.9 g, 67 mmol) is heated in carbon tetrachloride (133 ml) to near reflux in the presence of n-bromosuccinimide (11.9 g, 67 mmol, 1.0 eq.). 2,2'Azobisisobutyronitrile (2.2 g, 13.3 mmol, 0.2 eq.) is added and the resulting mixture is refluxed for two hours. After cooling, the reaction mixture is filtered through a glass-fritted funnel, and the filtrate is concentrated. The residue is triturated with petroleum ether and toluene to afford 6.42 g of 3-Bromomethylbenzo[b]thiophene (42%).
The title amine is prepared from 3-(bromomethyl)-benzo[B]thiophene in a similar fashion as described in US Patent 4,321,398.

Amine 18

The title amine is prepared from 3-(Bromomethyl)benzofuran (*J.Med.Chem.*, 40(17):2706-2725, 1997) in a similar fashion as described in US Patent No. 4,321,398.

Amine 19

A mixture of 2,3-dihydro-1H-indole (5.74 g, 48.2 mmol), and (S)-propylene oxide (2.8 g, 48.2 mmol) in ethanol (200 mL) is heated at reflux for 18 hours. The resulting mixture is cooled to room temperature, and evaporated to give a crude oil. The material is purified by flash chromatography (25% ethyl acetate/hexanes) to give 5.37 g (63%) of 2,3-dihydro-1-(2-hydroxypropyl)indole.

To a solution of 2,3-dihydro-1-(2-hydroxypropyl)indole (4.87 g, 27.5 mmol) in CH_2Cl_2 (150 mL) at 0°C, is added triethylamine (19.1 mL, 137.4 mmol), followed by methanesulfonyl chloride (4.24 mL, 54.9 mmol). The reaction is quenched after 10

minutes by addition of saturated $NaHCO_3$ solution. The reaction mixture is extracted with CH_2Cl_2, dried over $MgSO_4$ and evaporated. This crude material is taken up in dimethylformamide (150 ml), sodium azide added (3.57 g, 54.9 mmol), and the reaction mixture heated at 70°C for 7 hours. Diethyl ether and water is added to the cooled reaction mixture, and the water layer extracted several times with diethyl ether. The organic extracts are combined, washed with brine several times, dried over Na_2SO_4, and concentrated. The residue is purified by flash chromatography (15% ethyl acetate/hexanes) to give 4.44 g (80%) of 2,3-dihydro-1-(2-azidopropyl)indole.

2,3-Dihydro-1-(2-azidopropyl)indole (3.93 g, 19.5 mmol) and triphenylphosphine (6.38 g, 24.3 mmol) is dissolved in tetrahydrofuran (350 mL) and water (526 microliters, 29.2 mmol) is added. The reaction mixture is heated at reflux for 8 hours, cooled to room temperature, and concentrated. This crude residue is diluted with methanol, and passed over a cation exchange column to remove the excess triphenyl phosphine and byproducts. Flash chromatography (90:10:1 CH_2Cl_2/methanol/NH_4OH) provides the 1.05 g of the title amine (31%).

Amine 20

To a mixture of Boc-L-alanine (5 g, 24.4 mmol), indoline (3.2 ml, 29 mmol), and N,N-diisopropylethylamine (9.2 mL, 53 mmol) in dimethylformamide (130 mL) is added EDC (6.1 g, 32 mmol) and hydroxybenzotriazole (3.9 g, 29 mmol). The resulting mixture is stirred at room temperature overnight. The mixture is partitioned between ethyl acetate and H_2O. The aqueous phase is extracted with ethyl acetate, and the combined organic phases are washed with brine, dried ($MgSO_4$), and concentrated. The residue is purified by trituration with hexane to give 6.1 g of the Boc-protected title amine (80%).

To a mixture of the Boc-protected amine from above (4.0 g, 13.8 mmol) in CH_2Cl_2 (20 mL) at 0°C is added trifluoroacetic acid (5 mL). Additional trifluoroacetic acid (5 mL) is added after 1 hour and 2 hours. After 2.5 hours, the mixture is neutralized with a saturated aqueous solution of $NaHCO_3$. The aqueous phase is extracted with CH_2Cl_2 (2x), and the combined organic phases are dried ($MgSO_4$) and concentrated to provide 2.0 g (77%) of the title amine.

Amine 21

The title amine is prepared from Boc-D-alanine (5 g, 24.4 mmol) and indoline (3.2 ml, 29 mmol) by a procedure substantially similar to that described above for Amine 20.

Amine 22

To a solution of [2-(7-cyanomethoxy-1H-indol-3-yl)-1,1-dimethyl-ethyl]-carbamic acid tert-butyl ester (3.8 mmol) is added 2 N NaOH (10.0 mL, 20 mmol). The reaction mixture is reluxed for 2 hours. The reaction mixture is cooled to room temperature, evaporated to about 10 mL, acidified to pH 3.0 with 1 N HCl. The mixture is extracted with ethyl acetate (2 x 50 mL), the combined organic layer washed with brine and dried (Na_2SO_4). Evaporation to dryness afford [3-(2-tert-butoxycarbonylamino-2-methyl-propyl)-1H-indol-7-yloxy]-acetic acid (1.3 g, 95%). FDMS m/e = 363.2 (M^+ +1).
To a solution of [3-(2-tert-butoxycarbonylamino-2-methyl-propyl)-1H-indol-7-yloxy]acetic acid (480 mg, 1.32 mmol) in dimethylformamide (5.0 mL) is added methyl amine (1.52 mL, 1.0 M in tetrahydrofuran, 1.52 mmol) and Bop reagents (670 mg, 1.52 mmol). The reaction mixture is stirred at room temperature for 3 hours before evaporation to dryness. The resulting residue is chromatographed (30% ethyl acetate/hexane) to give 500 mg of [1,1-dimethyl-2-(7-methylcarbamoylmethoxy-1H-indol-3-yl)-ethyl]-carbamic acid tert-butyl ester (75%). FDMS m/e = 375.1 (M^+ +1).

The title amine is prepared from [1,1-dimethyl-2-(7-methylcarbamoylmethoxy-1H-indol-3-yl)-ethyl]-carbamic acid tert-butyl ester as described for the alternate preparation of Amine 6 (66%). FDMS m/e = 276.1 (M^+ +1).

Amine 23

Trifluoro-methanesulfonic acid 3-(2-tert-butoxycarbonylamino-2-methyl-propyl)-1H-indol-7-yl ester (200 mg, 0.46 mmol), methyl acrylate (80 mg, 0.92 mmol) and triethylamine (0.40 mL, 3.0 mmol) is stirred in dimethylformamide (2.0 mL) at room temperature for 30 minutes. Dichlorobis(triphenylphosphine)palladium (31 mg, 0.045 mmol) is added, the reaction mixture is heated to 90^0C and allowed to stir overnight. The reaction is cooled to room temperature, poured into a separatory funnel containing ethyl acetate and brine (50 mL each) and the aqeous layer is extracted with ethyl acetate (50 mL). The combined organic layers are washed with brine, dried (Na_2SO_4) and evaporated. The residue is purified using silica gel chromatography (20% ethyl acetate/hexane) to give 140 mg of 3-[3-(2-tert-butoxycarbonylamino-2-methyl-propyl)-1H-indol-7-yl]-acrylic acid methyl ester (82%). FDMS m/e = 372.2 (M^+ +1).
The title compound is prepared from 3-[3-(2-tert-butoxycarbonylamino-2-methyl-propyl)-1H-indol-7-yl]-acrylic acid methyl ester as described for the alternate preparation of Amine 6 (82%). FDMS m/e = 277.2 (M^+ +1).

Amine 24

3-[3-(2-tert-Butoxycarbonylamino-2-methyl-propyl)-1H-indol-7-yl]-propionic acid methyl ester is prepared from 3-[3-(2-tert-butoxycarbonylamino-2-methyl-propyl)-1H-indol-7-yl]-acrylic acid methyl ester as described below for the preparation of {2-[7-(2-methanesulfonyl-ethyl)-1H-indol-3-yl]-1,1-dimethyl-ethyl}-carbamic acid tert-butyl ester (80%). FDMS m/e = 375.2 (M^+ +1).

The title amine is prepared from 3-[3-(2-tert-Butoxycarbonylamino-2-methyl-propyl)-1H-indol-7-yl]-propionic acid methyl ester as described for the alternate preparation of Amine 6 (100%).

Amine 25

3-[3-(2-tert-Butoxycarbonylamino-2-methyl-propyl)-1H-indol-7-yl]-acrylamide is prepared from [1,1-dimethyl-2-(7-trifluoromethanesulfonylmethyl-1H-indol-3-yl)-ethyl]-carbamic acid tert-butyl ester and acrylamide as described for the preparation of Amine 23 (98%). FDMS m/e = 356.2 (M^+ +1).

The title amine is prepared from 3-[3-(2-tert-butoxycarbonylamino-2-methyl-propyl)-1H-indol-7-yl]-acrylamide as described for the alternate preparation of Amine 6 (83%). FDMS m/e = 258.2 (M^+ +1).

Amine 26

{2-[7-(2-Carbamoyl-ethyl)-1H-indol-3-yl]-1,1-dimethyl-ethyl}-carbamic acid tert-butyl ester is prepared from 3-[3-(2-tert-butoxycarbonylamino-2-methyl-propyl)-1H-indol-7-yl]-acrylamide as described for the preparation of Amine 28 (100%). FDMS m/e = 360.2 (M^+ + 1).

The title amine is prepared from {2-[7-(2-carbamoyl-ethyl)-1H-indol-3-yl]-1,1-dimethyl-ethyl}-carbamic acid tert-butyl ester as described for the alternate preparation of Amine 6 (98%). FDMS m/e = 260.2 (M^+ + 1).

Amine 27

{2-[7-(2-Methanesulfonyl-vinyl)-1H-indol-3-yl]-1,1-dimethyl-ethyl}-carbamic acid tert-butyl ester is prepared from [1,1-dimethyl-2-(7-trifluoromethanesulfonylmethyl-1H-indol-3-yl)-ethyl]-carbamic acid tert-butyl ester and methyl vinyl sulfone as described for the preparation of Amine 23 (98%). FDMS m/e = 392.2 (M^+ +1).

The title amine is prepared from {2-[7-(2-methanesulfonyl-vinyl)-1H-indol-3-yl]-1,1-dimethyl-ethyl}-carbamic acid tert-butyl ester as described for the alternate preparation of Amine 6 (80%). FDMS m/e = 293.2 (M^+ + 1).

Amine 28

To a solution of {2-[7-(2-methanesulfonyl-vinyl)-1H-indol-3-yl]-1,1-dimethyl-ethyl}-carbamic acid tert-butyl ester (0.40 g, 1.02 mmol) in methanol (20.0 mL) is added 10% Pd/C (0.10 g) in methanol (2.0 mL). The reaction mixture is purged with hydrogen and hydrogenation is carried out with a hydrogen balloon overnight. The reaction mixture is filtered and the filtrate is evaporated to dryness to give 320 mg of {2-[7-(2-methanesulfonyl-ethyl)-1H-indol-3-yl]-1,1-dimethyl-ethyl}-carbamic acid tert-butyl ester (80%). FDMS m/e = 395.2 (M^+ +1).

The title amine is prepared from {2-[7-(2-methanesulfonyl-ethyl)-1H-indol-3-yl]-1,1-dimethyl-ethyl}-carbamic acid tert-butyl ester as described for the alternate preparation of Amine 6 (92%). FDMS m/e = 295.2 (M^+ +1).

Amine 29

{2-[7-(2-Cyano-vinyl)-1H-indol-3-yl]-1,1-dimethyl-ethyl}-carbamic acid tert-butyl ester is prepared from [1,1-dimethyl-2-(7-trifluoromethanesulfonylmethyl-1H-indol-3-yl)-ethyl]-carbamic acid tert-butyl ester and acrylonitrile as described for the preparation of Amine 23 (85%). FDMS m/e = 339.2 (M^+ +1).

The title amine is prepared from {2-[7-(2-Cyano-vinyl)-1H-indol-3-yl]-1,1-dimethyl-ethyl}-carbamic acid tert-butyl ester as described for the alternate preparation of Amine 6 (94%). FDMS m/e = 240.2 (M^+ +1).

Amine 30

{2-[7-(2-Cyano-ethyl)-1H-indol-3-yl]-1,1-dimethyl-ethyl}-carbamic acid tert-butyl ester is prepared from {2-[7-(2-cyano-vinyl)-1H-indol-3-yl]-1,1-dimethyl-ethyl}-carbamic acid tert-butyl ester as described for the preparation of Amine 28 (86%). FDMS m/e = 341.2 (M^+ +1).

The title amine is prepared from {2-[7-(2-Cyano-ethyl)-1H-indol-3-yl]-1,1-dimethyl-ethyl}-carbamic acid tert-butyl ester as described for the alternate preparation of Amine 6 (86%). FDMS m/e = 242.2 (M^+ +1).

Amine 31

{1,1-Dimethyl-2-[7-(2-[1,2,4]triazol-1-yl-vinyl)-1H-indol-3-yl]-ethyl}-carbamic acid tert-butyl ester is prepared from [1,1-dimethyl-2-(7-trifluoromethanesulfonylmethyl-1H-indol-3-yl)-ethyl]-carbamic acid tert-butyl ester and 1-vinyl-1,2,4-triazole as described for the preparation of Amine 23 (93%). FDMS m/e = 381.2 (M^+ +1).

The title amine is prepared from {1,1-dimethyl-2-[7-(2-[1,2,4]triazol-1-yl-vinyl)-1H-indol-3-yl]-ethyl}-carbamic acid tert-butyl ester as described for the alternate preparation of Amine 6 (56%). FDMS m/e = 282.2 (M^+ +1).

Amine 32

(1-Methyl-1H-indol-3-yl)-acetonitrile (*J. Org. Chem.*, 63:6053-6058, 1998) is converted to 1-(1-methyl-1H-indol-3-yl)-cyclopentanecarbonitrile and then said carbonitrile compound is converted to the title amine via procedures described in *Eur. J. Med. Chem.*, 31:123-132, 1996.

Amine 34

To a vigorously stirred solution of 2-bromo-4,6-difluoro aniline (100 g, 0.48 mol) in pyridine (400 mL), at 0^0C, is added ethyl chloroformate (70 ml, 0.73 mol) at a rate to keep the temperature below 5^0C. When addition is complete, the mixture is stirred at 0^0C-5^0C an additional 2 hours while monitoring by TLC (20% ethyl acetate/hexane, UV). The reaction is then allowed to warm to room temperature, filtered and the filtrate concentrated. The residue is dissolved in diethyl ether/ethyl acetate (500 ml/250 ml) and washed with H_2O, 2.5 N HCl, aqueous $NaHCO_3$, brine, dried (Na_2SO_4), filtered, concentrated, and triturated with petroleum ether to give 126 g of 2-bromo-4,6-difluoro-N-carbethoxy aniline (94%).

In a 2L flask, 2-bromo-4,6-difluoro-N-carbethoxy aniline (42 g, 150 mmol) in CH_3CN (500 mL) is degassed with vacuum and purged with N_2. Dichlorobis(triphenylphosphine)palladium(II) (10.5 g, 15 mmol, 10 mol%), followed by CuI (710 mg, 4 mmol, 2.5 mol%) and triethyl amine (41 mL) are added and rinsed in with 100 mL of CH_3CN. Trimethylsilyl acetylene (31.8 ml, 225 mmol) is added and reaction is refluxed under N_2. Approximately 2 hours later, the starting material is consumed, indicated by TLC (20% ethyl acetate/hexane, UV). The reaction is cooled, filtered, concentrated, and the residue is dissolved in ethyl acetate, washed with H_2O, brine, dried (Na_2SO_4), filtered, concentrated, and is purified by flash chromatography (SiO_2, ethyl acetate/hexane gradient) to yield 30 g of 2-(trimethylsilylethynyl)-4,6-difluoro-N-carbethoxyaniline (71%).

Fresh sodium ethoxide is prepared by carefully adding NaH (16 g of 60% oil dispersion, 400 mmol) to 550 mL of ethanol under N_2. 2-(Trimethylsilylethynyl)-4,6-difluoro-N-carbethoxyaniline (28 g, 100 mmol) in 150 mL of ethanol is added and reaction is stirred at room temperature approximately 45 minutes, while monitoring by TLC (20% ethyl acetate/hexane, UV) until all the starting material is consumed. The mixture is heated to reflux and monitored by TLC until the intermediate material is consumed (approx. 1 hour). Reaction is cooled to room temperature, concentrated, diethylether is added, washed with H_2O, brine, dried (Na_2SO_4), filtered, concentrated, and is purified by flash chromatography (SiO_2, ethyl acetate/hexane gradient) to yield 12 g of 5,7-difluoro-indole (78%).

The 1.0 M ICl in CH_2Cl_2 (43 ml, 43 mmol) is added to a solution of 5,7-difluoro-indole (6 g, 39 mmol) in 35 ml pyridine under N_2 at 0°C and the resulting mixture is stirred for 30 minutes. The reaction is diluted with toluene and washed with brine, 1N HCl, 1N NaOH, dried (Na_2SO_4), filtered and concentrated. The crude 3-iodo-5,7-difluoroindole is stirred in toluene (85 ml) and 5 N NaOH (70 ml), tetrabutylammonium bromide (1.25 g, 3.9 mmol), then benzenesulfonyl chloride (6.2 ml, 48 mmol) are added and the resulting mixture is stirred 24 hours. The two phase reaction mixture is diluted with toluene, washed with brine, dried(Na_2SO_4), filtered, concentrated and the residue is triturated with diethyl ether/petroleum ether. The resulting solid is filtered to give 14.2 g of N-Benzenesulfonyl-3-iodo-5,7-difluoroindole (87%).

A 3.0 M diethyl ether solution of ethylmagnesium bromide (7.3 ml, 21.8 mmol) is added under N_2 at 0°C to a 95 ml tetrahydrofuran solution of N-benzenesulfonyl-3-iodo-5,7-difluoro-indole (8.4 g, 20 mmol). The resulting mixture is stirred for 20 minutes at 0°C, allowed to warm to room temperature over 20 minutes, then recooled to 0°C. A 20 ml tetrahydrofuran solution of (S) N,N dibenzyl-2-aminopropanal (*Syn. Lett.*, 1997,2, 223-224, 5.1 g, 22 mmol) is added to the reaction mixture and the resulting mixture is stirred 1 hour as it warmed to room temp. The reaction is quenched with aqueous NH_4Cl, extracted with ethyl acetate, washed with brine, dried (Na_2SO_4), filtered, concentrated, and the residue is purified by flash chromatography (SiO_2, ethyl acetate/hexane gradient) to yield 8.4 g of 2-(N,N-dibenzylamino)-1-(1-benzenesulfonyl-5,7-difluoro-1H-indol-3-yl)-propan-1-ol. (77%)

Lithium aluminum hydride (LAH) (0.7 g, 18 mmol) is added portionwise to a dioxane/tetrahydrofuran (90 ml/10 ml) solution of 2-(N,N-dibenzylamino)-1-(1-benzenesulfonyl-5,7-difluoro-1H-indol-3-yl)-propan-1-ol (1.9 g, 3.3 mmol) under N_2 at 0°C. After the addition is complete, the reaction is allowed to warm to room temperature, then is refluxed for 1 hour. The reaction is quenched with H_2O and 15% aqueous NaOH, filtered, and the filtrate is diluted with ethyl acetate, washed with brine, dried (Na_2SO_4), filtered, concentrated, and the residue is purified by flash chromatography (SiO_2, ethyl acetate/hexane gradient) to yield 1.2 g of dibenzyl-[2-(5,7-difluoro-1H-indol-3-yl)-1(S)-methyl-ethyl]-amine (86%).

A 100 ml ethanol mixture of dibenzyl-[2-(5,7-difluoro-1H-indol-3-yl)-1(S)-methyl-ethyl]-amine (930 mg, 2.4 mmol), ammonium formate (1.5 g, 24 mmol), and 10% palladium on charcoal (250 mg, 0.24 mmol) is reluxed 1 hour, cooled, filtered, and concentrated. The residue is purified by flash chromatography using a variable mixture of 90:10:1 CH_2Cl_2/methanol/NH_4OH to give 420 mg of the title amine (83%).

Amine 35

The title amine is prepared from N-benzenesulfonyl-3-iodo-5,7-difluoro-indole and (R) N,N dibenzyl-2-aminopropanal by a procedure substantially similar to that described for Amine 34.

Amines 33 and 36

The title amines are prepared as described in *J. Med. Chem.*, 40:2762-2769, 1997.

Amine 37

NaH (180 mg of 60% oil dispersion, 4.5 mmol) is added to a solution of dibenzyl-[2-(5,7-difluoro-1H-indol-3-yl)-1(R)-methyl-ethyl]-amine (1.4 g, 3.6 mmol) in 20 ml dimethylformamide under N_2 at 0°C. The resulting mixture is stirred for 20 minutes, then is allowed to warm to room temperature over 20 minutes. A 5 ml solution of iodomethane in dimethylformamide (7.2 mmol) is added dropwise and the reaction mixture is stirred for 1 hour. The reaction is quenched with cold aqueous $NaHCO_3$, xtracted with ethyl acetate, washed with brine, dried (Na_2SO_4), filtered, concentrated and is purified by flash chromatography (SiO_2, ethyl acetate/hexane gradient) to yield 1.3 g of dibenzyl-[2-(5,7-difluoro-1-methyl-1H-indol-3-yl)-1(R)-methyl-ethyl]-amine (89%).

Dibenzyl-[2-(5,7-difluoro-1-methyl-1H-indol-3-yl)-1(R)-methyl-ethyl]-amine (1.23 g, 3 mmol) is deprotected in the same manner as Amine 34 to give 500 mg of the title amine (76%).

Amine 38

$POCl_3$ (10.9 ml, 71 mmol) is added dropwise to 21 ml of dimethylformamide under N_2 at 10-20°C, is stirred 15 minutes, then a 13 ml dimethylformamide solution of 5-methoxy-6-fluoro-indole (*J. Med. Chem.*, 22:63-69, 1979; 10.7 g, 64.7 mmol) is added at a rate to keep the reaction temperature between 10 and 20°C. After the addition is complete, the mixture is stirred for 1 hour. Crushed ice and aqeuous NaOH (12.5 g/50 ml H_2O) is added to reaction. The resulting mixture is heated to reflux with a heat gun for 1 minute, cooled to 10°C, and is filtered to give 11.8 g of 6-fluoro-5-methoxy-1H-indole-3-carbaldehyde (95%).

A mixture of nitroethane(44 ml, 611 mmol), 6-fluoro-5-methoxy-1H-indole-3-carbaldehyde (11.8 g, 61 mmol), and ammonium acetate(1.78 g, 23 mmol) is stirred at

100°C for 3 hours, allowed to cool, and is filtered to give 14 g of 6-fluoro-5-methoxy-3-(2-nitro-propenyl)-1H-indole (92%).

A 45 ml tetrahydro solution of 6-fluoro-5-methoxy-3-(2-nitro-propenyl)-1H-indole (2.83 g, 11,3 mmol) is added dropwise to a 60 ml tetrahydrofuran suspension of LAH (2.14 g, 56.5 mmol) at 0°C, and the resulting mixture is allowed to warm to room temperature, then is refluxed for 1 hour. The reaction is quenched with H_2O and 15% aqueous NaOH, then is filtered, concentrated, and the filtrate is diluted with ethyl acetate, washed with brine, dried (Na_2SO_4), filtered, concentrated, and the residue is purified by flash chromatography (90:10:1 CH_2Cl_2/methanol/NH_4OH) to give 1 g of the title amine (41%).

Amine 39

A 0 °C solution of 4-hydroxyindole (20 g, 150 mmol) in 500 ml of dimethylformamide is treated with NaH (60% dispersion in mineral oil; 6.6 g, 165 mmol). After 30 minutes, bromoacetonitrile (11.5 ml, 165 mmol) is added, and the resulting mixture is allowed to slowly warm to ambient temperature and stir for 3 days. The reaction mixture is diluted with ethyl acetate and washed 3 times with H_2O. The organic layer is dried over Na_2SO_4 and concentrated *in vacuo*. The crude residue is purified by normal phase HPLC (SiO_2; 5% step gradient of 0 to 20% ethyl acetate in hexanes) to give 25 g of (1*H*-indol-4-yloxy)acetonitrile (97%).

A 0°C solution of (1*H*-indol-4-yloxy)acetonitrile (5.93 g, 34.4 mmol) in 175 ml of tetrahydrofuran is treated with NaH (60% dispersion in mineral oil; 1.65 g, 41.3 mmol). After 1 hour, (*S*)-(-)-propylene oxide (4 g, 68.9 mmol) is added, and the resulting mixture is allowed to slowly warm to ambient temperature and stir for 3 days. The reaction mixture is quenched with H_2O and extracted with ethyl acetate. The organic layer is dried over Na_2SO_4 and concentrated *in vacuo*. Purification of the crude residue (SiO_2; 10% step gradient of 0 to 40% ethyl acetate in hexanes) affords 2.1 g of the alkylated product (26%).

A 0°C solution of the alkylated product (1.8 g, 7.82 mmol) in 40 ml of CH_2Cl_2 and 3.3 ml of triethylamine is treated with methanesulfonyl chloride (1.2 ml, 15.6 mmol). After 1 hour, the reaction mixture is diluted with ethyl acetate (100 ml) and 1M aqueous

Na_2CO_3 solution (100 ml). The organic layer is washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. The crude mesylate is dissolved in 40 ml of dimethylformamide, and NaN_3 (1.0 g, 15.6 mmol) is added. The resulting mixture is heated at 60°C for 4.5 hours, then poured into H_2O (100 ml) and extracted with ethyl acetate (2 x 100 ml). The combined organic extracts are washed with brine (100 ml), dried over Na_2SO_4 and concentrated *in vacuo*. The crude azide is dissolved in 25 ml of tetrahydrofuran and treated with triphenylphosphine (2.56 g, 9.78 mmol). After stirring at room temperature for 1 hour, the reaction mixture is heated at 60°C for 3 hours. Water (10 ml) is added to hydrolyze the intermediate aza-ylide and heating is continued for an additional 3 hours. Upon cooling to ambient temperature, the reaction mixture is diluted with ethyl acetate (200 ml) and brine (200 ml). The organic layer is washed with brine (100 ml), dried over Na_2SO_4 and concentrated *in vacuo*. Purification of the crude residue (SiO_2; 100% $CHCl_3$ then 2.5% 2M NH_3/methanol in $CHCl_3$) affords 1.65 g (7.2 mmol; 92%) of the title amine.

Amines 40 and 41

The title Amines are prepared from methyl indole-4-carboxylate and methyl indole-5-carboxylate, respectively, substantially as described for Amine 39.

Amine 46

A 0°C solution of indole (7 g, 59.8 mmol) in 200 ml of dimethylformamide is treated with NaH (60% dispersion in mineral oil; 3.1 g, 77.7 mmol). After 20 minutes, bromoacetonitrile (4.2 ml, 59.8 mmol) is added, and the resulting mixture is allowed to slowly warm to ambient temperature and stir overnight. The reaction mixture is diluted with ethyl acetate (500 ml) and washed with H_2O (3 x 200 ml). The organic layer is dried over Na_2SO_4 and concentrated *in vacuo*. The crude residue is purified by flash chromatography (SiO_2; 5% then 20% ethyl acetate in hexanes) to give 2.53 g of indol-1-yl-acetonitrile (27%).

A solution of indol-1-yl-acetonitrile (2.5 g, 16 mmol) in 100 ml of ethanol and 15 ml of anhydrous NH_3 is treated with Raney nickel (300 mg). The resulting mixture is

heated for 8 hours (80°C) under an atmosphere of H_2 (300 psi). The reaction mixture is filtered over celite and concentrated *in vacuo*. Purification of the crude residue (SiO_2; 2% then 4% 2M NH_3/methanol in $CHCl_3$) affords 715 mg of the title amine (28%).

Amines 42, 43, 44 and 48

The title amines are prepared from 5-hydroxyindole, 4-hydroxy-2-methylindole, indole and 6-hydroxyindole, respectively, substantially as described for Amine 39.

Amine 49

A slurry of 4-fluoro-3-(dimethylaminomethyl)-1*H*-indole (4.3 g, 22.4 mmol) in 14.1 ml of 2-nitropropane is treated with solid NaOH (941 mg, 23.5 mmol), and the resulting mixture is heated at reflux overnight. After cooling to ambient temperature, the reaction mixture is acidified with 10% aqueous acetic acid (25 ml) and stirring is continued for 30 minutes. The reaction mixture is diluted with ethyl acetate (50 ml) and brine (50 ml). The layers are separated, and the organic layer is washed with brine (50 ml), dried over Na_2SO_4 and concentrated *in vacuo* to give 3.71 g of 4-fluoro-3-(2-methyl-2-nitropropyl)-1*H*-indole (76%).

A solution of 4-fluoro-3-(2-methyl-2-nitropropyl)-1*H*-indole (3.7 g, 17.0 mmol) in 95 ml of ethanol and 70 ml of ethyl acetate is treated with 5% Pd/C (900 mg) and the resulting mixture is shaken for 6 hours at ambient temperature under an atmosphere of H_2 (60 psi). Additional 5% Pd/C (900 mg) is added, and the reaction mixture is re-subjected to H_2 at 60 psi while being heated overnight at 50°C. The reaction mixture is filtered over celite and concentrated *in vacuo*. Purification of the crude residue (SiO_2; 1% step gradient of 0 to 10% 2M NH_3/methanol in $CHCl_3$) affords 1.16 g of the title amine (33%).

Amine 50

Amine 50 is prepared from 5-fluoro-3-(dimethylaminomethyl)-1*H*-indole in a method similar to that described for the preparation of Amine 49.

Amine 51

Methyl indole-4-carboxylate (7.0 g, 40 mmol) and Eschenmoser's salt (*N,N*-dimethylmethyleneammonium iodide; 7.8 g, 42 mmol) are combined in 130 ml of acetic acid. After heating at 65°C for 2 hours, the reaction mixture is concentrated *in vacuo*. The resulting solid is triturated with ethyl acetate, filtered and dried *in vacuo* to give 3-dimethylaminomethyl-1*H*-indole-4-carboxylic acid methyl ester hydroiodide in quantitative yield.

A 0 °C solution of 3-dimethylaminomethyl-1*H*-indole-4-carboxylic acid methyl ester hydroiodide (19 g, 52.7 mmol) in 75 ml of methanol and 75 ml of 2-nitropropane is treated with dimethyl sulfate (10 ml, 105.5 mmol) and solid sodium methoxide (6.3 g, 110.6 mmol) sequentially. The resulting mixture is allowed to warm to ambient temperature, and, after stirring overnight, the reaction mixture is diluted with ethyl acetate (300 ml) and saturated aqueous NH_4Cl solution (500 ml). The aqueous layer is extracted with ethyl acetate (200 ml), and the combined organic layers are dried over Na_2SO_4 and concentrated *in vacuo* to give 3-(2-methyl-2-nitropropyl)-1*H*-indole-4-carboxylic acid methyl ester in quantitative yield.

A solution of 3-(2-methyl-2-nitropropyl)-1*H*-indole-4-carboxylic acid methyl ester (14.8 g, 53.6 mmol) in 70 ml of tetrahydrofuran and 70 ml of ethyl acetate is treated with Raney nickel (3.3 g) and the resulting mixture is heated overnight (60 °C) under an atmosphere of H_2 (60 psi). The reaction mixture is filtered over celite and concentrated *in vacuo*. Purification of the crude residue (SiO_2; 2.5% step gradient of 2.5 to 20% 2M NH_3/methanol in $CHCl_3$) affords 9.21 g of the title amine (71%).

Amine 53

A solution of Amine 52 (1.0 g, 4.06 mmol) and NH_4Cl (800 mg, 15 mmol) in 100 ml of methanol is charged with 5 ml of anhydrous NH_3. The resulting mixture is sealed in a bomb and heated at 150°C for 40 hours. The reaction mixture is cooled and concentrated *in vacuo*. The crude residue is purified by radial chromatography (SiO_2; 10% 2M NH_3/methanol in $CHCl_3$) to afford 344 mg of the title amine (37%).

Amine 55

A 0 °C solution of 1,2-diamino-2-methylpropane (650 ml, 6.21 mmol), indole-3-carboxylic acid (1.0 g, 6.21 mmol) and *N,N*-diisopropylethylamine (2.7 ml, 15.2 mmol) in 30 ml of CH_2Cl_2 is treated with 1-[3-dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (1.2 g, 6.21 mmol). The resulting mixture is allowed to warm to ambient temperature and stir overnight. The reaction mixture is washed with H_2O, dried over Na_2SO_4 and concentrated *in vacuo*. Purification of the crude residue (SiO_2; 10% 2M NH_3/methanol in $CHCl_3$) affords 752 mg of the title amine (52%).

Amine 57

6-Fluoro-3-(2-methyl-2-nitropropyl)-1*H*-indole is prepared from 6-fluoro-3-(dimethylaminomethyl)-1*H*-indole by a method similar to that described for Amine 49, paragraph 1.

A solution of 6-fluoro-3-(2-methyl-2-nitropropyl)-1*H*-indole (1.16 g, 4.91 mmol) in 6 ml of tetrahydrofuran and 12 ml of methanol is treated with $CuSO_4 \cdot 5H_2O$ (400 mg, 1.35 mmol) and $NaBH_4$ (882 mg, 23.3 mmol). The resulting mixture is stirred at ambient temperature for 30 minutes and then diluted with H_2O (20 ml), CH_2Cl_2 (20 ml) and concentrated NH_4OH (5 ml). After 1 hour, the layers are separated, and the organic layer is dried over Na_2SO_4 and concentrated *in vacuo* to afford 951 mg of the title amine (94%).

Amine 58

6-Benzyloxyindole-3-carboxaldehyde is converted to 2-(6-benzyloxy-1*H*-indoyl-3-yl)-1,1-dimethylethylamine by sequentially following the procedures detailed for Amine 61, 1st paragraph, then for Amine 57, 1st and 2nd paragraphs.

A solution of 2-(6-benzyloxy-1*H*-indoyl-3-yl)-1,1-dimethylethylamine (4.9 g, 16.6 mmol) in 125 ml of CH_2Cl_2 is treated with t-butyloxycarbonyl anhydride (BOC_2O; 4.0 ml, 17.5 mmol). After stirring overnight at ambient temperature, the reaction mixture is diluted with H_2O, and the layers are separated. The organic layer is dried over Na_2SO_4 and concentrated *in vacuo*. The crude residue is purified by flash chromatography (SiO_2; 20% ethyl acetate in hexanes) to give 5.01 g of [2-(6-benzyloxy-1*H*-indoyl-3-yl)-1,1-dimethylethyl]carbamic acid *tert*-butyl ester (76%).

A solution of [2-(6-benzyloxy-1*H*-indoyl-3-yl)-1,1-dimethylethyl]carbamic acid *tert*-butyl ester (4.62 g, 11.7 mmol) in 300 ml of ethanol is treated with 5% Pd/C (1.0 g), and the resulting mixture is shaken under an atmosphere of H_2 at 60 psi overnight at ambient temperature. The reaction mixture is filtered over celite and concentrated *in vacuo*. The crude phenol is dissolved in 100 ml of dimethylformamide and treated with triton-B (8.5 ml, 17.6 mmol) and bromoacetonitrile (900 microliters, 12.8 mmol). After 1.5 hours, the reaction mixture is diluted with H_2O (100 ml), and the aqueous layer is extracted with ethyl acetate (3 x 100 ml). The combined organic extracts are washed with H_2O (2 x 100 ml), dried over Na_2SO_4 and concentrated *in vacuo*. The crude residue is purified by flash chromatography (SiO_2; 20% ethyl acetate in hexanes) affording 954 mg of BOC protected amine 58 (24%).

The BOC protected amine is deprotected substantially as described for Amine 6 to give the title amine 58 in 66% yield.

Amine 59

The title amine is prepared from 5-benzyloxy-3-(dimethylaminomethyl)-1*H*-indole by following the procedures detailed for Amine 57, 1st and 2nd paragraphs, followed by the methods described for Amine 58, 2nd – 4th paragraphs.

Amine 60

Amine 60 is prepared from 7-fluoroindole by sequentially following the methods described for Amine 51, 1st paragraph; Amine 49, 1st paragraph; and Amine 51, 3rd paragraph.

Amine 61

A solution of methyl 3-formylindole-6-carboxylate (8.0 g, 39.3 mmol) in 270 ml methanol is treated with dimethylamine (40% aqueous; 267 ml, 2.56 mol) at ambient temperature. After 45 minutes, $NaBH_4$ (4.45 g, 118.1 mmol) is added, and the resulting mixture is heated at 55°C for 3 hours. The reaction mixture is allowed to cool then is diluted with $CHCl_3$ (200 ml) and brine (150 ml). The organic layer is washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. The crude residue is purified by flash chromatography (SiO_2; 100% ethyl acetate then 20% 2M NH_3/methanol in $CHCl_3$) to give 9.07 g of 3-dimethylamino-methyl-1*H*-indole-6-carboxylic acid methyl ester (99%). Amine 61 is prepared from 3-dimethylaminomethyl-1*H*-indole-6-carboxylic acid methyl ester by essentially following the procedures detailed in Amine 49, 1st paragraph; and Amine 51, 3rd paragraph.

Amines 52, 56, 62, 65 and 87

The title amines are prepared from methyl indole-5-carboxylate, 5-cyanoindole, methyl indole-7-carboxylate, 6-cyanoindole and 4-cyanoindole, respectively, in a method similar to that described for the preparation of Amine 51.

Amine 63

Amine 63 is prepared from Amine 62 in 61% yield by essentially following the procedure described for Amine 53.

Amine 64

The title amine is prepared as described for Amines 8a and 8b, 1st-6th paragraphs.

Amine 66

A solution of [2-(7-hydroxy-1H-indol-3-yl)-1,1-dimethyl-ethyl]-carbamic acid tert-butyl ester (609 mg, 2.0 mmol) is dissolved in dry dimethylformamide (30 ml) under a nitrogen atmosphere and treated with sodium hydride (84 mg, 2.1 mmol, 60% dispersion in oil) added portion-wise over a 10 minute period. The mixture is cooled in an ice/water bath and methyl-2-chloroacetate (434 mg, 4.0 mmol) is added drop-wise over 20 minutes. The ice bath is removed and the mixture stirred at room temperature for 15 hours. The reaction is then quenched with saturated brine and extracted with ethyl acetate. The ethyl acetate layer is dried and concentrated to give a crude residue, which is purified by silica gel chromatography (gradient elution, chloroform with 1%-10% of 20% methanol in acetonitrile) to give 230 mg of [2-(7-(methoxycarbomethoxy)-1H-indol-3-yl)-1,1-dimethyl-ethyl]-carbamic acid tert-butyl ester (30%).

A solution of methanesulfonamide (106 mg, 1.12 mmol) and trimethyl aluminum (2.0 M in hexanes, 0.56 ml, 1.12 mmol) in dry dichloromethane (5.0 ml) is stirred at room temperature under a nitrogen atmosphere for 20 minutes. A solution of [2-(7-(methoxycarbomethoxy)-1H-indol-3-yl)-1,1-dimethyl-ethyl]-carbamic acid tert-butyl ester (160 mg, 0.425 mmol) in dry dichloromethane (1.5 ml) is added and the mixture is heated under reflux for 15 hours. The mixture is cooled to room temperature and quenched with 1 N HCl solution (3.4 ml) and partitioned between ethyl acetate and water. The organic extracts are dried over anhydrous Na_2SO_4, filtered and the solvent evaporated to give 220 mg of [2-(7-(methanesulfonamidylcarbomethoxy)-1H-indol-3-yl)-1,1-dimethyl-ethyl]-carbamic acid tert-butyl ester (90%).

The title amine is prepared from [2-(7-(methanesulfonamidylcarbomethoxy)-1H-indol-3-yl)-1,1-dimethyl-ethyl]-carbamic acid tert-butyl ester as described for the preparation of Amine 1 (108 mg, 70%).

Amine 67

[2-(7-Cyanomethoxy-1H-indol-3-yl)-1,1-dimethyl-ethyl]-carbamic acid tert-butyl ester (500 mg, 1.46 mmol) is dissolved in borane in tetrahydrofuran (3.0 ml of a 1M solution, 3.0 mmol) under a nitrogen atmosphere and the resulting mixture is stirred at room temperature for 18 hours. The mixture is then hydrolyzed by the addition of methanol saturated with HCl gas (1.5 ml) followed by stirring at room temperature for 30 minutes. The solvent is evaporated and the residue treated with saturated aqueous sodium bicarbonate (20 ml). The aqueous mixture is extracted with ethyl acetate (3 x 25ml). The combined ethyl acetate layers are dried and concentrated to give a crude residue, which is purified by elution from SCX resin (20% of 2M NH_3 in methanol in $CHCl_3$) to give after evaporation 390 mg of [2-(7-(2-aminoethoxy)-1H-indol-3-yl)-1,1-dimethyl-ethyl]-carbamic acid tert-butyl ester (77%).

[2-(7-(2-Aminoethoxy)-1H-indol-3-yl)-1,1-dimethyl-ethyl]-carbamic acid tert-butyl ester (270 mg, 0.78 mmol) and 1*H*-benzotriazol-1-yl methanesulfonate (*Tet. Lett.*, 40:117-120, 1999; 170 mg, 0.82 mmol) in dry dimethylformamide (6.0 ml) is stirred at room temperature under a nitrogen atmosphere for 3 hours. The mixture is diluted with water (20 ml) and extracted with ethyl acetate (2 x 20 ml). The combined organic extracts are washed with brine, dried over anhydrous Na_2SO_4, filtered and the solvent evaporated. The residue is taken up in 5% 2M NH_3 in methanol in $CHCl_3$ (5 ml) and the solid removed by filtration. Evaporation of the filtrate gives 270 mg of 2-(7-(2-methanesulfonylaminoethoxy)-1H-indol-3-yl)-1,1-dimethyl-ethyl]-carbamic acid tert-butyl ester (82%).

2-(7-(2-methanesulfonylaminoethoxy)-1H-indol-3-yl)-1,1-dimethyl-ethyl]-carbamic acid tert-butyl ester (350 mg, 0.82 mmol) is deprotected with 4.0M HCl in dioxane to give 170 mg of the tiile compound (89%).

Amines 68-71

The title amines are prepared from trifluoro-methanesulfonic acid 3-(2-tert-butoxycarbonylamino-2-methyl-propyl)-1H-indol-7-yl ester and: 4-methoxycarbonylbenzeneboronic acid; 4-acetamidylbenzeneboronic acid; 3-

methoxycarbonylbenzeboronic acid; and 5-methoxycaronylthiophen-2-ylboronic acid, respectively, using the procedure described for the preparation of Amine 2.

Amine 72

The title amine is prepared from [1,1-dimethyl-2-(7-trifluoromethanesulfonylmethyl-1H-indol-3-yl)-ethyl]-carbamic acid tert-butyl ester and 1-vinylimidazole as described for the preparation of Amine 23 (36%) FDMS m/e = 282.2 ($M^+ + 1$).

Amine 73

(2-{7-[2-(4-Cyano-phenyl)-vinyl]-1H-indol-3-yl}-1,1-dimethyl-ethyl)-carbamic acid tert-butyl ester is prepared from [1,1-dimethyl-2-(7-trifluoromethanesulfonylmethyl-1H-indol-3-yl)-ethyl]-carbamic acid tert-butyl ester and 4-cyanostyrene as described for the preparation of Amine 23 (93%). FDMS m/e = 315.2 ($M^+ +1$).
The title amine is prepared from (2-{7-[2-(4-cyano-phenyl)-vinyl]-1H-indol-3-yl}-1,1-dimethyl-ethyl)-carbamic acid tert-butyl ester as described for the preparation of Amine 28. FDMS m/e = 318.2 ($M^+ +1$).

Amine 74

{1,1-Dimethyl-2-[7-(2-pyrazin-2-yl-vinyl)-1H-indol-3-yl]-ethyl}-carbamic acid tert-butyl ester is prepared from [1,1-dimethyl-2-(7-trifluoromethanesulfonylmethyl-1H-indol-3-yl)-ethyl]-carbamic acid tert-butyl ester and 2-vinylpyrazine as described for the preparation of Amine 23 (99%). FDMS m/e = 393.2 ($M^+ +1$)

The Boc-protecting group on {1,1-dimethyl-2-[7-(2-pyrazin-2-yl-vinyl)-1H-indol-3-yl]-ethyl}-carbamic acid tert-butyl ester is removed as described in Amine 6 to give the title amine (94%) FDMS m/e = 293.2 ($M^+ + 1$).

Amine 75

The title amine is prepared from [1,1-dimethyl-2-(7-trifluoromethanesulfonylmethyl-1H-indol-3-yl)-ethyl]-carbamic acid tert-butyl ester and p-sulfonamido styrene as described for the preparation of Amine 23 (70%). FDMS m/e = 370.2 (M^+ + 1).

Amine 76

Trifluoro-methanesulfonic acid 3-(2-tert-butoxycarbonylamino-2-methyl-propyl)-1H-indol-6-yl ester is prepared from 6-benzyloxy gramine and 2-nitropropane as described in the preparation of Amine 1, 1st-5th paragraphs. Trifluoromethanesulfonic acid 3-(2-tert-butoxycarbonylamino-2-methyl-propyl)-1H-indol-6-yl ester and acrylonitrile are reacted and the Boc-protecting group is removed from the resulting product as described in the prepararation of Amine 23 to give the title amine (75%). FDMS m/e = 240.2 (M^+ +1).

Amine 77

The 7-nitroindole (20.0 g, 123.3 mmol) and Eschenmoser's salt (24.0 g, 129.5 mmol) are suspended in glacial acetic acid (500 mL) and stirred at 65 °C for 1 hour. The reaction mixture is cooled and the resulting solid filtered, and washed with ethyl acetate (2 x 50 mL). This solid is then dried in a vacuum oven overnight to yield 39.3 g of the desired 7-nitrogramine hydroiodide salt (89.4%).

The 7-nitrogramine salt (2.0 g, 5.8 mmol) is suspended in a mixture of 2-nitropropane (9.5 mL) and methanol (9.5 mL). Dimethylsulfate (1.09 mL, 11.5 mmol) is added dropwise via syringe, and the resulting yellow solution is stirred at room temperature for 5 minutes. Sodium methoxide (0.62 g, 11.5 mmol) is then added in one portion, and the mixture is stirred overnight at room temperature. The reaction is quenched by addition of saturated NH_4Cl solution and ethyl acetate. The aqueous layer is extracted with ethyl acetate, and the combined organic layers are washed with brine, and dried over Na_2SO_4 to give 1.0 g of 3-(2-nitro-2-methylpropyl)-7-nitroindole (69%).

3-(2-Nitro-2-methylpropyl)-7-nitroindole (1.89 g, 7.2 mmol) is dissolved in ethyl acetate (75 mL) and 10% Pd/C is added (750 mg). The mixture is stirred under a balloon of nitrogen for 2-3 hours. The mixture is filtered to remove the Pd/C, and the filtrate is evaporated to give a crude oil. This crude 3-(2-nitro-2-methylpropyl)-7-aminoindole is immediately dissolved in pyridine (100 mL) and the solution is cooled with an ice bath to 0°C. Benzenesulfonyl chloride is added slowly, and the mixture is stirred for 5 minutes at this temperature before removing the ice bath. The reaction mixture is stirred overnight before being quenched by addition of 1N HCl and ethyl acetate. The aqueous layer is extracted with ethyl acetate several times and the combined organic extracts are washed twice with brine and dried over Na_2SO_4 to give a crude oil. The crude material is purified by flash chromatography (25% ethyl acetate/hexanes) to provide 1.9 g of 3-(2-nitro-2-methylpropyl)-7-benzenesulfonamidyl-indole (71%).

3-(2-Nitro-2-methylpropyl)-7-benzenesulfonamidyl-indole (1.90 g, 5.1 mmol) is charged to a Parr reaction vessel and is dissolved in 3A-ethanol (500 mL). Raney Nickel (5 g) is added to the solution. The reaction is pressurized with hydrogen and is hydrogenated overnight at 60 °C under a hydrogen pressure of 60 psi. When the reaction is complete, the reaction mixture is cooled to ambient temperature and the Raney Nickel is removed by vacuum filtration. The solvent is evaporated to give the title amine.

Amine 78

3-(2-Nitro-2-methylpropyl)-7-methanesulfonamidyl-indole is prepared from crude 3-(2-nitro-2-methylpropyl)-7-aminoindole and methanesulfonyl chloride and 3-(2-nitro-2-methylpropyl)-7-methanesulfonamidyl-indole is converted to the title amine by the procedure described for Amine 77 (2.3 g).

Amine 79

The Boc-protected title amine is prepared from Boc-α-methylalanine and indoline by the procedure described above for Amine 20 except that the reaction is conducted in dichloromethane and the crude Boc-protected amine is purified by normal phase flash chromatography (silica gel, 20-60% ethyl acetate/hexanes).

To a mixture of the Boc-protected title amine (1.0 g, 3.3 mmol) in dioxane (8 mL) at room temperature is added 4M HCl/dioxane (8 mL). The reaction mixture is stirred overnight at room temperature, and then concentrated. The resulting material is dissolved in methanol (10 mL), purified using a cation exchange column, and concentrated to give 640 mg of the title amine (95%).

Amine 80

To a solution of {1,1-dimethyl-2-[7-(2-[1,2,4]triazol-1-yl-vinyl)-1H-indol-3-yl]-ethyl}-carbamic acid tert-butyl ester (1.0 g, 2.55 mmol) in methanol (20.0 mL), is added 10% Pd/C (0.50 g) in methanol (2.0 mL). The reaction mixture is purged with hydrogen and hydrogenation is carried out with a hydrogen balloon overnight. The reaction mixture is filtered, and the filtrate is evaporated to dryness to give 850 mg of {2-[7-(2-methanesulfonyl-ethyl)-1H-indol-3-yl]-1,1-dimethyl-ethyl}-carbamic acid tert-butyl ester (81%). FDMS m/e = 395.2 (M^+ + 1).

To solution of {1,1-Dimethyl-2-[7-(2-[1,2,4]triazol-1-yl-ethyl)-1H-indol-3-yl]-ethyl}-carbamic acid tert-butyl ester (220 mg, 0.57 mmol) in dioxane (5.0 mL) at room temperature is added 4N HCl (5.0 mL). The reaction mixture is stirred at room temperature for 1 hour. The reaction mixture is evaporated to dryness, residue is taken up with water (25.0 mL), saturated $NaHCO_3$ (5.0 mL) is added, and the mixture is extracted with ethyl acetate (2 x 50 mL). The organic extracts are washed with brine, dried (Na_2SO_4) and evaporated to dryness to give 150 mg of the title amine (90%).

Amine 81

3-Trifluoromethyl-bromobenzene (1 equivalent) is dissolved in dimethylsulfoxide (3 ml/mmol) under argon and bis-(pinacolato)-diboron (1.1 equivalents), potassium acetate (3 equivalents) and 1,1'-bis(diphenylphosphino)ferrocene)palladium(II)dichloride-dichlormethane complex (0.03 equivalents) are added. The resulting mixture is heated to 80°C and then stirred for two hours at this temperature. The mixture is cooled to room temperature, and trifluoro-methansulfonic acid 3-(2-tert-butoxycarbonylamino-2-methyl-propyl)-1H-indol-7-yl ester (0.8 equivalents), 1,1'-bis(diphenylphosphino)

ferrocene)palladium(II)dichloride-dichlormethane (0.03 equivalents) and 2M Na_2CO_3 (5 equivalents) are added under argon. The resulting mixture is heated to 80°C and then allowed to stir overnight at this temperature. The mixture is diluted with water and extracted with ethyl acetate or CH_2Cl_2. The organic extract is washed once with brine, then dried over Na_2SO_4, filtered and evaporated. The residue is chromatographed (silica gel, CH_2Cl_2/ethanolic NH_3, 98/2) to give the Boc-protected title compound.

The Boc-protected amine is dissolved in 5N HCl in isopropanol (5 ml/mmol) and stirred overnight at room temperature. The mixture is evaporated, dissolved in ethanol and loaded onto a 5 g SCX column conditioned with methanol. The column is washed twice with 5 ml ethanol to remove impurities. The title compound is then eluted with 5 ml ethanolic NH_3 and 5 ml ethanol. Evaporation of the solvent gives the deprotected amine.

Amines 82-84

The title amines are prepared from trifluoro-methansulfonic acid 3-(2-tert-butoxycarbonylamino-2-methyl-propyl)-1H-indol-7-yl ester and: ethyl 3-bromobenzoate; 3'-bromoacetophenone; and 4'-bromoacetophenone, respectively, using the procedure described for the preparation of Amine 81.

Amine 85

Amine 85 is prepared by hydrolysis of the methyl ester of Amine 62 by essentially following the procedure detailed for Amine 86.

Amine 86

A solution Amine 61 (2 g, 8.12 mmol) in 24 ml of tetrahydrofuran and 8 ml of MeOH is treated with 1M aqueous LiOH (8.1 ml). The resulting mixture is heated overnight at 60 °C. An additional portion of 1M aqueous LiOH (2 ml) is added and heating is continued for 24 hours to drive the hydrolysis to completion. The reaction mixture is concentrated *in vacuo* to give the crude lithium salt as a white solid.

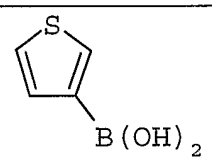
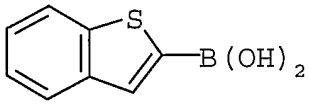
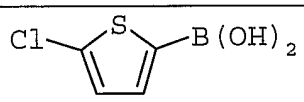
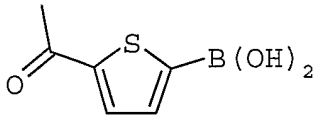
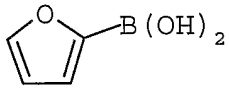
Amine 88

Amine 88 is prepared from indole-2-carboxylic acid and 1,2-diamino-2-methylpropane by essentially following the procedure detailed for Amine 55.

Boronic Acids

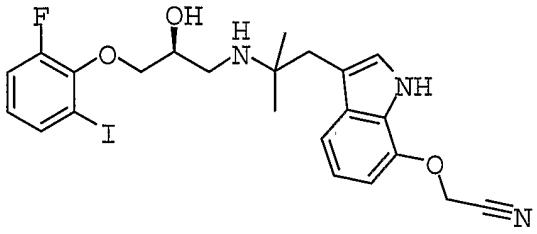
Boronic Acids 1-5 are obtained from commercial sources for use as described in Scheme 2. These boronic acids are pictured below in Table 3.

Table 3

 1	 2	 3
 4	 5	

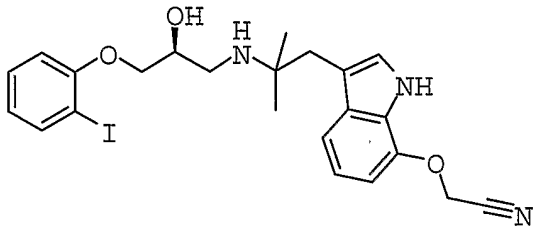
Aryl Halides of Formula V

Aryl Halide 1



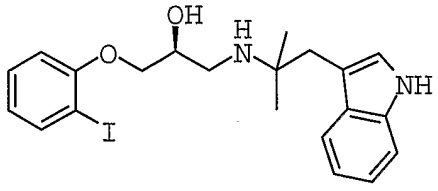
A solution of Epoxide 22 (496 mg, 1.69 mmol) and Amine 6 (410 mg, 1.69 mmol) in dry ethanol (10 ml) is heated at 110°C overnight. After evaporation of the solvent, the residue is purified via flash chromatography (silica gel, dichloromethane/ethanol 95:5 to 85:15) to give 150 mg of the title compound (17%). MS m/e = 538.2 (M^+ + 1).

Aryl Halide 2



The title compound is prepared from Epoxide 31 and Amine 6 as described above for Aryl Halide 1.

Aryl Halide 3



The title compound is prepared from Epoxide 31 and Amine 11 as described above for Aryl Halide 1.

Representative Procedure 1: Amination of Epoxide

A vial is charged with a solution of single amine of formula III (0.2M in ethanol or t-butanol, 90 micromolar) and a solution of a single epoxide of formula II (0.2M in dimethylsulfoxide, 80 micromolar). The vial is sealed and heated to 80°C for 24-48 hours. The solution is cooled to room temperature, diluted with methanol, and passed over a cation exchange column, eluting the basic material with 1N methanolic ammonia.

Representative Procedure 2: Amination of Epoxide

A stirred mixture of an epoxide of formula II (1 equivalent) and an amine of formula III (1-2 equivalents) in ethanol, methanol, n-butanol or t-butanol is heated at 70-80°C for 2-72 hours. The solvent is evaporated to dryness to give a crude oil that is optionally diluted with methanol or ethanol and passed over a cation exchange column (eluting the free base product with 1N methanolic ammonia) before further purification.

The final products prepared via Representative Procedure 1 or 2 may be further purified by flash or radial chromatography. Typical chromatography conditions include: a) using a variable mixture of 25:5:1 chloroform/methanol/ammonium hydroxide and 9:1 chloroform/methanol; b) a variable mixture of 90:10:1 CH_2Cl_2/ethanolic NH_3 gradient; c) dichloromethane/6-12% methanol, 0.15-0.35M ammonia in dichloromethane gradient; d) methylene chloride with a step gradient to 2-8% methanol; e) chloroform/2.0M ammonia in methanol, from 0-10% to 6-20% gradient elution or f) isocratic 6-8% 2M ammonia in methanol: 92-94% dichloromethane.

Alternatively, the final products may be purified on C18 bonded silica gel using either mass guided or UV guided reverse phase liquid chromatography (acetonitrile/water with 0.01% hydrochloric acid or 0.1% trifluoroacetic acid). When purification of a compound of the present invention results in production of a free base, the free base thus prepared may be salified, e.g., by dissolution of the free base in CH_2Cl_2 or diethylether, adding 1M ethanolic HCl or a solution of HCl in diethylether, and evaporating the volatiles, or as described in more detail below.

For example, a hydrochloride salt may be prepared by dissolving the free base in dichloromethane, diethylether, or a mixture of ethyl acetate and methanol and adding 1M ethanolic HCl, a solution of HCl in diethylether, or 0.5M ammonium chloride. The

resulting mixture is allowed to stir for a short time, e.g., for five minutes, before evaporating the volatiles and optionally triturating in diethyl ether to give the hydrochloride salt.

The oxalate salts may be prepared by dissolving the free base in a small amount of ethyl acetate, optionally adding methanol for solubitity. The resulting solution is treated with 1 equivalent of a 0.5M solution of oxalic acid in ethyl acetate. The reaction mixture is either concentrated *in vacuo* or centrifuged, separated, and the solids are dried, to give the oxalate salt.

To prepare a succinate salt, the free base may be dissolved in a small amount of ethyl acetate or methanol and then treated with 1 equivalent of succinic acid in methanol. The resulting slurry is dissolved in the minimum amount of methanol then concentrated *in vacuo* to give the succinate salt.

The table below sets out representative combinations of Amines and Epoxides that are reacted as described in Representative Procedure 1 or 2. Preparation of desired product is confirmed via mass spectral analysis (MSA). Emax ± Standard Error Mean (SEM) data, discussed in the "Demonstration of Function" section below, is also included for said compounds where available. The Emax values represent the average of at least 3 runs except as otherwise indicated.

Table 4

E.g.	Epoxide	Amine	MSA	Isolated Form	Emax (%) ± SEM
1	3	6	459.2	Free Base	64.1 ± 4.5
2	3	8	445.4	Free Base	44.5 ± 4.6
3	3	9	477.2	Free Base	68.9 ± 2.6
4	3	10	463.3	Free Base	52.3 ± 1.7
5	10	6	460.2	Hydrochloride	66.0 ± 3.6
6	11	6	461.5	Trifluoro Acetate	55.0 ± 3.4
7	9	6	461.3	Trifluoro Acetate	58.4 ± 1.7
8	8	6	461.3	Trifluoro Acetate	82.2 ± 3.8
9	8	8	447.5	Trifluoro Acetate	49.5 ± 3.3
10	14	6	475.0	Trifluoro Acetate	63.2 ± 5.3
11	15	11	446.0	Hydrochloride	69.0 ± 2.3

12	15	6	501.3	Trifluoro Acetate	77.7 ± 4.6
13	16	11	435.3	Trifluoro Acetate	63.4 ± 0.3
14	16	6	490.2	Trifluoro Acetate	75.2 ± 3.0
15	17	11	446.3	Trifluoro Acetate	50.2 ± 7.3
16	17	6	501.5	Trifluoro Acetate	54.2 ± 2.2
17	18	11	435.2	Trifluoro Acetate	43.1 ± 3.0
18	18	6	490.1	Trifluoro Acetate	52.3 ± 0.7
19	19	11	446.2	Trifluoro Acetate	49.1 ± 4.6
20	19	6	501.3	Trifluoro Acetate	59.1 ± 3.1
21	20	11	435.1	Trifluoro Acetate	61.3 ± 3.2
22	20	6	490.3	Trifluoro Acetate	66.0 ± 0.9
23	5	6	461.2	Hydrochloride	Not Tested
24	2	6	477.2	Hydrochloride	Not Tested
25	1	77	576.1	Free Base	89.6 ± 10.9
26	4	77	561.2	Hydrochloride	70.9 ± 5.4
27	1	78	514.1	Hydrochloride	81.0 ± 3.2
28	4	78	499.1	Hydrochloride	58.5 ± 0.5
29	28	78	514.2	Hydrochloride	68.5 ± 1.3
30	29	78	593.2	Hydrochloride	90.0 ± 6.6
31	11	11	406.2	Hydrochloride	62.4 ± 2.1
32	3	11	404.2	Free Base	58.9 ± 1.9
33	8	11	406.0	Free Base	75.9 ± 1.9
34	9	11	406.2	Free Base	64.5 ± 2.1
35	27	11	429.2	Free Base	50.3 ± 2.2
36	14	11	420.2	Free Base	63.9 ± 1.6
37	1	81	565.2	Hydrochloride	82.0 ± 4.3
38	4	81	550.4	Hydrochloride	78.0 ± 2.8
39	3	81	548.4	Hydrochloride	71.7 ± 3.0
40	1	82	569.2	Hydrochloride	73.3 ± 4.6
41	4	82	554.4	Hydrochloride	73.1 ± 1.0
42	3	82	552.2	Hydrochloride	61.0 ± 4.5
43	1	68	555.2	Hydrochloride	66.6 ± 3.1
44	4	68	540.2	Hydrochloride	38.5 ± 2.3
45	3	68	538.4	Hydrochloride	41.9 ± 4.5
46	1	83	539.4	Hydrochloride	68.2 ± 2.2
47	4	83	524.4	Hydrochloride	69.2 ± 2.0
48	1	84	539.2	Hydrochloride	60.4 ± 6.0
49	4	84	524.4	Hydrochloride	44.2 ± 1.2
50	3	84	522.6	Hydrochloride	38.4 ± 3.2
51	30	11	457.0	Hydrochloride	58.3 ± 1.3
52	30	6	512.1	Hydrochloride	74.0 ± 3.1
53	29	78	593.2	Hydrochloride	90.0 ± 6.6
54	29	85	544.1	Trifluoroacetate	79.0 ± 3.5
55	29	86	544.1	Trifluoroacetate	78.4 ± 0.2
56	1	78	514.1	Hydrochloride	81.0 ± 3.2

57	4	78	499.1	Hydrochloride	58.5 ± 0.5
58	28	78	514.2	Hydrochloride	68.5 ± 1.3
59	28	6	476.4	Trifluoroacetate	70.4 ± 4.0
60	28	11	421.3	Trifluoroacetate	86.5 ± 5.9
61	30	85	465.2	Hydrochloride	56.6 ± 2.7
62	30	86	465.2	Hydrochloride	63.8 ± 0.5
63	1	44	517.2	Oxalate	55.7 ± 0.8
64	1	46	393.2	Hydrochloride	22.2 ± 4.5
65	1	47	393.2	Hydrochloride	34.5 ± 7.3
66	2	44	408.2	Hydrochloride	34.8 ± 3.2
67	1	48	462.2	Hydrochloride	28.6 ± 3.4
68	2	11	422.2	Hydrochloride	53.2 ± 1.6
69	1	51	479.2	Hydrochloride	39.1 ± 7.1
70	1	52	479.2	Hydrochloride	37.3 ± 2.7
71	1	53	464.1	Hydrochloride	47.4 ± 1.8
72	1	54	421.2	Hydrochloride	48.0 ± 2.1
73	1	55	464.1	Hydrochloride	32.1 ± 3.3
74	1	56	446.2	Hydrochloride	28.3 ± 2.6
75	1	61	479.2	Hydrochloride	47.2 ± 0.3
76	1	62	479.2	Hydrochloride	67.6 ± 5.2
77	1	65	446.2	Hydrochloride	73.9 ± 1.3
78	4	65	431.2	Hydrochloride	58.6 ± 0.9
79	23	11	422.0	Hydrochloride	58.2 ± 2.3
80	24	11	424.2	Hydrochloride	43.4 ± 2.0
81	25	11	424.2	Hydrochloride	35.1 ± 2.1
82	7	11	423.2	Hydrochloride	45.5 ± 3.5
83	6	11	422.2	Hydrochloride	73.7 ± 2.0
84	26	11	423.2	Hydrochloride	34.3 ± 2.8
85	1	18	422.0	Hydrochloride	66.8 ± 3.2
86	4	18	407.0	Hydrochloride	52.5 ± 3.1
87	16	85	479.2	Hydrochloride	76.5 ± 2.7
88	20	85	479.2	Hydrochloride	71.0 ± 6.5
89	18	85	479.2	Hydrochloride	49.1 ± 1.9
90	15	85	490.2	Hydrochloride	90.4 ± 3.8
91	19	85	490.2	Hydrochloride	54.7 ± 2.8
92	17	85	490.2	Hydrochloride	60.2 ± 1.8
93	16	86	479.2	Hydrochloride	73.9 ± 2.0
94	20	86	479.2	Hydrochloride	64.0 ± 2.6
95	18	86	479.2	Hydrochloride	51.5 ± 3.3
96	15	86	490.2	Hydrochloride	74.1 ± 2.4
97	19	86	490.2	Hydrochloride	71.3 ± 0.8
98	17	86	490.2	Hydrochloride	57.7 ± 0.3
99	1	87	446.2	Hydrochloride	62.6 ± 4.7
100	1	88	NC	Hydrochloride	< 10
101	1	6	476.0	Succinate	76.5 ± 12.6

102	1	1	540.0	Succinate	69.0 ± 2.2
103	4	1	525.0	Succinate	57.1 ± 2.4
104	1	2	565.0	Succinate	59.2 ± 1.0
105	4	2	550.0	Succinate	69.1 ± 3.8
106	1	3	503.0	Succinate	78.0 ± 8.5
107	4	3	488.0	Succinate	57.9 ± 6.2
108	1	4	503.0	Succinate	71.5 ± 7.9
109	4	4	488.0	Succinate	68.0 ± 4.1
110	1	5	633.0	Succinate	72.7 ± 5.3
111	4	5	618.0	Succinate	86.0 ± 4.0
112	1	12	539.0	Succinate	97.7 ± 5.9
113	4	12	524.0	Succinate	76.5 ± 3.0
114	1	13	539.0	Succinate	72.1 ± 5.0
115	1	14	539.0	Succinate	83.3 ± 4.0
116	4	14	524.0	Succinate	58.1 ± 1.6
117	1	15	572.0	Succinate	67.6 ± 3.9
118	1	16	471.9	Oxalate	40.3 ± 2.9
119	4	16	457.9	Oxalate	35.2 ± 3.5
120	1	17	438.2	Oxalate	68.0 ± 4.9
121	13	17	438.9	Oxalate	39.1 ± 1.3
122	12	17	455.9	Oxalate	66.1 ± 2.9
123	21	17	495.9	Oxalate	44.4 ± 5.2
124	21	11	479.0	Oxalate	36.1 ± 7.6
125	13	11	422.2	Oxalate	59.2 ± 2.2
126	12	11	439.0	Oxalate	76.1 ± 2.9
127	4	17	423.2	Oxalate	50.1 ± 7.4
128	1	19	409.1	Hydrochloride	46.5 ± 3.0
129	4	19	394.3	Hydrochloride	35.2 ± 3.3
130	1	20	423.2	Hydrochloride	36.3 ± 1.8
131	1	21	423.2	Hydrochloride	23.6 ± 1.7
132	4	6	461.2	Free Base	53.6 ± 1.4
133	4	6	461.0	Succinate	60.6 ± 2.4
134	4	8	447.1	Free Base	59.6 ± 4.4
135	4	8	447.1	Free Base	30.0 ± 3.9
136	4	22	495.0	Free Base	47.9 ± 3.6
137	1	6	476.2	Free Base	65.5 ± 4.7
138	1	8	462.1	Free Base	54.8 ± 8.0
139	1	25	490.2	Succinate	86.5 ± 5.5
140	1	26	492.2	Succinate	83.5 ± 2.7
141	1	27	525.1	Succinate	65.0 ± 2.0
142	1	28	527.2	Succinate	82.1 ± 1.4
143	1	29	472.1	Succinate	66.4 ± 8.7
144	1	30	474.1	Succinate	73.3 ± 5.9
145	1	24	507.1	Succinate	79.3 ± 7.1
146	1	31	514.1	Succinate	47.3 ± 2.3

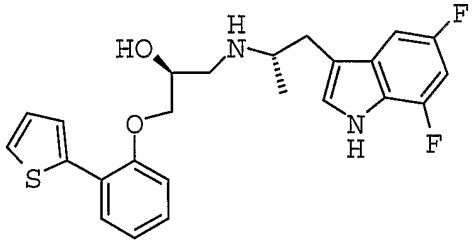
147	1	23	505.2	Free Base	Not Tested
148	4	32	446.3	Free Base	18.9 ± 1.5
149	1	32	461.3	Free Base	< 10
150	4	39	447.1	Oxalate	46.6 ± 1.9
151	6	39	463.0	Oxalate	52.4 ± 4.3
152	1	39	462.3	Oxalate	63.1 ± 4.4
153	1	40	465.2	Oxalate	45.2 ± 8.4
154	1	41	465.2	Oxalate	32.4 ± 8.1
155	1	42	462.2	Oxalate	58.7 ± 13.4
156	1	43	476.2	Oxalate	41.9 ± 9.3
157	1	11	421.2	Oxalate	51.3 ± 7.8
158	1	57	439.2	Oxalate	69.6 ± 4.8
159	2	57	440.2	Oxalate	53.0 ± 1.8
160	7	6	478.2	Oxalate	44.3 ± 3.9
161	7	8b	464.2	Oxalate	21.7 ± 3.1
162	1	49	439.2	Hydrochloride	64.2 ± 7.6
163	1	50	439.2	Hydrochloride	57.1 ± 5.8
164	4	11	406.2	Hydrochloride	53.9 ± 2.6
165	4	44	392.2	Hydrochloride	37.1 ± 4.0
166	4	49	424.2	Hydrochloride	47.8 ± 0.6
167	4	50	424.2	Hydrochloride	40.8 ± 1.3
168	1	58	476.2	Hydrochloride	62.1 ± 3.3
169	1	59	476.2	Hydrochloride	51.9 ± 3.4
170	1	60	439.2	Hydrochloride	71.2 ± 1.2
171	2	60	440.2	Hydrochloride	56.0 ± 1.5
172	4	57	424.2	Hydrochloride	55.0 ± 1.1
173	4	60	424.2	Hydrochloride	50.2 ± 1.5
174	1	63	463.6	Hydrochloride	57.6 ± 0.6
175	4	63	448.5	Hydrochloride	41.1 ± 3.5
176	1	66	572.0	Trifluoroacetate	79.0 ± 2.9
177	1	67	558.0	Free Base	73.8 ± 1.5
178	1	68	555.0	Succinate	72.5 ± 2.2
179	1	69	554.0	Succinate	71.5 ± 1.1
180	1	70	555.0	Succinate	Not Tested
181	1	71	561.0	Free Base	Not Tested
181	4	68	540.0	Succinate	39.6 ± 0.7
183	4	69	539.0	Succinate	47.7 ± 1.6
184	4	70	540.0	Succinate	Not Tested
185	1	24	507.2	Succinate	79.3 ± 7.1
186	1	72	513.0	Succinate	66.5 ± 0.4
187	1	73	550.2	Succinate	77.9 ± 0.7
188	1	74	525.1	Succinate	70.5 ± 3.8
189	1	75	602.3	Succinate	64.5 ± 1.7
190	1	76	472.2	Succinate	69.3 ± 1.3
191	29	11	500.1	Hydrochloride	85.6 ± 7.8

192	1	79	437.2	Hydrochloride	55.6 ± 6.0
193	4	79	422.2	Hydrochloride	32.0 ± 5.5

Alternate Preparation of Example 1

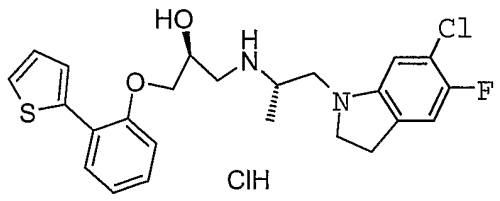
Amine 6 (12.08 g, 43.2 mmol, 1.10 equivalents) is dissolved in acetonitrile (86 mL) containing N-(trimethylsilyl)acetamide (95% pure, 5.1 g, 39.2 mmol, 1.0 equivalent - warmed to effect dissolution). Epoxide 3 is then added (8.0 g, 96% pure, 1.0 equivalent) and the solution is allowed to stand at 24-26°C for 45 hours after which water (10 mL) and acetic acid (6.3 g) are added. After 1.5 hours, the bulk of the solvents are removed under vacuum (25 °C, 10 mm, 16 hours). The resulting glass is partitioned between ethyl acetate (250 mL) and 1 N NaOH (300 mL). The aqueous layer is washed with ethyl acetate (100 mL). The organic layers are combined and washed with water (2x100 mL), saturated brine solution (100 mL), dried (20 g molecular sieves) and evaporated under vacuum. The residue is chromatographed (linear gradient of 0% to 35% methanol in ethyl acetate) to afford, after evaporation of the solvent, 14.4 g of the title compound (87%). IR ($CHCl_3$): 3478 cm^{-1}; UV (ethanol): λ(ε)279 (9000), 246 (10,970), 219 (55370); ES MS: 458.2396.

Example 194



A stirred mixture of Epoxide 1 (1 equivalent), Amine 34 (1.0-1.2 eq) and ytterbium trifluoromethane sulfonate hydrate (0.1 equivalent) in 10 ml CH_3CN is heated at 80°C for 20-60 hours. Upon completion, the reaction is diluted with ethyl acetate, washed with brine, dried (Na_2SO_4), and the solvent is evaporated to dryness. The ethanolamine product is purified by flash chromatography using a variable mixture of 90:10:1 CH_2Cl_2/methanol/NH_4OH. MS(ES+) 443.1. Emax (SEM) = 25.6 (1.8).

Example 195



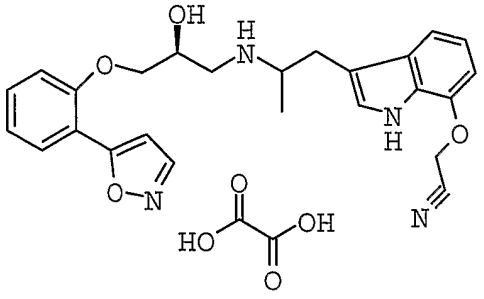
Epoxide 1 (232 mg, 1 mmol), Amine 33 (255 mg, 1.1 mmol), and ytterbium trifluoromethane sulfonate hydrate (62 mg, 0.1 mmol) in 10 ml acetonitrile are reacted and purified as in Example 194 to give 92 mg of the free base of the title compound (20%). A 5 ml methanol solution of the free base (92 mg, 0.2 mmol) and NH_4Cl (11 mg, 0.2 mmol) is stirred for 5 minutes at room temperature, concentrated, triturated in diethylether, filtered, and dried to give 95 mg of the title compound. MS(ES+) 459.1(free base). Emax (SEM) = 8.9 (1.7).

The table below sets out representative combinations of Amines and Epoxides that are reacted as described above in Example 194.

Table 5

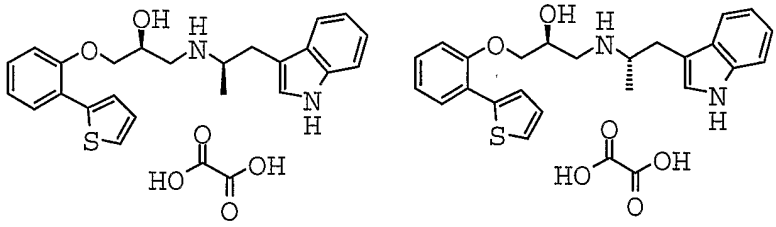
E.g.	Epoxide	Amine	MSA	Isolated Form	Emax (%) ± SEM
196	1	36	443.1	Free Base	15.8 ± 2.6
197	1	37	457.2	Free Base	34.5 ± 4.2
198	1	38	455.2	Free Base	12.5 ± 1.1

Example 199



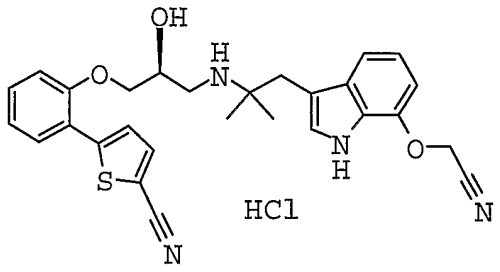
A solution of Amine 64 (105 mg, 0.457 mmol) and Epoxide 5 (82.6 mg, 0.381 mmol) in 2 ml of acetonitrile is treated with ytterbium trifluoromethane sulfonate hydrate (23.6 mg, 0.038 mmol). The resulting mixture is heated at 60°C over 3 days and then quenched with H_2O and extracted with ethyl acetate (3 x 50 ml). The combined organic extracts are dried over Na_2SO_4 and concentrated *in vacuo*. The crude residue is purified by radial chromatography (SiO_2; 3% 2M NH_3/methanol in $CHCl_3$) to give 51 mg (30%) of the free base. The free base is dissolved in a small amount of ethyl acetate, optionally adding methanol for solubitity. The resulting solution is treated with 1 equivalent of a 0.5M solution of oxalic acid in ethyl acetate. The reaction mixture is either concentrated *in vacuo* or centrifuged, separated, and the solids are dried, to give the title compound. MS 448.1. Emax (SEM) = 22.8 (n = 1).

Examples 200 & 201



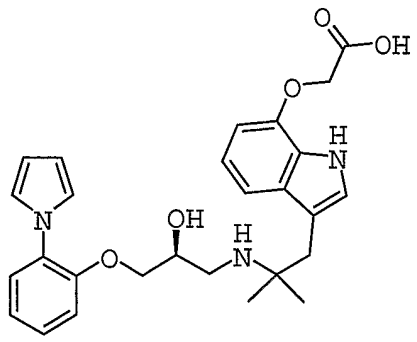
Racemic Amine 45 and Epoxide 1 are coupled in a fashion similar to that described in Representative Procedure 2 to give a mixture of the free bases of the title compounds. The title compounds are separated, one from the other, by normal phase chiral HPLC (Chiralpak AD; 15% 3A ethanol in heptane with 0.2% dimethylethylamine) to give the free base of Example 200 (faster eluting) in 40% yield and the free base of Example 201 in 35% yield. The oxalate salts are prepared by separately dissolving each of the free base isomers in a small amount of ethyl acetate, optionally adding methanol for solubility. The resulting solution is treated with 1 equivalent of a 0.5M solution of oxalic acid in ethyl acetate. The reaction mixture is either concentrated *in vacuo* or centrifuged, separated, and the solids are dried, to give the oxalate salts. Emax (SEM) = 28.8 (4.4) and 36.3 (9.8), respectively.

Example 202



To a solution of Amine 6 (11.9 g, 48.8 mmol) dissolved in ethanol (120 mL) is added a solution of Epoxide 15 (12.0 g, 43.6 mmol) dissolved in ethanol (30 mL). The solution is heated to reflux and the solution is stirred at the reflux temperature for 19 hours. The solvent is removed *in vacuo* and the solid is purified by Biotage chromatography (97.9:2:0.1 dichloromethane:methanol:concentrated ammonia hydroxide gradient to 95.9:4:0.1 dichloromethane:methanol: concentrated ammonia hydroxide as an eluent) to give 9.6 g of a solid. The solid is dissolved in 1,4 dioxane (100 mL) and 4 M HCl in dioxane (4.8 mL, 19.2 mmol) is added. The solution is stirred for 5 minutes and the solid is collected by vacuum filtration. The solid is dissolved in dichloromethane (100 mL) and cooled to 0°C in ice. The precipitate is collected by vacuum filtration and the filter cake is slurried in ethyl acetate (100 mL) and heated at a reflux for 1 hour. The mixture is filtered to give 9.44 g of the title compound (39%). FDMS m/e = 501.2 (M^++1). Emax (SEM) = 85.0 (3.5).

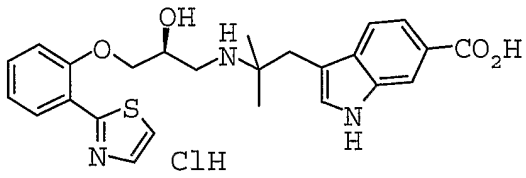
Example 203



Epoxide 3 is reacted with Amine 7 according to the Representative Procedure 2. The crude amination mixture (290 mg) is dissolved in 10 ml ethanol, 2M NaOH (2 ml) is

added and the resulting mixture is left to stir at room temperature overnight. The solution is neutralized with acetic acid and loaded on a SCX column. After washing with ethanol, the product is eluted with 10% NH_3 in ethanol. The fractions containing product are combined and evaporated to yield 220 mg of the title compound (80%). MS (positive ion): 478.4. Emax (SEM) = 73.8 (8.0).

Example 204



A solution of Amine 61 (1.2 equiv) and Epoxide 2 in t-butanol (0.2 M) is heated at 80°C for 24 hours. The solution of the crude free base is treated directly with crushed solid NaOH (5 equivalents). The resulting mixture is heated for 3 days at 70°C then concentrated. Purification of the crude product by reverse phase HPLC (YMC ODSA C18 5micrometer column, gradient of 5-95% CH_3CN in H_2O with 0.01% HCl, 20 ml/minute, over 12 minutes) affords the title compound. MS 466.0. Emax (SEM) = 67.0 (2.6).

The table below sets out representative combinations of Amines and Epoxides that are reacted as described above in Example 204.

Table 6

E.g.	Epoxide	Amine	MSA	Isolated Form	Emax (%) ± SEM
205	23	61	466.0	Hydrochloride	51.1 ± 3.8
206	5	62	450.0	Hydrochloride	42.0 ± 4.3
207	23	62	466.0	Hydrochloride	48.2 ± 3.3
208	13	62	466.0	Hydrochloride	58.2 ± 3.1
209	4	62	450.0	Hydrochloride	58.0 ± 2.6

Representative Procedure 5: Suzuki Coupling

Procedure 5(a)

A compound of formula V (6.4 mmol) is dissolved in 50 ml of dry dioxane and thoroughly flushed with argon. Palladium(0) tetrakis(triphenylphosphine) (750 mg, 0.64 mmol) is added under argon and stirred at ambient temperature until the mixture becomes homogenous. The clear solution is divided into aliquots of 2 ml, and each testing tube is charged with 2 equivalents of an aryl boronic acid and 500 microliters of 2M aqueous sodium carbonate under argon. The testing tubes are sealed and heated in a microwave oven (MLS ETHOS 1600) for 35 minutes and 100°C at 1000W. After complete conversion the samples are diluted with 2 ml of water and extracted with 3 ml of dichloromethane. Extraction is repeated with 2 ml of dichloromethane. The organic solutions are collected and dried over sodium sulfate. The organic filtrate is treated with pre-treated Amberlyst 15 (3 to 4 g each). (Prior to use Amberlyst 15 is prewashed with dichloromethane, ethanol then dichloromethane until the filtrate is colorless). The suspensions are shaken for 30 minutes on an orbital shaker and filtered. The Amberlyst is repeatedly rinsed with dichloromethane/ethanol 1:1 (4 x 3 ml) and then repeatedly treated with dichloromethane/ethanolic ammonia 1:1. Finally the resin is treated with ethanolic ammonia overnight. The alkaline filtrates are collected and evaporated.

Procedure 5(b)

A mixture of an aryl halide of formula V (1.2 mmol), a boronic acid (2.4 mmol), palladium(0) tetrakis(triphenylphosphine) (0.06 mmol), and 2M aqueous sodium carbonate (1.5 ml) in dioxane (20 ml) is heated overnight at 100°C in a sealed tube. The mixture is poured into water and extracted two times with ethyl acetate. The combined organic layers are washed with brine, dried over sodium sulfate, and concentrated under reduced pressure.

The final products prepared via Suzuki coupling may be purified by normal phase chromatography (silica gel, dichloromethane/ethanolic ammonia) providing the free bases or by reverse phase chromatography (acetonitrile/0.1% trifluoroacetic acid or 0.01% HCl in water) providing the trifluoro acetate or hydrochloride salts. The final products existing as salts may also be prepared in a separate salification step by dissolution of the

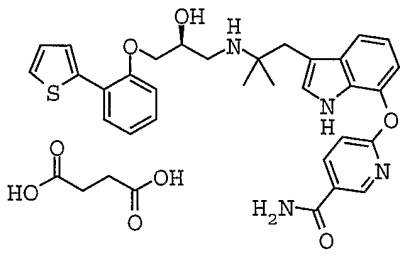
free base in ethanol or dichloromethane and treatment of the solution with acid, e.g., 1N ethanolic HCl. Removal of all volatiles under reduced pressure, affords the desired salt.

The table below sets out representative combinations of aryl halides and boronic acids that are reacted as described above in Representative Procedure 5(a) or 5(b).

Table 7

E.g.	Aryl Halide	Boronic Acid	MSA	Isolated Form	Emax (%) ± SEM
210	1	1	494.4	Trifluoroacetate	30.8 ± 3.5
211	3	4	576.6	Trifluoroacetate	84.2 ± 1.5
212	3	5	441.0	Hydrochloride	66.2 ± 2.6
213	3	3	491.5	Hydrochloride	82.2 ± 4.8
214	3	2	507.1	Hydrochloride	67.1 ± 4.8
215	2	4	631.7	Trifluoroacetate	82.4 ± 1.2
216	2	5	573.6	Trifluoroacetate	82.7 ± 1.9
217	2	3	624.1	Trifluoroacetate	79.2 ± 1.6
218	2	2	639.7	Trifluoroacetate	73.9 ± 2.0

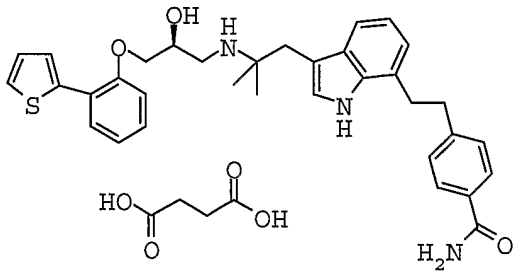
Example 219



Potassium carbonate (14 mg) is added to 2 mL of dimethylsulfoxide. The mixture is stirred under nitrogen, and heated to 50^{0}C for 30 minutes. The mixture is cooled to room temperature, and the compound of Example 115 (27 mg) dissolved in 2 mL of dimethylsulfoxide is added to the mixture, followed by the addition of 0.5 mL of water dropwise. The mixture is allowed to stir for 10 to 15 minutes, then 0.1 mL of 30% hydrogen peroxide is added dropwise. After 20 minutes, 15 mL of saturated aqueous

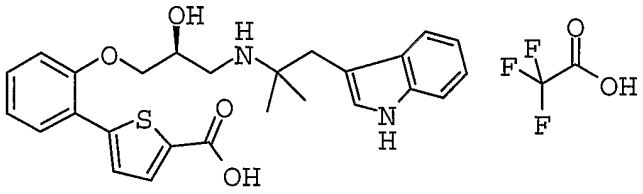
sodium sulfite solution and 5 mL water is added and the mixture is extracted 3 times with 40 mL of ethyl acetate. The combined organic layers are dried with sodium sulfate, filtered and evaporated to give 28 mg of the free base of the title compound (100%). The free base is dissolved in methanol and 1 equivalent of succinic acid (6 mg) is added. The solvent is evaporated to obtain the title compound. FDMS m/e = 557 (M^++1 of free base).

Example 220



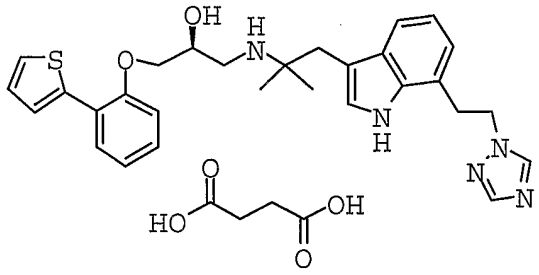
The title compuond is prepared from the compound of Example 187 as described for the preparation of Example 219. FDMS m/e = 568.1 (M^+ +1)

Example 221



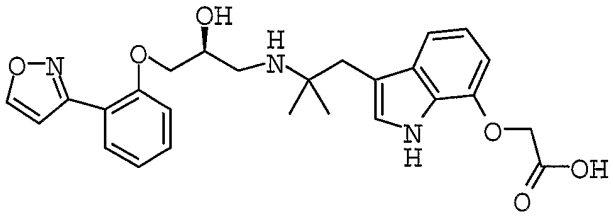
The crude residue containing the compound of Example 124 is dissolved in tetrahydrofuran and 1.2 equivalents of lithium hydroxide is added. The reaction mixture is stirred at ambient temperature overnight. The reaction is concentrated, and purified on C18 bonded silica gel using reverse phase liquid chromatography (acetonitrile/water with 0.1% trifluoroacetic acid). FDMS m/e 465.2.

Example 222



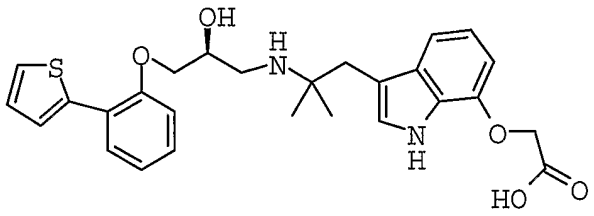
To a solution of the compound of Example 146 (1.02 mmol) in methanol is added 10% Pd/C (100 mg/mmol of substrate) in methanol. The reaction mixture is purged with hydrogen and hydrogenation is carried out with a hydrogen balloon overnight. The reaction mixture is filtered and the filtrate is evaporated to dryness to give the title compound. FDMS m/e = 516.2 (M^+ +1).

Example 223



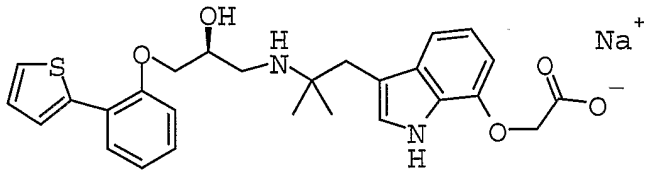
To a solution of the compound of Example 132 (200 mg, 0.43 mmol) in methanol is added 2N NaOH (1.0 mL). The reaction mixture is heated to relux and is stirred at reflux for 18 hours. The reaction mixture is cooled to room temperature and evaporated to dryness. The residue is taken up in water (20 mL), acidified to pH 5.0 with 1.0 N HCl, and extracted with ethyl acetate (2 x 25 mL). The combined organic extracts are washed with brine, dried (Na_2SO_4) and filtered. The filtrate is evaporated to dryness to afford 50 mg of the title compound (25%). FDMS m/e = 480.1 (M^+ +1).

Example 224



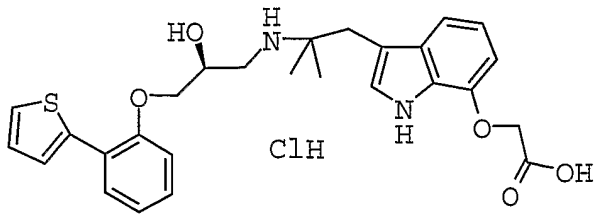
The title compound is prepared from the compound of Example 137 (200 mg, 0.43 mmol) by a procedure substantially similar to that described for Example 223 to give 50 mg of the title compound (85%). FDMS m/e = 495.2 (M^+ +1).

Example 225



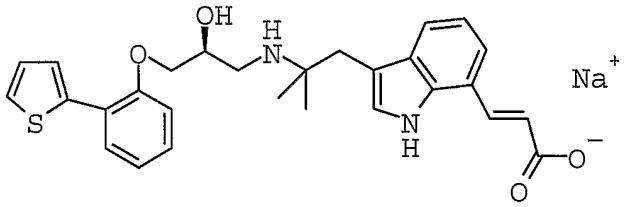
The compound of Example 224 (0.15 mmol) is dissolved in methanol (0.015 mmol of solute/mL). 2 N NaOH is added, the reaction mixture is heated to relux and then stirred for 1.5 hours. The reaction is cooled to room temperature and the mixture is evaporated to about 2 mL and the residue is diluted to 20 mL with water. The resulting solution is passed through a C18 cartridge, washed eith water (50 mL) and eluted with methanol (25 mL). The organic layer is evaporated to give a white solid (90%). FDMS m/e = 495.2 (M^+ +1).

Example 226



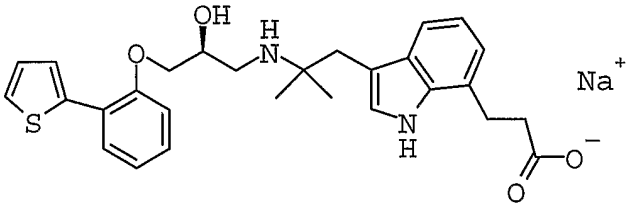
To a solution of the compound of Example 224 (146 mg, 0.30 mmol) in methanol (10 mL) is added NH_4Cl (15.8 mg, 0.30 mmole). The resulting solution is evaporated to dryness. The residue is taken up in ethyl acetate and evaporated to dryness to give 155 mg of the title compound (100%). FDMS m/e = 495.1 (M^+ +1).

Example 227



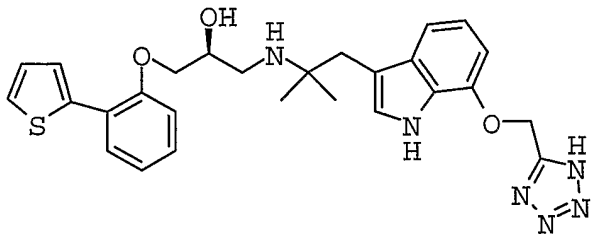
To a solution of the compound of Example 147 in methanol (5 mL) is added 1N NaOH (1.0 mL). The resulting solution is refluxed for 1 hour. The reaction mixture is cooled to room temperature and evaporated to dryness. The residue is taken up in water (10.0 mL), passed through a C18 cartridge, eluted with methanol (20 mL) and evaporated to dryness to give 45 mg of the title compound (50%). FDMS m/e 491.3 (M^+ +1).

Example 228



The title compound is prepared from the compound of Example 145 by a procedure substantially similar to that described for the preparation of Example 227. FDMS m/e = 493.1 (M^+ +1).

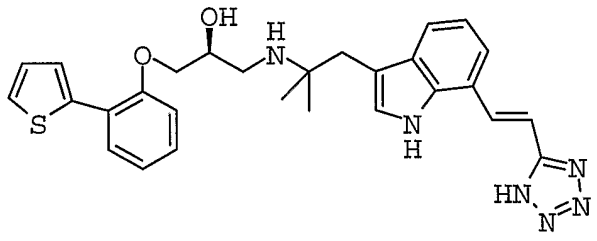
Example 229



$HO_2C{\cdot}CH_2CH_2CO_2H$

To a solution of the compound of Example 137 (250 mg, 0.52 mmol) in toluene (50 mL) is added dimethyltin oxide (43 mg, 0.26 mmol) and azidotrimethylsilane (600 mg, 5.2 mmol). The reaction mixture is heated to relux overnight. The reaction mixture is cooled to room temperature, evaporated to dryness. The resulting residue is chromatographed with 20% methanol (2N ammonia) in dichloromethane to give 150 mg of the free base of the title compound (56%). Succinic acid (34.1 mg, 0.289 mmol) in methanol (1.0 mL) is added and the resulting mixture is allowed to stir before evaporating to dryness to give 18 mg of the title compound (100%). FDMS m/e = 519.3 (M^+ +1).

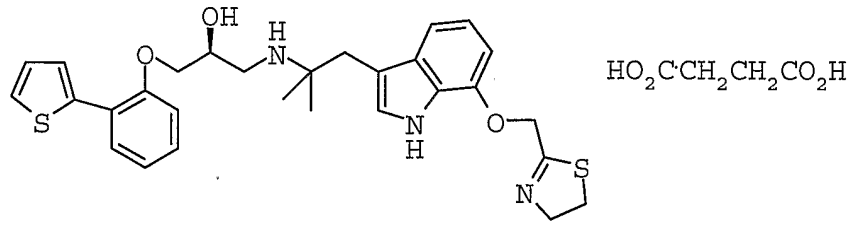
Example 230



$HO_2C{\cdot}CH_2CH_2CO_2H$

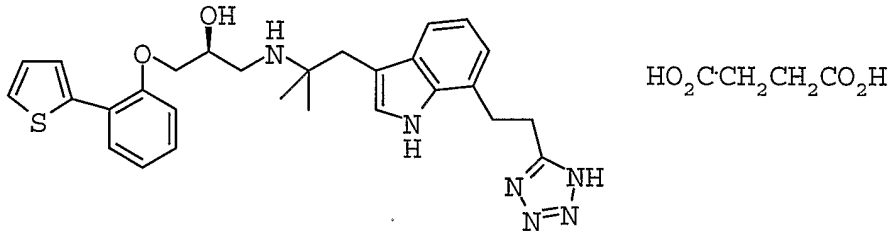
The free base of the title compound is prepared from the compound of Example 143 (76 mg, 0.16 mmol) and azidotrimethylsilane (190 mg, 1.62 mmol) by a procedure substantially analogous to that described in Example 229 to give the title compound. FDMS m/e = 515.2 (M^+ +1).

Example 231



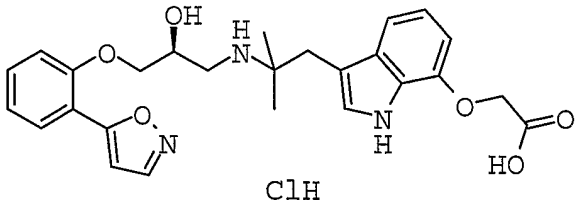
To a solution of the compound of Example 137 (87 mg, 0.18 mmol) in ethanol (10.0 mL), is added cysteamine (25 mg, 0.22 mmol). The resulting mixture is reluxed overnight. The reaction mixture is cooled to room temperature and evaporated to dryness. The resulting residue is chromatographed (5% methanol (2N ammonia) in dichloromathane) to give 42 mg of the free base of the title compound (44%). The succinate salt is prepared as described in Example 229 to give the title compound. FDMS m/e = 536.0 (M^+ +1).

Example 232



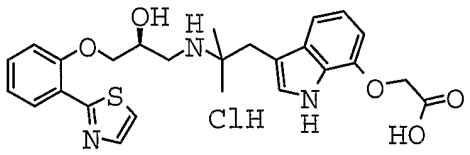
The title compound is prepared from the compound of Example 144 and azidotrimethylsilane by a procedure substantially analogous to that described in Example 229 to give the title compound. FDMS m/e = 517.2 (M^+ + 1).

Example 233

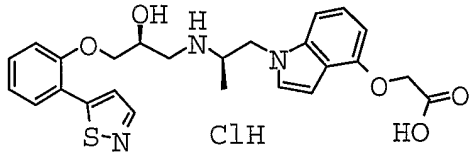


A solution of the compound of Example 23 (0.185 mmol) in 1.5 ml of t-butanol is treated with NaOH (100 mg). Ethanol (1.5 ml) is added to aid solubility, and the resulting mixture is heated at 80°C for 6 hours. The reaction mixture is concentrated *in vacuo* and purified by reverse phase HPLC (YMC ODSA C18 5 micrometer column, gradient of 5-95% CH_3CN in H_2O with 0.01% HCl, 20 ml/minute, over 12 minutes) to give 28.2 mg of the title compound (30%).

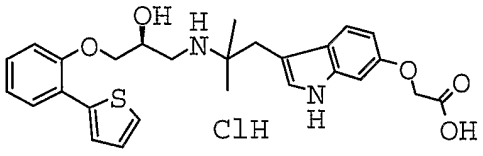
Examples 234-237



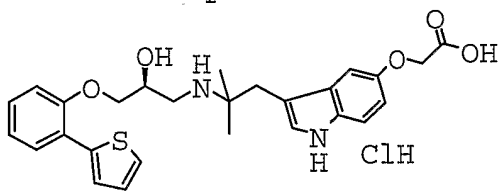
Example 234



Example 235



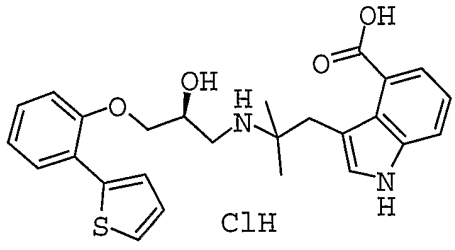
Example 236



Example 237

The title compounds are separately prepared from the compound of Examples 24, 151, 168 and 169, respectively, in a manner similar to that described in Example 233.

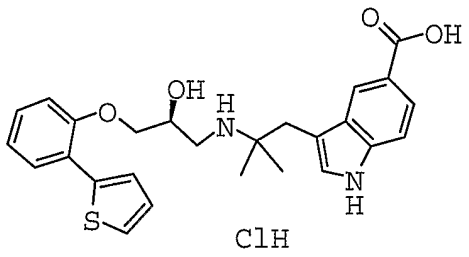
Example 238



A solution of crude free base of the product from Example 69 (195 mg, 0.408 mmol) in 1.2 ml of 3:1:1 tetrahydrofuran:methanol:H_2O is treated with LiOH (30 mg, 1.25 mmol). The resulting mixture is heated for 2 days at 70°C then concentrated *in*

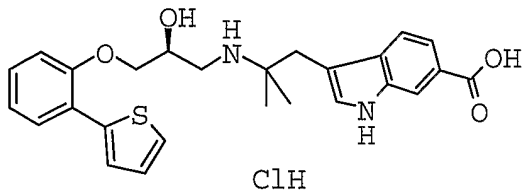
vacuo. Purification of the crude product by reverse phase HPLC (YMC ODSA C18 5 micrometer column, gradient of 5-95% CH_3CN in H_2O with 0.01% HCl, 20 ml/minute, over 12 minutes) affords 88.2 mg of the title compound (43%).

Examples 239-241



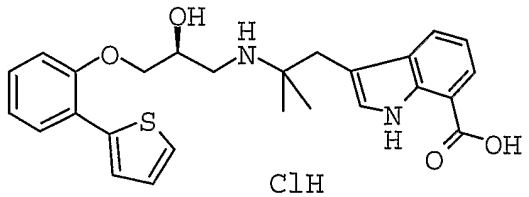
ClH

Example 239



ClH

Example 240

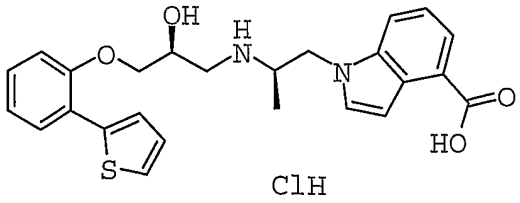


ClH

Example 241

The title compounds are separately prepared by hydrolysis of crude free base of the product from Examples 70, 75 and 76, respectively, in a method similar to that detailed in Example 238.

Example 242

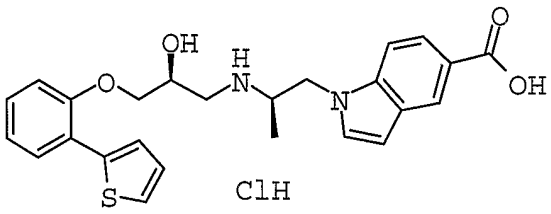


ClH

A solution of the free base of the compound of Example 153 (87.6 mg, 0.189 mmol) in 1.2 ml of 3:1:1 tetrahydrofuran:methanol:H_2O is treated with LiOH (7 mg, 0.282 mmol). The resulting mixture is stirred at ambient temperature for 11 days. Additional LiOH (7 mg, 0.282 mmol) is added, and the mixture is heated overnight at

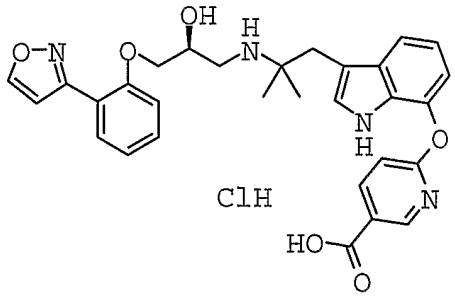
70°C then concentrated *in vacuo*. Purification of the crude product by reverse phase HPLC (YMC ODSA C18 5 micrometer column, gradient of 5-95% CH_3CN in H_2O with 0.01% HCl, 20 ml/minute, over 12 minutes) affords 31 mg of the title compound (34%).

Example 243



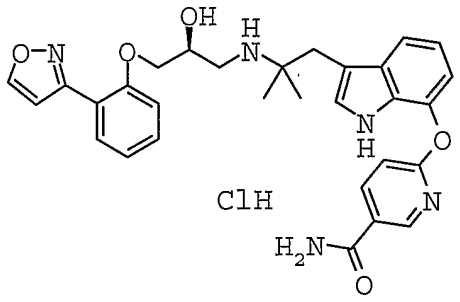
The title compound is prepared in 54% yield by hydrolysis of the free base of the compound of Example 154 with LiOH in a manner similar to that described in Example 242.

Example 244



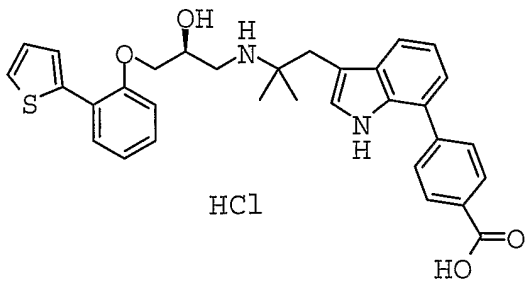
The compound of Example 116 (97 mg) is dissolved in 6 mL of methanol. Sodium hydroxide (2N, 3 mL) is added and the mixture is refluxed for 16 hours. Water (10 ml) is added and the pH of the mixture is adjusted to 3 using 1N hydrochloric acid. The aqueous mixture is extracted with ethyl acetate (3 x 50 mL). The combined organic extracts are dried with anhydrous sodium sulfate, filtered, and the solvent is evaporated. The product is purified using HPLC (5-95% solvent B in 3.8 minutes on YMC ODS-A (0.46x50mm), solvent A = 0.1% hydrochloric acid/water, solvent B = 0.1% hydrochloric acid/acetonitrile) to give 15.9 mg of the title compound. FDMS m/e = 543 (M^++1 of free base).

Example 245



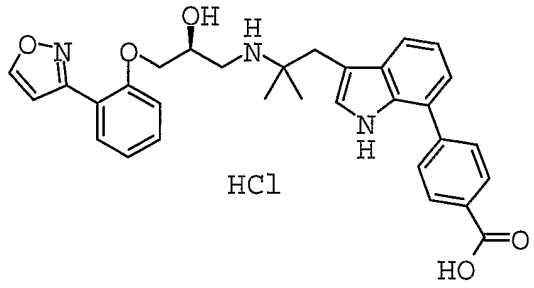
The crude title compound is prepared from he compound of Example 116 (97 mg) via the procedure described in Example 219. The crude product is purified using HPLC (5-95% solvent B in 3.8 minutes on YMC ODS-A (0.46x50mm), solvent A = 0.1% hydrochloric acid/water, solvent B = 0.1% hydrochloric acid/acetonitrile) to give 60.8 mg of the title compound. FDMS m/e = 542 (M^++1 of free base).

Example 246



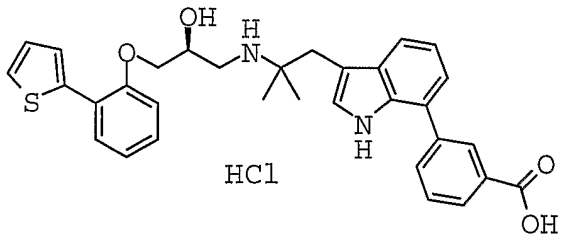
To a solution of the compound of Example 178 (103 mg, 0.186 mmol) in methanol (5mL) is added sodium hydroxide (0.93 mL, 2M, 1.86 mmol). The mixture is refluxed for 4 hours then diluted with HCl and extracted three times with ethyl acetate. The combined extracts are dried over sodium sulfate, filtered and evaporated. The residue is chromatographed by reverse phase HPLC (acetonitrile/0.01% HCl in water) to give the title compound (41%). FDMS m/e = 541 (M^++1 of free base).

Example 247



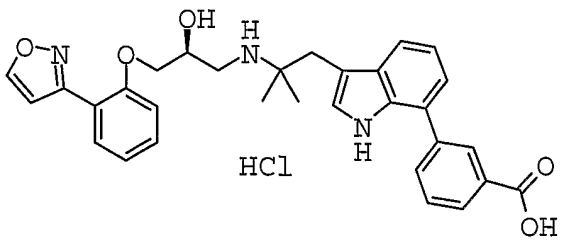
The compound of Example 182 is converted to the title compound via the procedure described for the preparation of the compound of Example 246 (57%). FDMS m/e = 526 (M^++1 of free base).

Example 248



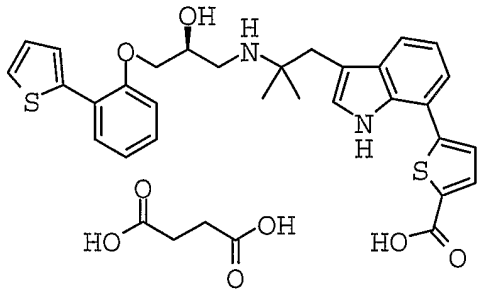
The compound of Example 180 is converted to the title compound via the procedure described for the preparation of the compound of Example 246 (88%). FDMS m/e = 541 (M^++1 of free base).

Example 249



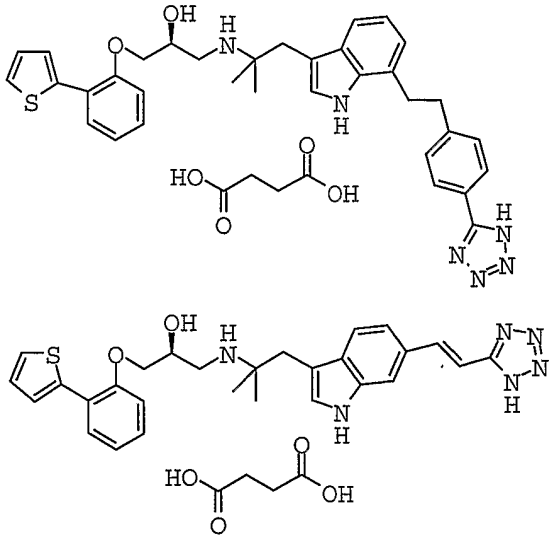
The compound of Example 184 is converted to the title compound via the procedure described for the preparation of the compound of Example 246 (32%). FDMS m/e = 526 (M^++1 of free base).

Example 250



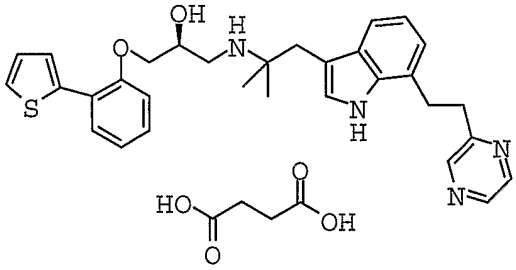
The compound of Example 181 is converted to the title compound via the procedure described for the preparation of the compound of Example 246 except that chromatography on the crude free base is not performed. Instead, the crude free base is dissolved in a small amount of ethyl acetate and treated with 1 equivalent of succinic acid in methanol. The resulting slurry is dissolved in the minimum amount of methanol then concentrated *in vacuo* to give the title compound (78%). FDMS m/e = 547 (M^++1 of free base).

Examples 251 and 252

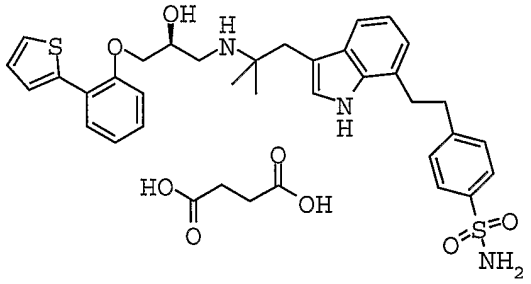


The title compounds are separately prepared from the compound of Examples 187 and 190, respectively, as described in Example 229. FDMS m/e = 593.1 (M^+ +1) and FDMS m/e = 515.2 (M^+ +1).

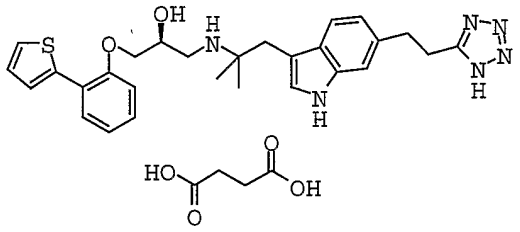
Example 253



Example 254

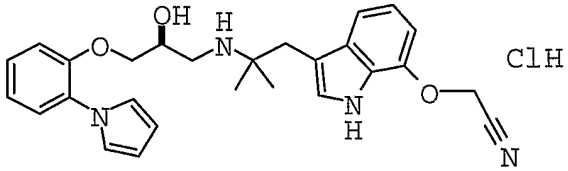


Example 255



The title compounds are separately prepared from the compound of Example 188, the compound of Example 189 and the compound of Example 252, respectively, as described for the preparation of Example 222. FDMS m/e = 527.2 (M^+ +1), 604.2 (M^+ +1) and FDMS m/e = 517.24 (M^+ +1).

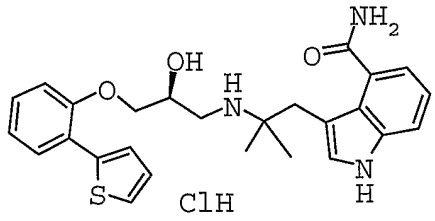
Example 256



The compound of Example 1 (8.87 g, 18.8 g, 1.00 equivalent) is treated all at once with concentrated HCl (1.57 mL, 0.95 equivalents) in ethyl acetate (221 mL, 25 °C). The

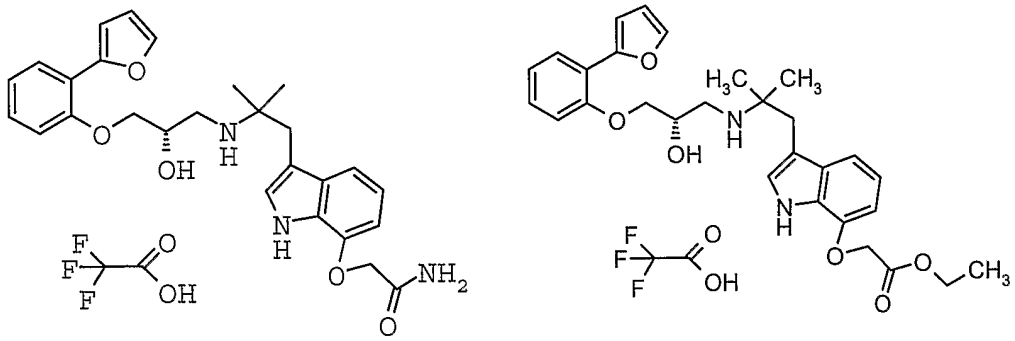
ethyl acetate is evaporated under vacuum and the solid stirred with 250 mL of diethyl ether (3 hours) after which the mixture is filtered and the resulting solid dried under a stream of nitrogen to afford 8.98 g of the title compound (93%). MS: 459.2.

Example 257



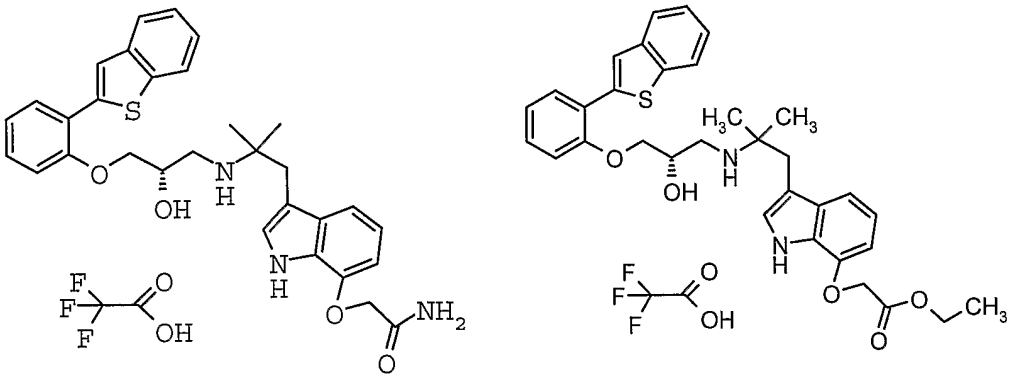
A solution of the crude free base of Example 99 (285 mg, 0.64 mmol) in 7.5 ml of dimethylsulfoxide is treated with powdered K_2CO_3 (177 mg, 1.28 mmol). The resulting mixture is cooled to 0°C, and 73 µl of 30% H_2O_2 is added dropwise. After stirring overnight, 1 ml of 20% KOH and an additional 200 µl of 30% H_2O_2 is added to the reaction mixture. After stirring overnight, 20 ml of H_2O is added, and the resulting mixture is cooled in an ice-H_2O bath for 1 hour, then extracted with $CHCl_3$. The organic layer is washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. The residue is purified by reverse phase HPLC (YMC ODSA C18 5µm column, gradient of 5-95% CH_3CN in H_2O with 0.01% HCl, 20 ml/minute, over 12 minutes) to give 25 mg of the title compound (8%). MS 464.2.

Examples 258 and 259



To a solution of the compound of Example 216 in dry ethanol is added 10% HCl in ethanol and the mixture is stirred at room temperature. The solvent is evaporated, the residue re-dissolved in ethanol and loaded on a SCX column. After washing with ethanol, the products are eluted with 10% NH_3 in ethanol, evaporated, separated and purified via preparative HPLC (C18 bonded silica gel reverse phase liquid chromatography (acetonitrile/water with 0.1% trifluoroacetic acid) to give the title compounds.

Examples 260 and 261



The title compounds are prepared as described for Examples 258 and 259 from the compound of Example 218.

The table below sets out Emax data collected for the compounds of Examples 219-261.

Table 8

E.g.	Emax (%) ± SEM	E.g.	Emax (%) ± SEM	E.g.	Emax (%) ± SEM
219	85.9 ± 9.4	234	66.4 ± 6.4	249	68.8 ± 7.8
220	81.2 ± 0.6	235	76.7 ± 4.4	250	92.5 ± 5.1
221	74.6 ± 3.6	236	88.4 ± 3.9	251	86.3 ± 3.4
222	81.2 ± 0.9	237	73.9 ± 2.9	252	82.3 ± 4.0
223	56.1 ± 2.8	238	< 10	253	81.6 ± 4.0
224	94.3 ± 4.6	239	69.6 ± 3.5	254	80.9 ± 4.9

225	78.1 ± 4.6	240	78.7 ± 2.4	255	83.9 ± 3.2
226	70.3 ± 5.7	241	70.1 ± 0.6	256	71.4 ± 2.7
227	87.5 ± 7.5	242	59.6 ± 2.8	257	81.8 ± 8.5
228	79.5 ± 0.6	243	48.4 ± 2.5	258	76.8 ± 2.1
229	83.0 ± 2.5	244	77.0 ± 2.1	259	84.2 ± 2.9
230	81.3 ± 2.4	245	63.3 ± 3.0	260	77.0 ± 3.4
231	85.0 ± 4.9	246	79.2 ± 3.4	261	75.8 ± 3.8
232	79.5 ± 1.7	247	54.6 ± 2.4		
233	52.4 ± 6.0	248	84.1 ± 1.8		

Demonstration of Function

The genes encoding the human β_1-adrenergic receptor (Frielle *et al.*, *Proc. Natl. Acad. Sci.*, 84:7920-7924, 1987), the human β_2-adrenergic receptor (Kobika *et al.*, *Proc. Natl. Acad. Sci.*, 84:46-50, 1987, Emorine *et al.*, *Proc. Natl. Acad. Sci.*, 84:6995-6999, 1987) and the human β3 adrenergic receptor (Granneman *et al.*, *Molecular Pharmacology*, 44(2):264-70, 1993) are individually subcloned into a phd expression vector (Grinnell *et al.*, *Bio/Technology*, 5:1189-1192, 1987) and transfected into the DXB-11 Chinese hamster ovary (CHO) cell line by calcium phosphate precipitation methodology. The stably transfected cells are grown to 95% confluency in 95% Dulbecco's modified Eagles Medium (DMEM), 5% fetal bovine serum and 0.01% proline. Media is removed and the cells are washed with phosphate buffered (pH 7.4) saline (without magnesium and calcium). Cells are then lifted using an enzyme free cell dissociation solution (Specialty Media, Lavallette, New Jersey) and pelleted by centrifugation.

Cells from each of the above cell lines are resuspended and added (20,000/well) to a 96-well plate. Cells are incubated at 37°C with representative compounds of the invention for 20 minutes in buffer (Hank's balanced salt solution, 10 mM HEPES, 0.1% BSA, 1 mM L-ascorbic acid, 0.2% dimethyl sulfoxide, 1 mM 3-isobutyl-1-methylxanthine, pH 7.4). After halting the incubation with quench buffer (50 mM Na Acetate, 0.25% Triton X-100, pH 5.8), the c-AMP level is quantified by scintillation proximity assay (SPA) using a modification of the commercially available c-AMP kit

(Amersham, Arlington Heights, IL) with rabbit anti-cAMP antibody (ICN Biomedicals, Aurora, Ohio) for the kit.

Sigmoidal dose response curves, from the whole cell receptor coupled c-AMP assay are fit to a four parameter logistic equation using non linear regression: $y=(a-d)/(1+(Dose/c)^b)+d$ where a and d are responses at zero and maximal dose, b is the slope factor and c is the EC_{50} as previously described (DeLean et al., *Am. J. Physiol.*, 235, E97-E102, 1978). EC_{50} is assessed as the concentration producing 50% of the maximum response to each agonist.

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. The % intrinsic activity (Emax) of representative compounds of the invention is assessed relative to isoproterenol by the compound's maximal response divided by the isoproterenol maximal response times 100.

In vitro Rat Atrial Tachycardia

Male rats (250-350 g) (Harlan Sprague Dawley, Indianapolis, Indiana, USA) are killed by cervical dislocation. Hearts are removed and the left and right atria are dissected and mounted with thread in tissue baths containing 10 mls of modified Krebs' solution. Initial resting tension is 1.5-2.0 g at the outset of the experiment (*Naunyn-Schmied Arch. Pharmacol.*, 320:145, 1982). Tissues are allowed to equilibrate approximately 30 minutes with vigorous oxygenation before exposure to a compound of the invention. To evaluate the ability of test compounds to increase heart rate, representative compounds of the present invention are added cumulatively once the atrial rate reached a steady state from the previous addition. Compound addition is continued until no further increase in atrial rate occurred or until a concentration of 10^{-4}M is reached. The increase in beats per minute (bpm) is measured for each concentration of test compound by means of a BioPac System (*Br. J. of Pharmacol.*, 126:1018-1024, 1999).

Utilities

As agonists of the β_3 receptor, the salts of the present invention are useful in treating conditions in human and non-human animals in which the β_3 receptor has been demonstrated to play a role.

The diseases, disorders or conditions for which compounds of the present invention are useful in treating include, but are not limited to, (1) diabetes mellitus, (2) hyperglycemia, (3) obesity, (4) hyperlipidemia, (5) hypertriglyceridemia, (6) hypercholesterolemia, (7) atherosclerosis of coronary, cerebrovascular and peripheral arteries, (8) hypertension, (9) disorders of the gall bladder including acute and chronic cholecystitis, (10) depression, (11) elevated intra-ocular pressure and glaucoma, (12) non-specific diarrhea dumping syndrome, (13) hepatic steatosis [fatty degeneration of the liver], and obesity dependent diseases/disorders such as: (14) gastrointestinal disorders including peptid ulcer, esophagitis, gastritis and duodenitis, (including that induced by H. pylori), intestinal ulcerations (including inflammatory bowel disease, ulcerative colitis, Crohn's disease and proctitis) and gastrointestinal ulcerations, (15) irritable bowel syndrome and other disorders needing decreased gut motility, (16) diabetic retinopathy, (17) neuropathic bladder dysfunction, (18) osteoarthritis, (19) restrictive lung disease, (20) obstructive sleep apnea, (21) congestive heart failure, (22) venous stasis and skin disorders related to venous stasis, (23) decreased libido (in both males and females), and (24) acute and chronic cystitis. The term "obesity dependent" means that the symptoms of said diseases will be ameliorated via the present salt's effect on the patient's weight.

Human patients in need of obesity treatment are typically those with a body mass index (BMI) >27 or those with a BMI ≥25 when co-morbidities, e.g., hypertension, sleep apnea and/or osteoarthritis, are present. A patient population at particular need of treatment are those with a BMI >30 or >27 with co-morbities.

Human patients in need of hypertension treatment are frequently overweight individuals, i.e., those with a BMI ≥25, but may also be of normal body weight (*i.e.*, BMI <25).

Human patients in need of type 2 diabetes treatment are typically individuals with a BMI <25, *i.e.*, individuals that are not overweight.

Formulation

The compound of formula I is preferably formulated in a unit dosage form prior to administration. Therefore, yet another embodiment of the present invention is a pharmaceutical formulation comprising a compound of formula I and a pharmaceutical carrier.

The present pharmaceutical formulations are prepared by known procedures using well-known and readily available ingredients. In making the formulations of the present invention, the active ingredient (formula I compound) 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.

Formulation 1

Tablets

Ingredient	Quantity (mg/tablet)
Active Ingredient	5 – 500
Cellulose, microcrystalline	200 - 650
Silicon dioxide, fumed	10 - 650

Stearate acid	5 - 15

The components are blended and compressed to form tablets.

Formulation 2

Suspensions

Ingredient	Quantity (mg/5 ml)
Active Ingredient	5 – 500 mg
Sodium carboxymethyl cellulose	50 mg
Syrup	1.25 mg
Benzoic acid solution	0.10 ml
Flavor	q.v.
Color	q.v.
Purified water to	5 ml

The medicament is passed through a No. 45 mesh U.S. sieve and mixed with the sodium carboxymethyl cellulose and syrup to form a smooth paste. The benzoic acid solution, flavor, and color are diluted with some of the water and added, with stirring. Sufficient water is then added to produce the required volume.

Formulation 3

Intravenous Solution

Ingredient	Quantity
Active Ingredient	25 mg
Isotonic saline	1,000 ml

The solution of the above ingredients is intravenously administered to a patient at a rate of about 1 ml per minute.

Dose

The specific dose administered is determined by the particular circumstances surrounding each situation. These circumstances include, the route of administration, the prior medical history of the recipient, the pathological condition or symptom being treated, the severity of the condition/symptom being treated, and the age and sex of the recipient. However, it will be understood that the therapeutic dosage administered will be determined by the physician in the light of the relevant circumstances.

Generally, an effective minimum daily dose of a compound of formula I is about 5, 10, 15, or 20 mg. Typically, an effective maximum dose is about 500, 100, 60, 50, or 40 mg. Most typically, the dose ranges between 15 mg and 60 mg. The exact dose may be determined, in accordance with the standard practice in the medical arts of "dose titrating" the recipient; that is, initially administering a low dose of the compound, and gradually increasing the does until the desired therapeutic effect is observed.

Route of Administration

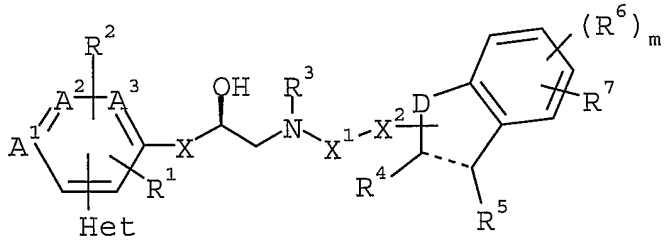
The compounds can be administered by a variety of routes including the oral, rectal, transdermal, subcutaneous, topical, intravenous, intramuscular or intranasal routes.

Combination Therapy

The compound of formula I may be used in combination with other drugs that are used in the treatment of the diseases or conditions for which the present salts are useful, e.g., treatment of obesity and/or type 2 diabetes. Such other drug(s) may be administered, by a route and in an amount commonly used therefore, contemporaneously or sequentially with a compound of the present invention. When a compound of the present invention is used contemporaneously with one or more other drugs, a pharmaceutical unit dosage form containing such other drugs in addition to the present salt is preferred. Accordingly, the pharmaceutical compositions of the present invention include those that also contain one or more other active ingredients, in addition to a compound of the present invention.

WE CLAIM:

1. A compound of formula I:



I;

wherein:

the dashed line represents a single or double bond;

m is 0, 1 or 2;

A^1, A^2 and A^3 are carbon or nitrogen provided that only one of A^1, A^2 and A^3 can be nitrogen;

D is NR^8, O or S;

Het is an optionally substituted, optionally benzofused 5 or 6 membered heterocyclic ring;

R^1 and R^2 are independently H, halo, hydroxy, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_4 haloalkyl, or SO_2(C_1-C_6 alkyl);

R^3 is H or C_1-C_6 alkyl;

R^4 forms a bond with X^2 or is H, cyano, C_1-C_6 alkyl, $CONR^9R^9$ or CO_2R^9;

R^5 forms a bond with X^2 or is H or C_1-C_6 alkyl;

R^6 is independently at each occurrence halo, hydroxy, cyano, C_1-C_6 alkyl, C_1-C_4 haloalkyl or C_1-C_6 alkoxy;

R^7 is H, CO_2R^{10}, $CONR^{10}R^{10}$, $CH{=}CHR^{11}$, $CH_2CH_2R^{11}$, $NR^{10}R^{10}$, $NR^{10}SO_2R^{10}$, $O(CR^{12}R^{13})_nR^{14}$, $O(CR^{12}R^{13})_pR^{15}$, SO_2R^{10}, $SO_2NR^{10}R^{10}$, optionally substituted phenyl or optionally substituted heterocycle;

R^8 forms a bond with X^2 or is H or C_1-C_6 alkyl;

R^9 and R^{10} are independently at each occurrence H, C_1-C_6 alkyl or phenyl; or when two R^9 or two R^{10} moieties are connected to the same nitrogen atom, then said R^9

or R^{10} moieties may combine with the nitrogen to which they are attached to form a pyrollidinyl, piperidinyl or hexamethyleneimino ring;

R^{11} is cyano, CO_2R^{16}, $CONR^{16}R^{16}$, $CONR^{16}SO_2R^{16}$, SO_2R^{16}, heterocycle or optionally substituted phenyl;

R^{12} and R^{13} are independently at each occurrence H or C_1-C_6 alkyl;

R^{14} is hydrogen, CO_2R^{17}, $CONR^{17}R^{17}$, SO_2R^{17}, $SO_2NR^{17}R^{17}$, optionally substituted phenyl or optionally substituted heterocycle,

R^{15} is cyano, $NR^{18}R^{18}$, $NR^{18}SO_2R^{18}$ or OR^{18};

R^{16}, R^{17} and R^{18} are independently at each occurrence H, C_1-C_6 alkyl or phenyl; or when two R^{16} or two R^{17} or two R^{18} moieties are connected to the same nitrogen atom, then said R^{16} or R^{17} or R^{18} moieties may combine with the nitrogen to which they are attached to form a pyrollidinyl, piperidinyl or hexamethyleneimino ring;

n is 0, 1, 2 or 3;

p is 1, 2 or 3;

X is absent or is OCH_2 or SCH_2;

X^1 is absent or is $(CR^{19}R^{20})_q$;

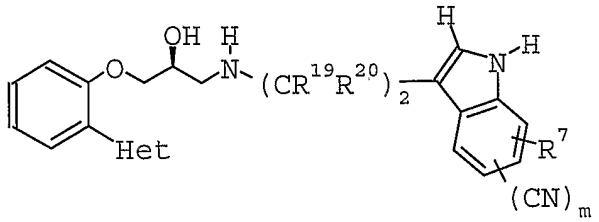
X^2 is absent or is CO, $CONR^{21}$ or $NR^{21}CO$;

q is 1, 2, 3, 4 or 5;

R^{19} and R^{20} are independently at each occurrence H or C_1-C_6 alkyl; or R^{19} and R^{20} combine with the carbon to which they are both attached to form a C_3-C_7 carbocyclic ring; and

R^{21} is H or C_1-C_6 alkyl; or a pharmaceutical salt thereof.

2. The compound of Claim 1 of the formula:



wherein:

m is 0 or 1;

Het is selected from benzothiophene; furan; isoxazole; oxazole; pyrrole; tetrazole and thiophene; wherein said Het moieties are optionally substituted once with methyl, cyano, SO_2NH_2 or $COCH_3$;

R^7 is H, CO_2H; $CH_2CH_2R^{11}$; thienyl substituted once with CO_2H; phenyl substituted once with CO_2H; $OCH_2CONHSO_2(C_1\text{-}C_4$ alkyl); $OCH_2CH_2NHSO_2(C_1\text{-}C_4$ alkyl); OCH_2CN; $OCH_2CO_2R^{17}$; $OCH_2CONR^{18}R^{18}$; O(pyridine) wherein said pyridine moieity is substituted once with cyano or CO_2H; OCH_2(tetrazole); OCH_2(4,5-dihydrothiazole); or $NHSO_2R^{10}$;

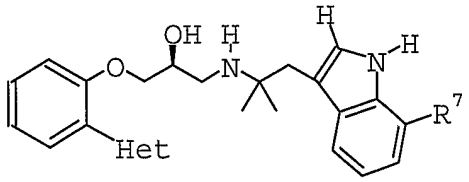
R^{10} is $C_1\text{-}C_4$ alkyl or phenyl;

R^{11} is CO_2R^{16}; $CONR^{16}R^{16}$; 1,2,3,4-tetrazole; or phenyl substituted once with $SO_2NR^{22}R^{22}$;

R^{16}, R^{17}, R^{18} and R^{22} are independently H or $C_1\text{-}C_4$ alkyl at each occurrence; and

R^{19} and R^{20} are independently H or methyl at each occurrence; or a pharmaceutical salt thereof.

3. The compound of Claim 1 or 2 of the formula:



;

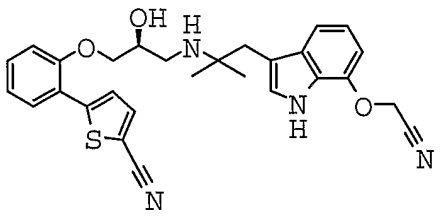
wherein:

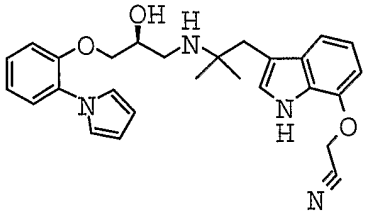
Het is thien-2-yl optionally substituted once with cyano, SO_2NH_2 or $COCH_3$;

R^7 is H; CO_2H; $CH_2CH_2R^{11}$; OCH_2CN; OCH_2CO_2H; OCH_2(tetrazole); thienyl substituted once with CO_2H or phenyl substituted once with CO_2H; or $NHSO_2R^{10}$; and

R^{11} is 1,2,3,4-tetrazole; or a pharmaceutical salt thereof.

4. The compound of Claim 1 or 2 which is selected from:





or a pharmaceutical salt thereof.

5. The compound of any one of Claims 1-4 which is the hydrochloride salt.

6. A method of treating Type 2 Diabetes comprising administering to a patient in need thereof a compound of any one of Claims 1-5.

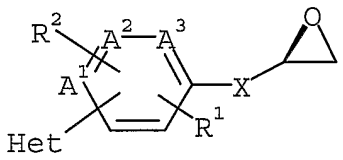
7. A method of treating obesity comprising administering to a patient in need thereof a compound of any one of Claims 1-5.

8. A method of agonizing the β_3 receptor comprising administering to a patient in need thereof a compound of any one of Claims 1-5.

9. A pharmaceutical formulation comprising a compound of any one of Claims 1-5 and a pharmaceutical carrier.

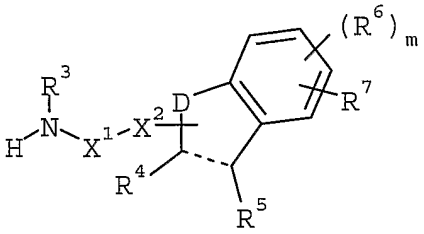
10. A compound of any one of Claims 1-5 for use in treating Type 2 diabetes or obesity or for use in agonizing the β_3 receptor.

11. A process for preparing a compound of any one of Claims 1-5 which comprises reacting a compound of formula II:



II;

with a compound of formula III:



III;

in the presence of a suitable solvent.

INTERNATIONAL SEARCH REPORT

Internati Application No
PCT/US 02/21317

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D403/12 C07D409/12 C07D413/12 C07D409/14 C07D417/12
A61P3/04 A61P3/10 A61K31/41 A61K31/38

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
5 November 2002	13/11/2002

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Baston, E

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

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