Abstract:

Title: COMPOUNDS AND COMPOSITIONS AS PPAR MODULATORS

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.
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 60/734,592, filed 07 November 2005. The foil disclosure of this application is incorporated herein by reference in its 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.

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 are useful as therapeutic agents in the treatment of such diseases.

SUMMARY OF THE INVENTION

In one aspect, the present invention provides compounds of Formula I:
in which:
n is selected from 0, 1, 2 and 3;
W is selected from N and CH;
Y is selected from O, S, (CEb)_{1.2} and CR_{4,5}; wherein R_{4b} and R_{4,5} are independently selected from hydrogen and Ci-alkyl;
Z is selected from S and O;
R_i is selected from -XiCR_{3}R_{8}X_{2}CO_{2}R_{7}, -XiSCR_{3}ReX_{2}CO_{2}R_{7} and -XOCR_{5}X_{2}CO_{2}R_{7}; wherein Xi and X2 are independently selected from a bond and Ci-4alkylene; and R_{3} and R_{6} are independently selected from hydrogen, Ci\^alkyl and Ci-4alkoxy; or R_{5} and R_{6} together with the carbon atom to which R_{5} and R_{6} are attached form C_{3-12}cycloalkyl; and R_{7} is selected from hydrogen and Ci-alkyl; each
R_2 is independently selected from halo, Ci\^alkyl, Ci\^alkoxy, Ci-4alkylthio and C_{3-12}cycloalkyl;
R_3 is Ci-alkyl;

[0004] R_4 is selected from Ci-4alkyl, halo, halo-substituted-C_{1-4}alkyl and halo-substituted-Ci-4alkoxy; 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.

[0005] 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.

[0006] In a third aspect, the present invention provides a method of treating a disease in an animal in which modulation of PPAR 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 or a N-oxide
derivative, individual isomers and mixture of isomers thereof, or a pharmaceutically
acceptable salt thereof.

[0007] 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 activity contributes to the pathology and/or symptomology of the disease.

[0008] 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**

[0009] "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. Ci-galkoxy
includes, methoxy, ethoxy, and the like. Halo-substituted alkyl includes trifluoromethyl,
pentafluoroethyl, and the like.

[0010] "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. "C6-iocycloalkyl" means an aryl as described above connected via a alkylene
grouping. For example, Ce-iocycloalkyl includes phenethyl, benzyl, etc.

[0011] "Cycloalkyl" means a saturated or partially unsaturated, monocyclic, fused
bicyclic or bridged polycyclic ring assembly containing the number of ring atoms indicated.
For example, C3-iocycloalkyl 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. Ci^alkyl or a nitrogen protecting
group. For example, Ca₄-heterocycloalkyl as used in this application to describe compounds of the invention includes morpholino, pyrrolidinyl, piperazinyl, piperidinyl, piperidinylone, 1,4-dioxo-8-aza-spiro[4.5]dec-8-yl, etc.

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

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

Description of the Preferred Embodiments

The present invention provides compounds, compositions and methods for the treatment of diseases in which modulation of the activity of one or more PPARs 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.

In one embodiment, with reference to compounds of Formula I:

- n is selected from 0, 1 and 2;
- W is selected from N and CH;
- Y is selected from O, S and CH₂;
- Z is selected from S and O;
- Rᵢ is selected from -X₁OCR₅R₆X₂CO₂H, -X₁OCR₅R₆X₂CO₂H and -X₁OCR₅R₆X₂CO₂H; wherein X₁ and X₂ are independently selected from a bond and C₄ₐlkoxy; and R₅ and R₆ are independently selected from hydrogen, C₄ₐlkoxy and C₄ₐlkoxy; or R₅ and R₆ together with the carbon atom to which R₅ and R₆ are attached form C₃₋₅cycloalkyl; and each
- R₂ is independently selected from halo, Cⁱᵗ-alkoxy, Cⁱᵗ-alkoxy and C₃₋₅cycloalkyl;
- R₃ is selected from Cⁱᵗ-alkoxy;
- R₄ is halo-substituted-Cⁱᵗ-alkoxy.
In another embodiment, Y is selected from O and S; and R_i is selected from
-CH_2CR_5R_6CO_2H, -SCR_5R_6CO_2H, -CR_5ReCH_2CO_2H and -CR_5R_6CO_2H;
wherein R_5 and R_6 are independently selected from hydrogen, methyl, methoxy and ethoxy;
or Rs and R_6 together with the carbon atom to which R_5 and R_6 are attached form
cyclopentyl.

In another embodiment, each R_2 is independently selected from methyl and
cyclopropyl; and R_3 is selected from methyl and isopropyl.

Preferred compounds of the invention are selected from: 2-Ethoxy-3-{4-[4-(2-
isopropoxy-pyrimidin-5-yl)-5-(4-trifluoromethoxy-phenyl)-oxazol-2-ylmethoxy]-phenyl}-
propionic acid; 2-Ethoxy-3-[3-[4-(2-isopropoxy-pyrimidin-5-yl)-5-(4-trifluoromethoxy-
phenyl)-oxazol-2-ylmethoxy]-phenyl] -propionic acid; 4-[4-(2-Isopropoxy-pyrimidin-5-yl)-
5-(4-trifluoromethoxy-phenyl)-oxazol-2-ylmethoxy]-2-methyl-phenoxy] -acetic acid; 3-[4-
(2-Isopropoxy-pyrimidin-5-yl)-5-(4-trifluoromethoxy-phenyl)-oxazol-2-ylmethoxy]-2-
methyl-phenyl] -propionic acid; 3-[2-Cyclopropyl-5-[4-(2-isopropoxy-pyrimidin-5-yl)-5-(4-
trifluoromethoxy-phenyl)-oxazol-2-ylmethoxy]-phenyl] -propionic acid; 3-[5-Cyclopropyl-
4-[4-(2-isopropoxy-pyrimidin-5-yl)-5-(4-trifluoromethoxy-phenyl)-oxazol-2-ylmethoxy]-2-
methyl-phenyl] -propionic acid; 3-[2-Cyclopropyl-3-[4-(2-isopropoxy-pyrimidin-5-yl)-5-(4-
trifluoromethoxy-phenyl)-oxazol-2-ylmethoxy]-phenyl] -propionic acid; 2-[4-[4-(2-
Isopropoxy-pyrimidin-5-yl)-5-(4-trifluoromethoxy-phenyl)-oxazol-2-ylmethoxy]-3-methyl-
phenoxy] -2-methyl-propionic acid; 3-[4-[4-(2-Isopropoxy-pyrimidin-5-yl)-5-(4-
trifluoromethoxy-phenyl)-oxazol-2-ylmethoxy]-phenyl] -2-methyl-propionic acid; 3-[4-[4-
(2-Isopropoxy-pyrimidin-5-yl)-5-(4-trifluoromethoxy-phenyl)-oxazol-2-ylmethoxy]-phenyl]-
butyric acid; 2-[4-[4-(2-Isopropoxy-pyrimidin-5-yl)-5-(4-trifluoromethoxy-phenyl)-
oxazol-2-ylmethoxy]-2-methyl-phenoxy] -2-methyl-propionic acid; 4-[4-(2-Isopropoxy-
pyrimidin-5-yl)-5-(4-trifluoromethoxy-phenyl)-oxazol-2-ylmethoxy]-2,3-dimethyl-
phenoxy] -acetic acid; 2-[4-[4-(2-Isopropoxy-pyrimidin-5-yl)-5-(4-trifluoromethoxy-
phenyl)-oxazol-2-ylmethysulfanyl]-2,5-dimethyl-phenoxy] -2-methyl-propionic acid; 2-[4-
(2-Isopropoxy-pyrimidin-5-yl)-5-(4-trifluoromethoxy-phenyl)-oxazol-2-ylmethoxy]-2,3-
dimethyl-phenoxy] -2-methyl-propionic acid; 2-Ethoxy-3-[4-[4-(2-isopropoxy-pyrimidin-5-
yl)-5-(4-trifluoromethoxy-phenyl)-oxazol-2-ylmethoxy]-2-methyl-phenyl] -propionic acid;
2-[4-[4-(2-Isopropoxy-pyrimidin-5-yl)-5-(4-trifluoromethoxy-phenyl)-oxazol-2-ylmethoxy]-

2,5-dimethyl-phenoxy} -2-methyl-propionic acid; 2-Ethoxy-3- \{4-[4-(2-isopropoxy-pyrimidin-5-yl)-5-(4-trifluoromethoxy-phenyl)-oxazol-2-ylmethoxy]-2,5-dimethyl-phenyl\} -propionic acid; 2-Cyclopropyl-5-[4-(2-isopropoxy-pyrimidin-5-yl)-5-(4-trifluoromethoxy-phenyl)-oxazol-2-ylmethoxy]-phenyl]-acetic acid; 3-Cyclopropyl-5-[4-(2-isopropoxy-pyrimidin-5-yl)-5-(4-trifluoromethoxy-phenyl)-oxazol-2-ylmethoxy]-phenyl]-acetic acid; 4-Cyclopropyl-3-[4-(2-isopropoxy-pyrimidin-5-yl)-5-(4-trifluoromethoxy-phenyl)-oxazol-2-ylmethoxy]-phenyl]-acetic acid; 2-Cyclopropyl-3-[4-(2-isopropoxy-pyrimidin-5-yl)-5-(4-trifluoromethoxy-phenyl)-oxazol-2-ylmethoxy]-phenyl]-acetic acid; 3-Cyclopropyl-4-[4-(2-isopropoxy-pyrimidin-5-yl)-5-(4-trifluoromethoxy-phenyl)-oxazol-2-ylmethoxy]-phenyl]-acetic acid; 2-Cyclopropyl-2-[4-(2-isopropoxy-pyrimidin-5-yl)-5-(4-trifluoromethoxy-phenyl)-oxazol-2-ylmethoxy]-phenyl]-acetic acid; 3-Cyclopropyl-2-[4-(2-isopropoxy-pyrimidin-5-yl)-5-(4-trifluoromethoxy-phenyl)-oxazol-2-ylmethoxy]-phenyl]-acetic acid; 1-[3-[4-(2-Isopropoxy-pyrimidin-5-yl)-5-(4-trifluoromethoxy-phenyl)-oxazol-2-ylmethoxy]-phenyl]-cyclopentane-carboxylic acid; 3-[4-[4-(2-Isopropoxy-pyrimidin-5-yl)-5-(4-trifluoromethoxy-phenyl)-oxazol-2-ylmethoxy]-2,5-dimethyl-phenyl]-2-methyl-propionic acid; 4-[4-(2-Isopropoxy-pyrimidin-5-yl)-5-(4-trifluoromethoxy-phenyl)-oxazol-2-ylmethoxy]-2,5-dimethyl-phenoxacyclic acid.

Further preferred compounds of Formula I are detailed in the Examples and table, infra.
Pharmacology and Utility

[0016] 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 contributes to the pathology and/or symptomology of the disease.

[0017] Such compounds may therefore be employed for the treatment of prophylaxis, dyslipidemia, hyperlipidemia, hypercholesteremia, atherosclerosis, atherogenesis, hypertriglyceridemia, heart failure, hyper cholesterolemia, 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.

[0018] 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.

[0019] 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).

[0020] 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**

[0021] 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.

[0022] 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 polyvinylpyrrolidone; 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.

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

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

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:

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 sensitizers such as protein tyrosine phosphatase-1B (PTP-1B) inhibitors such as PTP-1 12; 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; glycolgen phosphorylase A inhibitors such as BAY R3401; biguanides such as metformin; alpha-glucosidase inhibitors such as acarbose; GLP-I (glucagon like peptide-1), GLP-I analogs such as Exendin-4 and GLP-I 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)-I- [4-5-methyl-2-(4-trifluoromethyl-phenyl)-oxazol-4-ylmethoxy]-benzenesulfonyl]-2,3-dihydro-l 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;

b) hypolipidemic agents such as 3-hydroxy-3-methyl-glutaryl coenzyme A (HMG-CoA) reductase inhibitors, e.g., lovastatin, pravastatin, 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, bremoripteine, dexemphetamine, amphetamine, fenfluramine, dexfenfluuramine, sibutramine, orlistat, dexfenfluuramine, 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, chlorthiazide, hydrochlorothiazide, amiloride; angiotensin converting enzyme (ACE) inhibitors such as benazepril, captopril, enalapril, fosinopril, lisinopril, moexipril, perindopril, 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, nisoldipine and verapamil; aldosterone receptor antagonists; and aldosterone synthase inhibitors;

- e) a HDL increasing compound;
- f) Cholesterol absorption modulator such as Zetia® and KT6-971;
- g) Apo-Al 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 (\{N-{5-[4-(4-methyl-piperazino-methyl)-benzoylamido3-2-methylphenyl]-4-(3-pyridyl)-2-pyrimidine-amine\}) described in the European patent application EP-A-O 564 409 as example 21 or 4-Methyl-N-[3-(4-methyl-imidazol-1-yl)-5-trifuoromethyl- phenyl]-3-(4-pyridin-3-yl-pyrimidin-2-ylamino)-benzamide described in the patent application WO 04/005281 as example 92; and
- m) an agent interacting with a 5-HT₃ receptor and/or an agent interacting with 5-HT₄ receptor such as tegaserod described in the US patent No. 5510353 as example 13, tegaserod hydrogen maleate, cisapride, cilansetron;
- or, in each case a pharmaceutically acceptable salt thereof; and optionally a pharmaceutically acceptable carrier.
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-lH-indole-2-carboxylic acid, a sulfonylurea receptor ligand, aliskiren, valsartan, orlistat or a statin such as pravastatin, simvastatin, fluvastatin or pravastatin.

Preferably the pharmaceutical combinations contain 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.

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.

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.

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.

[0045] 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-IB) inhibitors, GLP-I receptor mimetics; metformin; alpha-glucosidase inhibitors, such as acarbose; GLP-I (glucagon like peptide-1), GLP-I analogs, such as Exendin-4, and GLP-I 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, fiuvastatin, dalvastatin, atorvastatin, rosuvastatin, fluidostatin 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.

[0046] 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.

[0047] 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.

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

[0048] 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.

[0049] Compounds of Formula I, in which R₄ is cyclic (e.g. cycloalkyl, heterocycloalkyl, aryl and heteroaryl), can be prepared by proceeding as in reaction scheme I:

Reactions Scheme 1

\[
\begin{align*}
&\text{(2)} \\
\text{\(\rightarrow\)} \\
&\text{(3)} \\
\text{\(\rightarrow\)} \\
&\text{I}
\end{align*}
\]

[0050] in which n, R₁, R₂, R₃, Y, Z and W are as defined for Formula I in the Summary of the Invention. Q is a halogen, preferably Cl or Br; and R³⁰ is independently selected from hydrogen, C₆alkyl or the R³⁰ 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(Ph₄), or the like), a suitable base (e.g., Na₂CO₃, 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.

[0051] Compounds of Formula I, in which R is defined by -XiCRsReX₂CO₂R₇ (shown below), -XiSCR₅ReXiCO₂R₇ and -XiOCR₅ReXaCO₂R₇, wherein R₇ is an alkyl group e.g., methyl for a compound of formula 6 converting to hydrogen in formula I, can be prepared by proceeding as in reaction scheme 2:

Reactions Scheme 2

[0052] in which n, R₁, R₂, R₃, R₄, Rs, R₇, Xi, Xz, Y, Z and W are as defined for Formula I. 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°C to about 50°C and takes up to about 30 hours to complete.

[0053] Compounds of Formula I can be prepared by proceeding as in reaction scheme 3:

Reactions Scheme 3
in which \( n, R_i, R, R_3, R_4, Y, Z \) and \( W \) are as defined for Formula I in the Summary of the Invention. Compounds of Formula I 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\(^\circ\)C and takes up to about 30 hours to complete.

Compounds of Formula (2), where \( Y \) is S or O, can be prepared by proceeding as in reaction scheme 4:

Reactions Scheme 4

in which \( n, R_i, R, R_3, R_4, Y, Z \) and \( W \) are as defined for Formula I in the Summary of the Invention; \( Y \) is S or O; 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 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\(^\circ\)C and takes up to about 24 hours to complete.

Compounds of Formula (2), in which \( Y \) is S or O, can be prepared by proceeding as in reaction scheme 5:
Reactions Scheme 5

(14) \rightarrow (2)

in which n, R₁, R₂, R₃, R₄, Y, Z and W are as defined for Formula I in the Summary of the Invention. 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.

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

**Additional Processes for Making Compounds of the Invention**

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.

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.).
[0062] 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.

[0063] 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).

[0064] 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.

[0065] 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.

[0066] 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.

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

(a) that of reaction scheme 1, 2, 3, 4 or 5; and
(b) optionally converting a compound of the invention into a pharmaceutically acceptable salt;
(c) optionally converting a salt form of a compound of the invention to a non-salt form;
(d) optionally converting an unoxidized form of a compound of the invention into a pharmaceutically acceptable N-oxide;
(e) optionally converting an N-oxide form of a compound of the invention to its unoxidized form;
(f) optionally resolving an individual isomer of a compound of the invention from a mixture of isomers;
(g) optionally converting a non-derivatized compound of the invention into a pharmaceutically acceptable prodrug derivative; and
(h) optionally converting a prodrug derivative of a compound of the invention to its non-derivatized form.

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.

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

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.

Intermediate 5: 4-Bromo-2-bromomethyl-5-(4-trifluoromethoxy-phenyl)-oxazole.

**Step A**: 1,1,1,3,3,3-Hexamethyldisilazane (8.93 g, 55.35 mmol) is dissolved in dry THF (50 mL) in a flame-dried three-necked flask, and cooled to 0°C. M-Butyllithium (2.5 M in hexanes, 21.55 mL, 53.88 mmol) is added dropwise. After stirring the resulting solution for 10 min at 0°C, it is cooled to -78°C. 4'-(Trifluoromethoxy)acetophenone 1 (10.0 g, 48.98 mmol) dissolved in dry THF (64 mL) is added dropwise over 30 min. The reaction is stirred for 45 min at -78°C. 2,2,2-Trifluoroethyltrifluoroacetate (11.43 g, 58.78 mmol) is added rapidly. After 20 min, the reaction is poured into a separation funnel containing 200 mL of 5% aqueous HCl and extracted with 250 mL diethyl ether. The organic layer is washed with brine, dried over MgSO₄, and concentrated. The residue is dissolved in acetonitrile (50 mL), then water (0.88 mL, 48.98 mmol) and triethylamine (7.43 g, 73.47 mmol) are added. Freshly prepared methanesulfonyl azide (8.98 g, 73.47 mmol) in a solution of acetonitrile (16 mL) is added over 30 min at rt. [Methanesulfonyl azide is prepared from the following procedure: Methanesulfonyl chloride (8.85 g, 73.47 mmol) is dissolved in acetone (50 mL). Sodium azide (7.56 g, 116.0 mmol) is then added over 30 min. The reaction is stirred for 1.5 h at rt, then it is filtered, and washed with acetone. The filtrate is concentrated and used crude.] The reaction is kept stirring for 1 h, then concentrated. The residue is diluted with diethyl ether (200 mL), washed with 10% NaOH three times, and then with brine. It is dried
over MgSO₄, filtered and concentrated to give crude product, which is purified by silica gel chromatography (ether/hexane, gradient) to give 2-diazo-4'-trifluoromethoxyacetophenone 2 as a yellow solid: ¹H-NMR (400 MHz, CDCl₃) δ = 7.82 (d, J = 8.8 Hz, 2H), 7.29 (d, J = 8.8 Hz, 2H), 5.89 (s, IH). MS calcd. for C₉H₆F₃N₂O₂ (M⁺) 230.0, found 203.0 (M+H⁺-N₂).

**Step B:** Aluminum chloride (19.6 g, 146.78 mmol) is carefully added in portions into anhydrous acetonitrile (200 mL). 2-Diazo-4'-trifluoromethoxyacetophenone 2 (16.89 g, 73.39 mmol) dissolved in anhydrous acetonitrile (200 mL) is added by syringe dropwise over 30 min at rt with an outlet to release generated nitrogen. The reaction is stirred for 45 min, then it is poured into diethyl ether (500 mL). The solution is carefully quenched with 0.2 N HCl, then treated with 1 N NaOH to pH 9-10. The organic layer is separated. The aqueous layer is extracted twice with diethyl ether. The combined organic layers are washed with water and brine, dried (MgSO₄), filtered, and concentrated to give crude product, which is purified by silica gel chromatography (ether/hexane gradient) to give 2-methyl-5-(4-trifluoromethoxy-phenyl)-oxazole 3 as an oil: ¹H-NMR (400 MHz, CDCl₃) δ = 7.56 (d, J = 8.8 Hz, 2H), 7.19 (d, J = 8.8 Hz, 2H), 7.13 (s, IH), 2.46 (s, 3H). MS calcd. for C₉H₆F₃NO₂ (M+H⁺) 244.1, found 244.0.

**Step C:** 2-Methyl-5-(4-trifluoromethoxy-phenyl)-oxazole 3 (3.07 g, 12.62 mmol) is dissolved in chloroform (100 mL), then bromine (649 µL, 12.62 mmol) is added dropwise and the mixture is stirred at rt for 15 h. The solution is diluted with CH₂Cl₂ (100 mL) and washed with saturated NaHCO₃ (150 mL) and brine (130 mL). The organic layer is dried (MgSO₄), filtered and concentrated to give crude product, which is purified by silica gel chromatography with ether/hexane (gradient) to give 4-bromo-2-methyl-5-(4-trifluoromethoxy-phenyl)-oxazole 4 as an oil: ¹H-NMR (400 MHz, CDCl₃) δ = 7.86 (d, 2H, J = 8.6 Hz), 7.22 (d, 2H, J = 8.6 Hz), 2.47 (s, 3H). MS calcd. for C₉H₉BrF₃NO₂ (M+H⁺) 321.9, found 321.9.

**Step D:** Al-Bromosuccinimide (4.89 g, 27.5 mmol) is added to a solution of 4-bromo-2-methyl-5-(4-trifluoromethoxy-phenyl)-oxazole 4 (2.0 g, 6.25 mmol) in carbon tetrachloride (40 mL). The above solution is stirred at 75°C for 20 h. The solution is diluted with CH₂Cl₂.
(100 mL) and washed with saturated aqueous Na₂CO₃ and brine. The organic layer is dried (MgSO₄), filtered and concentrated to give crude product, which is purified by silica gel chromatography with hexane/ether (gradient) to give 4-bromo-2-bromomethyl-5-(4-trifluoromethoxy-phenyl)-oxazole 5 as a white solid: ¹H-NMR (400 MHz, CDCl₃) δ = 7.91 (d, 2H, J = 8.6 Hz) 5.725 (d, 2H, J = 8.6 Hz) 5.41 (s, 3H). MS calcld. for CuH₇Br₂F₃NO₂ (MH-H⁺) 399.9, found 399.8.

Interimde 10: (2-Cyclopropyl-5-hydroxy-phenyl)-acetic acid ethyl ester.

Step A: (3-Hydroxy-phenyl)-acetic acid (10 g, 65.7 mmol) is dissolved in EtOH (60 mL). Catalytic amounts of thionyl chloride (~0.5 mL) are added and the solution is stirred for 6 h at rt. The solvent is removed in vacuo to give (3-hydroxy-phenyl)-acetic acid ethyl ester 6 (11.8 g, quant): MS calcld. for C₁₀H₁₃O₃ (M+H⁺) 181.1, found 181.0.

Step B: (3-Hydroxy-phenyl)-acetic acid ethyl ester 6 (5.93 g, 32.9 mmol) and imidazole (6.72 g, 98.7 mmol) are dissolved in DMF (16 mL) and stirred at rt for 10 min. Then TBDMSCl (7.44 g, 49.4 mmol) dissolved in DMF (4 mL) is added slowly and the mixture is stirred at rt overnight. Then water (50 mL) is added and the mixture is extracted with ether twice. The organic layers are combined, washed with water and brine, dried over MgSO₄, filtered and concentrated to give [3-(tc/V-butyl-dimethyl-silylxyloxy)-phenyl]-acetic acid ethyl ester 7 as an oil: ¹H-NMR (400 MHz, CDCl₃) δ = 6.97 (t, J = 7.8 Hz, 1H), 6.67 (d, J = 7.6 Hz, 1H), 6.59 (s, 1H), 6.54 (d, J = 8.1 Hz, 1H), 3.95 (q, J = 7.1 Hz, 2H), 3.35 (s, 2H), 1.05 (t, J = 7.1 Hz, 1H), 0.79 (s, 1H), 0.00 (s, 6H); MS calcld. for C₁₆H₂₇O₃Si (M+H⁺) 295.2, found 295.1.
Step C: [3-(tert-/Butyl-dimethyl-silanyloxy)-phenyl]-acetic acid ethyl ester 7 (9.20 g, 31.2 mmol) and potassium acetate (3.10 g, 31.2 mmol) are dissolved in acetic acid (120 mL) and cooled to 15°C. Bromine (1.60 mL, 31.2 mmol) dissolved in HOAc (60 mL) is added at a rate that kept the temperature at approx. 15°C, then the mixture is stirred at this temperature for 2 h. Insoluble salts are filtered and the filtrate is concentrated. The remainder is taken up in ether and washed with saturated sodium bicarbonate, water and brine. The organic layer is dried over MgSO₄, filtered and concentrated. The remainder is purified by flash chromatography (EtOAc/Hexanes gradient) to afford [2-bromo-5-(tert-butyl-dimethyl-silanyloxy)-phenyl]-acetic acid ethyl ester 8 as a colourless oil: ¹H-NMR (400 MHz, CDCl₃) δ= 7.19 (d, J = 8.6 Hz, 1H), 6.61 (d, J = 2.9 Hz, 5H), 6.44 (dd, J = 8.6 Hz, J = 2.9 Hz), 3.99 (q, J = 7.1 Hz, 2H), 3.51 (s, 6H), 1.07 (t, J = 7.1 Hz, 3H), 0.78 (s, 9H), 0.00 (s, 6H); MS calcd. for C₁₉H₂₆O₂BrSi (M+H⁺) 373.1, found 373.0.

Step D: [2-Bromo-5-(tert-/butyl-dimethyl-silanyloxy)-phenyl]-acetic acid ethyl ester 8 (1.00 g, 2.68 mmol), potassium phosphate (1.99 g, 9.38 mmol) and cyclopropylboronic acid (0.35 g, 4.02 mmol) are dissolved in toluene (12 mL). Tricyclohexylphosphine (0.23 g, 0.80 mmol), palladium acetate (0.09 g, 0.40 mmol) and water (0.6 mL) are added and the mixture is heated to 100°C overnight. Then the mixture is diluted with EtOAc (160 mL) and washed with water and brine successively. The organic layer is dried over MgSO₄, filtered and concentrated to afford crude [5-(tert-/butyl-dimethyl-silanyloxy)-2-cyclopropyl-phenyl]-acetic acid ethyl ester 9 as a colourless oil: ¹H-NMR (400 MHz, CDCl₃) δ= 6.91 (d, J = 8.3 Hz, 1H), 6.72 (d, J = 2.6 Hz, 3H), 6.65 (dd, J = 8.3 Hz, J = 2.6 Hz, 1H), 4.15 (q, J = 7.1 Hz, 2H), 3.76 (s, 2H), 1.84 (m, 1H), 1.24 (t, J = 7.1 Hz, 3H), 0.97 (s, 9H), 0.87 (m, 2H), 0.57 (m, 2H), 0.00 (s, 6H); MS calcd. for C₁₁H₃O₂Si (M-HH⁺) 335.2, found 335.1.

Step E: Crude [5-(tert-/butyl-dimethyl-silanyloxy)-2-cyclopropyl-phenyl]-acetic acid ethyl ester 9 is dissolved in a mixture of THF (5 mL) and TBAF (5 mL of a 1.0-M solution in THF) and stirred at rt for 90 min. Water (75 mL) is added and the mixture is extracted with EtOAc (100 mL) twice. The organic layers are combined, washed with 0.1 M HCl and brine, dried over MgSO₄, filtered and concentrated. The remainder is purified by reverse
phase HPLC (HkO/MeCN gradient) to afford (2-cyclopropyl-5-hydroxy-phenyl)-acetic acid ethyl ester 10 as an oil: $^1$H-NMR (400 MHz, CDCl$_3$) $\delta = 6.92$ (d, $J = 8.3$ Hz, IH), 6.71 (d, $J = 2.6$ Hz, IH), 6.64 (dd, $J = 8.3$ Hz, $J = 2.6$ Hz, IH), 4.16 (q, $J = 7.1$ Hz, 2H), 3.76 (s, 2H), 1.80 (m, IH), 1.25 (t, $J = 7.1$ Hz, 3H), 0.85 (m, 2H), 0.55 (m, 2H); MS calcd. for C$_{13}$H$_{17}$O$_3$ (M+H$^+$) 221.1, found 221.0.

Intermediate 15: (3-Cyclopropyl-5-hydroxy-phenyl)-acetic acid methyl ester.

**Step A**: (3,5-Dihydroxy-phenyl)-acetic acid (5 g, 29.7 mmol) is dissolved in MeOH (25 mL). Catalytic amounts of thionyl chloride (~0.25 mL) are added and the solution is stirred at rt overnight. The solvent is removed in vacuo to give (3,5-dihydroxy-phenyl)-acetic acid methyl ester 11 (5.44 g, quant.): MS calcd. for C$_9$H$_{11}$O$_4$ (M+H$^+$) 183.1, found 183.0.

**Step B**: (3,5-Dihydroxy-phenyl)-acetic acid methyl ester 11 (2.50 g, 13.9 mmol) and imidazole (3.78 g, 55.5 mmol) are dissolved in DMF (10 mL) and stirred at rt for 10 min. Then TBDMScI (1.67 g, 11.1 mmol) dissolved in DMF (4 mL) is added slowly and the mixture is stirred at rt for 8 h. Water (50 mL) is added and the mixture is extracted with ether twice. The organic layers are combined, washed with water and brine, dried over MgSO$_4$, filtered and concentrated. The crude product is dissolved in DCM/hexanes(1:9) and filtered to give a mixture of bisilylated sideproduct and [3-(fer^-butyl-dimethyl-silanyloxy)-5-hydroxy-phenyl]-acetic acid methyl ester 12 as a colourless oil: MS calcd. for C$_{15}$H$_{28}$O$_4$Si (M+H$^+$) 297.1, found 297.1.
Step C: [3-((tert-butyl-dimethyl-silanyloxy)-5-hydroxy-phenyl)-acetic acid methyl ester 12 (1.81 g, 6.1 mmol) and triethyl amine (0.85 mL, 6.1 mmol) are dissolved in DCM (30 mL) and cooled to 0°C. Triflic anhydride (1.03 mL, 6.1 mmol) dissolved in DCM (20 mL) is added dropwise, then the mixture is stirred at 0°C for 3 h. The solution is washed with saturated sodium bicarbonate, water and brine. The organic layer is dried over MgSO₄, filtered and concentrated. The remainder is purified by flash chromatography (EtOAc/Hexanes gradient) to afford [3-(tert-butyl-dimethyl-silanyloxy)-5-trifluoromethanesulfonyloxy-phenyl]-acetic acid methyl ester 13 as a colourless oil: ¹H-NMR (400 MHz, CDCl₃) δ = 6.61 (s, 1H), 6.58 (s, 1H), 6.44 (s, 1H), 3.49 (s, 3H), 3.37 (s, 2H), 0.76 (s, 9H), 0.00 (s, 6H); MS calcd. for C₁₅H₂₄F₃O₆Si (M+H⁺) 429.1, found 429.1.

Step D: [3-(tert-butyl-dimethyl-silanyloxy)-5-trifluoromethanesulfonyloxy-phenyl]-acetic acid methyl ester 13 (0.5 g, 1.13 mmol), potassium phosphate (0.84 g, 3.96 mmol) and cyclopropylboronic acid (0.13 g, 1.472 mmol) are dissolved in toluene (6 mL). Tricyclohexylphosphine (32 mg, 0.11 mmol), palladium acetate (13 mg, 0.06 mmol) and water (0.3 mL) are added and the mixture is heated to 100°C overnight. Then the mixture is diluted with EtOAc (100 mL) and washed with water and brine successively. The organic layer is dried over MgSO₄, filtered and concentrated to afford crude [3-(tert-butyl-dimethyl-silanyloxy)-5-cyclopropyl-phenyl]-acetic acid methyl ester 14 as a colourless oil: MS calcd. for C₁₈H₂₉O₅Si (M+H⁺) 321.2, found 321.1.

Step E: Crude [3-((tert-butyl-dimethyl-silanyloxy)-5-cyclopropyl-phenyl]-acetic acid methyl ester 14 (0.22 g, 0.69 mmol) is dissolved in a mixture of THF (5 mL) and TBAF (5 mL of a 1.0-M solution in THF) and stirred at rt for 90 min. Water (75 mL) is added and the mixture is extracted with EtOAc (100 mL) twice. The organic layers are combined, washed with 0.1 M HCl and brine, dried over MgSO₄, filtered and concentrated. The remainder is purified by reverse phase HPLC (H₂O/MeCN gradient) to afford (3-cyclopropyl-5-hydroxy-phenyl)-acetic acid methyl ester 15 as an oil: ¹H-NMR (400 MHz, CDCl₃) δ = 6.56 (s, 1H), 6.55 (s, 1H), 6.43 (s, 1H), 3.69 (s, 3H), 3.53 (s, 2H), 1.81 (m, 1H), 0.92 (m, 2H), 0.66 (m, 2H); MS calcd. for C₁₂H₁₅O₃ (MH-H⁺) 207.1, found 207.1.
Intermediates 17 and 18: (4-Bromo-3-hydroxy-phenyl)-acetic acid methyl ester and (2-bromo-3-hydroxy-phenyl)-acetic acid methyl ester.

Step A: (3-Hydroxy-phenyl)-acetic acid (3.0 g, 19.7 mmol) is dissolved in MeOH (50 mL). Catalytic amounts of thionyl chloride (~0.1 mL) are added and the solution is stirred for 6 h at rt. The solvent is removed in vacuo to give (3-hydroxy-phenyl)-acetic acid methyl ester 16 (3.2 g, quant.): MS calcd. for C₉H₉O₃ (IVH-H⁺) 167.1, found 167.0.

Step B: tert-Butylamine (5 mL, 48 mmol) is dissolved in toluene (40 mL) and cooled to -30°C, then bromine (1.2 mL, 24 mmol) is added dropwise and stirred at -30°C for 0.5 h. The mixture is cooled to -78°C and a solution of (3-hydroxy-phenyl)-acetic acid methyl ester 16 (4 g, 24 mmol) in DCM (20 mL) is added dropwise and stirred at rt for 16 h. 1 N HCl (20 mL) is added and the mixture is extracted with DCM (50 mL) and washed with a saturated solution of NaHCO₃ (50 mL), then brine (20 mL). The organic layer is dried over MgSO₄, filtered and concentrated. The regioisomers are separated and purified by reverse phase HPLC (H₂O/MeCN gradient) to afford 17 (4-bromo-3-hydroxy-phenyl)-acetic acid methyl ester: ¹H-NMR (400 MHz, CDCl₃) δ = 7.39 (d, J = 8.4 Hz, IH), 6.95 (d, J = 2.0 Hz, IH), 6.73 (dd, J = 2.0, 8.4 Hz, IH), 3.70 (s, 3H), 3.55 (s, 2H); MS calcd. for C₉H₇BrO₃ (M+H⁺) 244.9, found 245.0 and 18 (2-bromo-3-hydroxy-phenyl)-acetic acid methyl ester: ¹H-NMR (400 MHz, CDCl₃) δ = 7.17 (t, J = 8.0 Hz, IH), 6.94 (dd, J = 1.2, 8.0 Hz, IH), 6.86 (dd, J = 1.2, 8.0 Hz, IH), 3.79 (s, 2H), 3.72 (s, 3H); MS calcd. for C₉H₇BrO₃ (M+H⁺) 244.9, found 245.0.
**Intermediate 21**: (4-Cyclopropyl-3-hydroxy-phenyl)-acetic acid methyl ester.

**Step A**: (4-Bromo-3-hydroxy-phenyl)-acetic acid methyl ester 17 (751 mg, 2.09 mmol) and TBDMSCl (346 mg, 2.30 mmol) are dissolved in DCM (4 mL). Triethylamine (0.44 mL, 3.13 mmol) and DMAP (25 mg, 0.21 mmol) are added and the mixture is stirred at rt for 2 h. Water (10 mL) is added and the mixture is extracted with DCM. The organic layer is washed with 1 N HCl and brine, dried over MgSO₄, filtered, concentrated and purified by flash chromatography (EtOAc/Hexanes gradient) to afford [4-bromo-3-(tert-butyl-dimethyl-silanyloxy)-phenyl]-acetic acid methyl ester 19 as an oil: MS calcd. for C₁₅H₂₄BrO₃Si (M+H⁺) 359.1, found 359.0.

**Step B**: [4-Bromo-3-(tert-butyl-dimethyl-silanyloxy)-phenyl]-acetic acid methyl ester 19 (663 mg, 1.85 mmol), potassium phosphate (1.37 g, 6.47 mmol) and cyclopropylboronic acid (0.19 g, 2.22 mmol) are dissolved in toluene (40 mL). Tricyclohexylphosphine (42 mg, 0.18 mmol), palladium acetate (26 mg, 0.09 mmol) and water (2 mL) are added and the mixture is heated to 100°C overnight. The mixture is diluted with EtOAc (160 mL) and washed with water and brine successively. The organic layer is dried over MgSO₄, filtered, concentrated and purified by flash chromatography (EtOAc/Hexanes gradient) to afford [3-(tert-butyl-dimethyl-silanyloxy)-4-cyclopropyl-phenyl]-acetic acid methyl ester 20 as a colourless oil: ¹H-NMR (400 MHz, CDCl₃) δ = 6.77 (d, J = 2.4 Hz, 1H), 6.73 (m, 2H), 3.67
(s, 3H), 3.53 (s, 2H), 2.10 (m, 1H), 1.03 (s, 9H), 0.89 (m, 2H), 0.61 (m, 2H), 0.23 (s, 6H); MS calcd. for C$_8$H$_{29}$O$_3$Si (M+H$^+$) 321.2, found 321.1.

Step C: [3-(ferf-Butyl-dimethyl-silanyloxy)-4-cyclopropyl-phenyl]-acetic acid methyl ester 20 (479 mg, 1.49 mmol) is dissolved in a mixture of THF (20 mL) and TBAF (1.8 mL, 1.79 mmol) and stirred at rt for 90 min. 1 N HCl (40 mL) is added and the mixture is extracted with EtOAc (40 mL). The organic layer is washed with 1 N HCl and brine, dried over MgSO$_4$, filtered and concentrated to afford (4-cyclopropyl-3-hydroxy-phenyl)-acetic acid methyl ester 21 (0.42 g, quant.) as an oil: $^1$H-NMR (400 MHz, CDCl$_3$) $\delta$ = 7.00 (d, $J$ = 7.6 Hz, 1H), 6.79 (d, $J$ = 1.6 Hz, 1H), 6.75 (dd, $J$ = 1.6, 7.6 Hz, 1H), 3.69 (s, 3H), 3.55 (s, 2H), 1.79 (m, 5H), 0.95 (m, 2H), 0.63 (m, 2H). MS calcd. for C$_{12}$H$_{15}$O$_3$ (M+H$^+$) 207.1, found 207.0.

Intermediate 22: (2-Cyclopropyl-3-hydroxy-phenyl)-acetic acid methyl ester.

Following the procedure for Intermediate 21, except substituting bromide 18 for bromide 17, the title compound is prepared as a clear liquid: $^1$H-NMR (400 MHz, CDCl$_3$) $\delta$ = 7.12 (t, $J$ = 7.6 Hz, 1H), 6.82 (dd, $J$ = 1.2, 8.4 Hz, 1H), 6.78 (dd, $J$ = 1.2, 7.6 Hz, 1H), 3.86 (s, 2H), 3.70 (s, 3H), 1.62 (m, 1H), 1.60 (m, 2H), 0.63 (m, 2H). MS calcd. for C$_{12}$H$_{15}$O$_3$ (M+H$^+$) 207.1, found 207.0.

Intermediate 25: (±)-2-Ethoxy-3-(4-hydroxy-phenyl)-propionic acid ethyl ester.

28
**Step A**: 4-Hydroxybenzaldehyde (7.03 g, 57.6 mmol) is dissolved in acetonitrile (60 mL). Powdered potassium carbonate (11.98 g, 86.7 mmol) is added while stirring, followed by dropwise addition of the benzyl bromide (7 mL, 59 mmol). The mixture is vigorously stirred under nitrogen for 3 h. Filtration and concentration yielded 4-benzyloxy-benzaldehyde 23 (12.4 g, quant.) as a white solid: $^1$H-NMR (400 MHz, CDCl$_3$) $\delta$ = 9.89 (s, 1H), 7.84 (d, $J = 8.8$ Hz, 2H), 7.40 (m, 5H), 7.08 (d, $J = 8.8$ Hz, 2H), 5.16 (s, 2H). MS calcd. for C$_7$H$_7$O$_2$ (M+H$^+$) 213.1, found 213.2.

**Step B**: 4-Benzoyloxy-benzaldehyde 23 (1.24 g, 5.84 mmol) and ethyl ethoxyacetate (1.2 mL, 8.8 mmol) are dissolved in dry THF (30 mL). Solid potassium tert-butoxide (1.45 g, 12.9 mmol) is added and the mixture is stirred under nitrogen overnight. The resulting suspension is filtered through Celite 545. The solids are thoroughly washed with THF. The combined organic solutions are concentrated to yield 3-(4-benzyloxy-phenyl)-2-ethoxy-acrylic acid ethyl ester 24 as an oil. The crude material is used as such in the next step: $^1$H-NMR (400 MHz, CDCl$_3$) $\delta$ = 7.75 (d, $J = 8.8$ Hz, 2H), 7.37 (m, 5H), 6.96 (d, $J = 8.8$ Hz, 2H), 6.95 (s, 1H), 5.09 (s, 2H), 4.29 (q, $J = 7.2$ Hz, 2H), 3.98 (q, $J = 7.1$ Hz, 2H), 1.35 (m, 6H). MS calcd. for C$_{20}$H$_{23}$O$_4$ (M-J-H$^+$) 327.2, found 327.2.

**Step C**: 3-(4-Benzoyloxy-phenyl)-2-ethoxy-acrylic acid ethyl ester 24 (0.80 g, 2.45 mmol) is dissolved in ethanol (40 mL). The solution is degassed with nitrogen, then treated with a catalytic amount of 5% palladium black on carbon (0.28 g, 0.13 mmol). The solution is shaken under 60 psi hydrogen for 5 h. Filtration and concentration yielded (±)-2-ethoxy-3-(4-hydroxy-phenyl)-propionic acid ethyl ester 25 as an oil. $^1$H-NMR (400 MHz, CDCl$_3$) $\delta$ = 7.10 (d, $J = 8.4$ Hz, 2H), 6.74 (d, $J = 8.4$ Hz, 2H), 4.18 (q, $J = 7.2$ Hz, 2H), 3.97 (t, $J = 6.9$ Hz, 1H), 3.60 (m, 1H), 3.36 (m, 1H), 2.94 (d, $J = 6.6$ Hz, 2H), 1.23 (t, $J = 7.2$ Hz, 3H), 1.17 (t, $J = 7.0$ Hz, 3H). MS calcd. for C$_9$H$_{14}$O$_4$ (M+H$^+$) 239.1, found 239.1.

**Intermediate 26**: (±)-2-Ethoxy-3-(4-hydroxy-2-methyl-phenyl)-propionic acid ethyl ester.
Following the procedure for Intermediate 25, except substituting 4-hydroxy-2-methylbenzaldehyde for 4-hydroxybenzaldehyde, the title compound is prepared as a clear oil: MS calcd. for $\text{C}_{14}\text{H}_{20}\text{NaO}_4$ (M+Na$^+$) 275.1, found 275.1.

Intermediate 27: (±)-2-Ethoxy-3-(3-hydroxy-phenyl)-propionic acid ethyl ester.

Following the procedure for Intermediate 25, except substituting 3-hydroxy-benzaldehyde for 4-hydroxybenzaldehyde, the title compound is prepared as a clear oil: $^1$H-NMR (400 MHz, CDCl$_3$) $\delta$ = 7.15 (t, $J$ = 7.8 Hz, 1H), 6.80 (dd, $J$ = 7.6, 1.6 Hz, 1H), 6.75 (dd, $J$ = 2.3, 1.6 Hz, 1H), 6.71 (dd, $J$ = 8.0, 2.3 Hz, 1H), 4.18 (qd, $J$ = 7.1, 0.9 Hz, 2H), 3.97 (dd, $J$ = 7.4, 5.8 Hz, 1H), 3.61 (m, 1H), 3.37 (m, 1H), 2.98 (s, 1H), 2.96 (d, $J$ = 2.8 Hz, 1H), 1.23 (t, $J$ = 7.2 Hz, 3H), 1.17 (t, $J$ = 7.0 Hz, 3H). MS calcd. for $\text{C}_{13}\text{H}_{18}\text{NaO}_4$ (M+Na$^+$) 261.1, found 261.1.

Intermediate 28: (±)-2-Ethoxy-3-(4-hydroxy-2,5-dimethyl-phenyl)-propionic acid ethyl ester.

Following the procedure for Intermediate 25, except substituting 4-hydroxy-2,5-dimethylbenzaldehyde for 4-hydroxybenzaldehyde, the title compound is prepared as a clear oil: MS calcd. for $\text{C}_{14}\text{H}_{20}\text{NaO}_4$ (M+Na$^+$) 275.1, found 275.2.
Intermediate 31: 3-(4-Hydroxy-2-mβthyl-phenyl)-propionic acid methyl ester.

Step A: 4-Bromo-3-methyl-phenol (25.11 g, 134 mmol) is dissolved in acetonitrile (125 mL). Powdered potassium carbonate (25.69 g, 186 mmol) is added while stirring, followed by dropwise addition of benzyl bromide (17 mL, 143 mmol). The mixture is vigorously stirred under nitrogen for 6 h. Filtration through a plug of Celite 545 and concentration yielded 4-benzyloxy-1-bromo-2-methyl-benzene 29 as an off-white solid: ^1^H-NMR (400 MHz, CDCl$_3$) $\delta$ = 7.35 (m, 6H), 6.87 (d, $J$ = 2.8 Hz, IH), 6.68 (dd, $J$ = 8.8, 2.8 Hz, IH), 5.02 (s, 2H), 2.36 (s, 3H).

Step B: 4-Benzylloxy-1-bromo-2-methyl-benzene 29 (24.0 g, 86.6 mmol), tri-o-tolylphosphane (15.00 g, 49.3 mmol), ethyl diisopropylamine (35 mL, 212 mmol) and methyl acrylate (35 mL, 388 mmol) are dissolved in acetonitrile (200 mL). The mixture is degassed with argon. Solid palladium(II) acetate (4.00 g, 17.8 mmol) is added and the mixture is heated to 100°C for 18 h. The mixture is cooled and filtered through a plug of Celite 545. Concentration and silica gel purification (0-40% gradient of ethyl acetate in hexanes) yielded 3-(4-benzyloxy-2-methyl-phenyl)-acrylic acid ethyl ester 30 as an oil (30.8 g, quant.): ^1^H-NMR (400 MHz, CDCl$_3$) $\delta$ = 7.92 (d, $J$ = 15.8 Hz, IH), 7.52 (d, $J$ = 9.4 Hz, IH), 7.39 (m, 5H), 6.82 (m, 2H), 6.26 (d, $J$ = 15.8 Hz, IH), 5.08 (s, 2H), 3.80 (s, 3H), 2.42 (s, 3H). MS calcd. for C$_{19}$H$_{16}$O$_3$ (M+H) $^+$ 283.2, found 283.2.

Step C: 3-(4-Benzylloxy-2-methyl-phenyl)-acrylic acid ethyl ester 30 from Step B above is dissolved in ethyl acetate (200 mL) and ethanol (20 mL). The solution is degassed with nitrogen, then treated with 5% palladium black on carbon (1.15 g, 1.08 mmol, 1 mol%). The solution is shaken under 40 psi hydrogen for 15 h. Filtration and concentration yielded 3-(4-hydroxy-2-methyl-phenyl)-propionic acid methyl ester 31 as an oil: ^1^H-NMR (400 MHz, CDCl$_3$) $\delta$ = 6.98 (d, $J$ = 8.1 Hz, IH), 6.64 (d, $J$ = 2.6 Hz, IH), 6.60 (dd, $J$ = 8.1, 2.6 Hz, IH),
4.93 (s, IH), 3.68 (s, IH) 2.86 (t, $J = 8.8$ Hz, 2H), 2.55 (d, $J = 8.8$ Hz, 2H), 2.26 (s, 3H).

MS calcd. for C$_n$H$_i$NaO$_3$ (M+Na$^+$) 217.1, found 217.1.

**Intermediate 34:** (±)-3-(4-Hydroxy-phenyl)-2-methyl-propionic acid methyl ester.

**Step A:** 4-Bromophenol (3.55 g, 20.5 mmol) is dissolved in acetonitrile (50 mL). Powdered potassium carbonate (3.86 g, 27.9 mmol) is added while stirring, followed by dropwise addition of benzyl bromide (2.4 mL, 20.2 mmol). The mixture is vigorously stirred under nitrogen for 6 h. Filtration and concentration yielded 4-benzyloxy-bromobenzene 32 (5.52 g, quant.) as an oil that slowly solidified: $^1$H-NMR (400 MHz, CDCl$_3$) $\delta = 7.37$, (m, 7H), 6.87 (m, 2H), 5.07 (s, 2H).

**Step B:** 4-Benzyloxy-bromobenzene 32 (1.30 g, 5.2 mmol), tri-$\sigma$-tolyl-phosphane (0.98 g, 3.2 mmol), ethyl diisopropylamine (2 mL, 12.1 mmol) and methyl methacrylate (2.20 mL, 20.7 mmol) are dissolved in propionitrile (100 mL). The mixture is degassed with argon. Solid palladium(II) acetate (0.26 g, 1.2 mmol) is added and the mixture is heated to 100°C for 18 h. The mixture is cooled and filtered through a plug of Celite 545. Concentration and silica gel purification (10-60% gradient of ethyl acetate in hexanes) yielded a 1:1 mixture of isomeric olefins 33 as an oil. Used the mixture as such in the next step: MS calcd. for C$_{i8}$H$_{i9}$O$_3$ (MH-H$_2$O) 283.1, found 283.1.

**Step C:** The 1:1 olefin mixture 33 from **Step B** above is dissolved in ethyl acetate (50 mL) and ethanol (10 mL). The solution is degassed with nitrogen, then treated with a catalytic amount of 5% palladium black on carbon (0.50 g, 7 mol%). The solution is shaken under 60 psi hydrogen for 15 h. Filtration and concentration yielded (±)-3-(4-hydroxy-phenyl)-2-methyl-propionic acid methyl ester 34 as an oil: $^1$H-NMR (400 MHz, CDCl$_3$) $\delta = 7.01$ (d, $J$
 Intermediate 35: (±)-3-(4-Hydroxy-phenyl)-butyric acid methyl ester.

Following the procedure for Intermediate 34, except substituting methyl crotonate for methyl methacrylate in Step B, the title compound is prepared as a clear liquid: \textsuperscript{1}H-NMR (400 MHz, CDCl\textsubscript{3}) \( \delta = 7.08 \) (d, \( J = 8.9 \) Hz, 2H), 6.75 (d, \( J = 8.6 \) Hz, 2H), 4.91 (s, 1H), 3.62 (s, 3H), 3.22 (m, 1H), 2.55 (m, 2H), 1.27 (d, \( J = 7.0 \) Hz, 3H). MS calcd. for C\textsubscript{n}H\textsubscript{14}NaO\textsubscript{3} (M+Na\textsuperscript{+}) 217.1, found 217.1.

Intermediate 36: (±)-3-(4-Hydroxy-2,5-dimethyl-phenyl)-2-methyl-propionic acid methyl ester.

Following the procedure for Intermediate 34, except substituting the appropriate aryl bromide in Step B, the title compound is prepared as a clear liquid: \textsuperscript{1}H-NMR (400 MHz, CDCl\textsubscript{3}) \( \delta = 6.83 \) (s, 1H), 6.83 (s, 1H), 4.70 (s, 1H), 3.64 (s, 3H), 2.93 (dd, \( J = 6.6, 13.6 \) Hz, 1H), 2.67 (m, 1H), 2.55 (dd, \( J = 8.0, 13.6 \) Hz, 1H), 2.22 (s, 3H), 2.18 (s, 3H), 1.15 (d, \( J = 6.9 \) Hz, 3H).
Intermediate 41: 3-(2-Cyclopropyl-5-hydroxy-phenyl)-propionic acid methyl ester.

Step A: 3-(3-Hydroxy-phenyl)-propionic acid (24.88 g, 149.7 mmol) is dissolved in methanol (50 mL). Thionyl chloride (5 mL, 68.7 mmol) is added dropwise with vigorous stirring. The mixture is stirred at 60°C for 3 h. Cooling and concentration yielded 3-(3-hydroxy-phenyl)-propionic acid methyl ester 37 (29.26 g, quant.) as an oil: 1H-NMR (400 MHz, CDCl$_3$) δ = 7.15 (dd, J = 8.4, 7.6 Hz, 1H), 6.75 (d, J = 7.6 Hz, 1H), 6.69 (m, 2H), 3.68 (s, 3H), 2.90 (t, J = 7.6 Hz, 2H), 2.63 (t, J = 7.6 Hz, 2H).

Step B: 3-(3-Hydroxy-phenyl)-propionic acid methyl ester 37 (3.16 g, 17.5 mmol) is dissolved in DCM (40 mL). Powdered calcium carbonate (2.27 g, 22.7 mmol) is added. While the suspension is vigorously stirred, a solution of bromine (0.90 mL, 17.6 mmol) in DCM (30 mL) is added dropwise. After the addition is completed, the suspension is treated with 0.2 g sodium bisulfite in water (5 mL). The organic layer is dried over MgSO$_4$, filtered and concentrated to yield 3-(2-bromo-5-hydroxy-phenyl)-propionic acid methyl ester 38 as a colourless oil: 1H-NMR (400 MHz, CDCl$_3$) δ = 7.36 (d, J = 8.6 Hz, 1H), 6.76 (d, J = 3.0 Hz, 1H), 6.60 (dd, J = 8.6, 3.0 Hz, 3H), 5.46 (s, 1H), 3.69 (s, 3H), 3.00 (t, J = 7.9 Hz, 2H), 2.65 (t, J = 7.9 Hz, 2H).

Step C: 3-(2-Bromo-5-hydroxy-phenyl)-propionic acid methyl ester 38 (4.45 g, 17.2 mmol) is dissolved in DCM (80 mL). Imidazole (1.45 g, 21.3 mmol) is added and the mixture is stirred at rt until it became homogenous. tert-Butydimethylchlorosilane (2.66 g, 17.7 mmol) is added and the mixture is stirred at rt for 18 h. Washing with water, drying over
MgSO₄ and concentration yielded 3-[2-bromo-5-(?eⁿ-butyl-dimethyl-silanyloxy)-phenyl]-propionic acid methyl ester 39 as an oil: ¹H-NMR (400 MHz, CDCl₃) (two major rotamers are present; the data is given for the most abundant isomer) δ = 7.35 (d, J = 8.6 Hz, IH), 6.74 (d, J = 2.9 Hz, IH), 6.58 (dd, J = 8.6, 2.9 Hz, IH), 3.69 (s, 3H), 2.99 (t, J = 8.2 Hz, 2H), 2.63 (t, J = 8.2 Hz, 2H), 0.97 (s, 9H), 0.18 (s, 6H). MS calcd. for C₁₃H₁₇O₃ (M+H⁺) 221.1, found 221.1.

Step D: 3-[2-Bromo-5-(?eⁿ-butyl-dimethyl-silanyloxy)-phenyl]-propionic acid methyl ester 39 (5.74 g, 15.4 mmol) is dissolved in toluene (165 mL). Cyclopropylboronic acid (2.22 g, 25.8 mmol), potassium phosphate (11.71 g, 55.2 mmol), and tricyclohexyl-phosphane (1.81 g, 6.5 mmol) are added, followed by water (10 mL). The mixture is degassed with argon. Palladium(II) acetate (0.70 g, 3.1 mmol) is added. The mixture is heated to 95°C for 3.5 h. Cooling, separation of the organic layer, drying over MgSO₄ and concentration, followed by silica gel chromatography (0—25% gradient, ethyl acetate in hexanes) yielded 3-[5-(ter/-Butyl-dimethyl-silanyloxy)-2-cyclopropyl-phenyl]-propionic acid methyl ester 40 as an oil: ¹H-NMR (400 MHz, CDCl₃) δ = 6.84 (d, J = 8.3 Hz, IH), 6.63 (d, J = 2.5 Hz, IH), 6.59 (dd, J = 8.3, 2.5 Hz, IH), 3.70 (s, 3H), 3.08 (t, J = 7.8 Hz, 2H), 2.64 (t, J = 7.8 Hz, 2H), 1.83 (m, IH), 0.97 (s, 9H), 0.88 (m, 2H), 0.58 (m, 2H), 0.16 (s, 6H). MS calcd. for C₁₉H₂₄BrO₃Si (M+H⁺) 373.1, found 373.1.

Step E: 3-[5-(ter/-Butyl-dimethyl-silanyloxy)-2-cyclopropyl-phenyl]-propionic acid methyl ester 40 (2.87 g, 8.6 mmol) is dissolved in THF (30 mL). A 1 M solution of tetra-(ra-butyl)ammonium fluoride in THF (10 mL, 10 mmol) is added. The mixture is stirred at rt for 4 h. Concentration to dryness and purification by silica gel chromatography (10-60% gradient, ethyl acetate in hexanes) yielded 3-(2-cyclopropyl-5-hydroxy-phenyl)-propionic acid methyl ester 41: ¹H-NMR (400 MHz, CDCl₃) δ = 6.87 (d, J = 8.3 Hz, IH), 6.65 (d, J = 2.7 Hz, IH), 6.60 (dd, J = 8.3, 2.7 Hz, IH), 4.96 (s, IH), 3.70 (s, 3H), 3.09 (t, J = 7.8 Hz, 2H), 2.65 (t, J = 7.8 Hz, 2H), 1.82 (m, IH), 0.88 (m, 2H), 0.58 (m, 2H). MS calcd. for C₁₇H₁₇O₃ (M+H⁺) 221.1, found 221.1.
Intermediate 45: 3-(5-Cyclopropyl-4-hydroxy-2-methyl-phenyl)-propionic acid methyl ester.

**Step A**: 3-(4-Hydroxy-2-methyl-phenyl)-propionic acid methyl ester 31 (2.50 g, 12.9 mmol) is dissolved in DCM (60 mL) and cooled to 0°C. Powdered calcium carbonate (2.27 g, 22.7 mmol) is added. While the suspension is vigorously stirred, a solution of bromine (0.90 mL, 17.6 mmol) in DCM (20 mL) is added dropwise. After the addition is completed, the suspension is warmed up to rt and treated with 0.2 g sodium bisulfite and 5 mL water, followed by drying over MgSO₄, filtration and concentration to yield 3-(5-bromo-4-hydroxy-2-methyl-phenyl)-propionic acid methyl ester 42 (3.67 g, quant.) as a colourless oil that slowly solidified. ¹H-NMR (400 MHz, CDCl₃) δ = 7.21 (s, 1H), 6.82 (s, 1H), 5.30 (s, 1H), 3.69 (s, 3H), 2.85 (t, J = 7.5 Hz, 2H), 2.54 (t, J = 7.5 Hz, 2H), 2.24 (s, 3H).

**Step B**: 3-(5-Bromo-4-hydroxy-2-methyl-phenyl)-propionic acid methyl ester 42 (from **Step A** above) is dissolved in DCM (45 mL). Imidazole (1.12 g, 16.5 mmol) is added and the mixture is stirred at rt until it became homogenous. tert-Butyl dimethylchlorosilane (2.10 g, 13.9 mmol) is added and the mixture is stirred at rt for 18 h. Washing with water, drying the organic phase over MgSCU and concentration yielded 3-[5-bromo-4-(tert-butyl-dimethyl-silanyloxy)-2-methyl-phenyl]-propionic acid methyl ester 43 as an oil: ¹H-NMR (400 MHz, CDCl₃) δ = 7.25 (s, 1H), 6.65 (s, 1H), 3.68 (s, 3H), 2.83 (t, J = 7.6 Hz, 2H), 2.54 (t, J = 7.6 Hz, 2H), 2.21 (s, 3H), 1.03 (s, 9H), 0.23 (s, 6H).
Step C: 3-[5-Bromo-4-(ter-butyl-dimethyl-silanyloxy)-2-methyl-phenyl]-propionic acid methyl ester 43 (4.67 g, 12.1 mmol) is dissolved in toluene (70 mL). Cyclopropylboronic acid (1.95 g, 22.7 mmol), potassium phosphate (9.15 g, 43.1 mmol), and tricyclohexyl-phosphane (1.44 g, 5.13 mmol) are added, followed by water (10 mL). The mixture is degassed with argon. Palladium(II) acetate (0.55 g, 2.45 mmol) is added. The mixture is heated to 95°C for 3.5 h. Cooling, separation of the organic layer, drying over MgSCU and concentration, followed by silica gel chromatography (0-20% gradient, ethyl acetate in hexanes) yielded 3-[4-(ter/-butyl-dimethyl-silanyloxy)-5-cyclopropyl-2-methyl-phenyl]-propionic acid methyl ester 4 as an oil: 1H-NMR (400 MHz, CDCl3) δ = 6.56 (s, IH), 6.54 (s, IH), 3.67 (s, 3H), 2.81 (t, J = 7.7 Hz, 2H), 2.51 (t, J = 7.7 Hz, 2H), 2.21 (s, 3H), 1.76 (m, IH), 1.01 (s, 9H), 0.85 (m, 2H), 0.57 (m, 2H), 0.22 (s, 6H). MS calcd. for C20H33O3Si (M+H+) 349.2, found 349.2.

Step D: 3-[4-(ter/-Butyl-dimethyl-silanyloxy)-5-cyclopropyl-2-methyl-phenyl]-propionic acid methyl ester 44 (4.23 g, 12.1 mmol) is dissolved in THF (60 mL). A 1 M solution of tetra-(n-butyl)ammonium fluoride in THF (18 mL, 18 mmol) is added. The mixture is stirred at rt for 4 h. Concentration to dryness and purification by silica gel chromatography (10-30% gradient, ethyl acetate in hexanes) yielded 3-(5-cyclopropyl-4-hydroxy-2-methyl-phenyl)-propionic acid methyl ester 45: 1H-NMR (400 MHz, CDCl3) δ = 6.84 (s, IH), 6.67 (s, IH), 5.30 (s, IH), 3.68 (s, 3H), 2.84 (t, J = 7.7 Hz, 2H), 2.53 (t, J = 7.7 Hz, 2H), 2.24 (s, 3H), 1.74 (m, IH), 0.93 (m, 2H), 0.60 (m, 2H). MS calcd. for C14H19O3 (M+H+) 235.1, found 235.1.
Intermediate 48. (4-Hydroxy-2-methyl-phenoxy)-acetic acid methyl ester.

Step A: (2-Methylphenoxy)acetic acid ethyl ester (66.03 g, 340 mmol) is dissolved in dichloroethane (400 mL). Aluminum chloride (100.02 g, 750 mmol) is added and the light-brown mixture is stirred for 10 minutes at rt. Acetyl chloride (35 mL, 493 mmol) is added dropwise using an addition funnel. The rate of addition is adjusted to maintain a relatively slow emission of hydrogen chloride gas. The resulting dark brown solution is allowed to cool off to rt, then is poured over 300 g of crushed ice. The mixture is diluted with DCM (300 mL) and washed successively with water, saturated NaHCO₃ solution, water, saturated NH₄Cl solution, and brine. The organic layer is dried over Na₂SO₄, filtered and concentrated to afford 46 as a brown oil that solidified as a crystalline mass: ¹H-NMR (400MHz, CDCl₃) 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).

Step B: (4-Acetyl-2-methyl-phenoxy)-acetic acid ethyl ester (76.5 g, 324 mmol), 77% mCPBA (100.3 g, 407 mmol) and p-TsOH (13 g, 68 mmol) in dichloroethane (450 mL) are heated to 50°C for 30 h. The reaction mixture is then washed with 1 M KI (2x500 mL) and NaHSO₃ (2x500 mL). The organic layer is dried (MgSO₄), filtered and concentrated to afford 47 as a brown syrup.
Step C: A solution of (4-acetoxy-2-methyl-phenoxy)-acetic acid ethyl ester 47 (from step B above) in dry MeOH (400 mL) is combined with a 0.5 M solution of NaOMe in MeOH (650 mL, 325 mmol) and stirred for 2 h at rt. The solution is neutralized with 1 M HCl and washed with H₂O (2x500 mL). The organic layer is dried (Na₂SO₄), filtered, and concentrated to afford 48 as a light-brown solid: ¹H-NMR (400MHz, CDCl₃) δ = 6.58 (d, J = 2.8 Hz, 1H), 6.54 (d, J = 8.4 Hz, 1H), 6.50 (dd, J = 2.8, 8.4 Hz, 1H), 4.7 (or. s, 1H), 4.54 (s, 2H), 3.73 (s, 3H), 2.17 (s, 3H). MS calcd. for CI₀H₁₃O₄ (M+H⁺) 197.1, found 197.4.

Intermediate 52: (5-Cyclopropyl-4-hydroxy-2-methyl-phenoxy)-acetic acid methyl ester.

Step A: Intermediate 48 (5 g, 26 mmol) is dissolved in DCM (100 mL). Bromine (1.44 mL, 28 mmol) in DCM (20 mL) is added dropwise and stirred at rt for 2 h. The mixture is washed with aqueous saturated NaHCO₃ (2x100 mL) and brine (20 mL), dried over MgSO₄, filtered, and concentrated. The residue is recrystallized from EtOAc/Hexanes to afford 49 (5-bromo-4-hydroxy-2-methyl-phenoxy)-acetic acid methyl ester: ¹H-NMR (400 MHz, CDCl₃) δ = 7.01 (s, 1H), 6.98 (s, 1H), 5.31 (s, 1H), 4.74 (s, 2H), 3.97 (s, 3H), 2.39 (s, 3H); MS calcd. for CI₀H₁₂BrO₄ (M+Na⁺) 275.0, found 297.0 (M+Na⁺).

Step B: ((5-Bromo-4-hydroxy-2-methyl-phenoxy)-acetic acid methyl ester 49 (25.5 mmol) and TBDMSCl (4.23 g, 28.0 mmol) are dissolved in DCM (100 mL). Triethylamine (5.4 mL, 38.2 mmol) and DMAP (311 mg, 2.5 mmol) are added and the mixture is stirred at rt for
2 h. The mixture is washed with 1 N HCl and brine, dried over MgSO₄, filtered, concentrated and purified by flash chromatography (EtOAc/Hexanes gradient) to afford [5-bromo-4-(f bent-butyl-dimethyl-silanyloxy)-2-methyl-phenoxy]-acetic acid methyl ester so as an oil: MS calcd. for C₁₁H₂₆BrO₄Si (MH-H⁺) 389.1, found 389.0.

Step C: [5-Bromo-4-(ter/-butyl-dimethyl-silanyloxy)-2-methyl-phenoxy]-acetic acid methyl ester 50 (2.75 g, 7.0 mmol), potassium phosphate (5.2 g, 24.5 mmol) and cyclopropylboronic acid (0.72 g, 8.4 mmol) are dissolved in toluene (80 mL). Tricyclohexylphosphine (157 mg, 0.7 mmol), palladium acetate (98 mg, 0.35 mmol) and water (4 mL) are added and the mixture is heated to 100°C overnight. The mixture is diluted with EtOAc (140 mL) and washed with water and brine successively. The organic layer is dried over MgSO₄, filtered, and concentrated to afford crude [4-(ter/-butyl-dimethyl-silanyloxy)-5-cyclopropyl-2-methyl-phenoxy]-acetic acid methyl ester 51 which is used directly in the next step: MS calcd. for C₁₉H₂₁O₄Si (MH-H⁺) 351.2, found 351.2.

Step D: [4-(rerr-Butyl-dimethyl-silanyloxy)-5-cyclopropyl-2-methyl-phenoxy]-acetic acid methyl ester 51 (1.0 g, 3.1 mmol) is dissolved in a mixture of THF (30 mL) and TBAF (3.7 mL, 3.7 mmol) and stirred at rt for 90 min. 1 N HCl (40 mL) is added and the mixture is extracted with EtOAc (40 mL). The organic layer is washed with 1 N HCl and brine, dried over MgSO₄, filtered and concentrated. The residue is triturated with hexanes to afford (5-cyclopropyl-4-hydroxy-2-methyl-phenoxy)-acetic acid methyl ester 52 as an off-white powder. ¹H-NMR (400 MHz, CDCl₃) δ = 6.67 (s, 1H), 6.50 (s, 1H), 4.56 (s, 2H), 3.80 (s, 3H), 2.22 (s, 3H), 1.76 (m, 1H), 0.94 (m, 2H), 0.59 (m, 2H). MS calcd. for C₁₇H₁₉O₄ (M+H⁺) 237.1, found 237.0.

Intermediate 53: (4-Hydroxy-phenoxy)-acetic acid methyl ester.
(4-Hydroxy-phenoxy)-acetic acid (10.98 g, 65.3 mmol) is dissolved in methanol (50 mL). Catalytic concentrated sulfuric acid (0.2 mL) is added and the mixture is heated to reflux overnight. Cooling, treatment with solid NaHCCb and activated charcoal, drying over MgSO₄, filtration and concentration yielded a white solid (12.86 g, quant): ¹H-NMR (400 MHz, CDCl₃) δ = 7.80 (d, J = 9.2 Hz, 2H), 6.75 (d, J = 9.2 Hz, 2H), 4.58 (s, 2H), 3.80 (s, 3H). MS calcd. for C₉H₇O₄ (M+H⁺) 183.1, found 183.0.

**Intermediate 54:** (3-Cyclopropyl-4-hydroxy-phenoxy)-acetic acid methyl ester.

Following the procedure for intermediate 52, except substituting intermediate 53 for intermediate 48 in step A, the title compound is prepared as a clear solid: ¹H-NMR (400 MHz, CDCl₃) δ = 6.77 (dd, J = 1.2, 7.6 Hz, 1H), 6.68 (m, 2H), 4.56 (s, 2H), 3.80 (s, 3H), 1.81 (m, 1H), 0.96 (m, 2H), 0.64 (m, 2H). MS calcd. for C₁₂H₁₅O₄ (M+H⁺) 223.1, found 223.0.
Intermediate 59: 3-(2-Cyclopropyl-3-hydroxy-phenyl)-propionic acid methyl ester.

Step A: N-Bromosuccinimide (7.56 g, 42.5 mmol) is suspended in DCM (50 mL). tert-Butylamine (5 mL, 47.5 mmol) is added in one portion. After 45 min, the white precipitate is filtered off and the clear filtrate is used as such.

3-(3-Hydroxy-phenyl)-propionic acid methyl ester (7.56 g, 42 mmol) is dissolved in DCM (25 mL) and cooled to -78°C. The clear filtrate prepared above is added dropwise with stirring. After 30 min, the mixture is warmed up and concentrated to yield a mixture of 55 and 56. Trituration with DCM resulted in the precipitation of dibrominated sideproduct and is filtered off. Silica gel chromatography purification (10-100% ethyl acetate in hexanes) of the filtrate yielded 3-(2-bromo-3-hydroxy-phenyl)-propionic acid methyl ester 55 and 3-(4-bromo-3-hydroxy-phenyl)-propionic acid methyl ester 56: ¹H-NMR (400 MHz, CDCl₃) δ = 7.14 (t, J = 7.8 Hz, 1H), 6.90 (dd, J = 8.2, 1.4 Hz, 1H), 6.82 (dd, J = 7.4, 1.4 Hz, 1H), 5.68 (s, 1H), 3.69 (s, 3H), 3.07 (t, J = 8.0 Hz, 2H), 2.65 (t, J = 8.0 Hz, 2H). 56: ¹H-NMR (400 MHz, CDCl₃) δ = 7.35 (d, J = 8.4 Hz, 1H), 6.87 (d, J = 2.0 Hz, 1H), 6.66 (dd,
\( J = 8.4, 2.0 \text{ Hz, IH}, 5.45 (s, \text{ IH}), 3.67 (s, \text{ 3H}), 2.88 (t, J = 7.6 \text{ Hz, 2H}) \), 2.61 (t, \( J = 7.6 \text{ Hz, 2H} \)).

Step B: 3-(2-Bromo-3-hydroxy-phenyl)-propionic acid methyl ester 55 (0.86 g, 3.32 mmol) is dissolved in DCM (15 mL). Imidazole (0.36 g, 5.3 mmol) is added and the mixture is stirred at rt until homogenous. tert-Butyl dimethylchlorosilane (0.55 g, 3.6 mmol) is added and the mixture is stirred at rt for 18 h. Washing with water, drying over MgSO\(_4\) and concentration yielded 3-[2-bromo-3-(førf-butyl-dimethyl-silanyloxy)-phenyl]-propionic acid methyl ester 57 as an oil: ^1\text{H}-\text{NMR} (400 \text{ MHz, } \text{CDCl}_3) \delta = 7.07 (t, J = 7.6 \text{ Hz, IH}), 6.83 (dd, \( J = 7.6, 1.2 \text{ Hz, 2H} \)), 6.28 (dd, \( J = 8.0, 1.6 \text{ Hz, IH} \)), 3.67 (s, 3H), 3.06 (t, \( J = 7.6 \text{ Hz, 2H} \)). 2.63 (t, \( J = 7.6 \text{ Hz, 2H} \)) 1.03 (s, 9H), 0.34 (s, 6H). MS calcd. for \text{C}_6\text{H}_{26}\text{BrO}_3\text{Si} (M+H*) 373.1, found 372.6.

Step C: 3-(2-Bromo-3-(ter/-butyl-dimethyl-silanyloxy)-phenyl)-propionic acid methyl ester 57 (1.18 g, 3.16 mmol) is dissolved in toluene (25 mL). Cyclopropylboronic acid (0.55 g, 6.4 mmol), potassium phosphate (2.60 g, 12.2 mmol), and tricyclohexyl-phosphane (0.38 g, 1.36 mmol) are added, followed by water (5 mL). The mixture is degassed with argon. Palladium(II) acetate (0.16 g, 0.71 mmol) is added and the mixture is heated to 95\(^\circ\text{C}\) for 4 h. Cooling, separation of the organic layer, drying over MgSO\(_4\) and concentration, followed by silica gel chromatography (0-30% gradient, ethyl acetate in hexanes) yielded 3-[3-(ter/-butyl-dimethyl-silanyloxy)-2-cyclopropyl-phenyl]-propionic acid methyl ester 58 as an oil: ^1\text{H}-\text{NMR} (400 \text{ MHz, } \text{CDCl}_3) \delta = 7.01 (t, J = 7.8 \text{ Hz, IH}), 6.75 (d, \( J = 7.6 \text{ Hz, 2H} \)), 6.64 (d, \( J = 8.0, \text{ Hz, IH} \)), 3.68 (s, 3H), 3.17 (t, \( J = 7.9 \text{ Hz, 2H} \)), 2.63 (t, \( J = 7.9 \text{ Hz, 2H} \)), 1.54 (m, IH), 1.03 (s, 9H), 0.96 (m, 2H), 0.62 (m, 2H), 0.34 (s, 6H). MS calcd. for \text{C}_9\text{H}_{32}\text{O}_3\text{Si} (M+H*) 335.2, found 335.2.

Step D: 3-[3-(ter/-Butyl-dimethyl-silanyloxy)-2-cyclopropyl-phenyl]-propionic acid methyl ester 58 (0.72 g, 2.2 mmol) is dissolved in THF (3 mL). A 1 M solution of tetra-(n-butyl)ammonium fluoride in THF (4 mL, 4 mmol) is added and the mixture is stirred at rt for 18 h. Concentration to dryness and purification by silica gel chromatography (5-50% gradient, ethyl acetate in hexanes) yielded 3-(2-cyclopropyl-3-hydroxy-phenyl)- propionic acid methyl ester.
acid methyl ester 59: $^1$H-NMR (400 MHz, CDCl$_3$) $\delta = 7.09$ (t, $J = 7.9$ Hz, 1H), 6.76 (dd, $J = 8.1, 0.9$ Hz, 1H), 6.72 (d, $J = 7.6$ Hz, 1H), 5.93 (s, 3H), 3.69 (s, 2H), 3.15 (t, $J = 7.8$ Hz, 2H), 2.63 (t, $J = 7.8$ Hz, 2H), 1.59 (m, 1H), 1.14 (m, 2H), 0.65 (m, 2H). MS calcd. for C$_{13}$H$_7$O$_3$ (M+H$^+$) 221.1, found 221.1.

Intermediate 60: 3-(4-Cyclopropyl-3-hydroxy-phenyl)-propionic acid methyl ester.

Following the procedure for Intermediate 59, except substituting intermediate 56 for intermediate 55 in step B, the title compound is prepared as a clear oil: $^1$H-NMR (400 MHz, CDCl$_3$) $\delta = 6.99$ (d, $J = 7.7$ Hz, 1H), 6.71 (d, $J = 1.5$ Hz, 1H), 6.69 (dd, $J = 7.7, 1.5$ Hz, 1H), 5.47 (s, 1H), 3.67 (s, 3H), 2.88 (t, $J = 7.6$ Hz, 2H), 2.61 (t, $J = 7.6$ Hz, 2H), 1.76 (m, 1H), 0.94 (m, 2H), 0.62 (m, 2H). MS calcd. for C$_{13}$H$_7$O$_3$ (M+H$^+$) 221.1, found 221.1.

Intermediate 66: 2-(4-Hydroxy-2-methyl-phenoxy)-2-methyl-propionic acid methyl ester.

Step A: 4-Benzylxy-phenol (32.04 g, 160 mmol) is dissolved in of DCM (550 mL) and methanol (20 mL). Powdered calcium carbonate (21.83 g, 218 mmol) is suspended into the solution. While stirring vigorously, a solution of bromine (8.30 mL, 162 mmol) in DCM (50 mL) is added dropwise. After the addition is completed, the suspension is stirred at rt for 30 min, then the solids are filtered off. The filtrate is dried over solid NaHCO$_3$ and MgSO$_4$. 44
then filtered and concentrated to yield an oil. Recrystallization from diethyl ether/petroleum ether at -20°C yielded 4-benzyloxy-2-bromo-phenol 61 as a colourless oil that slowly solidified: 1H-NMR (400 MHz, CDCl₃) δ = 7.38 (m, 5H), 7.10 (d, J = 2.8 Hz, IH), 6.94 (d, J = 8.9 Hz, IH), 6.87 (dd, J = 8.9, 2.8 Hz, IH), 4.99 (s, 2H).

Step B: 4-Benzylxoy-2-bromo-phenol 61 (43.6 g, 156 mmol) is dissolved in DCM (400 mL). Imidazole (14.9 g, 219 mmol) is added and the mixture is stirred at rt until homogenous. tert-Butyl dimethylchlorosilane (23.6 g, 156.6 mmol) is added and the mixture is stirred at rt for 18 h. Washing with water, drying over MgSO₄ and concentration yielded (4-benzyloxy-2-bromo-phenoxy)-tert-butyl-dimethyl-silane 62 as an oil: 1H-NMR (400 MHz, CDCl₃) δ = 7.40 (m, 5H), 7.10 (s, IH), 6.79 (s, 2H) 4.98 (s, 2H) 1.03 (s, 9H) 0.22 (s, 6H).

Step C: (4-Benzylxoy-2-bromo-phenoxy)-fer/-butyl-dimethyl-silane 62 (10.05 g, 25.6 mmol) is dissolved in dimethylformamide (45 mL). The mixture is degassed with argon. Dichloro bis(triphenylphosphino)palladium(II) (3.49 g, 4.97 mmol) is added, followed by tetramethyltin (5.0 mL, 36.3 mmol). The mixture is heated to 100°C for 3 h, after which it became homogenous. Cooling, concentration, and silica gel chromatography purification (0-50% gradient, ethyl acetate in hexanes) yielded (4-benzyloxy-2-methyl-phenoxy)-tert-butyl-dimethyl-silane 63 as a white solid: 1H-NMR (400 MHz, CDCl₃) δ = 7.42 (m, 2H), 7.37 (m, 2H), 7.31 (m, IH), 6.79 (d, J = 2.2 Hz, IH), 6.67 (m, 2H) 4.99 (s, 2H) 2.18 (s, 3H), 1.01 (s, 9H), 0.18 (s, 6H). MS calcd. for C₂₀H₂₉O₂Si (M+H⁺) 329.2, found 329.2.

Step D: (4-Benzylxoy-2-methyl-phenoxy)-tert-butyl-dimethyl-silane 63 (5.03 g, 15.3 mmol) is dissolved in THF (30 mL). A 1 M solution of tetra-(<"butyl)ammonium fluoride in THF (18 mL, 18 mmol) is added. Then the mixture is stirred at rt for 4 h. Concentration to dryness and purification by silica gel chromatography (10-30% gradient, ethyl acetate in hexanes) yielded 4-benzyloxy-2-methyl-phenol 64: 1H-NMR (400 MHz, CDCl₃) δ = 7.42 (m, 4H), 7.31 (m, IH), 6.78 (s, IH), 6.69 (s, 2H), 4.99 (s, 2H), 2.27 (s, 3H).
**Step E:** 4-Benzylolxy-2-methyl-phenol (3.06 g, 14.3 mmol) is dissolved in acetonitrile (60 mL). Powdered cesium carbonate (8.71 g, 26.7 mmol) is added to the vigorously stirred solution. 2-Bromo-2-methyl-propionic acid methyl ester (2.20 mL, 17.0 mmol) is added and the mixture is stirred at 60°C for 6 h. Filtration and concentration yielded 2-(4-benzyloxy-2-methyl-phenoxy)-2-methyl-propionic acid methyl ester (5.1 g, quant.) as an oil: $^1$H-NMR (400 MHz, CDCl$_3$) δ = 7.37 (m, 5H), 6.80 (d, J = 2.4 Hz, IH), 6.65 (d, J = 2.8 Hz, IH), 6.64 (s, IH), 4.98 (s, 2H), 3.80 (s, 3H), 2.21 (s, 3H), 1.54 (s, 6H). MS calcd. for C$_{19}$H$_{22}$NaO$_4$ (M+Na$^+$) 337.2, found 337.2.

**Step F:** 2-(4-Benzylolxy-2-methyl-phenoxy)-2-methyl-propionic acid methyl ester (5.11 g, 14.3 mmol) is dissolved in ethanol (120 mL). The solution is degassed with nitrogen, then treated with a catalytic amount of 5% palladium black on carbon (1.50 g, 4 mol%). The solution is shaken under 60 psi hydrogen for 15 h. Filtration and concentration yielded an oil. Silica gel chromatography (hexanes to 60% ethyl acetate in hexanites) afforded 2-(4-hydroxy-2-methyl-phenoxy)-2-methyl-propionic acid methyl ester (3.42 g, quant.) as an oil: $^1$H-NMR (400 MHz, CDCl$_3$) δ = 6.64 (d, J = 3.0 Hz, IH), 6.59 (d, J = 8.7 Hz, IH), 6.51 (dd, J = 8.7, 3.1 Hz, IH), 4.62 (s, IH), 3.80 (s, 3H), 2.19 (s, 3H), 1.53 (s, 6H). MS calcd. for C$_{12}$H$_{16}$NaO$_4$ (M+Na$^+$) 247.1, found 247.1.

**Intermediate 67:** 2-(4-Hydroxy-2-methyl-phenoxy)-2-methyl-propionic acid methyl ester.

2-Methyl-hydroquinone (1.01 g, 8.13 mmol) is dissolved in acetonitrile (15 mL). Powdered cesium carbonate (2.86 g, 8.78 mmol) is added to the vigorously stirred solution. 2-Bromo-2-methyl-propionic acid methyl ester (1.10 mL, 8.50 mmol) dissolved in acetonitrile (5 mL) is added dropwise. The mixture is stirred at it for 6 h. Filtration and concentration, followed by purification by silica gel chromatography (10-70% gradient, ethyl acetate in hexanes)
yielded 2-(4-hydroxy-2-methyl-phenoxy)-2-methyl-propionic acid methyl ester as and oil: 

$^{1}$H-NMR (400 MHz, CDCl$_3$) $\delta$ = 6.61 (m, 3H), 4.53 (s, IH), 3.73 (s, 3H), 2.19 (s, 3H), 1.53 (s, 6H). The structure is confirmed by a NOESY experiment (the resonance at 1.53 ppm has a medium-strength positive nOe with the aromatic signals around 6.61 ppm, no nOe is observed with the methyl group at 2.19 ppm). MS calcd. for C$_{13}$H$_{17}$O$_4$ (MH$^+$) 225.1, found 225.1.

Intermede 68: 2-(4-Hydroxy-2,3-dimethyl-phenoxy)-2-methyl-propionic acid methyl ester.

Following the procedure for Intermediate 67, except substituting the appropriate hydroquinone, the title compound is prepared as a clear liquid: $^{1}$H-NMR (400 MHz, CDCl$_3$) $\delta$ = 6.50 (s, 2H), 4.55 (s, IH), 2.05 (s, 3H), 2.04 (s, 3H), 1.52 (s, 6H). MS calcd. for C$_{13}$H$_{18}$NaO$_4$ (M+Na$^+$) 261.1, found 261.1.

Intermediate 69: (4-Hydroxy-2,3-dimethyl-phenoxy)-acetic acid methyl ester.

Following the procedure for Intermediate 67, except substituting the appropriate hydroquinone and bromoacetate, the title compound is prepared as a clear oil: $^{1}$H-NMR (400 MHz, CDCl$_3$) $\delta$ = 7.56 (d, $\nu$ = 8.8 Hz, IH), 7.52 (s, $J$ = 8.8 Hz, IH), 4.57 (s, 2H), 4.47
(s, 1H), 3.80 (s, 3H), 2.23 (s, 3H), 2.17 (s, 3H). MS calcd. for C₇H₁₈O₄ (M+Na+) 233.1, found 233.1.

Intermediate 71: 2-(4-Hydroxy-2,5-dimethyl-phenoxy)-2-methyl-propionic acid methyl ester.

Step A: 2,5-Dimethylquinone (5.41 g, 39.7 mmol) is suspended in diethyl ether (70 mL). Water (100 mL) is added, followed by solid sodium dithionite (20.30 g, 116.6 mmol). The resulting mixture is shaken vigorously. The initially yellow mixture turned deep red, then colourless. Separation of the organic layer, washing with water and brine, drying over Na₂SO₄ and concentration yielded 2,5-dimethylhydroquinone 70 as a white solid: ¹H-NMR (400 MHz, DMSO-de) δ = 8.32 (s, 2H), 6.45 (s, 2H), 1.99 (s, 6H).

Step B: 2,5-Dimethylhydroquinone 70 (3.73 g, 27 mmol) is dissolved in dimethylformamide (20 mL) and acetonitrile (60 mL). powdered cesium carbonate (9.16 g, 28.1 g) is added to the vigorously stirred solution, followed by 2-bromo-2-methyl-propionic acid methyl ester (3.50 mL, 27.0 mmol). The mixture is stirred at 75°C for 18 h. Filtration and concentration, followed by purification by silica gel chromatography (5-30% gradient, ethyl acetate in hexanes) yielded 2-(4-hydroxy-2,5-dimethyl-phenoxy)-2-methyl-propionic acid methyl ester 71 as a white solid and oil. The chromatography also yielded recovered hydroquinone 70. 71: ¹H-NMR (400 MHz, CDCl₃) δ = 6.57 (s, 1H), 6.50 (s, 1H), 4.44 (s, 1H), 2.15 (s, 3H), 2.14 (s, 3H), 1.52 (s, 6H). MS calcd. for C₁₃H₁₈O₄ (M-I-Na+) 261.1, found 261.1.
Intermediate 72: (4-Hydroxy-2,5-dimethyl-phenoxy)-acetic acid methyl ester.

Following the procedure for Intermediate 71, except substituting the appropriate bromoacetate, the title compound is prepared as a clear oil: $^1$H-NMR (400 MHz, CDCl$_3$) $\delta =$ 6.60 (s, 1H), 6.53 (s, 1H), 4.58 (s, 2H), 3.60 (s, 3H), 2.22 (s, 3H), 2.19 (s, 3H). MS calcd. for C$_{11}$H$_{15}$O$_4$ (M+H$^+$) 211.1, found 211.1.

Intermediate 74: 2-(4-Mercapto-2,5-dimethyl-phenoxy)-2-methyl-propionic acid methyl ester.

Step A: 2,5-Dimethylphenol (10.04 g, 82.2 mmol) is dissolved in methanol (40 mL). Sodium thiocyanate (15.87 g, 195.8 mmol) and sodium bromide (7.37 g, 71.6 mmol) are added and the mixture is stirred at 0°C. Bromine (4.50 mL, 87.6 mmol) dissolved in methanol (40 mL) is added dropwise while stirring vigorously. Upon completion of the addition, the mixture is stirred at 50°C for 1 h. The mixture is cooled and concentrated. The residue is taken up in ethyl acetate and filtered. The filtrate is washed with saturated aqueous NaHCO$_3$, water, and brine, dried over Na$_2$SO$_4$ and concentrated to afford 2,5-dimethyl-4-thiocyanato-phenol 72 as an oil that solidified upon drying under high vacuum: $^1$H-NMR (400 MHz, CDCl$_3$) $\delta =$ 7.38 (s, 1H), 6.73 (s, 1H), 5.22 (s, 1H), 2.45 (s, 3H), 2.21 (s, 3H).

Step B: 2,5-Dimethyl-4-thiocyanato-phenol 72 (5.75 g, 32.1 mmol) is dissolved in acetonitrile (25 mL). Powdered cesium carbonate (15.32 g, 47.0 mmol) is added. Then 2-bromo-2-methyl-propionic acid methyl ester (4.50 mL, 34.8 mmol) is added and the mixture is stirred at 60°C for 18 h. Filtration and concentration, followed by silica gel chromatography (0-50% ethyl acetate in hexanes) yielded 2-(2,5-dimethyl-4-thiocyanato-phenoxy)-2-methyl-propionic acid methyl ester 73 as an oil: $^1$H-NMR (400 MHz, CDCl$_3$) (rotamers are present; the data given is for the most abundant isomer) $\delta =$ 7.39 (s, 1H), 6.50
Step C: 2-(2,5-dimethyl-4-thiocyanato-phenoxy)-2-methyl-propionic acid methyl ester 73 (3.88 g, 13.9 mmol) is dissolved in methanol (50 mL). Potassium dihydrogenphosphate (0.23 g, 1.69 mmol), water (6 mL), and dithiothreitol (2.80 g, 18.2 mmol) are added and the mixture is stirred at reflux for 3 h. After cooling and concentration, the residue is taken up in ethyl acetate, washed with water and brine, dried over Na$_2$SO$_4$ and concentrated to yield an oil. Silica gel chromatography purification (0-65% ethyl acetate in hexanes) afforded 2-(4-mercapto-2,5-dimethyl-phenoxy)-2-methyl-propionic acid methyl ester 74 as a colourless oil: $^1$H-NMR (400 MHz, CDCl$_3$) $\delta$ = 7.09 (s, 1H), 6.47 (s, 1H), 3.79 (s, 3H), 3.10 (s, 1H), 2.24 (s, 3H), 2.15 (s, 3H), 1.56 (s, 6H).

Intermediate 75: (4-Mercapto-2,5-dimethyl-phenoxy)-acetic acid methyl ester.

Following the procedure for Intermediate 74, except substituting the appropriate bromoacetate, the title compound is prepared as a clear liquid: $^1$H-NMR (400 MHz, CDCl$_3$) $\delta$ = 7.11 (s, 1H), 6.53 (s, 1H), 4.61 (s, 2H), 3.80 (s, 3H), 3.11 (s, 1H), 2.30 (s, 3H), 2.21 (s, 3H).

Intermediate 77: 2-(4-Hydroxy-2,5-dimethyl-phenylsulfanyl)-2-methyl-propionic acid methyl ester.
**Step A**: 2,5-Dimethyl-4-thiocyanato-phenol 72 (1.50 g, 8.4 mmol) is dissolved in methanol (30 mL). Potassium dihydrogenphosphate (0.32 g, 2.35 mmol), water (4 mL), and dithiothreitol (2.17 g, 14.1 mmol) are added and the mixture is stirred at reflux for 3 h. After cooling and concentration, the residue is taken up in ethyl acetate, washed with water and brine, dried 

\[\text{OeTNaSO}_4\] and concentrated to yield an oil. Silica gel chromatography purification (0-65% ethyl acetate in hexanes) afforded 4-mercapto-2,5-dimethyl-phenol 76 as a colourless wax: 1H-NMR (400 MHz, CDCl₃) δ = 7.10 (s, 1H), 6.63 (s, 1H), 4.81 (s, 1H), 3.08 (s, 1H), 2.28 (s, 3H), 2.17 (s, 3H). MS calcd. for C₈H₈O₂S (M-I-H⁺) 155.1, found 155.0.

**Step B**: 4-Mercapto-2,5-dimethyl-phenol 76 (0.44 g, 2.85 mmol) is dissolved in acetonitrile (5 mL). Powdered cesium carbonate (1.55 g, 4.8 mmol) is added. Then 2-bromo-2-methyl-propionic acid methyl ester (0.350 mL, 2.7 mmol) is added and the mixture is stirred at 25°C for 3 h. Filtration and concentration, followed by silica gel chromatography (10—50% ethyl acetate in hexanes) yielded 2-(4-hydroxy-2,5-dimethyl-phenylsulfanyl)-2-methyl-propionic acid methyl ester 77 as a wax: 1H-NMR (400 MHz, CDCl₃) δ = 7.17 (s, 1H), 6.66 (s, 1H), 4.94 (s, 1H), 3.67 (s, 3H), 2.36 (s, 3H), 2.18 (s, 3H), 1.46 (S, 6H). MS calcd. for C₁₃H₁₉O₃S (M+Na⁺) 255.1, found 255.1.

**Intermediate 79**: 2-(3-Hydroxy-phenyl)-2-methyl-propionic acid methyl ester.

**Step A**: To a flame-dried round bottom flask charged with NaH (3.33 g, 60% in mineral oil, 83.3 mmol) in dry THF (30 mL) is added (3-methoxy-phenyl)-acetic acid methyl ester (5.00 g, 27.8 mmol) dissolved in dry THF (15 mL) over 30 min. The reaction is stirred for an additional 3 h at rt, then it is cooled to 0°C. Iodomethane (9.23 g, 65.0 mmol) is added over a period of 30 min and the reaction is stirred at rt for 3 days. The reaction is poured into a
mixture of 3 N HCl (50 mL) and ice (50 mL) and extracted with ethyl acetate. The organic phase is washed with 10% NaHSO₃, water and brine, dried over MgSO₄, filtered and concentrated. Silica gel chromatography (0-10% ethyl acetate in hexanes) yielded 2-(3-methoxy-phenyl)-2-methyl-propionic acid methyl ester 78 as a colourless oil: ¹H-NMR (400 MHz, CDCl₃) δ = 7.30 (t, J = 8.0 Hz, IH), 6.98-6.96 (m, IH), 6.94 (t, J = 2.2 Hz, IH), 6.85 (dd, J = 2.4 Hz, J = 8.0 Hz, IH), 3.86 (s, 3H), 3.71 (s, 3H), 1.63 (s, 6H); MS calcd. for C₁₂H₁₆O₃ (MH-Na⁺) 231.1, found 231.1.

**Step B:** 2-(3-Methoxy-phenyl)-2-methyl-propionic acid methyl ester 78 (2.77 g, 13.3 mmol) is dissolved in dry DCM (17 mL). The solution is cooled to -65°C. Boron tribromide (4.33 g, 17.3 mmol) dissolved in DCM (17 mL) is added. The reaction mixture is stirred at -65°C for 90 min. Then the mixture is quenched with MeOH. Solvents are removed *in vacuo*, the remainder is diluted with ethyl acetate and washed with 0.2 N HCl. The aqueous phase is extracted with ethyl acetate. The organic layers are combined, washed with water and brine, dried over MgSO₄, filtered and concentrated. Silica gel chromatography (0-25% ethyl acetate in hexanes) yielded 79 as a light yellow oil. ¹H-NMR (400 MHz, CDCl₃) δ = 7.25 (t, J = 8.0 Hz, IH), 6.97-6.94 (m, IH), 6.88 (s, IH), 6.79-6.76 (m, IH), 3.72 (s, 3H), 1.62 (s, 6H); MS calcd. for C₁₁H₁₄O₃ (M+Na⁺) 217.1, found 217.1.

![Chemical Structure](image)

**Intermediate 80:** 2-(3-Hydroxy-phenoxy)-2-methyl-propionic acid methyl ester.

Resorcinol (1.10 g, 10.0 mmol) is dissolved in dry DMF (10 mL). NaH (0.44 g, 60% in mineral oil, 11.0 mmol) is added in portions. Then the mixture is stirred for 30 min at rt. 2-Bromo-2-methyl-propionic acid methyl ester (2.17 g, 12.0 mmol) is added slowly. The mixture is heated to 70°C overnight. The solvent is evaporated. The remainder is taken up in water and extracted with ethyl acetate three times. The combined organic layers are washed with brine, dried over MgSO₄, filtered and concentrated. Silica gel chromatography
purification (0-20% ethyl acetate in hexanes) afforded 80 as a colourless oil: $^1$H-NMR (400 MHz, CDCl$_3$) $\delta = 6.97$ (t, $J = 8.2$ Hz, IH), 6.38 (d, $J = 8.0$ Hz, IH), 6.29-6.26 (m, 2H), 3.67 (s, 3H), 1.49 (s, 6H); MS calcd. for C$_n$H$_{15}$O$_4$ (M+H$^+$) 211.1, found 211.1.

**Intermediate 81:** 1-(3-Hydroxy-phenyl)-cyclopentanecarboxylic acid methyl ester.

1-(3-Butoxy-phenyl)-cyclopentanecarboxylic acid (0.55 g, 2.0 mmol) is dissolved in dry DCM (5 mL). The solution is cooled to 0°C. boron tribromide (0.79 g, 3.1 mmol) dissolved in DCM (2 mL) is added. The mixture is warmed to rt and stirred for 4 h at this temperature. Then the mixture is quenched with MeOH. Solvents are removed in vacuo, the remainder is diluted with ethyl acetate and washed with 0.2 N HCl. The aqueous phase is extracted with ethyl acetate. The organic layers are combined, washed with water and brine, dried over MgSO$_4$, filtered and concentrated. Silica gel chromatography (0-25% ethyl acetate in hexanes) afforded 81 as a colourless oil: $^1$H-NMR (400 MHz, CDCl$_3$) $\delta = 7.17$ (t, $J = 8.0$ Hz, IH), 6.94 (d, $J = 7.6$ Hz, IH), 6.86 (s, IH), 6.72 (dd, $J = 1.0$ Hz, $J = 7.8$ Hz, IH), 5.16 (s, IH), 3.62 (s, 3H), 2.63-2.59 (m, 2H), 1.93-1.89 (m, 2H), 1.88-1.65 (m, 4H); MS calcd. for C$_{13}$H$_{16}$NaO$_3$ (M+Na$^+$) 243.1, found 243.2.

**Intermediate 83:** 2-(4-Hydroxy-phenoxy)-2-methyl-propionic acid methyl ester.

**Step A:** 4-(Benzyloxy)phenol (5.0 g, 25 mmol) is dissolved in DMF (40 mL). To the solution is added NaH (60% dispersion, 1.1 g, 27.5 mmol) in portions while it is kept at rt. After stirring the suspension for 30 min at rt methyl-α-bromoisobutyrate (9.05 g, 50 mmol)
is added dropwise. The mixture is stirred at 50°C for 3 h, then concentrated. The remainder is diluted with water (200 mL) and extracted with EtOAc (3x150 mL). The organic layer is separated and dried over MgSO₄, filtered and concentrated. The crude product is purified by flash chromatography (silica, Hex/EtOAc gradient) to afford 2-(4-benzyloxy-phenoxy)-2-methyl-propionic acid methyl ester 82 as a clear oil: ¹H-NMR (400MHz, CDCl₃) δ = 7.44-7.33 (m, 5H), 6.85 (m, 4H), 5.01 (s, 2H), 3.78 (s, 3H), 1.55 (s, 6H). MS calculated for C₁₈H₂₁O₄ (M+H⁺) 301.1, found 301.4.

Step B: 2-(4-Benzyloxy-phenoxy)-2-methyl-propionic acid methyl ester (0.5 g, 1.7 mmol) is dissolved in EtOH (15 mL). After addition of a catalytic amount of palladium(O) on charcoal the mixture is subjected to 1 atm hydrogen and stirred for 5 h at rt. Then the mixture is filtered through Celite 545, the solvent is removed and the remainder dried on high vacuum to yield 2-(4-hydroxy-phenoxy)-2-methyl-propionic acid methyl ester 83 as a brownish oil: ¹H-NMR (400MHz, CDCl₃) δ = 6.76 (d, J = 9.0 Hz, 2H), 6.69 (d, J = 9.0 Hz, 2H), 3.78 (s, 3H), 1.53 (s, 6H). MS calculated for C₁₈H₁₆O₄ (M+H⁺) 211.1, found 211.3.

Intermediate 84: (±)-2-(4-Hydroxy-phenoxy)-propionic acid methyl ester.

(±)-2-(4-Hydroxy-phenoxy)-propionic acid (10.0 g, 54.9 mmol) is dissolved in methanol (30 mL). Catalytic thionyl chloride (2 mL) is added and the mixture is heated to reflux overnight. Cooling, treatment with solid NaHCO₃ and activated charcoal, drying over MgSO₄, filtration and concentration yielded the title compound 84 as a white solid: ¹H-NMR (400 MHz, CDCl₃) δ = 6.77 (d, J = 9.2 Hz, 2H), 6.72 (d, J = 9.2 Hz, 2H), 4.67 (q, J = 6.8 Hz, IH), 3.76 (s, 3H), 1.59 (d, J = 6.8 Hz, 3H). MS calcd. for C₂₆H₂₄NaO₄ (M+Na⁺) 219.1, found 219.1.
Intermediate 91. 3-(4-Hydroxy-2,5-dimethyl-phenyl)-2,2-dimethyl-propionic acid methyl ester.

**Step A:** 4-Methoxy-2,5-dimethyl-benzaldehyde 85 (1.24 g, 7.55 mmol) is dissolved in dry dichloromethane (12 mL). Neat boron tribromide (1.75 g, 18.5 mmol) is added dropwise, with stirring. A tan-coloured precipitate started to form. The suspension is stirred at room temperature for 5 d. The homogenous mixture is poured over 150 g ice. After the ice melted, the solid phenol 86 is isolated by filtration and dried (1.28 g, quantitative). \(^1\)H-NMR (400 MHz, dms-o-d\(_6\)) \(\delta = 10.40\) (s, IH), 9.98 (s, IH), 7.54 (s, IH), 6.68 (s, IH), 3.36 (s, IH), 2.49 (s, 3H), 2.13 (s, 3H).

**Step B:** 4-Hydroxy-2,5-dimethyl-benzaldehyde 86 (30.56 g, 0.2 mol) is dissolved in acetonitrile (150 mL). Benzyl bromide (24 mL, 0.2 mol) is added, followed by powdered potassium carbonate (36.92 g, 0.27 mol). The mixture is stirred at 60°C for 18h. Cooling and concentration, followed by silica gel chromatography (0—20% ethyl acetate in hexanes) yielded 4-benzyloxy-2,5-dimethyl-benzaldehyde 87 as a colorless oil. \(^1\)H-NMR (400 MHz, CDCl\(_3\)) \(\delta = 10.13\) (s, IH), 7.61 (s, IH), 7.43 (m, 5H), 6.72 (s, IH), 5.15 (s, 2H), 2.63 (s, 3H), 2.28 (s, 3H). MS calcd. for C\(_{16}\)H\(_{17}\)O\(_2\) (M+H\(^+\)) 241.1, found 241.1.

**Step C:** 4-Benzyloxy-2,5-dimethyl-benzaldehyde 87 (4.77 g, 20 mmol) is dissolved in diethyl ether (30 mL). Sodium borohydride (1.0 g, 27 mmol) is added in one portion, followed by 5 mL absolute ethanol. The mixture is vigorously stirred for 3h at room
temperature, then carefully poured over 100 mL IN aqueous HCl. Extraction with ethyl acetate, washing with water and brine, then concentration yielded (4-benzyloxy-2,5-dimethyl-phenyl)-methanol 88 as a soft solid. 1H-NMR (400 MHz, CDCl₃) δ = 7.39 (m, 5H), 7.11 (s, IH), 6.73 (s, IH), 5.07 (s, 2H), 4.61 (s, 2H), 2.35 (s, 3H), 2.25 (s, 3H).

Step D: (4-Benzyloxy-2,5-dimethyl-phenyl)-methanol 88 (4.79 g, 19.7 mmol) and ethyl diisopropylamine (6.0 mL, 34.4 mmol) are dissolved in dichloromethane (80 mL). Acetic anhydride (2.5 mL, 26.4 mmol) is added in one portion and the mixture is stirred at room temperature for 18h. Washing with IN HCl, water, saturated aqueous NaHCO₃, saturated aqueous NH₄Cl and brine, followed by drying over MgSO₄ and concentration yields acetic acid 4-benzyloxy-2,5-dimethyl-benzyl ester 89 as an oil (4.93 g, quant.). 1H-NMR (400 MHz, CDCl₃) δ = 7.39 (m, 5H), 7.11 (s, IH), 6.73 (s, IH), 5.07 (s, 2H), 5.04 (s, 2H), 2.32 (s, 3H), 2.24 (s, 3H), 2.07 (s, 3H).

Step E: Acetic acid 4-benzyloxy-2,5-dimethyl-benzyl ester 89 (0.56 g, 2 mmol) is dissolved in dry dichloromethane (5 mL). (l-Methoxy-2-methyl-propenyloxy)-trimethylsilane (1 mL, 5 mmol) and magnesium perchlorate (0.09 g, 0.4 mmol) are added and the suspension is stirred overnight. Filtration and silica gel chromatography (0-30% ethyl acetate in hexanes) yielded 3-(4-benzyloxy-2,5-dimethyl-phenyl)-2,2-dimethyl-propionic acid methyl ester 90 as an oil. 1H-NMR (400 MHz, CDCl₃) δ = 7.37 (m, 5H), 6.81 (s, IH), 6.67 (s, IH), 5.02 (s, 2H), 2.82 (s, 3H), 2.25 (s, 3H), 2.20 (s, 3H), 1.18 (s, 6H).

Step F: 3-(4-Benzzyloxy-2,5-dimethyl-phenyl)-2,2-dimethyl-propionic acid methyl ester 90 (0.45 g, 1.4 mmol) is dissolved in ethanol (20 mL). Palladium black on carbon (5%; 0.16 g, 5 mol%) is added and the mixture is vigorously stirred under 1 atm. hydrogen for 18h. Filtration and concentration yielded 3-(4-hydroxy-2,5-dimethyl-phenyl)-2,2-dimethyl-propionic acid methyl ester 91 as an oil. 1H-NMR (400 MHz, CDCl₃) δ = 6.75 (s, IH), 6.56 (s, IH), 3.67 (s, 3H), 2.80 (s, 2H), 2.20 (s, 3H), 2.16 (s, 3H), 1.17 (s, 6H).
Intermediate 93. 2-Isopropoxy-5-pyrimidineboronic acid.

Step A: NaH (5.2 g, 130 mmol) is suspended in isopropanol (50 mL). The mixture is stirred for 30 min at 60°C. After the gas evolution ceased, 2-chloro-5-bromopyrimidine (10.0 g, 52 mmol) dissolved in isopropanol (100 mL) is added and the mixture is heated to reflux for 24 h. The solvent is removed in vacuo, and the remainder is taken up in H₂O and extracted with EtOAc. The organic layer is separated, dried over MgSO₄, filtered and concentrated to afford 2-isopropoxy-5-bromo-pyrimidine 92 as a light brown oil.

Step B: 2-Isopropoxy-5-bromo-pyrimidine 92 (0.65 g, 3 mmol) is dissolved in dry ether (10 mL) and cooled to -78°C under argon. n-Butyllithium (1.6 M in hexane, 2.81 mL, 4.5 mmol) is added dropwise and the mixture is stirred at -78°C for 2 h. Then triisopropyl borate (1.72 mL, 7.5 mmol) is added quickly and the mixture is stirred for another 2 h at -78°C. The mixture is allowed to warm to rt, quenched with H₂O (20 mL) and stirred overnight at rt. The ether is removed in vacuo, the aqueous layer is adjusted to pH 10 (with 2 M NaOH) and washed with ether. Then the aqueous layer is adjusted to pH 3 (with 48% aq. HBr) and extracted with EtOAc three times. The organic layer is separated and dried over MgSO₄, filtered and concentrated to afford 2-isopropoxy-5-pyrimidineboronic acid 93 as a white solid: MS calcd. for C₇H₁₂BN₂O₃ (MfH⁺) 183.1, found 183.1.

Intermediate 97: 4-Bromo-2-bromomethyl-5-(4-trifluoromethoxy-phenyl)-thiazole.
Step A: 4-Iodotrifluoromethoxyphenyl (49.5 g, 171.6 mmol) is dissolved in DMF (800 mL), then 2-methylthiazole (8.50 g, 85.5 mmol), triphenylphosphine (3.6 g, 13.73 mmol), cesium carbonate (55.9 g, 171.6 mmol), palladium(II) acetate (3.01 g, 13.7 mmol) are added and the mixture is stirred at 140°C for 24 hours. The reaction mixture is subsequently filtered through Celite 545 and washed with sat. K2CO₃ and EtOAc. The filtrate is diluted with EtOAc and washed with saturated NaHCO₃, brine and water. The organic layer is dried (MgSO₄), filtered and concentrated to give crude product, which is purified by silic gel chromatography (ether/hexane, gradient) to give 2-methyl-5-(4-trifluoromethoxy-phenyl)-thiazole 95.

Step E: Following the procedure of intermediate 4, except substituting 2-methyl-5-(4-trifluoromethoxy-phenyl)-thiazole for 2-methyl-5-(4-trifluoromethoxy-phenyl)-oxazole and without adding pyridine in step E, 4-bromo-2-methyl-5-(4-trifluoromethoxy-phenyl)-thiazole 96 is prepared as a colorless oil: ¹H-NMR (400 MHz, CDCl₃) δ = 7.56 (m, 2H), 7.21 (m, 2H), 2.67 (s, 3H). MS calculated for C₈H₈BrF₃NOS (M+H⁺) 337.9, found 337.9.

Step F: Following the procedure of intermediate 5, except substituting 4-bromo-2-methyl-5-(4-trifluoromethoxy-phenyl)-thiazole for 4-bromo-2-methyl-5-(4-trifluoromethoxy-phenyl)-oxazole in step F, 4-bromo-2-bromomethyl-5-(4-trifluoromethoxy-phenyl)-thiazole 97 is prepared as a yellow oil: ¹H-NMR (400 MHz, CDCl₃) δ = 7.59 (m, 2H), 7.23 (m, 2H), 4.63 (s, 2H). MS calculated for CuH₇Br₂F₃NOS (M+2H⁺) 416.9, found 416.8.
Example A1: (±)-2-Ethoxy-3-{4-[4-(2-isopropoxy-pyrimidin-5-yl)-5-(4-trifluoromethoxy-phenyl)-oxazol-2-ylmethoxy]-phenyl}-propionic acid.

Step A: Intermediate 25 (±)-2-ethoxy-3-(4-hydroxy-phenyl)-propionic acid ethyl ester (0.051 g, 0.21 mmol) is dissolved in acetonitrile (3 mL). Powdered cesium carbonate (0.12 g, 0.37 mmol) is added, followed by Intermediate 5, 4-bromo-2-bromomethyl-5-(4-trifluoromethoxy-phenyl)-oxazole (0.086 g, 0.22 mmol). After 4 h of vigorous stirring at it, the mixture is filtered and concentrated to yield 3-{4-[4-bromo-5-(4-trifluoromethoxy-phenyl)-oxazol-2-ylmethoxy]-phenyl}-2-ethoxy-propionic acid ethyl ester 98 as an oil. The crude material is used as such in the next step. MS calcd. for C_{24}H_{24}BrFsNOO (M+H*) 558.1, found 558.1.

Step B: Crude (±)-3-{4-[4-bromo-5-(4-trifluoromethoxy-phenyl)-oxazol-2-ylmethoxy-phenyl]2-ethoxy-propionic acid ethyl ester 98 (~0.21 mmol), 2-isopropoxy-pyrimidin-5-ylboronic acid (0.045 g, 0.25 mmol) and potassium carbonate (0.06 g, 0.43 mmol) are dissolved in 1,2-dimethoxyethane (2 mL) and water (0.2 mL). The mixture is degassed with argon. Tetrakis-(triphenylphosphino)palladium(0) (0.02 g, 8 mol%) is added and the mixture is heated to 170°C for 10 min. using a microwave oven to give crude (±)-2-ethoxy-3-{4-[4-(2-isopropoxy-pyrimidin-5-yl)-5-(4-trifluoromethoxy-phenyl)-oxazol-2-ylmethoxy]-phenyl] -propionic acid ethyl ester 99: MS calcd. for C_{33}H_{33}F_{3}N_{3}O_{7} (MH-H^+) 616.2, found 616.2.
Step C: To the crude mixture containing (dh)-2-ethoxy-3-{4-[4-(2-isopropoxy-pyrimidin-5-y1)-5-(4-trifluoromethoxy-phenyl)-oxazol-2-ylmethoxy]-phenyl}-propionic acid ethyl ester 99 is added a 1 M solution of LiOH in H₂O (0.6 mL). The mixture is stirred for 12 h at 50°C. The mixture is acidified with 1 M HCl (0.8 mL) and extracted with DCM twice. The organic layer is washed with brine, dried (MgSO₄), filtered, concentrated and purified on reverse phase HPLC (H₂O:MeCN gradient) to afford the title compound as an oil: ¹H-NMR (400 MHz, CDCl₃) δ = 8.80 (s, 2H), 7.61 (d, J = 8.4 Hz, 2H), 7.26 (d, J = 8.4 Hz, 2H), 7.21 (d, J = 8.0 Hz, 2H), 6.99 (d, J = 8.0 Hz, 2H), 5.33 (septet, J = 5.8 Hz, 1H), 5.20 (s, 2H), 4.06 (dd, J = 6.1, 4.4 Hz, IH), 3.62 (qd, J = 6.6, 5.0 Hz, IH), 3.45 (qd, J = 6.6, 5.0 Hz, IH), 3.09 (dd, J = 14.1, 3.5 Hz, IH), 2.98 (dd, J = 14.1, 7.7 Hz, IH), 1.43 (d, J = 5.8 Hz, 6H), 1.17 (t, J = 6.6 Hz, 3H). MS calcd. for C₃₂H₂₇F₃N₃O₇ (M+H⁺) 588.2, found 588.2.

[0078] By repeating the procedures described in the above example A1, using appropriate starting materials, the following compounds of Formula I, as identified in Table 1, are obtained.

<table>
<thead>
<tr>
<th>Compound Number</th>
<th>Compound Structure</th>
<th>Physical Data</th>
</tr>
</thead>
<tbody>
<tr>
<td>A2</td>
<td><img src="image" alt="Compound A2" /></td>
<td>¹H NMR (400 MHz, CDCl₃) δ = 8.80 (s, 2H), 7.61 (d, J = 8.7 Hz, 2H), 7.25 (m, 4H), 6.95 (m, 2H), 5.33 (septet, J = 6.1 Hz, 1H), 5.21 (s, 2H), 4.10 (m, 1H), 3.61 (m, 1H), 3.44 (m, 1H), 3.13 (dd, J = 14.3, 3.9 Hz, 1H), 3.01 (dd, J = 14.1, 7.7 Hz, 1H), 1.43 (d, J = 6.0 Hz, 6H), 1.16 (t, J = 6.8 Hz, 3H). MS calcd. for C₃₂H₂₇F₃N₃O₇ (M+H⁺) 588.2, found 588.2.</td>
</tr>
<tr>
<td>A3</td>
<td><img src="image" alt="Compound A3" /></td>
<td>¹H NMR (400 MHz, CDCl₃) 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), 2.82 (s, 3H), 1.42 (d, J = 6.2 Hz, 6H). MS calcd. for C₃₂H₂₇F₃N₃O₇ (M+H⁺) 602.1, found 602.1.</td>
</tr>
<tr>
<td>A4</td>
<td><img src="image" alt="Compound A4" /></td>
<td>¹H NMR (400 MHz, CDCl₃) δ = 8.64 (s, 2H), 7.62 (d, J = 8.8 Hz, 2H), 7.30 (d, J = 8.4 Hz, 2H), 7.02 (d, J = 8.4 Hz, 1H), 6.80-6.47 (m, 2H), 5.26 (septet, J = 6.2 Hz, 1H), 5.14 (s, 2H), 2.77 (t, J = 7.8 Hz, 2H), 2.42 (t, J = 7.8 Hz, 2H), 2.21 (s, 3H), 1.31 (d, J = 6.0 Hz, 6H). MS calcd. for C₃₂H₂₇F₃N₃O₇ (M+H⁺) 558.2, found 558.1.</td>
</tr>
<tr>
<td>Compound</td>
<td>Compound Structure</td>
<td>Physical Data</td>
</tr>
<tr>
<td>----------</td>
<td>-------------------</td>
<td>--------------</td>
</tr>
<tr>
<td>A5</td>
<td><img src="image" alt="A5 Structure" /></td>
<td>$^1$H NMR (400 MHz, CDCl$<em>3$) $\delta = 8.70$ (s, 2H), 7.61 (d, J = 8.8 Hz, 2H), 7.26 (m, 2H), 6.97 (d, J = 8.4 Hz, 1H), 6.90 (d, J = 8.2 Hz, 1H), 6.83 (dd, J = 8.4, 2.2 Hz, 2H), 5.32 (septet, J = 6.2 Hz, 1H), 5.18 (s, 2H), 3.14 (t, J = 7.5 Hz, 2H), 1.85 (m, 1H), 1.43 (d, J = 6.2 Hz, 6H), 0.92 (m, 2H), 0.61 (m, 2H). MS calcd. for C$</em>{18}$H$<em>{27}$F$</em>{23}$N$<em>{2}$O$</em>{5}$(M+H$^+$) 584.2, found 584.2.</td>
</tr>
<tr>
<td>A6</td>
<td><img src="image" alt="A6 Structure" /></td>
<td>$^1$H NMR (400 MHz, CDCl$<em>3$) $\delta = 8.75$ (s, 2H), 7.61 (d, J = 8.8 Hz, 2H), 7.26 (m, 2H), 6.85 (s, 1H), 6.62 (s, 1H), 5.32 (septet, J = 6.0 Hz, 1H), 5.21 (s, 2H), 2.85 (t, J = 7.2 Hz, 2H), 2.52 (s, J = 7.2 Hz, 2H), 2.29 (s, 3H), 2.13 (m, 1H), 1.41 (d, J = 6.0 Hz, 6H), 0.90 (m, 2H), 0.62 (m, 2H). MS calcd. for C$</em>{18}$H$<em>{27}$F$</em>{23}$N$<em>{2}$O$</em>{5}$(M+H$^+$) 598.2, found 598.1.</td>
</tr>
<tr>
<td>A7</td>
<td><img src="image" alt="A7 Structure" /></td>
<td>$^1$H NMR (400 MHz, CDCl$<em>3$) $\delta = 8.76$ (s, 2H), 7.61 (d, J = 8.8 Hz, 2H), 7.27 (d, J = 8.8 Hz, 2H), 7.15 (t, J = 7.6 Hz, 1H), 6.91 (d, J = 7.6 Hz, 1H), 6.89 (d, J = 7.6 Hz, 1H), 5.32 (septet, J = 6.0 Hz, 1H), 5.21 (s, 2H), 3.21 (m, 1H), 1.42 (d, J = 6.0 Hz, 6H), 1.05 (m, 2H), 0.79 (m, 2H). MS calcd. for C$</em>{18}$H$<em>{27}$F$</em>{23}$N$<em>{2}$O$</em>{5}$(M+H$^+$) 584.2, found 584.1.</td>
</tr>
<tr>
<td>A8</td>
<td><img src="image" alt="A8 Structure" /></td>
<td>$^1$H NMR (400 MHz, CDCl$<em>3$) $\delta = 8.75$ (s, 2H), 7.61 (d, J = 8.8 Hz, 2H), 7.27 (d, J = 8.8 Hz, 2H), 6.93 (t, J = 8.6 Hz, 1H), 6.81 (m, 3H), 5.32 (septet, J = 6.4 Hz, 1H), 5.19 (s, 2H), 2.50 (s, 3H), 1.57 (s, 6H), 1.42 (d, J = 6.4 Hz, 6H). MS calcd. for C$</em>{18}$H$<em>{27}$F$</em>{23}$N$<em>{2}$O$</em>{5}$(M+H$^+$) 588.2, found 588.2.</td>
</tr>
<tr>
<td>A9</td>
<td><img src="image" alt="A9 Structure" /></td>
<td>$^1$H NMR (400 MHz, CDCl$<em>3$) $\delta = 8.74$ (s, 2H), 7.61 (d, J = 8.8 Hz, 2H), 7.25 (d, J = 8.8 Hz, 2H), 7.14 (d, J = 8.6 Hz, 2H), 6.98 (dd, J = 8.6 Hz, 2H), 5.32 (septet, J = 6.2 Hz, 1H), 5.19 (s, 2H), 3.01 (dd, J = 13.4, 6.5 Hz, 1H), 2.73 (ddq, J = 7.6, 6.5, 6.0 Hz, 1H), 2.65 (dd, J = 13.4, 7.6 Hz, 1H), 1.43 (d, J = 6.2 Hz, 6H), 1.18 (d, J = 6.0 Hz, 3H). MS calcd. for C$</em>{18}$H$<em>{27}$F$</em>{23}$N$<em>{2}$O$</em>{5}$(M+H$^+$) 588.2, found 588.2.</td>
</tr>
<tr>
<td>A10</td>
<td><img src="image" alt="A10 Structure" /></td>
<td>$^1$H NMR (400 MHz, CDCl$<em>3$) $\delta = 8.74$ (s, 2H), 7.61 (d, J = 8.8 Hz, 2H), 7.26 (d, J = 8.8 Hz, 2H), 7.19 (d, J = 8.8 Hz, 2H), 6.99 (d, J = 8.8 Hz, 2H), 5.32 (septet, J = 6.2 Hz, 1H), 5.20 (s, 2H), 3.26 (m, 1H), 2.61 (m, 2H), 1.43 (d, J = 6.2 Hz, 6H), 1.31 (d, J = 6.8 Hz, 3H). MS calcd. for C$</em>{18}$H$<em>{27}$F$</em>{23}$N$<em>{2}$O$</em>{5}$(M+H$^+$) 588.2, found 588.2.</td>
</tr>
<tr>
<td>A11</td>
<td><img src="image" alt="A11 Structure" /></td>
<td>$^1$H NMR (400 MHz, CDCl$<em>3$) $\delta = 8.85$ (s, 2H), 7.61 (d, J = 8.6 Hz, 2H), 7.28 (d, J = 8.6 Hz, 2H), 6.89 (d, J = 2.4 Hz, 1H), 6.84 (d, J = 8.8 Hz, 1H), 6.78 (dd, J = 8.8, 2.4 Hz, 1H), 5.35 (septet, J = 6.0 Hz, 1H), 5.17 (s, 2H), 2.24 (s, 3H), 1.58 (s, 6H), 1.44 (d, J = 6.0 Hz, 6H). $^3$F-FNMR (376 MHz, CDCl$<em>3$) $\delta = -57.7$ ppm. MS calcd. for C$</em>{18}$H$</em>{27}$F$<em>{23}$N$</em>{2}$O$_{5}$(M+H$^+$) 588.2, found 588.2.</td>
</tr>
<tr>
<td>A12</td>
<td><img src="image" alt="A12 Structure" /></td>
<td>$^1$H NMR (400 MHz, CDCl$<em>3$) $\delta = 8.81$ (s, 2H), 7.60 (d, J = 8.6 Hz, 2H), 7.28 (d, J = 8.6 Hz, 2H), 6.61 (d, J = 8.8 Hz, 1H), 6.60 (d, J = 8.8 Hz, 1H), 5.35 (septet, J = 6.0 Hz, 1H), 5.16 (s, 2H), 4.63 (s, 6H), 2.22 (s, 6H), 1.43 (d, J = 6.0 Hz, 6H). $^3$F-FNMR (376 MHz, CDCl$<em>3$) $\delta = -57.75$ ppm. MS calcd. for C$</em>{18}$H$</em>{27}$F$<em>{23}$N$</em>{2}$O$_{5}$(M+H$^+$) 574.2, found 574.2.</td>
</tr>
<tr>
<td>Compound Number</td>
<td>Compound Structure</td>
<td>Physical Data</td>
</tr>
<tr>
<td>-----------------</td>
<td>-------------------</td>
<td>---------------</td>
</tr>
<tr>
<td>A13</td>
<td><img src="image" alt="Structure A13" /></td>
<td>$^1$H NMR (400 MHz, CDCl$<em>3$) $\delta$ = 8.56 (s, 2H), 7.56 (d, $J$ = 8.6 Hz, 2H), 7.50 (d, $J$ = 8.9 Hz, 1H), 7.29 (d, $J$ = 8.8 Hz, 2H), 6.64 (s, 1H), 5.30 (septet, $J$ = 6.1 Hz, 1H), 3.98 (s, 2H), 2.18 (s, 2H), 1.67 (s, 6H), 1.47 (d, $J$ = 6.1 Hz, 6H). MS calcld. for C$</em>{30}$H$<em>{27}$F$</em>{13}$N$<em>{3}$O$</em>{2}$ (M+H$^+$) 618.2, found 618.2.</td>
</tr>
<tr>
<td>A14</td>
<td><img src="image" alt="Structure A14" /></td>
<td>$^1$H NMR (400 MHz, CDCl$<em>3$) $\delta$ = 8.68 (s, 2H), 7.50 (d, $J$ = 8.8 Hz, 2H), 7.30 (s, 1H), 7.27 (d, $J$ = 8.6 Hz, 2H), 6.64 (s, 1H), 5.30 (septet, $J$ = 6.1 Hz, 1H), 3.98 (s, 2H), 2.18 (s, 2H), 1.67 (s, 6H), 1.47 (d, $J$ = 6.1 Hz, 6H). MS calcld. for C$</em>{30}$H$<em>{27}$F$</em>{13}$N$<em>{3}$O$</em>{2}$ (M+H$^+$) 602.2, found 602.2.</td>
</tr>
<tr>
<td>A15</td>
<td><img src="image" alt="Structure A15" /></td>
<td>$^1$H NMR (400 MHz, CDCl$<em>3$) $\delta$ = 8.83 (s, 2H), 7.61 (d, $J$ = 8.8 Hz, 2H), 7.27 (d, $J$ = 8.8 Hz, 2H), 6.84 (s, 1H), 6.72 (s, 1H), 5.34 (septet, $J$ = 6.2 Hz, 1H), 5.19 (s, 2H), 4.03 (dd, $J$ = 7.8, 3.5 Hz, 1H), 3.62 (qd, $J$ = 6.5, 5.0 Hz, 2H), 3.45 (qd, $J$ = 6.5, 5.0 Hz, 1H), 5.37 (m, 1H), 3.37 (m, 1H), 2.97 (dd, $J$ = 14.4, 3.5 Hz, 1H), 1.97 (dd, $J$ = 14.4, 7.8 Hz, 1H), 2.36 (s, 3H), 2.44 (dd, $J$ = 5.5 Hz, 6H), 1.13 (t, $J$ = 6.8 Hz, 3H). MS calcld. for C$</em>{30}$H$<em>{27}$F$</em>{13}$N$<em>{3}$O$</em>{2}$ (M+H$^+$) 602.2, found 602.2.</td>
</tr>
<tr>
<td>A16</td>
<td><img src="image" alt="Structure A16" /></td>
<td>$^1$H NMR (400 MHz, CDCl$<em>3$) $\delta$ = 8.78 (s, 2H), 7.61 (d, $J$ = 8.8 Hz, 2H), 7.27 (d, $J$ = 8.8 Hz, 2H), 6.84 (s, 1H), 6.72 (s, 1H), 5.34 (septet, $J$ = 6.1 Hz, 1H), 5.16 (s, 2H), 2.22 (s, 3H), 2.20 (s, 3H), 1.56 (s, 6H), 1.43 (d, $J$ = 6.1 Hz, 6H). MS calcld. for C$</em>{30}$H$<em>{27}$F$</em>{13}$N$<em>{3}$O$</em>{2}$ (M+H$^+$) 602.2, found 602.2.</td>
</tr>
<tr>
<td>A17</td>
<td><img src="image" alt="Structure A17" /></td>
<td>$^1$H NMR (400 MHz, CDCl$<em>3$) $\delta$ = 8.84 (s, 2H), 7.61 (d, $J$ = 8.9 Hz, 2H), 7.29 (d, $J$ = 8.9 Hz, 2H), 7.01 (s, 1H), 6.81 (s, 1H), 5.36 (septet, $J$ = 6.2 Hz, 1H), 5.21 (s, 2H), 4.03 (dd, $J$ = 8.4, 4.3 Hz, 1H), 3.59 (m, 1H), 3.36 (m, 1H), 3.08 (dd, $J$ = 14.3, 4.4 Hz, 1H), 2.94 (dd, $J$ = 14.3, 8.5 Hz, 1H), 2.34 (s, 3H), 2.22 (s, 3H), 2.44 (d, $J$ = 6.1 Hz, 6H), 1.14 (t, $J$ = 7.0 Hz, 3H). MS calcld. for C$</em>{30}$H$<em>{27}$F$</em>{13}$N$<em>{3}$O$</em>{2}$ (M+H$^+$) 616.2, found 616.2.</td>
</tr>
<tr>
<td>A18</td>
<td><img src="image" alt="Structure A18" /></td>
<td>$^1$H NMR (400 MHz, CD$<em>2$OD) $\delta$ = 8.64 (s, 2H), 7.62 (d, $J$ = 9.2 Hz, 2H), 7.29 (d, $J$ = 8.4 Hz, 2H), 6.95-6.80 (m, 3H), 5.26 (septet, $J$ = 6.2 Hz, 1H), 5.16 (s, 2H), 3.72 (s, 2H), 1.82-1.72 (m, 1H), 1.31 (d, $J$ = 6.0 Hz, 6H), 0.82-0.77 (m, 2H), 0.49-0.45 (m, 2H). MS calcld. for C$</em>{30}$H$<em>{27}$F$</em>{13}$N$<em>{3}$O$</em>{2}$ (M+H$^+$) 570.1, found 570.1.</td>
</tr>
<tr>
<td>A19</td>
<td><img src="image" alt="Structure A19" /></td>
<td>$^1$H NMR (400 MHz, CD$<em>2$OD) $\delta$ = 8.64 (s, 2H), 7.63 (d, $J$ = 8.8 Hz, 2H), 7.29 (d, $J$ = 8.0 Hz, 2H), 6.71 (s, 1H), 6.60 (s, 1H), 6.58 (s, 1H), 5.26 (septet, $J$ = 6.2 Hz, 1H), 5.16 (s, 2H), 3.48 (s, 2H), 1.18-1.75 (m, 1H), 1.31 (d, $J$ = 6.0 Hz, 6H), 0.82-0.82 (m, 2H), 0.49-0.45 (m, 2H). MS calcld. for C$</em>{30}$H$<em>{27}$F$</em>{13}$N$<em>{3}$O$</em>{2}$ (M+H$^+$) 570.1, found 570.1.</td>
</tr>
<tr>
<td>A20</td>
<td><img src="image" alt="Structure A20" /></td>
<td>$^1$H NMR (400 MHz, CD$<em>2$OD) $\delta$ = 8.56 (s, 2H), 7.62 (d, $J$ = 9.2 Hz, 2H), 7.30 (d, $J$ = 8.0 Hz, 2H), 6.99 (s, 1H), 6.76-6.72 (m, 2H), 5.27 (septet, $J$ = 6.2 Hz, 1H), 5.23 (s, 2H), 3.48 (s, 2H), 1.12-2.06 (m, 1H), 1.12 (d, $J$ = 6.0 Hz, 6H), 0.82-0.78 (m, 2H), 0.55-0.51 (m, 2H). MS calcld. for C$</em>{30}$H$<em>{27}$F$</em>{13}$N$<em>{3}$O$</em>{2}$ (M+H$^+$) 570.2, found 570.1.</td>
</tr>
<tr>
<td>Compound Number</td>
<td>Compound Structure</td>
<td>Physical Data</td>
</tr>
<tr>
<td>-----------------</td>
<td>-------------------</td>
<td>---------------</td>
</tr>
<tr>
<td>A21</td>
<td><img src="https://example.com/image1.png" alt="Image" /></td>
<td>$^1$H-NMR (400 MHz, CD$_2$(OD)) $\delta$ = 8.64 (s, 2H), 7.62 (d, $J$ = 8.8 Hz, 2H), 7.31 (d, $J$ = 8.4 Hz, 2H), 7.07 (t, $J$ = 8.0 Hz, 1H), 6.94 (d, $J$ = 7.6 Hz, 1H), 6.82 (d, $J$ = 7.6 Hz, 1H). 5.26 (septet, $J$ = 6.2 Hz, 1H), 5.19 (s, 2H), 3.78 (s, 2H), 1.58-1.51 (m, 1H), 1.31 (d, $J$ = 6.4 Hz, 6H). MS calcd. for C$_9$H$_9$F$_2$N$_2$O$_4$ (M+H$^+$) 570.2, found 570.1.</td>
</tr>
<tr>
<td>A22</td>
<td><img src="https://example.com/image2.png" alt="Image" /></td>
<td>$^1$H-NMR (400 MHz, CD$_2$(OD)) $\delta$ = 8.63 (s, 2H), 7.61 (d, $J$ = 8.8 Hz, 2H), 7.30 (d, $J$ = 8.0 Hz, 2H), 6.96 (d, $J$ = 9.2 Hz, 1H), 6.02 (dd, $J$ = 2.8 Hz, $J$ = 8.8 Hz, 1H), 6.37 (d, $J$ = 3.2 Hz, 1H), 5.26 (septet, $J$ = 6.2 Hz, 1H), 4.48 (s, 2H), 2.15-2.07 (m, 1H), 1.31 (d, $J$ = 6.4 Hz, 6H), 0.83-0.79 (m, 2H), 0.56-0.52 (m, 2H). MS calcd. for C$_9$H$_9$F$_2$N$_2$O$_4$ (M+H$^+$) 586.2, found 586.1.</td>
</tr>
<tr>
<td>A23</td>
<td><img src="https://example.com/image3.png" alt="Image" /></td>
<td>$^1$H-NMR (400 MHz, CD$<em>2$(OD)) $\delta$ = 8.50 (s, 2H), 7.47 (d, $J$ = 8.8 Hz, 2H), 7.17 (t, $J$ = 8.0 Hz, 1H), 6.95 (s, 1H), 6.91-6.83 (m, 2H), 5.26 (septet, $J$ = 6.2 Hz, 1H), 5.19 (s, 2H), 3.50 (s, 2H), 1.31 (d, $J$ = 6.0 Hz, 6H). MS calcd. for C$</em>{10}$H$_{10}$F$_2$N$_2$O$_4$ (M+H$^+$) 600.2, found 600.1.</td>
</tr>
<tr>
<td>A24</td>
<td><img src="https://example.com/image4.png" alt="Image" /></td>
<td>$^1$H-NMR (400 MHz, CD$<em>2$(OD)) $\delta$ = 8.64 (s, 2H), 7.62 (d, $J$ = 8.8 Hz, 2H), 7.29 (d, $J$ = 8.0 Hz, 2H), 7.17 (t, $J$ = 8.0 Hz, 1H), 6.88 (s, 1H), 6.84-6.78 (m, 2H), 5.26 (septet, $J$ = 6.2 Hz, 1H), 5.17 (s, 2H), 2.81 (t, $J$ = 7.6 Hz, 2H), 2.50 (s, $J$ = 7.8 Hz, 2H), 1.31 (d, $J$ = 6.4 Hz, 6H). MS calcd. for C$</em>{11}$H$_{11}$F$_2$N$_2$O$_4$ (M+H$^+$) 644.2, found 644.1.</td>
</tr>
<tr>
<td>A25</td>
<td><img src="https://example.com/image5.png" alt="Image" /></td>
<td>$^1$H-NMR (400 MHz, CD$<em>2$(OD)) $\delta$ = 8.78 (s, 2H), 7.76 (d, $J$ = 9.2 Hz, 2H), 7.45 (d, $J$ = 8.0 Hz, 2H), 7.08 (d, $J$ = 8.8 Hz, 2H), 6.94 (d, $J$ = 9.2 Hz, 2H), 5.41 (septet, $J$ = 6.2 Hz, 1H), 5.27 (s, 2H), 4.80-4.75 (m, 1H), 1.62 (d, $J$ = 6.8 Hz, 3H), 1.46 (d, $J$ = 6.4 Hz, 6H). MS calcd. for C$</em>{12}$H$_{12}$F$_2$N$_2$O$_4$ (M+H$^+$) 694.2, found 694.1.</td>
</tr>
<tr>
<td>A26</td>
<td><img src="https://example.com/image6.png" alt="Image" /></td>
<td>$^1$H-NMR (400 MHz, CD$<em>2$(OD)) $\delta$ = 8.49 (s, 2H), 7.47 (d, $J$ = 8.8 Hz, 2H), 7.15 (d, $J$ = 8.0 Hz, 2H), 6.77 (d, $J$ = 9.2 Hz, 2H), 6.69 (d, $J$ = 9.2 Hz, 2H), 5.12 (septet, $J$ = 6.2 Hz, 1H), 4.99 (s, 2H), 1.27 (s, 6H), 1.17 (d, $J$ = 6.0 Hz, 6H). MS calcd. for C$</em>{13}$H$_{13}$F$_2$N$_2$O$_4$ (M+H$^+$) 744.2, found 744.1.</td>
</tr>
<tr>
<td>A27</td>
<td><img src="https://example.com/image7.png" alt="Image" /></td>
<td>$^1$H-NMR (400 MHz, CD$<em>2$(OD)) $\delta$ = 8.55 (s, 2H), 7.52 (d, $J$ = 8.8 Hz, 2H), 7.19 (d, $J$ = 8.4 Hz, 2H), 7.08 (t, $J$ = 8.4 Hz, 1H), 6.91 (s, 1H), 6.85 (d, $J$ = 8.4 Hz, 1H), 6.79 (d, $J$ = 8.4 Hz, 1H), 5.15 (septet, $J$ = 6.2 Hz, 1H), 5.09 (s, 2H), 1.34 (s, 6H), 1.20 (d, $J$ = 6.0 Hz, 6H). MS calcd. for C$</em>{14}$H$_{14}$F$_2$N$_2$O$_4$ (M+H$^+$) 794.2, found 794.2.</td>
</tr>
<tr>
<td>A28</td>
<td><img src="https://example.com/image8.png" alt="Image" /></td>
<td>$^1$H-NMR (400 MHz, CD$<em>2$(OD)) $\delta$ = 8.65 (s, 2H), 7.63 (d, $J$ = 8.8 Hz, 2H), 7.30 (d, $J$ = 8.0 Hz, 2H), 7.10 (t, $J$ = 8.4 Hz, 1H), 6.66 (d, $J$ = 8.4 Hz, 1H), 6.53 (s, 3H), 6.47 (d, $J$ = 8.4 Hz, 1H), 5.26 (septet, $J$ = 6.2 Hz, 1H), 5.16 (s, 2H), 1.46 (s, 6H), 1.32 (d, $J$ = 6.0 Hz, 6H). MS calcd. for C$</em>{15}$H$_{15}$F$_2$N$_2$O$_4$ (M+H$^+$) 844.2, found 844.2.</td>
</tr>
<tr>
<td>Compound Number</td>
<td>Compound Structure</td>
<td>Physical Data</td>
</tr>
<tr>
<td>-----------------</td>
<td>-------------------</td>
<td>---------------</td>
</tr>
<tr>
<td>A30</td>
<td><img src="image" alt="Structure A30" /></td>
<td>$^1$H NMR 400 MHz and/or MS (m/z)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>$^1$H NMR (400 MHz, CDCl$<em>3$) $\delta$ = 8.85 (s, 2H), 7.62 (d, $J = 8.8$ Hz, 2H), 7.30 (d, $J = 8.0$ Hz, 2H), 7.16 (d, $J = 7.6$ Hz, 1H), 7.03 (s, 1H), 6.96 (d, $J = 8.0$ Hz, 1H), 6.88 (d, $J = 6.4$ Hz, 1H), 5.26 (septet, $J = 6.2$ Hz, 1H), 5.19 (s, 2H), 2.57-2.48 (m, 2H), 1.83-1.72 (m, 2H), 1.67-1.59 (m, 4H), 1.31 (d, $J = 6.0$ Hz, 6H). MS calc'd for C$</em>{24}$H$<em>{25}$F$</em>{2}$N$<em>{4}$O$</em>{5}$ (M+H$^+$) 584.2, found 584.2.</td>
</tr>
<tr>
<td>A31</td>
<td><img src="image" alt="Structure A31" /></td>
<td>$^1$H NMR (400 MHz, CDCl$<em>3$) $\delta$ = 8.82 (s, 2H), 7.62 (d, $J = 8.6$ Hz, 2H), 7.29 (d, $J = 8.6$ Hz, 2H), 6.86 (s, 1H), 6.61 (s, 1H), 5.36 (septet, $J = 6.1$ Hz, 1H), 5.17 (s, 2H), 4.64 (s, 2H), 2.27 (s, 3H), 2.23 (s, 3H), 1.44 (d, $J = 6.1$ Hz, 6H). MS calc'd for C$</em>{24}$H$<em>{25}$F$</em>{2}$N$<em>{4}$O$</em>{5}$ (M+H$^+$) 586.2, found 586.1.</td>
</tr>
<tr>
<td>A32</td>
<td><img src="image" alt="Structure A32" /></td>
<td>$^1$H NMR (400 MHz, CDCl$<em>3$) $\delta$ = 8.82 (s, 2H), 7.54 (d, $J = 8.6$ Hz, 2H), 7.31 (s, 1H), 7.25 (d, $J = 8.6$ Hz, 2H), 6.59 (s, 1H), 5.29 (septet, $J = 6.1$ Hz, 1H), 4.68 (s, 2H), 4.02 (s, 2H), 2.25 (s, 3H), 2.19 (s, 3H), 1.42 (d, $J = 6.1$ Hz, 6H). MS calc'd for C$</em>{24}$H$<em>{25}$F$</em>{2}$N$<em>{4}$O$</em>{5}$ (M+H$^+$) 590.2, found 590.1.</td>
</tr>
<tr>
<td>A33</td>
<td><img src="image" alt="Structure A33" /></td>
<td>$^1$H NMR (400 MHz, CDCl$<em>3$) $\delta$ = 8.77 (s, 2H), 7.62 (d, $J = 8.8$ Hz, 2H), 7.26 (d, $J = 8.8$ Hz, 2H), 6.93 (s, 1H), 6.82 (s, 1H), 5.32 (septet, $J = 6.1$ Hz, 1H), 5.19 (s, 2H), 2.88 (s, 2H), 2.30 (s, 3H), 2.19 (s, 3H), 1.43 (d, $J = 6.1$ Hz, 6H), 1.21 (s, 6H). MS calc'd for C$</em>{24}$H$<em>{25}$F$</em>{2}$N$<em>{4}$O$</em>{5}$ (M+H$^+$) 600.2, found 600.2.</td>
</tr>
<tr>
<td>A34</td>
<td><img src="image" alt="Structure A34" /></td>
<td>$^1$H NMR (400 MHz, CDCl$<em>3$) $\delta$ = 8.82 (s, 2H), 7.60 (d, $J = 8.8$ Hz, 2H), 7.28 (d, $J = 8.8$ Hz, 2H), 7.26 (s, 1H), 6.92 (s, 1H), 5.33 (septet, $J = 6.1$ Hz, 1H), 5.21 (s, 2H), 2.48 (s, 3H), 2.20 (s, 3H), 1.46 (s, 6H), 1.43 (d, $J = 6.1$ Hz, 6H), 1.21 (s, 6H). MS calc'd for C$</em>{24}$H$<em>{25}$F$</em>{2}$N$<em>{4}$O$</em>{5}$ (M+H$^+$) 618.3, found 618.2.</td>
</tr>
<tr>
<td>A35</td>
<td><img src="image" alt="Structure A35" /></td>
<td>$^1$H NMR (400 MHz, CDCl$<em>3$) $\delta$ = 8.5 (br, 1H), 7.61 (d, $J = 8.7$ Hz, 2H), 7.24 (d, $J = 8.7$ Hz, 2H), 6.84 (s, 1H), 6.71 (s, 1H), 6.5 (br, 2H), 5.16 (s, 2H), 4.00 (s, 3H), 2.22 (s, 3H), 2.19 (s, 3H), 1.56 (s, 6H). MS calc'd for C$</em>{24}$H$<em>{25}$F$</em>{2}$N$<em>{4}$O$</em>{5}$ (M+H$^+$) 573.2, found 573.2.</td>
</tr>
<tr>
<td>A36</td>
<td><img src="image" alt="Structure A36" /></td>
<td>$^1$H NMR (400 MHz, CDCl$<em>3$) $\delta$ = 8.75 (br, 2H), 7.41 (d, $J = 8.6$ Hz, 2H), 7.25 (d, $J = 8.6$ Hz, 2H), 6.75 (s, 2H), 5.33 (s, 2H), 5.28 (m, 1H), 2.24 (s, 3H), 1.57 (s, 6H), 1.41 (d, $J = 6.0$ Hz, 6H). MS calc'd for C$</em>{24}$H$<em>{25}$F$</em>{2}$N$<em>{4}$O$</em>{5}$ (M+H$^+$) 618.3, found 618.2.</td>
</tr>
<tr>
<td>A37</td>
<td><img src="image" alt="Structure A37" /></td>
<td>$^1$H NMR (400 MHz, CDCl$<em>3$) $\delta$ = 7.85 (br, 2H), 7.62 (d, $J = 8.6$ Hz, 1H), 7.32 (d, $J = 8.4$ Hz, 2H), 7.23 (d, $J = 8.6$ Hz, 1H), 7.14 (d, $J = 8.4$ Hz, 2H), 6.69 (s, 1H), 6.68 (s, 1H), 5.26 (s, 2H), 3.91 (s, 3H), 2.17 (s, 6H), 1.51 (s, 6H). MS calc'd for C$</em>{24}$H$<em>{25}$F$</em>{2}$N$<em>{4}$O$</em>{5}$ (M+H$^+$) 589.2, found 589.2.</td>
</tr>
<tr>
<td>A38</td>
<td><img src="image" alt="Structure A38" /></td>
<td>$^1$H NMR (400 MHz, CDCl$<em>3$) $\delta$ = 7.85 (br, 2H), 7.62 (d, $J = 8.6$ Hz, 1H), 7.32 (d, $J = 8.4$ Hz, 2H), 7.23 (d, $J = 8.6$ Hz, 1H), 7.14 (d, $J = 8.4$ Hz, 2H), 6.69 (s, 1H), 6.68 (s, 1H), 5.26 (s, 2H), 3.91 (s, 3H), 2.17 (s, 6H), 1.51 (s, 6H). MS calc'd for C$</em>{24}$H$<em>{25}$F$</em>{2}$N$<em>{4}$O$</em>{5}$ (M+H$^+$) 589.2, found 589.2.</td>
</tr>
</tbody>
</table>
Transcriptional Assay

[0079] 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.

[0080] 293T human embryonic kidney cells (8x10⁶) are seeded in a 175cm² 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 170,000 cells/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% CO₂ 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 1µM. Test compound (500nM) is added to each well of cells in the assay plate and the cells are incubated at 37°C, 5.0% CO₂ 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.

[0081] 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 halfway 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.

[0082] 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 and/or PPARα and/or PPARγ of less than 5µM, more preferably less than 1µM, more preferably less than 500nm, more preferably less than 100nM. Compounds of the invention preferably have an EC₅₀ for PPARδ that is less than or equal to PPARα which in turn has an EC₅₀ that is at least 10-fold less than PPARγ.

[0083] 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:

![Diagram of Formula I]

in which:

- \( n \) is selected from 0, 1, 2 and 3;
- \( W \) is selected from N and CH;
- \( Y \) is selected from O, S, (CH)\(_2\) and \( \text{CR}_4 \text{R}_5 \); wherein \( \text{R}_4 \) and \( \text{R}_5 \) are independently selected from hydrogen and Ci-6alkyl;
- \( Z \) is selected from S and O;
- \( \text{R}_i \) is selected from \(-\text{XiCR}_3\text{R}_6\text{CO}_2\text{R}_7\), \(-\text{Xi\text{SCR}_3\text{Re}_2\text{CO}_2\text{R}_7}\) and \(-\text{XiOCR}_5\text{Re}_2\text{CO}_2\text{R}_7\); wherein \( \text{X}_i \) and \( \text{X}_2 \) are independently selected from a bond and \( \text{C}_4 \text{alkylene} \), and \( \text{R}_5 \) and \( \text{R}_6 \) are independently selected from hydrogen, \( \text{C}_4 \text{alkyl} \) and \( \text{C}_4 \text{alkoxy} \); or \( \text{R}_5 \) and \( \text{R}_6 \) together with the carbon atom to which \( \text{R}_s \) and \( \text{R}_6 \) are attached form \( \text{C}_3\text{-i}2\text{cycloalkyl} \); and \( \text{R}_7 \) is selected from hydrogen and \( \text{Ci}7\text{alkyl} \); each
  - \( \text{R}_2 \) is independently selected from halo, \( \text{Ci}7\text{alkyl} \), \( \text{Ci}4\text{alkoxy} \), \( \text{Ci}8\text{alkylthio} \) and \( \text{C}_3\text{-i}2\text{cycloalkyl} \);
  - \( \text{R}_3 \) is \( \text{Ci}8\text{alkyl} \);
  - \( \text{R}_4 \) is selected from \( \text{C}4\text{alkyl} \), \( \text{halo} \), \( \text{halo-substituted-C}_4\text{alkyl} \) and \( \text{halo-substituted-C}_4\text{alkoxy} \);
- and the pharmaceutically acceptable salts, hydrates, solvates, isomers and prodrugs thereof.

2. The compound of claim 1 in which:

- \( n \) is selected from 0, 1 and 2;
- \( W \) is selected from N and CH;
Y is selected from O, S and CH₂;
Z is selected from S and O;
R₁ is selected from -XiCR₅Rₓ₂CO₂H, -XIOCR₅Rₓ₂ICO₂H and -X₁OCR₅Rₓ₂CO₂H; wherein X₁ and X₂ are independently selected from a bond and C₁₄alkylene; and R₅ and R₆ are independently selected from hydrogen, C₁₄alkyl and C₁₄alkoxy; or R₅ and R₆ together with the carbon atom to which R₅ and R₆ are attached form C₃₋₁₂cycloalkyl; and each

R₂ is independently selected from halo, C₁₋₄alkoxy, C₁₋₄alkyl and C₃₋₁₂cycloalkyl;
R₃ is selected from C₁₋₄alkoxy; and
R₄ is halo-substituted-C₁₋₄alkoxy.

3. The compound of claim 2 in which Y is selected from O and S; and R₁ is selected from -CH₂CR₅R₆CO₂H, -OCR₅R₆CO₂H, -SCR₅R₆CO₂H, -CR₅R₆CH₂CO₂H and -C₅R₆CO₂H; wherein R₅ and R₆ are independently selected from hydrogen, methyl, methoxy and ethoxy; or R₅ and R₆ together with the carbon atom to which R₅ and R₆ are attached form cyclopentyl.

4. The compound of claim 3 in which each R₂ is independently selected from methyl and cyclopropyl; and R₃ is selected from methyl and isopropyl.

5. The compound of claim 1 selected from: 2-Ethoxy-3-[4-{4-(2-isopropoxy-pyrimidin-5-yl)-5-(4-trifluoromethoxy-phenyl)-oxazol-2-ylmethoxy]-phenyl]-propionic acid; 2-Ethoxy-3-{3-[4-(24sopropoxy-pyrimidin-5-yl)-5-(4-trifluoromethoxy-phenyl)-oxazol-2-ylmethoxy]-phenyl}-propionic acid; 4-{4-(2-Isopropoxy-pyrimidin-5-yl)-5-(4-trifluoromethoxy-phenyl)-oxazol-2-ylmethoxy]-2-methyl-phenoxy]-acetic acid; 3- {4-{4-(2-Isopropoxy-pyrimidin-5-yl)-5-(4-trifluoromethoxy-phenyl)-oxazol-2-ylmethoxy]-2-methyl-phenyl}-propionic acid; 3- {3-Cyclopropyl-5-[4-(2-isopropoxy-pyrimidin-5-yl)-5-(4-trifluoromethoxy-phenyl)-oxazol-2-ylmethoxy]-2-methyl-phenyl}-propionic acid; 3- {5-Cyclopropyl-4-[4-(2-isopropoxy-pyrimidin-5-yl)-5-(4-trifluoromethoxy-phenyl)-oxazol-2-ylmethoxy]-2-methyl-phenyl}-propionic acid; 3- {2-Cyclopropyl-3-[4-(2-isopropoxy-pyrimidin-5-yl)-5-(4-trifluoromethoxy-phenyl)-oxazol-2-ylmethoxy]-2-methyl-phenyl}-propionic acid; 3- {2-Cyclopropyl-3-[4-(2-isopropoxy-pyrimidin-5-yl)-5-(4
trifluoromethoxy-phenyl)-oxazol-2-ylmethoxy]-phenyl}-propionic acid; 2-{4-[4-(2-
Isoproxy-pyrimidin-5-yl)-5-(4-trifluoromethoxy-phenyl)-oxazol-2-ylmethoxy]-3-methyl-
phenoxy} -2-methyl-propionic acid; 3- {4-[4-(2-Isoproxy-pyrimidin-5-yl)-5-(4-
trifluoromethoxy-phenyl)-oxazol-2-ylmethoxy]-phenyl} -2-methyl-propionic acid; 3- {4-[4-
(2-Isoproxy-pyrimidin-5-yl)-5-(4-trifluoromethoxy-phenyl)-oxazol-2-ylmethoxy]-phenyl} -butyric acid; 2- {4-[4-(2-Isoproxy-pyrimidin-5-yl)-5-(4-trifluoromethoxy-phenyl)-oxazol-2-ylmethoxy]-2-methyl-phenoxy} -2-methyl-propionic acid; 4-[4-(2-Isoproxy-
pyrimidin-5-yl)-5-(4-trifluoromethoxy-phenyl)-oxazol-2-ylmethoxy]-phenyl} -2-methyl-
propionic acid; 2-{4-[4-(2-Isoproxy-pyrimidin-5-yl)-5-(4-trifluoromethoxy-phenyl)-
phenyl} -acetic acid; 2- {4-[4-(2-Isoproxy-pyrimidin-5-yl)-5-(4-trifluoromethoxy-
phenyl)-oxazol-2-ylmethoxy]-2,5-dimethyl-phenoxy} -2-methyl-propionic acid; 2-Ethoxy-3- 
{4-[4-(2-isoproxy-pyrimidin-5-yl)-5-(4-trifluoromethoxy-phenyl)-oxazol-2-ylmethoxy]-
2-methyl-phenyl} -propionic acid; 2- {4-[4-(2-Isoproxy-pyrimidin-5-yl)-5-(4-trifluoro-
methoxy-phenyl)-oxazol-2-ylmethoxy]-2,5-dimethyl-phenoxy} -2-methyl-propionic acid; 2-Ethoxy-3- 
{4-[4-(2-isoproxy-pyrimidin-5-yl)-5-(4-trifluoromethoxy-phenyl)-oxazol-2-ylmethoxy]-
2-methyl-phenyl} -propionic acid; 2-Cyclopropyl-5- 
{4-[(2-isoproxy-pyrimidin-5-yl)-5-(4-trifluoromethoxy-phenyl)-oxazol-2-ylmethoxy]-
phenyl} -acetic acid; 3-Cyclopropyl-5- 
{4-[(2-isoproxy-pyrimidin-5-yl)-5-(4-trifluoromethoxy-phenyl)-oxazol-2-ylmethoxy]-
phenyl} -acetic acid; 4-Cyclopropyl-3- 
{4-[(2-isoproxy-pyrimidin-5-yl)-5-(4-trifluoromethoxy-phenyl)-oxazol-2-ylmethoxy]-
phenyl} -acetic acid; 3-Cyclopropyl-4- 
{4-[(2-isoproxy-pyrimidin-5-yl)-5-(4-trifluoromethoxy-phenyl)-oxazol-2-ylmethoxy]-
phenyl} -acetic acid; 5-Cyclopropyl-4- 
{4-[(2-isoproxy-pyrimidin-5-yl)-5-(4-trifluoromethoxy-phenyl)-oxazol-2-ylmethoxy]-
2-methyl-phenyl} -acetic acid; 3-[4-(2-
Isoproxy-pyrimidin-5-yl)-5-(4-trifluoromethoxy-phenyl)-oxazol-2-ylmethoxy]-phenyl} -acetic acid; 3- 
{3-[4-(2-Isoproxy-pyrimidin-5-yl)-5-(4-trifluoromethoxy-phenyl)-oxazol-2-ylmethoxy]-
phenyl} -propionic acid; 2- {4-[4-(2-Isoproxy-pyrimidin-5-yl)-5-(4-
trifluoromethoxy-phenyl)-oxazol-2-ylmethoxy]-phenyl} -propionic acid; 2- {4-[4-(2-
Isoproxy-pyrimidin-5-yl)-5-(4-trifluoromethoxy-phenyl)-oxazol-2-ylmethoxy]-phenyl} -
2-methyl-propionic acid; 2-{3-[4-(2-Isoproxy-pyrimidin-5-yl)-5-(4-trifluoronomethoxy-
phenyl)-oxazol-2-ylmethoxy]-phenyl}-2-propionic acid; 2-{3-[4-(2-Isopropoxy-pyrimidin-5-yl)-5-(4-trifluoromethoxy-phenyl)-oxazol-2-ylmethoxy]-phenyl} -propionic acid; 1-{3-[4-(2-Isopropoxy-pyrimidin-5-yl)-5-(4-trifluoromethoxy-phenyl)-oxazol-2-ylmethoxy]-phenyl} -cyclopentanecarboxylic acid; 3-{4-[4-(2-Isopropoxy-pyrimidin-5-yl)-5-(4-trifluoromethoxy-phenyl)-oxazol-2-ylmethoxy]-2,5-dimethyl-phenyl}-2-methyl-propionic acid; 4-[4-(2-Isopropoxy-pyrimidin-5-yl)-5-(4-trifluoromethoxy-phenyl)-oxazol-2-ylmethoxy]-2,5-dimethyl-phenoxy} -acetic acid; 4-[4-(2-Isopropoxy-pyrimidin-5-yl)-5-(4-trifluoromethoxy-phenyl)-oxazol-2-ylmethoxy]-2,5-dimethylphenylsulfanyl}-2,5-dimethyl-propionic acid; and 2-{4-(2-Isopropoxy-pyrimidin-5-yl)-5-(4-trifluoromethoxy-phenyl)-oxazol-2-ylmethoxy]-2,5-dimethyl-phenoxy} -acetic acid; 3-{4-(2-Isopropoxy-pyrimidin-5-yl)-5-(4-trifluoromethoxy-phenyl)-oxazol-2-ylmethoxy]-2,5-dimethyl-phenyl}-2,2-dimethyl-propionic acid; and 2-{4-(2-Isopropoxy-pyrimidin-5-yl)-5-(4-trifluoromethoxy-phenyl)-oxazol-2-ylmethoxy]-2,5-dimethyl-phenylsulfanyl}-2-methyl-propionic acid.

6. A method for treating a disease or disorder in an animal in which modulation of PPAR 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 PPAR activity is at least one PPAR selected from PPARα, PPARδ and PPARγ.

8. The method of claim 7 in which the PPAR activity is both PPARα and PPARδ.

9. 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.
10. 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.

11. 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 PPAR activity contributes to the pathology and/or symptomology of the disease.

12. The use of claim 11 in which the PPAR activity is at least one PPAR selected from PPARα, PPARδ and PPARγ.

13. The use of claim 12 in which the PPAR activity is both PPARα and PPARδ.

14. 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.

15. 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; insulinotrophic sulfonylurea receptor ligands such as meglitinides, e.g., nateglinide and repaglinide; insulin sensitizer such as protein tyrosine phosphatase-IB (PTP-IB) inhibitors such as PTP-12; 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-I (glucagon like peptide-1), GLP-I analogs such as Exendin-4 and GLP-I 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 (2^\text{nd}-l-{4-[5-methyl-2-(4-trifluoromethyl-phenyl)-oxazol-4-ylmethoxy]-benzenesulfonyl}) -2,3-dihydro-1H-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, fluvastatin, dalvastatin, atorvastatin, rosuvastatin and rivastatin; squalene synthase inhibitors; FXR (famesoid 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, chlorothiazide, hydrochlorothiazide, amiloride; angiotensin converting enzyme (ACE) inhibitors such as benazepril, captopril, enalapril, fosinopril, lisinopril, moexipril, perindopril, quinapril, ramipril andtrandolapril; 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-66-1 132, RO-66-1 168; β-adrenergic receptor blockers such as acebutolol, atenolol, betaxolol, bisoproloU 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-Al analogues and mimetics;
h) thrombin inhibitors such as Xirnelagatran;
   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. fernara, 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)-benzamid; and
   m) an agent interacting with a 5-HT3 receptor and/or an agent interacting with 5-HT4 receptor such as tegaserod, tegaserod hydrogen maleate, cisapride, cilansetron;
   or, in each case a pharmaceutically acceptable salt thereof; and optionally a pharmaceutically acceptable carrier.

16. A pharmaceutical composition according to claim 14 or a combination according to claim 15, 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.

17. 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.
18. Use of a compound according to any of claims 1 to 5, or a pharmaceutical composition according to claim 14 or a combination according to claim 15, 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.
A. CLASSIFICATION OF SUBJECT MATTER

<table>
<thead>
<tr>
<th>Category</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
<th>Relevant to claim No</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>WO 03/043985 A (NOVARTIS AG [CH]; NOVARTIS PHARMA GMBH [AT]; BACH ANDREW THOMAS [US]); 30 May 2003 (2003-05-30) cited in the application claims 1,20-26</td>
<td>1,6-18</td>
</tr>
<tr>
<td>A</td>
<td>WO 96/38442 A (SEARLE &amp; CO [US]; ROGERS KATHY L &amp; HF [US]; TALLEY JOHN J [US]; SIKORS) 5 December 1996 (1996-12-05) claims 1,10-17; examples 2,3,6,8,14,16</td>
<td>1,9,14,16-18</td>
</tr>
<tr>
<td>A</td>
<td>WO 96/03392 A (SEARLE &amp; CO [US]; TALLEY JOHN J [US]; CARTER JEFFERY S [US]; COLLINS P) 8 February 1996 (1996-02-08) claims 1,12,23,34-38; examples 1,21,33,34,36-38,41,43,44</td>
<td>1,9,14,16-18</td>
</tr>
</tbody>
</table>

Further documents are listed in the continuation of Box C

See patent family annex

Date of the actual completion of the international search: 11 April 2007

Date of mailing of the international search report: 19/04/2007

Name and mailing address of the ISA/Authorized officer:

European Patent Office, P B 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel (+31-70) 340-2040, Tx 31 651 bpm nl,
Fax (+31-70) 340-3016

Has s, Chr i stian

Form PCT/ISA/210 (second sheet) (April 2009)
<table>
<thead>
<tr>
<th>Category</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
<th>Relevant to claim No</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>wo 96/36617 A (SEARLE &amp; CO [US]; TALLEY JOHN J [US]; BERTENSHAW STEPHEN [US]; ROGIER) 21 November 1996 (1996-11-21) c l aims 1,10-16; examples 15,28-31</td>
<td>1,9, 14, 16-18</td>
</tr>
<tr>
<td>A</td>
<td>EP 0 442 448 A (SQUIBB BRISTOL MYERS CO [US]) 21 August 1991 (1991-08-21) cl aims 1,10-12; examples</td>
<td>1,14, 17</td>
</tr>
<tr>
<td>A</td>
<td>EP 0 434 034 A (SQUIBB BRISTOL MYERS CO [US]) 26 June 1991 (1991-06-26) cl aims 1,11,12; examples</td>
<td>1,14, 17</td>
</tr>
<tr>
<td>P, X</td>
<td>wo 2005/116016 A (IRM LLC [US]; EPPLE ROBERT [US]; XIE YONGPING [US]; WANG XING [US]; CO) 8 December 2005 (2005-12-08) page 40, example E1; page 48, compound no. C3; page 49, compound no. C6; page 54, compound no. C22; page 60, compound no. E2; cl aims</td>
<td>1-18</td>
</tr>
<tr>
<td>P, X</td>
<td>wo 2005/116000 A (IRM LLC [US]; EPPLE ROBERT [US]; COW CHRISTOPHER [US]; XIE YONGPing [U]) 8 December 2005 (2005-12-08) page 76, example L1; page 77, example M; page 122, compound F96; page 163, compounds L21 and L22; page 164, compound M2; cl aims</td>
<td>1-4,6-18</td>
</tr>
</tbody>
</table>
INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2006/043587

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.
   because they relate to subject matter not required to be searched by this Authority, namely
   Although claims 6-10 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.
   because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [X] Claims Nos.
   because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [X] As all required additional search fees were timely paid by the applicant, this International Search Report covers all claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [X] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [X] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.

Remark on Protest
[X] The additional search fees were accompanied by the applicant's protest.
[ ] No protest accompanied the payment of additional search fees.
<table>
<thead>
<tr>
<th>Patent document cited in search report</th>
<th>Publication date</th>
<th>Patent family member(s)</th>
<th>Publication date</th>
</tr>
</thead>
<tbody>
<tr>
<td>wo 03043985 A</td>
<td>30-05-2003</td>
<td>AU 2002352073 A</td>
<td>10-06-2003</td>
</tr>
<tr>
<td></td>
<td></td>
<td>BR 0214305 A</td>
<td>26-10-2004</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CA 2463154 A</td>
<td>30-05-2003</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CN 1589260 A</td>
<td>02-03-2005</td>
</tr>
<tr>
<td></td>
<td></td>
<td>EP 1448523 A</td>
<td>25-08-2004</td>
</tr>
<tr>
<td></td>
<td></td>
<td>HU 0402236 A2</td>
<td>28-02-2005</td>
</tr>
<tr>
<td></td>
<td></td>
<td>JP 2005511634 T</td>
<td>28-04-2005</td>
</tr>
<tr>
<td></td>
<td></td>
<td>KR 20050044556 A</td>
<td>12-05-2005</td>
</tr>
<tr>
<td></td>
<td></td>
<td>MX PA04004869 A</td>
<td>11-04-2005</td>
</tr>
<tr>
<td></td>
<td></td>
<td>NZ 532080 A</td>
<td>31-08-2006</td>
</tr>
<tr>
<td></td>
<td></td>
<td>US 2004248936 Al</td>
<td>09-12-2004</td>
</tr>
<tr>
<td>wo 9638442 A</td>
<td>05-12-1996</td>
<td>AT 221885 T</td>
<td>15-08-2002</td>
</tr>
<tr>
<td></td>
<td></td>
<td>AT 246188 T</td>
<td>15-08-2003</td>
</tr>
<tr>
<td></td>
<td></td>
<td>AU 6027996 A</td>
<td>18-12-1996</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CA 2223091 Al</td>
<td>05-12-1996</td>
</tr>
<tr>
<td></td>
<td></td>
<td>DE 69622894 D1</td>
<td>12-09-2002</td>
</tr>
<tr>
<td></td>
<td></td>
<td>DE 69622894 T2</td>
<td>30-04-2003</td>
</tr>
<tr>
<td></td>
<td></td>
<td>DE 69629290 D1</td>
<td>04-09-2003</td>
</tr>
<tr>
<td></td>
<td></td>
<td>DE 69629290 T2</td>
<td>22-04-2004</td>
</tr>
<tr>
<td></td>
<td></td>
<td>DK 0995747 T3</td>
<td>25-11-2002</td>
</tr>
<tr>
<td></td>
<td></td>
<td>DK 828736 T3</td>
<td>24-11-2003</td>
</tr>
<tr>
<td></td>
<td></td>
<td>ES 2181614 T3</td>
<td>01-03-2003</td>
</tr>
<tr>
<td></td>
<td></td>
<td>ES 2205035 T3</td>
<td>01-05-2004</td>
</tr>
<tr>
<td></td>
<td></td>
<td>HK 1027802 A</td>
<td>08-11-2002</td>
</tr>
<tr>
<td></td>
<td></td>
<td>PT 995747 T</td>
<td>31-12-2002</td>
</tr>
<tr>
<td></td>
<td></td>
<td>PT 828736 T</td>
<td>31-12-2003</td>
</tr>
<tr>
<td></td>
<td></td>
<td>US 5643933 A</td>
<td>01-07-1997</td>
</tr>
<tr>
<td>wo 9603392 A</td>
<td>08-02-1996</td>
<td>AU 3201095 A</td>
<td>22-02-1996</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CA 2195847 A</td>
<td>08-02-1996</td>
</tr>
<tr>
<td></td>
<td></td>
<td>EP 0772606 A</td>
<td>14-05-1997</td>
</tr>
<tr>
<td></td>
<td></td>
<td>JP 10504542 T</td>
<td>06-05-1998</td>
</tr>
<tr>
<td></td>
<td></td>
<td>us 5668161 A</td>
<td>16-09-1997</td>
</tr>
<tr>
<td>wo 9636617 A</td>
<td>21-11-1996</td>
<td>AU 5860396 A</td>
<td>29-11-1996</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CA 2221692 A</td>
<td>21-11-1996</td>
</tr>
<tr>
<td></td>
<td></td>
<td>EP 0825989 A</td>
<td>04-03-1998</td>
</tr>
<tr>
<td></td>
<td></td>
<td>JP 11509835 T</td>
<td>31-08-1999</td>
</tr>
<tr>
<td>ep 0442448 A</td>
<td>21-08-1991</td>
<td>CA 2036192 Al</td>
<td>14-08-1991</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CN 1052667 A</td>
<td>03-07-1991</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CN 1101042 A</td>
<td>05-04-1995</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CN 1101041 A</td>
<td>05-04-1995</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CN 1101043 A</td>
<td>05-04-1995</td>
</tr>
<tr>
<td></td>
<td></td>
<td>FI 906213 A</td>
<td>21-06-1991</td>
</tr>
<tr>
<td></td>
<td></td>
<td>HU 591116 A2</td>
<td>28-04-1992</td>
</tr>
<tr>
<td></td>
<td></td>
<td>JP 4217966 A</td>
<td>07-08-1992</td>
</tr>
<tr>
<td></td>
<td></td>
<td>NO 905444 A</td>
<td>21-06-1991</td>
</tr>
<tr>
<td></td>
<td></td>
<td>NZ 236474 A</td>
<td>27-07-1993</td>
</tr>
<tr>
<td></td>
<td></td>
<td>PT 96276 A</td>
<td>30-09-1991</td>
</tr>
<tr>
<td>wo 2005116016 A</td>
<td>08-12-2005</td>
<td>AR 049186 Al</td>
<td>05-07-2006</td>
</tr>
<tr>
<td></td>
<td></td>
<td>AU 2005247930 Al</td>
<td>08-12-2005</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CA 2563819 Al</td>
<td>08-12-2005</td>
</tr>
</tbody>
</table>

Form PCT/ISA/210 (patent family annex) (April 2005)
<table>
<thead>
<tr>
<th>Patent document cited in search report</th>
<th>Publication date</th>
<th>Patent family member(s)</th>
<th>Publication date</th>
</tr>
</thead>
<tbody>
<tr>
<td>WO 2005116000 A</td>
<td>08-12-2005</td>
<td>AR 049284 A1</td>
<td>12-07-2006</td>
</tr>
<tr>
<td></td>
<td></td>
<td>AU 2005247931 A1</td>
<td>08-12-2005</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CA 2563818 A1</td>
<td>08-12-2005</td>
</tr>
</tbody>
</table>