TITLE OF THE INVENTION

HETEROCYCLE-SUBSTITUTED 3-ALKYL AZETIDINE DERIVATIVES

BACKGROUND OF THE INVENTION

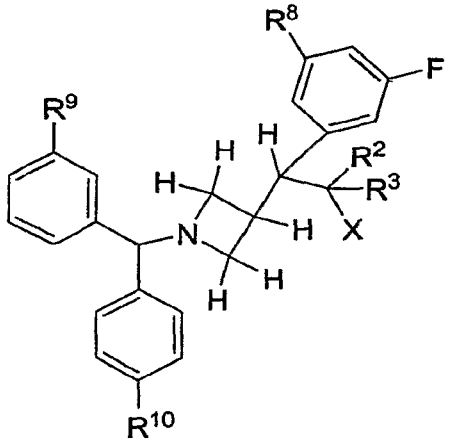
Marijuana (*Cannabis sativa L.*) and its derivatives have been used for centuries for medicinal and recreational purposes. A major active ingredient in marijuana and hashish has been determined to be Δ^9-tetrahydrocannabinol (Δ^9-THC). Detailed research has revealed that the biological action of Δ^9-THC and other members of the cannabinoid family occurs through two G-protein coupled receptors termed CB1 and CB2. The CB1 receptor is primarily found in the central and peripheral nervous systems and to a lesser extent in several peripheral organs. The CB2 receptor is found primarily in lymphoid tissues and cells. Three endogenous ligands for the cannabinoid receptors derived from arachidonic acid have been identified (anandamide, 2-arachidonoyl glycerol, and 2-arachidonyl glycerol ether). Each is an agonist with activities similar to Δ^9-THC, including sedation, hypothermia, intestinal immobility, antinociception, analgesia, catalepsy, anti-emesis, and appetite stimulation.

There are at least two CB1 modulators characterized as an inverse agonista or an antagonists, N-(1-piperidinyl)-5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methylpyrazole-3-carboxamide (SR141716A), and 3-(4-chlorophenyl-N'-(4-chlorophenyl)sulfonyl-N-methyl-4-phenyl-4,5-dihydro-1H-pyrazole-1-carboxamide (SLV-319), in clinical trials for treatment of eating disorders and/or smoking cessation at this time. There still remains a need for potent low molecular weight CB1 modulators that have pharmacokinetic and pharmacodynamic properties suitable for use as human pharmaceuticals.

US 6,355,631, US 6,479,479 and PCT publications WO 01/64632, 01/64633, 01/64634, and 05/000809 are directed to azetidine derivatives as cannabinoid antagonists.

SUMMARY OF THE INVENTION

The present invention is concerned with azetidine derivatives of general formula I:



(I)

and pharmaceutically acceptable salts thereof which are modulators of and, in particular, antagonists and/or inverse agonists of the Cannabinoid-1 (CB1) receptor and are useful in the treatment, prevention or suppression of diseases mediated by the Cannabinoid-1 (CB1) receptor. In one aspect, the invention

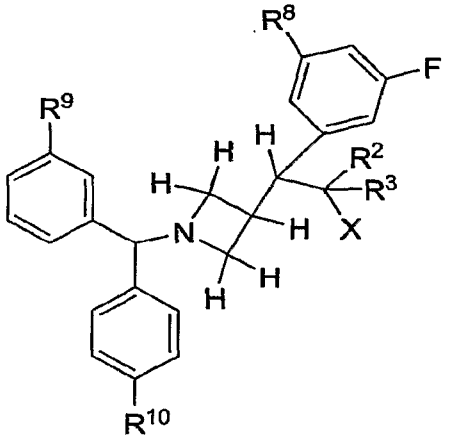
is concerned with the use of these novel compounds to selectively antagonize the Cannabinoid-1 (CB1) receptor. As such, compounds of the present invention are useful as centrally acting drugs in the treatment of psychosis, memory deficits, cognitive disorders, Alzheimer's disease, migraine, neuropathy, neuro-inflammatory disorders including multiple sclerosis and Guillain-Barre syndrome and the inflammatory sequelae of viral encephalitis, cerebral vascular accidents, and head trauma, anxiety disorders, stress, epilepsy, Parkinson's disease, movement disorders, and schizophrenia. The compounds are also useful for the treatment of substance abuse disorders, particularly abuse and/or addiction to opiates, alcohol, marijuana, and nicotine, including smoking cessation. The compounds are also useful for the treatment of obesity or eating disorders associated with excessive food intake and complications associated therewith, including left ventricular hypertrophy. The compounds are also useful for the treatment of constipation and chronic intestinal pseudo-obstruction. The compounds are also useful for the treatment of cirrhosis of the liver. The compounds are also useful for the treatment of asthma.

The present invention is also concerned with treatment of these conditions, and the use of compounds of the present invention for manufacture of a medicament useful in treating these conditions. The present invention is also concerned with treatment of these conditions through a combination of compounds of formula I and other currently available pharmaceuticals.

The invention is also concerned with pharmaceutical formulations comprising one of the compounds as an active ingredient, as well as processes for preparing the compounds of this invention.

DETAILED DESCRIPTION OF THE INVENTION

The compounds of the present invention are represented by structural formula I:



(I).

In one embodiment of this invention, X is selected from:

(1) hydroxy,

(2) NH_2,

(3) methyl, and

(4) methoxy.

In yet another subclass of this class, X is methyl.

In one embodiment of the present invention, R^2 and R^3 are each independently selected from:

(1) hydrogen,
(2) methyl,
(3) fluoro,
(4) hydroxyl, and
(5) trifluoromethyl,

provided that R^2 and R^3 are not both hydrogen when X is hydroxy, $-NH_2$, or methoxy.

In a subclass of this class, R^2 is selected from:

(1) hydrogen,
(2) methyl, and
(3) hydroxyl, and

R^3 is selected from:

(1) methyl, and
(2) hydroxyl.

In another subclass, R^2 is selected from:

(1) hydrogen,
(2) fluoro,
(3) methyl, and
(4) hydroxyl, and

R^3 is selected from methyl, and hydroxyl.

In another subclass of the present invention, R^2 and R^3 are each fluoro.

In still another subclass of the present invention, R^2 is fluoro and R^3 is methyl.

In one class, R^8 is selected from:

(1) R^{15},
(2) hydrogen,
(3) halogen,
(4) methyl,
(5) $-CF_3$,
(6) cyano, and
(7) SO_2CH_3.

In one subclass, R^8 is selected from:

(1) R^{15},
(2) hydrogen,
(3) halogen,
(4) chloro,
(5) fluoro, and
(6) cyano.

In another subclass, R^8 is selected from:

(1) R^{15},

(2) hydrogen,

(3) chloro,

(4) fluoro, and

(5) cyano.

In another subclass, R^8 is selected from:

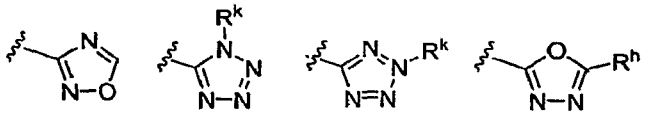
(1) R^{15},

(2) fluoro, and

(3) cyano.

In another subclass, R^8 is R^{15}.

In another subclass, R^8 is selected from:



In another subclass, R^8 is selected from:

(1) fluoro, and

(2) cyano.

In yet another class, R^9 is selected from:

(1) R^{15},

(2) hydrogen,

(3) fluoro

(4) chloro, and

(5) cyano.

In one subclass, R^9 is selected from:

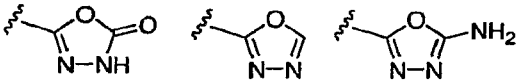
(1) R^{15},

(2) hydrogen, and

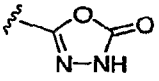
(3) cyano.

In another subclass, R^9 is R^{15}.

In still another subclass, R^9 is selected from:



In still another subclass, R^9 is:



In another subclass, R^9 is selected from:

(1) hydrogen, and

(2) cyano.

In another class of this embodiment, R^{10} is selected from:

(1) R^{15},
(2) hydrogen,
(3) fluoro,
(4) chloro,
(5) $-CF_3$,
(6) cyano, and
(7) methyl.

In another class of this embodiment, R^{10} is selected from:

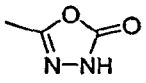
(1) R^{15},
(2) hydrogen,
(3) halogen, and
(4) cyano.

In another class of this embodiment, R^{10} is selected from:

(1) R^{15},
(2) hydrogen,
(3) chloro, and
(4) cyano.

In a subclass, R^{10} is R^{15}.

In another subclass, R^{10} is:



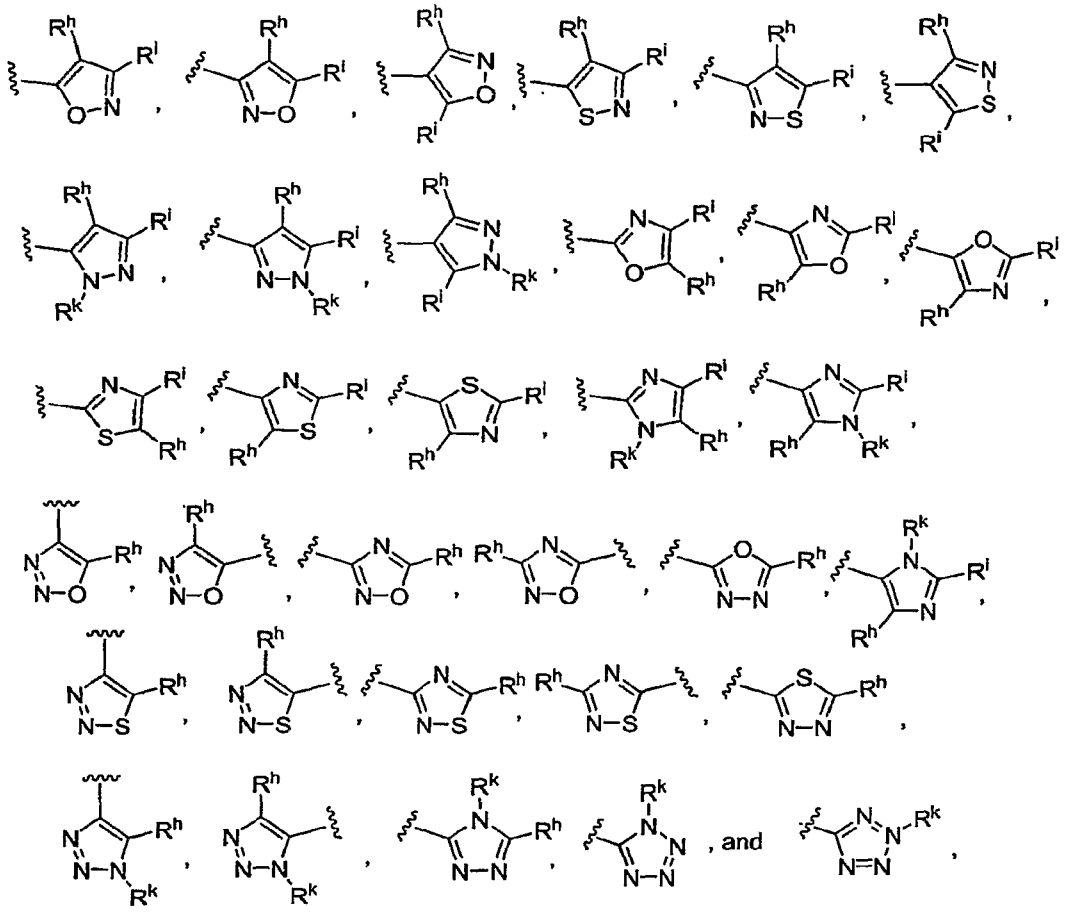
.

In another subclass, R^{10} is selected from:

(1) hydrogen,
(2) chloro, and
(3) cyano.

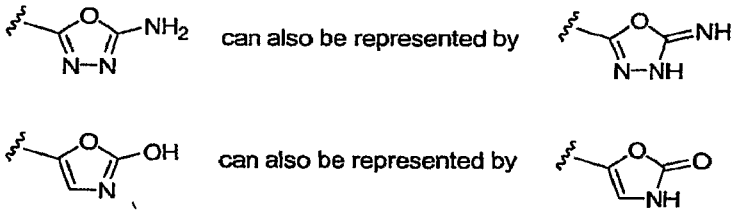
In yet another subclass, R^{10} is chloro.

In one embodiment of the present invention, each R^{15} is a 5-membered unsaturated heterocyclic ring selected from:

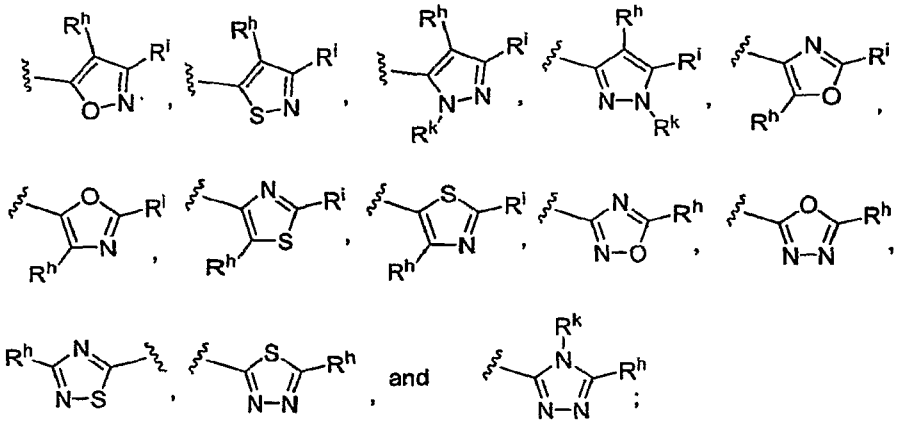


wherein: R^h and R^i are each independently selected from: –H, -OH, -SH, -NH_2, C_{1-3} alkyl, -CF_3; and each R^k is selected from: -H, and C_{1-3} alkyl.

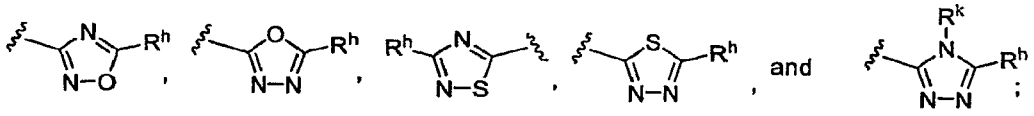
The substructures above can be considered to represent all possible tautomeric structures of the individual ring systems. For example:



In another class of the present invention, each R^{15} is independently selected from:

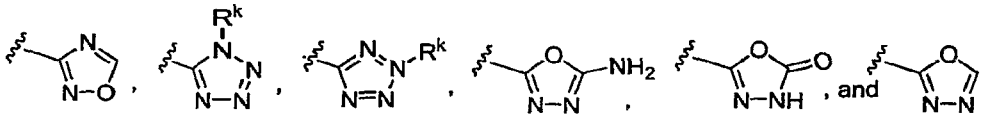


; wherein R^h and R^i are each independently selected from: –H, -OH, -SH, $-NH_2$, methyl, and $-CF_3$; and each R^k is selected from: -H, and methyl. In one subclass of the present invention, each R^{15} is independently selected from:



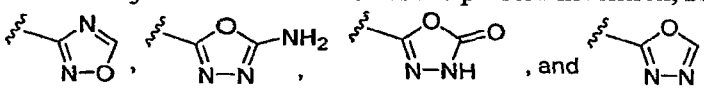
wherein R^h is selected from: –H, -OH, and $-NH_2$, and each R^k is selected from: -H, and methyl.

In one subclass of the present invention, each R^{15} is independently selected from:



wherein R^k is selected from hydrogen and methyl.

In yet another subclass of the present invention, R^{15} is selected from:



In one embodiment of the present invention, each R^h is independently selected from:

(1) –H,
(2) –OH,
(3) –SH,
(4) $-NH_2$,
(5) C_{1-3} alkyl, and
(6) $-CF_3$.

In one class of this embodiment, each R^h is independently selected from:

(1) –H,
(2) –OH,
(3) –SH,
(4) $-NH_2$,
(5) methyl, and
(6) $-CF_3$.

In one subclass of this class, each R^h is independently selected from:

(1) –H,

(2) –OH, and

(3) $–NH_2$.

In one embodiment of the present invention, each R^i is independently selected from:

(1) –H,

(2) –OH,

(3) –SH,

(4) $–NH_2$,

(5) C_{1-3} alkyl, and

(6) $-CF_3$.

In one class of this embodiment, each R^i is independently selected from:

(1) –H,

(2) –OH,

(3) –SH,

(4) $–NH_2$,

(5) methyl, and

(6) $-CF_3$.

In one subclass of this class, each R^i is independently selected from:

(1) –H,

(2) –OH, and

(3) $–NH_2$.

In another subclass of this class, each R^i is hydrogen.

In one embodiment, each R^k is independently selected from:

(1) –H, and

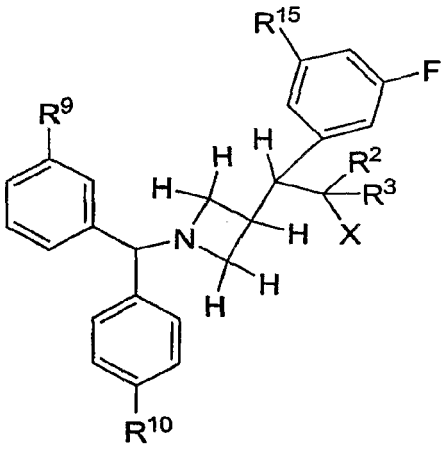
(2) C_{1-3} alkyl.

In one class, each R^k is independently selected from:

(1) –H, and

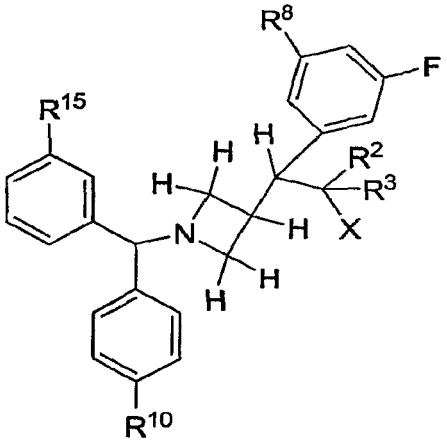
(2) methyl.

In one class are compounds of structural formula IA:



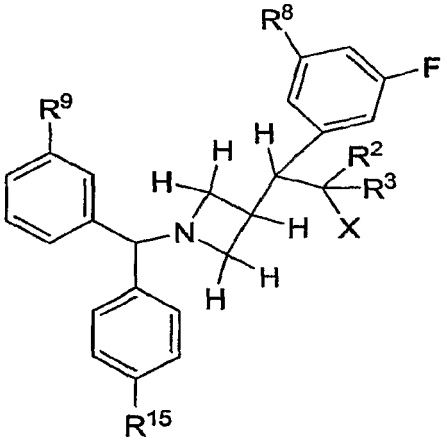
IA.

In another class are compounds of structural formula IB:



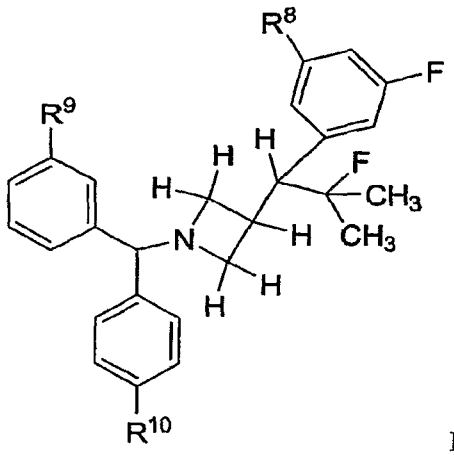
IB.

In still another class are compounds of structural formula IC:



IC.

In yet another class are compounds of structural formula ID:



ID.

In one embodiment of the present invention, only one of R^8, R^9, and R^{10} is R^{15}.

In one class, only R^8 is R^{15}.

In another class, only R^9 is R^{15}.

In still another class, only R^{10} is R^{15}.

"Alkyl", as well as other groups having the prefix "alk", such as alkoxy, alkanoyl, means carbon chains which may be linear or branched or combinations thereof. Examples of alkyl groups include methyl, ethyl, n-propyl, isopropyl, butyl, isobutyl, sec- and tert-butyl, pentyl, hexyl, heptyl, octyl, nonyl.

"Aryl" means mono- or bicyclic aromatic rings containing only carbon atoms. Examples of aryl include phenyl, naphthyl, and the like.

"Halogen" includes fluorine, chlorine, bromine and iodine.

Compounds of Formula I may contain one or more asymmetric centers and can thus occur as racemates and racemic mixtures, single enantiomers, diastereomeric mixtures and individual diastereomers. The present invention is meant to comprehend all such isomeric forms of the compounds of Formula I.

Some of the compounds described herein contain olefinic double bonds, and unless specified otherwise, are meant to include both E and Z geometric isomers.

Tautomers are defined as compounds that undergo rapid proton shifts from one atom of the compound to another atom of the compound. Some of the compounds described herein may exist as tautomers with different points of attachment of hydrogen. Such an example may be a ketone and its enol form known as keto-enol tautomers. The individual tautomers as well as mixture thereof are encompassed with compounds of Formula I.

Compounds of the Formula I may be separated into diastereoisomeric pairs of enantiomers by, for example, fractional crystallization from a suitable solvent, for example MeOH or ethyl acetate or a mixture thereof. The pair of enantiomers thus obtained may be separated into individual stereoisomers by conventional means, for example by the use of an optically active amine as a resolving agent or on a chiral HPLC column.

Alternatively, any enantiomer of a compound of the general Formula I may be obtained by stereospecific synthesis using optically pure starting materials or reagents of known configuration.

Furthermore, some of the crystalline forms for compounds of the present invention may exist as polymorphs and as such are intended to be included in the present invention. In addition, some of the compounds of the instant invention may form solvates with water or common organic solvents. Such solvates are encompassed within the scope of this invention.

It is generally preferable to administer compounds of the present invention as enantiomerically pure formulations. Racemic mixtures can be separated into their individual enantiomers by any of a number of conventional methods. These include chiral chromatography, derivatization with a chiral auxiliary followed by separation by chromatography or crystallization, and fractional crystallization of diastereomeric salts.

The term "pharmaceutically acceptable salts" refers to salts prepared from pharmaceutically acceptable non-toxic bases or acids including inorganic or organic bases and inorganic or organic acids. Salts derived from inorganic bases include aluminum, ammonium, calcium, copper, ferric, ferrous, lithium, magnesium, manganic salts, manganous, potassium, sodium, zinc, and the like. Particularly preferred are the ammonium, calcium, magnesium, potassium, and sodium salts. Salts derived from pharmaceutically acceptable organic non-toxic bases include salts of primary, secondary, and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic amines, and basic ion exchange resins, such as arginine, betaine, caffeine, choline, N,N'-dibenzylethylenediamine, diethylamine, 2-diethylaminoethanol, 2-dimethylaminoethanol, ethanolamine, ethylenediamine, N-ethyl-morpholine, N-ethylpiperidine, glucamine, glucosamine, histidine, hydrabamine, isopropylamine, lysine, methylglucamine, morpholine, piperazine, piperidine, polyamine resins, procaine, purines, theobromine, triethylamine, trimethylamine, tripropylamine, tromethamine, and the like. The term "pharmaceutically acceptable salt" further includes all acceptable salts such as acetate, lactobionate, benzenesulfonate, laurate, benzoate, malate, bicarbonate, maleate, bisulfate, mandelate, bitartrate, mesylate, borate, methylbromide, bromide, methylnitrate, calcium edetate, methylsulfate, camsylate, mucate, carbonate, napsylate, chloride, nitrate, clavulanate, N-methylglucamine, citrate, ammonium salt, dihydrochloride, oleate, edetate, oxalate, edisylate, pamoate (embonate), estolate, palmitate, esylate, pantothenate, fumarate, phosphate/diphosphate, gluceptate, polygalacturonate, gluconate, salicylate, glutamate, stearate, glycollylarsanilate, sulfate, hexylresorcinate, subacetate, hydrabamine, succinate, hydrobromide, tannate, hydrochloride, tartrate, hydroxynaphthoate, teoclate, iodide, tosylate, isothionate, triethiodide, lactate, panoate, valerate, and the like which can be used as a dosage form for modifying the solubility or hydrolysis characteristics or can be used in sustained release or pro-drug formulations.

It will be understood that, as used herein, references to the compounds of Formula I are meant to also include the pharmaceutically acceptable salts.

Compounds of the present invention are modulators of the CB1 receptor. In particular, the compounds of structural formula I are antagonists or inverse agonists of the CB1 receptor.

Compounds of this invention are modulators of the CB1 receptor and as such are useful as centrally acting drugs in the treatment of psychosis; memory deficits; cognitive disorders; Alzheimer's disease; migraine; neuropathy; neuro-inflammatory disorders including multiple sclerosis and Guillain-Barre syndrome and the inflammatory sequelae of viral encephalitis, cerebral vascular accidents, and head trauma; anxiety disorders; stress; epilepsy; Parkinson's disease; movement disorders; schizophrenia; substance abuse disorders, particularly to opiates, alcohol, marijuana, and nicotine; obesity or eating disorders associated with excessive food intake and complications associated therewith, including left ventricular hypertrophy, as well as treating or preventing obesity in other mammalian species, including canines and felines; cirrhosis of the liver; non-alcoholic fatty liver disease (NAFLD); non-alcoholic steatohepatitis (NASH); asthma; constipation; and chronic intestinal pseudo-obstruction. In particular, the compounds of this invention are antagonists/inverse agonists of the CB1 receptor. In particular, the compounds of the invention are useful for smoking cessation.

The compounds of the present invention possess a 5-membered, carbon-linked, partly or fully unsaturated, heterocylic moiety and are metabolized by both oxidative and nonoxidative mechanisms. This heterocyclic moiety is amenable to secondary metabolic processing and/or oxidative cleavage, which provides a favorable metabolic profile. The compounds of the present invention exhibit mixed mechanisms of metabolism or clearance. It is highly desirable that the clearance and/or excretion of drugs from targeted patients be mediated by more than one mechanism rather than be dependent upon a single mechanism to clear the drug from the patient. This is a desirable feature to avoid potential drug-drug interactions or genetic polymorphisms in a single clearance mechanism that might contribute to broad patient to patient variability. Likewise, mixed mechanisms of clearance may avoid undesirable rises in drug exposure in patients with compromised organ function; for example, liver function impairment or kidney disease. With multiple metabolic pathways available for clearance and/or excretion, compounds of the present invention may have more limited patient to patient variability in exposure and a greater safety profile.

The magnitude of prophylactic or therapeutic dose of a compound of Formula I will, of course, vary with the nature of the severity of the condition to be treated and with the particular compound of Formula I and its route of administration. It will also vary according to the age, weight and response of the individual patient. In general, the daily dose range lie within the range of from about 0.001 mg to about 100 mg per kg body weight of a mammal, preferably 0.01 mg to about 50 mg per kg, and most preferably 0.1 to 10 mg per kg, in single or divided doses. On the other hand, it may be necessary to use dosages outside these limits in some cases.

Another aspect of the present invention provides pharmaceutical compositions which comprises a compound of Formula I and a pharmaceutically acceptable carrier. The term "composition", as in pharmaceutical composition, is intended to encompass a product comprising the active ingredient(s), and the inert ingredient(s) (pharmaceutically acceptable excipients) 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 compositions of the present invention encompass any composition made by admixing a compound of Formula I, additional active ingredient(s), and pharmaceutically acceptable excipients.

Any suitable route of administration may be employed for providing a mammal, particularly a human or companion animal such as a dog or cat, with an effective dosage of a compound of the present invention. For example, oral, rectal, topical, parenteral, ocular, pulmonary, nasal, and the like may be employed. Dosage forms include tablets, troches, dispersions, suspensions, solutions, capsules, creams, ointments, aerosols, and the like.

The pharmaceutical compositions of the present invention comprise a compound of Formula I as an active ingredient or a pharmaceutically acceptable salt thereof, and may also contain a pharmaceutically acceptable carrier and optionally other therapeutic ingredients. By "pharmaceutically acceptable" it is meant the carrier, diluent or excipient must be compatible with the other ingredients of the formulation and not deleterious to the recipient thereof. The compositions include compositions suitable for oral, rectal, topical, parenteral (including subcutaneous, intramuscular, and intravenous), ocular (ophthalmic), pulmonary (aerosol inhalation), or nasal administration, although the most suitable route in any given case will depend on the nature and severity of the conditions being treated and on the nature of the active ingredient. They may be conveniently presented in unit dosage form and prepared by any of the methods well-known in the art of pharmacy.

Suitable topical formulations of a compound of formula I include transdermal devices, aerosols, creams, solutions, ointments, gels, lotions, dusting powders, and the like. The topical pharmaceutical compositions containing the compounds of the present invention ordinarily include about 0.005% to 5% by weight of the active compound in admixture with a pharmaceutically acceptable vehicle. Transdermal skin patches useful for administering the compounds of the present invention include those well known to those of ordinary skill in that art.

In practical use, the compounds of Formula I can be combined as the active ingredient in intimate admixture with a pharmaceutical carrier according to conventional pharmaceutical compounding techniques.

Pharmaceutical compositions of the present invention suitable for oral administration may be presented as discrete units such as capsules (including timed release and sustained release formulations), pills, cachets, powders, granules or tablets each containing a predetermined amount of the active ingredient, as a powder or granules or as a solution or a suspension in an aqueous liquid, a non-aqueous liquid, an oil-in-water emulsion or a water-in-oil liquid emulsion, including elixirs, tinctures, solutions, suspensions, syrups and emulsions. Desirably, each tablet, cachet, or capsule contains from about 0.01 to 1,000 mg, particularly 0.01, 0.05, 0.1, 0.5, 1.0, 2, 2.5, 3, 4, 5, 6, 7, 8, 9, 10, 12, 15, 25, 30, 40, 50, 75, 100, 125, 150, 175, 180, 200, 225, 250, 500, 750 and 1,000 milligrams of the active ingredient for the symptomatic adjustment of the dosage to the patient to be treated.

Additional suitable means of administration of the compounds of the present invention include injection, intravenous bolus or infusion, intraperitoneal, subcutaneous, intramuscular and topical, with or without occlusion.

Exemplifying the invention is a pharmaceutical composition comprising any of the compounds described above and a pharmaceutically acceptable carrier. Also exemplifying the invention is a pharmaceutical composition made by combining any of the compounds described above and a pharmaceutically acceptable carrier. An illustration of the invention is a process for making a pharmaceutical composition comprising combining any of the compounds described above and a pharmaceutically acceptable carrier.

The dose may be administered in a single daily dose or the total daily dosage may be administered in divided doses of two, three or four times daily. Furthermore, based on the properties of the individual compound selected for administration, the dose may be administered less frequently, e.g., weekly, twice weekly, monthly, etc. The unit dosage will, of course, be correspondingly larger for the less frequent administration.

When administered via intranasal routes, transdermal routes, by rectal or vaginal suppositories, or through a continual intravenous solution, the dosage administration will, of course, be continuous rather than intermittent throughout the dosage regimen.

The following are examples of representative pharmaceutical dosage forms for the compounds of Formula I:

Capsule	mg/capsule
Compound of Formula I	25
Lactose Powder	573.5
Magnesium Stearate	1.5
	600

Tablet	mg/tablet
Compound of Formula I	25
Microcrystalline Cellulose	415
Povidone	14.0
Pregelatinized Starch	43.5
Magnesium Stearate	2.5
	500

Compounds of Formula I may be used in combination with other drugs that are used in the treatment/prevention/suppression or amelioration of the diseases or conditions for which compounds of Formula I are useful. Such other drugs may be administered, by a route and in an amount commonly used therefor, contemporaneously or sequentially with a compound of Formula I. When a compound of Formula I is used contemporaneously with one or more other drugs, a pharmaceutical composition containing such other drugs in addition to the compound of Formula I 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 Formula I. Examples of other active ingredients that may be combined with a compound of Formula I include, but are not limited to: antipsychotic agents, cognition enhancing agents, anti-migraine agents, anti-asthmatic agents, antiinflammatory agents, anxiolytics, anti-Parkinson's agents, anti-epileptics, anorectic agents, serotonin reuptake inhibitors, other

anti-obesity agents, as well as antidiabetic agents, lipid lowering agents, and antihypertensive agents which may be administered separately or in the same pharmaceutical compositions.

Specific DP-IV inhibitors of use in combination with a compound of the present invention are selected from 7-[(3R)-3-amino-4-(2,4,5-trifluorophenyl)butanoyl]-3-(trifluoromethyl)-5,6,7,8-tetrahydro-1,2,4-triazolo[4,3-a]pyrazine. In particular, the compound of formula I is favorably combined with 7-[(3R)-3-amino-4-(2,4,5-trifluorophenyl)butanoyl]-3-(trifluoromethyl)-5,6,7,8-tetrahydro-1,2,4-triazolo[4,3-a]pyrazine, and pharmaceutically acceptable salts thereof.

The obesity-related disorders herein are associated with, caused by, or result from obesity. Examples of obesity-related disorders include overeating and bulimia, hypertension, diabetes, elevated plasma insulin concentrations and insulin resistance, dyslipidemias, hyperlipidemia, endometrial, breast, prostate and colon cancer, osteoarthritis, obstructive sleep apnea, cholelithiasis, gallstones, heart disease, abnormal heart rhythms and arrythmias, myocardial infarction, congestive heart failure, coronary heart disease, sudden death, stroke, polycystic ovarian disease, craniopharyngioma, the Prader-Willi Syndrome, Frohlich's syndrome, GH-deficient subjects, normal variant short stature, Turner's syndrome, and other pathological conditions showing reduced metabolic activity or a decrease in resting energy expenditure as a percentage of total fat-free mass, e.g, children with acute lymphoblastic leukemia. Further examples of obesity-related disorders are metabolic syndrome, also known as syndrome X, insulin resistance syndrome, sexual and reproductive dysfunction, such as infertility, hypogonadism in males and hirsutism in females, gastrointestinal motility disorders, such as obesity-related gastro-esophageal reflux, respiratory disorders, such as obesity-hypoventilation syndrome (Pickwickian syndrome), cardiovascular disorders, inflammation, such as systemic inflammation of the vasculature, arteriosclerosis, hypercholesterolemia, hyperuricaemia, lower back pain, gallbladder disease, gout, and kidney cancer. The compounds of the present invention are also useful for reducing the risk of secondary outcomes of obesity, such as reducing the risk of left ventricular hypertrophy.

The compounds of formula I are also useful for treating or preventing obesity and obesity-related disorders in cats and dogs. As such, the term "mammal" includes companion animals such as cats and dogs.

As used herein, the term "substance abuse disorders" includes substance dependence or abuse with or without physiological dependence. The substances associated with these disorders are: alcohol, amphetamines (or amphetamine-like substances), caffeine, cannabis, cocaine, hallucinogens, inhalants, marijuana, nicotine, opioids, phencyclidine (or phencyclidine-like compounds), sedative-hypnotics or benzodiazepines, and other (or unknown) substances and combinations of all of the above.

In particular, compounds of structural formula I are useful for aiding in stopping consumption of tobacco and are useful in treating nicotine dependence and nicotine withdrawal. For smoking cessation, the compound of form I may be used in combination with a nicotine agonist or a partial nicotine agonist, including varenicline and selective alpha-4 beta 2 nicotinic partial agonists such as SSR 591813, or a monoamine oxidase inhibitor (MAOI), or another active ingredient demonstrating efficacy in aiding

cessation of tobacco consumption; for example, an antidepressant such as bupropion, doxepine, ornortriptyline; or an anxiolytic such as buspirone or clonidine.

The method of treatment of this invention comprises a method of modulating the CB1 receptor and treating CB1 receptor mediated diseases by administering to a patient in need of such treatment a non-toxic therapeutically effective amount of a compound of this invention that selectively antagonizes the CB1 receptor in preference to the other CB or G-protein coupled receptors.

Abbreviations used in the following Schemes and Examples:

aq or aq.: aqueous; BOC or boc: benzyloxycarbonyl; brine: saturated sodium chloride solution; Bu: butyl; DBU: 1,8-diazabicyclo[5.4.0]undec-7-ene; DIEA: *N,N*-diisopropyl ethyl amine; DMAP: 4-dimethylaminopyridine; DMF: dimethylformamide; DMSO: dimethylsulfoxide; DPPF: 1,1'-bis-(diphenylphosphino)ferrocene; Et: ethyl; g or gm: gram; h or hr: hours; HOAc: acetic acid; HOBT: 1-hydroxybenzotriazole; HPLC: high pressure liquid chromatography; HPLC/MS: high pressure liquid chromatography/mass spectroscopy; in vacuo: rotoevaporation; iPr: isopropyl; LC-MS: liquid chromatography-mass spectrum; LHMDS: Lithium Hexamethyl Disilylamide-LiN($SiMe_3$)$_2$; M: molar; Me: methyl; mg: milligram; MHz: megahertz; min: minutes; mL: milliliter; mmol: millimole; MS or ms: mass spectrum; NaHMDS: sodium hexamethyl disilylamide Ph: phenyl; psi: pounds per square inch; rt or RT: room temperature; R_t: retention time; THF: tetrahydrofuran; TLC: thin layer chromatography; μL, μl, μL or μl: microliter.

Compounds of the present invention may be prepared by procedures illustrated in the accompanying schemes.

Compounds of the present invention may be prepared by procedures illustrated in the examples schemes, as well as by reference to procedures known to those of ordinary skill in the art, including those described in PCT Publication WO 05/000809.

PREPARATION 1

1-[Bis(4-chlorophenyl)methyl]azetidin-3-one

This compound was prepared according to the procedures in WO 05/000809, Preparation 1.

PREPARATION 2

1-[bis(4-phenyl)methyl]azetidin-3-one

This compound was prepared according to the procedures in WO 05/000809, Preparation 2.

PREPARATION 3

Methyl {1-[bis(4-chlorophenyl)methyl]azetidin-3-ylidene}(3,5-difluorophenyl)acetate

This compound was prepared according to the procedures in WO 05/000809, Preparation 3.

PREPARATION 4

Methyl {1-[bis(4-chlorophenyl)methyl]azetidin-3-ylidene}(3,5-difluorophenyl)acetate

This compound was prepared according to the procedures in WO 05/000809, Preparation 4.

PREPARATION 5

Methyl (3,5-difluorophenyl)[1-(diphenylmethyl)azetidin-3-ylidene]acetate

This compound was prepared according to the procedures in WO 05/000809, Preparation 5.

PREPARATION 6

Methyl{1-[bis(4-chlorophenyl)methyl]azetidin-3-yl}(3,5-difluorophenyl)acetate

This compound was prepared according to the procedures in WO 05/000809, Preparation 1.

PREPARATION 7

2-{1-[Bis(4-chlorophenyl)methyl]azetidin-3-yl}(3,5-difluorophenyl)ethanol

This compound was prepared according to the procedures in WO 05/000809, Preparation 7.

PREPARATION 8

{1-[Bis(4-chlorophenyl)methyl]azetidin-3-yl}(3,5-difluorophenyl)acetaldehyde

This compound was prepared according to the procedures in WO 05/000809, Preparation 8.

PREPARATION 9

3-[(*S*)-(4-Chlorophenyl)(3-hydroxyazetidin-1-yl)methyl]benzonitrile

This compound was prepared according to the procedures in WO 05/000809, Preparation 9.

PREPARATION 10

3-[(*S*)-(4-Chlorophenyl)(3-hydroxyazetidin-1-yl)methyl]benzonitrile, alternate preparation

Step 1 *N*-[(1*E*)-(3-cyanophenyl)methylene]-2-methylpropane-2-(*R*)sulfinamide

A solution of 19.0 g (157 mmole) of (*R*)-(+)-2-methylpropane-2-sulfinamide and 89.0 g (314 mmole) of titanium tetraisopropoxide in CH_2Cl_2 was stirred at room temperature for 10 min. Then a solution of 21.6 g (165 mmole) of 3-formylbenzonitrile in 10 mL CH_2Cl_2 was added, and the solution was stirred at room temperature. After 18 h, the reaction was quenched by the addition of 30 mL brine and the solution was rapidly stirred for 15 min. The mixture was filtered through a pad of CELITE and the residue was washed with 300 mL of CH_2Cl_2. The combined organic extracts were washed with brine, dried over Na_2SO_4 and concentrated. The residue was filtered through a pad of silica gel using 20% ethyl acetate-hexane to afford the title compound; ^{1}H-NMR($CDCl_3$) δ 1.31 (s, 9H), 7.65 (t, 1H, J = 7.8 Hz), 7.82 (d, 1H, J = 7.8 Hz), 8.07 (d, 1H, J = 7.8 Hz), 8.20 (s, 1H), 8.62 (s, 1H); Mass Spectrum: m/e = 235 (M+1).

Step 2 *N*-[(*S*)-(4-chlorophenyl)(3-cyanophenyl)methyl]-2-methylpropane-2-(*R*)- sulfinamide

A solution of 20 g (85.4 mmole) of *N*-[(1*E*)-(3-cyanophenyl)methylene]-2-methylpropane-2-(*R*)sulfonamide in 1000 mL toluene and 400 mL ether was cooled to -60 °C in a dry ice-acetone bath. Then 170 mL of a 1M solution of 4-chlorophenylmagnesium bromide in ether was added at a rate such that the temperature remained between -60 °C and -50 °C and the reaction was stirred at -60 °C for 6 h. The reaction was quenched by addition of 300 mL of saturated NH_4Cl solution and the layers were separated. The organic layer was washed with 300 mL aliquots of saturated NH_4Cl solution and brine, then was dried over Na_2SO_4 and concentrated. The residue was filtered through a pad of silica gel using 10 to 30% ethyl acetate hexane to afford the title compound with de > 96% as determined by analytical ChiralPak AD column; ^{1}H-NMR($CDCl_3$) δ 1.27 (s, 9H), 3.76 (s, 1H), 5.65 (d, 1H, J = 2.3 Hz), 7.24-7.7 (m, 8H).

Step 3 3-[(*S*)-amino(4-chlorophenyl)methyl]benzonitrile hydrochloride

To a solution of 850 mg (2.45 mmole) of *N*-[(*S*)-(4-chlorophenyl)(3-cyanophenyl)methyl]-2-methylpropane-2-(*R*)-sulfinamide in 20 mL of CH_3OH was added 2.5 mL of 4M HCL in dioxane. The solution was stirred at room temperature for 45 min, then was diluted with 40 mL ether. The solids were collected by filtration to afford the title compound as a white solid; ^{1}H-NMR($CDCl_3$) δ 1.6 (s, 2H, br), 5.24 (s, 1H), 7.24-7.78 (m, 8H).

Step 4 3-[(*S*)-(4-chlorophenyl)(3-hydroxyazetidin-1-yl)methyl]benzonitrile

To a mixture of 20.27 g (72.6 mmole) of 3-[(*S*)-[(3-chloro-2-hydroxypropyl)amino](4-chlorophenyl)methyl]benzonitrile hydrochloride and 21.3 g (245 mmole) of $NaHCO_3$ in 600 mL of isopropanol was added 14.4 mL (174 mmole) of epibromohydrin . The mixture was heated to reflux for 24 h, then was cooled and concentrated. The residue was partitioned between 750 mL portions of ether and water and the aqueous layer was washed with two 500 mL portions of ether. The combined organic extracts were washed with brine, dried over $MgSO_4$ and concentrated. The residue was purified by flash chromatography using 10-20% ethyl acetate in hexane to afford the title compound as a clear oil; ^{1}H-NMR($CDCl_3$) δ 1.6 (s, 2H, br), 5.24 (s, 1H), 7.24-7.78 (m, 8H).2.89 (m, 2H), 3.54 (m, 2H), 4.39 (s, 1H), 4.52 (m, 1H), 7.2-7.8 (m, 8H).

PREPARATION 11

1-{1-[(3-chlorophenyl)(4-chlorophenyl)methyl]azetidin-3-yl}-1-(3,5-difluorophenyl)-2-methylpropan-2-ol

A solution of 0.985 g (4.0 mmole) of finely powdered $CeCl_3$ (Strem Chemical Co.) in 10 mL anhydrous THF was stirred at room temperature under N_2. After 1h, the solution was cooled to – 78 °C in a dry ice-acetone bath and 2.5 mL of a 1.6M solution of methyllithium in ether was added dropwise at such a rate that the solids remained dispersed. After 30 minutes, a solution of 0.485 g (1.1 mmole) of methyl {1-[(3-chlorophenyl)(4-chlorophenyl)methyl]azetidin-3-yl}(3,5-difluorophenyl)acetate in 5 mL of THF was added and the solution was left stirring at -78 °C for 1 h. The reaction was quenched by addition of 0.1 mL CH_3OH, diluted with 40 mL of ether and allowed to warm to – 10 °C. Then aqueous NH_4Cl solution was added dropwise until the cerium salts precipitated onto the surface of the flask. The supernatant was decanted and the solids were triturated with two 20 mL portions of CH_2Cl_2 and two 20 mL portions of ether. The combined organic extracts were washed with saturated aqueous NH_4Cl solution and brine, dried over Na_2SO_4 and concentrated to afford the title compound as a mixture of 4 diastereomers. The mixture was purified by flash chromatography on silica gel using a step gradient of 3 column volumnes each of 1%, then 2%, then 4%, then 6% ethyl acetate-hexane to afford two diastereomers of the title compound. The enantiomers of the faster diastereomer were separated by chromatography on an AD column chiral using 6% isopropanol in heptane. Faster diastereomer: ^{1}H-NMR($CDCl_3$) δ 1.07 (s, 3H), 1.14 (S, 3H), 2.28 (t, 1H, J = 7.5Hz), 2.74 (d, 1H, J = 10.7Hz), 2.82 (t, 1H, J = 7.5 Hz), 3.10-3.16 (m, 2H), 3.62 (m, 1H), 4.20 (s, 1H), 6.67-6.73 (m, 3H), 7.21-7.33(m, 8H); Mass Spectrum: m/e = 476 (M+1 ^{35}Cl, ^{35}Cl) and 478 (M+1 ^{35}Cl, ^{37}Cl).

Slower diastereomer ^{1}H-NMR($CDCl_3$) δ 1.06 (s, 3H), 1.14 (S, 3H), 2.29 (t, 1H, J = 7.5Hz), 2.75 (d, 1H, J = 10.7Hz), 2.82 (t, 1H, J = 7.5 Hz), 3.10-3.16 (m, 2H), 3.62 (m, 1H), 4.22 (s, 1H), 6.67-6.73 (m, 3H), 7.21-7.33(m, 8H); Mass Spectrum: m/e = 476 (M+1 ^{35}Cl, ^{35}Cl) and 478 (M+1 ^{35}Cl, ^{37}Cl).

PREPARATION 12

3-((*S*)-(4-chlorophenyl){3-[(1*S*)-1-(3,5-difluorophenyl)-2-hydroxy-2-methylpropyl]azetidin-1-yl}methyl)benzonitrile

This compound was prepared according to the procedures in WO 05/000809, Example 49.

PREPARATION 13

3-((*S*)-(4-chlorophenyl){3-[(1*S*)-1-(3,5-difluorophenyl)-2-fluoro-2-methylpropyl]azetidin-1-yl}methyl)benzonitrile

This compound was prepared according to the procedures in WO 05/000809, Example 74.

PREPARATION 14

3-((*S*)-(4-chlorophenyl){3-[(1*S*)-1-(3,5-difluorophenyl)-2-hydroxy-2-methylpropyl]azetidin-1-yl}methyl)benzonitrile

This compound was prepared according to the procedures in WO 05/000809, Example 76.

PREPARATION 15

3-((*S*)-(4-chlorophenyl){3-[(1*S*)-1-(3,5-difluorophenyl)-2-hydroxy-2-methylpropyl]azetidin-1-yl}methyl)benzonitrile

This compound was prepared according to the procedures in WO 05/000809, Example 79.

PREPARATION 16

3-((1*S*)-1-{1-[(*S*)-(4-chlorophenyl)(3-cyanophenyl)methyl]azetidin-3-yl}-2-fluoro-2-methylpropyl)-5-fluorobenzonitrile

Step 1: Ethyl (2*R*)-(3-bromo-5-fluorophenyl)[1-(diphenylmethyl)-3-hydroxyazetidin-3-yl]acetate

The title compound was prepared from ethyl 3-bromo-5-fluorophenylacetate and 1-[bis-phenylmethyl]azetidin-3-one (Preparation 2) by the procedure described in Step 2 of Preparation 3 except that lithium hexamethyldisilamide was used instead of butyllithium to form the ketene acetal; Mass Spectrum: m/e = 498 (M+1, ^{79}Br), 500 (M+1, ^{81}Br)

Step 2: Ethyl (3-bromo-5-fluorophenyl)[1-(diphenylmethyl)azetidin-3-ylidene]acetate

The title compound was prepared from ethyl (2*R*)-(3-bromo-5-fluorophenyl)[1-(diphenylmethyl)-3-hydroxyazetidin-3-yl]acetate according to the procedures described in Preparation 5; Mass Spectrum: m/e = 480 (M+1, ^{79}Br), 482 (M+1, ^{81}Br)

Step 3 Ethyl (3-bromo-5-fluorophenyl)[1-(diphenylmethyl)azetidin-3-yl]acetate

The title compound was prepared from ethyl (3-bromo-5-fluorophenyl)[1-(diphenylmethyl) azetidin-3-ylidene]acetate according to the procedure described in Preparation 6 except that THF was used as the co-solvent; Mass Spectrum: m/e = 482 (M+1, ^{79}Br), 484 (M+1, ^{81}Br).

Step 4 1-(3-Bromo-5-fluorophenyl)-1-[1-(diphenylmethyl)azetidin-3-yl]-2-methylpropan-2-ol

The title compound was prepared from ethyl (3-bromo-5-fluorophenyl)[1-(diphenylmethyl) azetidin-3-yl]acetate according to the procedure described in Step 1 of Preparation 12; Mass Spectrum: m/e = 468 (M+1, ^{79}Br), 470 (M+1, ^{81}Br).

Step 5 (1*S*)-1-(3-bromo-5-fluorophenyl)-1-[1-(diphenylmethyl)azetidin-3-yl]-2-methylpropan-2- ol

The enantiomers of the product of Step 4 were separated by chromatography on a ChiralPak AD column using 3% isopropanol-heptane as described in Step 1 of Preparation 12; Mass Spectrum: m/e = 468 (M+1).

Step 6 3-[(1*S*)-1-(3-bromo-5-fluorophenyl)-2-fluoro-2-methylpropyl]-1-(diphenylmethyl) azetidine

The title compound was prepared from (1*S*)-1-(3-bromo-5-fluorophenyl)-1-[1-(diphenylmethyl) azetidin-3-yl]-2-methylpropan-2-ol according to the procedure described in Step 2 of Preparation 14; Mass Spectrum: m/e = 470 (M+1, ^{79}Br), 472 (M+1, ^{81}Br).

Step 7 3-[(1*S*)-1-(3-bromo-5-fluorophenyl)-2-fluoro-2-methylpropyl]azetidine

The title compound was prepared from 3-[(1*S*)-1-(3-bromo-5-fluorophenyl)-2-fluoro-2-methylpropyl]-1-(diphenylmethyl)azetidine according to the procedure described in Step 1 of Preparation 15; Mass Spectrum: m/e = 304 (M+1, ^{79}Br), 306 (M+1, ^{81}Br).

Step 8 3-[(*S*)-{3-[(1*S*)-1-(3-Bromo-5-fluorophenyl)-2-fluoro-2-methylpropyl]azetidin-1-yl}(4-chlorophenyl)methyl]benzonitrile

The title compound was prepared from 3-[(1*S*)-1-(3-bromo-5-fluorophenyl)-2-fluoro-2-methylpropyl]azetidine according to the procedure described in Step 2 of Preparation 15 except that DIEA was used instead of Cs_2CO_3; Mass Spectrum: m/e = 529 (M+1, ^{35}Cl, ^{79}Br), 531 (M+1, ^{35}Cl, ^{81}Br and ^{37}Cl, ^{79}Br), 576 (M+1, ^{35}Cl, ^{81}Br).

Step 9 3-((1*S*)-1-{1-[(*S*)-(4-chlorophenyl)(3-cyanophenyl)methyl]azetidin-3-yl}-2-fluoro-2-methylpropyl)-5-fluorobenzonitrile

A suspension of 143 mg (0.27 mmole) of 3-[(*S*)-{3-[(1*S*)-1-(3-bromo-5-fluorophenyl)-2-fluoro-2-methylpropyl]azetidin-1-yl}(4-chlorophenyl)methyl]benzonitrile, 0.026 mg (0.216 mmole) of Zn(CN)2, 5 mg (0.005 mmole) of tris(dibenzylideneacetone)dipalladium(0) and 8 mg (0.014 mmole) of 1, 1'-Bis(diphenylphosphino)ferrocene in 2.5 mL of dry DMF was degassed for 1h at rt. Then the solution was heated at 140 °C for 17h. The solution was concentrated under high vacuum and then was partitioned between 20 mL ether, 20 mL ethyl acetate and 10 mL water. The layers were separated and the aqueous layer was washed with two 20 mL portions of 1:1 ether-ethyl acetate. The combined organic layers were dried over Na_2SO_4 and concentrated. The residue was purified by preparatory TLC using 20% ethyl acetate-hexane to afford the title compound; Mass Spectrum: m/e = 476 (M+1, ^{35}Cl), 478 (M+1, ^{37}Cl).

PREPARATION 17

Ethyl 3-(1-{1-[(4-chlorophenyl)(3-cyanophenyl)methyl]azetidin-3-yl}-2-fluoro-2-methylpropyl)-5-fluorobenzoate

Step 1: 3-{1-[1-(diphenylmethyl)azetidin-3-yl]-2-fluoro-2-methylpropyl}-5-fluorobenzonitrile

A solution of 16.19g (34.42 mmol) of 3-[1-(3-bromo-5-fluorophenyl)-2-fluoro-2-methylpropyl]-1-(diphenylmethyl)azetidine, 3.23g (27.53 mmol) of zinc cyanide, 1.10g (1.2 mmol) of tris(dibenzylideneacetone)dipalladium, and 1.53g (2.75 mmol) of DPPF in 99 mL of DMF and 1 mL of water was degassed for 1 h at rt. Then it was stirred at 140 °C. After 17 h, it was concentrated to remove solvents. Then the mixture was poured into 300 mL of ether/ethyl acetate (1:1) and 100 mL aq $NaHCO_3$. The organic layer was dried over Na_2SO_4 and concentrated. The residue was purified by silica gel chromatography with hexanes/ethyl acetate to afford the title compound as a white solid; ^{1}H-NMR($CDCl_3$) δ 1.22(d, 3H, J= 21Hz), 1.30(d, 6H, J= 21Hz), 2.30 (t, 1H, J = 7.8Hz), 2.86-2.96 (m, 2H), 3.08-3.18 (m, 2H), 3.65 (t, 1H, J = 7Hz), 4.25 (s, 1H), 7.13-7.43 (m, 13H); Mass Spectrum: m/e = 417 (M+1).

Step 2: 3-{1-[1-(diphenylmethyl)azetidin-3-yl]-2-fluoro-2-methylpropyl}-5-fluorobenzoic acid

The reaction of mixture of 7.15g (17.18 mmol) of 3-{1-[1(diphenylmethyl)azetidin-3-yl]-2-fluoro-2-methylpropyl}-5-fluorobenzonitrile (Step 1), 125 mL of EtOH, and 70 mL of 5N NaOH was refluxed for 3.5h. Then it was adjusted to pH = 4-5 with 12N HCl and concentrated to remove solvents. To the residue was added 200 mL of $CH_2Cl_2$to dissolve the compound and it was filtered to remove the solid. The solid layer was washed with CH_2Cl_2 and the combined organic layers were concentrated to afford the title compound as white solid; Mass Spectrum: m/e = 436 (M+1).

Step 3: Ethyl 3-{1-[1-(diphenylmethyl)azetidin-3-yl]-2-fluoro-2-methylpropyl}-5-fluorobenzoate

A mixture of 7.5g (17.15 mmol) of 3-{1-[1-(diphenylmethyl)azetidin-3-yl]-2-fluoro-2-methylpropyl}-5-fluorobenzoic acid, 25 mL of 4N HCl in dioxane, and 200 mL of EtOH was refluxed. After 10h, it was concentrated to remove solvents. To the residue was added 150 mL of CH_2Cl_2 and 30 mL of H_2O and pH was adjusted to 7-8 with aq $NaHCO_3$, then extracted with CH_2Cl_2. The combined organic layer was dried over Na_2SO_4 and concentrated. The residue was purified by silica gel chromatography with hexanes/ethyl acetate to afford the title compound as an white solid; ^{1}H-NMR($CDCl_3$) δ 1.25(d, 3H, J= 22Hz), 1.30(d, 3H, J= 22Hz), 1.42 (t, 3H, J = 7.1Hz), 2.35 (t, 1H, J = 8 Hz), 2.89 (t, 1H, J = 8Hz), 2.97 (m, 1H), 3.12 (m, 1H), 3.24 (m, 1H), 3.68 (t, 1H, J = 6 Hz), 4.27 (s, 1H), 4.38 (q, 2H, J_1= 14, J_2 = 7Hz), 7.103-7.66 (m, 13H); Mass Spectrum: m/e = 464 (M+1).

Step 4: Ethyl 3-(1-azetidin-3-yl-2-fluoro-2-methylpropyl)-5-fluorobenzoate

Ethyl 3-{1-[1-(diphenylmethyl)azetidin-3-yl]-2-fluoro-2-methylpropyl}-5-fluorobenzoate (7.6g, 16.40 mmol) was hydrogenated in 150 mL of EtOH in the presence 3.4g of $Pd(OH)_2$ under 50 Psi pressure hydrogen for 24 h. Then it was filtered to remove the solid and washed with CH_2Cl_2. The combined organic layer was concentrated and washed with hexanes/ether to afford the title compound as an white solid. Mass Spectrum: m/e = 298 (M+1).

Step 5: Ethyl 3-(1-{1-[(4-chlorophenyl)(3-cyanophenyl)methyl]azetidin-3-yl}-2-fluoro-2-methylpropyl)-5-fluorobenzoate

The mixture of 4.90g (16.40mmol) of ethyl 3-(1-azetidin-3-yl-2-fluoro-2-methylpropyl)-5-fluorobenzoate, 8.17 g of 3-[bromo(4-chlorophenyl)methyl]benzonitrile, 6 mL(34.36 mmol) of DIEA in 40 mL of acetonitrile was refluxed for 4h, then concentrated *in vacuo*. The mixture was poured into 150 mL of CH_2Cl_2 and 30 mL of aq $NaHCO_3$. The organic layer was dried over Na_2S0_4 and concentrated. Two pairs of racemic compounds were separated by silica gel chromatography. Single diastereomers were separated by a chiral AD column; Mass Spectrum: m/e = 523 (M+1, ^{35}Cl), 525 (M+1, ^{37}Cl).

PREPARATION 18

Ethyl 3-(1-{1-[(4-cyanophenyl)(3-cyanophenyl)methyl]azetidin-3-yl}-2-fluoro-2-methylpropyl)-5-fluorobenzoate

Prepared from ethyl 3-(1-azetidin-3-yl-2-fluoro-2-methylpropyl)-5-fluorobenzoate and 3-[bromo(4-cyanophenyl)methyl]benzonitrile as described in Preparation 17, Part 5; Mass Spectrum: m/e = 514.

PREPARATION 19

3-((1*S*)-1-{1-[(*S*)-(4-chlorophenyl)(3-cyanophenyl)methyl]azetidin-3-yl}-2-fluoro-2-methylpropyl)-5-fluorobenzohydrazide

A mixture of 523 mg (0.41 mmol) of ethyl 3-(1-{1-[(4-chlorophenyl)(3-cyanophenyl)methyl] azetidin-3-yl}-2-fluoro-2-methylpropyl)-5-fluorobenzoate (Preparation 17), 0.6 mL(16.36 mmol) of hydrazine, and 4mL of EtOH was heated to reflux. After 8h, the mixture was concentrated to remove solvents to afford the of title compound as an white solid. ^1H-NMR($CDCl_3$) δ 1.20(d, 3H, J= 21Hz), 1.29(d, 3H, J= 21Hz), 2.32 (t, 3H, J = 7.1Hz), 2.85 (t, 1H, J = 8 Hz), 2.94 (m, 1H), 3.06 (m, 1H), 3.20 (m, 1H), 3.51 (s, 2H), 3.63 (t, 1H, J = 5 HZ), 4.26 (s, 1H), 7.06-7.71 (m, 11H); Mass Spectrum: m/e = 509 (M+1, ^{35}Cl), 511 (M+1, ^{37}Cl).

PREPARATION 20

3-[(4-chlorophenyl)(3-{2-fluoro-1-[3-fluoro-5-(hydroxymethyl)phenyl]-2-methylpropyl}azetidin-1-yl)methyl]benzonitrile

To the mixture of 42 mg (0.08 mmol) of ethyl 3-(1-{1-[(4-chlorophenyl)(3-cyanophenyl)methyl] azetidin-3-yl}-2-fluoro-2-methylpropyl)-5-fluorobenzoate in 3 mL of THF was added 0.18 mL (0.36 mmol) of 2 M $LiBH_4$ solution in THF and the solution was stirred overnight at rt. Then it was poured into 20 mL of CH_2Cl_2 and 5 mL of water. The water layer was extracted with CH_2Cl_2 and the combined organic layer was concentrated. The residue was purified by silica gel chromatography with hexane/ethyl acetate to afford the title compound as a white solid; Mass Spectrum: m/e = 481 (M+1, ^{35}Cl), 483 (M+1, ^{37}Cl).

PREPARATION 21

3-(1-{1-[(4-chlorophenyl)(3-cyanophenyl)methyl]azetidin-3-yl}-2-fluoro-2-methylpropyl)-5-fluorobenzoic acid

A mixture of 112 mg (0.214 mmol) of ethyl 3-(1-{1-[(4-chlorophenyl)(3-cyanophenyl)methyl] azetidin-3-yl}-2-fluoro-2-methylpropyl)-5-fluorobenzoate and 1.2 mL of 1M LiOH in 5 mL of EtOH was stirred for 2.5h at rt. The solution was adjusted to pH = 5-6 with 6N HCl and concentrated to remove solvents.

The residue was dissolve in 10 mL of CH_2Cl_2 and solids were removed by filtration. The solution was concentrated to afford the title compound as a white solid; Mass Spectrum: m/e = 495 (M+1, ^{35}Cl), 497 (M+1, ^{37}Cl).

PREPARATION 22

3-(1-{1-[(4-chlorophenyl)(3-cyanophenyl)methyl]azetidin-3-yl}-2-fluoro-2-methylpropyl)-5-fluoro-*N*-methylbenzamide

A solution of 46 mg (0.093 mmol) of 3-(1-{1-[(4-chlorophenyl)(3-cyanophenyl)methyl]azetidin-3-yl}-2-fluoro-2-methylpropyl)-5-fluorobenzoic acid, 39.2 mg (0.204 mmol) of *N*-(3-dimethyl-aminopropyl)-N-ethylcarbodiimide hydrochloride, 6.2 mg (0.046 mmol) of HOBT, 120 uL (0.23 mmol) of methyl amine (2M in THF), 48 uL (0.28 mmol) of DIEA in 2 mL of CH_2Cl_2 was stirred overnight at rt. Then it was concentrated. The residue was purified by silica gel chromatography with hexane/acetone to afford the title compound as a white solid; Mass Spectrum: m/e = 508 (M+1, ^{35}Cl), 510 (M+1, ^{37}Cl).

PREPARATION 23

3-(1-{1-[(4-chlorophenyl)(3-cyanophenyl)methyl]azetidin-3-yl}-2-fluoro-2-methylpropyl)-5-fluoro-*N,N*-dimethylbenzamide

Prepared from 3-(1-{1-[(4-chlorophenyl)(3-cyanophenyl)methyl]azetidin-3-yl}-2-fluoro-2-methylpropyl)-5-fluorobenzoic acid and dimethylamine according to the procedure described in Preparation 22; Mass Spectrum: m/e = 522 (M+1, ^{35}Cl), 524 (M+1, ^{37}Cl).

PREPARATION 24

3-(1-{1-[(4-chlorophenyl)(3-cyanophenyl)methyl]azetidin-3-yl}-2-fluoro-2-methylpropyl)-5-fluorobenzamide

Prepared from 3-(1-{1-[(4-chlorophenyl)(3-cyanophenyl)methyl]azetidin-3-yl}-2-fluoro-2-methylpropyl)-5-fluorobenzoic acid and ammonia according to the procedure described in Preparation 22; Mass Spectrum: m/e = 494 (M+1, ^{35}Cl), 496 (M+1, ^{37}Cl).

PREPARATION 25

Isopropyl 3-(1-{1-[(4-chlorophenyl)(3-cyanophenyl)methyl]azetidin-3-yl}-2-fluoro-2-methylpropyl)-5-fluorobenzoate

Prepared from 3-(1-{1-[(4-chlorophenyl)(3-cyanophenyl)methyl]azetidin-3-yl}-2-fluoro-2-methylpropyl)-5-fluorobenzoic acid and isopropanol according to the procedure described in Preparation 21; Mass Spectrum: m/e = 537 (M+1, ^{35}Cl), 539 (M+1, ^{37}Cl).

PREPARATION 26

Methyl 4-((*R*)-(3-cyanophenyl){3-[(1*S*)-1-(3,5-difluorophenyl)-2-fluoro-2-methylpropyl]azetidin-1-yl}methyl)benzoate

Step 1 Methyl 4-[(3-cyanophenyl)(hydroxy)methyl]benzoate

A solution of 3.0 g (15 mmole) of methyl 4-(chlorocarbonyl)benzoate and 183 mg (0.2 mmole) of tris(dibenzylideneacetone)dipalladium(0) was cooled to 0 °C under N_2. After 5 min, 32 mL of a 0.5 M solution of (3-cyanophenyl)(iodo)zinc in THF was added dropwise and the solution was stirred at rt.

After 4 h, the reaction was quenched by addition of saturated NH_4Cl solution and 30 mL ether. The layers were separated and the aqueous layer was washed with three 30 mL portions of ether. The combined organic extracts were washed with 30 mL of saturated $NaHCO_3$ solution and 30 mL brine before being dried over $MgSO_4$ and concentrated. The residue was dissolved in 50 mL of 1:5 CH_3OH-THF and cooled to 0 °C. To this was added 500 mg (13.5 mmole) of $NaBH_4$ in two portions over 10 minutes. After 20 min, the reaction was quenched by addition of 1 mL saturated Na_2SO_4 solution and concentrated. The resulting slurry was diluted with ether and filtered. The solid residue was washed with ether and the combined filtrates were washed with brine, dried over $Na_2SO_4$and concentrated to an oil that was purified by silica gel chromatography using a step-gradient of 10 to 25% EtOAc-hexane. Homogeneous fractions were combined and concentrated to afford the title compound as a white solid.

Step 2: Methyl 4-[(3-cyanophenyl)(hydroxy)methyl]benzoate

To a solution of 267 mg (1 mmole) of methyl 4-[(3-cyanophenyl)(hydroxy)methyl]benzoate in 3 mL of CH_2Cl_2 was added 66 uL (107 mg, 0.9 mmole) of $SOCl_2$. The solution was stirred under N_2 at rt for 1h, then was cooled to 0 °C in an ice bath. To this was added 140 uL (327 mg, 1.8 mmole) of $SOBr_2$ and the solution was stirred at 0 °C for 2h. The reaction was quenched by dropwise addition of saturated aqueous $NaHCO_3$ solution. The layers were separated and the aqueous layer was washed with two 20 mL portions of ether. The combined organic extracts were washed with brine, dried over $MgSO_4$ and concentrated. The resulting oil was used directly in the next step.

Step 3: Methyl 4-((*S*)-(3-cyanophenyl){3-[(1*S*)-1-(3,5-difluorophenyl)-2-fluoro-2-methylpropyl] azetidin-1-yl}methyl)benzoate

The title compound was prepared methyl 4-[bromo(3-cyanophenyl)methyl]benzoate and 3-[(1*S*)-1-(3,5-difluorophenyl)-2-fluoro-2-methylpropyl]azetidine (Step 1, Preparation 15) by the procedure described in Step 2 of Preparation 15. The product was purified by chromatography on an AD column using 30% isopropanol-heptane to afford the title compound; ^{1}H-NMR($CDCl_3$) δ 1.25 (t, J = 22 Hz, 6H), 2.33 (t, J = 6.5 Hz, 1H), 2.83-2.89 (m, 2H), 3.05-3.22 (m, 2H), 3.65 (m, 1H), 3.92 (s, 3H), 4.34 (s, 1H), 6.68-6.71 (m, 3H), 7.21-7.8 (m, 8H); Mass Spectrum: m/e = 493 (M+1).

PREPARATION 27

Methyl 4-((*S*)-(3-cyanophenyl){3-[(1*S*)-1-(3,5-difluorophenyl)-2-fluoro-2-methylpropyl]azetidin-1-yl}methyl)benzoate

Further elution of the AD column from Example Preparation 26, Step 3, afforded the title compound; ^{1}H-NMR($CDCl_3$) δ 1.25 (t, J = 22 Hz, 6H), 2.33 (t, J = 6.5 Hz, 1H), 2.83-2.89 (m, 2H), 3.05-3.22 (m, 2H), 3.65 (m, 1H), 4.02 (s, 3H), 4.34 (s, 1H), 6.68-6.71 (m, 3H), 7.21-7.8 (m, 8H); Mass Spectrum: m/e = 493 (M+1).

PREPARATION 28

Isopropyl 4-((*S*)-(3-cyanophenyl){3-[(1*S*)-1-(3,5-difluorophenyl)-2-fluoro-2-methylpropyl]azetidin-1-yl}methyl)benzoate

A solution of 10 mg (0.02 mmole) of methyl 4-((*S*)-(3-cyanophenyl){3-[(1*S*)-1-(3,5-difluorophenyl)-2-fluoro-2-methylpropyl]azetidin-1-yl}methyl)benzoate in 2 mL ispopropanol was cooled to 0 °C. To this was added 2 drops of a 1.6M solution of butyllithium in hexane and the solution was allowed to warm to room temperature over 3 h. The reaction was quenched by addition of 2 drops of saturated $NaHCO_3$ solution and the solution was concentrated. The residue was triturated with CH_2Cl_2, and the solution concentrated. The residue was filtered through a plug of silica gel using 35% EtOAc-hexane to afford the title compound; ^{1}H-NMR($CDCl_3$) δ 1.21 (t, J = 10 Hz, 6H), 1.36 (t, J = 22 Hz, 3H), 1.3 (t, J = 22 Hz, 3H), 2.37 (t, J = 6.5 Hz, 1H), 2.83-2.89 (m, 2H), 3.05-3.22 (m, 2H), 3.65 (m, 1H), 4.02 (s, 3H), 4.34 (s, 1H), 6.68-6.71 (m, 3H), 7.21-7.8 (m, 8H); Mass Spectrum: m/e = 521 (M+1).

PREPARATION 29

Ethyl 4-((*S*)-(3-cyanophenyl){3-[(1*S*)-1-(3,5-difluorophenyl)-2-fluoro-2-methylpropyl]azetidin-1-yl}methyl)benzoate

The title compound was prepared from methyl 4-((*S*)-(3-cyanophenyl){3-[(1*S*)-1-(3,5-difluorophenyl)-2-fluoro-2-methylpropyl]azetidin-1-yl}methyl)benzoate according to the procedures described in Preparation 28 except that ethanol was used instead of isopropanol as the solvent; Mass Spectrum: m/e = 507 (M+1)

PREPARATION 30

3-((S)-(4-chlorophenyl){3-[(1S)-1-(3,5-difluorophenyl)-2-fluoro-2-methylpropyl]azetidin-1-yl}methyl)benzohydrazide

The title compound was prepared from methyl 4-((*S*)-(3-cyanophenyl){3-[(1*S*)-1-(3,5-difluorophenyl)-2-fluoro-2-methylpropyl]azetidin-1-yl}methyl)benzoate according to the procedure listed in Preparation 19; Mass Spectrum: m/e = 493 (M+1).

PREPARATION 31

Methyl (2*S*)-(3-bromo-5-fluorophenyl){1-[(*S*)-(4-chlorophenyl)(3-cyanophenyl)methyl]azetidin-3-yl}acetate

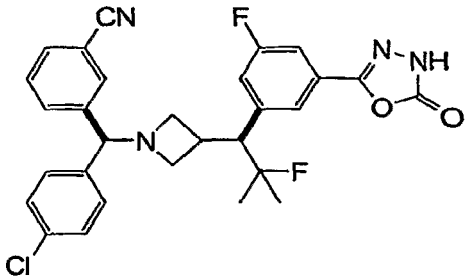
Step 1 Methyl (2*R*)-(3-bromo-5-fluorophenyl){1-[(*S*)-(4-chlorophenyl)(3-cyanophenyl)methyl] azetidin-3-yl}acetate

Further elution of the column in Example 26, Step 7 afforded methyl (2*R*)-(3-bromo-5-fluorophenyl){1-[(*S*)-(4-chlorophenyl)(3-cyanophenyl)methyl]azetidin-3-yl}acetate; ^{1}H-NMR($CDCl_3$) δ 2.67(t, 1H, J = 6.2 Hz), 2.90(dd, 1H, J_1 = 7.3 Hz, J_2 = 5.5 Hz), 3.09- 3.13(m, 2H), 3.43(t, 1H, J = 7.3 Hz), 3.68(s, 3H), 3.82(d, 1H, J = 10.7 Hz), 4.34(s, 1H), 6.96 (d, 1H, J = 8.9Hz), 7.17(d, 1H, J = 8.1 Hz), 7.20 (d, 1H, J = 12Hz), 7.26-7.32 (m, 5H), 7.40 (t, 1H, J =7.6 Hz), 7.50 (d, 1H, J = 7.7Hz), 7.60 (d, 1H, J = 8.0Hz), 7.70 (s, 1H); Mass Spectrum: m/e = 527 527(M+1, ^{35}Cl ^{79}Br), 529 (M+1, ^{37}Cl^{79}Br/^{35}Cl ^{81}Br), 531 (M+1, ^{37}Cl ^{11}Br).

Step 2 Methyl (2*S*)-(3-bromo-5-fluorophenyl){1-[(*S*)-(4-chlorophenyl)(3-cyanophenyl)methyl] azetidin-3-yl}acetate

To a solution of 20.56g (38.95 mmol) of methyl (2*R*)-(3-bromo-5-fluorophenyl){1-[(*S*)-(4-chlorophenyl)(3-cyanophenyl)methyl]azetidin-3-yl}acetatein 250 mL of THF, A solution of 40.90 mL (40.9 mmol) of lithium bis(trimethylsilyl)amide(1M in THF) was added and the reaction mixture was stirred for 50 min. at -78°C. Then the reaction was quenched with 1N HCl (PH = 7-8) at 0°C. The mixture was transferred into 200 mL ether and the water layer was extracted with CH_2Cl_2 (100 mL x2). The combined organic layer was dried over Na_2S04 and concentrated. The residue was separated by silica gel chromatography with cyclohexane/ethyl acetate to afford the title compound, methyl (2*S*)-(3-bromo-5-fluorophenyl){1-[(*S*)-(4-chlorophenyl)(3-cyanophenyl)methyl]azetidin-3-yl}acetate; ^{1}H-NMR($CDCl_3$) δ 2.66(t, 1H, J = 6.2 Hz), 2.92(dd, 1H, J_1 = 7.5 Hz, J_2 = 5.7 Hz), 3.08- 3.16(m, 2H), 3.41(t, 1H, J = 7.2 Hz), 3.69(s, 3H), 3.83(d, 1H, J = 10.7 Hz), 4.34(s, 1H), 6.96 (d, 1H, J = 8.9Hz), 7.17(d, 1H, J = 8.0 Hz), 7.20 (d, 1H, J = 12Hz), 7.27-7.32 (m, 5H), 7.39 (t, 1H, J =7.6 Hz), 7.50 (d, 1H, J = 7.5Hz), 7.60 (d, 1H, J = 7.5Hz), 7.70 (s, 1H); Mass Spectrum: m/e = 527(M+1, ^{35}Cl ^{79}Br), 529 (M+1, ^{37}Cl^{79}Br/^{35}Cl ^{81}Br), 531 (M+1, ^{37}Cl ^{81}Br). Further elution of the column afforded methyl (2*R*)-(3-bromo-5-fluorophenyl){1-[(*S*)-(4-chlorophenyl)(3-cyanophenyl)methyl]azetidin-3-yl}acetate; ^{1}H-NMR($CDCl_3$) δ 2.67(t, 1H, J = 6.2 Hz), 2.90(dd, 1H, J_1 = 7.3 Hz, J_2 = 5.5 Hz), 3.09- 3.13(m, 2H), 3.43(t, 1H, J = 7.3 Hz), 3.68(s, 3H), 3.82(d, 1H, J = 10.7 Hz), 4.34(s, 1H), 6.96 (d, 1H, J = 8.9Hz), 7.17(d, 1H, J = 8.1 Hz), 7.20 (d, 1H, J = 12Hz), 7.26-7.32 (m, 5H), 7.40 (t, 1H, J =7.6 Hz), 7.50 (d, 1H, J = 7.7Hz), 7.60 (d, 1H, J = 8.0Hz), 7.70 (s, 1H); Mass Spectrum: m/e = 527 (M+1, ^{35}Cl ^{79}Br), 529 (M+1, ^{37}Cl^{79}Br/^{35}Cl ^{81}Br), 531 (M+1, ^{37}Cl ^{81}Br).

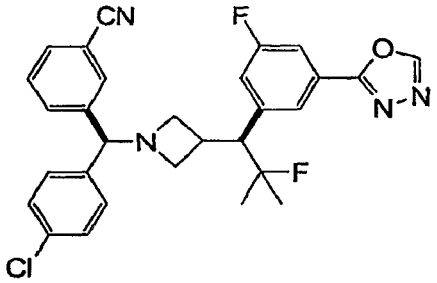
EXAMPLE 1



3-[(*S*)-(4-chlorophenyl)(3-{(1*S*)-2-fluoro-1-[3-fluoro-5-(5-oxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)phenyl]-2-methylpropyl}azetidin-1-yl)methyl]benzonitrile

To a solution of 44 mg (0.86 mmol) of 3-((1*S*)-1-{1-[(*S*)-(4-chlorophenyl)(3-cyanophenyl) methyl]azetidin-3-yl}-2-fluoro-2-methylpropyl)-5-fluorobenzohydrazide (Preparation 19) in 2 mL CH_2Cl_2 was added 11.3 uL(0.215 mmol) of phosgene solution (20% in toluene) at 0°C, followed by stirring at rt. After 1.5h, the solution was concentrated *in vacuo* to remove solvents and 2mL of 2N NH_3 in MeOH was added and the solution was concentrated again. The residue was purified by silica gel chromatography with CH_2Cl_2 / acetone to afford the title compound as a white solid; ^{1}H-NMR($CDCl_3$) δ 1.22(d, 3H, J= 22Hz), 1.28(d, 3H, J= 22Hz), 2.36 (t, 1H, J = 8Hz), 2.91 (t, 1H, J = 8 Hz), 2.96 (m, 1H), 3.12 (t, 1H, J = 7 Hz), 3.27 (m, 1H), 3.64 (t, 1H, J = 6 HZ), 4.30 (s, 1H), 7.06-7.71 (m, 12H); Mass Spectrum: m/e = 535 (M+1, ^{35}Cl), 537 (M+1, ^{37}Cl).

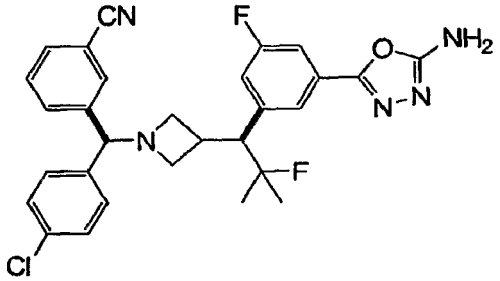
EXAMPLE 2



3-[(*S*)-(4-chlorophenyl)(3-{(1*S*)-2-fluoro-1-[3-fluoro-5-(1,3,4-oxadiazol-2-yl)phenyl]-2-methylpropyl}azetidin-1-yl)methyl]benzonitrile

A solution of 41 mg (0.081 mmol) of 3-((1*S*)-1-{1-[(*S*)-(4-chlorophenyl)(3-cyanophenyl)methyl] azetidin-3-yl}-2-fluoro-2-methylpropyl)-5-fluorobenzohydrazide and 1.5 mL triethyl orthofomate in 2 mL of xylene was stirred for 3.5 at 125°C, followed by concentration to remove solvents. The residue was purified by silica gel chromatography with hexane/ethyl acetate/ammonia in MeOH to afford the title compound as a white solid; ^{1}H-NMR($CDCl_3$) δ 1.23(d, 3H, J= 22Hz), 1.29(d, 3H, J= 22Hz), 2.34 (t, 1H, J = 8Hz), 2.89 (t, 1H, J = 8 Hz), 2.98 (m, 1H), 3.02 (t, 1H, J = 11 Hz), 3.25 (m, 1H), 3.63 (t, 1H, J = 6 HZ), 4.23 (s, 1H), 7.11-7.73 (m, 11H), 8.51(s, 1H); Mass Spectrum: m/e = 519 (M+1, ^{35}Cl), 521 (M+1, ^{37}Cl).

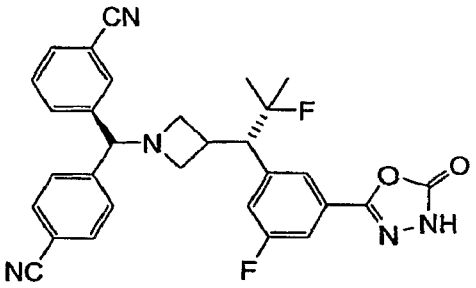
EXAMPLE 3



3-[(*S*)-(3-{(1*S*)-1-[3-(5-amino-1,3,4-oxadiazol-2-yl)-5-fluorophenyl]-2-fluoro-2-methylpropyl} azetidin-1-yl)(4-chlorophenyl)methyl]benzonitrile

To a mixture of 53 mg (0.104 mmol) of 3-((1*S*)-1-{1-[(*S*)-(4-chlorophenyl)(3-cyanophenyl) methyl]azetidin-3-yl}-2-fluoro-2-methylpropyl)-5-fluorobenzohydrazide in 3 mL of dioxane, 11.4 mg (0.135 mmol) of $NaHCO_3$ in 1 mL of water was added 13 mg (0.125mmol) cyanogen bromide and the solution was stirred at rt. After 2.5h, it was concentrated to remove solvents. The residue was dissolved in 20 mL of CH_2Cl_2 and 5 mL of water and the pH was adjusted to 7-8 with aq $NaHCO_3$. The aqueous layer was extracted with CH_2Cl_2,and the combined organic layer was concentrated. The residue was purified by silica gel chromatography with CH_2Cl_2/ acetone to afford the title compound as a white solid; ^{1}H-NMR ($CDCl_3$) δ 1.22(d, 3H, J= 22Hz), 1.28(d, 3H, J= 22Hz), 2.34 (br, 1H) 2.88 (br, 1H), 2.96 (m, 1H), 3.10 (dr, 1H), 3.24 (m, 1H), 3.63 (br, 1H), 4.27 (s, 1H), 5.50(s, 2H), 7.01-7.66 (m, 11H);Mass Spectrum: m/e = 534 (M+1, ^{35}Cl), 536 (M+1, ^{37}Cl).

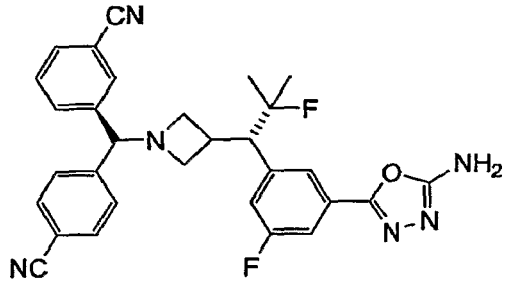
EXAMPLE 4



3-[(*S*)-(4-cyanophenyl)(3-{(1*S*)-2-fluoro-1-[3-fluoro-5-(5-oxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)phenyl]-2-methylpropyl}azetidin-1-yl)methyl]benzonitrile

Prepared from ethyl 3-(1-{1-[(4-cyanophenyl)(3-cyanophenyl)methyl]azetidin-3-yl}-2-fluoro-2-methylpropyl)-5-fluorobenzoate (Preparation 18) according to the procedures in Preparation 19 and Example 1; Mass Spectrum: m/e = 526 (M+1).

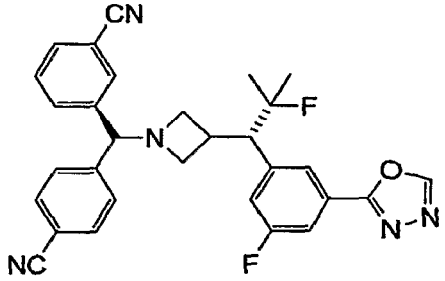
EXAMPLE 5



3-[(*S*)-(3-{(1*S*)-1-[3-(5-amino-1,3,4-oxadiazol-2-yl)-5-fluorophenyl]-2-fluoro-2-methylpropyl} azetidin-1-yl)(4-cyanophenyl)methyl]benzonitrile

Prepared from ethyl 3-(1-{1-[(4-cyanophenyl)(3-cyanophenyl)methyl]azetidin-3-yl}-2-fluoro-2-methylpropyl)-5-fluorobenzoate (Preparation 18) according to the procedures in Preparation 19 and Example 3; Mass Spectrum: m/e = 525 (M+1).

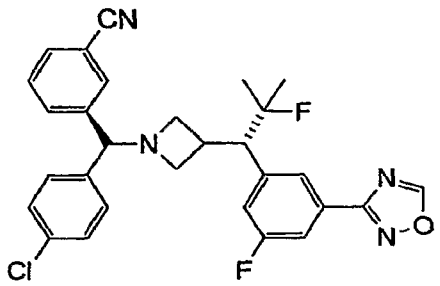
EXAMPLE 6



3-[(*S*)-(4-cyanophenyl)(3-{(1*S*)-2-fluoro-1-[3-fluoro-5-(1,3,4-oxadiazol-2-yl)phenyl]-2-methylpropyl}azetidin-1-yl)methyl]benzonitrile

Prepared from ethyl 3-(1-{1-[(4-cyanophenyl)(3-cyanophenyl)methyl]azetidin-3-yl}-2-fluoro-2-methylpropyl)-5-fluorobenzoate (Preparation 18) according to the procedures in Preparation 19 and Example 2; Mass Spectrum: m/e = 510 (M+1).

EXAMPLE 7



3-[(*S*)-(4-chlorophenyl)(3-{(1*S*)-2-fluoro-1-[3-fluoro-5-(1,2,4-oxadiazol-3-yl)phenyl]-2-methylpropyl}azetidin-1-yl)methyl]benzonitrile

Step 1: 3-[(*S*)-{3-[(1*S*)-1-(3-bromo-5-fluorophenyl)-2-fluoro-2-methylpropyl]azetidin-1-yl}(4-chlorophenyl)methyl]-N'-hydroxybenzenecarboximidamide

The mixture of 240 mg (0.45 mmol) of 3-[(*S*)-{3-[(1S)-1-(3-bromo-5-fluorophenyl)-2-fluoro-2-methylpropyl]azetidin-1-yl}(4-chlorophenyl)methyl]benzonitrile, 47.2 mg (0.68 mmol) of hydroxylamine hydrochloride, 0.124 mL (0.9mmol) of triethylamine, and 5 mL of ethanol was heated to reflux for 4h. The solution was concentrated and the residue was poured into 20 mL of CH_2Cl_2 and 5 mL of aq $NaHCO_3$ (PH>7). The aqueous layer was extracted with two 10 mL portions of CH_2Cl_2. The combined organic layer was dried over Na_2S04 and concentrated to afford the title compound as a white solid; Mass Spectrum: m/e = 562 (M+1, ^{35}Cl), 564 (M+1, ^{37}Cl).

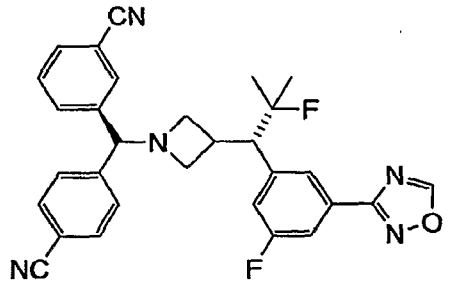
Step 2: 3-{3-[(*S*)-{3-[(1*S*)-1-(3-bromo-5-fluorophenyl)-2-fluoro-2-methyl propyl]azetidin-1-yl} (4-chlorophenyl)methyl]phenyl}-1,2,4-oxadiazole

A mixture of 70 mg (0.125mmol) of 3-[(*S*)-{3-[(1*S*)-1-(3-bromo-5-fluoro phenyl)-2-fluoro-2-methylpropyl]azetidin-1-yl}(4-chlorophenyl)methyl]-*N*'-hydroxybenzenecarboximidamide, 1.5 mL of triethyl orthoformate, and 2 mL of xylene was stirred for 4h at 125-130°C. Then it was concentrated, and the residue was purified by silica gel chromatography with hexanes/acetone to afford the title compound as a white solid; Mass Spectrum: m/e = 572 (M+1, ^{35}Cl), 574 (M+1, ^{37}Cl).

Step 3: 3-[(1*S*)-1-(1-{(*S*)-(4-chlorophenyl)[3-(1,2,4-oxadiazol-3-yl)phenyl]-methyl}azetidin-3-yl)-2-fluoro-2-methylpropyl]-5-fluorobenzonitrile

A mixture of 60 mg (0.104 mmol) of 3-{3-[(*S*)-{3-[(1*S*)-1-(3-bromo-5-fluorophenyl)-2-fluoro-2-methyl propyl]azetidin-1-yl}(4-chlorophenyl)methyl]phenyl}-1,2,4-oxadiazole, 48.5 mg (0.84 mmol) of zinc cyanide, 4 mg (0.004 mmol) of tris(dibenzylideneacetone)-dipalladium, and 5 mg (0.009 mmol) of DPPF in 3 mL of DMF/H_2O (99/1) was degassed with N_2 for 1 h at rt. Then it was stirred at 135°C. After 14 h, the reaction mixture was concentrated to remove solvents. Then the mixture was poured into 20 mL of CH_2Cl_2 and 5 mL of aq $NaHCO_3$ (pH> 7). The aqueous layer was extracted with CH_2Cl_2 and the combined organic layer was dried over Na_2S04 and concentrated. The residue was purified by silica gel chromatography with hexanes / acetone to afford the title compound as a white solid; Mass Spectrum: m/e = 519 (M+1, ^{35}Cl), 521 (M+1, ^{37}Cl).

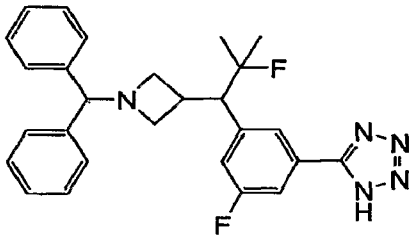
EXAMPLE 8



3-[(1*S*)-1-(1-{(*S*)-(4-cyanophenyl)[3-(1,2,4-oxadiazol-3-yl)phenyl]-methyl}azetidin-3-yl)-2-fluoro-2-methylpropyl]-5-fluorobenzonitrile

Further elution of the column in Example 7, Step 3 afforded the title compound; Mass Spectrum: m/e = 510 (M+1).

EXAMPLE 9

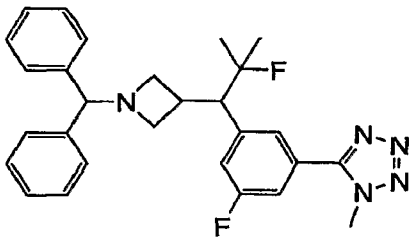


5-(3-{1-[1-(diphenylmethyl)azetidin-3-yl]-2-fluoro-2-methylpropyl}-5-fluorophenyl)-1*H*-tetrazole

A mixture of 1.17 g (2.81 mmol) of 3-{1-[1(diphenylmethyl)azetidin-3-yl]-2-fluoro-2-methylpropyl}-5-fluorobenzonitrile, 914 mg (14.06 mmol) of sodium azide, and 715 mg (14.05mmol) of ammonium chloride in 15 mL of DMF was stirred for 16 h. Then it was concentrated to remove solvents. The residue was purified by silica gel chromatography with CH_2Cl_2/MeOH/NH_3 (2M) in MeOH to afford the title compound as a white solid;

^{1}H-NMR($CDCl_3$) δ 1.26(s, 3H), 1.30(s, 3H), 3.80 (br, 1H) 4.12 (br, 1H), 6.90-7.93 (m, 13H), 8.21(d, 1H, J = 14 Hz); Mass Spectrum: m/e = 460 (M+1).

EXAMPLE 10

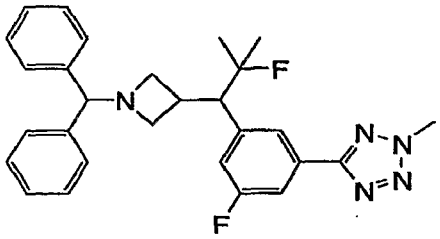


5-(3-{1-[1-(diphenylmethyl)azetidin-3-yl]-2-fluoro-2-methylpropyl}-5-fluorophenyl)-1-methyl-1*H*-tetrazole

The reaction of mixture of 1.31 g (2.85 mmol) 5-(3-{1-[1-(diphenylmethyl)azetidin-3-yl]-2-fluoro-2-methylpropyl}-5-fluorophenyl)-1*H*-tetrazole, 0.36 mL (5.70 mmol) methyl iodide, and 1.77 mL (9.97 mmol) DIEA in 8 mL MeCN was heated to reflux for 2.5 h. Then it was concentrated to remove the solvents. Then it was added 20 mL of CH_2Cl_2 and 5 mL of water and adjust pH = 7-8 with aq $NaHCO_3$.

The water layer was extracted with CH_2Cl_2, and the combined organic layer was concentrated. The residue was separated by silica gel chromatography with CH_2Cl_2/ MeOH / NH_3 (2M) in MeOH to afford the title compound; ^{1}H-NMR($CDCl_3$) δ 1.22(d, 3H, J= 22Hz), 1.29(d, 3H, J= 22Hz), 2.37 (t, 1H, J = 8 Hz), 2.90 (t, 1H, J = 8 Hz), 3.00 (m, 1H), 3.14 (m, 1H), 3.22 (m, 1H), 3.68 (J, 1H, J = 6Hz), 4.19 (s, 3H), 4.26 (s, 1H), 7.12-7.43 (m, 13H);Mass Spectrum: m/e = 474 (M+1).

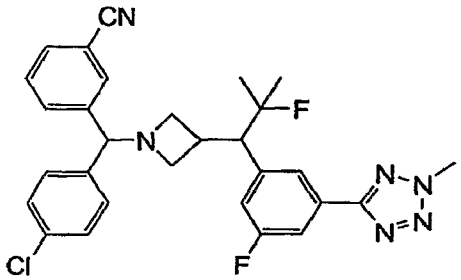
EXAMPLE 11



5-(3-{1-[1-(diphenylmethyl)azetidin-3-yl]-2-fluoro-2-methylpropyl}-5-fluorophenyl)-2-methyl-2H-tetrazole

Further elution of the column in Example 10 afforded the title compound; ^{1}H-NMR($CDCl_3$) δ 1.24(d, 3H, J= 20Hz), 1.29(d, 3H, J= 20Hz), 2.40 (t, 1H, J = 8 Hz), 2.90 (t, 1H, J = 8 Hz), 3.00 (m, 1H), 3.15 (m, 1H), 3.24 (m, 1H), 3.68 (m, 1H), 4.27 (s, 1H), 4.42 (s, 3H), 7.01-7.44 (m, 11H), 7.70 (m, 1H), 7.77(s, 1H); Mass Spectrum: m/e = 474 (M+1).

EXAMPLE 12



Step 1: 5-[3-(1-azetidin-3-yl-2-fluoro-2-methylpropyl)-5-fluorophenyl]-2-methyl-2*H*-tetrazole

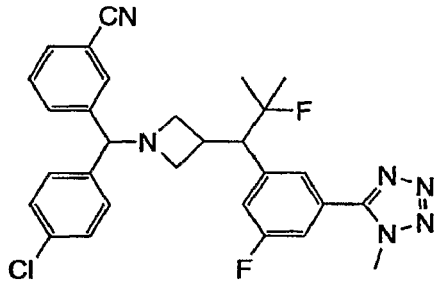
A solution of 370 mg (0.78 mmol) of 5-(3-{1-[1-(diphenylmethyl)azetidin-3-yl]-2-fluoro-2-methylpropyl}-5-fluorophenyl)-2-methyl-2*H*-tetrazole in 20 mL of EtOH was shaken in presence 200 mg of $Pd(OH)_2$ under 50 Psi pressure hydrogen for 24 h. Then it was filtered to remove the solid and washed with CH_2Cl_2. The combined organic layer was concentrated and washed with hexanes/ethyl ether to afford the title compound as a white solid; Mass Spectrum: m/e = 308 (M+1).

Step 2: 3-[(4-chlorophenyl)(3-{2-fluoro-1-[3-fluoro-5-(2-methyl-2*H*-tetrazol-5-yl)phenyl]-2-methylpropyl}azetidin-1-yl)methyl]benzonitrile

A mixture of 240 mg (0.78 mmol) of 5-[3-(1-azetidin-3-yl-2-fluoro-2-methylpropyl)-5-fluorophenyl]-2-methyl-2*H*-tetrazole, 530 mg (1.56 mmol) of 3-[bromo(4-chlorophenyl) methyl]benzonitrile, 1.1 mL(6.26 mmol) of DIEA in 8 mL of acetonitrile was heated to reflux for 4h. Then, it was concentrated. The mixture was poured into 30 mL of CH_2Cl_2 and 5 mL of aq $NaHCO_3$. The organic layer was dried over Na_2S0_4 and concentrated. The compounds were purified by silica gel chromatography. Single

diastereomers were separated by a chiral AD column; Mass Spectrum: m/e = 533 (M+1, ^{35}Cl), 535 (M+1, ^{37}Cl).

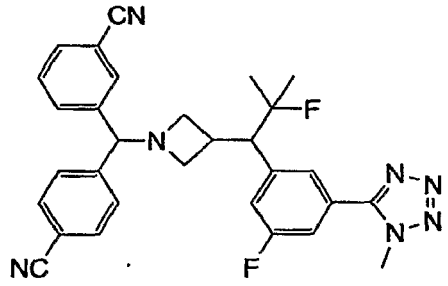
EXAMPLE 13



3-[(4-chlorophenyl)(3-{2-fluoro-1-[3-fluoro-5-(1-methyl-1*H*-tetrazol-5-yl)phenyl]-2-methylpropyl}azetidin-1-yl)methyl]benzonitrile

The title compound was prepared from 5-(3-{1-[1-(diphenylmethyl)azetidin-3-yl]-2-fluoro-2-methylpropyl}-5-fluorophenyl)-1-methyl-1*H*-tetrazole according to the procedures described in Example 12; Mass Spectrum: m/e = 533 (M+1, ^{35}Cl), 535 (M+1, ^{37}Cl).

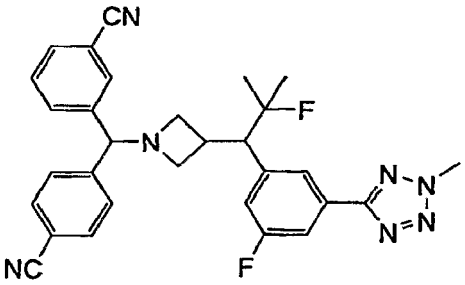
EXAMPLE 14



3-[(4-cyanophenyl)(3-{2-fluoro-1-[3-fluoro-5-(1-methyl-1*H*-tetrazol-5-yl)phenyl]-2-methylpropyl}azetidin-1-yl)methyl]benzonitrile

The title compound was prepared from 5-(3-{1-[1-(diphenylmethyl)azetidin-3-yl]-2-fluoro-2-methylpropyl}-5-fluorophenyl)-1*H*-tetrazole according to the procedures described in Examples 10 and 13; Mass Spectrum: m/e = 524 (M+1).

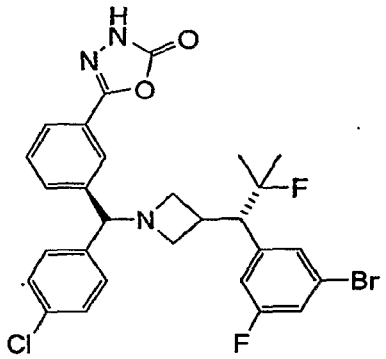
EXAMPLE 15



3-[(4-cyanophenyl)(3-{2-fluoro-1-[3-fluoro-5-(2-methyl-2*H*-tetrazol-5-yl)phenyl]-2-methylpropyl}azetidin-1-yl)methyl]benzonitrile

The title compound was prepared from 5-(3-{1-[1-(diphenylmethyl)azetidin-3-yl]-2-fluoro-2-methylpropyl}-5-fluorophenyl)-1*H*-tetrazole according to the procedures described in Examples 11 and 12; Mass Spectrum: m/e = 524 (M+1).

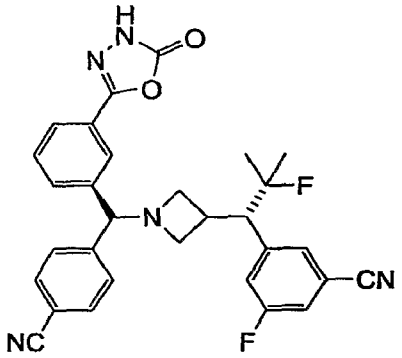
EXAMPLE 16



5-{3-[(*S*)-{3-[(1*S*)-1-(3-bromo-5-fluorophenyl)-2-fluoro-2-methylpropyl]azetidin-1-yl}(4-chlorophenyl)methyl]phenyl}-1,3,4-oxadiazol-2(3*H*)-one

The title compound was prepared from 3-[{3-[1-(3-bromo-5-fluorophenyl)-2-fluoro-2-methylpropyl]azetidin-1-yl}(4-chlorophenyl)methyl]benzonitrile according to the procedures in Preparation 19 and Example 1; Mass Spectrum: m/e = 588 (M+1, $^{35}Cl\ ^{79}Br$), 590 (M+1, $^{37}Cl^{79}Br/^{35}Cl\ ^{81}Br$), 592 (M+1, $^{37}Cl\ ^{81}Br$).

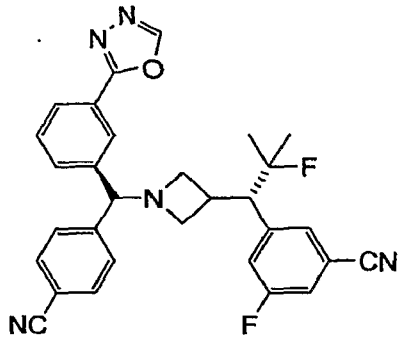
EXAMPLE 17



3-[(1*S*)-1-(1-{(*S*)-(4-cyanophenyl)[3-(5-oxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)phenyl]methyl} azetidin-3-yl)-2-fluoro-2-methylpropyl]-5-fluorobenzonitrile

The title compound was prepared from 3-[{3-[1-(3-bromo-5-fluorophenyl)-2-fluoro-2-methylpropyl]azetidin-1-yl}(4-cyanophenyl)methyl]benzonitrile according to the procedures described in Preparation 19 and Example 1 and in Preparation 16, Step 9; Mass Spectrum: m/e = 525 (M+1).

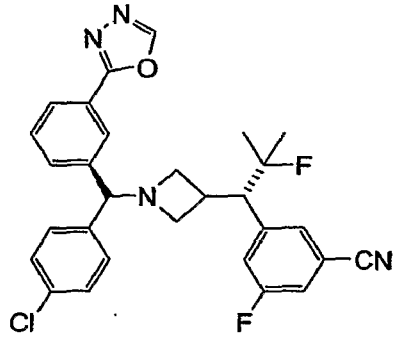
EXAMPLE 18



3-[(1*S*)-1-(1-{(*S*)-(4-cyanophenyl)[3-(1,3,4-oxadiazol-2-yl)phenyl]methyl}azetidin-3-yl)-2-fluoro-2-methylpropyl]-5-fluorobenzonitrile

The title compound was prepared from 3-[{3-[1-(3-bromo-5-fluorophenyl)-2-fluoro-2-methylpropyl]azetidin-1-yl}(4-cyanophenyl)methyl]benzonitrile according to the procedures described in Preparation 19, in Example 2, and in Preparation 16, Step 9; Mass Spectrum: m/e = 510 (M+1).

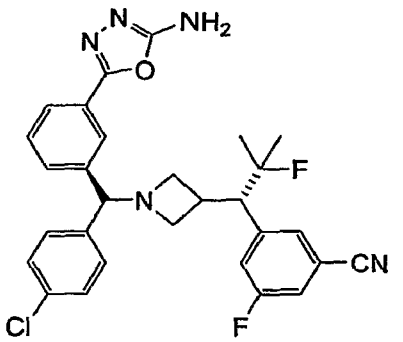
EXAMPLE 19



3-[(1*S*)-1-(1-{(*S*)-(4-chlorophenyl)[3-(1,3,4-oxadiazol-2-yl)phenyl]methyl}azetidin-3-yl)-2-fluoro-2-methylpropyl]-5-fluorobenzonitrile

The title compound was prepared from 5-{3-[(*S*)-{3-[(1*S*)-1-(3-bromo-5-fluorophenyl)-2-fluoro-2-methylpropyl]azetidin-1-yl}(4-chlorophenyl)methyl]phenyl}-1,3,4-oxadiazol-2(3*H*)-one according to the procedure listed in Preparation 19, Example 2, and in Preparation 16, Step 9; Mass Spectrum: m/e = 519 (M+1, ^{35}Cl), 537 (M+1, ^{37}Cl).

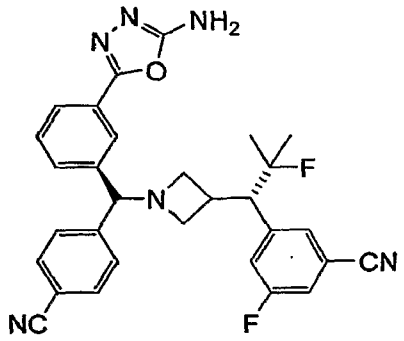
EXAMPLE 20



3-((1*S*)-1-{1-[(*S*)-[3-(5-amino-1,3,4-oxadiazol-2-yl)phenyl](4-chlorophenyl)methyl]azetidin-3-yl}-2-fluoro-2-methylpropyl)-5-fluorobenzonitrile

The title compound was prepared from 5-{3-[(*S*)-{3-[(1*S*)-1-(3-bromo-5-fluorophenyl)-2-fluoro-2-methylpropyl]azetidin-1-yl}(4-chlorophenyl)methyl]phenyl}-1,3,4-oxadiazol-2(3*H*)-one according to the procedure listed in Preparation 19, in Example 3, and in Preparation 16, Step 9; Mass Spectrum: m/e = 534 (M+1, ^{35}Cl), 536 (M+1, ^{37}Cl).

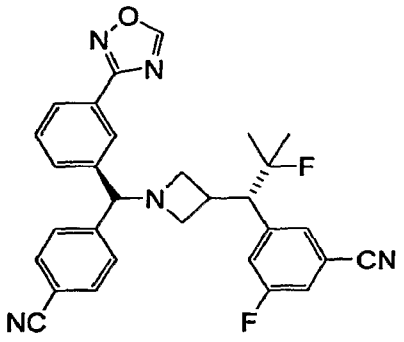
EXAMPLE 21



3-((1*S*)-1-{1-[(*S*)-[3-(5-amino-1,3,4-oxadiazol-2-yl)phenyl](4-cyanophenyl)methyl]azetidin-3-yl}-2-fluoro-2-methylpropyl)-5-fluorobenzonitrile

The title compound was prepared from 3-[{3-[1-(3-bromo-5-fluorophenyl)-2-fluoro-2-methylpropyl]azetidin-1-yl}(4-cyanophenyl)methyl]benzonitrile according to the procedures described in Preparation 19, in Example 2, and in Preparation 16, Step 9; Mass Spectrum: m/e = 525 (M+1).

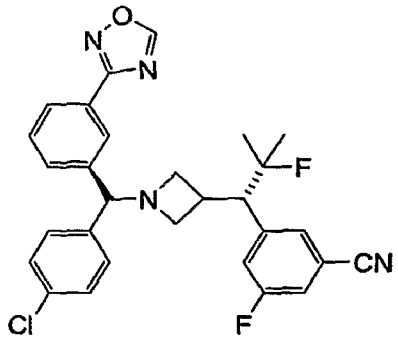
EXAMPLE 22



3-[(1*S*)-1-(1-{(*S*)-(4-cyanophenyl)[3-(1,2,4-oxadiazol-3-yl)phenyl]methyl}azetidin-3-yl)-2-fluoro-2-methylpropyl]-5-fluorobenzonitrile

The title compound was prepared from 3-[{3-[1-(3-bromo-5-fluorophenyl)-2-fluoro-2-methylpropyl]azetidin-1-yl}(4-cyanophenyl)methyl]benzonitrile according to the procedures described in Example 7 and Preparation 16, Step 9; Mass Spectrum: m/e = 510 (M+1).

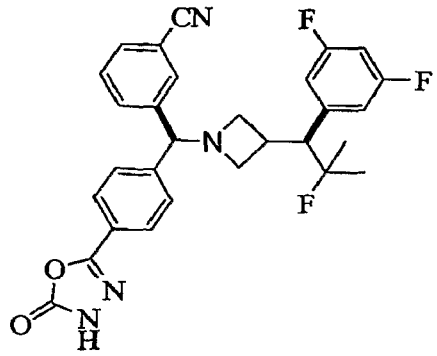
EXAMPLE 23



3-[(1*S*)-1-(1-{(*S*)-(4-chlorophenyl)[3-(1,2,4-oxadiazol-3-yl)phenyl]methyl}azetidin-3-yl)-2-fluoro-2-methylpropyl]-5-fluorobenzonitrile

The title compound was prepared from 5-{3-[(*S*)-{3-[(1*S*)-1-(3-bromo-5-fluorophenyl)-2-fluoro-2-methylpropyl]azetidin-1-yl}(4-chlorophenyl)methyl]phenyl}-1,3,4-oxadiazol-2(3*H*)-one according to the procedure listed in Example 8 and in Preparation 16, Step 9; Mass Spectrum: m/e = 519 (M+1, ^{35}Cl), 521 (M+1, ^{37}Cl).

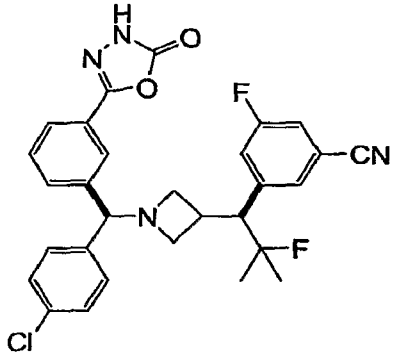
EXAMPLE 24



5-[3-((*S*)-(4-chlorophenyl){3-[(1*S*)-1-(3,5-difluorophenyl)-2-fluoro-2-methylpropyl] azetidin-1-yl}methyl)phenyl]-1,3,4-oxadiazol-2(3*H*)-one

The title compound was prepared from 3-((*S*)-(4-chlorophenyl){3-[(1*S*)-1-(3,5-difluorophenyl)-2-fluoro-2-methylpropyl]azetidin-1-yl}methyl)benzohydrazide according to the procedure listed in Example 1; Mass Spectrum: m/e = 518 (M+1).

EXAMPLE 25



3-[(1*S*)-1-(1-{(*S*)-(4-chlorophenyl)[3-(5-oxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)phenyl]methyl} azetidin-3-yl)-2-fluoro-2-methylpropyl]-5-fluorobenzonitrile

3-[(*S*)-(4-Chlorophenyl)(3-hydroxyazetidin-1-yl)methyl]benzonitrile

Step 1 *N*-[(1*E*)-(3-cyanophenyl)methylene]-2-methylpropane-2-(*R*)sulfinamide

A solution of 19.0 g (157 mmole) of (R)-(+)-2-methylpropane-2-sulfinamide and 89.0 g (314 mmole) of titanium tetraisopropoxide in CH_2Cl_2 was stirred at room temperature for 10 min. Then a solution of 21.6 g (165 mmole) of 3-formylbenzonitrile in 10 mL CH_2Cl_2 was added, and the solution was stirred at room temperature. After 18 h, the reaction was quenched by the addition of 30 mL brine and the solution was rapidly stirred for 15 min. The mixture was filtered through a pad of CELITE and the residue was washed with 300 mL of CH_2Cl_2. The combined organic extracts were washed with brine, dried over Na_2SO_4 and concentrated. The residue was filtered through a pad of silica gel using 20% ethyl acetate-hexane to afford the title compound; ^{1}H-NMR($CDCl_3$) δ 1.31 (s, 9H), 7.65 (t, 1H, J = 7.8 Hz), 7.82 (d, 1H, J = 7.8 Hz), 8.07 (d, 1H, J = 7.8 Hz), 8.20 (s, 1H), 8.62 (s, 1H); Mass Spectrum: m/e = 235 (M+1).

Step 2 *N*-[(*S*)-(4-chlorophenyl)(3-cyanophenyl)methyl]-2-methylpropane-2-(*R*)-sulfinamide

A solution of 20 g (85.4 mmole) of *N*-[(1*E*)-(3-cyanophenyl)methylene]-2-methylpropane-2-(*R*)sulfonamide in 1000 mL toluene and 400 mL ether was cooled to -60 °C in a dry ice-acetone bath. Then 170 mL of a 1M solution of 4-chlorophenylmagnesium bromide in ether was added at a rate such that the temperature remained between -40 °C and -30 °C and the reaction was stirred at -30 °C for 6 h. The reaction was quenched by addition of 300 mL of saturated NH_4Cl solution and the layers were separated. The organic layer was washed with three 300 mL aliquots of saturated NH_4Cl solution and brine, then was dried over Na_2SO_4 and concentrated. The residue was filtered through a pad of silica gel using 10 to 30% ethyl acetate hexane to afford the title compound with de > 99% as determined by analytical ChiralPak AD column; ; ^{1}H-NMR($CDCl_3$) δ 1.27 (s, 9H), 3.76 (s, 1H), 5.65 (d, 1H, J = 2.3 Hz), 7.24-7.7 (m, 8H).

Step 3 3-[(*S*)-amino(4-chlorophenyl)methyl]benzonitrile hydrochloride

To a solution of 850 mg (2.45 mmole) of *N*-[(*S*)-(4-chlorophenyl)(3-cyanophenyl)methyl]-2-methylpropane-2-(*R*)-sulfinamide in 20 mL of CH_3OH was added 2.5 mL of 4M HCL in dioxane. The solution was stirred at room temperature for 45 min, then was diluted with 40 mL ether. The solids were collected by filtration to afford the title compound as a white solid; ^{1}H-NMR($CDCl_3$) δ 1.6 (s, 2H, br), 5.24 (s, 1H), 7.24-7.78 (m, 8H).

Step 4 3-[(*S*)-(4-chlorophenyl)(3-hydroxyazetidin-1-yl)methyl]benzonitrile

To a mixture of 20.27 g (72.6 mmole) of 3-[(*S*)-[(3-chloro-2-hydroxypropyl)amino](4-chlorophenyl)methyl]benzonitrile hydrochloride and 21.3 g (245 mmole) of $NaHCO_3$ in 600 mL of isopropanol was added 14.4 mL (174 mmole) of epibromohydrin . The mixture was heated to reflux for 24 h, then was cooled and concentrated. The residue was partitioned between 750 mL portions of ether and water and the aqueous layer was washed with two 500 mL portions of ether. The combined organic extracts were washed with brine, dried over $MgSO_4$ and concentrated. The residue was purified by

flash chromatography using 10-20% ethyl acetate in hexane to afford the title compound as a clear oil; ^{1}H-NMR($CDCl_3$) δ 1.6 (s, 2H, br), 5.24 (s, 1H), 7.24-7.78 (m, 8H).2.89 (m, 2H), 3.54 (m, 2H), 4.39 (s, 1H), 4.52 (m, 1H), 7.2-7.8 (m, 8H).

Step 5: 3-[(*S*)-(4-chlorophenyl)(3-oxoazetidin-1-yl)methyl]benzonitrile

To a solution of 21.1 mL (0.24 mol) of oxalyl chloride in 500 mL CH_2Cl_2, a solution of 34.2 mL (0.48 mol) of DMSO in 50 mL CH_2Cl_2 was added slowly at -78°C. After the reaction mixture was stirred for 30 min., a solution of 36.02 g (0.12 mol) of 3-[(*S*)-(4-chlorophenyl)(3-hydroxyazetidin-1-yl)methyl]benzonitrile in 50 mL of CH_2Cl_2 was added and stirred for another 45 min. Then 82.8 mL (0.60 mol) of triethylamine was added and the mixture was stirred for 30 min. at -78°C. The mixture was warmed to rt and stirring continued for 30 min. Then the mixture was poured into 1000 mL of ether and 200 mL of aq $NaHCO_3$. The water layer was extracted with two 200 mL portions of ether. The combined organic layers were dried over Na_2S0_4 and concentrated. The residue was purified by silica gel chromatography with hexanes / ethyl acetate to afford the title compound as a white solid; ^{1}H-NMR($CDCl_3$) δ 4.03- 4.07(m, 4H), 4.65(s, 1H), 7.33-7.43 (m, 4H), 7.45 (t, 1H, J =7.8 Hz), 7.56 (d, 1H, J = 7.5Hz), 7.72 (d, 1H, J = 7.5Hz), 7.81 (s, 1H); Mass Spectrum: m/e = 297, (M+1, ^{35}Cl), 299 (M+1, ^{37}Cl).

Step 6 Methyl (3-bromo-5-fluorophenyl){1-[(*S*)-(4-chlorophenyl)(3-cyanophenyl)methyl] azetidin-3-ylidene}acetate

To a solution of 14.55g (58.87 mmol) of methyl (3-bromo-5-fluorophenyl)acetate in 200 mL of THF at -78°C, was added a solution of 56.80 mL (56.80 mmol) (1M in THF) of LHMDS. After the reaction mixture was stirred for 30 min., a solution of 15.60 g (52.57 mmol) of 3-[(*S*)-(4-chlorophenyl)(3-oxoazetidin-1-yl)methyl]benzonitrile in 50 mL of THF was added and the mixture was stirred for 2.5h at -78°C. Then 8.35g (68.33 mmol) of DMAP, 14.65 mL (84.09 mmol) of DIEA, and 8.72 mL (110.38 mmol) of methanesulfonyl chloride were added, and the mixture was stirred for 1h at -78°C. The mixture was then allowed to warm to rt and was stirred at rt for 12h. The mixture was poured into 300 mL of ether and 100 mL of water. The water layer was extracted with ether (100 mL x2). The combined organic layer was dried over Na_2S0_4 and concentrated. The residue was purified by silica gel chromatography with hexanes / ethyl acetate to afford the title compound as a white solid; ^{1}H-NMR($CDCl_3$) δ 3.75(s, 3H), 3.87(s, 2H), 4.23-4.29(m, 2H), 4.59(s, 1H), 6.92 (d, 1H, J = 12Hz), 7.18(s, 1H), 7.20 (d, 1H, J = 12Hz), 7.31- 7.38 (dd, 4H, J J_11 =28.4 Hz, J_2 = 8.5Hz), 7.42 (t, 1H, J =7.7 Hz), 7.54 (d, 1H, J = 7.6Hz), 7.66 (d, 1H, J = 7.6Hz), 7.76 (s, 1H); Mass Spectrum: m/e = 525, (M+1, ^{35}Cl ^{79}Br), 527 (M+1, ^{37}Cl^{79}Br/^{35}Cl^{81}Br), 529 (M+1, ^{37}Cl ^{81}Br).

Step 7 methyl (2*S*)-(3-bromo-5-fluorophenyl){1-[(*S*)-(4-chlorophenyl)(3-cyanophenyl)methyl] azetidin-3-yl}acetate

To a solution of 27.15g (51.64 mmol) of methyl (3-bromo-5-fluorophenyl){1-[(*S*)-(4-chlorophenyl)(3-cyanophenyl)methyl]azetidin-3-ylidene}acetate in 120 mL of THF and 220 mL of MeOH, were added small portions of sodium borohydride (total: 740 mg, 31.05 mmol) at -5-0°C. The mixture stirred at -5-

0°C and the reaction was followed by HPLC. Then the reaction was quenched with 2N HCl at 0°C (to pH = 7- 7.5) and concentrated to remove the organic solvents. The residue was dissolved in 300 mL of CH_2Cl_2 and 300 mL water, and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (100 mL x2). The combined organic layer was dried over Na_2S0_4 and concentrated. The residue was separated by silica gel chromatography with cyclohexane/ethyl acetate to afford the methyl (2*S*)-(3-bromo-5-fluorophenyl){1-[(S)-(4-chlorophenyl)(3-cyanophenyl)methyl]azetidin-3-yl}acetate; ^{1}H-NMR($CDCl_3$) δ 2.66(t, 1H, J = 6.2 Hz), 2.92(dd, 1H, J_1 = 7.5 Hz, J_2 = 5.7 Hz), 3.08- 3.16(m, 2H), 3.41(t, 1H, J = 7.2 Hz), 3.69(s, 3H), 3.83(d, 1H, J = 10.7 Hz), 4.34(s, 1H), 6.96 (d, 1H, J = 8.9Hz), 7.17(d, 1H, J = 8.0 Hz), 7.20 (d, 1H, J = 12Hz), 7.27-7.32 (m, 5H), 7.39 (t, 1H, J =7.6 Hz), 7.50 (d, 1H, J = 7.5Hz), 7.60 (d, 1H, J = 7.5Hz), 7.70 (s, 1H); Mass Spectrum: m/e = 527(M+1, ^{35}Cl ^{79}Br), 529 (M+1, ^{37}Cl^{79}Br/^{35}Cl ^{81}Br), 531 (M+1, ^{37}Cl ^{81}Br).

Further elution of the column afforded methyl (2*R*)-(3-bromo-5-fluorophenyl){1-[(*S*)-(4-chlorophenyl)(3-cyanophenyl)methyl]azetidin-3-yl}acetate; ^{1}H-NMR($CDCl_3$) δ 2.67(t, 1H, J = 6.2 Hz), 2.90(dd, 1H, J_1 = 7.3 Hz, J_2 = 5.5 Hz), 3.09- 3.13(m, 2H), 3.43(t, 1H, J = 7.3 Hz), 3.68(s, 3H), 3.82(d, 1H, J = 10.7 Hz), 4.34(s, 1H), 6.96 (d, 1H, J = 8.9Hz), 7.17(d, 1H, J = 8.1 Hz), 7.20 (d, 1H, J = 12Hz), 7.26-7.32 (m, 5H), 7.40 (t, 1H, J =7.6 Hz), 7.50 (d, 1H, J = 7.7Hz), 7.60 (d, 1H, J = 8.0Hz), 7.70 (s, 1H); Mass Spectrum: m/e = 527 (M+1, ^{35}Cl ^{79}Br), 529 (M+1, ^{37}Cl^{79}Br/^{35}Cl ^{81}Br), 531 (M+1, ^{37}Cl ^{81}Br).

Step 8 3-[(*S*)-{3-[(1*S*)-1-(3-bromo-5-fluorophenyl)-2-hydroxy-2-methylpropyl]azetidin-1-yl}(4-chlorophenyl)methyl]benzonitrile

A portion of 7.84 g (31.80 mmol) of cerium (III) chloride (anhydrous) was stirred for 30 min under N_2 at rt. Then 120 mL of THF (anhydrous) was added, and the slurry was stirred for another 30 min at rt. Then the reaction mixture was cooled to -78°C and a solution of 14.9 mL (23.80 mmol) methyllithium (1.6M in ether) was added dropwise. After addition was complete, the mixture was stirred for 30 min at -78°C. Then a solution of 6.0g (11.36 mmol) of methyl (2*S*)-(3-bromo-5-fluorophenyl){1-[(*S*)-(4-chlorophenyl)(3-cyanophenyl)methyl]azetidin-3-yl}acetate in 30 mL of THF was added, and the reaction mixture was stirred for 1.5h at -78°C. The reaction was quenched by dropwise addition of 20 mL water and warmed slowly to rt. The pH was adjusted to 7-8 with aq $NaHCO_3$. The solid residue was washed with CH_2Cl_2 (300 mLx4). The combined organic layer was dried over Na_2S0_4 and concentrated. The residue was purified by silica gel chromatography with hexane / ethyl acetate to afford the title compound as a white solid; ^{1}H-NMR($CDCl_3$) δ 1.10 (s, 3H), 1.15 (s, 3H), 2.28(t, 1H, J = 7.8 Hz), 2.71(d, 1H, J_1 = 11 Hz), 2.84 (t, 1H, J = 7.5 Hz), 3.09- 3.18(m, 2H), 3.60 (m, 1H), 4.25(s, 1H), 6.86 (d, 1H, J = 9.4Hz), 7.10-7.13(m, 2H), 7.28-7.34 (m, 4H), 7.36 (t, 1H, J =7.8 Hz), 7.46 (d, 1H, J = 7.5Hz), 7.57 (d, 1H, J = 7.5Hz), 7.67 (s, 1H); Mass Spectrum: m/e = 527, (M+1, ^{35}Cl ^{79}Br), 529 (M+1, ^{37}Cl^{79}Br/^{35}Cl ^{81}Br), 531 (M+1, ^{37}Cl ^{81}Br).

Step 9 3-[(*S*)-{3-[(1*S*)-1-(3-bromo-5-fluorophenyl)-2-fluoro-2-methylpropyl]azetidin-1-yl}(4-chlorophenyl)methyl]benzonitrile

A mixture of 6.90 g (13.07 mmol) of 3-[(*S*)-{3-[(1*S*)-1-(3-bromo-5-fluorophenyl)-2-hydroxy-2-methylpropyl]azetidin-1-yl}(4-chlorophenyl)methyl]benzonitrile, 50 mL of hydrogen fluoride pyridine (HF 70%), and 60 mL of 1,2-dichloroethane was stirred at 40-42°C for 16 h. Then the reaction mixture was poured slowly to a mixture of 250 mL of water, 74 g of NaOH, 300 mL of aq $NaHCO_3$, 300g of ice and 500mL of CH_2Cl_2 with rapid stirring. The pH of the mixture was adjusted to 7-8, and the mixture was filtered to remove solids. The aqueous layer was extracted with three 300 mL portions of CH_2Cl_2. The combined organic layer was dried over Na_2S0_4 and concentrated. The residue was purified by silica gel chromatography with hexane/ethyl acetate to afford the title compound as a white solid; ^{1}H-NMR($CDCl_3$) δ 1.25 (t, 6H, J = 11.8Hz), 2.32(t, 1H, J = 7.5 Hz), 2.83-2.89(m, 2H), 3.09- 3.17(m, 2H), 3.59 (m, 1H), 4.26(s, 1H), 6.85 (d, 1H, J = 9.1Hz), 7.10-7.14(m, 2H), 7.28-7.33 (m, 4H), 7.36 (t, 1H, J =7.2 Hz), 7.46 (d, 1H, J = 7.8Hz), 7.56 (d, 1H, J = 7.7Hz), 7.67 (s, 1H); Mass Spectrum: m/e = 529, (M+1, ^{35}Cl ^{79}Br), 531 (M+1, ^{37}Cl^{79}Br/^{35}Cl ^{81}Br), 533 (M+1, ^{37}Cl ^{81}Br).

Step 10 3-[(*S*)-{3-[(1*S*)-1-(3-bromo-5-fluorophenyl)-2-fluoro-2-methylpropyl]azetidin-1-yl}(4-chlorophenyl)methyl]benzoic acid

A mixture of 5.52g (10.4 mmol) of 3-[(*S*)-{3-[(1*S*)-1-(3-bromo-5-fluorophenyl)-2-fluoro-2-methylpropyl]azetidin-1-yl}(4-chlorophenyl)methyl]benzonitrile, 65 mL of EtOH, and 40 mL of 5N NaOH was heated to reflux for 4h (with monitoring by HPLC). Then the pH solution was adjusted to 4-5 with 12N HCl and the solution was concentrated to remove organic solvents. The residue was dissolved in 200 mL of CH_2Cl_2 and filtered to remove undissolved solid. The solid residue was triturated with two 200 mL portions of CH_2Cl_2 and the combined organic layers were concentrated to the title compound as white solid; Mass Spectrum: m/e = 548, (M+1, ^{35}Cl ^{79}Br), 550 (M+1, ^{37}Cl^{79}Br/^{35}Cl ^{81}Br), 552 (M+1, ^{37}Cl ^{81}Br).

Step 11: Ethyl 3-[(*S*)-{3-[(1*S*)-1-(3-bromo-5-fluorophenyl)-2-fluoro-2-methylpropyl]azetidin-1-yl}(4-chlorophenyl)methyl]benzoate

To a mixture of 5.72g (10.4 mmol) of 3-[(*S*)-{3-[(1*S*)-1-(3-bromo-5-fluorophenyl)-2-fluoro-2-methylpropyl]azetidin-1-yl}(4-chlorophenyl)methyl]benzoic acid in 230 mL of EtOH, was added a solution of 25 mL of 4N HCl in dioxane. After 7.5h at reflux, the solution was cooled and concentrated to remove solvents. To the residue were added 150 mL of CH_2Cl_2 and 30 mL of H_2O and the pH was adjusted to 7-8 with aq $NaHCO_3$. The aqueous layer was extracted with three 100 mL portions of $CH_2Cl_2$and the combined organic layer was dried over Na_2SO_4 and concentrated. The residue was purified by silica gel chromatography with hexanes/ethyl acetate to afford the title compound as a white solid; ^{1}H-NMR($CDCl_3$) δ 1.25 (d, 3H, J_1 = 22Hz), 1.27 (d, 3H, J_1 = 22Hz), 1.40(t, 3H, J = 7.1 Hz), 2.34(t, 1H, J = 7.5 Hz), 2.83-2.89(m, 2H), 3.10- 3.15(m, 2H), 3.62 (m, 1H), 4.30(s, 1H), 4.38 (q, 2H, J_1 = 14.2Hz, J_2 = 7.1Hz), 6.85 (d, 1H, J = 9.4Hz), 7.10-7.11(m, 2H), 7.26-7.38 (m, 5H), 7.55 (d, 1H, J = 7.8Hz), 7.86 (d, 1H, J = 7.7Hz), 8.05 (s, 1H); Mass Spectrum: m/e = 576, (M+1, ^{35}Cl ^{79}Br), 578 (M+1, ^{37}Cl^{79}Br/^{35}Cl ^{81}Br), 580 (M+1, ^{37}Cl ^{81}Br).

Step 12: Ethyl 3-((*S*)-(4-chlorophenyl){3-[(1*S*)-1-(3-cyano-5-fluorophenyl)-2-fluoro-2-methyl-propyl]azetidin-1-yl}methyl)benzoate

A mixture of 5.64g (9.77 mmol) of ethyl 3-[(*S*)-{3-[(1*S*)-1-(3-bromo-5-fluorophenyl)-2-fluoro-2-methylpropyl]azetidin-1-yl}(4-chlorophenyl)methyl]benzoate, 700 mg (5.96 mmol) of zinc cyanide, 179 mg (0.195 mmol) of tris(dibenzylideneacetone)dipalladium, and 270 mg (0.489 mmol) of DPPF in 99 mL of DMF and 1 mL of water was degassed with N_2 for 1 h at rt. Then it was stirred at 125°C. After 12 h, the reaction mixture was concentrated to remove solvents. The residue was poured into 200 mL of CH_2Cl_2 and 50 mL of aq $NaHCO_3$ (pH= 7-8). The aqueous layer was extracted with $CH_2Cl_2$and the combined organic layer was dried over Na_2SO_4 and concentrated. The residue was purified by silica gel chromatography with hexanes / ethyl acetate to afford the title compound as a white solid; ^{1}H-NMR($CDCl_3$) δ 1.23 (d, 3H, J_1 = 21.7Hz), 1.28 (d, 3H, J_1 = 21.7Hz), 1.40(t, 3H, J = 7.1 Hz), 2.29(t, 1H, J = 7.5 Hz), 2.85-2.95(m, 2H), 3.05(m, 1H), 3.18(m, 1H), 3.64 (t, 1H, J = 6.7 Hz), 4.29(s, 1H), 4.37 (q, 2H, J_1 = 14.2Hz, J_2 = 7.1Hz), 7.16 (d, 1H, J = 9.3Hz), 7.23 (d, 1H, J = 7.8Hz), 7.27-7.38(m, 6H), 7.55 (d, 1H, J = 7.8Hz), 7.86 (d, 1H, J = 7.7Hz), 8.0 (s, 1H); Mass Spectrum: m/e = 523, (M+1, ^{35}Cl), 525 (M+1, ^{37}Cl).

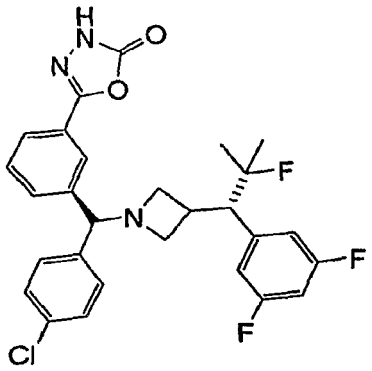
Step 13 3-((*S*)-(4-chlorophenyl){3-[(1*S*)-1-(3-cyano-5-fluorophenyl)-2-fluoro-2-methylpropyl] azetidin-1-yl}methyl)benzohydrazide

A mixture of 3.06 g (5.85 mmol) of ethyl 3-((*S*)-(4-chlorophenyl){3-[(1*S*)-1-(3-cyano-5-fluorophenyl)-2-fluoro-2-methylpropyl]azetidin-1-yl}methyl)benzoate, 13 mL (16.36 mmol) of hydrazine, and 85mL of EtOH was heated to reflux. After 8h, the solvents were removed to afford the title compound as a white solid.; ^{1}H-NMR($CDCl_3$) δ 1.22 (d, 3H, J_1 = 21.7Hz), 1.28 (d, 3H, J_1 = 21.7Hz), 2.29(t, 1H, J = 7.5 Hz), 2.85-2.94(m, 2H), 3.07(m, 1H), 3.15(m, 1H), 3.62 (t, 1H, J = 6.6 Hz), 4.29(s, 1H), 7.16 (d, 1H, J = 9.1Hz), 7.22 (d, 1H, J = 7.5Hz), 7.25-7.36(m, 6H), 7.50-7.54 (m, 2H), 7.77 (s, 1H); Mass Spectrum: m/e = 509, (M+1, ^{35}Cl), 511 (M+1, ^{37}Cl).

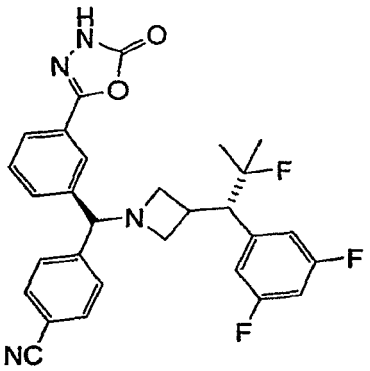
Step 14 3-[(1*S*)-1-(1-{(*S*)-(4-chlorophenyl)[3-(5-oxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)phenyl] methyl}azetidin-3-yl)-2-fluoro-2-methylpropyl]-5-fluorobenzonitrile

To a solution of 3.0g (5.85 mmol) of 3-((*S*)-(4-chlorophenyl){3-[(1*S*)-1-(3-cyano-5-fluorophenyl)-2-fluoro-2-methylpropyl]azetidin-1-yl}methyl)benzohydrazide in 100 mL of CH_2Cl_2 was added 3.73 mL (7.1 mmol) of phosgene solution (20% in toluene). The solution was stirred for 1.5 h at 0°C. The solution was concentrated ,and to the residue was added 6mL of 2N NH_3 in MeOH, and the mixture was concentrated again. The residue was purified by silica gel chromatography with CH_2Cl_2 / acetone to afford the title compound as a white solid; ^{1}H-NMR($CDCl_3$) δ 1.26 (d, 3H, J_1 = 22.1Hz), 1.30 (d, 3H, J_1 = 21.7Hz), 2.39(t, 1H, J = 8.0 Hz), 2.93-3.0(m, 2H), 3.12(t, 1H, J = 7.3Hz), 3.33(m, 1H), 3.69 (t, 1H, J = 6.8 Hz), 4.35(s, 1H), 7.20 (d, 1H, J = 9.7Hz), 7.23 (d, 1H, J = 7.3Hz), 7.29-7.40(m, 7H), 7.48 (d, 1H, J = 7.8 Hz), 7.68 (d, 1H, J = 7.8 Hz), 7.97 (s, 1H); Mass Spectrum: m/e = 535, (M+1, ^{35}Cl), 537 (M+1, ^{37}Cl).

EXAMPLES 26 and 27



26



27

The following compounds were prepared according to procedures outlined above, and applying skill of one ordinarily skilled in the art.

Example 26: 5-[3-((*S*)-(4-chlorophenyl){3-[(1*S*)-1-(3,5-difluorophenyl)-2-fluoro-2-methylpropyl]azetidin-1-yl}methyl)phenyl]-1,3,4-oxadiazol-2(3*H*)-one

Mass Spectrum: m/e = 528, 530 (M+1).

Example 27: 4-{(*S*)-{3-[(1*S*)-1-(3,5-difluorophenyl)-2-fluoro-2-methylpropyl]azetidin-1-yl}[3-(5-oxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)phenyl]methyl}-benzonitrile

Mass Spectrum: m/e = 519 (M+1).

BIOLOGICAL EXAMPLE 1

Cannabinoid Receptor-1 (CB1) Binding Assay.

This assay is described in Biological Example 1 of WO 05/00809.

The binding assay for CB2 receptor is done similarly with recombinant human CB2 receptor expressed in CHO cells.

Compounds of Examples 1-27 have IC_{50}s of less than 1 micromolar in the CB1 binding assay. The compounds of Examples 1-27 are selective CB1 antagonist/inverse agonist compounds having IC50s 100-fold greater in the CB2 binding assay than in the CB1 assay, and generally have IC50s of greater than one micromolar in the CB2 binding assay.

BIOLOGICAL EXAMPLE 2

Cannabinoid Receptor-1 (CB1) Functional Activity Assay.

This assay is described in Biological Example 2 of WO 05/00809.

CB1 antagonist/inverse agonist compounds of the present invention generally have EC50s of less than 1 micromolar in the CB1 functional assay and selective CB1 antagonist/inverse agonists have generally have EC_{50}s of greater than 1 micromolar in the CB2 functional assay.

BIOLOGICAL EXAMPLE 3

Acute food intake studies in rats or mice: General Procedure

This assay is described in Biological Example 1 of WO 05/00809.

BIOLOGICAL EXAMPLE 4

Chronic weight reduction studies in rats or mice: General Procedure

This assay is described in Biological Example 1 of WO 05/00809.

BIOLOGICAL EXAMPLE 5

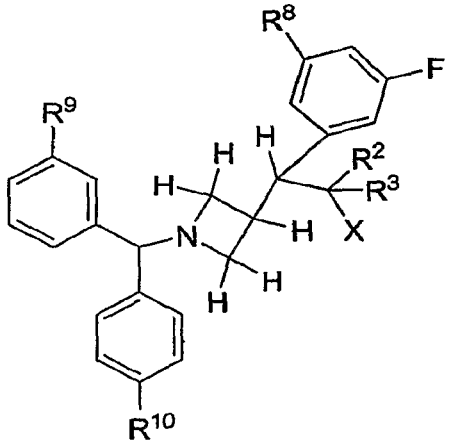
Tail suspension test

This assay is described in Biological Example 1 of WO 05/00809.

While the invention has been described and illustrated with reference to certain particular embodiments thereof, those skilled in the art will appreciate that various changes, modifications and substitutions can be made therein without departing from the spirit and scope of the invention. For example, effective dosages other than the particular dosages as set forth herein above may be applicable as a consequence of variations in the responsiveness of the mammal being treated for any of the indications for the compounds of the invention indicated above. Likewise, the specific pharmacological responses observed may vary according to and depending upon the particular active compound selected or whether there are present pharmaceutical carriers, as well as the type of formulation and mode of administration employed, and such expected variations or differences in the results are contemplated in accordance with the objects and practices of the present invention. It is intended, therefore, that the invention be defined by the scope of the claims which follow and that such claims be interpreted as broadly as is reasonable.

WHAT IS CLAIMED IS:

1. A compound of structural formula I:



(I)

wherein:

X is selected from:

(1) hydroxy,
(2) NH_2,
(3) methyl, and
(4) methoxy;

R^2 and R^3 are each independently selected from:

(1) hydrogen,
(2) methyl,
(3) fluoro,
(4) hydroxyl, and
(5) trifluoromethyl,

provided that R^2 and R^3 are not both hydrogen when X is hydroxy, $-NH_2$, or methoxy;

R^8 is selected from:

(1) R^{15},
(2) hydrogen,
(3) halogen,
(4) methyl,
(5) $-CF_3$,
(6) cyano, and
(7) SO_2CH_3;

R^9 is selected from:

(1) R^{15},
(2) hydrogen,
(3) fluoro

(4) chloro, and

(5) cyano;

R^{10} is selected from:

(1) R^{15},

(2) hydrogen,

(3) fluoro,

(4) chloro,

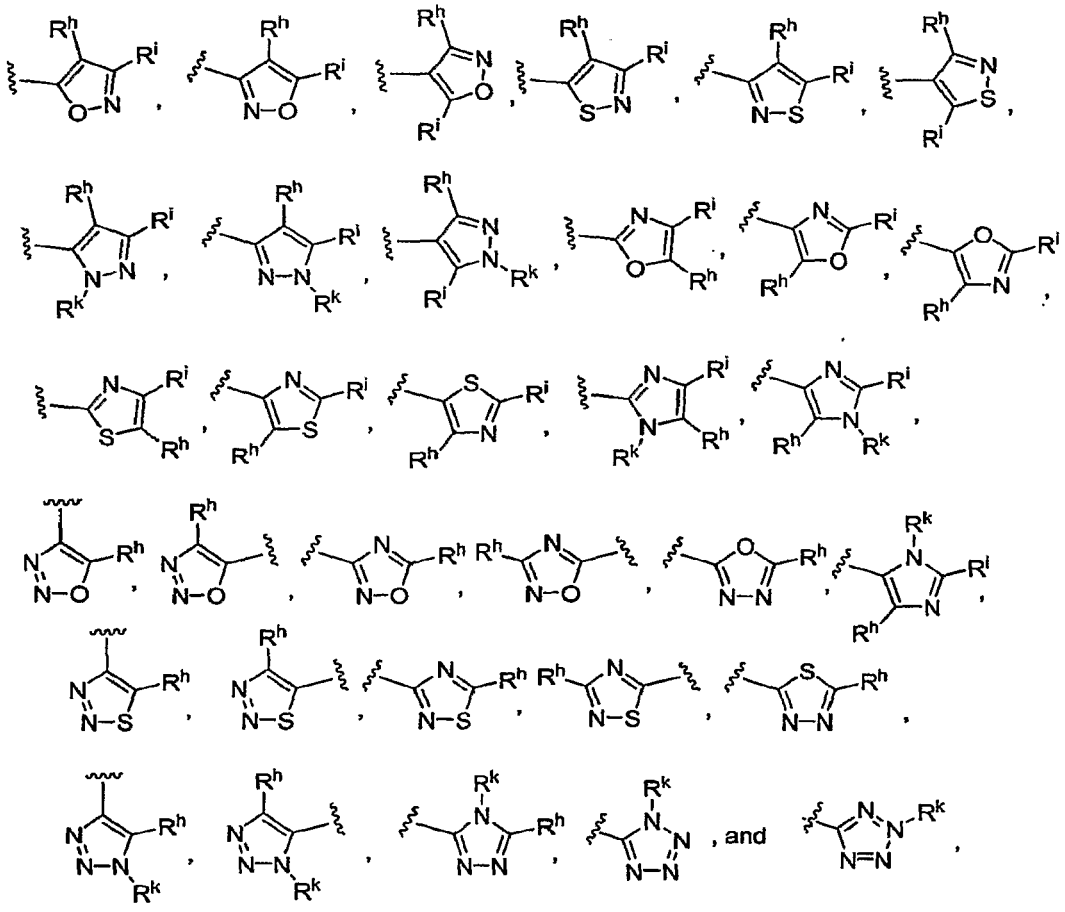
(5) $-CF_3$,

(6) cyano, and

(7) methyl;

provided that at least one of R^8, R^9, and R^{10} is R^{15};

each R^{15} is a 5-membered unsaturated heterocyclic ring selected from:



each R^h is independently selected from:

(1) –H,

(2) –OH,

(3) –SH,

(4) $-NH_2$,

(5) C_{1-3} alkyl, and

(6) -CF_3;

each R^i is independently selected from:

(1) –H,

(2) –OH,

(3) –SH,

(4) –NH_2,

(5) C_{1-3} alkyl, and

(6) -CF_3;

each R^k is independently selected from:

(1) –H, and

(2) C_{1-3} alkyl;

n is selected from 0, 1, and 2;

or a pharmaceutically acceptable salt or solvate thereof.

2. The compound according to Claim 1, wherein:

X is methyl

R^2 is selected from:

(1) hydrogen,

(2) fluoro,

(3) methyl, and

(4) hydroxyl;

R^3 is selected from methyl, and hydroxyl;

R^8 is selected from:

(1) R^{15},

(2) fluoro, and

(3) cyano;

R^9 is selected from:

(1) R^{15},

(2) hydrogen, and

(3) cyano;

R^{10} is selected from:

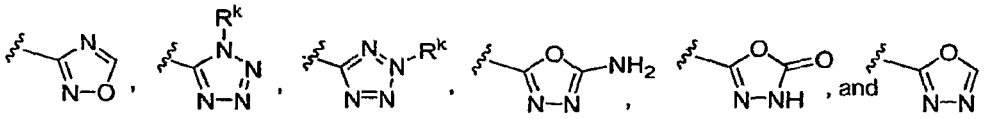
(1) R^{15},

(2) hydrogen,

(3) chloro, and

(4) cyano;

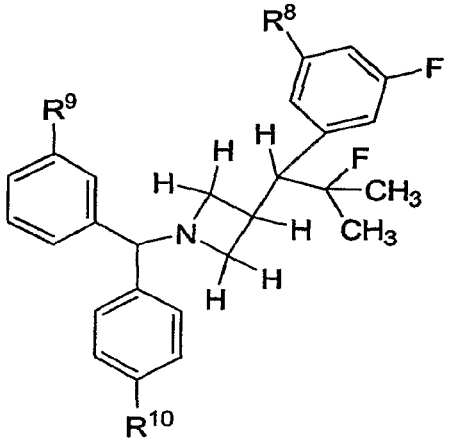
each R^{15} is independently selected from:



wherein R^k is selected from hydrogen and methyl;

or a pharmaceutically acceptable salt or solvate thereof.

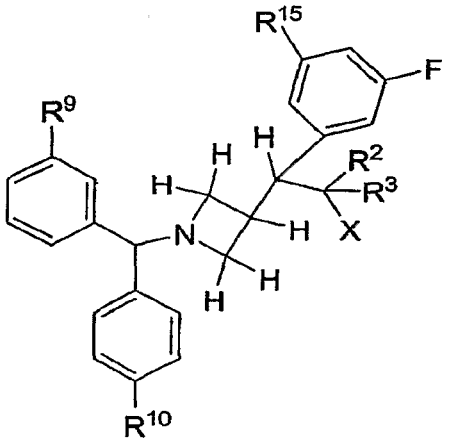
3. The compound according to Claim 2, of structural formula:



wherein only one of R^8, R^9, and R^{10} is R^{15}, or a pharmaceutically acceptable salt thereof.

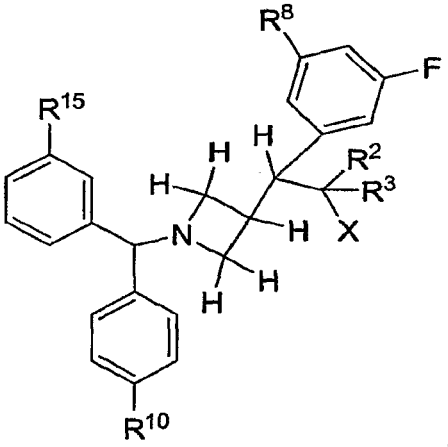
4. The compound according to Claim 1, selected from:

(a)



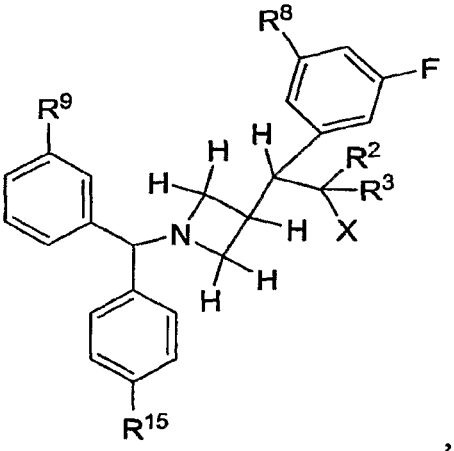
,

(b)



, and

(c)



,

or a pharmaceutically acceptable salt or solvate thereof.

5. A compound according to Claim 1, selected from:

(1) 3-[(*S*)-(4-chlorophenyl)(3-{(1*S*)-2-fluoro-1-[3-fluoro-5-(5-oxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)phenyl]-2-methylpropyl}azetidin-1-yl)methyl]benzonitrile,

(2) 3-[(*S*)-(4-chlorophenyl)(3-{(1*S*)-2-fluoro-1-[3-fluoro-5-(1,3,4-oxadiazol-2-yl)phenyl]-2-methylpropyl}azetidin-1-yl)methyl]benzonitrile,

(3) 3-[(*S*)-(3-{(1*S*)-1-[3-(5-amino-1,3,4-oxadiazol-2-yl)-5-fluorophenyl]-2-fluoro-2-methylpropyl}azetidin-1-yl)(4-chlorophenyl)methyl]benzonitrile,

(4) 3-[(*S*)-(4-cyanophenyl)(3-{(1*S*)-2-fluoro-1-[3-fluoro-5-(5-oxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)phenyl]-2-methylpropyl}azetidin-1-yl)methyl]benzonitrile,

(5) 3-[(*S*)-(3-{(1*S*)-1-[3-(5-amino-1,3,4-oxadiazol-2-yl)-5-fluorophenyl]-2-fluoro-2-methylpropyl}azetidin-1-yl)(4-cyanophenyl)methyl]benzonitrile,

(6) 3-[(*S*)-(4-cyanophenyl)(3-{(1*S*)-2-fluoro-1-[3-fluoro-5-(1,3,4-oxadiazol-2-yl)phenyl]-2-methylpropyl}azetidin-1-yl)methyl]benzonitrile,

(7) 3-[(*S*)-(4-chlorophenyl)(3-{(1*S*)-2-fluoro-1-[3-fluoro-5-(1,2,4-oxadiazol-3-yl)phenyl]-2-methylpropyl}azetidin-1-yl)methyl]benzonitrile,

(8) 3-[(1*S*)-1-(1-{(*S*)-(4-cyanophenyl)[3-(1,2,4-oxadiazol-3-yl)phenyl]-methyl}azetidin-3-yl)-2-fluoro-2-methylpropyl]-5-fluorobenzonitrile,

(9) 5-(3-{1-[1-(diphenylmethyl)azetidin-3-yl]-2-fluoro-2-methylpropyl}-5-fluorophenyl)-1*H*-tetrazole,

(10) 5-(3-{1-[1-(diphenylmethyl)azetidin-3-yl]-2-fluoro-2-methylpropyl}-5-fluorophenyl)-1-methyl-1*H*-tetrazole,

(11) 5-(3-{1-[1-(diphenylmethyl)azetidin-3-yl]-2-fluoro-2-methylpropyl}-5-fluorophenyl)-2-methyl-2H-tetrazole,

(12) 3-[(4-chlorophenyl)(3-{2-fluoro-1-[3-fluoro-5-(2-methyl-2H-tetrazol-5-yl)phenyl]-2-methylpropyl}azetidin-1-yl)methyl]benzonitrile,

(13) 3-[(4-chlorophenyl)(3-{2-fluoro-1-[3-fluoro-5-(1-methyl-1*H*-tetrazol-5-yl)phenyl]-2-methylpropyl}azetidin-1-yl)methyl]benzonitrile,

(14) 3-[(4-cyanophenyl)(3-{2-fluoro-1-[3-fluoro-5-(1-methyl-1*H*-tetrazol-5-yl)phenyl]-2-methylpropyl}azetidin-1-yl)methyl]benzonitrile,

(15) 3-[(4-cyanophenyl)(3-{2-fluoro-1-[3-fluoro-5-(2-methyl-2*H*-tetrazol-5-yl)phenyl]-2-methylpropyl}azetidin-1-yl)methyl]benzonitrile,

(16) 5-{3-[(*S*)-{3-[(1*S*)-1-(3-bromo-5-fluorophenyl)-2-fluoro-2-methylpropyl]azetidin-1-yl}(4-chlorophenyl)methyl]phenyl}-1,3,4-oxadiazol-2(3*H*)-one,

(17) 3-[(1*S*)-1-(1-{(*S*)-(4-chlorophenyl)[3-(5-oxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)phenyl]methyl}azetidin-3-yl)-2-fluoro-2-methylpropyl]-5-fluorobenzonitrile,

(18) 3-[(1*S*)-1-(1-{(*S*)-(4-cyanophenyl)[3-(5-oxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)phenyl]methyl}azetidin-3-yl)-2-fluoro-2-methylpropyl]-5-fluorobenzonitrile,

(19) 3-[(1*S*)-1-(1-{(*S*)-(4-cyanophenyl)[3-(1,3,4-oxadiazol-2-yl)phenyl]methyl}azetidin-3-yl)-2-fluoro-2-methylpropyl]-5-fluorobenzonitrile,

(20) 3-[(1*S*)-1-(1-{(*S*)-(4-chlorophenyl)[3-(1,3,4-oxadiazol-2-yl)phenyl]methyl}azetidin-3-yl)-2-fluoro-2-methylpropyl]-5-fluorobenzonitrile,

(21) 3-((1*S*)-1-{1-[(*S*)-[3-(5-amino-1,3,4-oxadiazol-2-yl)phenyl](4-chlorophenyl)methyl]azetidin-3-yl}-2-fluoro-2-methylpropyl)-5-fluorobenzonitrile,

(22) 3-((1*S*)-1-{1-[(*S*)-[3-(5-amino-1,3,4-oxadiazol-2-yl)phenyl](4-cyanophenyl)methyl]azetidin-3-yl}-2-fluoro-2-methylpropyl)-5-fluorobenzonitrile,

(23) 3-[(1*S*)-1-(1-{(*S*)-(4-cyanophenyl)[3-(1,2,4-oxadiazol-3-yl)phenyl]methyl}azetidin-3-yl)-2-fluoro-2-methylpropyl]-5-fluorobenzonitrile,

(24) 3-[(1*S*)-1-(1-{(*S*)-(4-chlorophenyl)[3-(1,2,4-oxadiazol-3-yl)phenyl]methyl}azetidin-3-yl)-2-fluoro-2-methylpropyl]-5-fluorobenzonitrile,

(25) 5-[3-((*S*)-(4-chlorophenyl){3-[(1*S*)-1-(3,5-difluorophenyl)-2-fluoro-2-methylpropyl] azetidin-1-yl}methyl)phenyl]-1,3,4-oxadiazol-2(3*H*)-one,

(26) 5-[3-((*S*)-(4-chlorophenyl){3-[(1*S*)-1-(3,5-difluorophenyl)-2-fluoro-2-methylpropyl]azetidin-1-yl}methyl)phenyl]-1,3,4-oxadiazol-2(3*H*)-one,

(27) 4-{(*S*)-{3-[(1*S*)-1-(3,5-difluorophenyl)-2-fluoro-2-methylpropyl]azetidin-1-yl}[3-(5-oxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)phenyl]methyl}-benzonitrile,

and pharmaceutically acceptable salts and esters thereof.

6. The use of a compound according to Claim 1 for the manufacture of a medicament useful for treating a disease mediated by the Cannabinoid-1 receptor.

7. The use according to Claim 6, wherein the disease mediated by the Cannabinoid-1 receptor is selected from: psychosis, memory deficit, cognitive disorders, Alzheimer's disease, migraine, neuropathy, neuro-inflammatory disorders, cerebral vascular accidents, head trauma, anxiety disorders, stress, epilepsy, Parkinson's disease, schizophrenia, substance abuse disorders, constipation, chronic intestinal pseudo-obstruction, cirrhosis of the liver, asthma, obesity, and other eating disorders associated with excessive food intake.

8. The use according to Claim 7, wherein the substance abuse disorder is abuse of or addiction to a substance selected from: opiates, alcohol, marijuana, and nicotine, and the eating disorder associated with excessive food intake is selected from obesity, bulimia nervosa, and compulsive eating disorders.

9. The use of a compound according to Claim 1 for the manufacture of a medicament useful for preventing obesity in a person at risk for obesity.

10. A composition comprising a compound according to Claim 1 and a pharmaceutically acceptable carrier.