COMPOUNDS AND COMPOSITIONS AS PPAR MODULATORS

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims the benefit of priority to U.S. Provisional Patent Application Number 60/574,137, filed 24 May 2004, and U.S. Provisional Patent Application Number 60/649,671, filed 2 February 2005. The full disclosures of these applications are incorporated herein by reference in their entirety and for all purposes.

BACKGROUND OF THE INVENTION

Field of the Invention

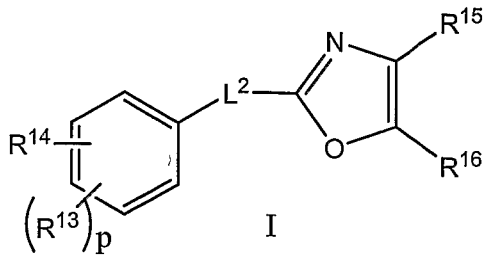
[0002] The invention provides compounds, pharmaceutical compositions comprising such compounds and methods of using such compounds to treat or prevent diseases or disorders associated with the activity of the Peroxisome Proliferator-Activated Receptor (PPAR) families, particularly the activity of PPARδ.

Background

[0003] Peroxisome Proliferator Activated Receptors (PPARs) are members of the nuclear hormone receptor super family, which are ligand-activated transcription factors regulating gene expression. Certain PPARs are associated with a number of disease states including dyslipidemia, hyperlipidemia, hypercholesteremia, atherosclerosis, atherogenesis, hypertriglyceridemia, heart failure, myocardial infarction, vascular diseases, cardiovascular diseases, hypertension, obesity, inflammation, arthritis, cancer, Alzheimer's disease, skin disorders, respiratory diseases, ophthalmic disorders, IBDs (irritable bowel disease), ulcerative colitis and Crohn's disease. Accordingly, molecules that modulate the activity of PPARs, particularly PPARδ, are useful as therapeutic agents in the treatment of such diseases.

SUMMARY OF THE INVENTION

[0004] In one aspect, the present invention provides compounds of Formula I:



I

[0005] in which:

[0006] p is an integer selected from 0 to 3;

[0007] L^2 is selected from –XOX–, $–XS(O)_{0-2}X–$ and $–XS(O)_{0-2}XO–$; wherein X is independently selected from a bond and C_{1-4}alkylene; wherein any alkylene of L^2 can be optionally substituted by 1 to 3 radicals selected from halo, C_{1-6}alkyl, C_{1-6}alkoxy, halo-substituted-C_{1-6}alkyl and halo-substituted-C_{1-6}alkoxy;

[0008] R^{13} is selected from halo, C_{1-6}alkyl, C_{1-6}alkoxy, hydroxy-C_{1-6}alkyl, halo-substituted-C_{1-6}alkyl, halo-substituted-C_{1-6}alkoxy, C_{6-10}aryl, C_{5-10}heteraryl, C_{3-12}cycloalkyl and C_{3-8}heterocycloalkyl; wherein any aryl, heteroaryl, cycloalkyl and heterocycloalkyl of R^{13} is optionally substituted with 1 to 3 radicals independently selected from halo, nitro, cyano, C_{1-6}alkyl, C_{1-6}alkoxy, hydroxy-C_{1-6}alkyl, halo-substituted-C_{1-6}alkyl and halo-substituted-C_{1-6}alkoxy;

[0009] R^{14} is selected from $-XOXC(O)OR^{17}$ and $-XC(O)OR^{17}$; wherein X is a bond or C_{1-4}alkylene; and R^{17} is selected from hydrogen and C_{1-6}alkyl;

[0010] R^{15} and R^{16} are independently selected from $–R^{18}$ and $–YR^{18}$; wherein Y is a selected from C_{1-6}alkylene, C_{2-6}alkenylene, C_{2-6}alkynylene, $–C(O)NR^{17}–$ and –OX–; X is a bond or C_{1-4}alkylene; R^{17} is selected from hydrogen and C_{1-6}alkyl; and R^{18} is selected from C_{3-12}cycloalkyl, C_{3-8}heterocycloalkyl, C_{6-10}aryl and C_{5-13}heteroaryl; or R^{15} and R^{16} together with the atoms to which R^{15} and R^{16} are attached form fused bicyclic or tricyclic C_{5-14}heteroaryl;

[0011] wherein any aryl, heteroaryl, cycloalkyl and heterocycloalkyl of R^{18}, or the combination of R^{15} and R^{16}, is optionally substituted with 1 to 3 radicals independently selected from halo, nitro, cyano, C_{1-6}alkyl, C_{1-6}alkoxy, C_{1-6}alkylthio, hydroxy-C_{1-6}alkyl,

halo-substituted-C_{1-6}alkyl, halo-substituted-C_{1-6}alkoxy, C_{3-12}cycloalkyl, C_{3-8}heterocycloalkyl, C_{6-10}aryl, C_{5-13}heteroaryl, $-XS(O)_{0-2}R^{17}$, $-XS(O)_{0-2}XR^{19}$, $-XNR^{17}R^{17}$, $-XNR^{17}S(O)_{0-2}R^{17}$, $-XNR^{17}C(O)R^{17}$, $-XC(O)NR^{17}R^{17}$, $-XNR^{17}C(O)R^{19}$, $-XC(O)NR^{17}R^{19}$, $-XC(O)R^{19}$, $-XNR^{17}XR^{19}$ and $-XOXR^{19}$; wherein any aryl, heteroaryl, cycloalkyl or heterocycloalkyl substituent is further optionally substituted with 1 to 3 radicals independently selected from halo, nitro, cyano, C_{1-6}alkyl, C_{1-6}alkoxy, C_{1-6}alkylthio, hydroxy-C_{1-6}alkyl, halo-substituted-C_{1-6}alkyl and halo-substituted-C_{1-6}alkoxy; wherein X is a bond or C_{1-4}alkylene; R^{17} is selected from hydrogen and C_{1-6}alkyl; and R^{19} is selected from C_{3-12}cycloalkyl, C_{3-8}heterocycloalkyl, C_{6-10}aryl and C_{5-10}heteroaryl; wherein any aryl, heteroaryl, cycloalkyl or heterocycloalkyl of R^{19} is optionally substituted with 1 to 3 radicals independently selected from halo, nitro, cyano, C_{1-6}alkyl, C_{1-6}alkoxy, halo-substituted-C_{1-6}alkyl and halo-substituted-C_{1-6}alkoxy; and the N-oxide derivatives, prodrug derivatives, protected derivatives, individual isomers and mixture of isomers thereof; and the pharmaceutically acceptable salts and solvates (e.g. hydrates) of such compounds.

[0012] In a second aspect, the present invention provides a pharmaceutical composition that contains a compound of Formula I or a N-oxide derivative, individual isomers and mixture of isomers thereof; or a pharmaceutically acceptable salt thereof, in admixture with one or more suitable excipients.

[0013] In a third aspect, the present invention provides a method of treating a disease in an animal in which modulation of PPAR activity, particularly PPARδ, can prevent, inhibit or ameliorate the pathology and/or symptomology of the diseases, which method comprises administering to the animal a therapeutically effective amount of a compound of Formula I or a N-oxide derivative, individual isomers and mixture of isomers thereof, or a pharmaceutically acceptable salt thereof.

[0014] In a fourth aspect, the present invention provides the use of a compound of Formula I in the manufacture of a medicament for treating a disease in an animal in which PPAR activity, particularly PPARδ activity contributes to the pathology and/or symptomology of the disease.

[0015] In a fifth aspect, the present invention provides a process for preparing compounds of Formula I and the N-oxide derivatives, prodrug derivatives, protected

derivatives, individual isomers and mixture of isomers thereof, and the pharmaceutically acceptable salts thereof.

DETAILED DESCRIPTION OF THE INVENTION

Definitions

[0016] "Alkyl" as a group and as a structural element of other groups, for example halo-substituted-alkyl and alkoxy, can be either straight-chained or branched. C_{1-6}alkoxy includes, methoxy, ethoxy, and the like. Halo-substituted alkyl includes trifluoromethyl, pentafluoroethyl, and the like.

[0017] "Aryl" means a monocyclic or fused bicyclic aromatic ring assembly containing six to ten ring carbon atoms. For example, aryl can be phenyl or naphthyl, preferably phenyl. "Arylene" means a divalent radical derived from an aryl group. "Heteroaryl" is as defined for aryl where one or more of the ring members are a heteroatom. For example heteroaryl includes pyridyl, indolyl, indazolyl, quinoxalinyl, quinolinyl, benzofuranyl, benzopyranyl, benzothiopyranyl, benzo[1,3]dioxole, imidazolyl, benzo-imidazolyl, pyrimidinyl, furanyl, oxazolyl, isoxazolyl, triazolyl, tetrazolyl, pyrazolyl, thienyl, etc. "C_{6-10}arylC_{0-4}alkyl" means an aryl as described above connected via a alkylene grouping. For example, C_{6-10}arylC_{0-4}alkyl includes phenethyl, benzyl, etc.

[0018] "Cycloalkyl" means a saturated or partially unsaturated, monocyclic, fused bicyclic or bridged polycyclic ring assembly containing the number of ring atoms indicated. For example, C_{3-10}cycloalkyl includes cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, etc. "Heterocycloalkyl" means cycloalkyl, as defined in this application, provided that one or more of the ring carbons indicated, are replaced by a moiety selected from -O-, -N=, -NR-, -C(O) -, -S-, -S(O) - or -$S(O)_2$-, wherein R is hydrogen, C_{1-4}alkyl or a nitrogen protecting group. For example, C_{3-8}heterocycloalkyl as used in this application to describe compounds of the invention includes morpholino, pyrrolidinyl, piperazinyl, piperidinyl, piperidinylone, 1,4-dioxa-8-aza-spiro[4.5]dec-8-yl, etc.

[0019] "Halogen" (or halo) preferably represents chloro or fluoro, but can also be bromo or iodo.

[0020] "Treat", "treating" and "treatment" refer to a method of alleviating or abating a disease and/or its attendant symptoms.

Description of the Preferred Embodiments

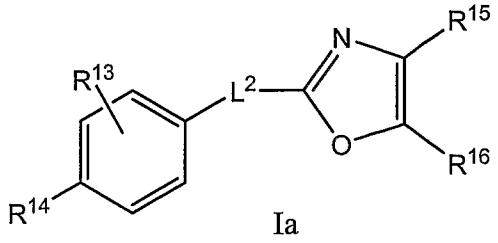
[0021] The present invention provides compounds, compositions and methods for the treatment of diseases in which modulation of PPARδ activity can prevent, inhibit or ameliorate the pathology and/or symptomology of the diseases, which method comprises administering to the animal a therapeutically effective amount of a compound of Formula I.

[0022] In one embodiment, with reference to compounds of Formula I, p is an integer selected from 0 to 3; L^2 is selected from –XOX–, $-XS(O)_{0-2}X-$ and $-XS(O)_{0-2}XO-$; wherein X is independently selected from a bond and C_{1-4}alkylene; wherein any alkylene of L^2 can be optionally substituted by 1 to 3 radicals selected from halo, C_{1-6}alkyl, C_{1-6}alkoxy, halo-substituted-C_{1-6}alkyl and halo-substituted-C_{1-6}alkoxy; and R^{13} is C_{1-6}alkyl, C_{1-6}alkoxy and halo.

[0023] In a further embodiment, R^{14} is selected from $-XOXC(O)OR^{17}$ and $-XC(O)OR^{17}$; wherein X is a bond or C_{1-4}alkylene; and R^{17} is selected from hydrogen and C_{1-6}alkyl; R^{15} and R^{16} are independently selected from $-R^{18}$ and $-YR^{18}$; wherein Y is a selected from C_{1-6}alkylene, C_{2-6}alkenylene, $-C(O)NR^{17}-$ and –OX–; X is a bond or C_{1-4}alkylene; R^{17} is selected from hydrogen and C_{1-6}alkyl; and R^{18} is selected from C_{6-10}aryl, C_{3-12}cycloalkyl and C_{5-13}heteroaryl; or R^{15} and R^{16} together with the atoms to which R^{15} and R^{16} are attached form fused bicyclic or tricyclic C_{5-14}heteroaryl; wherein any aryl, heteroaryl and cycloalkyl of R^{18}, or the combination of R^{15} and R^{16}, is optionally substituted with 1 to 3 radicals independently selected from halo, nitro, cyano, C_{1-6}alkyl, C_{1-6}alkoxy, C_{1-6}alkylthio, hydroxy-C_{1-6}alkyl, halo-substituted-C_{1-6}alkyl, halo-substituted-C_{1-6}alkoxy, C_{3-12}cycloalkyl, C_{3-8}heterocycloalkyl, C_{6-10}aryl optionally substituted with C_{1-6}alkoxy, C_{5-13}heteroaryl, $-XS(O)_{0-2}R^{17}$, $-XS(O)_{0-2}XR^{19}$, $-XNR^{17}R^{17}$, $-XNR^{17}S(O)_{0-2}R^{17}$, $-XNR^{17}C(O)R^{17}$, $-XC(O)NR^{17}R^{17}$, $-XNR^{17}C(O)R^{19}$, $-XC(O)NR^{17}R^{19}$, $-XC(O)R^{19}$, $-XNR^{17}XR^{19}$ and $-XOXR^{19}$; wherein X is a bond or C_{1-4}alkylene; R^{17} is selected from hydrogen and C_{1-6}alkyl; and R^{19} is selected from C_{6-10}aryl, C_{5-10}heteroaryl, C_{3-8}heterocycloalkyl and C_{3-12}cycloalkyl; wherein any aryl, heteroaryl, cycloalkyl or heterocycloalkyl of R^{19} is optionally substituted with 1 to 3 radicals

independently selected from halo, nitro, cyano, C_{1-6}alkyl, C_{1-6}alkoxy, halo-substituted-C_{1-6}alkyl and halo-substituted-C_{1-6}alkoxy.

[0024] In a further embodiment, the invention provides a compound of Formula Ia:



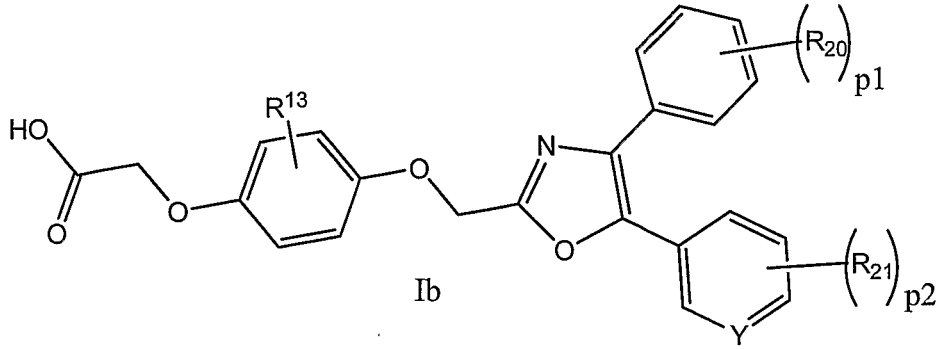
Ia

[0025] in which: L^2 is selected from $-S(O)_{0-2}(CH_2)_{1-4}O-$, $-O(CH_2)_{1-4}S(O)_{0-2}-$, $-CH_2S(O)_{0-2}-$, $-S(O)_{0-2}CH_2-$, $-S(O)_{0-2}-$, $-CH_2O-$ and $-OCH_2-$; R^{13} is selected from C_{1-6}alkyl, C_{1-6}alkoxy and halo; R^{14} is selected from $-OCH_2C(O)OH$ and $-CH_2C(O)OH$; R^{15} and R^{16} are independently selected from $-R^{18}$ and $-YR^{18}$; wherein Y is selected from C_{1-6}alkylene, C_{2-6}alkenylene, $-C(O)NH-$ and $-O(CH_2)_{1-3}-$; and R^{18} is selected from phenyl, biphenyl, cyclohexyl, naphthyl, benzo[1,3]dioxol-5-yl, benzo[b]furanyl, pyridinyl, pyrimidinyl, dibenzo-furan-2-yl, furanyl, benzo[b]thiophene, thiophenyl, phenoxathiin-4-yl, benzoxazolyl, 3-oxo-3,4-dihydro-2H-benzo[1,4]oxazin-6-yl, 2-oxo-2,3-dihydro-benzooxazol-6-yl, 2,3-dihydro-benzo[1,4]dioxin-6-yl, benzoxazolyl, 3,4-dihydro-2H-benzo[b][1,4]dioxepin-7-yl and quinolinyl; or R^{15} and R^{16} together with the atoms to which R^{15} and R^{16} are attached form 4,5-dihydro-naphtho[1,2-d]thiazol-2-yl, 4H-chromeno[4,3-d]thiazol-2-yl, 5,6-dihydro-4H-3-thia-1-aza-benzo[e]azulen-2-yl, benzthiazolyl, benzoxazolyl and 1-oxa-3-aza-cyclopenta[a]naphthalen-2-yl;

[0026] wherein any aryl, heteroaryl, cycloalkyl and heterocycloalkyl of R^{15}, R^{16} or the combination of R^{15} and R^{16}, is optionally substituted with 1 to 3 radicals independently selected from halo, cyano, nitro, methyl, isopropyl, isopropyl-sulfanyl, isopropyloxy, hydroxy-methyl, methyl-sulfanyl, methoxy, ethoxy, pentafluoroethoxy, trifluoromethyl, trifluoromethoxy, trifluoromethyl-sulfonyl, morpholino, phenoxy, benzoxy, ethyl-sulfonyl, dimethylamino, methyl-sulfonyl-amino, ethyl-sulfonyl, propyl, vinyl, propyloxy, *sec*-butoxy, trifluoromethyl-sulfanyl, dimethyl-amino-carbonyl, diethyl-amino-carbonyl, methyl-carbonyl-amino, methyl-carbonyl, cyclopentyl-oxy, isopropyl-methylamino-carbonyl, cyclopropyl-amino-carbonyl, cyclohexyl, morpholino, piperidinyl, indolyl, pyrrolidinyl,

pyrrolidinyl-carbonyl, 2,3-dihydro-benzofuran-5-yl piperidinyl-carbonyl, morpholino-carbonyl, isopropyl-methyl-amino, isopropyl-methyl-amino-carbonyl, diethyl-amino, and phenyl optionally substituted with methoxy.

[0027] In a further embodiment are compounds of Formula Ib:



Ib

[0028] in which p1 and p2 are independently selected from 0, 1 and 2; Y is selected from N and CH; R^{13} is selected from C_{1-6}alkyl, C_{1-6}alkoxy and halo; R^{20} is selected from trifluoromethyl and trifluoromethoxy; and R^{21} is selected from isopropyloxy and methoxy.

[0029] Preferred compounds of Formula I are detailed in the Examples, *infra*. A preferred compound of the invention is {4-[4-(6-isopropoxy-pyridin-3-yl)-5-(4-trifluoromethoxy-phenyl)-oxazol-2-ylmethoxy]-2-methyl-phenoxy}-acetic acid.

Pharmacology and Utility

[0030] Compounds of the invention modulate the activity of PPARs and, as such, are useful for treating diseases or disorders in which PPARs contributes to the pathology and/or symptomology of the disease. This invention further provides compounds of this invention for use in the preparation of medicaments for the treatment of diseases or disorders in which PPARs, particularly PPARδ, contributes to the pathology and/or symptomology of the disease.

[0031] Such compounds may therefore be employed for the treatment of prophylaxis, dyslipidemia, hyperlipidemia, hypercholesteremia, atherosclerosis, atherogenesis, hypertriglyceridemia, heart failure, hyper cholesteremia, myocardial infarction, vascular diseases, cardiovascular diseases, hypertension, obesity, cachexia, HIV wasting syndrome, inflammation, arthritis, cancer, Alzheimer's disease, anorexia, anorexia nervosa, bulimia, skin disorders, respiratory diseases, ophthalmic disorders, IBDs (irritable

bowel disease), ulcerative colitis and Crohn's disease. Preferably for the treatment of prophylaxis, dyslipidemia, hyperlipidemia, hypercholesteremia, atherosclerosis, atherogenesis, hypertriglyceridemia, cardiovascular diseases, hypertension, obesity, inflammation, cancer, skin disorders, IBDs (irritable bowel disease), ulcerative colitis and Crohn's disease.

[0032] Compounds of the invention can also be employed to treat long term critical illness, increase muscle mass and/or muscle strength, increase lean body mass, maintain muscle strength and function in the elderly, enhance muscle endurance and muscle function, and reverse or prevent frailty in the elderly.

[0033] Further, the compounds of the present invention may be employed in mammals as hypoglycemic agents for the treatment and prevention of conditions in which impaired glucose tolerance, hyperglycemia and insulin resistance are implicated, such as type-1 and type-2 diabetes, Impaired Glucose Metabolism (IGM), Impaired Glucose Tolerance (IGT), Impaired Fasting Glucose (IFG), and Syndrome X. Preferably type-1 and type-2 diabetes, Impaired Glucose Metabolism (IGM), Impaired Glucose Tolerance (IGT) and Impaired Fasting Glucose (IFG).

[0034] In accordance with the foregoing, the present invention further provides a method for preventing or treating any of the diseases or disorders described above in a subject in need of such treatment, which method comprises administering to said subject a therapeutically effective amount (*See, "Administration and Pharmaceutical Compositions", infra*) of a compound of the invention or a pharmaceutically acceptable salt thereof. For any of the above uses, the required dosage will vary depending on the mode of administration, the particular condition to be treated and the effect desired. The present invention also concerns: i) a compound of the invention or a pharmaceutically acceptable salt thereof for use as a medicament; and ii) the use of a compound of the invention or a pharmaceutically acceptable salt thereof for the manufacture of a medicament for preventing or treating any of the diseases or disorders described above.

Administration and Pharmaceutical Compositions

[0035] In general, compounds of the invention will be administered in therapeutically effective amounts via any of the usual and acceptable modes known in the

art, either singly or in combination with one or more therapeutic agents. A therapeutically effective amount can vary widely depending on the severity of the disease, the age and relative health of the subject, the potency of the compound used and other factors. In general, satisfactory results are indicated to be obtained systemically at daily dosages of from about 0.03 to 2.5mg/kg per body weight. An indicated daily dosage in the larger mammal, e.g. humans, is in the range from about 0.5mg to about 100mg, conveniently administered, e.g. in divided doses up to four times a day or in retard form. Suitable unit dosage forms for oral administration comprise from ca. 1 to 50mg active ingredient.

[0036] Compounds of the invention can be administered as pharmaceutical compositions by any conventional route, in particular enterally, e.g., orally, e.g., in the form of tablets or capsules, or parenterally, e.g., in the form of injectable solutions or suspensions, topically, e.g., in the form of lotions, gels, ointments or creams, or in a nasal or suppository form. Pharmaceutical compositions comprising a compound of the present invention in free form or in a pharmaceutically acceptable salt form in association with at least one pharmaceutically acceptable carrier or diluent can be manufactured in a conventional manner by mixing, granulating or coating methods. For example, oral compositions can be tablets or gelatin capsules comprising the active ingredient together with a) diluents, e.g., lactose, dextrose, sucrose, mannitol, sorbitol, cellulose and/or glycine; b) lubricants, e.g., silica, talcum, stearic acid, its magnesium or calcium salt and/or polyethyleneglycol; for tablets also c) binders, e.g., magnesium aluminum silicate, starch paste, gelatin, tragacanth, methylcellulose, sodium carboxymethylcellulose and or polyvinylpyrollidone; if desired d) disintegrants, e.g., starches, agar, alginic acid or its sodium salt, or effervescent mixtures; and/or e) absorbents, colorants, flavors and sweeteners. Injectable compositions can be aqueous isotonic solutions or suspensions, and suppositories can be prepared from fatty emulsions or suspensions. The compositions can be sterilized and/or contain adjuvants, such as preserving, stabilizing, wetting or emulsifying agents, solution promoters, salts for regulating the osmotic pressure and/or buffers. In addition, they can also contain other therapeutically valuable substances. Suitable formulations for transdermal applications include an effective amount of a compound of the present invention with a carrier. A carrier can include absorbable pharmacologically acceptable solvents to assist passage through the skin of the host. For example, transdermal devices are in the form of a bandage comprising

a backing member, a reservoir containing the compound optionally with carriers, optionally a rate controlling barrier to deliver the compound to the skin of the host at a controlled and predetermined rate over a prolonged period of time, and means to secure the device to the skin. Matrix transdermal formulations can also be used. Suitable formulations for topical application, e.g., to the skin and eyes, are preferably aqueous solutions, ointments, creams or gels well-known in the art. Such can contain solubilizers, stabilizers, tonicity enhancing agents, buffers and preservatives.

[0037] This invention also concerns a pharmaceutical composition comprising a therapeutically effective amount of a compound as described herein in combination with one or more pharmaceutically acceptable carriers.

[0038] Compounds of the invention can be administered in therapeutically effective amounts in combination with one or more therapeutic agents (pharmaceutical combinations).

[0039] Thus, the present invention also relates to pharmaceutical combinations, such as a combined preparation or pharmaceutical composition (fixed combination), comprising: 1) a compound of the invention as defined above or a pharmaceutical acceptable salt thereof; and 2) at least one active ingredient selected from:

[0040] a) anti-diabetic agents such as insulin, insulin derivatives and mimetics; insulin secretagogues such as the sulfonylureas, e.g., Glipizide, glyburide and Amaryl; insulinotropic sulfonylurea receptor ligands such as meglitinides, e.g., nateglinide and repaglinide; insulin sensitizer such as protein tyrosine phosphatase-1B (PTP-1B) inhibitors such as PTP-112; GSK3 (glycogen synthase kinase-3) inhibitors such as SB-517955, SB-4195052, SB-216763, NN-57-05441 and NN-57-05445; RXR ligands such as GW-0791 and AGN-194204; sodium-dependent glucose co-transporter inhibitors such as T-1095; glycogen phosphorylase A inhibitors such as BAY R3401; biguanides such as metformin; alpha-glucosidase inhibitors such as acarbose; GLP-1 (glucagon like peptide-1), GLP-1 analogs such as Exendin-4 and GLP-1 mimetics; DPPIV (dipeptidyl peptidase IV) inhibitors such as DPP728, LAF237 (vildagliptin - Example 1 of WO 00/34241), MK-0431, saxagliptin, GSK23A ; an AGE breaker; a thiazolidone derivative (glitazone) such as pioglitazone, rosiglitazone, or *(R)*-1-{4-[5-methyl-2-(4-trifluoromethyl-phenyl)-oxazol-4-ylmethoxy]-benzenesulfonyl}-2,3-dihydro-1*H*-indole-2-carboxylic acid described in the patent

application WO 03/043985, as compound 19 of Example 4, a non-glitazone type PPARγ agonist e.g. GI-262570;

[0041] b) hypolipidemic agents such as 3-hydroxy-3-methyl-glutaryl coenzyme A (HMG-CoA) reductase inhibitors, e.g., lovastatin, pitavastatin, simvastatin, pravastatin, cerivastatin, mevastatin, velostatin, fluvastatin, dalvastatin, atorvastatin, rosuvastatin and rivastatin; squalene synthase inhibitors; FXR (farnesoid X receptor) and LXR (liver X receptor) ligands; cholestyramine; fibrates; nicotinic acid and aspirin;

[0042] c) an anti-obesity agent or appetite regulating agent such as phentermine, leptin, bromocriptine, dexamphetamine, amphetamine, fenfluramine, dexfenfluramine, sibutramine, orlistat, dexfenfluramine, mazindol, phentermine, phendimetrazine, diethylpropion, fluoxetine, bupropion, topiramate, diethylpropion, benzphetamine, phenylpropanolamine or ecopipam, ephedrine, pseudoephedrine or cannabinoid receptor antagonists;

[0043] d) anti-hypertensive agents, e.g., loop diuretics such as ethacrynic acid, furosemide and torsemide; diuretics such as thiazide derivatives, chlorithiazide, hydrochlorothiazide, amiloride; angiotensin converting enzyme (ACE) inhibitors such as benazepril, captopril, enalapril, fosinopril, lisinopril, moexipril, perinodopril, quinapril, ramipril and trandolapril; inhibitors of the Na-K-ATPase membrane pump such as digoxin; neutralendopeptidase (NEP) inhibitors e.g. thiorphan, terteo-thiorphan, SQ29072; ECE inhibitors e.g. SLV306; ACE/NEP inhibitors such as omapatrilat, sampatrilat and fasidotril; angiotensin II antagonists such as candesartan, eprosartan, irbesartan, losartan, telmisartan and valsartan, in particular valsartan; renin inhibitors such as aliskiren, terlakiren, ditekiren, RO 66-1132, RO-66-1168; β-adrenergic receptor blockers such as acebutolol, atenolol, betaxolol, bisoprolol, metoprolol, nadolol, propranolol, sotalol and timolol; inotropic agents such as digoxin, dobutamine and milrinone; calcium channel blockers such as amlodipine, bepridil, diltiazem, felodipine, nicardipine, nimodipine, nifedipine, nisoldipine and verapamil; aldosterone receptor antagonists; and aldosterone synthase inhibitors;

[0044] e) a HDL increasing compound;

[0045] f) Cholesterol absorption modulator such as Zetia® and KT6-971;

[0046] g) Apo-A1 analogues and mimetics;

[0047] h) thrombin inhibitors such as Ximelagatran;

[0048] i) aldosterone inhibitors such as anastrazole, fadrazole, eplerenone;

[0049] j) Inhibitors of platelet aggregation such as aspirin, clopidogrel bisulfate;

[0050] k) estrogen, testosterone, a selective estrogen receptor modulator, a selective androgen receptor modulator;

[0051] l) a chemotherapeutic agent such as aromatase inhibitors e.g. femara, anti-estrogens, topoisomerase I inhibitors, topoisomerase II inhibitors, microtubule active agents, alkylating agents, antineoplastic antimetabolites, platin compounds, compounds decreasing the protein kinase activity such as a PDGF receptor tyrosine kinase inhibitor preferably Imatinib ({ N-{5-[4-(4-methyl-piperazino-methyl)-benzoylamido]-2-methylphenyl}-4-(3-pyridyl)-2-pyrimidine-amine }) described in the European patent application EP-A-0 564 409 as example 21 or 4-Methyl-N-[3-(4-methyl-imidazol-1-yl)-5-trifluoromethyl-phenyl]-3-(4-pyridin-3-yl-pyrimidin-2-ylamino)-benzamide described in the patent application WO 04/005281 as example 92; and

[0052] m) an agent interacting with a 5-HT_3 receptor and/or an agent interacting with 5-HT_4 receptor such as tegaserod described in the US patent No. 5510353 as example 13, tegaserod hydrogen maleate, cisapride, cilansetron;

[0053] or, in each case a pharmaceutically acceptable salt thereof; and optionally a pharmaceutically acceptable carrier.

[0054] Most preferred combination partners are tegaserod, imatinib, vildagliptin, metformin, a thiazolidone derivative (glitazone) such as pioglitazone, rosiglitazone, or *(R)*-1-{4-[5-methyl-2-(4-trifluoromethyl-phenyl)-oxazol-4-ylmethoxy]-benzenesulfonyl}-2,3-dihydro-1*H*-indole-2-carboxylic acid, a sulfonylurea receptor ligand, aliskiren, valsartan, orlistat or a statin such as pitavastatin, simvastatin, fluvastatin or pravastatin.

[0055] Preferably the pharmaceutical combinations contains a therapeutically effective amount of a compound of the invention as defined above, in a combination with a therapeutically effective amount of another therapeutic agent as described above, e.g., each at an effective therapeutic dose as reported in the art. Combination partners (1) and (2) can be administered together, one after the other or separately in one combined unit dosage form or in two separate unit dosage forms. The unit dosage form may also be a fixed combination.

[0056] The structure of the active agents identified by generic or trade names may be taken from the actual edition of the standard compendium "The Merck Index" or the

Physician's Desk Reference or from databases, e.g. Patents International (e.g. IMS World Publications) or Current Drugs. The corresponding content thereof is hereby incorporated by reference. Any person skilled in the art is fully enabled to identify the active agents and, based on these references, likewise enabled to manufacture and test the pharmaceutical indications and properties in standard test models, both in vitro and in vivo.

[0057] In another preferred aspect the invention concerns a pharmaceutical composition (fixed combination) comprising a therapeutically effective amount of a compound as described herein, in combination with a therapeutically effective amount of at least one active ingredient selected from the above described group a) to m), or, in each case a pharmaceutically acceptable salt thereof.

[0058] A pharmaceutical composition or combination as described herein for the manufacture of a medicament for the treatment of for the treatment of dyslipidemia, hyperlipidemia, hypercholesteremia, atherosclerosis, hypertriglyceridemia, heart failure, myocardial infarction, vascular diseases, cardiovascular diseases, hypertension, obesity, inflammation, arthritis, cancer, Alzheimer's disease, skin disorders, respiratory diseases, ophthalmic disorders, inflammatory bowel diseases, IBDs (irritable bowel disease), ulcerative colitis, Crohn's disease, conditions in which impaired glucose tolerance, hyperglycemia and insulin resistance are implicated, such as type-1 and type-2 diabetes, Impaired Glucose Metabolism (IGM), Impaired Glucose Tolerance (IGT), Impaired Fasting Glucose (IFG), and Syndrome-X.

[0059] Such therapeutic agents include estrogen, testosterone, a selective estrogen receptor modulator, a selective androgen receptor modulator, insulin, insulin derivatives and mimetics; insulin secretagogues such as the sulfonylureas, e.g., Glipizide and Amaryl; insulinotropic sulfonylurea receptor ligands, such as meglitinides, e.g., nateglinide and repaglinide; insulin sensitizers, such as protein tyrosine phosphatase-1B (PTP-1B) inhibitors, GSK3 (glycogen synthase kinase-3) inhibitors or RXR ligands; biguanides, such as metformin; alpha-glucosidase inhibitors, such as acarbose; GLP-1 (glucagon like peptide-1), GLP-1 analogs, such as Exendin-4, and GLP-1 mimetics; DPPIV (dipeptidyl peptidase IV) inhibitors, e.g. isoleucin-thiazolidide; DPP728 and LAF237, hypolipidemic agents, such as 3-hydroxy-3-methyl-glutaryl coenzyme A (HMG-CoA) reductase inhibitors, e.g., lovastatin, pitavastatin, simvastatin, pravastatin, cerivastatin, mevastatin, velostatin, fluvastatin,

dalvastatin, atorvastatin, rosuvastatin, fluindostatin and rivastatin, squalene synthase inhibitors or FXR (liver X receptor) and LXR (farnesoid X receptor) ligands, cholestyramine, fibrates, nicotinic acid and aspirin. A compound of the present invention may be administered either simultaneously, before or after the other active ingredient, either separately by the same or different route of administration or together in the same pharmaceutical formulation.

[0060] The invention also provides for pharmaceutical combinations, e.g. a kit, comprising: a) a first agent which is a compound of the invention as disclosed herein, in free form or in pharmaceutically acceptable salt form, and b) at least one co-agent. The kit can comprise instructions for its administration.

[0061] The terms "co-administration" or "combined administration" or the like as utilized herein are meant to encompass administration of the selected therapeutic agents to a single patient, and are intended to include treatment regimens in which the agents are not necessarily administered by the same route of administration or at the same time.

[0062] The term "pharmaceutical combination" as used herein means a product that results from the mixing or combining of more than one active ingredient and includes both fixed and non-fixed combinations of the active ingredients. The term "fixed combination" means that the active ingredients, e.g. a compound of Formula I and a co-agent, are both administered to a patient simultaneously in the form of a single entity or dosage. The term "non-fixed combination" means that the active ingredients, e.g. a compound of Formula I and a co-agent, are both administered to a patient as separate entities either simultaneously, concurrently or sequentially with no specific time limits, wherein such administration provides therapeutically effective levels of the 2 compounds in the body of the patient. The latter also applies to cocktail therapy, e.g. the administration of 3 or more active ingredients.

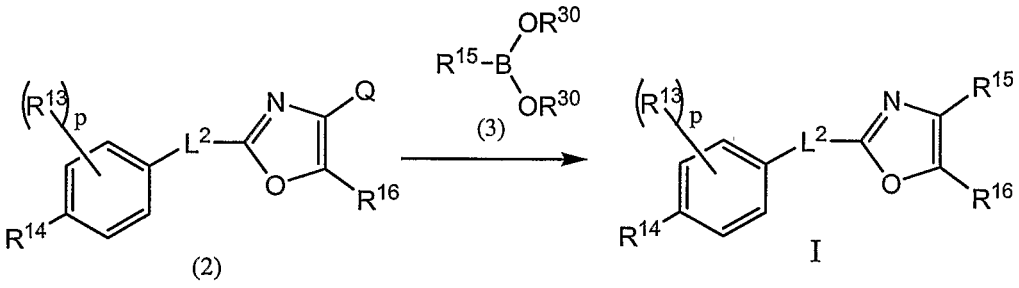
Processes for Making Compounds of the Invention

[0063] The present invention also includes processes for the preparation of compounds of the invention. In the reactions described, it can be necessary to protect reactive functional groups, for example hydroxy, amino, imino, thio or carboxy groups,

where these are desired in the final product, to avoid their unwanted participation in the reactions. Conventional protecting groups can be used in accordance with standard practice, for example, see T.W. Greene and P. G. M. Wuts in "Protective Groups in Organic Chemistry", John Wiley and Sons, 1991.

[0064] Compounds of Formula I, in which R^{15} is cyclic (e.g. cycloalkyl, heterocycloalkyl, aryl and heteroaryl), can be prepared by proceeding as in reaction scheme Ia:

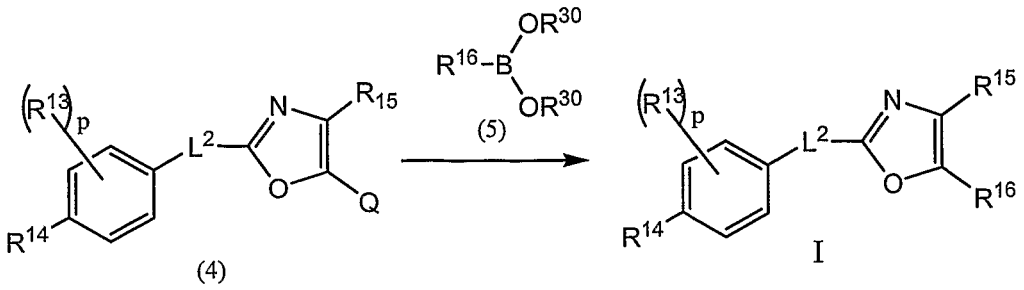
Reactions Scheme 1a



[0065] in which p, R^{13}, R^{14}, R^{16} and L^2 are as defined for Formula I in the Summary of the Invention. Q is a halogen, preferably Cl or Br; and R^{30} is independently selected from hydrogen, $C_{1\text{-}6}$alkyl or the R^{30} radicals can be cyclized. Compounds of Formula I are prepared by reacting a compound of formula 2 with a compound of formula 3 in the presence of a suitable catalyst (e.g., $Pd(Ph_3)_4$, or the like), a suitable base (e.g., Na_2CO_3, or the like) and a suitable solvent (e.g., water, ethanol, DME or the like). The reaction is carried out in the temperature range of about 120 to about 200°C (microwave) and takes up to about 20 minutes to complete.

[0066] Compounds of Formula I, in which R^{16} is cyclic (e.g. cycloalkyl, heterocycloalkyl, aryl and heteroaryl), can be prepared by proceeding as in reaction scheme Ib:

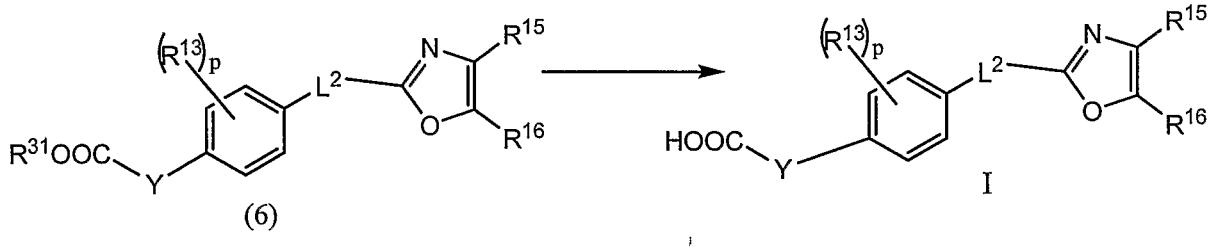
Reactions Scheme 1b



[0067] in which p, R^{13}, R^{14}, R^{16} and L^2 are as defined for Formula I in the Summary of the Invention. Q is a halogen, preferably Cl or Br; and R^{30} is independently selected from hydrogen, C_{1-6}alkyl or the R^{30} radicals can be cyclized. Compounds of Formula I are prepared by reacting a compound of formula 4 with a compound of formula 5 in the presence of a suitable catalyst (e.g., $Pd(Ph_3)_4$, or the like), a suitable base (e.g., Na_2CO_3, or the like) and a suitable solvent (e.g., water, ethanol, DME or the like). The reaction is carried out in the temperature range of about 120 to about 200°C (microwave) and takes up to about 20 minutes to complete.

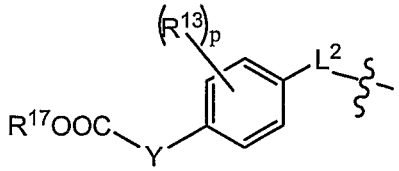
[0068] Compounds of Formula I, in which R^{14} is defined by –Y-$COOR^{31}$, can be prepared by proceeding as in reaction scheme 2:

Reactions Scheme 2



[0069] in which p, R^{13}, R^{15}, R^{16} and L^2 are as defined for Formula I in the Summary of the Invention; Y is –XOX– or –X– (wherein X is independently selected from a bond or C_{1-4}alkylene as defined in the Summary of the Invention) and R^{31} is an alkyl group, for example, methyl. Compounds of Formula I are prepared by reacting a compound of formula 4 in the presence of a suitable base (e.g., lithium hydroxide, or the like) and a suitable solvent (e.g., THF, water or the like). The reaction is carried out in the temperature range of about 0 to about 50°C and takes up to about 30 hours to complete.

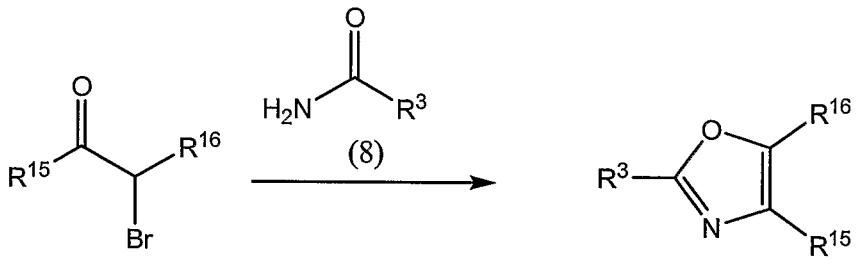
[0070] Compounds of Formula 9, in which R^3 is $-CH_3$, $-SH$, $-C(O)OC_2H_5$, $-CH_2OC(O)C(CH_3)_3$ or a group defined by:



(R^3)

[0071] wherein Y is –XOX– or –X–; and p, R^{13}, L^2, X and R^{17} are as defined in the Summary of the Invention), can be prepared by proceeding as in reaction scheme 3:

Reactions Scheme 3

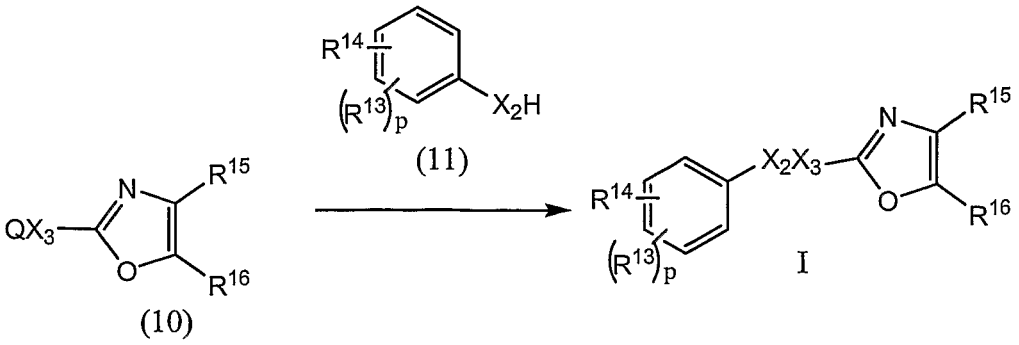


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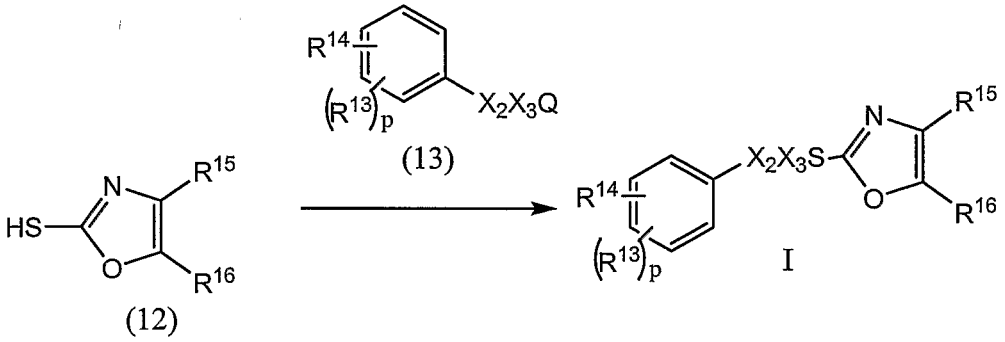
[0072] in which p, R^{13}, R^{17} and L^2 are as defined for Formula I in the Summary of the Invention; R^{15} and R^{16} independently are selected from hydrogen, alkyl or any cyclic radical (cycloalkyl, heterocycloalkyl, aryl and heteroaryl as defined in the Summary of the Invention). Compounds of Formula 9 are prepared by reacting a compound of formula 7 with a compound of formula 8 optionally in the presence of a solvent (e.g., ethanol, or the like). The reaction is carried out in the temperature range of about 10 to about 200°C and takes up to about 30 hours to complete.

[0073] Compounds of Formula I can be prepared by proceeding as in reaction scheme 4a and 4b:

Reactions Scheme 4a



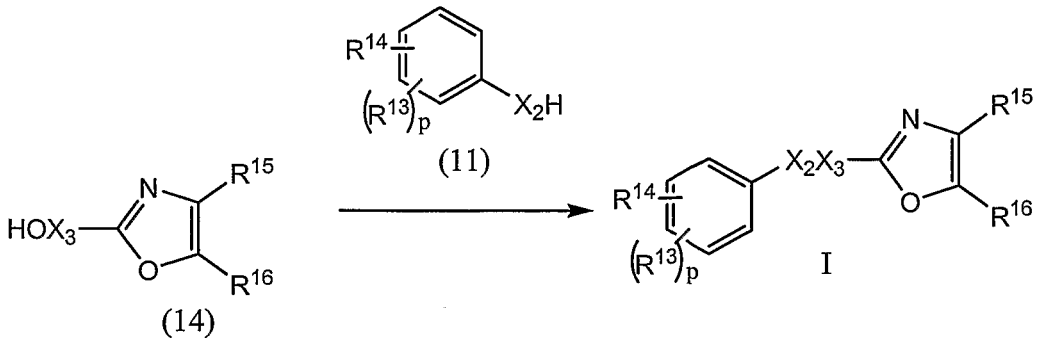
Reactions Scheme 4b



[0074] in which p, R^{13}, R^{14}, R^{15} and R^{16} are as defined for Formula I in the Summary of the Invention; X_2 is S or O; X_3 is a bond or C_{1-4}alkylene; and Q is a halo group, preferably Br or Cl. Compounds of Formula I are prepared by reacting a compound of formula 10 with a compound of formula 11 or a compound of formula 12 with a compound of formula 13 in the presence of a suitable solvent (e.g., cyanomethyl, ethanol or the like). The reaction is carried out in the temperature range of about 10 to about 80°C and takes up to about 24 hours to complete.

[0075] Compounds of Formula I can be prepared by proceeding as in reaction scheme 5:

Reactions Scheme 5



[0076] in which p, R^{13}, R^{14}, R^{15} and R^{16} are as defined for Formula I in the Summary of the Invention; X_2 is S or O; and X_3 is a bond or C_{1-4}alkylene. Compounds of Formula I are prepared by reacting a compound of formula 14 with a compound of formula 11 in the presence of a suitable solvent (e.g., DCM, THF or the like) and a suitable activating reagent (e.g., triphenylphosphine, diethylazodicarboxylate or the like). The reaction is carried out in the temperature range of about 0 to about 50°C and takes up to about 24 hours to complete.

[0077] Detailed reaction conditions are described in the examples, *infra*.

Additional Processes for Making Compounds of the Invention

[0078] A compound of the invention can be prepared as a pharmaceutically acceptable acid addition salt by reacting the free base form of the compound with a pharmaceutically acceptable inorganic or organic acid. Alternatively, a pharmaceutically acceptable base addition salt of a compound of the invention can be prepared by reacting the free acid form of the compound with a pharmaceutically acceptable inorganic or organic base. Alternatively, the salt forms of the compounds of the invention can be prepared using salts of the starting materials or intermediates.

[0079] The free acid or free base forms of the compounds of the invention can be prepared from the corresponding base addition salt or acid addition salt from, respectively. For example a compound of the invention in an acid addition salt form can be converted to the corresponding free base by treating with a suitable base (e.g., ammonium hydroxide solution, sodium hydroxide, and the like). A compound of the invention in a base addition

salt form can be converted to the corresponding free acid by treating with a suitable acid (e.g., hydrochloric acid, etc.).

[0080] Compounds of the invention in unoxidized form can be prepared from N-oxides of compounds of the invention by treating with a reducing agent (e.g., sulfur, sulfur dioxide, triphenyl phosphine, lithium borohydride, sodium borohydride, phosphorus trichloride, tribromide, or the like) in a suitable inert organic solvent (e.g. acetonitrile, ethanol, aqueous dioxane, or the like) at 0 to 80°C.

[0081] Prodrug derivatives of the compounds of the invention can be prepared by methods known to those of ordinary skill in the art (e.g., for further details see Saulnier et al., (1994), Bioorganic and Medicinal Chemistry Letters, Vol. 4, p. 1985). For example, appropriate prodrugs can be prepared by reacting a non-derivatized compound of the invention with a suitable carbamylating agent (e.g., 1,1-acyloxyalkylcarbanochloridate, para-nitrophenyl carbonate, or the like).

[0082] Protected derivatives of the compounds of the invention can be made by means known to those of ordinary skill in the art. A detailed description of techniques applicable to the creation of protecting groups and their removal can be found in T. W. Greene, "Protecting Groups in Organic Chemistry", 3rd edition, John Wiley and Sons, Inc., 1999.

[0083] Compounds of the present invention can be conveniently prepared, or formed during the process of the invention, as solvates (e.g., hydrates). Hydrates of compounds of the present invention can be conveniently prepared by recrystallization from an aqueous/organic solvent mixture, using organic solvents such as dioxin, tetrahydrofuran or methanol.

[0084] Compounds of the invention can be prepared as their individual stereoisomers by reacting a racemic mixture of the compound with an optically active resolving agent to form a pair of diastereoisomeric compounds, separating the diastereomers and recovering the optically pure enantiomers. While resolution of enantiomers can be carried out using covalent diastereomeric derivatives of the compounds of the invention, dissociable complexes are preferred (e.g., crystalline diastereomeric salts). Diastereomers have distinct physical properties (e.g., melting points, boiling points, solubilities, reactivity, etc.) and can be readily separated by taking advantage of these dissimilarities. The

diastereomers can be separated by chromatography, or preferably, by separation/resolution techniques based upon differences in solubility. The optically pure enantiomer is then recovered, along with the resolving agent, by any practical means that would not result in racemization. A more detailed description of the techniques applicable to the resolution of stereoisomers of compounds from their racemic mixture can be found in Jean Jacques, Andre Collet, Samuel H. Wilen, "Enantiomers, Racemates and Resolutions", John Wiley And Sons, Inc., 1981.

[0085] In summary, the compounds of Formula I can be made by a process, which involves:

[0086] (a) that of reaction scheme 1a, 1b, 2, 3, 4a, 4b or 5; and

[0087] (b) optionally converting a compound of the invention into a pharmaceutically acceptable salt;

[0088] (c) optionally converting a salt form of a compound of the invention to a non-salt form;

[0089] (d) optionally converting an unoxidized form of a compound of the invention into a pharmaceutically acceptable N-oxide;

[0090] (e) optionally converting an N-oxide form of a compound of the invention to its unoxidized form;

[0091] (f) optionally resolving an individual isomer of a compound of the invention from a mixture of isomers;

[0092] (g) optionally converting a non-derivatized compound of the invention into a pharmaceutically acceptable prodrug derivative; and

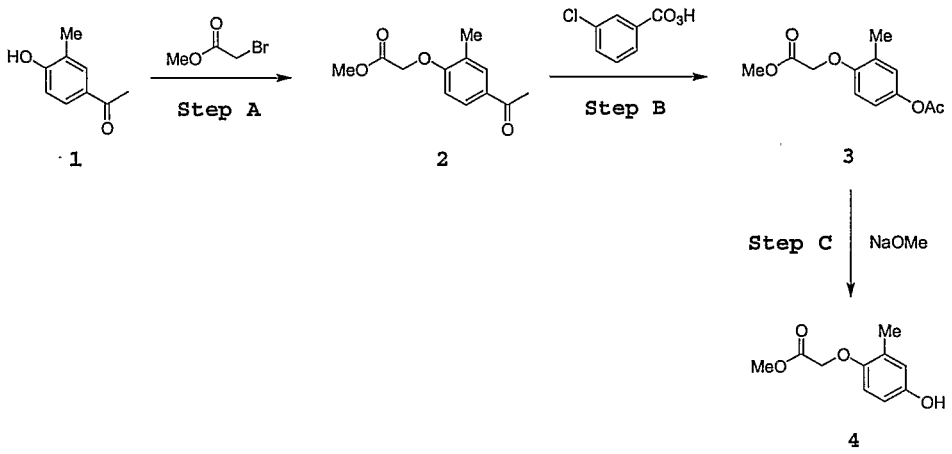
[0093] (h) optionally converting a prodrug derivative of a compound of the invention to its non-derivatized form.

[0094] Insofar as the production of the starting materials is not particularly described, the compounds are known or can be prepared analogously to methods known in the art or as disclosed in the Examples hereinafter.

[0095] One of skill in the art will appreciate that the above transformations are only representative of methods for preparation of the compounds of the present invention, and that other well known methods can similarly be used.

Examples

[0096] The present invention is further exemplified, but not limited, by the following intermediates and examples that illustrate the preparation of compounds of Formula I according to the invention.



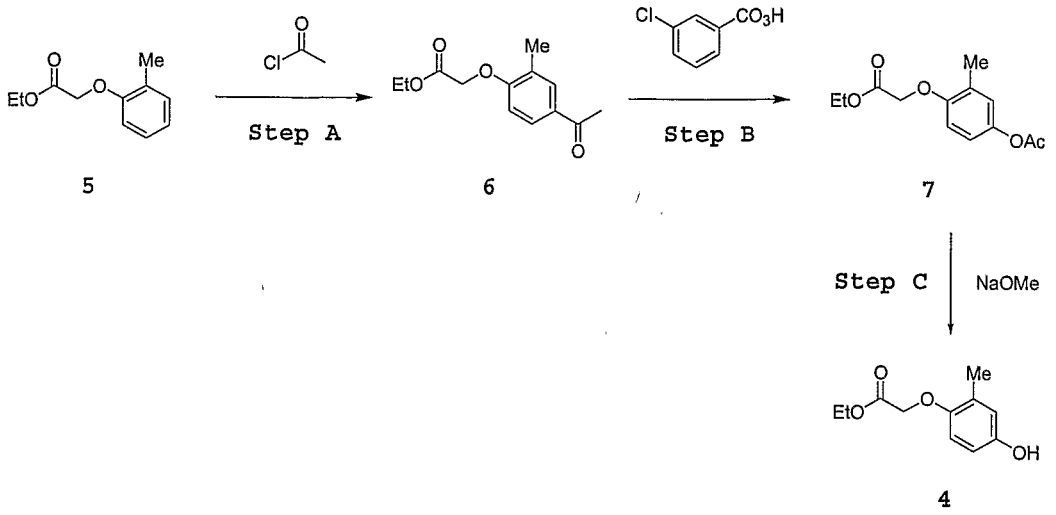
[0097] **Intermediate 4.** (4-Hydroxy-2-methyl-phenoxy)-acetic acid methyl ester.

[0098] **Step A:** 4'-Hydroxy-3'-methylacetophenone 1 (25 g, 166.4 mmol) and methyl-bromoacetate (25.5 g, 166.4 mmol) was dissolved in MeCN (600 mL). Cs_2CO_3 (117.8 g, 332.9 mmol) was added and the mixture was stirred overnight at rt. After insoluble salts were filtered and washed with MeCN, the solvent was removed and the remainder was taken up in EtOAc and washed subsequently with 1 M HCl (3x500 mL) and H_2O (2x500 mL). The organic layer was dried ($MgSO_4$), filtered and concentrated to afford 2 (35.9 g, 161.4 mmol, 97%) as a white solid.

[0099] **Step B:** (4-Acetyl-2-methyl-phenoxy)-acetic acid methyl ester 2 (33 g, 151.3 mmol), 77% mCPBA (54.9 g, 264.8 mmol) and p-TsOH (2.9 g, 15.1 mmol) in DCM (650 mL) were heated under reflux for 48 h. The reaction mixture was then washed with 1 M KI (2x500 mL) and $NaHSO_3$ (2x500 mL). The organic layer was dried ($MgSO_4$), filtered and concentrated to afford 3 (28.8 g, 121.0 mmol, 80%) as a brown syrup.

[00100] **Step C:** A solution of (4-acetoxy-2-methyl-phenoxy)-acetic acid methyl ester **3** (25 g, 105.0 mmol) in dry MeOH (400 mL) was combined with a 0.5 M solution of NaOMe in MeOH (210 mL, 105.0 mmol)and stirred for 1 h at rt. The solution was

neutralized with 1 M HCl and washed with H_2O (2x500 mL). The organic layer was dried ($MgSO_4$), filtered and concentrated to afford **4** (17.5 g, 89.3 mmol, 85%) as a brown solid: ^{1}H-NMR (400MHz, CD_3OD) δ = 6.65-6.51 (m, 3H), 4.60 (s, 2H), 3.75 (s, 3H), 2.19 (s, 3H). MS calcd. for $C_{10}H_{13}O_4$ ($M+H^+$) 197.1, found 197.2.



5 6 7 4

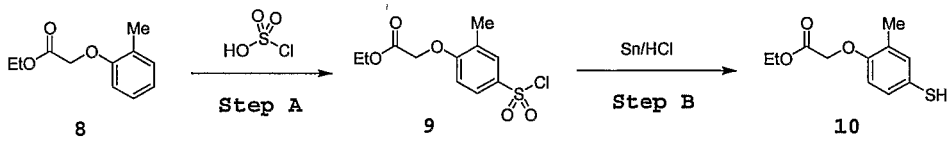
[00101] **Intermediate 4** (alternative route). (4-Hydroxy-2-methyl-phenoxy)-acetic acid methyl ester.

[00102] **Step A:** (2-Methylphenoxy)acetic acid ethyl ester 5 (66.03 g, 340 mmol) was dissolved in dichloroethane (400 mL). Aluminum chloride (100.02 g, 750 mmol, 2.2 equiv.) was added and the light-brown mixture was stirred for 10 minutes at room temperature until homogenous. Acetyl chloride (35 mL, 493 mmol, 1.45 equiv.) was added dropwise using an addition funnel. The rate of addition was adjusted to maintain a relatively slow emission of hydrogen chloride gas. The resulting dark brown solution was allowed to cool off to room temperature, then was poured over 300 g of crushed ice. The mixture was diluted with 300 mL dichloromethane and washed successively with water, saturated $NaHCO_3$ solution, water, saturated NH_4Cl solution, and brine. The organic layer was dried over Na_2SO_4, filtered and concentrated to afford 6 (76.54 g, 324 mmol, 95%) as a brown oil that solidified as a crystalline mass. ^{1}H-NMR (400MHz, $CDCl_3$) δ = 7.79 (d, J = 2.0 Hz, 1H), 7.77 (dd, J = 2.0, 8.4 Hz, 1H), 6.69 (d, J = 8.4 Hz, 1H), 4.71 (s, 2H), 4.26 (q, J = 7.2 Hz, 2H), 2.54 (s, 3H), 2.32 (s, 2H), 1.29 (t, J = 7.2 Hz, 3H).

[00103] **Step B:** (4-Acetyl-2-methyl-phenoxy)-acetic acid ethyl ester 6 (76.54 g, 324 mmol), 77% mCPBA (100.31 g, 407 mmol, 1.26 equiv.) and p-TsOH (13 g, 68 mmol,

21 mol%) in dichloroethane (450 mL) were heated to 50°C for 30 h. The reaction mixture was then washed with 1 M KI (2x500 mL) and $NaHSO_3$ (2x500 mL). The organic layer was dried ($MgSO_4$), filtered and concentrated to afford 7 as a brown syrup.

[00104] **Step C:** A solution of (4-acetoxy-2-methyl-phenoxy)-acetic acid ethyl ester 7 (from step B above) in dry MeOH (400 mL) was combined with a 0.5 M solution of NaOMe in MeOH (650 mL, 325 mmol)and stirred for 2 h at rt. The solution was neutralized with 1 M HCl and washed with H_2O (2x500 mL). The organic layer was dried (Na_2SO_4), filtered and concentrated to afford **4** (21.7 g, 111 mmol, 34%, two steps) as a light-brown solid: ^{1}H-NMR (400MHz, $CDCl_3$) δ = 6.58 (d, J = 2.8 Hz, 1H), 6.54 (d, J = 8.4 Hz), 6.50 (dd, J = 2.8, 8.4 Hz, 1H), 4.7 (br. s, 1H), 4.54 (s, 2H), 3.73 (s, 3H), 2.17 (s, 3H). MS calcd. for $C_{10}H_{13}O_4$ ($M+H^+$) 197.1, found 197.4.

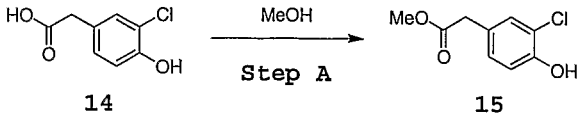


[00105] **Intermediate 10.** (4-Mercapto-2-methyl-phenoxy)-acetic acid ethyl ester.

[00106] **Step A:** A 500 mL three-necked round bottom flasked was charged with chlorosulfonic acid (25 mL, 373.9 mmol), flushed with nitrogen and cooled to 0 °C. Under nitrogen and vigorous stirring, ethyl (2-methylphenoxy) acetate 8 (40 g, 206.2 mmol) was added dropwise. The mixture was stirred at for 90 min at 0 °C, then poured on ice-water (200 mL). After the mixture was stirred for an additional 45 min at rt, the white precipitate was filtered, washed with ice-water and dried in vacuo to afford 9 (28.4 g, 97.0 mmol, 47%) as a white solid.

[00107] Step B: (4-Chlorosulfonyl-2-methyl-phenoxy)-acetic acid ethyl ester 9 (25 g, 85.4 mmol) and tin (50.8 g, 427 mmol) were suspended in EtOH and cooled to 0 °C. After a solution of 4 N HCl in dioxane (107 mL, 427 mmol) was added dropwise, the resulting mixture was heated to reflux for 3 h. Then the mixture was concentrated in vacuo, the remainder taken up in chloroform and filtered. The filtrate was concentrated in vacuo to a yellow oil, which was purified by chromatography (silica, Hex/EtOAc gradient) to afford 10 (15 g, 66.4 mmol, 78%) as a colourless oil: ^{1}H-NMR (400MHz, $CDCl_3$) δ = 7.14 (m, 1H),

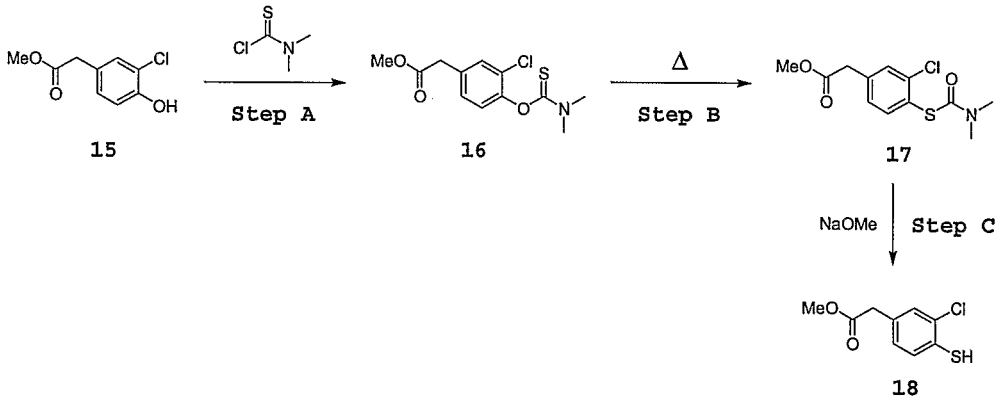
7.07-7.10 (m, 1H), 6.59 (m, 1H), 4.60 (s, 2H), 4.25 (q, J = 7.1 Hz, 2H), 3.33 (s, 1H), 2.24 (s, 3H), 1.29 (t, J = 7.1 Hz, 3H). MS calcd. for $C_{11}H_{14}O_3S$ ($M+H^+$) 227.1, found 227.4.



14 15

[00108] **Intermediate 15.** (3-Chloro-4-hydroxy-phenyl)-acetic acid methyl ester.

[00109] **Step A:** 3-Chloro-4-hydroxy-phenyl)-acetic acid 14 (20 g, 107 mmol) was dissolved in MeOH (250 mL) containing catalytic amounts of conc. H_2SO_4 (2.5 mL). The solution was heated to reflux overnight. The solvent was evaporated, the remainder was dissolved in DCM and washed with H_2O (3x200 mL). The organic layer was dried ($MgSO_4$), filtered and concentrated to afford 15 (21.5 g, 107 mmol, 100%) as a light yellow solid: ^{1}H-NMR (400MHz, CD_3OD) δ = 7.21 (d, J = 2.1 Hz, 1H), 7.01 (dd, J = 2.1 Hz, J = 8.3, 1H), 6.84 (d, J = 8.3 Hz, 1H), 3.67 (s, 3H), 3.54 (s, 2H). MS calcd. for $C_9H_{10}ClO_3$ ($M+H^+$) 201.0, found 201.2.



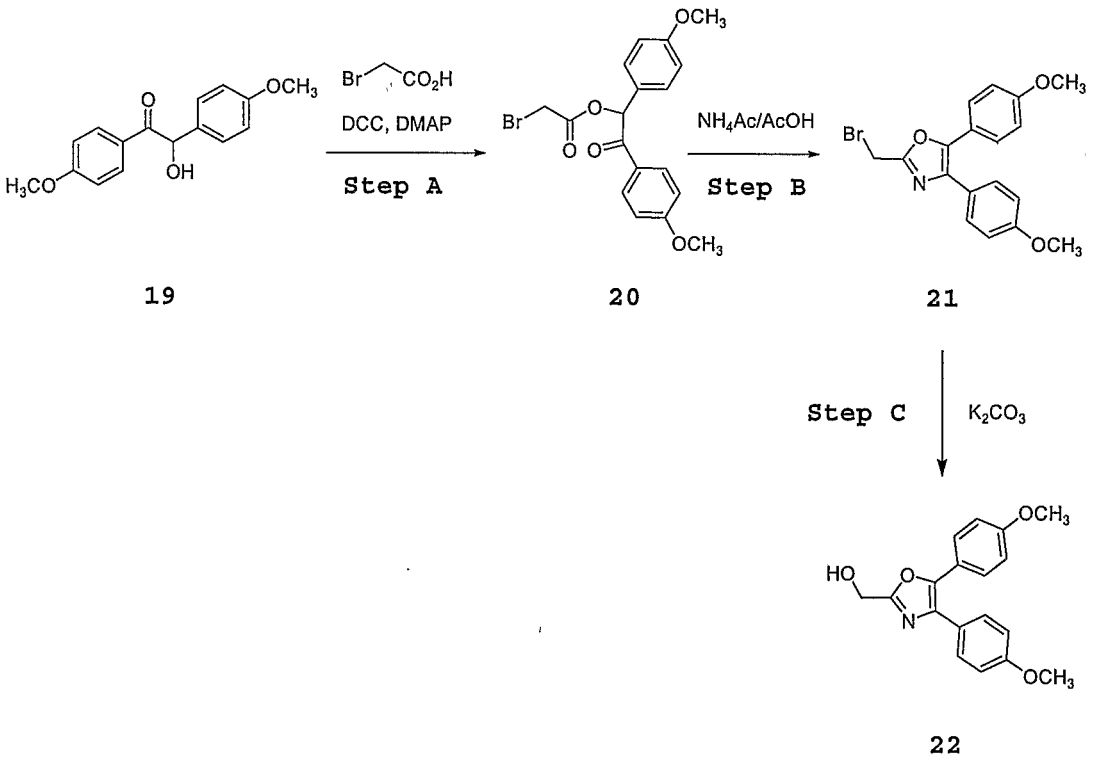
15 16 17 18

[00110] **Intermediate 18.** (3-Chloro-4-mercapto-phenyl)-acetic acid methyl ester.

[00111] **Step A:** 3-(Chloro-4-hydroxy-phenyl)-acetic acid methyl ester 15 (4.1 g, 21.4 mmol), dimethyl thiocarbamoylchloride (3.2 g, 25.6 mmol), Et_3N (5.9 mL, 42.8 mmol) and DMAP (261 mg, 2.14 mmol) were dissolved in dry dioxane (30 mL) and heated to reflux for 16 h under nitrogen. The reaction mixture was cooled to rt, diluted with EtOAc and washed with H_2O (3x50 mL). The organic layer was dried ($MgSO_4$), filtered and concentrated to afford 16 (5.2 g, 18.1 mmol, 85%) as a colourless oil.

[00112] **Step B:** (3-Chloro-4-dimethylthiocarbamoyloxy-phenyl)-acetic acid methyl ester 16 (5.2 g, 18.1 mmol) was transferred to a 250 mL three-necked round bottom flask equipped with a thermometer. Tetradecane (45 mL) was added and the mixture was heated to reflux (250 °C) overnight. After cooling to rt the solvent was decanted, the remaining oil was washed several times with hexanes and purified by chromatography (silica, Hex/EtOAc gradient) to afford 17 (3.1 g, 10.8 mmol, 60%) as a brown oil.

[00113] **Step C:** (3-Chloro-4-dimethylcarbamoylsulfanyl-phenyl)-acetic acid methyl ester 17 (3.1 g, 10.8 mmol) was dissolved in 0.5 M NaOMe solution. The mixture was heated to reflux for 4h, then acidified with 1 M HCl. The organic solvent was evaporated, the remainder was extracted into EtOAc (50 mL) and washed with H_2O (2x50 mL). The organic layer was dried ($MgSO_4$), filtered, concentrated and purified (silica, hexanes/EtOAc gradient) to afford 18 (1.5 g, 6.9 mmol, 64%) as a pale yellow oil: ^{1}H-NMR (400MHz, $CDCl_3$) δ = 7.30-7.26 (m, 2H), 7.06-7.03 (m, 1H) 3.87 (s, 1H), 3.69 (s, 3H), 3.55 (s, 2H). MS calcd. for $C_9H_{10}ClO_2S$ ($M+H^+$) 217.0, found 217.3.



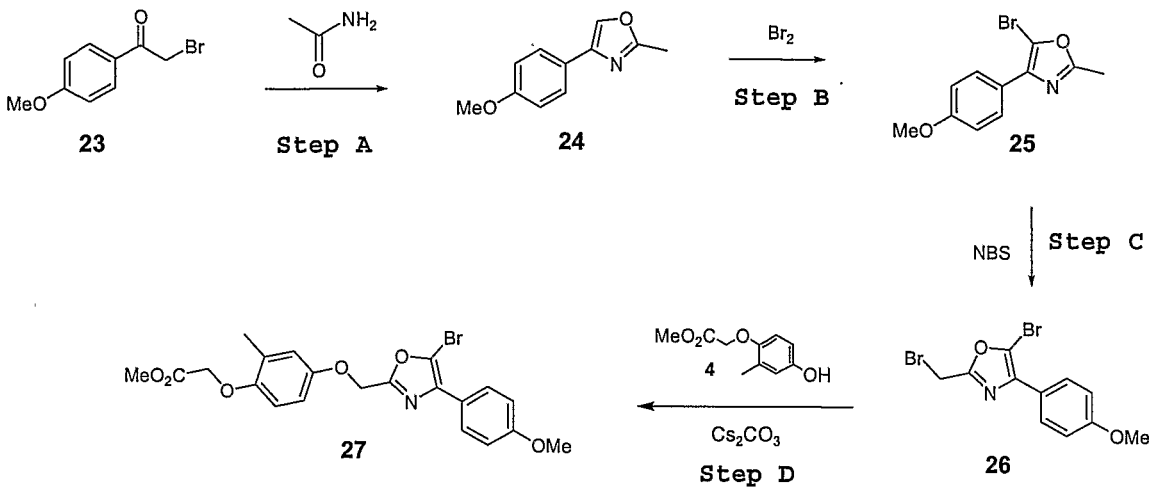
19 20 21 22

[00114] Intermediate 22. **2-Hydroxymethyl-4,5-bis-(4-methoxy-phenyl)-oxazole.**

[00115] **Step A:** A mixture of anisoin **19** (1.00 g, 3.49 mmol), bromoacetic acid (0.53 g, 3.84 mmol), 1,3-dicyclohexycarbodiimide (0.88 g, 4.23 mmol), DMAP (21.5 mg, 0.17 mmol) and CH_2Cl_2 (25 mL) was stirred at room temperature under an atmosphere of N_2. After 17 h, the mixture was filtered and concentrated to leave an oil, which was purified by flash chromatography. Elution with a mixtute of hexane and ethyl acetate (10:1) afforded bromo-acetic acid 1,2-bis-(4-methoxy-phenyl)-2-oxo-ethyl ester **20** (1.02 g, 2.59 mmol, 74%) as a slightly yellow solid: ^{1}H-NMR (400MHz, $CDCl_3$) δ = 7.89 (d, J = 8.4 Hz, 2H), 7.37 (d, J = 8.8 Hz, 2H), 6.90-6.84 (m, 5H), 4.03-3.96 (m, 2H), 3.82 (s, 3H), 3.77 (s, 3H).

[00116] **Step B:** A solution of bromo-acetic acid 1,2-bis-(4-methoxy-phenyl)-2-oxo-ethyl ester **20** (393.0 mg, 1.00 mmol) and NH_4OAc (384.0 mg, 5.0 mmol) in AcOH (6 mL) was heated at reflux for 1.5 h. Then the mixture was poured onto H_2O and extracted with CH_2Cl_2 to leave an oil. Flash chromatography using a mixture of hexane and ethyl acetate (10:1) as eluent afforded **21** (283.0 mg, 0.76 mmol, 76%) as a white solid: ^{1}H-NMR (400MHz, $CDCl_3$) δ = 7.58-7.50 (m, 4H), 6.90 (d, J = 8.0 Hz, 4H), 5.22 (s, 2H), 3.83 (s, 6H).

[00117] **Step C:** A mixture of intermediate 21 (75.0 mg, 0.20 mmol), potassium carbonate (110.4 mg, 0.80 mmol) and CH_3CN (5 mL) was heated at reflux for 2 h. The mixture was poured onto H_2O, EtOAc (50 mL) was added. The organic layer was dried and filtered. The solvent was removed in vacuo to afford 2-hydroxymethyl-4,5-bis-(4-methoxy-phenyl)-oxazole 22 (50.0 mg, 0.16 mmol, 80%) as a white solid. %): ^{1}H-NMR (400MHz, $CDCl_3$) δ = 7.49 (d, J = 8.8 Hz, 2H), 7.45 (d, J = 8.8 Hz, 2H), 6.84 (d, J = 5.2 Hz, 1H), 6.82 (d, J = 5.2 Hz, 2H), 4.72 (s, 2H), 3.77 (s, 6H). MS calcd. for $C_{18}H_{18}NO_4$ ($M+H^+$) 312.12, found 312.10.



[00118] **Intermediate 27:** {4-[5-bromo-4-(4-methoxy-phenyl)-oxazol-2-ylmethoxy]-2-methyl-phenoxy}-acetic acid methyl ester.

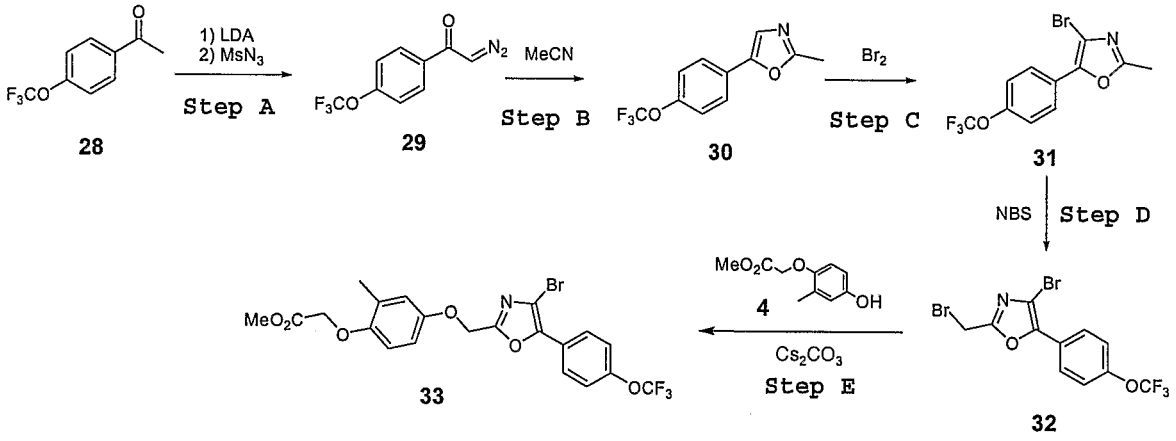
[00119] **Step A:** 2-Bromo-4'-methoxyacetophenone 23 (20.0 g, 87.3 mmol) and acetamide (15.5 g, 262.0 mmol) were heated to 150 ^{0}C for 2 hours. The mixture was cooled to rt, diluted with EtOAc and washed with saturated Na_2CO_3 and brine. The organic layer was dried ($MgSO_4$), filtered and concentrated to give crude product, which was purified by silica gel chromatography (EtOAc/hexane gradient) to give 4-(4-methoxy-phenyl)-2-methyl-oxazole 24 (10.3 g, 62 %) as a white solid: ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 7.65 (s, 1H), 7.56 (d, J=8.8 Hz, 2H), 6.85 (d, J=8.8 Hz, 2H), 3.76 (s, 3H), 2.44 (s, 3H). MS calcd. for $C_{11}H_{12}NO_2$ ($M+H^+$) 190.2, found 190.1.

[00120] Step B: 4-(4-Methoxy-phenyl)-2-methyl-oxazole 24 (212 mg, 1.12 mmol) was dissolved in carbon tetrachloride (10 mL), then bromine (63.3 µL, 1.23 mmol) was added and the mixture was stirred at rt for 30 min. The solid was collected by filtration, then dissolved in EtOAc (50 mL) and washed with saturated $NaHCO_3$ (20 mL) and brine (10 mL). The organic layer was dried ($MgSO_4$), filtered and concentrated to give 5-bromo-4-(4-methoxy-phenyl)-2-methyl-oxazole 25 as a white solid (240 mg, 80%): ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 7.78 (d, J=8.8 Hz, 2H), 6.88 (d, J=8.8 Hz, 2H), 3.77 (s, 3H), 2.43 (s, 3H). MS calcd. for $C_{11}H_{11}BrNO_2$ ($M+H^+$) 269.1, found 269.0.

[00121] **Step C:** N-bromosuccinimide (4.89 g, 27.5 mmol) was added to a solution of 5-bromo-4-(4-methoxy-phenyl)-2-methyl-oxazole 25 (6.7 g, 25.0 mmol) in carbon tetrachloride (250 mL). The above solution was stirred at room temperature for 15 hours.

Then the mixture was washed with saturated Na_2CO_3 and brine. The organic layer was dried ($MgSO_4$), filtered and concentrated to give crude product, which was purified by silic gel chromatography with hexane/ether (gradient) to give 5-bromo-2-bromomethyl-4-(4-methoxy-phenyl)-oxazole 26 (3.3 g, 38 %) as a white solid: ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 7.87 (d, J= 8.8 Hz, 2H), 6.97 (d, J=8.8 Hz, 2H), 4.46 (s, 2H), 3.85 (s, 3H). MS calcd. for $C_{11}H_{10}Br_2NO_2$ ($M+H^+$) 348.0, found 347.9.

[00122] **Step D:** A mixture of 5-bromo-2-bromomethyl-4-(4-methoxy-phenyl)-oxazole (2.75 g, 7.92 mmol) 26, (4-hydroxy-2-methyl-phenoxy)-acetic acid methyl ester 4 (1.24 g, 6.34 mmol) and Cs_2CO_3 (3.01 g, 9.48 mmol) in MeCN (200mL) was stirred at rt for 1 h. The mixture was filtered, then concentrated to give crude product, which was purified by silic gel chromatography with EtOAc/hexane (gradient) to give {4-[5-bromo-4-(4-methoxy-phenyl)-oxazol-2-ylmethoxy]-2-methyl-phenoxy}-acetic acid methyl ester 27 (2.51 g, 86 %) as a solid: ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 7.81 (d, J=9.8 Hz, 2H), 6.90 (d, J=9.8 Hz, 2H), 6.80 (d, J=3.2 Hz, 1H), 6.71 (m, 1H), 6.58 (m, 1H), 4.99 (s, 2H), 4.52 (s, 2H), 3.78 (s, 3H), 3.72 (s, 3H), 2.20 (s, 3H). MS calcd. for $C_{21}H_{21}BrNO_6$ ($M+H^+$) 463.3, found 463.0.



[00123] **Intermediate 33:** {4-[4-bromo-5-(4-trifluoromethoxy-phenyl)-oxazol-2-ylmethoxy]-2-methyl-phenoxy}-acetic acid methyl ester.

[00124] **Step A:** 1,1,1,3,3,3-hexamethyldisilazane (8.93 g, 55.35 mmol) was dissolved in dry THF (50 mL) in a flame dried three-necked flask, and cooled to 0°C. n-Butyl lithium (2.5 M in hexanes, 21.55 mL, 53.88 mmol) was added dropwise. After stirring the resulting solution for 10 min at 0°C, it was cooled to -78°C. 4'-(trifluoromethoxy)acetophenone 28 (10.0 g, 48.98 mmol) dissolved in dry THF (64 mL) was

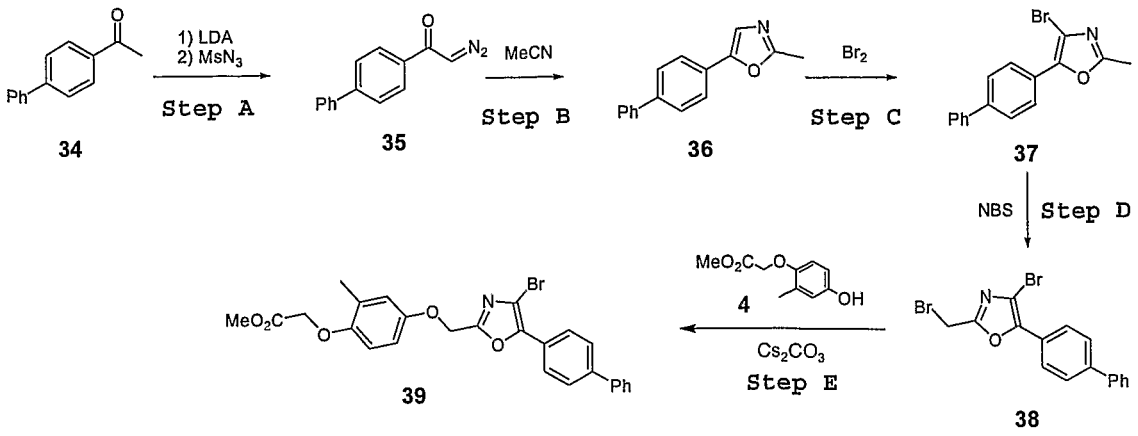
added dropwise over 30 min. The reaction was kept stirring for 45 min at -78°C. 2,2,2-trifluoroethyltrifluoroacetate (11.43 g, 58.78 mmol) was added rapidly. After 20 min, the reaction was poured into a separation funnel containing 200 mL of 5% HCl and extracted with 250 mL diethyl ether. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated. The residue was dissolved in acetonitril (50 mL), then water (0.88 mL, 48.98 mmol) and triethylamine (7.43 g, 73.47 mmol) were added. Freshly prepared methanesulfonyl azide (8.98 g, 73.47 mmol) in a solution of acetonitrile (16 mL) was added over 30 min at room temperature. [Methanesulfonyl azide was prepared from the following procedure: methanesulfonyl chloride (8.85 g, 73.47 mmol) was dissolved in acetone (50 mL). Sodium azide (7.56 g, 116.0 mmol) was then added over 30 min. The reaction was stirred for 1.5 h at rt, then it was filtered, and washed with acetone. The mixture was concentrated to give crude product.] The reaction was kept stirring for 1 h, then concentrated. The residue was diluted with diethyl ether (200 mL), washed with 10% NaOH three times, and then with brine. It was dried over $MgSO_4$, filtered and concentrated to give crude product, which was purified by silica gel chromatography (ether/hexane, gradient) to give 2-diazo-4'-trifluoromethoxyacetophenone (29) (7.93 g, 70 %) as a yellow solid: ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 7.82 (d, J=8.8 Hz, 2H), 7.29 (d, J=8.8 Hz, 2H), 5.89 (s, 1H). MS calcd. for $C_9H_6F_3N_2O_2$ (M^+) 230.0, found 203.0 ($M+H^+-N_2$).

[00125] **Step B:** Aluminum chloride (19.6 g, 146.78 mmol) was carefully added in portions into anhydrous acetonitrile (200 mL). 2-Diazo-4'-trifluoromethoxyacetophenone 29 (16.89 g, 73.39 mmol) dissolved in anhydrous acetonitrile (200 mL) was added by syringe dropwise over 30 min at rt with an outlet to release generated nitrogen. The reaction was stirred for 45 min, then it was poured into ditheyl ether (500 mL). The solution was carefully quenched with 0.2 N HCl. Then it was basified with 1 N NaOH to PH = 9-10. The organic layer was separated. The aqueous layer was extracted twice with diethyl ether. The combined organic layers were washed with water and brine, dried ($MgSO_4$), filtered, and concentrated to give crude product, which was purified by silica gel chromatography (ether/hexane gradient) to give 2-methyl-5-(4-trifluoromethoxy-phenyl)-oxazole 30 (14.0 g, 78 %) as an oil: ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 7.56 (d, J=8.8 Hz, 2H), 7.19 (d, J=8.8 Hz, 2H), 7.13 (s, 1H), 2.46 (s, 3H). MS calcd. for $C_{11}H_9F_3NO_2$ ($M+H^+$) 244.1, found 244.0.

[00126] **Step C:** 2-Methyl-5-(4-trifluoromethoxy-phenyl)-oxazole 30 (3.07 g, 12.62 mmol) was dissolved in chloroform (100 mL), then bromine (648.7 μL, 12.62 mmol) was added dropwise and the mixture was stirred at rt for 15 h. The solution was diluted with CH_2Cl_2 (100 mL) and washed with saturated $NaHCO_3$ (150 mL) and brine (130 mL). The organic layer was dried ($MgSO_4$), filtered and concentrated to give crude product, which was purified by silic gel chromatography with ether/hexane (gradient) to give 4-bromo-2-methyl-5-(4-trifluoromethoxy-phenyl)-oxazole 31 as an oil (2.0 g, 49.4%): ^{1}H-NMR (400 MHz, $CDCl_3$) δ =7.86 (d, 2H, J=8.6 Hz), 7.22 (d, 2H, J=8.6 Hz), 2.47 (s, 3H). MS calcd. for $C_{11}H_8BrF_3NO_2$ ($M+H^+$) 321.9, found 321.9.

[00127] **Step D:** N-bromosuccinimide (4.89 g, 27.5 mmol) was added to a solution of 4-bromo-2-methyl-5-(4-trifluoromethoxy-phenyl)-oxazole 31 (2.0 g, 6.25 mmol) in carbon tetrachloride (40 mL). The above solution was stirred at 75^{0}C for 20 h. The solution was diluted with CH_2Cl_2 (100 mL) and washed with saturated aqueous Na_2CO_3 and brine. The organic layer was dried ($MgSO_4$), filtered and concentrated to give crude product, which was purified by silic gel chromatography with hexane/ether (gradient) to give 4-bromo-2-bromomethyl-5-(4-trifluoromethoxy-phenyl)-oxazole 32 (1.64 g, 66.0 %) as a white solid: ^{1}H-NMR (400 MHz, $CDCl_3$) δ =7.91 (d, 2H, J=8.6 Hz), 7.25 (d, 2H, J=8.6 Hz), 4.41 (s, 3H). MS calcd. for $C_{11}H_7Br_2F_3NO_2$ ($M+H^+$) 399.9, found 399.8.

[00128] **Step E:** A mixture of 4-bromo-2-bromomethyl-5-(4-trifluoromethoxy-phenyl)-oxazole 32 (895 mg, 2.232 mmol), (4-hydroxy-2-methyl-phenoxy)-acetic acid methyl ester 4 (482 mg, 2.455 mmol) and Cs_2CO_3 (836 mg, 2.567 mmol) in MeCN (50mL) was stirred at rt for 3 h. The mixture was filtered, then concentrated to give crude product, which was purified by silic gel chromatography with EtOAc/hexane (gradient) to give {4-[4-bromo-5-(4-trifluoromethoxy-phenyl)-oxazol-2-ylmethoxy]-2-methyl-phenoxy}-acetic acid methyl ester 33 (926 mg, 80.0 %) as a solid: ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 7.89 (d, J=8.4 Hz, 2H), 7.23 (d, J=8.4 Hz, 2H), 6.79 (d, J=3.2 Hz, 1H), 6.70 (m, 1H), 6.59 (m, 1H), 5.03 (s, 2H), 4.53 (s, 2H), 3.72 (s, 3H), 3.72 (s, 3H), 2.21 (s, 3H). MS calcd. for $C_{21}H_{18}BrF_3NO_6$ ($M+H^+$) 516.0, found 516.9.



[00129] **Intermediate 39:** [4-(5-Biphenyl-4-yl-4-bromo-oxazol-2-ylmethoxy)-2-methyl-phenoxy]-acetic acid methyl ester.

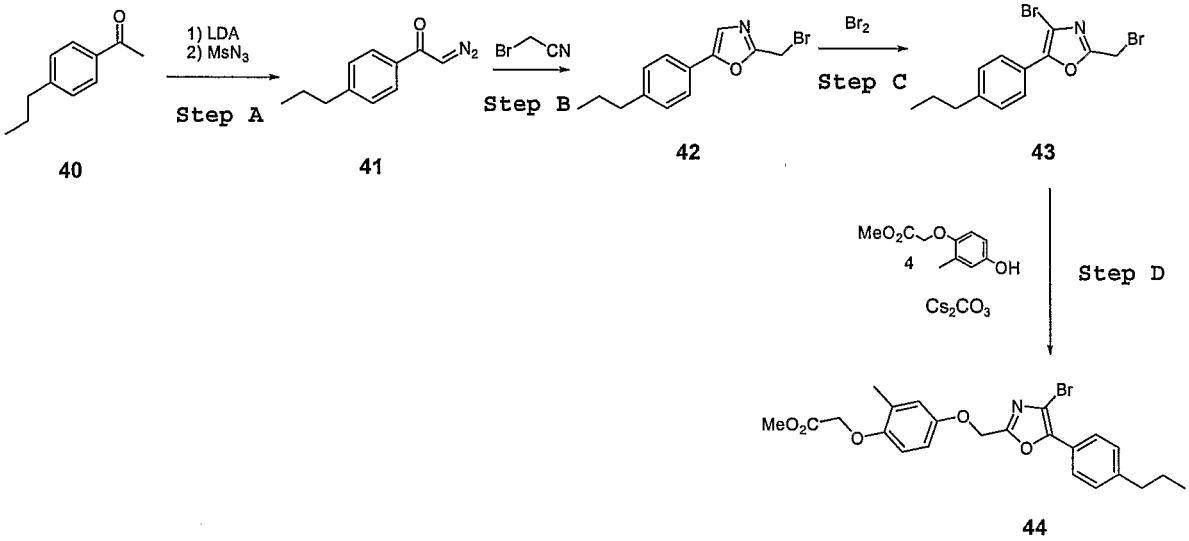
[00130] **Step A:** Following the procedure of Intermediate 33, step A, except substituting 4'-phenylacetophenone 34 for 4'-(trifluoromethoxy)acetophenone 28 in step A, 1-biphenyl-4-yl-2-diazo-ethanone 35 (7.20 g, 43%) was obtained as a yellow solid: ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 7.72 (d, J = 8.4 Hz, 2H), 7.55 (d, J = 8.4 Hz, 2H), 7.49 (d, J = 7.2 Hz, 2H), 7.35-7.24 (m, 3H), 5.81 (s, 1H). MS calcd. for $C_{14}H_{11}N_2O$ (M^+) 223.0, found 195.0 ($M+H^+-N_2$).

[00131] **Step B:** Following the procedure of Intermediate 33, step B, 5-biphenyl-4-yl-2-methyl-oxazole 36 (6.05 g, 80%) was obtained as a white solid: ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 7.70-7.61 (m, 6H), 7.48-7.36 (m, 3H), 7.25 (s, 1H), 2.58 (s, 3H). MS calcd. for $C_{16}H_{14}NO$ ($M+H^+$) 236.1, found 236.0.

[00132] **Step C:** Following the procedure of Intermediate 33, step C, 5-biphenyl-4-yl-4-bromo-2-methyl-oxazole 37 (1.45 g, 54%) was obtained as a light yellow solid: ^{1}H-NMR (400 MHz, $CDCl_3$) δ =7.80 (d, J = 8.8 Hz, 2H), 7.51 (d, J = 8.8 Hz, 2H), 7.46 (d, J = 8.4 Hz, 2H), 7.30-7.17 (m, 3H), 2.36 (s, 3H). MS calcd. for $C_{16}H_{13}BrNO$ ($M+H^+$) 314.0, found 313.9.

[00133] **Step D:** Following the procedure of Intermediate 33, step D, 5-biphenyl-4-yl-4-bromo-2-bromomethyl-oxazole 38 (1.36 g, 79%) was obtained as a light yellow solid: ^{1}H-NMR (400 MHz, $CDCl_3$) δ =7.95 (d, J=8.4 Hz, 2H), 7.64 (d, J=8.8 Hz, 2H), 7.57 (d, J=7.2 Hz, 2H), 7.42-7.32(m, 3H), 4.43 (s, 3H). MS calcd. for $C_{16}H_{12}Br_2NO$ ($M+H^+$) 391.9, found 391.9.

[00134] **Step E**: Following the procedure of Intermediate 33, step E, [4-(5-Biphenyl-4-yl-4-bromo-oxazol-2-ylmethoxy)-2-methyl-phenoxy]-acetic acid methyl ester 39 (492 mg, 36%) was obtained as a light yellow solid: ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 8.21 (d, J = 8.4 Hz, 2H), 7.89 (d, J = 8.4 Hz, 2H), 7.83 (d, J = 8.0 Hz, 2H), 7.68-7.56 (m, 3H), 7.08 (d, J = 3.2 Hz, 1H), 7.00-6.85 (m, 2H), 5.30 (s, 2H), 4.80 (s, 2H), 3.99 (s, 3H), 2.48 (s, 3H). MS calcd. for $C_{26}H_{23}BrNO_5$ ($M+H^+$) 508.1, found 508.0.



[00135] **Intermediate 44:** {4-[4-Bromo-5-(4-propyl-phenyl)-oxazol-2-ylmethoxy]-2-methyl-phenoxy}-acetic acid methyl ester.

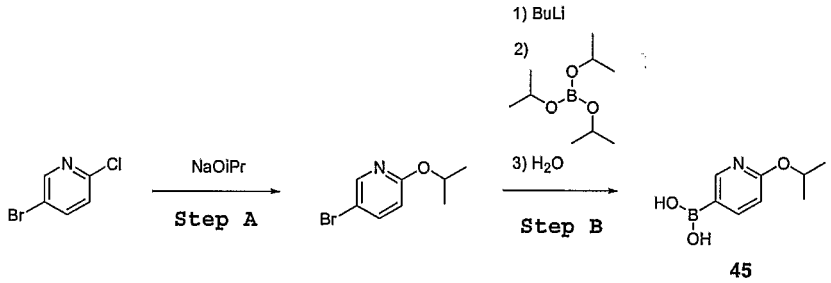
[00136] **Step A:** Following the procedure of Intermediate 33, step A, except substituting 4'-propylacetophenone 40 for 4'-(trifluoromethoxy)acetophenone 28 in step A, 2-diazo-4'-propylacetophenone 41 (16.2 g, 93 %) was obtained as a yellow solid: ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 7.62 (d, J=8.4 Hz, 2H), 7.19 (d, J=8.4 Hz, 2H), 5.81 (s, 1H), 2.56 (t, J = 7.8 Hz, 2 H), 1.62-1.54 (m, 2H), 0.87 (t, J = 7.2 Hz, 3H). MS calcd. for $C_{11}H_{13}N_2O$ ($M+H^+$) 189.0, found 161.1($M-N_2+H^+$).

[00137] Step B: Following the procedure of Intermediate 33, step B, except substituting bromoacetonitrile for acetonitrile. 2-Bromomethyl-5-(4-propyl-phenyl)-oxazole 42 (5.3 g, 72 %) was obtained as a white solid: ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 7.34 (d, J=8.4 Hz, 2H), 7.04 (s, 1H), 7.02 (d, J=8.4 Hz, 2H), 4.44-4.30 (m, 2H), 2.38 (t, J = 7.6 Hz, 2H), 1.47-1.38 (m, 2H), 0.72 (t, J = 7.4 Hz, 3H). MS calcd. for $C_{13}H_{15}BrNO$ ($M+H^+$) 280.0, found 280.0.

[00138] Step C: Following the procedure of Intermediate 33, step C, 4-Bromo-2-bromomethyl-5-(4-propyl-phenyl)-oxazole 43 (2.7 g, 53 %) was obtained as a light yellow solid: ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 7.85 (d, J=8.4 Hz, 2H), 7.28 (d, J=8.0 Hz, 2H), 4.63-4.48 (m, 2H), 2.63 (t, J = 7.6 Hz, 2H), 1.71-1.62 (m, 2H), 0.96 (t, J = 7.4 Hz, 3H). MS calcd. for $C_{13}H_{14}Br_2NO$ ($M+H^+$) 357.9, found 357.9.

[00139] Step D: Following the procedure of Intermediate 33, step E, {4-[4-Bromo-5-(4-propyl-phenyl)-oxazol-2-ylmethoxy]-2-methyl-phenoxy}-acetic acid methyl ester 44 (1.4 g, 100 %) was obtained as a light yellow solid: ^{1}H-NMR (400 MHz, CD_3OD) δ = 7.71 (d, J=8.4 Hz, 2H), 7.19 (d, J=8.4 Hz, 2H), 6.78 (d, J = 2.8 Hz, 1H), 6.70-6.61 (m, 2H), 5.00 (s, 2H), 4.54 (s, 2H), 3.65 (s, 3H), 2.51 (t, J = 7.6 Hz, 2H), 1.60-1.51 (m, 2H), 0.84 (t, J = 7.2 Hz, 3H). MS calcd. for $C_{23}H_{25}BrNO_5$ ($M+H^+$) 474.1, found 474.0.

[00140] Intermediate 45: 2-Isopropoxy-5-pyridineboronic acid.

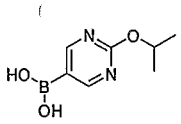


[00141] **Step A:** NaH (5.2 g, 130 mmol) was suspended in isopropanol (50 mL). The mixture was stirred for 30 min at 60°C. After the gas evolution ceased, 2-chloro-5-bromopyridine (10.0 g, 52 mmol) dissolved in isopropanol (100 mL) was added and the mixture was heated to reflux for 24 h. The solvent was removed in vacuo, and the remainder was taken up in H_2O and extracted with EtOAc. The organic layer was seperated and dried over $MgSO_4$, filtered and concentrated to afford 2-isopropoxy-5-bromo-pyridine (8.4 g, 39 mmol, 75%) as a light brown oil: ^{1}H-NMR (400MHz, $CDCl_3$) δ = 8.10 (d, J = 2.5 Hz, 1H), 7.54 (dd, J = 2.5 Hz, J = 8.8 Hz, 1H), 6.52 (d, J = 8.8 Hz, 1H), 5.17 (m, 1H), 1.26 (d, J = 6.2 Hz, 6H). MS calcd. for $C_8H_{11}BrNO$ ($M+H^+$) 216.0, found 215.9.

[00142] **Step B:** 2-Isopropoxy-5-bromo-pyridine (0.65 g, 3 mmol) was dissolved in dry ether (10 mL) and cooled to -78°C under argon. Butyl lithium (1.6 M in hexane, 2.81

mL, 4.5 mmol) was added dropwise and the mixture was stirred at -78°C for 2h. Then triisopropyl borate (1.72 mL, 7.5 mmol) was added quickly and the mixture was stirred for another 2 h at -78°C. The mixture was allowed to warm to rt, quenched with H_2O (20 mL) and stirred overnight at rt. The ether was removed in vacuo, the aqueous layer was adjusted to pH 10 (with 2 M NaOH) and washed with ether. Then the aqueous layer was adjusted to pH 3 (with 48% aq. HBr) and extracted with EtOAc three times. The organic layer was seperated and dried over $MgSO_4$, filtered and concentrated to afford 2-isopropoxy-5-pyridineboronic acid **45** (0.42 g, 2.3 mmol, 77%) as a colourless glass: MS calcd. for $C_8H_{13}BNO_3$ ($M+H^+$) 182.1, found 182.1.

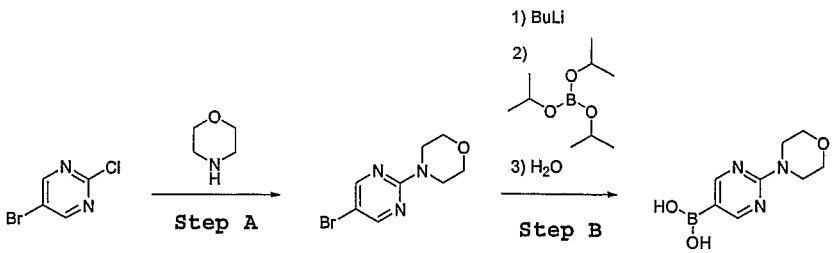
[00143] **Intermediate 46.** 2-Isopropoxy-5-pyrimidineboronic acid.



46

[00144] Following the procedure of Intermediate 45, except substituting 2-chloro-5-bromopyrimidine for 2-chloro-5-bromopyridine in Step A, the title compound was prepared as a white solid (0.15 g, 0.8 mmol, 27%): MS calcd. for $C_7H_{12}BN_2O_3$ ($M+H^+$) 183.1, found 183.1.

[00145] **Intermediate 47:** 2-Morpholino-5-pyrimidineboronic acid.

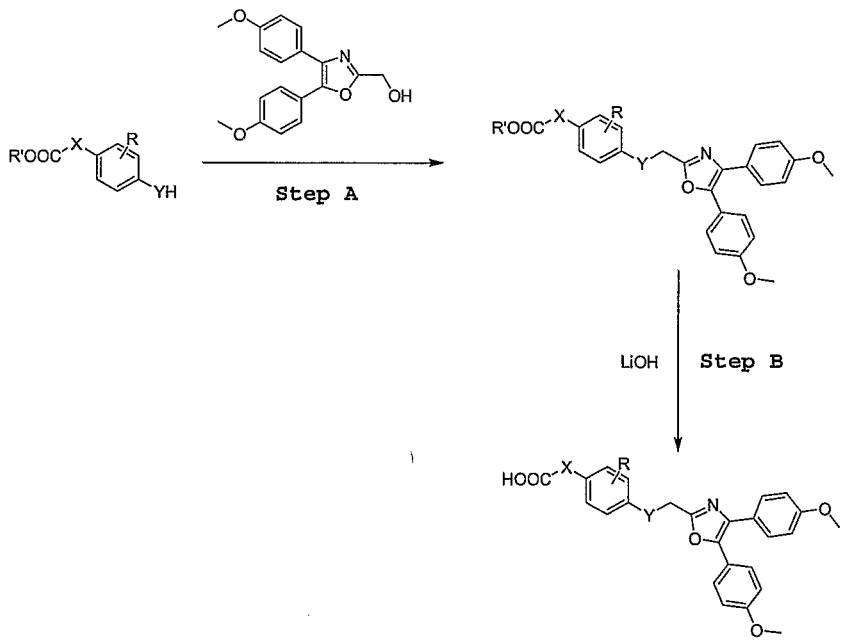


47

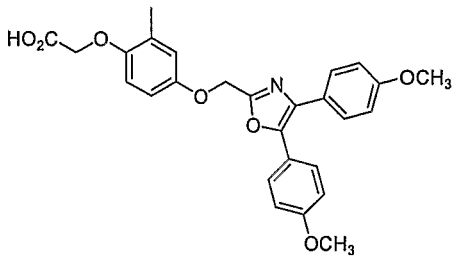
[00146] **Step A:** Morpholine (5.4 mL, 62.4 mmol) was dissolved in MeCN (250 mL). K_2CO_3 (8.6 g, 62.4 mmol) was added and the mixture was stirred at rt for 1h. Then 2-chloro-5-bromo-pyrimidine (10.0 g, 52 mmol) was added and the mixture was heated to reflux for 5 h. The solvent was partially removed in vacuo and the remainder was taken up in

H_2O and extracted with EtOAc. The organic layer was seperated and dried over $MgSO_4$, filtered and concentrated to afford 2-isopropoxy-5-bromo-pyrimidine (10.1 g, 41.1 mmol, 80%) as a light brown oil: ^{1}H-NMR (400MHz, $CDCl_3$) δ = 8.24 (s, 2H), 3.69 (m, 8H). MS calcd. for $C_8H_{11}BrN_3O$ ($M+H^+$) 244.0, found 243.9.

[00147] **Step B:** Following the procedure of Intermediate 45 Step B, except substituting 2-isopropoxy-5-bromo-pyrimidine for 2-isopropoxy-5-bromo-pyridine, the title compound was prepared as a white solid (0.38 g, 1.8 mmol, 60%): MS calcd. for $C_8H_{13}BN_3O_3$ ($M+H^+$) 210.1, found 210.1.

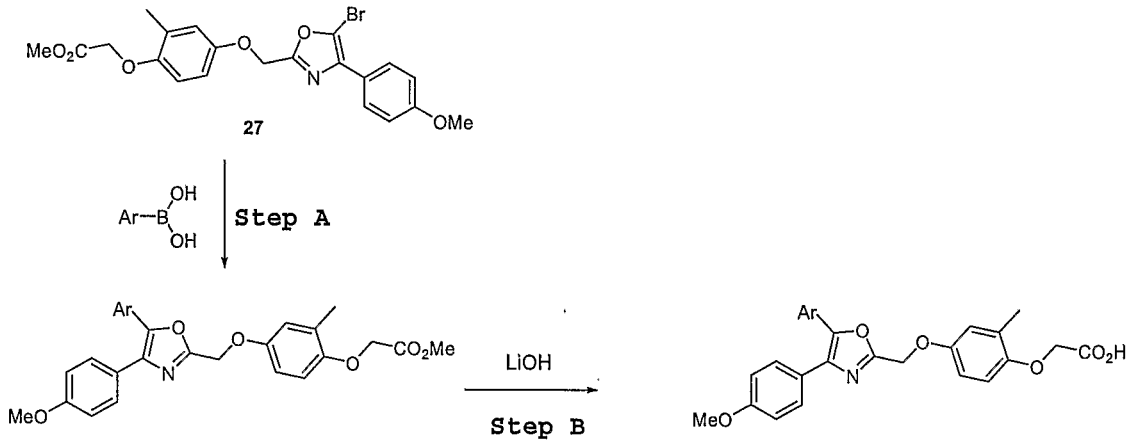


[00148] Example A1. {4-[4,5-Bis-(4-methoxy-phenyl)-oxazol-2-ylmethoxy]-2-methyl-phenoxy}-acetic acid.

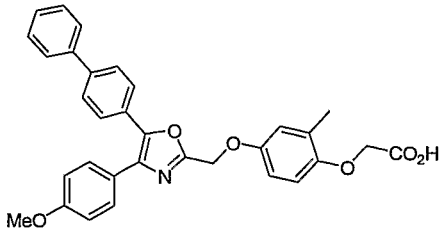


[00149] **Step A:** Intermediate 22 (25 mg, 0.08 mmol), intermediate 4 (18 mg, 0.09 mmol) and triphenylphosphine (30 mg, 0.11 mmol) were dissolved in dry DCM (1 mL) and cooled to 0 °C. After the slow addition of diethyl azodicarboxylate (24 □L, 0.15 mmol) the solution was stirred at rt overnight. The solvent was removed to afford crude {4-[4,5-Bis-(4-methoxy-phenyl)-oxazol-2-ylmethoxy]-2-methyl-phenoxy}-acetic acid methyl ester which was used without further purification in step B.

[00150] **Step B:** The crude {4-[4,5-Bis-(4-methoxy-phenyl)-oxazol-2-ylmethoxy]-2-methyl-phenoxy}-acetic acid methyl ester was dissolved in THF (1 mL), a solution of 1 M LiOH in H_2O (0.2 mL) was added and the mixture was stirred overnight at rt. The mixture was acidified with 1 M HCl (0.25 mL), EtOAc (10 mL) was added and the organic layer washed with H_2O (3x5 mL). The organic layer was dried ($MgSO_4$), filtered, concentrated and purified on reverse phase HPLC (H_2O/MeCN gradient) to afford the title compound A1 (10.4 mg, 0.022 mmol, 27%) as a white solid: ^{1}H-NMR (400MHz, CD_3OD) δ = 7.40-7.37 (m, 4H), 6.81-6.87 (m, 5H), 6.74-6.66 (m, 2H), 5.04 (s, 2H), 4.52 (s, 2H), 3.73 (s, 3H), 3.72 (s, 3H), 2.16 (s, 3H). MS calcd. for $C_{27}H_{26}NO_7$ ($M+H^+$) 476.16, found 476.10.

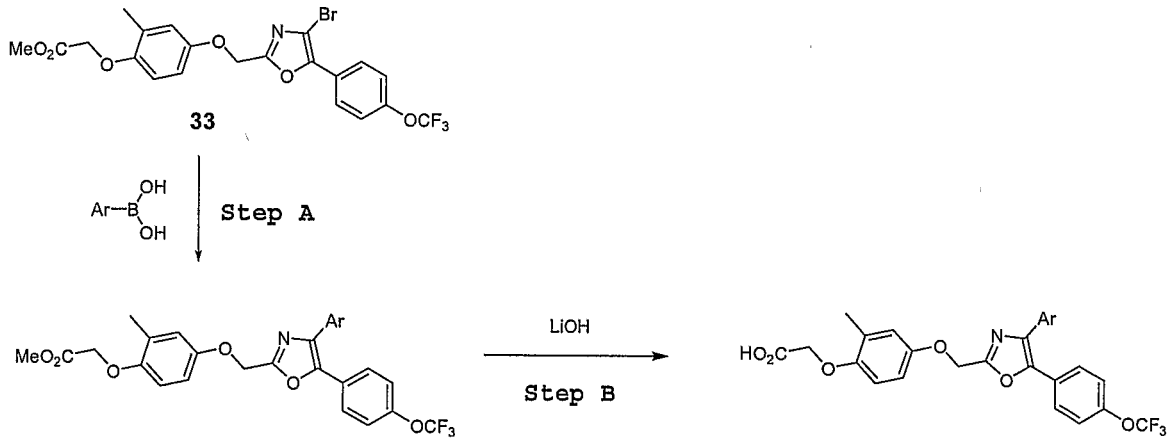


[00151] **Example B1:** {4-[5-Biphenyl-4-yl-4-(4-methoxy-phenyl)-oxazol-2-ylmethoxy]-2-methyl-phenoxy}-acetic acid.

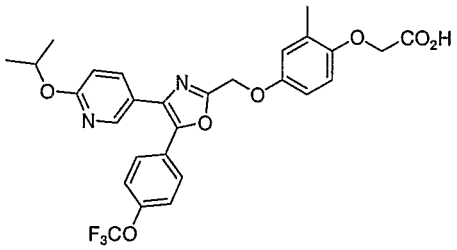


[00152] **Step A:** A mixture of {4-[5-bromo-4-(4-methoxy-phenyl)-oxazol-2-ylmethoxy]-2-methyl-phenoxy}-acetic acid methyl ester **27** (30.0 mg, 0.064 mmol), 4-biphenylboronic acid (25.7 mg, 0.13 mmol), tetrakis (triphenylphosphine) palladium (7.9 mg, 0.006 mmol), potassium carbonate (35.8 mg, 0.26 mmol), 1,4-dioxane (1 mL), EtOH (0.4 mL) and H_2O (0.2 mL) in a sealed vial was heated to 120°C and stirred at this temperature overnight. The reaction mixture was cooled to room temperature and used in the next step without further purification. MS calcd. for $C_{33}H_{30}NO_6$ ($M+H^+$) 536.2, found 536.2.

[00153] **Step B:** $LiOH.H_2O$ (13.6 mg, 0.32 mmol) was added to the reaction mixture from step A. The mixture was stirred at room temperature for 2 h, and then filtered. The filtrate was purified on reverse phase HPLC (H_2O/MeCN gradient) to afford the title compound B1 (15.0 mg, 0.029 mmol, 45%) as a white solid: ^{1}H-NMR (400MHz, CD_3OD) δ = 7.63-7.57 (m, 6H), 7.49-7.47 (m, 2H), 7.38 (t, J = 7.4 Hz, 2H), 7.28 (t, J = 7.6 Hz, 1H), 6.93-6.91 (m, 2H), 6.87 (d, J = 2.8 Hz, 1H), 6.79-6.69 (m, 2H), 5.11 (s, 2H), 4.54 (s, 2H), 3.75 (s, 3H), 2.17 (s, 3H). MS calcd. for $C_{32}H_{28}NO_6$ ($M+H^+$) 522.2, found 522.2.

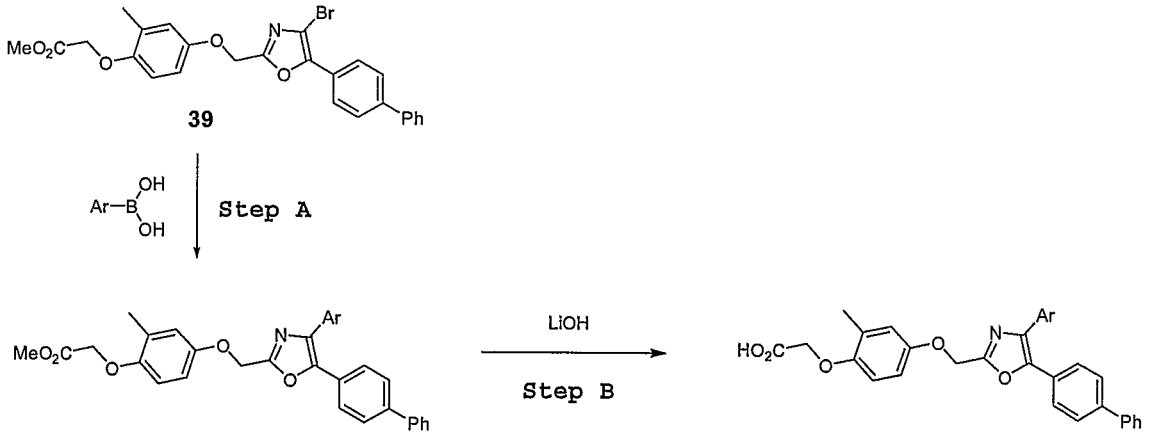


[00154] **Example C1:** {4-[4-(6-Isopropoxy-pyridin-3-yl)-5-(4-trifluoromethoxy-phenyl)-oxazol-2-ylmethoxy]-2-methyl-phenoxy}-acetic acid.

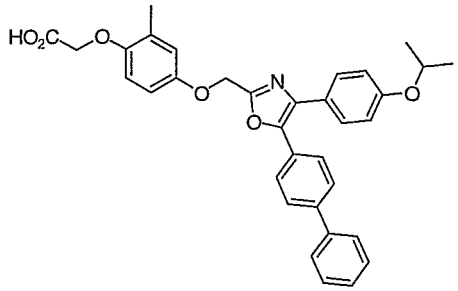


[00155] **Step A:** A mixture of {4-[4-bromo-5-(4-trifluoromethoxy-phenyl)-oxazol-2-ylmethoxy]-2-methyl-phenoxy}-acetic acid methyl ester **33** (150 mg, 0.29 mmol), 2-isopropoxy-5-pyridineboronic acid **45** (63.1 mg, 0.35 mmol), tetrakis triphenylphosphine) palladium (33.5 mg, 0.029 mmol) and potassium carbonate (1 M in H_2O, 1.2 mL, 1.2 mmol) was suspended in 1,4-dioxane (6.0 mL) and EtOH (3.0 mL). The mixture was heated to 120°C in a sealed vial for 10 h, then cooled to room temperature and used in the next step without further purification. MS calcd. for $C_{29}H_{28}F_3N_2O_7$ ($M+H^+$) 573.2, found 573.2.

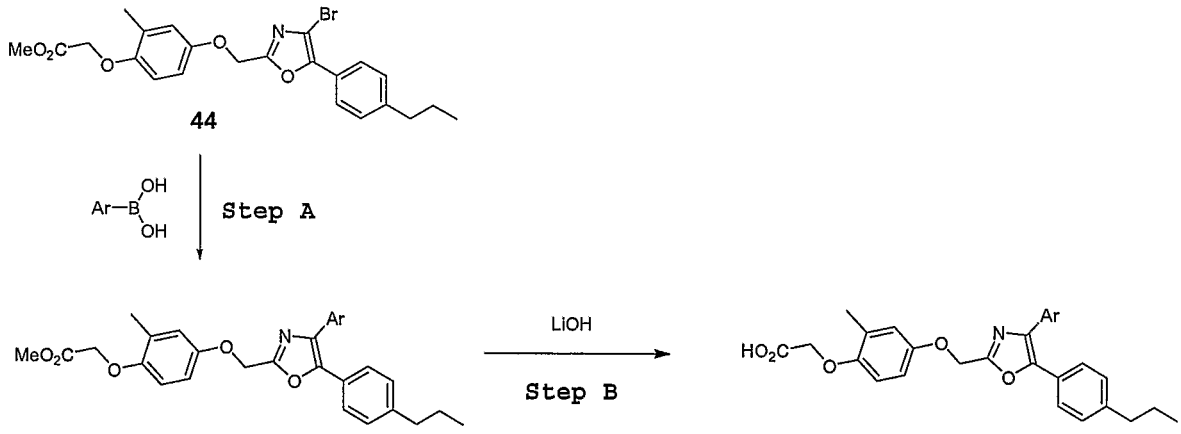
[00156] **Step B:** $LiOH.H_2O$ (61 mg, 1.45 mmol) was added to the reaction mixture from step A. The mixture was stirred at room temperature for 2 h, and then filtered. The filtrate was purified on reverse phase HPLC (H_2O/MeCN gradient) to afford the title compound **C1** as a white solid (83.0 mg, 0.15 mmol, 52%): ^{1}H-NMR (400MHz, CD_3OD) δ = 8.36 (d, J = 2.4 Hz, 1H), 7.90 (dd, J = 8.8 Hz, J = 2.4 Hz, 1H), 7.70 (d, J = 9.2 Hz, 2H), 7.38 (d, J = 8.0 Hz, 2H), 6.93 (d, J = 3.2 Hz, 1H), 6.88-6.77 (m, 3H), 5.28 (m, 1H), 5.20 (s, 2H), 4.63 (s, 2H), 2.26 (s, 3H), 1.38 (d, J = 6.0 Hz, 6H). MS calcd. for $C_{28}H_{26}F_3N_2O_7$ ($M+H^+$) 559.2, found 558.9.



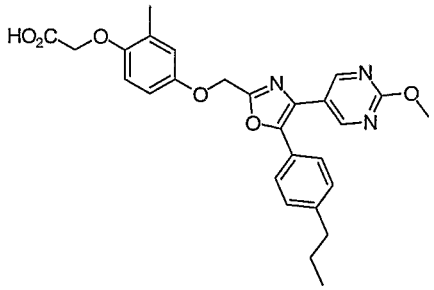
Example D1: {4-[5-Biphenyl-4-yl-4-(4-isopropoxy-phenyl)-oxazol-2-ylmethoxy]-2-methyl-phenoxy}-acetic acid.



[00157] Following the procedure of example C1, except substituting intermediate 39 for intermediate 33, and substituting 4-isopropoxyphenylboronic acid for 2-isopropoxy-5-pyridineboronic acid in step A, the title compound D1 was prepared as a white solid (9.2 mg, 0.17 mmol, 43%): ^{1}H-NMR (400MHz, CD_3OD) δ = 7.59-7.55 (m, 6H), 7.44 (d, J = 8.8 Hz, 2H), 7.35 (t, J = 7.6 Hz, 2H), 7.26 (t, J = 7.4 Hz, 1H), 6.88 (d, J = 8.8 Hz, 2H), 6.85 (d, J = 2.8 Hz, 2H), 6.79-6.68 (m, 2H), 5.08 (s, 2H), 4.56 (m, 1H), 4.52 (s, 2H), 2.17 (s, 3H), 1.26 (d, J = 6.0 Hz, 6H). MS calcd. for $C_{34}H_{32}NO_6$ ($M+H^+$) 550.2, found 550.2.



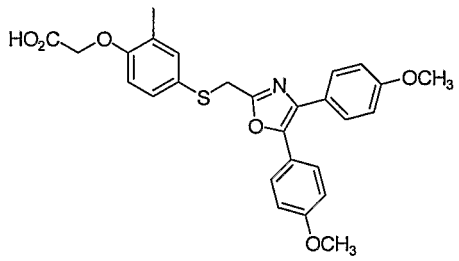
[00158] Example E1: {4-[4-(2-Methoxy-pyrimidin-5-yl)-5-(4-propyl-phenyl)-oxazol-2-ylmethoxy]-2-methyl-phenoxy}-acetic acid.

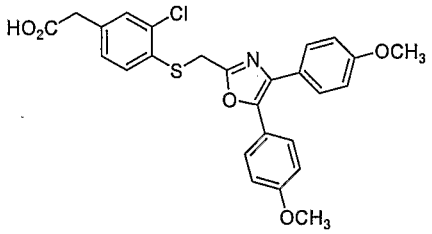
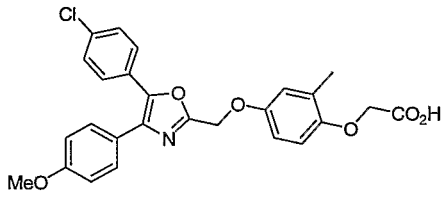
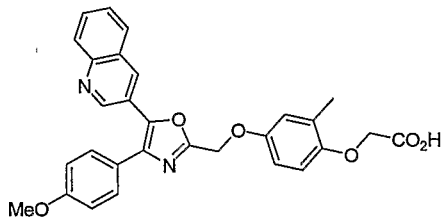


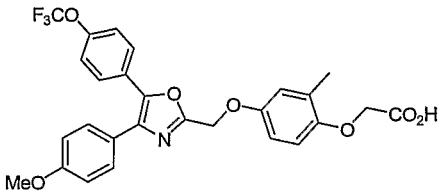
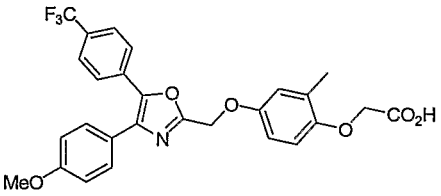
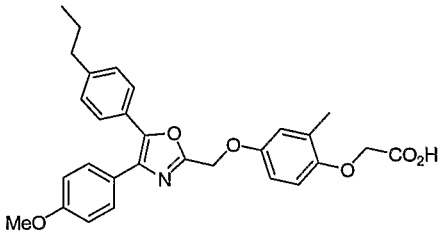
[00159] Following the procedure of Example D1, except substituting intermediate 44 for intermediate 33, and 2-methoxypyrimidine-5-boronic acid for 2-isopropoxy-5-pyridineboronic acid in step A, the title compound E1 was prepared as a white solid (8.6 mg, 0.018 mmol, 55%): ^{1}H-NMR (400MHz, CD_3OD) δ = 8.66 (s, 2H), 7.41 (d, J = 8.0 Hz, 2H), 7.21 (d, J = 8.0 Hz, 2H), 6.83 (d, J = 2.8 Hz, 1H), 6.77-6.67 (m, 2H), 5.09 (s, 2H), 4.53 (s, 2H), 3.95 (s, 3H), 2.56 (t, J = 7.6 Hz, 2H), 2.16 (s, 3H), 1.61-1.55 (m, 2H), 0.87 (t, J = 7.4 Hz, 3H). MS calcd. for $C_{27}H_{28}N_3O_6$ ($M+H^+$) 490.2, found 490.2.

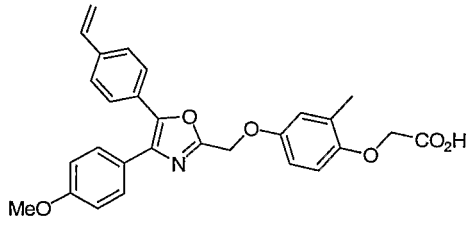
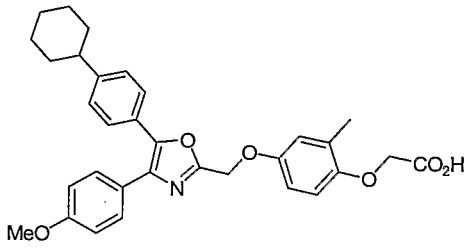
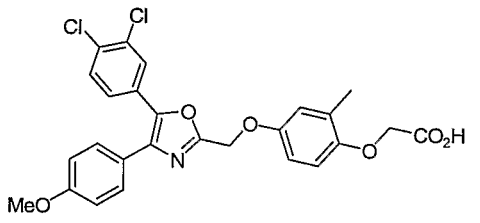
[00160] By repeating the procedures described in the above examples, using appropriate starting materials, the following compounds of Formula I, as identified in Table 1, are obtained.

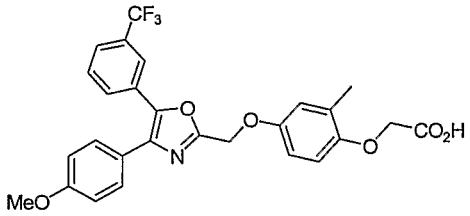
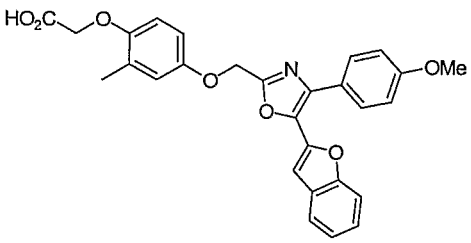
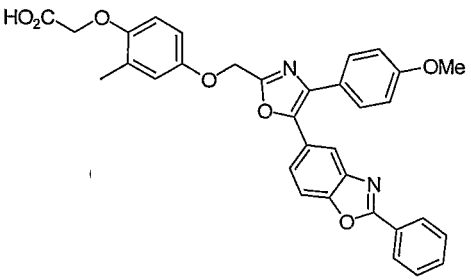
***Table* 1**

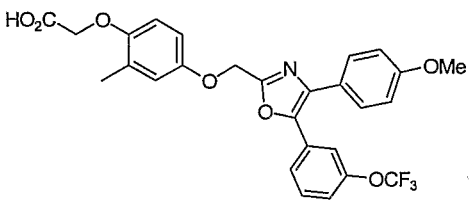
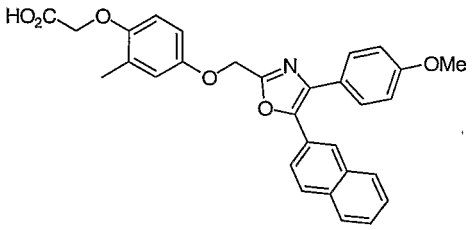
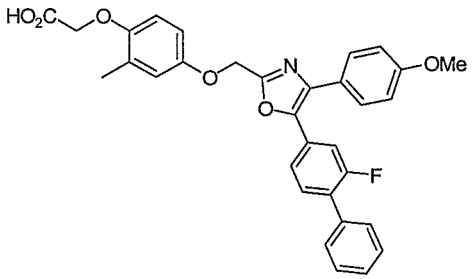
Compound Number	**Compound Structure**	**Physical Data ^{1}H NMR 400 MHz (DMSO-d_6) and/or MS (m/z)**
A2		^{1}H-NMR (400MHz, CD_3OD) δ = 7.29 (d, J = 8.0 Hz, 2H), 7.23 (d, J = 8.4 Hz, 2H), 7.18 (d, J = 8.8 Hz, 1H), 7.13 (s, 1H), 6.86-6.81 (m, 4H), 6.67 (d, J = 8.4 Hz, 1H), 4.58 (s, 2H), 4.01 (s, 2H), 3.73 (s, 6H), 2.01 (s, 3H). MS calcd. for $C_{27}H_{26}NO_6S$ ($M+H^+$) 492.14, found 492.10.

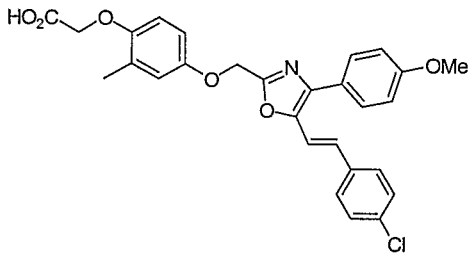
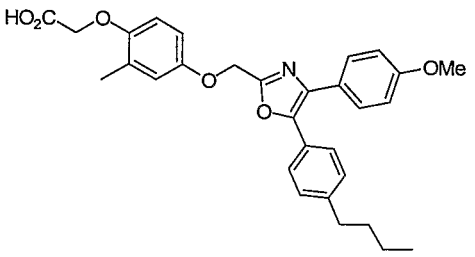
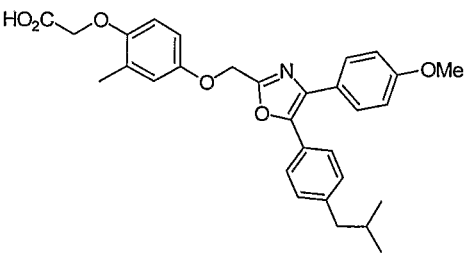
Compound Number	Compound Structure	Physical Data ^{1}H NMR 400 MHz (DMSO-d_6) and/or MS (m/z)
A3		^{1}H-NMR (400MHz, CD_3OD) δ = 7.47 (d, J = 8.0 Hz, 1H), 7.33 (d, J = 1.6 Hz, 1H), 7.30 (d, J = 8.8 Hz, 2H), 7.23 (d, J = 8.8 Hz, 2H), 7.12 (dd, J = 2.0 Hz, J = 8.0 Hz, 1H), 6.79-6.85 (m, 4H), 4.21 (s, 2H), 3.72 (s, 6H), 3.52 (s, 2H). MS calcd. for $C_{26}H_{23}ClNO_5S$ ($M+H^+$) 496.09, found 496.00.
B2		^{1}H-NMR (400MHz, CD_3OD) δ = 7.49(d, J = 8.4 Hz, 2H), 7.44 (d, J = 8.8 Hz, 2H), 7.37 (d, J = 8.4 Hz, 2H), 6.92 (d, J = 8.8 Hz, 2H), 6.85 (d, J = 2.8 Hz, 1H), 6.79-6.69 (m, 2H), 5.09 (s, 2H), 4.55 (s, 2H), 3.75 (s, 3H), 2.16 (s, 3H). MS calcd. for $C_{26}H_{23}ClNO_6$ ($M+H^+$) 480.1, found 480.1.
B3		^{1}H-NMR (400MHz, CD_3OD) δ = 8.94(s, 1H), 8.61 (s, 1H), 8.01-7.95 (m, 2H), 7.80-7.63 (m, 2H), 7.53 (d, J = 8.8 Hz, 2H), 6.96 (d, J = 8.8 Hz, 1H), 6.89 (d, J = 3.2 Hz, 1H), 6.83-6.70 (m, 2H), 5.17 (s, 2H), 4.56 (s, 2H), 3.76 (s, 3H), 2.17 (s, 3H). MS calcd. for $C_{29}H_{25}N_2O_6$ ($M+H^+$) 497.2, found 497.2.

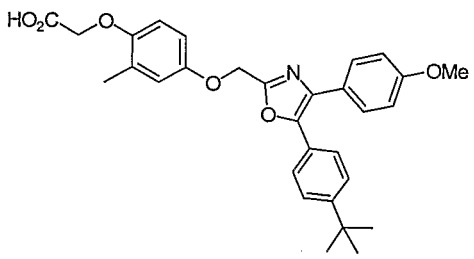
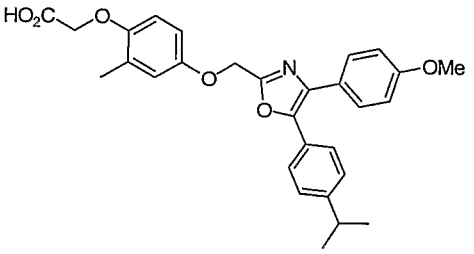
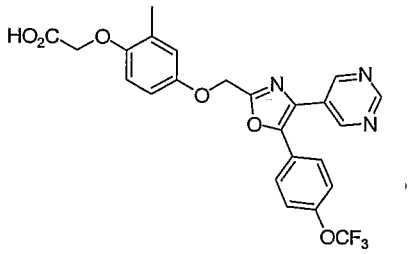
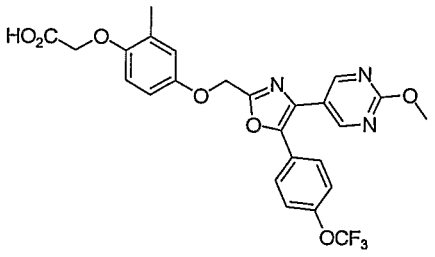
Compound Number	Compound Structure	Physical Data ^{1}H NMR 400 MHz (DMSO-d_6) and/or MS (m/z)
B4		^{1}H-NMR (400MHz, CD_3OD) δ = 7.59 (d, J = 8.8 Hz, 2H), 7.43 (d, J = 9.2 Hz, 2H), 7.24 (d, J = 8.4 Hz, 2H), 6.92 (d, J = 8.8 Hz, 2H), 6.84 (d, J = 2.8 Hz, 1H), 6.79-6.68 (m, 2H), 5.08 (s, 2H), 4.53 (s, 2H), 3.75 (s, 3H), 2.17 (s, 3H). MS calcd. for $C_{27}H_{23}F_3NO_7$ ($M+H^+$) 530.1, found 530.0.
B5		^{1}H-NMR (400MHz, CD_3OD) δ = 7.67-7.59(m, 4H), 7.43 (d, J = 8.8 Hz, 2H), 6.93 (d, J = 8.8 Hz, 2H), 6.85 (d, J = 2.8 Hz, 1H), 6.79-6.69 (m, 2H), 5.10 (s, 2H), 4.53 (s, 2H), 3.75 (s, 3H), 2.17 (s, 3H). MS calcd. for $C_{27}H_{23}F_3NO_6$ ($M+H^+$) 514.1, found 514.1.
B6		^{1}H-NMR (400MHz, CD_3OD) δ = 7.41-7.35 (m, 4H), 7.11 (d, J = 8.4 Hz, 2H), 6.87 (d, J = 8.8 Hz, 2H), 6.82 (d, J = 2.4 Hz, 1H), 6.76-6.65 (m, 2H), 5.03 (s, 2H), 4.51 (s, 2H), 3.72 (s, 3H), 2.50 (t, J = 7.6 Hz, 2H), 2.15 (s, 3H), 1.59-1.50 (m, 2H), 0.85 (t, J = 7.4 Hz, 3H). MS calcd. for $C_{29}H_{30}NO_6$ ($M+H^+$) 488.2, found 488.2.

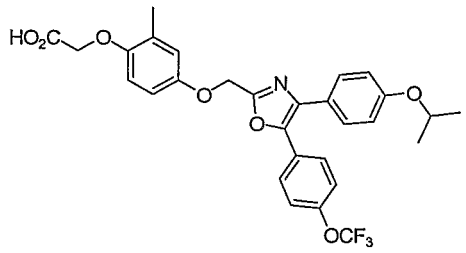
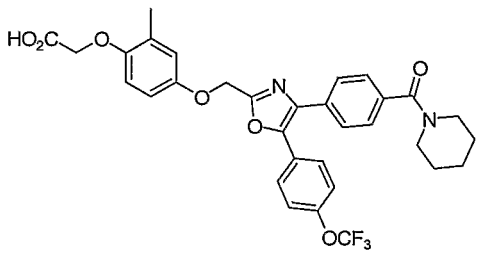
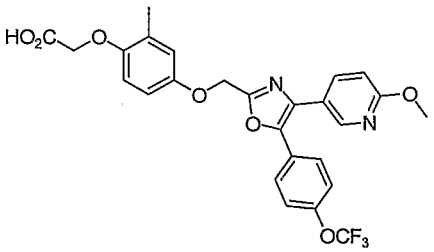
Compound Number	Compound Structure	Physical Data ^{1}H NMR 400 MHz (DMSO-d_6) and/or MS (m/z)
B7		^{1}H-NMR (400MHz, CD_3OD) δ = 7.46-7.37 (m, 6H), 6.90 (d, J = 8.8 Hz, 2H), 6.84 (d, J = 2.8 Hz, 2H), 6.78-6.62 (m, 3H), 5.77 (d, J = 17.6 Hz, 1H), 5.21 (d, J = 10.8 Hz, 1H), 5.07 (s, 2H), 4.54 (s, 2H), 3.74 (s, 3H), 2.16 (s, 3H). MS calcd. for $C_{28}H_{26}NO_6$ ($M+H^+$) 472.2, found 472.2.
B8		^{1}H-NMR (400MHz, CD_3OD) δ = 7.44-7.38 (m, 4H), 7.17 (d, J = 8.0 Hz, 2H), 6.89 (d, J = 8.8 Hz, 2H), 6.84 (d, J = 2.8 Hz, 1H), 6.78-6.68 (m, 2H), 5.06 (s, 2H), 4.54 (s, 2H), 3.73 (s, 3H), 2.50-2.42 (m, 1H), 2.16 (s, 3H), 1.77-1.65 (m, 5H), 1.38-1.19 (m, 5H). MS calcd. for $C_{32}H_{34}NO_6$ ($M+H^+$) 528.2, found 528.2.
B9		^{1}H-NMR (400MHz, CD_3OD) δ = 7.65 (d, J = 2.0 Hz, 1H), 7.52-7.40 (m, 4H), 6.95 (d, J = 8.4 Hz, 2H), 6.86 (d, J = 2.8 Hz, 1H), 6.80-6.69 (m, 2H), 5.11 (s, 2H), 4.54 (s, 2H), 3.76 (s, 3H), 2.16 (s, 3H). MS calcd. for $C_{26}H_{22}Cl_2NO_6$ ($M+H^+$) 514.1, found 514.1.

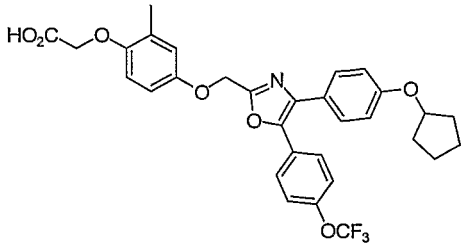
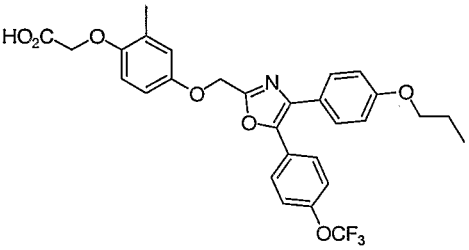
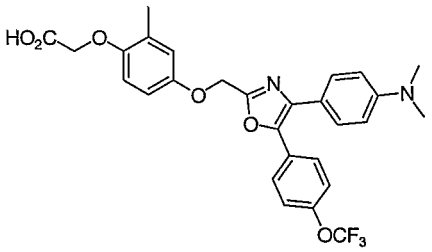
Compound Number	Compound Structure	Physical Data ^{1}H NMR 400 MHz (DMSO-d_6) and/or MS (m/z)
B10		MS calcd. for $C_{27}H_{23}F_3NO_6$ ($M+H^+$) 514.1, found 514.1.
B11		^{1}H-NMR (400MHz, CD_3OD) δ = 7.75-7.73 (m, 2H), 7.60 (d, J = 7.6 Hz, 1H), 7.47 (d, J = 8.0 Hz, 1H), 7.30-7.19 (m, 2H), 7.11 (s, 1H), 6.99-6.96 (m, 2H), 6.88 (d, J = 2.8 Hz, 1H), 6.82-6.70 (m, 2H), 5.14 (s, 2H), 4.55 (s, 2H), 3.78 (s, 3H), 2.17 (s, 3H). MS calcd. for $C_{28}H_{24}NO_7$ ($M+H^+$) 486.2, found 486.1.
B12		^{1}H-NMR (400MHz, CD_3OD) δ = 8.36-9.34 (m, 2H), 8.00 (s, 1H), 7.95 (d, J = 8.4 Hz, 1H), 7.77-7.66 (m, 6H), 7.13 (d, J = 8.8 Hz, 2H), 7.08 (d, J = 2.8 Hz, 2H), 7.00-6.90 (m, 2H), 5.33 (s, 2H), 4.75 (s, 2H), 3.93 (s, 3H), 2.34 (s, 3H). MS calcd. for $C_{33}H_{27}N_2O_7$ ($M+H^+$) 563.2, found 563.2.

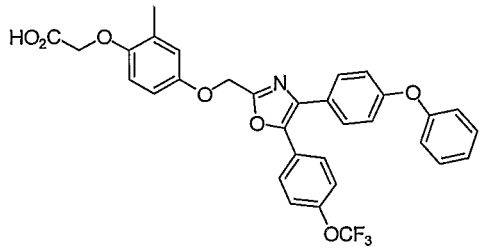
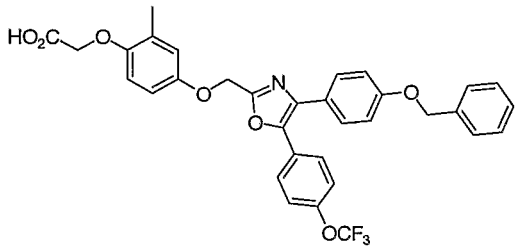
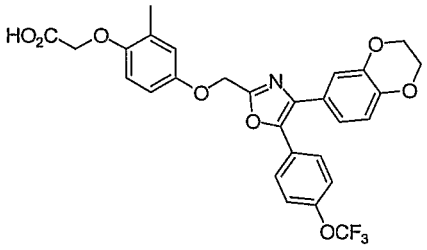
Compound Number	Compound Structure	Physical Data ^{1}H NMR 400 MHz (DMSO-d_6) and/or MS (m/z)
B13		^{1}H-NMR (400MHz, CD_3OD) δ = 7.49-7.38 (m, 4H), 7.33 (s, 1H), 7.18 (d, J = 7.6 Hz, 1H), 6.91 (d, J = 8.8 Hz, 1H), 6.84 (d, J = 2.8 Hz, 1H), 6.78-6.67 (m, 2H), 5.09 (s, 2H), 4.53 (s, 2H), 3.75 (s, 3H), 2.16 (s, 3H). MS calcd. for $C_{27}H_{23}F_3NO_7$ ($M+H^+$) 530.1, found 530.1.
B14		^{1}H-NMR (400MHz, CD_3OD) δ = 8.06 (s, 1H), 7.84-7.79 (m, 3H), 7.59-7.45 (m, 5H), 6.93 (d, J = 8.4 Hz, 2H), 6.89 (d, J = 2.8 Hz, 1H), 6.83-6.71 (m, 2H), 5.14 (s, 2H), 4.56 (s, 2H), 3.75 (s, 3H), 2.17 (s, 3H). MS calcd. for $C_{30}H_{26}NO_6$ ($M+H^+$) 496.2, found 496.2.
B15		^{1}H-NMR (400MHz, CD_3OD) δ = 7.51-7.31 (m, 9H), 6.96 (d, J = 8.8 Hz, 2H), 6.88 (d, J = 2.8 Hz, 1H), 6.82-6.70 (m, 2H), 5.12 (s, 2H), 4.56 (s, 2H), 3.76 (s, 3H), 2.17 (s, 3H). MS calcd. for $C_{32}H_{27}FNO_6$ ($M+H^+$) 540.2, found 540.2.

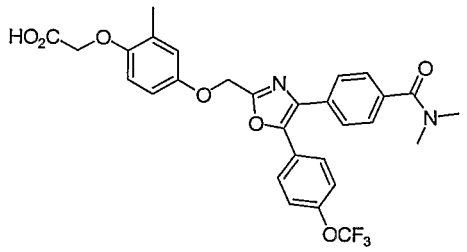
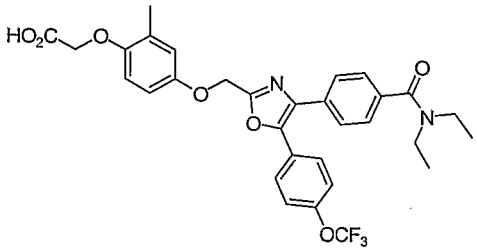
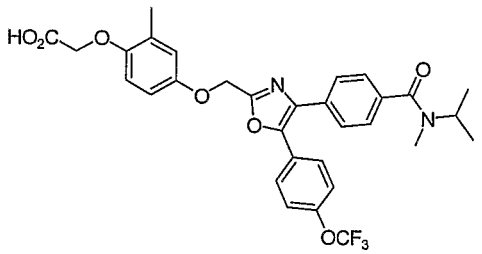
Compound Number	Compound Structure	Physical Data ^{1}H NMR 400 MHz (DMSO-d_6) and/or MS (m/z)
B16		^{1}H-NMR (400MHz, CD_3OD) δ = 7.56 (d, J = 8.4 Hz, 2H), 7.45 (d, J = 8.4 Hz, 2H), 7.27 (d, J = 8.4 Hz, 2H), 7.13-7.04 (m, 2H), 6.97 (d, J = 8.4 Hz, 2H), 6.84 (d, J = 2.4 Hz, 1H), 6.77-6.67 (m, 2H), 5.05 (s, 2H), 4.53 (s, 2H), 3.76 (s, 3H), 2.17 (s, 3H). MS calcd. for $C_{28}H_{25}ClNO_6$ ($M+H^+$) 506.1, found 506.1.
B17		^{1}H-NMR (400MHz, CD_3OD) δ = 7.45-7.38 (m, 4H), 7.15 (d, J = 8.4 Hz, 2H), 6.90 (d, J = 8.8 Hz, 2H), 6.86 (d, J = 2.8 Hz, 1H), 6.80-6.69 (m, 2H), 5.08 (s, 2H), 4.55 (s, 2H), 3.76 (s, 3H), 2.56 (t, J = 7.8 Hz, 2H), 2.19 (s, 3H), 1.58-1.22 (m, 4H), 0.88 (t, J = 7.4 Hz, 3H). MS calcd. for $C_{30}H_{32}NO_6$ ($M+H^+$) 502.2, found 502.2.
B18		^{1}H-NMR (400MHz, CD_3OD) δ = 7.46-7.41 (m, 4H), 7.14 (d, J = 8.0 Hz, 2H), 6.93 (d, J = 8.4 Hz, 2H), 6.88 (d, J = 2.8 Hz, 1H), 6.82-6.72 (m, 2H), 5.10 (s, 2H), 4.57 (s, 2H), 3.78 (s, 3H), 2.46 (d, J = 7.2 Hz, 2H), 2.21 (s, 3H), 1.90-1.79 (m, 1H), 0.88 (d, J = 6.8 Hz, 3H). MS calcd. for $C_{30}H_{32}NO_6$ ($M+H^+$) 502.2, found 502.2.

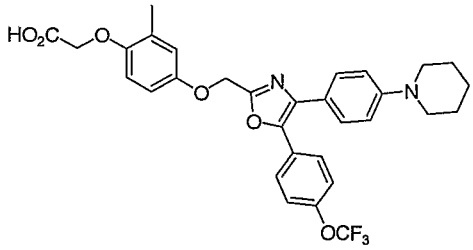
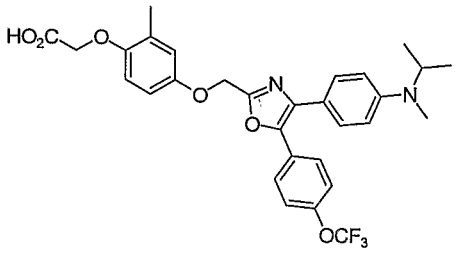
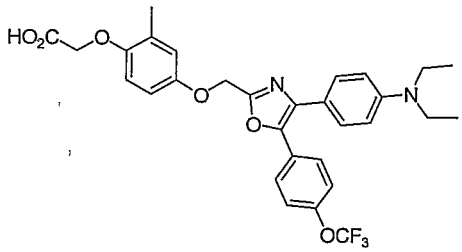
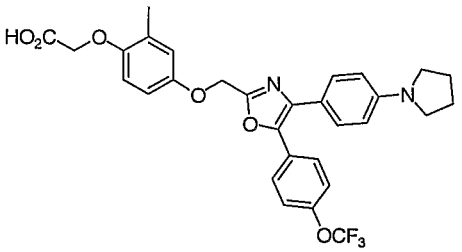
Compound Number	Compound Structure	Physical Data ^{1}H NMR 400 MHz (DMSO-d_6) and/or MS (m/z)
B19		^{1}H-NMR (400MHz, CD_3OD) δ = 7.55-7.44 (m, 6H), 6.99 (d, J = 8.4 Hz, 2H), 6.94 (d, J = 2.4 Hz, 1H), 6.88-6.78 (m, 2H), 5.16 (s, 2H), 4.62 (s, 2H), 3.82 (s, 3H), 2.24 (s, 3H), 1.32 (s, 9H). MS calcd. for $C_{30}H_{32}NO_6$ ($M+H^+$) 502.2, found 502.2.
B20		^{1}H-NMR (400MHz, CD_3OD) δ = 7.55-7.49 (m, 4H), 7.31 (d, J = 8.0 Hz, 2H), 6.99 (d, J = 8.8 Hz, 2H), 6.94 (d, J = 2.4 Hz, 2H), 6.89-6.78 (m, 2H), 5.17 (s, 2H), 4.63 (s, 2H), 3.82 (s, 3H), 2.96-2.89 (m, 1H), 2.24 (s, 3H), 1.26 (d, J = 7.2 Hz, 6H). MS calcd. for $C_{29}H_{30}NO_6$ ($M+H^+$) 488.2, found 488.1.
C2		^{1}H-NMR (400MHz, CD_3OD) δ = 9.09 (s, 1H), 8.92 (s, 2H), 7.67 (d, J = 8.8 Hz, 2H), 7.37 (d, J = 8.4 Hz, 2H), 6.87 (d, J = 2.4 Hz, 1H), 6.81-6.70 (m, 2H), 5.17 (s, 2H), 4.55 (s, 2H), 2.16 (s, 3H). MS calcd. for $C_{24}H_{19}F_3N_3O_6$ ($M+H^+$) 502.1, found 502.1.
C3		^{1}H-NMR (400MHz, CD_3OD) δ = 8.66 (s, 2H), 7.62 (d, J = 8.8 Hz, 2H), 7.30 (d, J = 8.0 Hz, 2H), 6.83 (d, J = 2.8 Hz, 1H), 6.77-6.66 (m, 2H), 5.11 (s, 2H), 4.53 (s, 2H), 3.96 (s, 3H), 2.15 (s, 3H). MS calcd. for $C_{25}H_{21}F_3N_3O_7$ ($M+H^+$) 532.1, found 532.1.

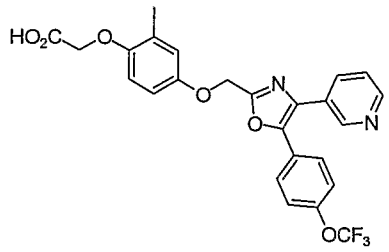
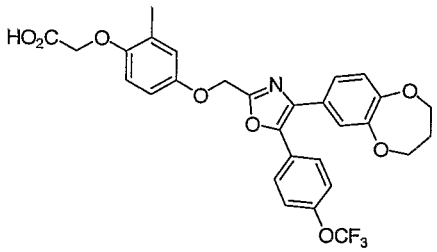
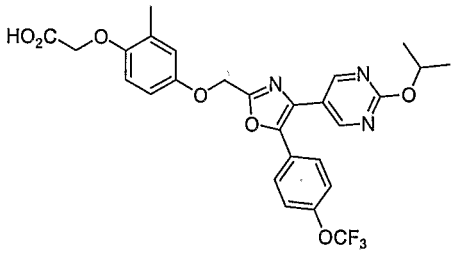
Compound Number	Compound Structure	Physical Data ^{1}H NMR 400 MHz (DMSO-d_6) and/or MS (m/z)
C4		^{1}H-NMR (400MHz, CD_3OD) δ = 7.69 (d, J = 8.8 Hz, 2H), 7.50 (d, J = 8.8 Hz, 2H), 7.34 (d, J = 8.8 Hz, 2H), 6.98 (d, J = 8.8 Hz, 2H), 6.93 (d, J = 3.2 Hz, 1H), 6.87-6.77 (m, 2H), 5.18 (s, 2H), 4.69 (m, 1H), 4.59 (s, 2H), 2.26 (s, 3H), 1.35 (d, J = 6.0 Hz, 6H). MS calcd. for $C_{29}H_{27}F_3NO_7$ ($M+H^+$) 558.2, found 558.2.
C5		^{1}H-NMR (400MHz, CD_3OD) δ = 7.62-7.59 (m, 4H), 7.38 (d, J = 8.4 Hz, 2H), 7.27 (d, J = 8.8 Hz, 2H), 6.84 (d, J = 2.8 Hz, 1H), 6.78-6.67 (m, 2H), 5.11 (s, 2H), 4.53 (s, 2H), 3.63 (bs, 2H), 3.34 (bs, 2H), 2.16 (s, 3H), 1.64-1.45 (m, 6H). MS calcd. for $C_{32}H_{30}F_3N_2O_7$ ($M+H^+$) 611.2, found 611.2.
C6		^{1}H-NMR (400MHz, CD_3OD) δ = 8.28 (d, J = 2.4 Hz, 1H), 7.79 (dd, J = 2.4 Hz, J = 8.8 Hz, 1H), 7.60 (d, J = 8.8 Hz, 2H), 7.30 (d, J = 8.4 Hz, 2H), 6.85 (d, J = 2.8 Hz, 1H), 6.81-6.68 (m, 3H), 5.11 (s, 2H), 4.54 (s, 2H), 3.85 (s, 3H), 2.16 (s, 3H). MS calcd. for $C_{26}H_{22}F_3N_2O_7$ ($M+H^+$) 531.1, found 531.1.

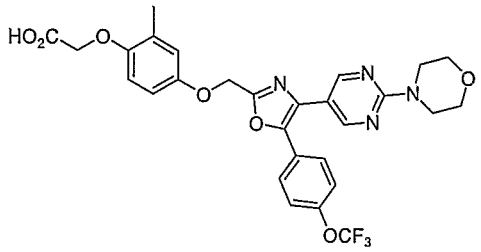
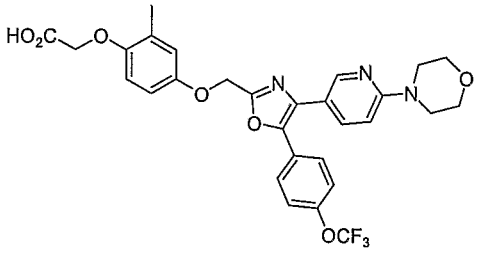
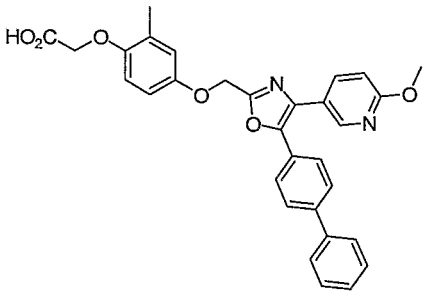
Compound Number	Compound Structure	Physical Data ^{1}H NMR 400 MHz (DMSO-d_6) and/or MS (m/z)
C7		^{1}H-NMR (400MHz, CD_3OD) δ = 7.59 (d, J = 8.8 Hz, 2H), 7.40 (d, J = 8.8 Hz, 2H), 7.24 (d, J = 8.4 Hz, 2H), 6.87 (d, J = 8.4 Hz, 2H), 6.83 (d, J = 2.8 Hz, 1H), 6.77-6.67 (m, 2H), 5.08 (s, 2H), 4.87-4.75 (m, 1H), 4.48 (s, 2H), 2.16 (s, 3H), 1.96-1.58 (m, 8H). MS calcd. for $C_{31}H_{29}F_3NO_7$ ($M+H^+$) 584.2, found 584.1.
C8		^{1}H-NMR (400MHz, CD_3OD) δ = 7.67 (d, J = 8.8 Hz, 2H), 7.49 (d, J = 8.8 Hz, 2H), 7.31 (d, J = 8.0 Hz, 2H), 6.99 (d, J = 8.8 Hz, 2H), 6.92 (d, J = 2.8 Hz, 1H), 6.86-6.76 (m, 2H), 5.16 (s, 2H), 4.61 (s, 2H), 3.97 (t, J = 6.4 Hz, 2H), 2.25 (s, 3H), 1.84-1.78 (m, 2H), 1.04 (t, J = 7.6 Hz, 3H). MS calcd. for $C_{29}H_{27}F_3NO_7$ ($M+H^+$) 558.2, found 558.2.
C9		MS calcd. for $C_{28}H_{26}F_3N_2O_6$ ($M+H^+$) 543.2, found 543.2.

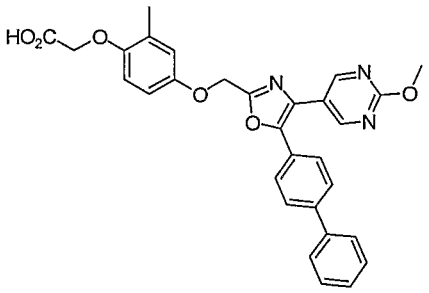
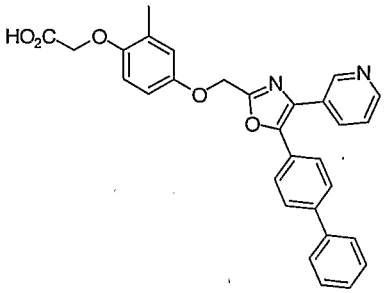
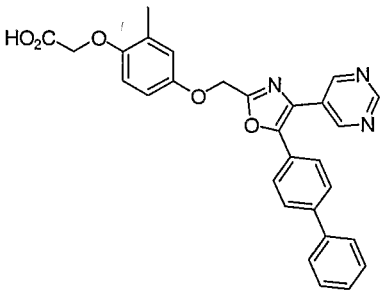
Compound Number	Compound Structure	Physical Data ^{1}H NMR 400 MHz (DMSO-d_6) and/or MS (m/z)
C10		^{1}H-NMR (400MHz, CD_3OD) δ = 7.60 (d, J = 8.8 Hz, 2H), 7.49 (d, J = 8.8 Hz, 2H), 7.32-7.23 (m, 4H), 7.07 (t, J = 7.4 Hz, 1H), 7.00-6.92 (m, 4H), 6.83 (d, J = 2.8 Hz, 1H), 6.78-6.67 (m, 2H), 5.09 (s, 2H), 4.53 (s, 2H), 2.16 (s, 3H). MS calcd. for $C_{32}H_{25}F_3NO_7$ ($M+H^+$) 592.2, found 592.1.
C11		^{1}H-NMR (400MHz, CD_3OD) δ = 7.57 (d, J = 8.8 Hz, 2H), 7.42 (d, J = 8.8 Hz, 2H), 7.37-7.20 (m, 7H), 6.98 (d, J = 8.8 Hz, 2H), 6.83 (d, J = 2.8 Hz, 1H), 6.77-6.67 (m, 2H), 5.07 (s, 2H), 5.04 (s, 2H), 4.52 (s, 2H), 2.16 (s, 3H). MS calcd. for $C_{33}H_{27}F_3NO_7$ ($M+H^+$) 606.2, found 606.1.
C12		^{1}H-NMR (400MHz, CD_3OD) δ = 7.59 (d, J = 8.8 Hz, 2H), 7.24 (d, J = 8.0 Hz, 2H), 6.97-6.92 (m, 2H), 6.83 (d, J = 2.8 Hz, 1H), 6.79-6.67 (m, 3H), 5.07 (s, 2H), 4.53 (s, 2H), 4.20-5.15 (m, 4H), 2.16 (s, 3H). MS calcd. for $C_{28}H_{23}F_3NO_8$ ($M+H^+$) 558.1, found 558.1.

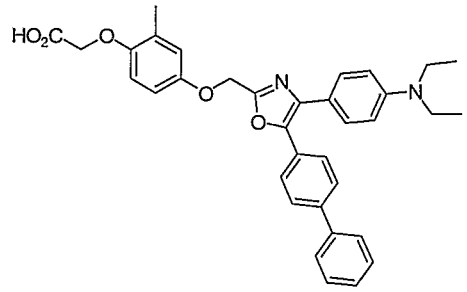
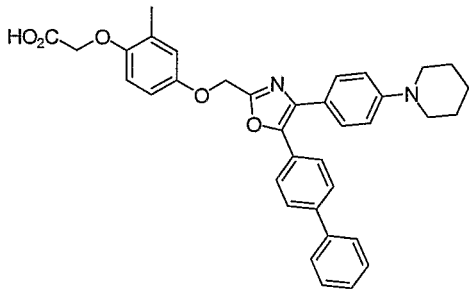
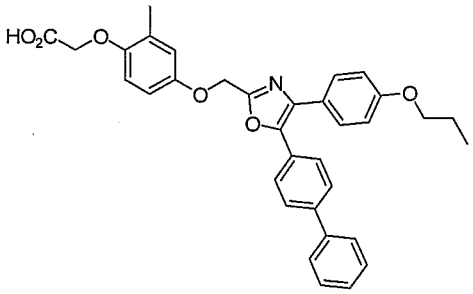
Compound Number	Compound Structure	Physical Data ^{1}H NMR 400 MHz (DMSO-d_6) and/or MS (m/z)
C13		^{1}H-NMR (400MHz, CD_3OD) δ = 7.61-7.58 (m, 4H), 7.41 (d, J = 8.8 Hz, 2H), 7.26 (d, J = 8.0 Hz, 2H), 6.83 (d, J = 3.2 Hz, 1H), 6.78-6.67 (m, 2H), 5.10 (s, 2H), 4.52 (s, 2H), 3.02 (s, 3H), 2.95 (s, 3H), 2.16 (s, 3H). MS calcd. for $C_{29}H_{26}F_3N_2O_7$ ($M+H^+$) 571.2, found 571.1.
C14		^{1}H-NMR (400MHz, CD_3OD) δ = 7.61-7.57 (m, 4H), 7.36 (d, J = 8.0 Hz, 2H), 7.25 (d, J = 8.0 Hz, 2H), 6.83 (d, J = 2.8 Hz, 1H), 6.78-6.66 (m, 2H), 5.10 (s, 2H), 4.52 (s, 2H), 3.51-3.43 (m, 4H), 2.16 (s, 3H), 1.18-1.04 (m, 6H). MS calcd. for $C_{31}H_{30}F_3N_2O_7$ ($M+H^+$) 599.2, found 599.2.
C15		^{1}H-NMR (400MHz, CD_3OD) δ = 7.61-7.58 (m, 4H), 7.40-7.31 (m, 2H), 7.25 (d, J = 8.4 Hz, 2H), 6.83 (d, J = 3.2 Hz, 1H), 6.78-6.67 (m, 2H), 5.10 (s, 2H), 4.52 (s, 2H), 3.97-3.84 (m, 1H), 2.86-2.78 (m, 3H), 2.15 (s, 3H), 1.19-1.09 (m, 6H). MS calcd. for $C_{31}H_{30}F_3N_2O_7$ ($M+H^+$) 599.2, found 599.2.

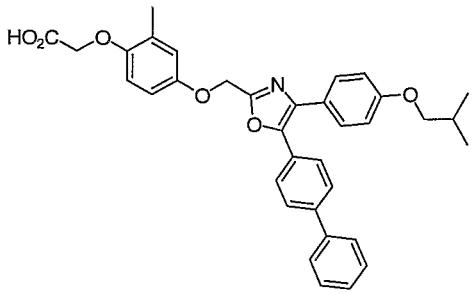
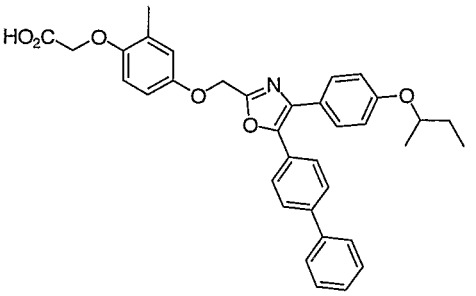
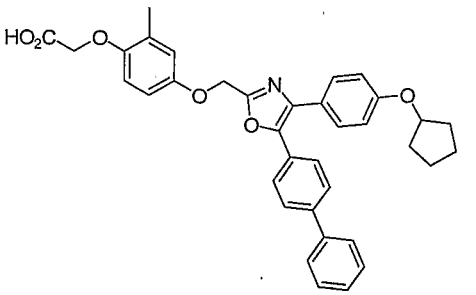
Compound Number	Compound Structure	Physical Data ^{1}H NMR 400 MHz (DMSO-d_6) and/or MS (m/z)
C16		^{1}H-NMR (400MHz, CD_3OD) δ = 7.73-7.68 (m, 4H), 7.50 (d, J = 8.8 Hz, 2H), 7.37 (d, J = 8.4 Hz, 2H), 6.93 (d, J = 2.8 Hz, 1H), 6.88-6.77 (m, 2H), 5.20 (s, 2H), 4.63 (s, 2H), 3.56-3.53 (m, 4H), 2.26 (s, 3H), 1.98-1.75 (m, 6H), MS calcd. for $C_{31}H_{30}F_3N_2O_6$ ($M+H^+$) 583.2, found 583.2.
C17		^{1}H-NMR (400MHz, CD_3OD) δ = 7.62-7.57 (m, 4H), 7.26-7.21 (m, 4H), 6.83 (d, J = 2.8 Hz, 1H), 6.77-6.66 (m, 2H), 5.09 (s, 2H), 4.53 (s, 2H), 4.00-3.94 (m, 1H), 3.01 (s, 3H), 2.16 (s, 3H), 1.20 (s, 3H), 1.19 (s, 3H). MS calcd. for $C_{30}H_{30}F_3N_2O_6$ ($M+H^+$) 571.2, found 571.2.
C18		MS calcd. for $C_{30}H_{30}F_3N_2O_6$ ($M+H^+$) 571.2, found 571.2.
C19		^{1}H-NMR (400MHz, CD_3OD) δ = 7.58 (d, J = 8.8 Hz, 2H), 7.31-7.17 (m, 4H), 6.82 (d, J = 2.8 Hz, 1H), 6.76-6.66 (m, 2H), 5.04 (s, 2H), 4.52 (s, 2H), 3.24-3.07 (m, 4H), 2.15 (s, 3H), 1.96-1.93 (m, 4H). MS calcd. for $C_{30}H_{28}F_3N_2O_6$ ($M+H^+$) 569.2, found 569.2.

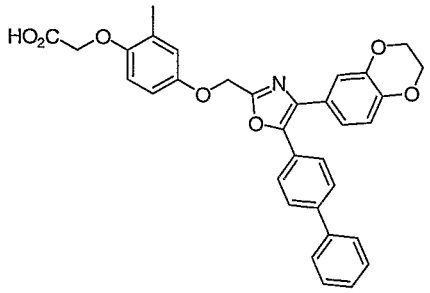
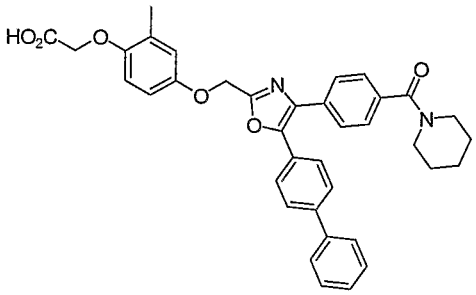
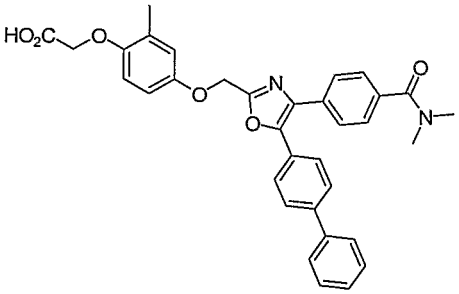
Compound Number	Compound Structure	Physical Data ^{1}H NMR 400 MHz (DMSO-d_6) and/or MS (m/z)
C20		^{1}H-NMR (400MHz, CD_3OD) δ = 8.89 (bs, 1H), 8.69 (bs, 1H), 8.13 (d, J = 7.6 Hz, 1H), 7.81 (d, J = 8.8 Hz, 2H), 7.61-7.52 (m, 3H), 7.05 (d, J = 2.0 Hz, 1H), 6.99-6.88 (m, 2H), 5.33 (s, 2H), 4.73 (s, 2H), 2.33 (s, 3H). MS calcd. for $C_{25}H_{20}F_3N_2O_6$ ($M+H^+$) 501.1, found 501.1.
C21		^{1}H-NMR (400MHz, CD_3OD) δ = 7.59-7.56 (m, 2H), 7.24 (d, J = 8.0 Hz, 2H), 7.09-7.02 (m, 2H), 6.90 (d, J = 8.4 Hz, 1H), 6.83 (d, J = 2.8 Hz, 1H), 6.77-6.67 (m, 2H), 5.07 (s, 2H), 4.53 (s, 2H), 4.15-4.10 (m, 4H), 2.16 (s, 3H), 2.15-2.05 (m, 2H). MS calcd. for $C_{29}H_{25}F_3NO_8$ ($M+H^+$) 572.2, found 572.1.
C22		^{1}H-NMR (400MHz, $CDCl_3$) δ = 8.75 (s, 2H), 7.96 (d, J = 8.7 Hz, 1H), 7.60 (d, J = 8.7 Hz, 1H), 7.30 (d, J = 8.6 Hz, 1H), 7.25 (d, J = 8.6 Hz, 1H), 6.90-6.68 (m, 3H), 5.32 (m, 1H), 5.16 (s, 2H), 4.64 (s, 2H), 2.28 (s, 3H), 1.42 (d, J = 6.2 Hz, 6H). MS calcd. for $C_{27}H_{25}F_3N_3O_7$ ($M+H^+$) 602.1, found 602.1.

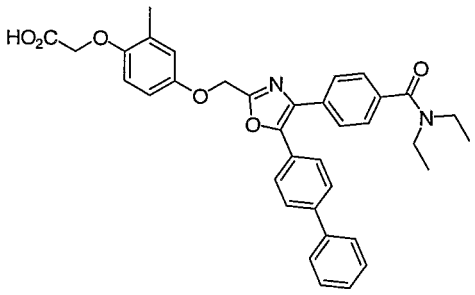
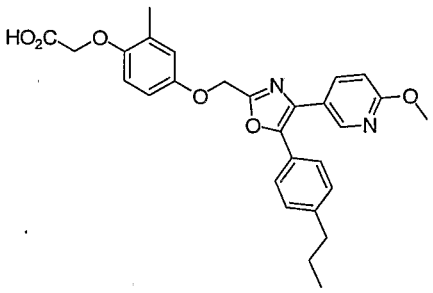
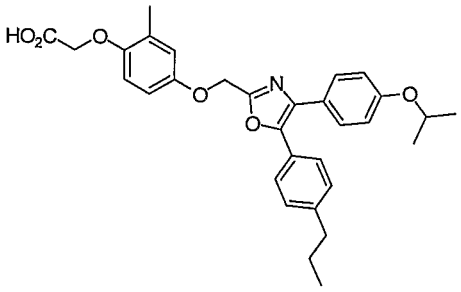
Compound Number	Compound Structure	Physical Data ^{1}H NMR 400 MHz (DMSO-d_6) and/or MS (m/z)
C23		^{1}H-NMR (400MHz, $CDCl_3$) δ = 8.33 (s, 2H), 7.37 (d, J = 8.3 Hz, 2H), 7.00 (d, J = 8.3 Hz, 2H), 6.64-6.43 (m, 3H), 4.90 (s, 2H), 4.38 (s, 2H), 3.61 (m, 4H), 3.55 (m, 4H), 2.02 (s, 3H). MS calcd. for $C_{28}H_{26}F_3N_4O_7$ ($M+H^+$) 587.2, found 587.2.
C24		^{1}H-NMR (400MHz, $CDCl_3$) δ = 8.36 (s, 1H), 7.37 (dd, J = 2.2 Hz, J = 9.0 Hz, 1H), 7.58 (d, J = 8.5 Hz, 2H), 7.27 (d, J = 8.5 Hz, 2H), 6.91-6.68 (m, 3H), 5.15 (s, 2H), 4.64 (s, 2H), 3.89 (m, 4H), 3.72 (m, 4H), 2.26 (s, 3H). MS calcd. for $C_{29}H_{27}F_3N_3O_7$ ($M+H^+$) 586.2, found 586.3.
D2		^{1}H-NMR (400MHz, CD_3OD) δ = 8.32 (bs, 1H), 7.84 (dd, J = 8.8 Hz, J = 2.0 Hz, 1H), 7.61-7.54 (m, 6H), 7.36 (t, J = 7.4 Hz, 2H), 7.27 (t, J = 7.2 Hz, 1H), 6.84-6.67 (m, 4H), 5.10 (s, 2H), 4.53 (s, 2H), 3.87 (s, 3H), 2.17 (s, 3H). MS calcd. for $C_{31}H_{27}N_2O_6$ ($M+H^+$) 523.2, found 523.2.

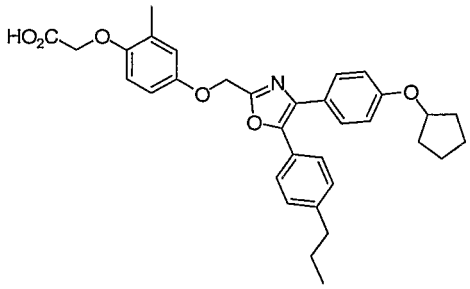
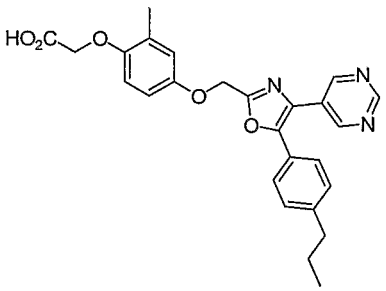
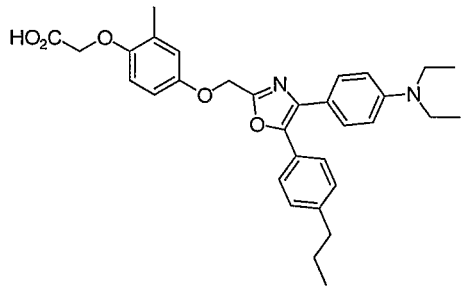
Compound Number	Compound Structure	Physical Data ^{1}H NMR 400 MHz (DMSO-d_6) and/or MS (m/z)
D3		^{1}H-NMR (400MHz, CD_3OD) δ = 8.74 (s, 2H), 7.75 (d, J = 8.4 Hz, 2H), 7.67 (d, J = 7.6 Hz, 2H), 7.61 (d, J = 8.4 Hz, 2H), 7.43 (t, J = 7.6 Hz, 2H), 7.33 (t, J = 7.2 Hz, 1H), 6.90 (d, J = 2.8 Hz, 1H), 6.83-6.71 (m, 2H), 5.20 (s, 2H), 4.56 (s, 2H), 3.91 (s, 3H), 2.12 (s, 3H). MS calcd. for $C_{30}H_{26}N_3O_6$ ($M+H^+$) 524.2, found 524.2.
D4		^{1}H-NMR (400MHz, CD_3OD) δ = 8.89 (bs, 1H), 8.64 (bs, 1H), 8.22 (d, J = 8.0 Hz, 1H), 7.80-7.56 (m, 7H), 7.49 (t, J = 7.4 Hz, 2H), 7.40 (t, J = 7.0 Hz, 1H), 6.96 (d, J = 2.8 Hz, 1H), 6.91-6.79 (m, 2H), 5.25 (s, 2H), 4.64 (s, 2H), 2.24 (s, 3H). MS calcd. for $C_{30}H_{25}N_2O_6$ ($M+H^+$) 493.2, found 493.0.
D5		^{1}H-NMR (400MHz, CD_3OD) δ = 9.08 (s, 1H), 8.96 (s, 2H), 7.72-7.31 (m, 9H), 6.88 (d, J = 2.8 Hz, 1H), 6.80-6.70 (m, 2H), 5.17 (s, 2H), 4.56 (s, 2H), 2.17 (s, 3H). MS calcd. for $C_{36}H_{35}N_2O_5$ ($M+H^+$) 494.2, found 494.1.

Compound Number	Compound Structure	Physical Data ^{1}H NMR 400 MHz (DMSO-d_6) and/or MS (m/z)
D6		^{1}H-NMR (400MHz, CD_3OD) δ = 7.74 (d, J = 8.0 Hz, 2H), 7.63-7.56 (m, 6H), 7.38-7.26 (m, 5H), 6.84 (d, J = 2.8 Hz, 1H), 6.79-6.67 (m, 2H), 5.11 (s, 2H), 4.53 (s, 2H), 3.56 (q, J = 7.2 Hz, 4H), 2.16 (s, 3H), 1.09 (t, J = 7.2 Hz, 6H). MS calcd. for $C_{35}H_{35}N_2O_5$ ($M+H^+$) 563.3, found 563.3.
D7		^{1}H-NMR (400MHz, CD_3OD) δ = 7.69 (d, J = 8.8 Hz, 2H), 7.62-7.55 (m, 6H), 7.42-7.26 (m, 5H), 6.85 (d, J = 2.8 Hz, 1H), 6.79-6.68 (m, 2H), 5.11 (s, 2H), 4.53 (s, 2H), 3.47-3.45 (s, 4H), 2.17 (s, 3H), 1.90-1.66 (s, 6H). MS calcd. for $C_{36}H_{35}N_2O_5$ ($M+H^+$) 575.3, found 575.2.
D8		^{1}H-NMR (400MHz, CD_3OD) δ = 7.64-7.57 (m, 6H), 7.48-7.29 (m, 5H), 6.92 (d, J = 8.8 Hz, 2H), 6.87 (d, J = 2.8 Hz, 1H), 6.81-6.70 (m, 2H), 5.11 (s, 2H), 4.56 (s, 2H), 3.90 (t, J = 6.4 Hz, 2H), 2.17 (s, 3H), 1.77-1.68 (m, 2H), 0.97 (t, J = 7.4 Hz, 3H). MS calcd. for $C_{34}H_{32}NO_6$ ($M+H^+$) 550.2, found 550.2.

Compound Number	Compound Structure	Physical Data ^{1}H NMR 400 MHz (DMSO-d_6) and/or MS (m/z)
D9		^{1}H-NMR (400MHz, CD_3OD) δ = 7.63-7.57 (m, 6H), 7.49-7.27 (m, 5H), 6.92 (d, J = 8.8 Hz, 2H), 6.87 (d, J = 2.8 Hz, 1H), 6.81-6.70 (m, 2H), 5.11 (s, 2H), 4.56 (s, 2H), 3.71 (d, J = 6.8 Hz, 2H), 2.17 (s, 3H), 2.04-1.94 (m, 1H), 0.97 (d, J = 6.8 Hz, 6H). MS calcd. for $C_{35}H_{34}NO_6$ ($M+H^+$) 564.2, found 564.2.
D10		^{1}H-NMR (400MHz, CD_3OD) δ = 7.64-7.58 (m, 6H), 7.48-7.27 (m, 5H), 6.90 (d, J = 8.8 Hz, 2H), 6.87 (d, J = 2.8 Hz, 1H), 6.81-6.70 (m, 2H), 5.11 (s, 2H), 4.54 (s, 2H), 4.38-4.30 (m, 1H), 2.17 (s, 3H), 1.75-1.55 (m, 2H), 1.22 (d, J = 6.0 Hz, 3H) 0.91 (t, J = 7.4 Hz, 3H). MS calcd. for $C_{35}H_{34}NO_6$ ($M+H^+$) 564.2, found 564.2.
D11		^{1}H-NMR (400MHz, CD_3OD) δ = 7.66-7.58 (m, 6H), 7.47-7.27 (m, 5H), 6.88-6.86 (m, 3H), 6.81-6.70 (m, 2H), 5.11 (s, 2H), 4.85-4.75 (m, 1H), 4.54 (s, 2H), 2.17 (s, 3H), 1.89-1.57 (m, 8H). MS calcd. for $C_{36}H_{34}NO_6$ ($M+H^+$) 576.2, found 576.2.

Compound Number	Compound Structure	Physical Data ^{1}H NMR 400 MHz (DMSO-d_6) and/or MS (m/z)
D12		^{1}H-NMR (400MHz, CD_3OD) δ = 7.60-7.55 (m, 6H), 7.37-7.24 (m, 3H), 7.01-6.96 (m, 2H), 6.84 (d, J = 2.8 Hz, 1H), 6.80-6.68 (m, 4H), 5.07 (s, 2H), 4.53 (s, 2H), 4.20-4.16 (m, 4H), 2.17 (s, 3H). MS calcd. for $C_{33}H_{28}NO_7$ ($M+H^+$) 550.2, found 550.1.
D13		^{1}H-NMR (400MHz, CD_3OD) δ = 7.65-7.55 (m, 8H), 7.37-7.25 (m, 5H), 6.84 (d, J = 3.2 Hz, 1H), 6.79-6.67 (m, 2H), 5.10 (s, 2H), 4.52 (s, 2H), 3.62 (bs, 2H), 3.34 (bs, 2H), 2.16 (s, 3H), 1.65-1.47 (m, 6H). MS calcd. for $C_{37}H_{35}N_2O_6$ ($M+H^+$) 603.2, found 603.2.
D14		^{1}H-NMR (400MHz, CD_3OD) δ = 7.65 (d, J = 8.0 Hz, 2H), 7.60-7.54 (m, 5H), 7.40-7.33 (m, 4H), 7.26 (t, J = 7.4 Hz, 1H), 6.84 (d, J = 2.8 Hz, 1H), 6.79-6.67 (m, 2H), 5.10 (s, 2H), 4.52 (s, 2H), 3.02 (s, 3H), 2.95 (s, 3H), 2.16 (s, 3H). MS calcd. for $C_{34}H_{31}N_2O_6$ ($M+H^+$) 563.2, found 563.2.

Compound Number	Compound Structure	Physical Data ^{1}H NMR 400 MHz (DMSO-d_6) and/or MS (m/z)
D15		^{1}H-NMR (400MHz, CD_3OD) δ = 7.65 (d, J = 8.0 Hz, 2H), 7.62-7.53 (m, 5H), 7.39-7.33 (m, 4H), 7.26 (t, J = 7.4 Hz, 1H), 6.84 (d, J = 2.8 Hz, 1H), 6.79-6.66 (m, 2H), 5.10 (s, 2H), 4.52 (s, 2H), 3.52-3.15 (m, 4H), 2.16 (s, 3H), 1.21-1.00 (m, 6H). MS calcd. for $C_{36}H_{35}N_2O_6$ ($M+H^+$) 591.2, found 591.2.
E2		^{1}H-NMR (400MHz, CD_3OD) δ = 8.25 (d, J = 2.0 Hz, 1H), 7.78 (dd, J = 8.8 Hz, J = 2.4 Hz, 1H), 7.38 (d, J = 8.0 Hz, 2H), 7.17 (d, J = 8.4 Hz, 2H), 6.83 (d, J = 2.8 Hz, 1H), 6.77-6.66 (m, 3H), 5.07 (s, 2H), 4.52 (m, 1H), 3.84 (s, 3H), 2.52 (t, J = 7.6 Hz, 2H), 2.15 (s, 3H), 1.59-1.53 (m, 2H), 0.86 (t, J = 7.2 Hz, 3H). MS calcd. for $C_{28}H_{29}N_2O_6$ ($M+H^+$) 489.2, found 489.1.
E3		^{1}H-NMR (400MHz, CD_3OD) δ = 7.52-7.48 (m, 4H), 7.26 (d, J = 8.0 Hz, 1H), 6.95-6.93 (m, 3H), 6.89-6.78 (m, 2H), 5.16 (s, 2H), 4.67-4.61 (m, 1H), 4.63 (s, 2H), 2.59 (t, J = 7.6 Hz, 2H), 2.24 (s, 3H), 1.68-1.62 (m, 2H), 1.33 (d, J = 6.0 Hz, 6H), 0.95 (t, J = 7.4 Hz, 3H). MS calcd. for $C_{31}H_{34}NO_6$ ($M+H^+$) 516.2, found 516.3.

Compound Number	Compound Structure	Physical Data ^{1}H NMR 400 MHz (DMSO-d_6) and/or MS (m/z)
E4		^{1}H-NMR (400MHz, CD_3OD) δ = 7.45 (d, J = 8.4 Hz, 4H), 7.19 (d, J = 8.0 Hz, 2H), 6.89-6.87 (m, 3H), 6.83-6.73 (m, 2H), 5.11 (s, 2H), 4.83-4.80 (m, 1H), 4.59 (s, 2H), 2.57 (t, J = 7.6 Hz, 2H), 2.22 (s, 3H), 1.97-1.58 (m, 11H), 0.92 (t, J = 7.2 Hz, 3H). MS calcd. for $C_{33}H_{36}NO_6$ ($M+H^+$) 542.3, found 542.3.
E5		^{1}H-NMR (400MHz, CD_3OD) δ =9.07 (bs, 1H), 8.90 (bs, 2H), 7.43 (d, J = 8.0 Hz, 4H), 7.24 (d, J = 8.0 Hz, 2H), 6.84-6.70 (m, 4H), 5.12 (s, 2H), 4.52 (s, 2H), 2.58-2.54 (m, 2H), 2.16 (s, 3H), 1.63-1.54 (m, 2H), 0.87 (t, J = 7.4 Hz, 3H). MS calcd. for $C_{26}H_{26}N_3O_5$ ($M+H^+$) 460.2, found 460.1.
E6		MS calcd. for $C_{32}H_{37}N_2O_5$ ($M+H^+$) 529.3, found 529.2.

Transcriptional Assay

[00161] Transfection assays are used to assess the ability of compounds of the invention to modulate the transcriptional activity of the PPARs. Briefly, expression vectors for chimeric proteins containing the DNA binding domain of yeast GAL4 fused to the ligand-binding domain (LBD) of either PPARδ PPARα or PPARγ are introduced via transient transfection into mammalian cells, together with a reporter plasmid where the luciferase gene is under the control of a GAL4 binding site. Upon exposure to a PPAR modulator, PPAR transcriptional activity varies, and this can be monitored by changes in luciferase levels. If transfected cells are exposed to a PPAR agonist, PPAR-dependent transcriptional activity increases and luciferase levels rise.

[00162] 293T human embryonic kidney cells ($8x10^6$) are seeded in a $175cm^2$ flask a day prior to the start of the experiment in 10% FBS, 1% Penicillin/Streptomycin/Fungizome, DMEM Media. The cells are harvested by washing with PBS (30ml) and then dissociating using trypsin (0.05%; 3ml). The trypsin is inactivated by the addition of assay media (DMEM, CA-dextran fetal bovine serum (5%). The cells are spun down and resuspended to 170,000cells/ml. A Transfection mixture of GAL4-PPAR LBD expression plasmid (1μg), UAS-luciferase reporter plasmid (1μg), Fugene (3:1 ratio; 6μL) and serum-free media (200μL) was prepared and incubated for 15-40 minutes at room temperature. Transfection mixtures are added to the cells to give 0.16M cells/mL, and cells (50μl/well) are then plated into 384 white, solid-bottom, TC-treated plates. The cells are further incubated at 37°C, 5.0% CO_2 for 5-7 hours. A 12-point series of dilutions (3 fold serial dilutions) are prepared for each test compound in DMSO with a starting compound concentration of 10μM. Test compound (500nl) is added to each well of cells in the assay plate and the cells are incubated at 37°C, 5.0% CO_2 for 18-24 hours. The cell lysis/luciferase assay buffer, Bright-Glo™ (25%; 25μl; Promega), is added to each well. After a further incubation for 5 minutes at room temperature, the luciferase activity is measured.

[00163] Raw luminescence values are normalized by dividing them by the value of the DMSO control present on each plate. Normalized data is analyzed and dose-response

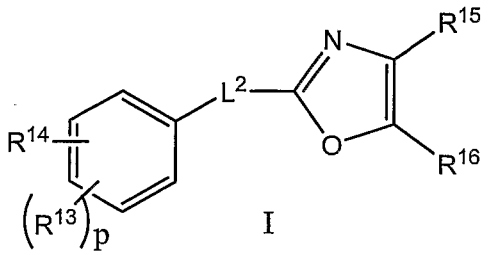
curves are fitted using Prizm graph fitting program. EC50 is defined as the concentration at which the compound elicits a response that is half way between the maximum and minimum values. Relative efficacy (or percent efficacy) is calculated by comparison of the response elicited by the compound with the maximum value obtained for a reference PPAR modulator.

[00164] Compounds of Formula I, in free form or in pharmaceutically acceptable salt form, exhibit valuable pharmacological properties, for example, as indicated by the *in vitro* tests described in this application. Compounds of the invention preferably have an EC50 for PPARδ of less than 1μM, more preferably less than 500nm, more preferably less than 100nM. Compounds of the invention are at least 100-fold selective for PPARδ over PPARγ.

[00165] It is understood that the examples and embodiments described herein are for illustrative purposes only and that various modifications or changes in light thereof will be suggested to persons skilled in the art and are to be included within the spirit and purview of this application and scope of the appended claims. All publications, patents, and patent applications cited herein are hereby incorporated by reference for all purposes.

WE CLAIM:

1. A compound of Formula I:



I

in which

p is an integer selected from 0 to 3;

L^2 is selected from –XOX–, $–XS(O)_{0-2}X–$ and $–XS(O)_{0-2}XO–$; wherein X is independently selected from a bond and C_{1-4}alkylene; wherein any alkylene of L^2 can be optionally substituted by 1 to 3 radicals selected from halo, C_{1-6}alkyl, C_{1-6}alkoxy, halo-substituted-C_{1-6}alkyl and halo-substituted-C_{1-6}alkoxy;

R^{13} is selected from halo, C_{1-6}alkyl, C_{1-6}alkoxy, hydroxy-C_{1-6}alkyl, halo-substituted-C_{1-6}alkyl, halo-substituted-C_{1-6}alkoxy, C_{6-10}aryl, C_{5-10}heteraryl, C_{3-12}cycloalkyl and C_{3-8}heterocycloalkyl; wherein any aryl, heteroaryl, cycloalkyl and heterocycloalkyl of R^{13} is optionally substituted with 1 to 3 radicals independently selected from halo, nitro, cyano, C_{1-6}alkyl, C_{1-6}alkoxy, hydroxy-C_{1-6}alkyl, halo-substituted-C_{1-6}alkyl and halo-substituted-C_{1-6}alkoxy;

R^{14} is selected from $-XOXC(O)OR^{17}$ and $-XC(O)OR^{17}$; wherein X is a bond or C_{1-4}alkylene; and R^{17} is selected from hydrogen and C_{1-6}alkyl;

R^{15} and R^{16} are independently selected from $–R^{18}$ and $–YR^{18}$; wherein Y is selected from C_{1-6}alkylene, C_{2-6}alkenylene, C_{2-6}alkynylene, $–C(O)NR^{17}–$ and –OX–; X is a bond or C_{1-4}alkylene; R^{17} is selected from hydrogen and C_{1-6}alkyl; and R^{18} is selected from C_{3-12}cycloalkyl, C_{3-8}heterocycloalkyl, C_{6-10}aryl and C_{5-13}heteroaryl; or R^{15} and R^{16} together with the atoms to which R^{15} and R^{16} are attached form fused bicyclic or tricyclic C_{5-14}heteroaryl;

wherein any aryl, heteroaryl, cycloalkyl and heterocycloalkyl of R^{18}, or the combination of R^{15} and R^{16}, is optionally substituted with 1 to 3 radicals independently selected from halo, nitro, cyano, C_{1-6}alkyl, C_{1-6}alkoxy, C_{1-6}alkylthio, hydroxy-C_{1-6}alkyl,

halo-substituted-C_{1-6}alkyl, halo-substituted-C_{1-6}alkoxy, C_{3-12}cycloalkyl, C_{3-8}heterocycloalkyl, C_{6-10}aryl, C_{5-13}heteroaryl, $-XS(O)_{0-2}R^{17}$, $-XS(O)_{0-2}XR^{19}$, $-XNR^{17}R^{17}$, $-XNR^{17}S(O)_{0-2}R^{17}$, $-XNR^{17}C(O)R^{17}$, $-XC(O)NR^{17}R^{17}$, $-XNR^{17}C(O)R^{19}$, $-XC(O)NR^{17}R^{19}$, $-XC(O)R^{19}$, $-XNR^{17}XR^{19}$ and $-XOXR^{19}$; wherein any aryl, heteroaryl, cycloalkyl or heterocycloalkyl substituent is further optionally substituted with 1 to 3 radicals independently selected from halo, nitro, cyano, C_{1-6}alkyl, C_{1-6}alkoxy, C_{1-6}alkylthio, hydroxy-C_{1-6}alkyl, halo-substituted-C_{1-6}alkyl and halo-substituted-C_{1-6}alkoxy; wherein X is a bond or C_{1-4}alkylene; R^{17} is selected from hydrogen and C_{1-6}alkyl; and R^{19} is selected from C_{3-12}cycloalkyl, C_{3-8}heterocycloalkyl, C_{6-10}aryl and C_{5-10}heteroaryl; wherein any aryl, heteroaryl, cycloalkyl or heterocycloalkyl of R^{19} is optionally substituted with 1 to 3 radicals independently selected from halo, nitro, cyano, C_{1-6}alkyl, C_{1-6}alkoxy, halo-substituted-C_{1-6}alkyl and halo-substituted-C_{1-6}alkoxy; and the pharmaceutically acceptable salts, hydrates, solvates, isomers and prodrugs thereof.

2. The compound of claim 1 in which:

p is an integer selected from 0 to 3;

L^2 is selected from $-XOX-$, $-XS(O)_{0-2}X-$ and $-XS(O)_{0-2}XO-$; wherein X is independently selected from a bond and C_{1-4}alkylene; wherein any alkylene of L^2 can be optionally substituted by 1 to 3 radicals selected from halo, C_{1-6}alkyl, C_{1-6}alkoxy, halo-substituted-C_{1-6}alkyl and halo-substituted-C_{1-6}alkoxy;

R^{13} is C_{1-6}alkyl, C_{1-6}alkoxy and halogen; and

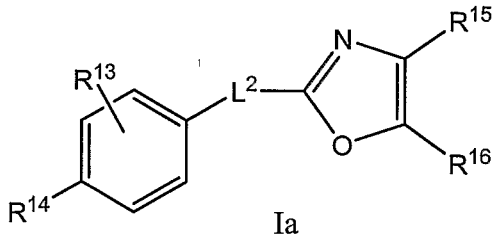
R^{14} is selected from $-XOXC(O)OR^{17}$ and $-XC(O)OR^{17}$; wherein X is a bond or C_{1-4}alkylene; and R^{17} is selected from hydrogen and C_{1-6}alkyl;

R^{15} and R^{16} are independently selected from $-R^{18}$ and $-YR^{18}$; wherein Y is selected from C_{1-6}alkylene, C_{2-6}alkenylene, $-C(O)NR^{17}-$ and $-OX-$; X is a bond or C_{1-4}alkylene; R^{17} is selected from hydrogen and C_{1-6}alkyl; and R^{18} is selected from C_{6-10}aryl, C_{3-12}cycloalkyl and C_{5-13}heteroaryl; or R^{15} and R^{16} together with the atoms to which R^{15} and R^{16} are attached form fused bicyclic or tricyclic C_{5-14}heteroaryl;

wherein any aryl, heteroaryl and cycloalkyl of R^{18}, or the combination of R^{15} and R^{16}, is optionally substituted with 1 to 3 radicals independently selected from halo, nitro, cyano, C_{1-6}alkyl, C_{1-6}alkoxy, C_{1-6}alkylthio, hydroxy-C_{1-6}alkyl, halo-substituted-C_{1-6}alkyl, halo-

substituted-C_{1-6}alkoxy, C_{3-12}cycloalkyl, C_{3-8}heterocycloalkyl, C_{6-10}aryl optionally substituted with C_{1-6}alkoxy, C_{5-13}heteroaryl, $-XS(O)_{0-2}R^{17}$, $-XS(O)_{0-2}XR^{19}$, $-XNR^{17}R^{17}$, $-XNR^{17}S(O)_{0-2}R^{17}$, $-XNR^{17}C(O)R^{17}$, $-XC(O)NR^{17}R^{17}$, $-XNR^{17}C(O)R^{19}$, $-XC(O)NR^{17}R^{19}$, $-XC(O)R^{19}$, $-XNR^{17}XR^{19}$ and $-XOXR^{19}$; wherein X is a bond or C_{1-4}alkylene; R^{17} is selected from hydrogen and C_{1-6}alkyl; and R^{19} is selected from C_{6-10}aryl, C_{5-10}heteroaryl, C_{3-8}heterocycloalkyl and C_{3-12}cycloalkyl; wherein any aryl, heteroaryl, cycloalkyl or heterocycloalkyl of R^{19} is optionally substituted with 1 to 3 radicals independently selected from halo, nitro, cyano, C_{1-6}alkyl, C_{1-6}alkoxy, halo-substituted-C_{1-6}alkyl and halo-substituted-C_{1-6}alkoxy.

3. The compound of claim 1 of Formula Ia:



Ia

L^2 is selected from $-S(O)_{0-2}(CH_2)_{1-4}O-$, $-O(CH_2)_{1-4}S(O)_{0-2}-$, $-CH_2S(O)_{0-2}-$, $-S(O)_{0-2}CH_2-$, $-S(O)_{0-2}-$, $-CH_2O-$ and $-OCH_2-$;

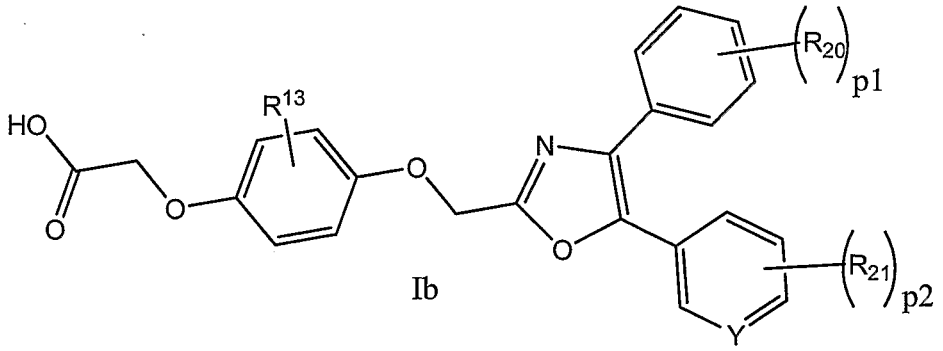
R^{13} is selected from C_{1-6}alkyl, C_{1-6}alkoxy and halo;

R^{14} is selected from $-OCH_2C(O)OH$ and $-CH_2C(O)OH$;

R^{15} and R^{16} are independently selected from $-R^{18}$ and $-YR^{18}$; wherein Y is selected from C_{1-6}alkylene, C_{2-6}alkenylene, $-C(O)NH-$ and $-O(CH_2)_{1-3}-$; and R^{18} is selected from phenyl, biphenyl, cyclohexyl, naphthyl, benzo[1,3]dioxol-5-yl, benzo[b]furanyl, pyridinyl, pyrimidinyl, dibenzo-furan-2-yl, furanyl, benzo[b]thiophene, thiophenyl, phenoxathiin-4-yl, benzoxazolyl, 3-oxo-3,4-dihydro-2H-benzo[1,4]oxazin-6-yl, 2-oxo-2,3-dihydro-benzooxazol-6-yl, 2,3-dihydro-benzo[1,4]dioxin-6-yl, benzoxazolyl, 3,4-dihydro-2H-benzo[b][1,4]dioxepin-7-yl and quinolinyl; or R^{15} and R^{16} together with the atoms to which R^{15} and R^{16} are attached form 4,5-dihydro-naphtho[1,2-d]thiazol-2-yl, 4H-chromeno[4,3-d]thiazol-2-yl, 5,6-dihydro-4H-3-thia-1-aza-benzo[e]azulen-2-yl, benzthiazolyl, benzoxazolyl and 1-oxa-3-aza-cyclopenta[a]naphthalen-2-yl;

wherein any aryl, heteroaryl, cycloalkyl and heterocycloalkyl of R^{15}, R^{16} or the combination of R^{15} and R^{16}, is optionally substituted with 1 to 3 radicals independently selected from halo, cyano, nitro, methyl, isopropyl, isopropyl-sulfanyl, isopropyloxy, hydroxy-methyl, methyl-sulfanyl, methoxy, ethoxy, pentafluoroethoxy, trifluoromethyl, trifluoromethoxy, trifluoromethyl-sulfonyl, morpholino, phenoxy, benzoxy, ethyl-sulfonyl, dimethylamino, methyl-sulfonyl-amino, ethyl-sulfonyl, propyl, vinyl, propyloxy, *sec*-butoxy, trifluoromethyl-sulfanyl, dimethyl-amino-carbonyl, diethyl-amino-carbonyl, methyl-carbonyl-amino, methyl-carbonyl, cyclopentyl-oxy, isopropyl-methylamino-carbonyl, cyclopropyl-amino-carbonyl, cyclohexyl, morpholino, piperidinyl, indolyl, pyrrolidinyl, pyrrolidinyl-carbonyl, 2,3-dihydro-benzofuran-5-yl piperidinyl-carbonyl, morpholino-carbonyl, isopropyl-methyl-amino, isopropyl-methyl-amino-carbonyl, diethyl-amino, and phenyl optionally substituted with methoxy.

4. The compound of claim 3 of Formula Ib:



Ib

in which:

p1 and p2 are independently selected from 0, 1 and 2;

Y is selected from N and CH;

R^{13} is selected from C_{1-6}alkyl, C_{1-6}alkoxy and halo;

R^{20} is selected from trifluoromethyl and trifluoromethoxy; and

R^{21} is selected from isopropyloxy and methoxy.

5. The compound of claim 4 that is {4-[4-(6-isopropoxy-pyridin-3-yl)-5-(4-trifluoromethoxy-phenyl)-oxazol-2-ylmethoxy]-2-methyl-phenoxy}-acetic acid.

6. A method for treating a disease or disorder in an animal in which modulation of PPARδ activity can prevent, inhibit or ameliorate the pathology and/or symptomology of the disease, which method comprises administering to the animal a therapeutically effective amount of a compound of Claim 1.

7. The method of claim 6 in which the disease or disorder is selected from the treatment of prophylaxis, dyslipidemia, hyperlipidemia, hypercholesteremia, atherosclerosis, atherogenesis, hypertriglyceridemia, heart failure, myocardial infarction, vascular diseases, cardiovascular diseases, hypertension, obesity, cachexia, inflammation, arthritis, cancer, anorexia, anorexia nervosa, bulimia, Alzheimer's disease, skin disorders, respiratory diseases, ophthalmic disorders, irritable bowel diseases, ulcerative colitis, Crohn's disease, type-1 diabetes, type-2 diabetes and Syndrome X.

8. The method of claim 6 in which the disease or disorder is selected from HIV wasting syndrome, long term critical illness, decreased muscle mass and/or muscle strength, decreased lean body mass, maintenance of muscle strength and function in the elderly, diminished muscle endurance and muscle function, and frailty in the elderly.

9. The use of a compound according to any of claims 1 to 5 in the manufacture of a medicament for treating a disease in an animal in which PPARδ activity contributes to the pathology and/or symptomology of the disease.

10. A pharmaceutical composition comprising a therapeutically effective amount of a compound of any of claim 1 to 5 in combination with one or more pharmaceutically acceptable excipients.

11. A pharmaceutical combination, especially a pharmaceutical composition, comprising: 1) a compound of any of claims 1 to 5 or a pharmaceutical acceptable salt thereof; and 2) at least one active ingredient selected from:

a) anti-diabetic agents such as insulin, insulin derivatives and mimetics; insulin secretagogues such as the sulfonylureas, e.g., Glipizide, glyburide and Amaryl;

insulinotropic sulfonylurea receptor ligands such as meglitinides, e.g., nateglinide and repaglinide; insulin sensitizer such as protein tyrosine phosphatase-1B (PTP-1B) inhibitors such as PTP-112; GSK3 (glycogen synthase kinase-3) inhibitors such as SB-517955, SB-4195052, SB-216763, NN-57-05441 and NN-57-05445; RXR ligands such as GW-0791 and AGN-194204; sodium-dependent glucose co-transporter inhibitors such as T-1095; glycogen phosphorylase A inhibitors such as BAY R3401; biguanides such as metformin; alpha-glucosidase inhibitors such as acarbose; GLP-1 (glucagon like peptide-1), GLP-1 analogs such as Exendin-4 and GLP-1 mimetics; dipeptidyl peptidase IV inhibitors such as DPP728, vildagliptin, MK-0431, saxagliptin, GSK23A ; an AGE breaker; a thiazolidone derivative (glitazone) such as pioglitazone, rosiglitazone, or *(R)*-1-{4-[5-methyl-2-(4-trifluoromethyl-phenyl)-oxazol-4-ylmethoxy]-benzenesulfonyl}-2,3-dihydro-1*H*-indole-2-carboxylic acid, a non-glitazone type PPARγ agonist e.g. GI-262570;

b) hypolipidemic agents such as 3-hydroxy-3-methyl-glutaryl coenzyme A (HMG-CoA) reductase inhibitors, e.g., lovastatin, pitavastatin, simvastatin, pravastatin, cerivastatin, mevastatin, velostatin, fluvastatin, dalvastatin, atorvastatin, rosuvastatin and rivastatin; squalene synthase inhibitors; FXR (farnesoid X receptor) and LXR (liver X receptor) ligands; cholestyramine; fibrates; nicotinic acid and aspirin;

c) an anti-obesity agent or appetite regulating agent such as phentermine, leptin, bromocriptine, dexamphetamine, amphetamine, fenfluramine, dexfenfluramine, sibutramine, orlistat, dexfenfluramine, mazindol, phentermine, phendimetrazine, diethylpropion, fluoxetine, bupropion, topiramate, diethylpropion, benzphetamine, phenylpropanolamine or ecopipam, ephedrine, pseudoephedrine or cannabinoid receptor antagonists;

d) anti-hypertensive agents, e.g., loop diuretics such as ethacrynic acid, furosemide and torsemide; diuretics such as thiazide derivatives, chlorithiazide, hydrochlorothiazide, amiloride; angiotensin converting enzyme (ACE) inhibitors such as benazepril, captopril, enalapril, fosinopril, lisinopril, moexipril, perinodopril, quinapril, ramipril and trandolapril; inhibitors of the Na-K-ATPase membrane pump such as digoxin; neutralendopeptidase (NEP) inhibitors e.g. thiorphan, terteo-thiorphan, SQ29072; ECE inhibitors e.g. SLV306; ACE/NEP inhibitors such as omapatrilat, sampatrilat and fasidotril; angiotensin II antagonists such as candesartan, eprosartan, irbesartan, losartan, telmisartan and valsartan, in particular valsartan; renin inhibitors such as aliskiren, terlakiren, ditekiren, RO 66-1132, RO-

66-1168; β-adrenergic receptor blockers such as acebutolol, atenolol, betaxolol, bisoprolol, metoprolol, nadolol, propranolol, sotalol and timolol; inotropic agents such as digoxin, dobutamine and milrinone; calcium channel blockers such as amlodipine, bepridil, diltiazem, felodipine, nicardipine, nimodipine, nifedipine, nisoldipine and verapamil; aldosterone receptor antagonists; and aldosterone synthase inhibitors;

e) a HDL increasing compound;

f) a cholesterol absorption modulator such as Zetia® and KT6-971;

g) Apo-A1 analogues and mimetics;

h) thrombin inhibitors such as Ximelagatran;

i) aldosterone inhibitors such as anastrazole, fadrazole, eplerenone;

j) Inhibitors of platelet aggregation such as aspirin, clopidogrel bisulfate;

k) estrogen, testosterone, a selective estrogen receptor modulator, a selective androgen receptor modulator;

l) a chemotherapeutic agent such as aromatase inhibitors e.g. femara, anti-estrogens, topoisomerase I inhibitors, topoisomerase II inhibitors, microtubule active agents, alkylating agents, antineoplastic antimetabolites, platin compounds, compounds decreasing the protein kinase activity such as a PDGF receptor tyrosine kinase inhibitor preferably Imatinib or 4-Methyl-N-[3-(4-methyl-imidazol-1-yl)-5-trifluoromethyl-phenyl]-3-(4-pyridin-3-yl-pyrimidin-2-ylamino)-benzamide; and

m) an agent interacting with a 5-HT_3 receptor and/or an agent interacting with 5-HT_4 receptor such as tegaserod, tegaserod hydrogen maleate, cisapride, cilansetron;

or, in each case a pharmaceutically acceptable salt thereof; and optionally a pharmaceutically acceptable carrier.

12. A pharmaceutical composition according to claim 10 or a combination according to claim 11, for the treatment or prevention of dyslipidemia, hyperlipidemia, hypercholesteremia, atherosclerosis, hypertriglyceridemia, heart failure, myocardial infarction, vascular diseases, cardiovascular diseases, hypertension, obesity, inflammation, arthritis, cancer, Alzheimer's disease, skin disorders, respiratory diseases, ophthalmic disorders, inflammatory bowel diseases, IBDs (irritable bowel disease), ulcerative colitis, Crohn's disease, conditions in which impaired glucose tolerance, hyperglycemia and insulin

resistance are implicated, such as type-1 and type-2 diabetes, Impaired Glucose Metabolism (IGM), Impaired Glucose Tolerance (IGT), Impaired Fasting Glucose (IFG), and Syndrome-X.

13. A compound according to any of claims 1 to 5, or a pharmaceutical composition according to claim 10 or a combination according to claim 11, for use as a medicament.

14. Use of a compound according to any of claims 1 to 5, or a pharmaceutical composition according to claim 10 or a combination according to claim 11, for the manufacture of a medicament for the treatment or prevention of dyslipidemia, hyperlipidemia, hypercholesteremia, atherosclerosis, hypertriglyceridemia, heart failure, myocardial infarction, vascular diseases, cardiovascular diseases, hypertension, obesity, inflammation, arthritis, cancer, Alzheimer's disease, skin disorders, respiratory diseases, ophthalmic disorders, inflammatory bowel diseases, IBDs (irritable bowel disease), ulcerative colitis, Crohn's disease, conditions in which impaired glucose tolerance, hyperglycemia and insulin resistance are implicated, such as type-1 and type-2 diabetes, Impaired Glucose Metabolism (IGM), Impaired Glucose Tolerance (IGT), Impaired Fasting Glucose (IFG), and Syndrome-X.