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(54) Title: COMPOUNDS AND COMPOSITIONS AS PPAR MODULATORS

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

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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 60/571,003, filed 14 May 2004. The full disclosure of this application is incorporated herein by reference in its entirety and for all purposes.

BACKGROUND OF THE INVENTION

Field of the Invention

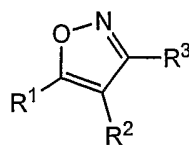
[0002] The invention provides compounds, pharmaceutical compositions comprising such compounds and methods of using such compounds to treat or prevent diseases or disorders associated with the activity of the Peroxisome Proliferator-Activated Receptor (PPAR) families, particularly the activity of PPAR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

Background

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

SUMMARY OF THE INVENTION

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



I

[0005] in which:

[0006] R^1 is selected from C_{1-6} alkyl, C_{3-12} cycloalkyl, C_{3-8} heterocycloalkyl, C_{6-10} aryl and C_{5-10} heteroaryl; wherein any alkyl, aryl, heteroaryl, cycloalkyl and heterocycloalkyl of R^1 is optionally substituted with 1 to 3 radicals independently selected from halo, nitro, cyano, C_{1-6} alkyl, C_{1-6} alkoxy, halo-substituted- C_{1-6} alkyl, halo-substituted- C_{1-6} alkoxy, $-XC(O)YR^5$ and $-XYC(O)R^5$; wherein X is a bond or C_{1-4} alkylene and Y is selected from a bond, O, S, and NR^6 ; and R^5 is selected from C_{1-6} alkyl, C_{3-12} cycloalkyl, C_{3-8} heterocycloalkyl, C_{6-10} aryl and C_{5-10} heteroaryl; and R^6 is selected from hydrogen, C_{1-6} alkyl, C_{3-12} cycloalkyl, C_{3-8} heterocycloalkyl, C_{6-10} aryl and C_{5-10} heteroaryl;

[0007] R^2 is selected from $-XOXOR^5$, $-XOR^5$, $-C(O)OR^5$, $-C(O)NR^4R^4$, $-C(O)NR^4XOR^4$, $-C(O)OXOR^5$, $-C(O)XOR^5$, $-C(O)NR^4XOR^5$, $-C(O)NR^4R^5$ and $-C(O)NR^4XR^5$; wherein X is a bond or C_{1-4} alkylene; R^4 is selected from hydrogen and C_{1-6} alkyl; R^5 is selected from C_{1-6} alkyl, C_{3-12} cycloalkyl, C_{3-8} heterocycloalkyl, C_{6-10} aryl and C_{5-10} heteroaryl; or R^4 and R^5 together with the nitrogen atom to which R^4 and R^5 are attached form C_{3-8} heterocycloalkyl or C_{5-10} heteroaryl;

[0008] wherein any alkylene group of R^2 is optionally substituted by halo, C_{1-6} alkyl and phenyl; wherein any aryl, heteroaryl, cycloalkyl and heterocycloalkyl of R^2 is optionally substituted with 1 to 3 radicals independently selected from halo, nitro, cyano, C_{1-6} alkyl, C_{1-6} alkoxy, halo-substituted- C_{1-6} alkyl and halo-substituted- C_{1-6} alkoxy;

[0009] R^3 is selected from C_{3-12} cycloalkyl, C_{3-8} heterocycloalkyl, C_{6-10} aryl and C_{5-10} heteroaryl; wherein any aryl, heteroaryl, cycloalkyl and heterocycloalkyl of R^3 is optionally substituted with 1 to 3 radicals independently selected from halo, nitro, cyano, C_{1-6} alkyl, C_{1-6} alkoxy, halo-substituted- C_{1-6} alkyl, halo-substituted- C_{1-6} alkoxy, $-XOXC(O)OR^5$, $-XC(O)OR^5$ wherein X is independently selected from a bond and C_{1-4} alkylene; and R^5 is selected from hydrogen and C_{1-6} alkyl; 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.

[0010] In a second aspect, the present invention provides a pharmaceutical composition which 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.

[0011] In a third aspect, the present invention provides a method of treating a disease in an animal in which modulation of PPAR activity, particularly PPAR δ , 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.

[0012] In a fourth aspect, the present invention provides the use of a compound of Formula I in the manufacture of a medicament for treating a disease in an animal in which PPAR activity, particularly PPAR δ , activity contributes to the pathology and/or symptomology of the disease.

[0013] 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

[0014] "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. C₁₋₆alkoxy includes, methoxy, ethoxy, and the like. Halo-substituted alkyl includes trifluoromethyl, pentafluoroethyl, and the like.

[0015] "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, quinoxaliny, quinolinyl, benzofuranyl, benzopyranyl, benzothiopyranyl, benzo[1,3]dioxole, imidazolyl, benzoimidazolyl, pyrimidinyl, furanyl, oxazolyl, isoxazolyl, triazolyl, tetrazolyl, pyrazolyl,

thienyl, etc. "C₆₋₁₀arylC₀₋₄alkyl" means an aryl as described above connected via a alkylene grouping. For example, C₆₋₁₀arylC₀₋₄alkyl includes phenethyl, benzyl, etc.

[0016] "Cycloalkyl" means a saturated or partially unsaturated, monocyclic, fused bicyclic or bridged polycyclic ring assembly containing the number of ring atoms indicated. For example, C₃₋₁₀cycloalkyl 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, C₁₋₄alkyl or a nitrogen protecting group. For example, C₃₋₈heterocycloalkyl 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.

[0017] "Halogen" (or halo) preferably represents chloro or fluoro, but can also be bromo or iodo.

[0018] "Treat", "treating" and "treatment" refer to a method of alleviating or abating a disease and/or its attendant symptoms.

Description of the Preferred Embodiments

[0019] The present invention provides compounds, compositions and methods for the treatment of diseases in which modulation of PPAR δ 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.

[0020] In one embodiment, with reference to compounds of Formula I: R¹ is selected from C₁₋₆alkyl, C₃₋₁₂cycloalkyl, C₅₋₁₀heteroaryl and C₆₋₁₀aryl; wherein any aryl or heteroaryl of R₁ is optionally substituted by 1 to 3 radicals independently selected from halo, nitro, C₁₋₆alkyl, C₁₋₆alkoxy, halo-substituted-C₁₋₆alkyl and -XC(O)OR⁵; wherein X is a bond or C₁₋₄alkylene; and R⁵ is selected from hydrogen and C₁₋₆alkyl; R² is selected from -XOXOR⁵, -XOR⁵, -C(O)NR⁴XOR⁴, -C(O)NR⁴XOR⁵, -C(O)OXOR⁵, -C(O)XOR⁵, -C(O)NR⁴R⁴, -C(O)NR⁴R⁵ and -C(O)NR⁴XR⁵; wherein X is a bond or C₁₋₄alkylene; R⁴ is selected from hydrogen and C₁₋₆alkyl; R⁵ is C₃₋₁₂cycloalkyl, C₃₋₈heterocycloalkyl, C₆₋₁₀aryl and C₅₋₁₀heteroaryl; or R⁴ and R⁵ together with the nitrogen atom to which R⁴ and R⁵ are attached form C₃₋₈heterocycloalkyl or C₅₋₁₀heteroaryl; wherein any alkylene group of R² is optionally substituted by C₁₋₆alkyl and phenyl; wherein any aryl, heteroaryl, cycloalkyl and

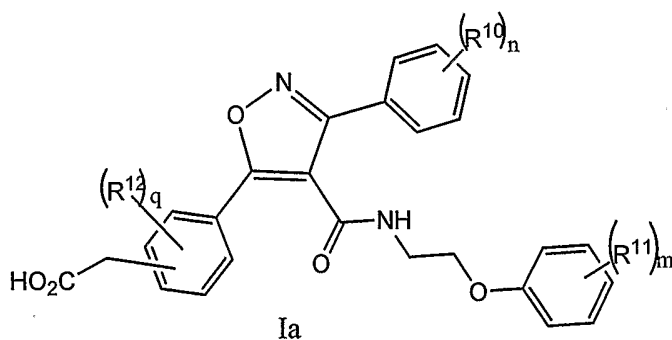
heterocycloalkyl of R^2 is optionally substituted with 1 to 3 radicals independently selected from halo, nitro, C_{1-6} alkyl, C_{1-6} alkoxy, halo-substituted- C_{1-6} alkyl and halo-substituted- C_{1-6} alkoxy; and R^3 is C_{6-10} aryl optionally substituted with 1 to 3 radicals independently selected from halo, C_{1-6} alkyl, C_{1-6} alkoxy, $-OXC(O)OR^5$ and $-XC(O)OR^5$ wherein X is a bond or C_{1-4} alkylene; and R^5 is selected from hydrogen and C_{1-6} alkyl.

[0021] In another embodiment, R^1 is selected from methyl, ethyl, t-butyl, propyl, cyclopropyl, isopropyl, pyridinyl, furanyl, thienyl and phenyl optionally substituted with 1 to 2 radicals independently selected from halo, methyl, nitro, methoxy, carboxymethyl and trifluoromethyl.

[0022] In a further embodiment, R^2 is selected from $-C(O)NHR^4$, $-C(O)NHR^5$, $-C(O)N(CH_3)CH_2R^5$, $-CH_2O(CH_2)_2OR^5$, $-CH_2OR^5$, $-C(O)NH(CH_2)_2OR^5$, $-C(O)O(CH_2)_2OR^5$, $-C(O)(CH_2)_3OR^5$, $-C(O)NH(CH_2)_{1-3}R^5$, $-C(O)NH(CH_2)_2OR^4$ and $-C(O)N(CH_3)(CH_2)_2OR^5$; wherein R^4 is selected from methyl and butyl; R^5 is selected from phenyl, cyclopentyl, furanyl, pyridinyl and naphthyl; or R^4 and R^5 together with the nitrogen atom to which R^4 and R^5 are attached form 3,4-dihydro-1H-isoquinolin-2-yl; wherein any alkylene group of R^2 is optionally substituted by a radical selected from methyl and phenyl; wherein any aryl, heteroaryl, cycloalkyl and heterocycloalkyl of R^2 is optionally substituted with 1 to 3 radicals independently selected from halo, nitro, methyl, trifluoromethyl, trifluoromethoxy and methoxy.

[0023] In a further embodiment, R^3 is phenyl optionally substituted with 1 to 3 radicals independently selected from halo, methyl, methoxy, $-OCH_2C(O)OH$, $-(CH_2)_2C(O)OH$ and $-CH_2C(O)OH$.

[0024] In another embodiment, are compounds of Formula Ia:



[0025] in which: q, m and n are independently selected from 0, 1 and 2; and R¹⁰, R¹¹ and R¹² are each independently selected from halo, C₁₋₆alkyl, nitro, C₁₋₆alkoxy and halo-substituted-C₁₋₆alkyl.

[0026] Preferred compounds of Formula I are detailed in the Examples and tables, *infra*. Further preferred compounds are selected from: (5-{4-[2-(2,4-Dichloro-phenoxy)-ethyl-carbamoyl]-5-phenyl-isoxazol-3-yl}-phenyl)-acetic acid; (3-Chloro-4-{4-[2-(2,4-dichloro-phenoxy)-ethylcarbamoyl]-5-phenyl-isoxazol-3-yl}-phenyl)-acetic acid; (3-Chloro-4-{4-[2-(2,4-dichloro-phenoxy)-ethylcarbamoyl]-5-p-tolyl-isoxazol-3-yl}-phenyl)-acetic acid; {3-Chloro-4-[4-[2-(2,4-dichloro-phenoxy)-ethylcarbamoyl]-5-(4-fluoro-phenyl)-isoxazol-3-yl]-phenyl}-acetic acid; {3-Chloro-4-[4-[2-(2,4-dichloro-phenoxy)-ethylcarbamoyl]-5-(4-nitro-phenyl)-isoxazol-3-yl]-phenyl}-acetic acid; (3-Chloro-4-{5-(2-chloro-phenyl)-4-[2-(2,4-dichloro-phenoxy)-ethylcarbamoyl]-isoxazol-3-yl}-phenyl)-acetic acid; (3-Chloro-4-{5-(4-chloro-phenyl)-4-[2-(2,4-dichloro-phenoxy)-ethylcarbamoyl]-isoxazol-3-yl}-phenyl)-acetic acid; {3-Chloro-4-[4-[2-(2,4-dichloro-phenoxy)-ethylcarbamoyl]-5-(2-methoxy-phenyl)-isoxazol-3-yl]-phenyl}-acetic acid; {3-Chloro-4-[4-[2-(2,4-dichloro-phenoxy)-ethylcarbamoyl]-5-(3-methoxy-phenyl)-isoxazol-3-yl]-phenyl}-acetic acid; {3-Chloro-4-[4-[2-(2,4-dichloro-phenoxy)-ethylcarbamoyl]-5-(4-methoxy-phenyl)-isoxazol-3-yl]-phenyl}-acetic acid; {3-Chloro-4-[4-[2-(2,4-dichloro-phenoxy)-ethylcarbamoyl]-5-(2-trifluoromethyl-phenyl)-isoxazol-3-yl]-phenyl}-acetic acid; {3-Chloro-4-[4-[2-(2,4-dichloro-phenoxy)-ethylcarbamoyl]-5-(3-trifluoromethyl-phenyl)-isoxazol-3-yl]-phenyl}-acetic acid; {3-Chloro-4-[4-[2-(2,4-dichloro-phenoxy)-ethylcarbamoyl]-5-(4-trifluoromethyl-phenyl)-isoxazol-3-yl]-phenyl}-acetic acid; (3-{4-[2-(2,4-Dichloro-phenoxy)-ethylcarbamoyl]-5-p-tolyl-isoxazol-3-yl}-phenyl)-acetic acid; {3-[4-[2-(2,4-Dichloro-phenoxy)-ethylcarbamoyl]-5-(4-fluoro-phenyl)-isoxazol-3-yl]-phenyl}-acetic acid; {3-[4-[2-(2,4-Dichloro-phenoxy)-ethylcarbamoyl]-5-(4-nitro-phenyl)-isoxazol-3-yl]-phenyl}-acetic acid; (3-{5-(2-Chloro-phenyl)-4-[2-(2,4-dichloro-phenoxy)-ethylcarbamoyl]-isoxazol-3-yl}-phenyl)-acetic acid; (3-{5-(3-Chloro-phenyl)-4-[2-(2,4-dichloro-phenoxy)-ethylcarbamoyl]-isoxazol-3-yl}-phenyl)-acetic acid; (3-{5-(4-Chloro-phenyl)-4-[2-(2,4-dichloro-phenoxy)-ethylcarbamoyl]-isoxazol-3-yl}-phenyl)-acetic acid; {3-[4-[2-(2,4-Dichloro-phenoxy)-ethylcarbamoyl]-5-(2-methoxy-phenyl)-isoxazol-3-yl]-phenyl}-acetic acid; {3-[4-[2-(2,4-Dichloro-phenoxy)-ethylcarbamoyl]-5-(3-methoxy-phenyl)-isoxazol-3-yl]-phenyl}-acetic acid; {3-[4-[2-(2,4-Dichloro-phenoxy)-

ethylcarbamoyl]-5-(4-methoxy-phenyl)-isoxazol-3-yl]-phenyl}-acetic acid; {3-[4-[2-(2,4-Dichloro-phenoxy)-ethylcarbamoyl]-5-(2-trifluoromethyl-phenyl)-isoxazol-3-yl]-phenyl}-acetic acid; {3-[4-[2-(2,4-Dichloro-phenoxy)-ethylcarbamoyl]-5-(3-trifluoromethyl-phenyl)-isoxazol-3-yl]-phenyl}-acetic acid; {3-[4-[2-(2,4-Dichloro-phenoxy)-ethylcarbamoyl]-5-(4-trifluoromethyl-phenyl)-isoxazol-3-yl]-phenyl}-acetic acid; (3-{4-[2-(2,4-Dichloro-phenoxy)-ethylcarbamoyl]-5-o-tolyl-isoxazol-3-yl}-phenyl)-acetic acid; and (3-{4-[2-(2,4-Dichloro-phenoxy)-ethylcarbamoyl]-5-m-tolyl-isoxazol-3-yl}-phenyl)-acetic acid.

[0027] Further preferred compounds are detailed in the examples and tables, *infra*.

Pharmacology and Utility

[0028] Compounds of the invention modulate the activity of PPARs and, as such, are useful for treating diseases or disorders in which PPARs contributes to the pathology and/or symptomology of the disease. This invention further provides compounds of this invention for use in the preparation of medicaments for the treatment of diseases or disorders in which PPARs, particularly PPAR δ , contributes to the pathology and/or symptomology of the disease.

[0029] Such compounds may therefore be employed for the treatment of prophylaxis, dyslipidemia, hyperlipidemia, hypercholesteremia, atherosclerosis, atherogenesis, hypertriglyceridemia, heart failure, hyper cholesteremia, myocardial infarction, vascular diseases, cardiovascular diseases, hypertension, obesity, cachexia, HIV wasting syndrome, inflammation, arthritis, cancer, Alzheimer's disease, anorexia, anorexia nervosa, bulimia, skin disorders, respiratory diseases, ophthalmic disorders, IBDs (irritable bowel disease), ulcerative colitis and Crohn's disease. Preferably for the treatment of prophylaxis, dyslipidemia, hyperlipidemia, hypercholesteremia, atherosclerosis, atherogenesis, hypertriglyceridemia, cardiovascular diseases, hypertension, obesity, inflammation, cancer, skin disorders, IBDs (irritable bowel disease), ulcerative colitis and Crohn's disease.

[0030] 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.

[0031] 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).

[0032] 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

[0033] 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.

[0034] 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.

[0035] This invention also concerns a pharmaceutical composition comprising a therapeutically effective amount of a compound as described herein in combination with one or more pharmaceutically acceptable carriers.

[0036] Compounds of the invention can be administered in therapeutically effective amounts in combination with one or more therapeutic agents (pharmaceutical combinations).

[0037] 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:

[0038] a) anti-diabetic agents such as insulin, insulin derivatives and mimetics; insulin secretagogues such as the sulfonylureas, e.g., Glipizide, glyburide and Amaryl; insulinotropic sulfonylurea receptor ligands such as meglitinides, e.g., nateglinide and repaglinide; insulin sensitizer such as protein tyrosine phosphatase-1B (PTP-1B) inhibitors such as PTP-112; GSK3 (glycogen synthase kinase-3) inhibitors such as SB-517955, SB-4195052, SB-216763, NN-57-05441 and NN-57-05445; RXR ligands such as GW-0791 and AGN-194204; sodium-dependent glucose co-transporter inhibitors such as T-1095; glycogen phosphorylase A inhibitors such as BAY R3401; biguanides such as metformin; alpha-glucosidase inhibitors such as acarbose; GLP-1 (glucagon like peptide-1), GLP-1 analogs such as Exendin-4 and GLP-1 mimetics; DPPIV (dipeptidyl peptidase IV) inhibitors such as DPP728, LAF237 (vildagliptin - Example 1 of WO 00/34241), MK-0431, saxagliptin, GSK23A ; an AGE breaker; a thiazolidone derivative (glitazone) such as pioglitazone, rosiglitazone, or (*R*)-1-{4-[5-methyl-2-(4-trifluoromethyl-phenyl)-oxazol-4-ylmethoxy]-benzenesulfonyl}-2,3-dihydro-1*H*-indole-2-carboxylic acid described in the patent application WO 03/043985, as compound 19 of Example 4, a non-glitazone type PPAR γ agonist e.g. GI-262570;

[0039] b) hypolipidemic agents such as 3-hydroxy-3-methyl-glutaryl coenzyme A (HMG-CoA) reductase inhibitors, e.g., lovastatin, pitavastatin, simvastatin, pravastatin, cerivastatin, mevastatin, velostatin, fluvastatin, dalvastatin, atorvastatin, rosuvastatin and rivastatin; squalene synthase inhibitors; FXR (farnesoid X receptor) and LXR (liver X receptor) ligands; cholestyramine; fibrates; nicotinic acid and aspirin;

[0040] 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;

[0041] d) anti-hypertensive agents, e.g., loop diuretics such as ethacrynic acid, furosemide and torsemide; diuretics such as thiazide derivatives, chlorithiazide, hydrochlorothiazide, amiloride; angiotensin converting enzyme (ACE) inhibitors such as benazepril, captopril, enalapril, fosinopril, lisinopril, moexipril, perinodopril, quinapril, ramipril 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 66-1132, 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, nifedipine, nimodipine, nifedipine, nisoldipine and verapamil; aldosterone receptor antagonists; and aldosterone synthase inhibitors;

[0042] e) a HDL increasing compound;

[0043] f) Cholesterol absorption modulator such as Zetia® and KT6-971;

[0044] g) Apo-A1 analogues and mimetics;

[0045] h) thrombin inhibitors such as Ximelagatran;

[0046] i) aldosterone inhibitors such as anastrozole, fadrazole, eplerenone;

[0047] j) Inhibitors of platelet aggregation such as aspirin, clopidogrel bisulfate;

[0048] k) estrogen, testosterone, a selective estrogen receptor modulator, a selective androgen receptor modulator;

[0049] l) a chemotherapeutic agent such as aromatase inhibitors e.g. femara, anti-estrogens, topoisomerase I inhibitors, topoisomerase II inhibitors, microtubule active agents, alkylating agents, antineoplastic antimetabolites, platin compounds, compounds decreasing the protein kinase activity such as a PDGF receptor tyrosine kinase inhibitor preferably Imatinib ({ N-{5-[4-(4-methyl-piperazino-methyl)-benzoylamido]-2-methylphenyl}-4-(3-pyridyl)-2-pyrimidine-amine }) described in the European patent application EP-A-0 564 409 as example 21 or 4-Methyl-N-[3-(4-methyl-imidazol-1-yl)-5-trifluoromethyl-phenyl]-3-(4-pyridin-3-yl-pyrimidin-2-ylamino)-benzamide described in the patent application WO 04/005281 as example 92; and

[0050] 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;

[0051] or, in each case a pharmaceutically acceptable salt thereof; and optionally a pharmaceutically acceptable carrier.

[0052] Most preferred combination partners are tegaserod, imatinib, vildagliptin, metformin, a thiazolidone derivative (glitazone) such as pioglitazone, rosiglitazone, or (*R*)-1-{4-[5-methyl-2-(4-trifluoromethyl-phenyl)-oxazol-4-ylmethoxy]-benzenesulfonyl}-2,3-dihydro-1*H*-indole-2-carboxylic acid, a sulfonyleurea receptor ligand, aliskiren, valsartan, orlistat or a statin such as pitavastatin, simvastatin, fluvastatin or pravastatin.

[0053] Preferably the pharmaceutical combinations contains a therapeutically effective amount of a compound of the invention as defined above, in a combination with a therapeutically effective amount of another therapeutic agent as described above, e.g., each at an effective therapeutic dose as reported in the art. Combination partners (1) and (2) can be administered together, one after the other or separately in one combined unit dosage form or in two separate unit dosage forms. The unit dosage form may also be a fixed combination.

[0054] 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.

[0055] 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.

[0056] 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.

[0057] Such therapeutic agents include estrogen, testosterone, a selective estrogen receptor modulator, a selective androgen receptor modulator, insulin, insulin derivatives and mimetics; insulin secretagogues such as the sulfonylureas, e.g., Glipizide and Amaryl; insulinotropic sulfonylurea receptor ligands, such as meglitinides, e.g., nateglinide and repaglinide; insulin sensitizers, such as protein tyrosine phosphatase-1B (PTP-1B) inhibitors, GSK3 (glycogen synthase kinase-3) inhibitors or RXR ligands; biguanides, such as metformin; alpha-glucosidase inhibitors, such as acarbose; GLP-1 (glucagon like peptide-1), GLP-1 analogs, such as Exendin-4, and GLP-1 mimetics; DPPIV (dipeptidyl peptidase IV) inhibitors, e.g. isoleucin-thiazolidide; DPP728 and LAF237, hypolipidemic agents, such as 3-hydroxy-3-methyl-glutaryl coenzyme A (HMG-CoA) reductase inhibitors, e.g., lovastatin, pitavastatin, simvastatin, pravastatin, cerivastatin, mevastatin, velostatin, fluvastatin, dalvastatin, atorvastatin, rosuvastatin, fluindostatin and rivastatin, squalene synthase inhibitors or FXR (liver X receptor) and LXR (farnesoid X receptor) ligands, cholestyramine, fibrates, nicotinic acid and aspirin. A compound of the present invention may be administered either simultaneously, before or after the other active ingredient, either separately by the same or different route of administration or together in the same pharmaceutical formulation.

[0058] 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.

[0059] 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.

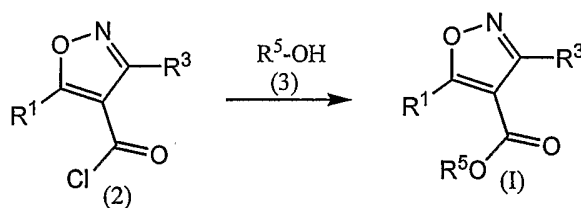
[0060] The term “pharmaceutical combination” as used herein means a product that results from the mixing or combining of more than one active ingredient and includes both fixed and non-fixed combinations of the active ingredients. The term “fixed combination” means that the active ingredients, e.g. a 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

[0061] 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.

[0062] Compounds of Formula I, in which R² is -C(O)OR⁵, can be prepared by proceeding as in the following Reaction Scheme 1:

Reactions Scheme 1

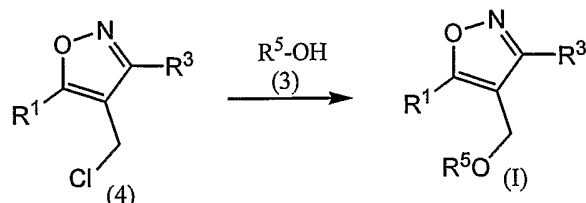


[0063] in which R¹, R³ and R⁵ are as defined for Formula I in the Summary of the Invention. Compounds of Formula I are prepared by reacting a compound of formula 2 with a compound of formula 3 in the presence of a suitable catalyst (e.g., dimethyl-tin chloride, or

the like) and a suitable solvent (e.g., THF, or the like). The reaction is carried out in the temperature range of 0 to 60°C and takes up to 20 hours to complete.

[0064] Compounds of Formula I, in which R² is -XOR⁵ (X is methylene), can be prepared by proceeding as in the following Reaction Scheme 2:

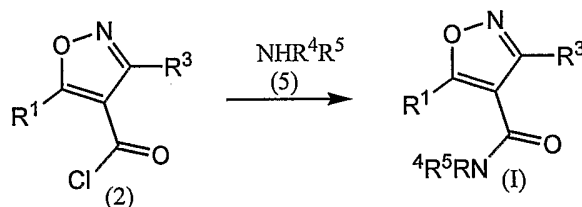
Reactions Scheme 2



[0065] in which R¹, R³ and R⁵ are as defined for Formula I in the Summary of the Invention. Compounds of Formula I are prepared by reacting a compound of formula 4 with a compound of formula 3 in the presence of a suitable base (e.g., sodium hydride, or the like) and a suitable solvent (e.g., dichloromethane, or the like). The reaction is carried out in the temperature range of 0 to 90°C and takes up to 8 hours to complete.

[0066] Compounds of Formula I, in which R² is -C(O)NR⁴R⁵, can be prepared by proceeding as in the following Reaction Scheme 3:

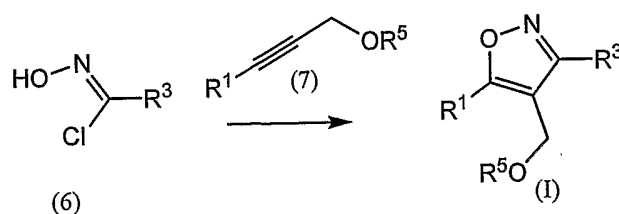
Reactions Scheme 3



[0067] in which R¹, R³, R⁴ and R⁵ are as defined for Formula I in the Summary of the Invention. Compounds of Formula I are prepared by reacting a compound of formula 2 with a compound of formula 5 in the presence of a suitable base (e.g., triethylamine, or the like) and a suitable solvent (e.g., dichloromethane, or the like). The reaction is carried out in the temperature range of 0 to 50°C and takes up to 8 hours to complete.

[0068] Compounds of Formula I, in which R¹ is methyl, can be prepared by proceeding as in the following Reaction Scheme 4:

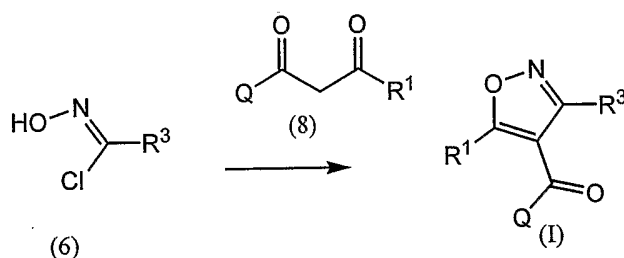
Reactions Scheme 4



[0069] in which R^1 , R^3 and R^5 are as defined for Formula I in the Summary of the Invention. Compounds of Formula I are prepared by reacting a compound of formula 6 with a compound of formula 7 in the presence of a suitable base (e.g., triethylamine, or the like) and optionally in the presence of a suitable solvent (e.g., dichloroethane, or the like). The reaction is carried out in the temperature range of 50 to 120°C and takes up to 15 hours to complete.

[0070] Compounds of Formula I, in which R^1 is methyl, can be prepared by proceeding as in the following Reaction Scheme 5:

Reactions Scheme 5



[0071] in which R^1 , R^3 , R^4 and R^5 are as defined for Formula I in the Summary of the Invention. Q represents $-\text{OR}^5$, $-\text{NR}^4\text{R}^4$, $-\text{NR}^4\text{XOR}^4$, $-\text{NR}^4\text{XOR}^5$, $-\text{NR}^4\text{R}^5$ and $-\text{NR}^4\text{XR}^5$ according to the definition of R^2 in the Summary of the Invention. Compounds of Formula I are prepared by reacting a compound of formula 6 with a compound of formula 8 in the presence of a suitable base (e.g., triethylamine, or the like) and a suitable solvent (e.g., dichloroethane, or the like). The reaction is carried out in the temperature range of 50 to 120°C and takes up to 15 hours to complete.

Additional Processes for Making Compounds of the Invention

[0072] 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.

[0073] 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 form, 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.)

[0074] 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.

[0075] 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).

[0076] 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.

[0077] 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.

[0078] 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.

[0079] In summary, the compounds of Formula I can be made by a process, which involves:

[0080] (a) that of reaction scheme 1, 2, 3, 4 or 5; and

[0081] (b) optionally converting a compound of the invention into a pharmaceutically acceptable salt;

[0082] (c) optionally converting a salt form of a compound of the invention to a non-salt form;

[0083] (d) optionally converting an unoxidized form of a compound of the invention into a pharmaceutically acceptable N-oxide;

[0084] (e) optionally converting an N-oxide form of a compound of the invention to its unoxidized form;

[0085] (f) optionally resolving an individual isomer of a compound of the invention from a mixture of isomers;

[0086] (g) optionally converting a non-derivatized compound of the invention into a pharmaceutically acceptable prodrug derivative; and

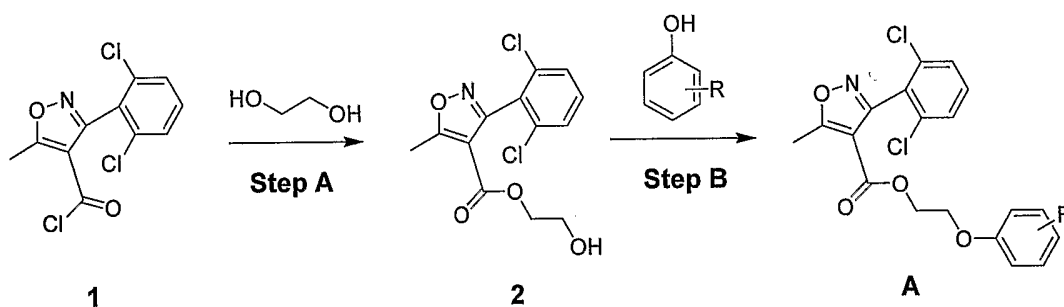
[0087] (h) optionally converting a prodrug derivative of a compound of the invention to its non-derivatized form.

[0088] 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.

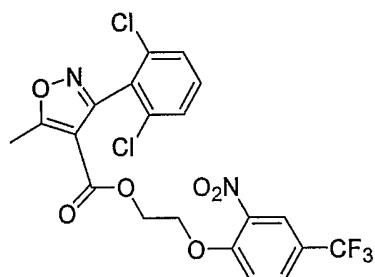
[0089] One of skill in the art will appreciate that the above transformations are only representative of methods for preparation of the compounds of the present invention, and that other well known methods can similarly be used.

Examples

[0090] The present invention is further exemplified, but not limited, by the following examples that illustrate the preparation of compounds of Formula I according to the invention.



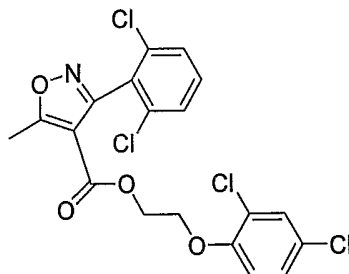
[0091] **Example A1.** 3-(2,6-Dichloro-phenyl)-5-methyl-isoxazole-4-carboxylic acid 2-(2-nitro-4-trifluoromethyl-phenoxy)-ethyl ester.



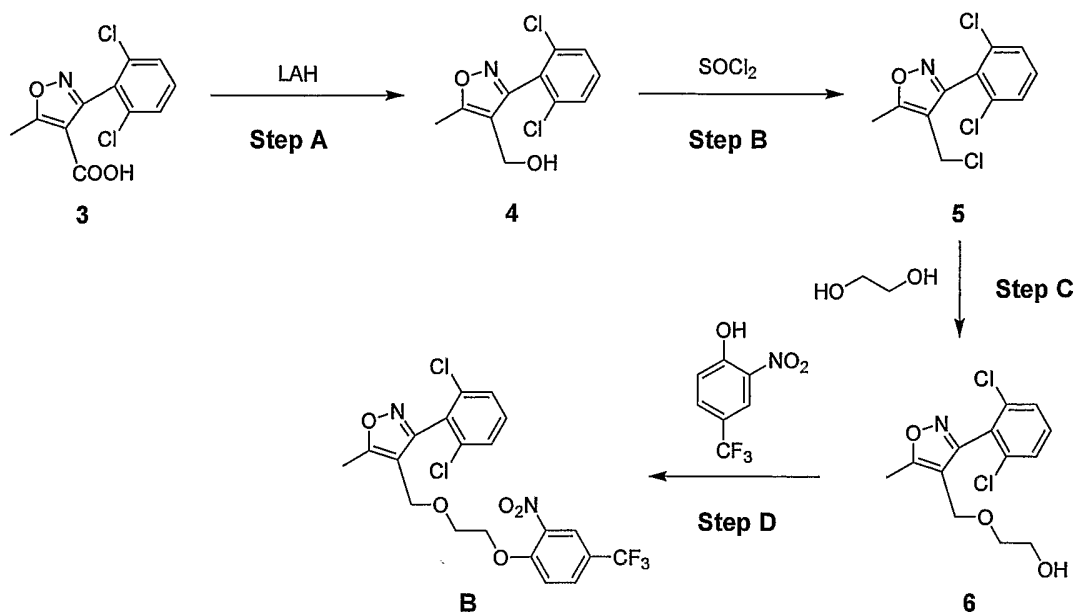
[0092] **Step A:** To a solution of ethylene glycol (0.62 g, 10 mmol) in THF (50 mL) is added a catalytic amount of dimethyl tin dichloride (5 mol%), K_2CO_3 (2.76 g, 20 mmol) and 3-(2,6-Dichloro-phenyl)-5-methyl-isoxazole-4-carbonyl chloride **1** (2.91 g, 10 mmol), successively, at room temperature. The mixture is stirred overnight at room temperature, then poured into water and extracted three times with DCM (300 mL). The organic layers are combined, dried ($MgSO_4$), filtered and concentrated to afford crude **2** as a white solid.

[0093] **Step B:** 3-(2,6-Dichloro-phenyl)-5-methyl-isoxazole-4-carboxylic acid 2-hydroxy-ethyl ester **2** (25 mg, 0.079 mmol), triphenylphosphine (31 mg, 0.119 mmol) and 2-nitro-4-trifluoromethyl-phenol (19.6 mg, 0.095 mmol) are dissolved in DCM (1 mL) and cooled to $0^\circ C$. Diethyl azodicarboxylate (27.5 mg, 0.158 mmol) is added dropwise, the solution is warmed to room temperature and stirred for 12 hours. Then the mixture is concentrated and purified on reverse phase HPLC ($H_2O/MeCN$ gradient) to afford the title compound **A1** as a yellow solid: MS calculated for $C_{20}H_{14}Cl_2F_3N_2O_6$ ($M+H^+$) 505.0, found 505.0.

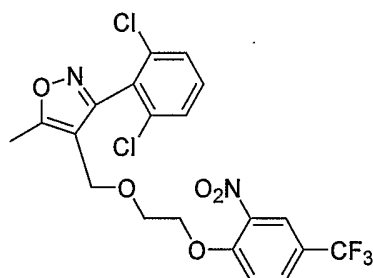
[0094] **Example A2.** 3-(2,6-Dichloro-phenyl)-5-methyl-isoxazole-4-carboxylic acid 2-(2,4-dichloro-phenoxy)-ethyl ester.



[0095] Following the procedure of Example **A1**, except substituting 2,4-dichloro-phenol for 2-nitro-4-trifluoromethyl-phenol in Step B, the title compound is prepared as a white solid: MS calculated for $C_{19}H_{14}Cl_4NO_4$ ($M+H^+$) 460.0, found 460.0.



[0096] **Example B.** 3-(2,6-Dichloro-phenyl)-5-methyl-4-[2-(2-nitro-4-trifluoromethyl-phenoxy)-ethoxymethyl]-isoxazole.

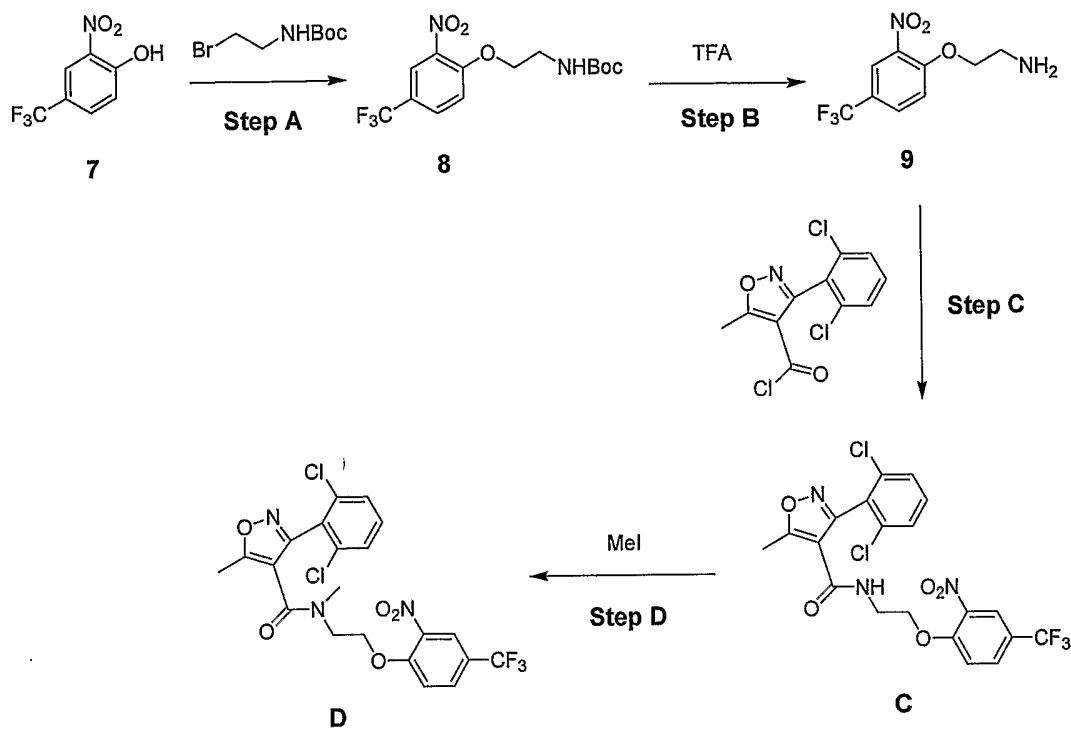


[0097] **Step A:** A solution of isoxazole **3** (5.0 g, 18.4 mmol) in dry THF (100 mL) is cooled to 0°C. LAH (27.8 mL of a 1 M solution in THF) is added dropwise and the reaction mixture is stirred at room temperature for 20 hours. Sodium sulfate decahydrate is added slowly together with THF (70 mL) and the mixture is stirred for another 1 hour at room temperature. The mixture is then filtered over celite, the solvent is evaporated and the remainder is purified by column chromatography using a DCM/MeOH gradient to yield intermediate **4** as a white solid: $^1\text{H-NMR}$ (400 MHz, CDCl_3) δ = 7.32-7.21 (m, 3H), 4.23 (s, 2H), 2.43 (s, 3H). MS calculated for $\text{C}_{11}\text{H}_{10}\text{Cl}_2\text{NO}_2$ ($\text{M}+\text{H}^+$) 258.0, found 258.2.

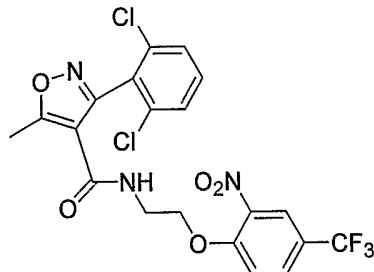
[0098] Step B: [3-(2,6-Dichloro-phenyl)-5-methyl-isoxazol-4-yl]-methanol **4** (1.23 g, 4.8 mmol) is dissolved in DCM (35 mL) and cooled to 0°C. Thionyl chloride (0.42 mL, 5.72 mmol) dissolved in DCM (15 mL) is added dropwise. After the addition is completed the reaction mixture is stirred at room temperature for 1 hour. Then the mixture is concentrated in vacuo and the remainder is purified by column chromatography using a DCM/MeOH gradient to yield intermediate **5** as a white solid: ¹H-NMR (400 MHz, CDCl₃) δ = 7.46-7.26 (m, 3H), 4.27 (s, 2H), 2.57 (s, 3H). MS calculated for C₁₁H₉Cl₃NO (M+H⁺) 276.0, found 276.2.

[0099] Step C: To a suspension of NaH (60% dispersion in mineral oil, 100 mg, 2.5 mmol) in ethylene glycol (10 mL) is added 4-Chloromethyl-3-(2,6-dichloro-phenyl)-5-methyl-isoxazole **5** (0.20 g, 0.72 mmol). The mixture is stirred at 80°C for 3 hours. The mixture is then acidified with 0.5 M HCl, diluted with H₂O and extracted three times with DCM. The organic layers are combined, dried (MgSO₄), filtered and concentrated. The remainder is purified by column chromatography using a DCM/MeOH gradient to afford intermediate **6** as colorless oil: ¹H-NMR (400 MHz, CDCl₃) δ = 7.37-7.19 (m, 3H), 4.19 (s, 2H), 3.52 (t, J = 4.5 Hz, 2H), 3.33 (t, J = 4.5 Hz, 2H), 2.47 (s, 3H). MS calculated for C₁₃H₁₄Cl₂NO₃ (M+H⁺) 302.0, found 302.2.

[00100] Step D: 2-[3-(2,6-Dichloro-phenyl)-5-methyl-isoxazol-4-ylmethoxy]-ethanol **6** (50 mg, 0.17 mmol), triphenylphosphine (66 mg, 0.25 mmol) and 2-nitro-4-trifluoromethyl-phenol (42 mg, 0.20 mmol) are dissolved in DCM (2 mL) and cooled to 0°C. Diethyl azodicarboxylate (58 mg, 0.34 mmol) is added dropwise, the solution is warmed to room temperature and stirred for 12 hours. Then the mixture is concentrated and purified on reverse phase HPLC (H₂O/MeCN gradient) to afford the title compound **B** as a white solid: ¹H-NMR (400 MHz, CDCl₃) δ = 8.11 (d, J = 1.9 Hz, 1H), 7.73 (dd, J = 8.8 Hz, J = 1.8 Hz, 1H), 7.38-7.26 (m, 3H), 7.12 (d, J = 8.8 Hz, 1H), 4.35 (s, 2H), 4.20 (t, J = 4.5 Hz, 2H), 3.71 (t, J = 4.5 Hz, 2H), 2.54 (s, 3H). MS calculated for C₂₀H₁₆Cl₂F₃N₂O₅ (M+H⁺) 491.0, found 491.1.



[00101] **Example C.** 3-(2,6-Dichloro-phenyl)-5-methyl-isoxazole-4-carboxylic acid [2-(2-nitro-4-trifluoromethyl-phenoxy)-ethyl]-amide.



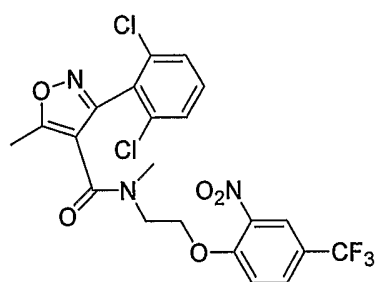
[00102] **Step A:** 2-nitro-4-trifluoromethyl-phenol 7 (0.5 g, 2.42 mmol) and (2-Bromoethyl)-carbamic acid tert-butyl ester (0.54 g, 2.42 mmol) are dissolved in MeCN. Cs_2CO_3 is added (1.58 g, 4.84 mmol) and the mixture is stirred at 90°C for 6 hours. The mixture is then filtered, concentrated in vacuo, diluted with H_2O and extracted three times with DCM. The organic layers are combined, dried (MgSO_4), filtered, and concentrated and the remainder purified by column chromatography using a DCM/MeOH gradient to afford intermediate 8 as a yellow solid: $^1\text{H-NMR}$ (400 MHz, CDCl_3) δ = 8.42 (d, J = 1.1 Hz, 1H), 8.37 (m, NH), 7.58 (dd, J = 9.0 Hz, J = 2.0 Hz, 1H), 6.92 (d, J = 9.0 Hz, 1H), 4.29 (t, J = 5.5 Hz, 2H), 3.60

(q, $J = 5.5$ Hz, 2H), 1.42 (s, 9H). MS calculated for $C_9H_{10}F_3N_2O_3$ ($M-Boc^+$) 251.1, found 251.2.

[00103] Step B: [2-(2-Nitro-4-trifluoromethyl-phenoxy)-ethyl]-carbamic acid tert-butyl ester **8** (0.81 g, 2.30 mmol) is dissolved in 5% trifluoroacetic acid in DCM (20 mL) and stirred at room temperature for 4 hours. The mixture is then concentrated, diluted with aqueous sat. K_2CO_3 and extracted three times with DCM. The organic layers are combined, dried ($MgSO_4$), filtered, and concentrated to afford intermediate **9** as a yellow oil: 1H -NMR (400 MHz, $CDCl_3$) $\delta = 8.49$ (d, $J = 1.1$ Hz, 1H), 7.63 (dd, $J = 9.0$ Hz, $J = 2.0$ Hz, 1H), 7.00 (d, $J = 9.0$ Hz, 1H), 3.99 (t, $J = 5.4$ Hz, 2H), 3.56 (q, $J = 5.3$ Hz, 2H), 1.63 (s, NH₂). MS calculated for $C_9H_{10}F_3N_2O_3$ ($M+H^+$) 251.1, found 251.2.

[00104] Step C: 2-(2-Nitro-4-trifluoromethyl-phenoxy)-ethylamine **9** (0.25 g, 1.00 mmol) and 3-(2,6-Dichloro-phenyl)-5-methyl-isoxazole-4-carbonyl chloride **1** (0.30 g, 1.00 mmol) are dissolved in DCM (25 mL). Triethyl amine (0.21 mL, 1.50 mmol) is added and the solution is stirred at room temperature for 2 hours. The solution is then washed three times with H_2O , concentrated and purified on reverse phase HPLC ($H_2O/MeCN$ gradient) to afford the title compound **C** as a yellow solid: 1H -NMR (400 MHz, $CDCl_3$) $\delta = 8.50$ (d, $J = 1.2$ Hz, 1H), 8.09 (m, NH), 7.64 (dd, $J = 9.0$ Hz, $J = 2.1$ Hz, 1H), 7.41-7.16 (m, 3H), 6.83 (d, $J = 9.0$ Hz, 1H), 4.40 (t, $J = 5.3$ Hz, 2H), 3.42 (q, $J = 5.3$ Hz, 2H), 2.81 (s, 3H). MS calculated for $C_{20}H_{15}Cl_2F_3N_3O_5$ ($M+H^+$) 504.0, found 504.2.

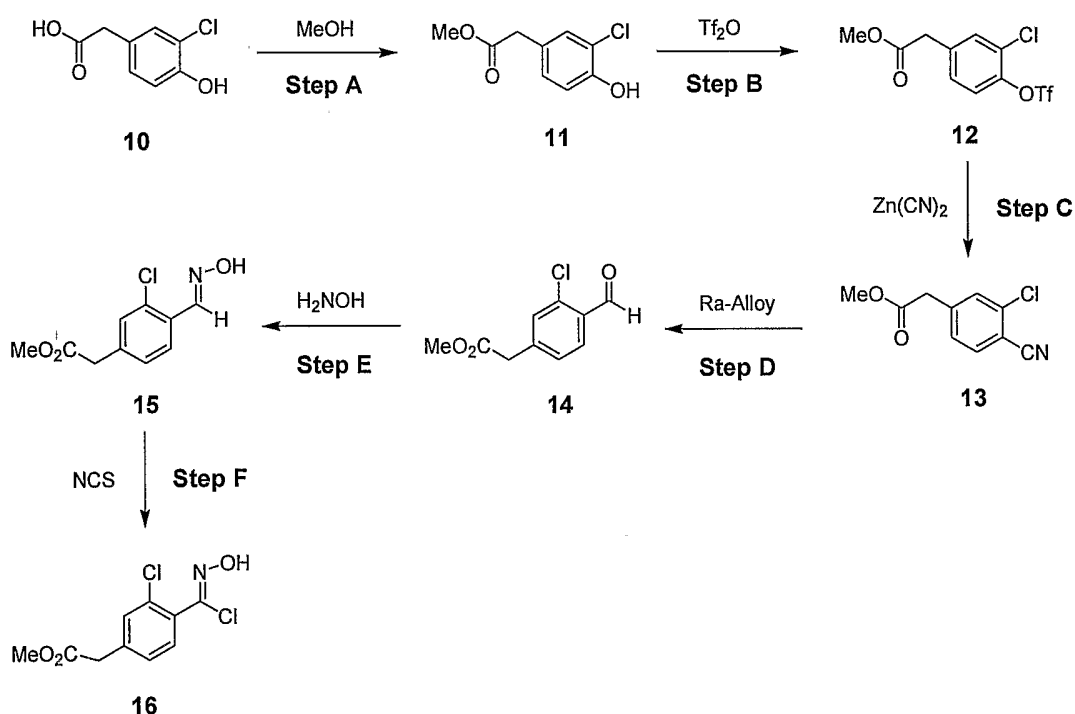
[00105] Example D. 3-(2,6-Dichloro-phenyl)-5-methyl-isoxazole-4-carboxylic acid methyl-[2-(2-nitro-4-trifluoromethyl-phenoxy)-ethyl]-amide.



[00106] Step D: 3-(2,6-Dichloro-phenyl)-5-methyl-isoxazole-4-carboxylic acid [2-(2-nitro-4-trifluoromethyl-phenoxy)-ethyl]-amide (Example C, 20 mg, 0.04 mmol) is dissolved in DMF (0.5 mL) and cooled to 0°C. Sodium hydride (60% in mineral oil, 2 mg, 0.05 mmol)

is added and the solution is stirred for 15 min at 0°C. Then methyl iodide (6.5 μ L, 0.05 mmol) is added and the mixture is stirred at room temperature for 2 hours. The reaction mixture is diluted with H₂O and extracted three times with DCM. The organic layers are combined, dried (MgSO₄), filtered, and concentrated. The remainder is purified on reverse phase HPLC (H₂O/MeCN gradient) to afford the title compound **D** as a yellow solid: MS calculated for C₂₁H₁₇Cl₂F₃N₃O₅ (M+H⁺) 518.0, found 518.2.

[00107] Intermediate **16**: [3-Chloro-4-(hydroxyimino-chloromethyl)-phenyl]-acetic acid methyl ester.



[00108] Step A: 3-Chloro-4-hydroxy-phenyl)-acetic acid **10** (20 g, 107 mmol) is dissolved in MeOH (250 mL) containing catalytic amounts of conc. H₂SO₄ (2.5 mL). The solution is heated to reflux overnight. The solvent is evaporated, the remainder is dissolved in DCM and washed with H₂O (3x200 mL). The organic layer is dried (MgSO₄), filtered and concentrated to afford **11** as a light yellow solid: ¹H-NMR (400MHz, CD₃OD) δ = 7.21 (d, J = 2.1 Hz, 1H), 7.01 (dd, J = 2.1 Hz, J = 8.3, 1H), 6.84 (d, J = 8.3 Hz, 1H), 3.67 (s, 3H), 3.54 (s, 2H). MS calculated for C₉H₁₀ClO₃ (M+H⁺) 201.0, found 201.2.

[00109] Step B: To a solution of (3-Chloro-4-hydroxy-phenyl)-acetic acid methyl ester 11 (15.9 g, 79.3 mmol) and triethylamine (11.04 mL, 79.3 mmol) in DCM (160 mL) triflic anhydride (13.33 mL, 79.3 mmol) is added dropwise at 0°C over a period of 2 hours. The reaction mixture is then diluted with EtOAc (300mL) and washed successively with NaHCO₃, brine and water. The organic layer is dried (MgSO₄), filtered and concentrated to afford (3-chloro-4-trifluoromethanesulfonyloxy-phenyl)-acetic acid methyl ester 12 as colorless oil: MS calculated for C₁₀H₉ClF₃O₅S (M+H⁺) 333.0, found 333.1.

[00110] Step C: A solution of (3-chloro-4-trifluoromethanesulfonyloxy-phenyl)-acetic acid methyl ester 12 (24.5 g, 73.6 mmol) in dry DMF (45 mL) is combined with zinc cyanide (8.91 g, 75.9 mmol) and tetrakis(triphenylphosphine) palladium (8.50 g, 7.4 mmol). The mixture is stirred for 34 hours at 80°C, then cooled to room temperature, diluted with EtOAc (150 mL) and poured into a saturated NaHCO₃ solution (150 mL). A white precipitate is removed by vacuum filtration. The organic layer of the filtrate is separated and washed with H₂O. The organic layer is dried (MgSO₄), filtered and concentrated. The remainder is purified by silica gel chromatography using 20% EtOAc/hexane to give (3-chloro-4-cyano-phenyl) acetic acid methyl ester 13 as a wax-like solid: ¹H-NMR (400MHz, CDCl₃) δ = 7.63 (d, J= 8.0 Hz, 1H), 7.47 (d, J= 1.2 Hz, 1H), 7.30 (dd, J= 1.2 Hz, J= 8.0 Hz, 1H), 3.72 (s, 3H), 3.69 (s, 2H). MS calculated for C₁₀H₉O₂ClN (M+H⁺) 210.0, found 210.0.

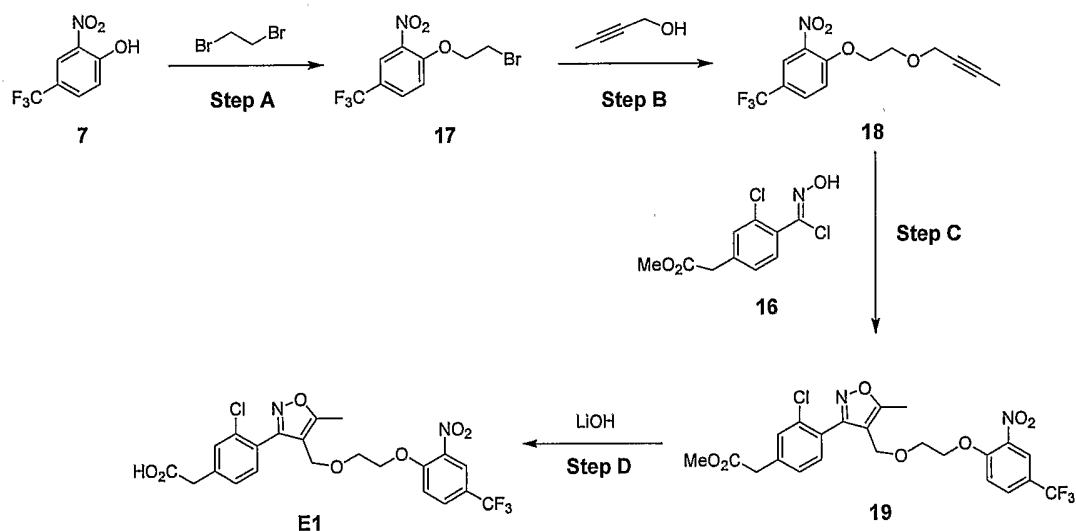
[00111] Step D: A solution of (3-chloro-4-cyano-phenyl) acetic acid methyl ester 13 (7.4 g, 35.3 mmol) in 88% formic acid (100 mL) is combined with Raney-alloy (9.0 g) and heated to reflux for 10 hours at 110°C. After cooling to room temperature, the alloy is removed by filtration over Celite. The filtrate is concentrated to ~10% of the original volume and diluted with EtOAc (250 mL) and washed three times with water (80 mL). The organic layer is dried (MgSO₄), filtered and concentrated to afford crude product, which is purified by silica gel chromatography using an EtOAc/hexane gradient to give (3-Chloro-4-formyl-phenyl)-acetic acid methyl ester 14 as a wax-like solid. Another amount of product 14 is collected by reesterification of saponified byproduct(3-Chloro-4-formyl-phenyl)-acetic acid: ¹H-NMR (400MHz, CDCl₃) δ = 10.31 (s, 1H), 7.84 (d, J= 8.0 Hz, 1H), 7.58 (s, 1H), 7.45 (d, J= 8.0 Hz, 1H), 3.86 (s, 3H), 3.64 (s, 2H). MS calculated for C₁₀H₁₀ClO₃ (M+H⁺) 213.0, found 213.3.

[00112] Step E: Hydroxylamine hydrochloride (2.45 g, 35.3 mmol) is dissolved in water (100 mL) and cooled to 0°C on an ice-bath. NaHCO₃ (4.44 g, 52.9 mmol) is added and

the solution is kept at 0°C for 20 minutes. Then (3-Chloro-4-formyl-phenyl)-acetic acid methyl ester **14** (5.00 g, 23.5 mmol) dissolved in MeOH (75 mL) is added slowly. A white precipitate formed immediately. The ice-bath is removed and the mixture is stirred at room temperature for 2 hours. The MeOH is removed in vacuo and the product is extracted three times with DCM. The organic layers are combined, dried (MgSO₄), filtered, and concentrated to afford the intermediate **15** as a white solid: ¹H-NMR (400MHz, CDCl₃) δ = 8.53 (s, 1H), 7.80 (d, J= 8.1 Hz, 1H), 7.33 (s, 1H), 7.19 (d, J= 8.0 Hz, 1H), 3.71 (s, 3H), 3.62 (s, 2H). MS calculated for C₁₀H₁₁ClNO₃ (M+H⁺) 228.0, found 228.3.

[00113] Step F: [3-Chloro-4-(hydroxyimino-methyl)-phenyl]-acetic acid methyl ester **15** (0.91 g, 4.0 mmol) and N-chlorosuccinimide (0.53 g, 4.0 mmol) are dissolved in DMF (20 mL). After adding catalytic amounts of HCl(g) to the solution, an exothermic reaction occurs. After 2 hours of stirring at room temperature the mixture is diluted with H₂O and extracted three times with ether to afford intermediate **16** as a wax-like solid, which is used immediately without further purification: MS calculated for C₁₀H₁₀Cl₂NO₃ (M+H⁺) 262.0, found 262.3.

[00114] Example E1: (3-Chloro-4-{5-methyl-4-[2-(2-nitro-4-trifluoromethyl-phenoxy)-ethoxymethyl]-isoxazol-3-yl}-phenyl)-acetic acid.



[00115] **Step A:** 2-nitro-4-trifluoromethyl-phenol **7** (1.3 g, 6.3 mmol) and 1,2-dibromoethane (2.71 mL, 31 mmol) are dissolved in MeCN. Cs₂CO₃ is added (4.1 g, 12.6 mmol) and the mixture is stirred at 90°C for 12 hours. The mixture is then filtered, concentrated in vacuo, diluted with H₂O and extracted three times with DCM. The organic layers are combined, dried (MgSO₄), filtered, and concentrated and the remainder purified by column chromatography using a hexanes/EtOAc gradient to afford intermediate **17** as a yellow solid: ¹H-NMR (400 MHz, CDCl₃) δ = 8.06 (d, J = 2.0 Hz, 1H), 7.73 (dd, J = 8.8 Hz, J = 2.0 Hz, 1H), 7.12 (d, J = 8.8 Hz, 1H), 4.42 (t, J = 6.4 Hz, 2H), 3.63 (t, J = 6.4 Hz, 2H). MS calculated for C₉H₈BrF₃NO₃ (M+H⁺) 314.0, found 314.2.

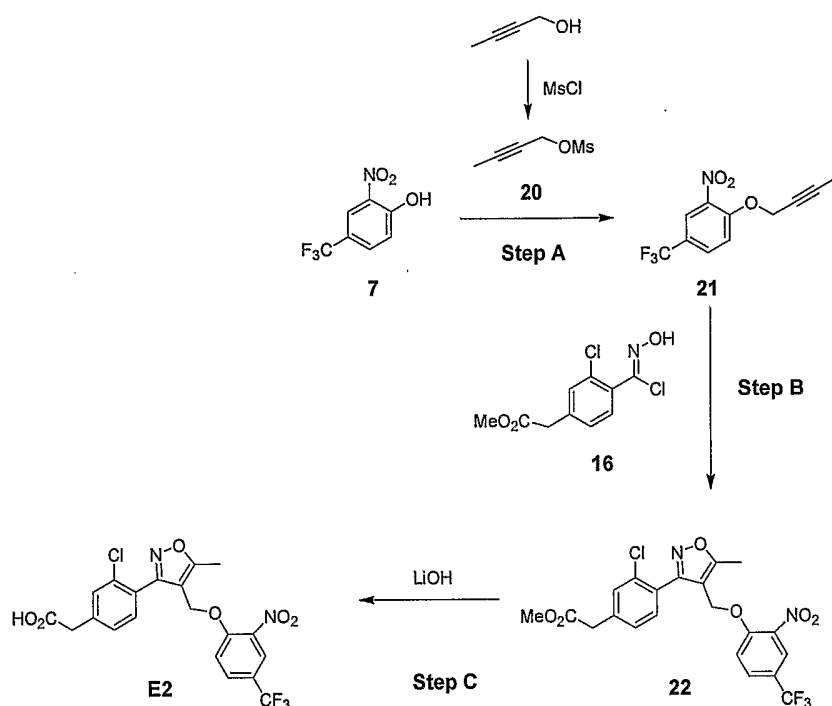
[00116] **Step B:** 1-(2-Bromo-ethoxy)-2-nitro-4-trifluoromethyl-benzene **17** (1.1 g, 3.5 mmol), 2-butyne-1-ol (0.53 mL, 7.0 mmol) and LiOH (0.6 g, 14.0 mmol) are dissolved in DMSO (10 mL). The mixture is stirred for 6 h at room temperature, diluted with H₂O and extracted three times with DCM. The organic layers are combined, dried (MgSO₄), filtered, and concentrated and the remainder purified by column chromatography using a hexanes/EtOAc gradient to afford intermediate **18** as a yellow oil: ¹H-NMR (400 MHz, CDCl₃) δ = 8.06 (d, J = 2.0 Hz, 1H), 7.71 (dd, J = 8.9 Hz, J = 2.0 Hz, 1H), 7.16 (d, J = 8.9 Hz, 1H), 4.29 (t, J = 4.7 Hz, 2H), 4.15 (q, J = 2.3 Hz, 2H), 3.87 (t, J = 4.7 Hz, 2H), 1.79 (t, J = 2.3 Hz, 3H). MS calculated for C₁₃H₁₃F₃NO₄ (M+H⁺) 304.1, found 304.3.

[00117] **Step C:** 1-(2-But-2-ynyloxy-ethoxy)-2-nitro-4-trifluoromethyl-benzene **18** (40 mg, 0.13 mmol) and chloroxime **16** (35 mg, 0.13 mmol) are dissolved in DCE (1 mL) together with triethylamine (50 μL, 0.36 mmol). The mixture is stirred for 10 h at 90°C. Then the mixture is concentrated in vacuo to yield crude (3-Chloro-4-{5-methyl-4-[2-(2-nitro-4-trifluoromethyl-phenoxy)-ethoxymethyl]-isoxazol-3-yl}-phenyl)-acetic acid methyl ester **19** as part of a mixture of two regioisomers, which is used in the next step without further purification. MS calculated for C₂₃H₂₁ClF₃N₂O₇ (M+H⁺) 529.1, found 529.3.

[00118] **Step D:** The crude (3-Chloro-4-{5-methyl-4-[2-(2-nitro-4-trifluoromethyl-phenoxy)-ethoxymethyl]-isoxazol-3-yl}-phenyl)-acetic acid methyl ester **19** is dissolved in THF (1 mL), a solution of 1 M LiOH in H₂O (0.2 mL) is added and the mixture is stirred overnight at 60°C. The mixture is acidified with 1 M HCl, EtOAc (10 mL) is added and the organic layer washed with H₂O (3x5 mL). The organic layer is dried (MgSO₄), filtered, concentrated and purified on reverse phase HPLC (H₂O/MeCN gradient) to afford the title compound **E1** as a white solid: ¹H-NMR (400 MHz, CDCl₃) δ = 8.03 (d, J = 2.0 Hz, 1H),

7.67 (dd, $J = 8.8$ Hz, $J = 1.9$ Hz, 1H), 7.33 (m, 2H), 7.18 (m, 1H), 7.05 (d, $J = 8.8$ Hz, 1H), 4.32 (s, 2H), 4.12 (t, $J = 4.5$ Hz, 2H), 3.66 (t, $J = 4.5$ Hz, 2H), 3.61 (s, 2H), 2.43 (s, 3H). MS calculated for $C_{22}H_{19}ClF_3N_2O_7$ ($M+H^+$) 515.1, found 515.3.

[00119] **Example E2:** {3-Chloro-4-[5-methyl-4-(2-nitro-4-trifluoromethyl-phenoxy)methyl]-isoxazol-3-yl]-phenyl}-acetic acid.



[00120] **Step A:** 2-Butyne-1-ol (1.4 g, 20 mmol) is dissolved in ether (50 mL) and cooled to 0°C . Triethylamine (3.3 mL, 24 mmol) is added to the solution. Methanesulfonyl chloride (1.6 mL, 22 mmol) is dissolved in ether (5 mL) and added dropwise to the reaction solution. The mixture is stirred for 30 minutes at 0°C , then filtered and concentrated to give crude methanesulfonic acid but-2-ynyl ester **20** (2.96 g, 20 mmol, quant.) as a colorless liquid: $^1\text{H-NMR}$ (400 MHz, CDCl_3) $\delta = 4.79$ (q, $J = 2.4$ Hz, 2H), 3.08 (s, 3H), 1.87 (t, $J = 2.4$ Hz, 3H).

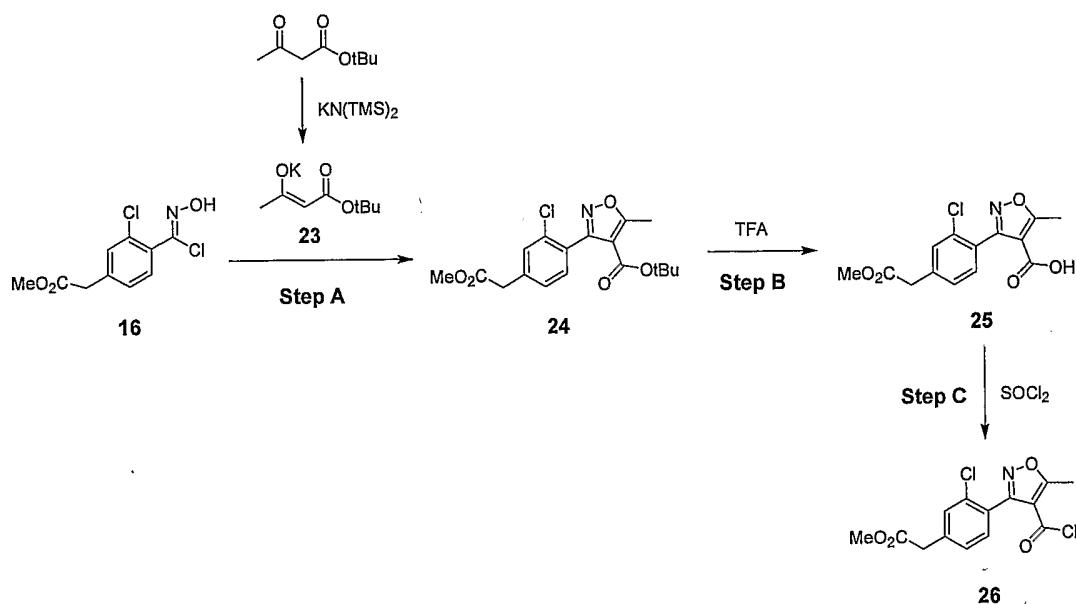
[00121] 2-nitro-4-trifluoromethylphenol **7** (4.1 g, 20 mmol) and methanesulfonic acid but-2-ynyl ester **20** (3.0 g, 20 mmol) are dissolved in MeCN. Cs_2CO_3 is added (13.0 g, 40 mmol) and the mixture is stirred at 90°C for 12 hours. The mixture is then filtered,

concentrated in vacuo, diluted with H₂O and extracted three times with DCM. The organic layers are combined, dried (MgSO₄), filtered, and concentrated and the remainder purified by column chromatography using a hexanes/EtOAc gradient to afford 1-but-2-ynyloxy-2-nitro-4-trifluoromethyl-benzene **21** as a yellow solid: ¹H-NMR (400 MHz, CDCl₃) δ = 8.06 (d, J = 1.7 Hz, 1H), 7.73 (dd, J = 8.8 Hz, J = 1.8 Hz, 1H), 7.30 (d, J = 8.8 Hz, 1H), 4.81 (q, J = 2.3 Hz, 2H), 1.79 (t, J = 2.3 Hz, 3H). MS calculated for C₁₁H₉F₃NO₃ (M+H⁺) 260.1, found 260.3.

[00122] Step B: 1-But-2-ynyloxy-2-nitro-4-trifluoromethyl-benzene **21** (34 mg, 0.13 mmol) and chloroxime **16** (35 mg, 0.13 mmol) are dissolved in DCE (1 mL) together with triethylamine (25 μL, 0.18 mmol). The mixture is stirred for 10 h at 90°C. Then the mixture is concentrated in vacuo to yield crude {3-Chloro-4-[5-methyl-4-(2-nitro-4-trifluoromethyl-phenoxy)methyl]-isoxazol-3-yl]-phenyl}-acetic acid methyl ester **22** as part of a mixture of two regioisomers, which is used in the next step without further purification. MS calculated for C₂₁H₁₇ClF₃N₂O₆ (M+H⁺) 485.1, found 485.3.

[00123] Step C: The crude {3-Chloro-4-[5-methyl-4-(2-nitro-4-trifluoromethyl-phenoxy)methyl]-isoxazol-3-yl]-phenyl}-acetic acid methyl ester **22** is dissolved in THF (1 mL), a solution of 1 M LiOH in H₂O (0.2 mL) is added and the mixture is stirred overnight at 60°C. The mixture is acidified with 1 M HCl, EtOAc (10 mL) is added and the organic layer washed with H₂O (3x5 mL). The organic layer is dried (MgSO₄), filtered, concentrated and purified on reverse phase HPLC (H₂O/MeCN gradient) to afford the title compound **E2** as a white solid: ¹H-NMR (400 MHz, CDCl₃) δ = 7.97 (d, J = 1.9 Hz, 1H), 7.61 (dd, J = 8.8 Hz, J = 1.8 Hz, 1H), 7.36 (m, 2H), 7.21 (m, 1H), 6.94 (d, J = 8.7 Hz, 1H), 4.94 (s, 2H), 3.63 (s, 2H), 2.51 (s, 3H). MS calculated for C₂₀H₁₅ClF₃N₂O₆ (M+H⁺) 471.1, found 471.3

[00124] Intermediate 26: [3-Chloro-4-(4-chlorocarbonyl-5-methyl-isoxazol-3-yl)-phenyl]-acetic acid methyl ester.



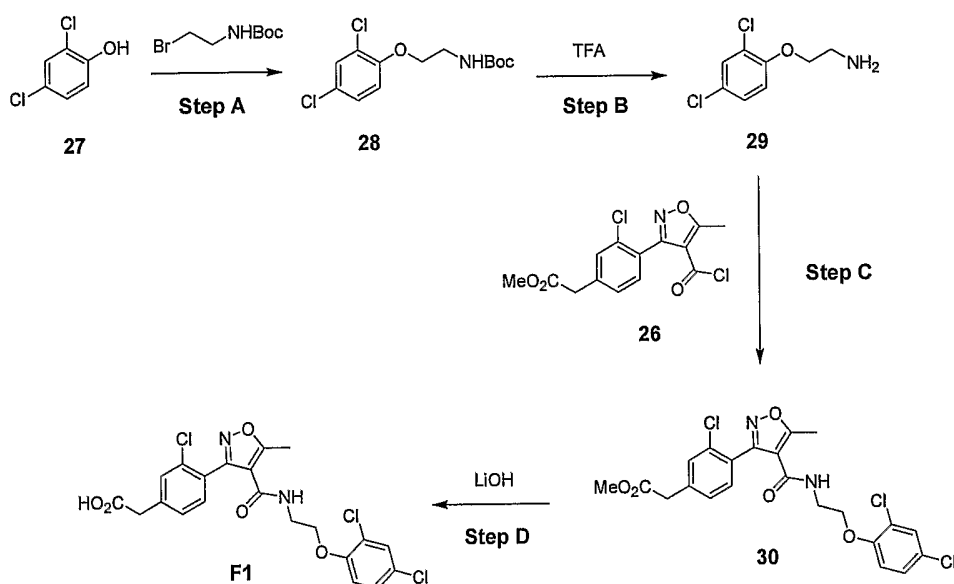
[00125] **Step A:** *tert*-Butyl acetoacetate (5.0 g, 32 mmol) is dissolved in ether (100 mL). Potassium bis(trimethylsilyl)amide (5.7 g, 29 mmol) is added slowly while stirring at room temperature. Then the mixture is concentrated and triturated with hexane. The precipitate is filtered and dried to yield crude potassium enolate **23** (4.6 g, 23 mmol, 81%). Enolate **23** (1.0 g, 5.0 mmol) is dissolved in MeCN (50 mL) and cooled to 0°C. Intermediate **16** (1.1 g, 4.2 mmol) dissolved in MeCN (10 mL) is added dropwise and the solution is stirred at 0 °C for 2 hours. The solvent is evaporated and the remainder is purified by column chromatography using a hexanes/EtOAc gradient to afford 3-(2-chloro-4-methoxycarbonylmethyl-phenyl)-5-methyl-isoxazole-4-carboxylic acid *tert*-butyl ester **24** as a white solid: ¹H-NMR (400 MHz, CDCl₃) δ = 7.41 (d, J = 1.5 Hz, 1H), 7.33 (d, J = 7.8 Hz, 1H), 7.25 (dd, J = 8.0 Hz, J = 1.5 Hz, 1H), 3.69 (s, 3H), 3.65 (s, 2H), 2.73 (s, 3H), 1.28 (s, 9H). MS calculated for C₁₈H₂₁ClNO₅ (M+H⁺) 366.1, found 366.4.

[00126] **Step B:** 3-(2-chloro-4-methoxycarbonylmethyl-phenyl)-5-methyl-isoxazole-4-carboxylic acid *tert*-butyl ester **24** (1.0 g, 2.7 mmol) is dissolved in trifluoroacetic acid (20 mL) and stirred at room temperature for 4 hours. Then the solvent is evaporated and the remainder is dried on high vacuum to afford 3-(2-Chloro-4-methoxycarbonylmethyl-phenyl)-5-methyl-isoxazole-4-carboxylic acid **25** as a white solid: ¹H-NMR (400 MHz, CDCl₃) δ = 10.36 (s, 1H), 7.42 (s, 1H), 7.36 (d, J = 7.8 Hz, 1H), 7.27 (dd, J = 8.4 Hz, J = 0.6

Hz, 1H), 3.74 (s, 3H), 3.68 (s, 2H), 2.78 (s, 3H). MS calculated for $C_{14}H_{13}ClNO_5$ ($M+H^+$) 310.0, found 310.3.

[00127] Step C: 3-(2-Chloro-4-methoxycarbonylmethyl-phenyl)-5-methyl-isoxazole-4-carboxylic acid **25** (0.6 g, 1.9 mmol) and thionyl chloride (155 μ L, 2.1 mmol) are dissolved in toluene (25 mL). The mixture is stirred at 120°C for 10 hours. Then the reaction mixture is cooled down to 0°C and triethylamine (600 μ L, 3.8 mmol) are added dropwise. The resulting solution containing crude [3-Chloro-4-(4-chlorocarbonyl-5-methyl-isoxazol-3-yl)-phenyl]-acetic acid methyl ester **26** is used without further purification: MS calculated for $C_{14}H_{12}Cl_2NO_4$ ($M+H^+$) 328.0, found 328.2.

[00128] Example F1: (3-Chloro-4-{4-[2-(2,4-dichloro-phenoxy)-ethylcarbamoyl]-5-methyl-isoxazol-3-yl}-phenyl)-acetic acid.



[00129] Step A: 2,4-Dichloro-phenol **27** (2.0 g, 12.3 mmol) and (2-Bromo-ethyl)-carbamic acid tert-butyl ester (2.75 g, 12.3 mmol) are dissolved in MeCN (40 mL). CS_2CO_3 is added (8.0 g, 24.6 mmol) and the mixture is stirred at 90°C for 6 hours. The mixture is then filtered, concentrated in vacuo, diluted with H_2O and extracted three times with DCM. The organic layers are combined, dried ($MgSO_4$), filtered, and concentrated and the

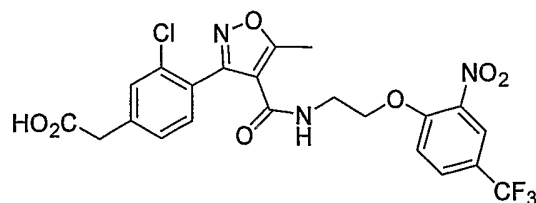
remainder purified by column chromatography using a DCM/MeOH gradient to afford intermediate **28** as a white solid: $^1\text{H-NMR}$ (400 MHz, CDCl_3) δ = 7.37 (d, J = 2.5 Hz, 1H), 7.18 (dd, J = 8.8 Hz, J = 2.5 Hz, 1H), 6.84 (d, J = 8.8 Hz, 1H), 5.03 (m, NH), 4.06 (t, J = 5.0 Hz, 2H), 3.57 (q, J = 5.2 Hz, 2H), 1.45 (s, 9H). MS calculated for $\text{C}_9\text{H}_{10}\text{Cl}_2\text{NO}_3$ (M-tBu^+) 251.1, found 251.1.

[00130] Step B: [2-(2,4-Dichloro-phenoxy)-ethyl]-carbamic acid tert-butyl ester **28** (0.81 g, 2.30 mmol) is dissolved in 60% trifluoroacetic acid in DCM (20 mL) and stirred at room temperature for 1 hour. The mixture is then concentrated, diluted with aqueous sat. K_2CO_3 and extracted three times with DCM. The organic layers are combined, dried (MgSO_4), filtered, and concentrated to afford intermediate **29** as a white solid: MS calculated for $\text{C}_8\text{H}_{10}\text{Cl}_2\text{NO}$ (M+H^+) 206.0, found 206.0.

[00131] Step C: A solution of 2-(2,4-Dichloro-phenoxy)-ethylamine **29** (17 mg, 0.08 mmol) in toluene (2 mL) is cooled to 0°C . A solution of intermediate **26** (0.08 mmol) and triethylamine (23 μL , 0.16 mmol) in MeCN (1 mL) is added and the solution is warmed to room temperature. After stirring at room temperature for 1 h the mixture is poured into H_2O and extracted three times with EtOAc. The organic layers are combined, dried (MgSO_4), filtered, and concentrated to afford crude (3-Chloro-4-{4-[2-(2,4-dichloro-phenoxy)-ethylcarbamoyl]-5-methyl-isoxazol-3-yl}-phenyl)-acetic acid methyl ester **30**.

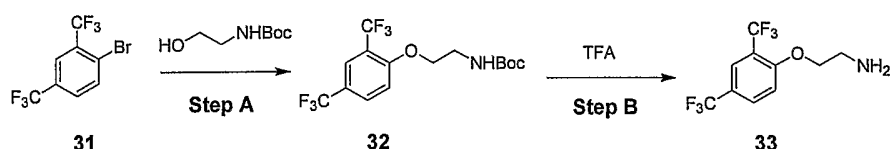
[00132] Step D: The crude (3-Chloro-4-{4-[2-(2,4-dichloro-phenoxy)-ethylcarbamoyl]-5-methyl-isoxazol-3-yl}-phenyl)-acetic acid methyl ester **30** is dissolved in THF (2 mL). A solution of 1 M LiOH in H_2O (0.2 mL) and MeOH (25 μL) is added and the mixture is stirred overnight at room temperature. The mixture is acidified with 1 M HCl, EtOAc (10 mL) is added and the organic layer washed with H_2O (3x5 mL). The organic layer is dried (MgSO_4), filtered, concentrated and purified on reverse phase HPLC ($\text{H}_2\text{O}/\text{MeCN}$ gradient) to afford the title compound **F1** as a white solid: $^1\text{H-NMR}$ (400 MHz, CDCl_3) δ = 7.40 (d, J = 8.2 Hz, 1H), 7.28 (d, J = 2.2 Hz, 1H), 7.21-19 (m, 2H), 7.12 (dd, J = 8.8 Hz, J = 2.5 Hz, 1H), 6.68 (d, J = 8.7 Hz, 1H), 5.74 (m, NH), 3.89 (t, J = 4.8 Hz, 2H), 3.63 (q, J = 5.0 Hz, 2H), 3.45 (s, 2H), 2.69 (s, 3H). MS calculated for $\text{C}_{21}\text{H}_{18}\text{Cl}_3\text{N}_2\text{O}_5$ (M+H^+) 483.0, found 483.3.

[00133] Example F2: (3-Chloro-4-{5-methyl-4-[2-(2-nitro-4-trifluoromethyl-phenoxy)-ethylcarbamoyl]-isoxazol-3-yl}-phenyl)-acetic acid.



[00134] Following the procedure of **Example F1**, except substituting intermediate **9** for intermediate **29** in **Step C**, the title compound **F2** is prepared as a white solid: $^1\text{H-NMR}$ (400 MHz, CDCl_3) δ = 8.39 (s, 1H), 7.98 (m, NH), 7.54 (d, J = 8.9 Hz, 1H), 7.29 (m, 2H), 7.17 (m, 1H), 6.75 (d, J = 9.1 Hz, 1H), 4.29 (t, J = 5.4 Hz, 2H), 3.52 (s, 2H), 3.36 (q, J = 5.2 Hz, 2H), 2.70 (s, 3H). MS calculated for $\text{C}_{22}\text{H}_{18}\text{ClF}_3\text{N}_3\text{O}_7$ ($\text{M}+\text{H}^+$) 528.1, found 528.3.

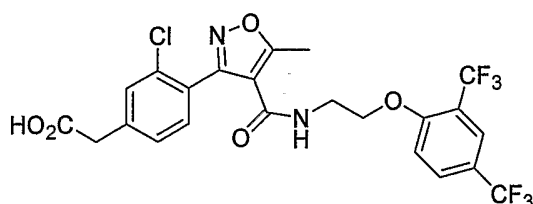
[00135] **Intermediate 33**. 2-(2,4-Bis-trifluoromethyl-phenoxy)-ethylamine.



[00136] **Step A:** (2-Hydroxy-ethyl)-carbamic acid *tert*-butyl ester (0.2 mL, 1.29 mmol) is dissolved in 3 mL dry dimethyl-acetamide. 2-Potassium-1,1,1,3,3,3-hexamethyl-disilazane (0.52 g, 2.6 mmol, 2 equiv.) is added, followed by 1-bromo-2,4-bis-trifluoromethyl-benzene **31** (0.26 mL, 1.5 mmol, 1.2 equiv.). The mixture is stirred at 60°C under nitrogen for 18 hours. The mixture is cooled, diluted with 50 mL water and extracted with dichloromethane (3 x 50 mL). The combined organic extracts are washed with water and 10% aqueous citric acid, dried over Na_2SO_4 and concentration. Silica gel chromatography (5% to 25% ethyl acetate in hexanes) yielded [2-(2,4-Bis-trifluoromethyl-phenoxy)-ethyl]-carbamic acid *tert*-butyl ester **32** as a colorless, mobile oil: $^1\text{H-NMR}$ (400 MHz, CDCl_3) δ = 7.61 (s, 1H), 7.00 (d, J = 8 Hz, 1H), 6.76 (d, J = 8 Hz, 1H), 5.10 (s, 1H), 4.26 (t, J = 4 Hz, 2H), 3.65 (m, 2H), 1.45 (s, 9H). $^{19}\text{F-NMR}$ (376 MHz, CDCl_3) δ = -61.5, -62.0. No molecular ion could be obtained; a loss of *tert*-butyl group is observed: MS calculated for $\text{C}_{11}\text{H}_{10}\text{F}_6\text{NO}_3$ ($\text{M}+\text{H}^+ - \text{C}_4\text{H}_8$) 318.1, found 318.3.

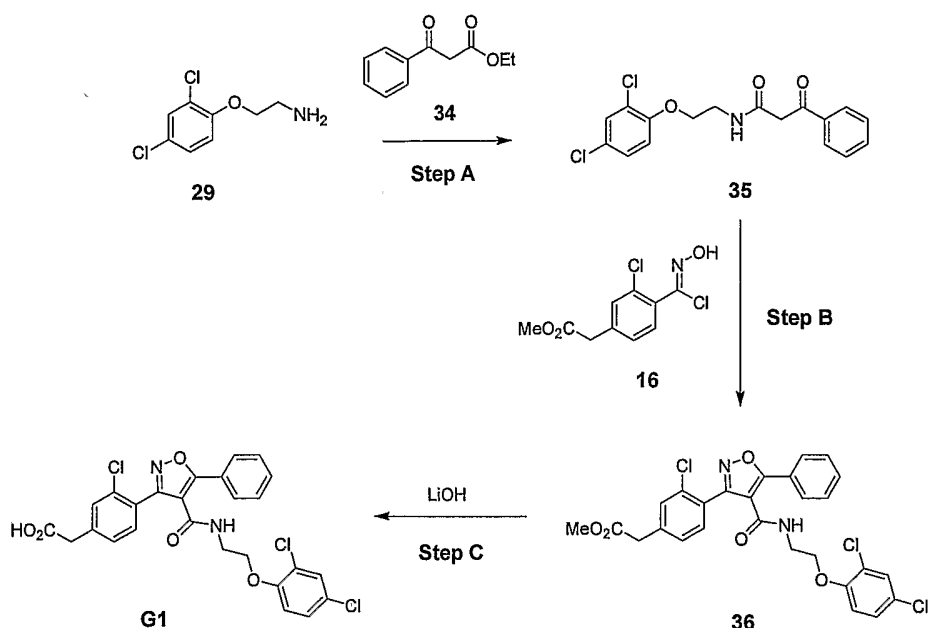
[00137] Step B: [2-(2,4-Bis-trifluoromethyl-phenoxy)-ethyl]-carbamic acid *tert*-butyl ester 32 from Step A above (0.23 g, 0.62 mmol) is dissolved in DCM (4 mL) and trifluoroacetic acid (2 mL). After 1 hour, the reaction is completed by LCMS. The mixture is then concentrated, diluted with aqueous saturated K_2CO_3 and extracted three times with DCM. The organic layers are combined, dried ($MgSO_4$), filtered, and concentrated to afford intermediate 33 as oil: MS calculated for $C_{10}H_{10}F_6NO$ ($M+H^+$) 274.07, found 274.3.

[00138] **Example F3:** (4-{4-[2-(2,4-Bis-trifluoromethyl-phenoxy)-ethylcarbamoyl]-5-methyl-isoxazol-3-yl}-3-chloro-phenyl)-acetic acid.



[00139] Following the procedure of **Example F1**, except substituting intermediate 33 for intermediate 29 in **Step C**, the title compound **F3** is prepared as a white solid: 1H -NMR (400 MHz, $CDCl_3$) δ = 7.73 (s, 1H), 7.70 (d, J = 9.0 Hz, 1H), 7.40 (d, J = 7.8 Hz, 1H), 7.27 (s, 1H), 7.23 (dd, J = 7.7 Hz, J = 1.4 Hz, 1H), 6.95 (d, J = 8.8 Hz, 1H), 5.63 (m, NH), 4.04 (t, J = 5.0 Hz, 2H), 3.65 (q, J = 5.1 Hz, 2H), 3.50 (s, 2H), 2.68 (s, 3H). MS calculated for $C_{23}H_{18}ClF_6N_2O_5$ ($M+H^+$) 551.1, found 551.3.

[00140] **Example G1:** (3-Chloro-4-{4-[2-(2,4-dichloro-phenoxy)-ethylcarbamoyl]-5-phenyl-isoxazol-3-yl}-phenyl)-acetic acid.



[00141] Step A: To a solution of 2-(2,4-Dichloro-phenoxy)-ethylamine **29** (412 mg, 2.0 mmol) in toluene (1.5 mL) is added ethyl benzoylacetate **34** (384 mg, 2.0 mmol). The mixture is heated to 160°C for 10 minutes in a microwave. The resulting mixture is concentrated and purified on reverse phase HPLC (H₂O/MeCN gradient) to afford N-[2-(2,4-dichloro-phenoxy)-ethyl]-3-oxo-3-phenyl-propionamide **35** as a white solid: ¹H-NMR (400 MHz, CDCl₃) δ = 7.98 (d, J = 7.2 Hz, 2H), 7.60-7.35 (m, 5H), 7.15 (dd, J = 2.5 Hz, J = 8.8 Hz, 1H), 6.83 (d, J = 8.8 Hz, 1H), 4.10 (t, J = 5.2 Hz, 2H), 3.98 (s, 2H), 3.76 (q, J = 5.3 Hz, 2H). MS calculated for C₁₇H₁₆Cl₂NO₃ (M+H⁺) 352.0, found 352.1.

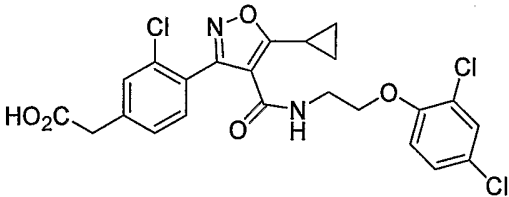
[00142] Step B: N-[2-(2,4-dichloro-phenoxy)-ethyl]-3-oxo-3-phenyl-propionamide **35** (300 mg, 0.85 mmol) is dissolved in CH₃CN (5 mL). Potassium bis(trimethylsilyl)amide (170 mg, 0.85 mmol) is added slowly while stirring at room temperature. Then the mixture is cooled to 0°C, and a solution of intermediate **16** (0.71 mmol) in CH₃CN (4 mL) is added dropwise. The mixture is stirred at room temperature for 3 hours, then concentrated to afford crude (3-Chloro-4-{4-[2-(2,4-dichloro-phenoxy)-ethylcarbamoyl]-5-phenyl-isoxazol-3-yl}-phenyl)-acetic acid methyl ester **36**.

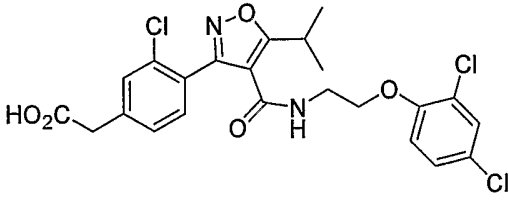
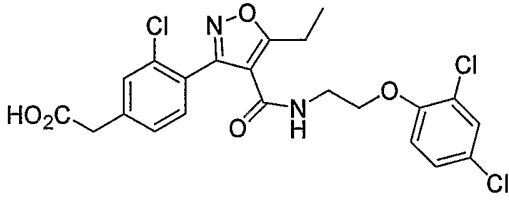
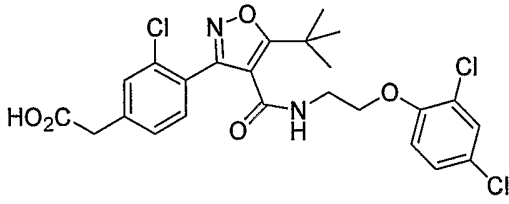
[00143] Step C: The crude (3-Chloro-4-{4-[2-(2,4-dichloro-phenoxy)-ethylcarbamoyl]-5-phenyl-isoxazol-3-yl}-phenyl)-acetic acid methyl ester **36** (0.85 mmol) is dissolved in THF (5 mL). A solution of 1 M LiOH in H₂O (2 mL) is added and the mixture is stirred overnight at room temperature. The mixture is acidified with 1 M HCl (3 mL),

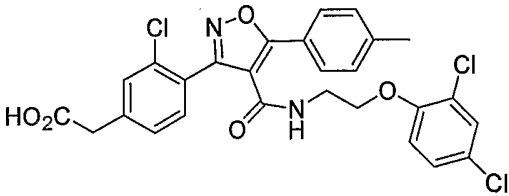
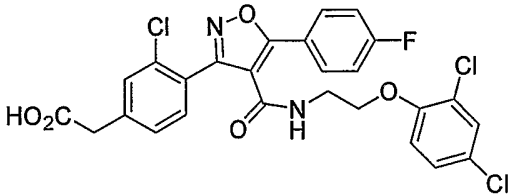
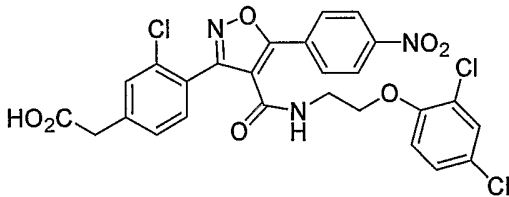
DCM (50 mL) is added and the organic layer washed with H₂O (3x30 mL). The organic layer is dried (MgSO₄), filtered, concentrated and purified on reverse phase HPLC (H₂O/MeCN gradient) to afford the title compound **G1** as a white solid: ¹H-NMR (400 MHz, CDCl₃) δ = 7.93 (dd, J = 1.8 Hz, J = 7.8 Hz, 2H), 7.52-7.23 (m, 7H), 7.17 (dd, J = 8.8 Hz, J = 2.5 Hz, 1H), 6.71 (d, J = 8.8 Hz, 1H), 6.15 (t, J = 5.3 Hz, NH), 3.92 (t, J = 4.8 Hz, 2H), 3.72 (q, J = 5.3 Hz, 2H), 3.50 (s, 2H). MS calculated for C₂₆H₂₀Cl₃N₂O₅ (M+H⁺) 545.0, found 545.3.

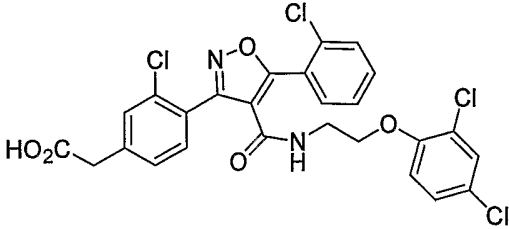
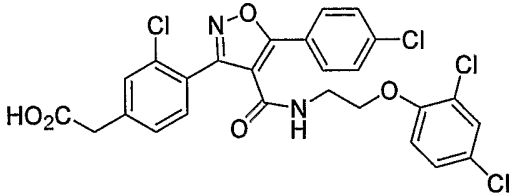
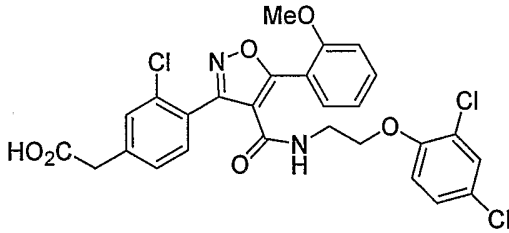
[00144] By repeating the procedure described in the above examples, using appropriate starting materials, the following compounds of Formula I are obtained as identified in Table 1.

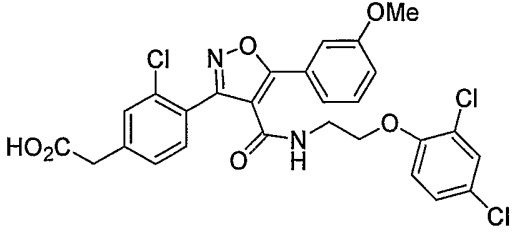
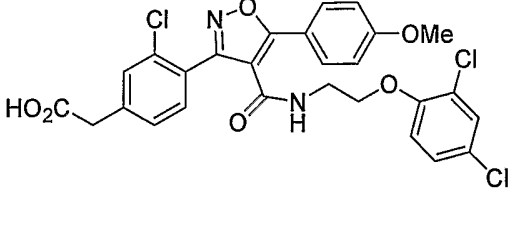
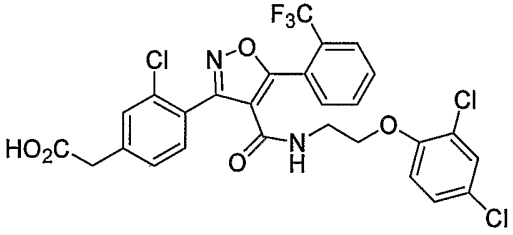
Table 1

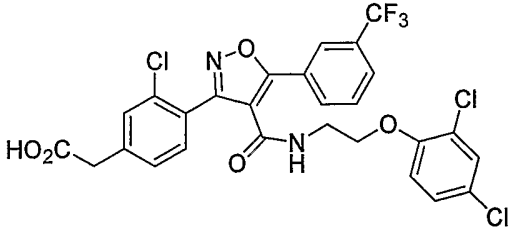
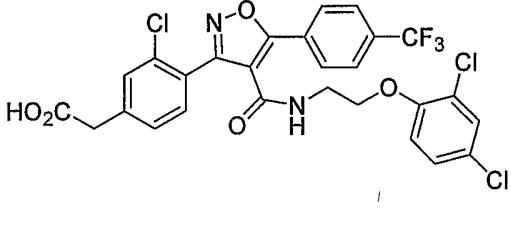
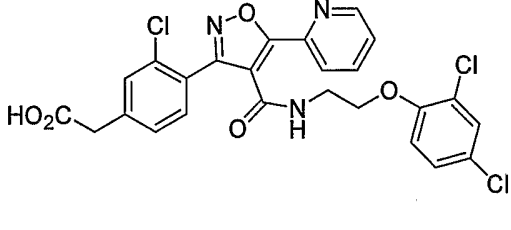
Compound Number	Compound Structure	Physical Data ¹ H NMR 400 MHz (DMSO- <i>d</i> ₆) and/or MS (m/z)
G2		¹ H-NMR (400 MHz, CDCl ₃) δ = 7.46 (d, J = 7.7 Hz, 1H), 7.37 (d, J = 2.5 Hz, 1H), 7.30-7.27 (m, 2H), 7.20 (dd, J = 8.8 Hz, J = 2.5 Hz, 1H), 6.77 (d, J = 8.8 Hz, 1H), 5.92 (t, J = 5.5 Hz, NH), 3.99 (t, J = 4.9 Hz, 2H), 3.74 (q, J = 5.2 Hz, 2H), 3.53 (s, 2H), 2.86 (m, 1H), 1.35 (m, 2H), 1.24 (m, 2H). MS calculated for C ₂₃ H ₂₀ Cl ₃ N ₂ O ₅ (M+H ⁺) 509.0, found 509.2.

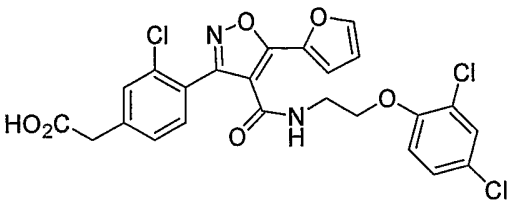
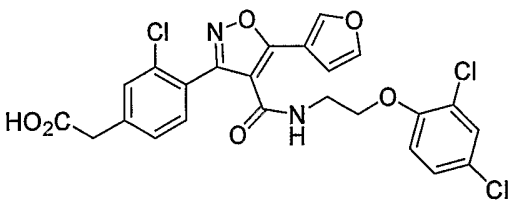
Compound Number	Compound Structure	Physical Data ¹ H NMR 400 MHz (DMSO- <i>d</i> ₆) and/or MS (m/z)
G3		¹ H-NMR (400 MHz, CDCl ₃) δ = 7.49 (d, J = 7.8 Hz, 1H), 7.37 (d, J = 2.5 Hz, 1H), 7.30-7.27 (m, 2H), 7.20 (dd, J = 8.8 Hz, J = 2.5 Hz, 1H), 6.76 (d, J = 8.8 Hz, 1H), 5.85 (t, J = 5.5 Hz, NH), 3.96 (t, J = 4.9 Hz, 2H), 3.84 (m, 1H), 3.72 (q, J = 5.2 Hz, 2H), 3.51 (s, 2H), 1.43 (d, J = 7.0 Hz, 6H). MS calculated for C ₂₃ H ₂₂ Cl ₃ N ₂ O ₅ (M+H ⁺) 511.1, found 511.3.
G4		¹ H-NMR (400 MHz, CDCl ₃) δ = 7.49 (d, J = 7.6 Hz, 1H), 7.37 (d, J = 2.5 Hz, 1H), 7.31-7.27 (m, 2H), 7.20 (dd, J = 8.8 Hz, J = 2.5 Hz, 1H), 6.76 (d, J = 8.8 Hz, 1H), 5.84 (t, J = 5.5 Hz, NH), 3.97 (t, J = 4.9 Hz, 2H), 3.72 (q, J = 5.2 Hz, 2H), 3.52 (s, 2H), 3.20 (q, J = 7.6 Hz, 2H), 1.41 (t, J = 7.6 Hz, 3H). MS calculated for C ₂₂ H ₂₀ Cl ₃ N ₂ O ₅ (M+H ⁺) 497.0, found 497.2.
G5		¹ H-NMR (400 MHz, CDCl ₃) δ = 7.36 (d, J = 7.9 Hz, 1H), 7.31 (d, J = 2.2 Hz, 1H), 7.13 (s, 2H), 7.11 (s, 1H), 6.63 (d, J = 8.8 Hz, 1H), 6.00 (t, J = 5.5 Hz, NH), 3.80 (t, J = 4.8 Hz, 2H), 3.64 (q, J = 5.1 Hz, 2H), 3.37 (s, 2H), 1.43 (s, 9H). MS calculated for C ₂₄ H ₂₄ Cl ₃ N ₂ O ₅ (M+H ⁺) 525.1, found 525.0.

Compound Number	Compound Structure	Physical Data ¹ H NMR 400 MHz (DMSO- <i>d</i> ₆) and/or MS (m/z)
G6		¹ H-NMR (400 MHz, CDCl ₃) δ = 7.79 (d, J = 8.0 Hz, 2H), 7.51 (d, J = 7.8 Hz, 1H), 7.34-7.16 (m, 6H), 6.73 (d, J = 8.8 Hz, 1H), 6.18 (t, J = 5.5 Hz, NH), 3.94 (t, J = 4.8 Hz, 2H), 3.74 (q, J = 5.1 Hz, 2H), 3.53 (s, 2H), 2.37 (s, 3H). MS calculated for C ₂₇ H ₂₂ Cl ₃ N ₂ O ₅ (M+H ⁺) 559.1, found 559.0.
G7		¹ H-NMR (400 MHz, CDCl ₃) δ = 8.24 (m, 2H), 7.74 (d, J = 7.8 Hz, 1H), 7.58-7.35 (m, 6H), 6.94 (d, J = 8.8 Hz, 1H), 6.32 (t, J = 5.5 Hz, NH), 4.14 (t, J = 4.8 Hz, 2H), 3.96 (q, J = 5.1 Hz, 2H), 3.72 (s, 2H). MS calculated for C ₂₆ H ₁₉ Cl ₃ FN ₂ O ₅ (M+H ⁺) 563.0, found 563.0.
G8		¹ H-NMR (400 MHz, CDCl ₃) δ = 8.31 (d, J = 8.9 Hz, 2H), 8.24 (d, J = 8.9 Hz, 2H), 7.54 (d, J = 8.2 Hz, 1H), 7.34-7.18 (m, 4H), 6.71 (d, J = 8.8 Hz, 1H), 6.12 (t, J = 5.5 Hz, NH), 3.92 (t, J = 4.7 Hz, 2H), 3.76 (q, J = 5.0 Hz, 2H), 3.49 (s, 2H). MS calculated for C ₂₆ H ₁₉ Cl ₃ N ₃ O ₇ (M+H ⁺) 590.0, found 590.0.

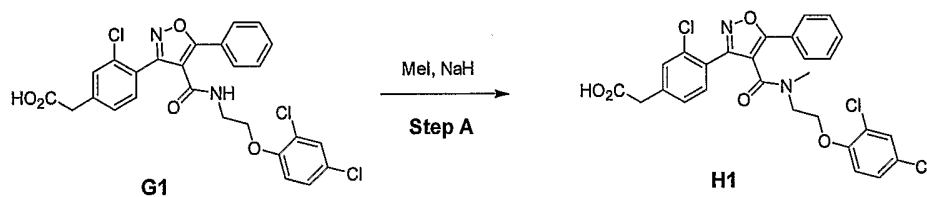
Compound Number	Compound Structure	Physical Data ¹ H NMR 400 MHz (DMSO- <i>d</i> ₆) and/or MS (m/z)
G9		¹ H-NMR (400 MHz, CDCl ₃) δ = 7.47-6.99 (m, 9H), 6.53 (d, J = 8.8 Hz, 1H), 5.91 (t, J = 5.5 Hz, NH), 3.75 (t, J = 4.7 Hz, 2H), 3.50 (q, J = 5.1 Hz, 2H), 3.43 (s, 2H). MS calculated for C ₂₆ H ₁₉ Cl ₄ N ₂ O ₅ (M+H ⁺) 579.0, found 579.0.
G10		¹ H-NMR (400 MHz, CDCl ₃) δ = 7.94 (d, J = 8.6 Hz, 2H), 7.52 (d, J = 11.8 Hz, 1H), 7.42 (d, J = 8.6 Hz, 2H), 7.36-7.18 (m, 4H), 6.71 (d, J = 8.8 Hz, 1H), 6.10 (t, J = 5.5 Hz, NH), 3.93 (t, J = 4.8 Hz, 2H), 3.74 (q, J = 5.1 Hz, 2H), 3.51 (s, 2H). MS calculated for C ₂₆ H ₁₉ Cl ₄ N ₂ O ₅ (M+H ⁺) 579.0, found 579.0.
G11		¹ H-NMR (400 MHz, CDCl ₃) δ = 7.67 (d, J = 2.6 Hz, 1H), 7.65 (d, J = 2.6 Hz, 1H), 7.61-7.12 (m, 6H), 6.99 (d, J = 8.4 Hz, 1H), 6.76 (d, J = 8.8 Hz, 1H), 6.56 (t, J = 5.5 Hz, NH), 3.99 (t, J = 4.8 Hz, 2H), 3.87 (s, 3H), 3.73 (q, J = 5.2 Hz, 2H), 3.65 (s, 2H). MS calculated for C ₂₇ H ₂₁ Cl ₃ N ₂ O ₆ (M+H ⁺) 575.1, found 575.0.

Compound Number	Compound Structure	Physical Data ¹ H NMR 400 MHz (DMSO- <i>d</i> ₆) and/or MS (m/z)
G12		¹ H-NMR (400 MHz, CDCl ₃) δ = 7.61-7.12 (m, 9H), 6.71 (d, J = 8.8 Hz, 1H), 6.19 (t, J = 5.5 Hz, NH), 3.93 (t, J = 4.8 Hz, 2H), 3.83 (s, 3H), 3.74 (q, J = 5.2 Hz, 2H), 3.53 (s, 2H). MS calculated for C ₂₇ H ₂₁ Cl ₃ N ₂ O ₆ (M+H ⁺) 575.1, found 575.0.
G13		¹ H-NMR (400 MHz, CDCl ₃) δ = 7.90 (d, J = 8.9 Hz, 2H), 7.51 (d, J = 7.8 Hz, 1H), 7.34-6.96 (m, 5H), 6.94 (d, J = 8.9 Hz, 2H), 6.72 (d, J = 8.8 Hz, 1H), 6.15 (t, J = 5.5 Hz, NH), 3.93 (t, J = 4.8 Hz, 2H), 3.83 (s, 3H), 3.74 (q, J = 5.2 Hz, 2H), 3.52 (s, 2H). MS calculated for C ₂₇ H ₂₁ Cl ₃ N ₂ O ₆ (M+H ⁺) 575.1, found 575.0.
G14		¹ H-NMR (400 MHz, CDCl ₃) δ = 7.80 (d, J = 7.7 Hz, 1H), 7.67-7.16 (m, 8H), 6.68 (d, J = 8.8 Hz, 1H), 5.89 (t, J = 5.5 Hz, NH), 3.85 (t, J = 4.8 Hz, 2H), 3.62 (q, J = 5.2 Hz, 2H), 3.60 (s, 2H). MS calculated for C ₂₇ H ₁₉ Cl ₃ F ₃ N ₂ O ₅ (M+H ⁺) 613.0, found 613.0.

Compound Number	Compound Structure	Physical Data ¹ H NMR 400 MHz (DMSO- <i>d</i> ₆) and/or MS (m/z)
G15		¹ H-NMR (400 MHz, CDCl ₃) δ = 8.26 (s, 1H), 8.16 (d, J = 8.0 Hz, 1H), 7.71 (d, J = 7.9 Hz, 1H), 7.58-7.12 (m, 6H), 6.67 (d, J = 8.8 Hz, 1H), 6.08 (t, J = 5.5 Hz, NH), 3.88 (t, J = 4.8 Hz, 2H), 3.70 (q, J = 5.2 Hz, 2H), 3.46 (s, 2H). MS calculated for C ₂₇ H ₁₉ Cl ₃ F ₃ N ₂ O ₅ (M+H ⁺) 613.0, found 613.0.
G16		¹ H-NMR (400 MHz, CDCl ₃) δ = 8.23 (d, J = 8.3 Hz, 2H), 7.82 (d, J = 8.3 Hz, 2H), 7.62 (d, J = 7.7 Hz, 1H), 7.44-7.27 (m, 4H), 6.81 (d, J = 8.8 Hz, 1H), 6.24 (t, J = 5.5 Hz, NH), 4.02 (t, J = 4.8 Hz, 2H), 3.84 (q, J = 5.2 Hz, 2H), 3.59 (s, 2H). MS calculated for C ₂₇ H ₁₉ Cl ₃ F ₃ N ₂ O ₅ (M+H ⁺) 613.0, found 613.0.
G17		¹ H-NMR (400 MHz, CDCl ₃) δ = 8.69 (d, J = 4.7 Hz, 1H), 8.20 (d, J = 8.0 Hz, 1H), 8.04-7.14 (m, 7H), 6.83 (d, J = 8.8 Hz, 1H), 5.74 (m, NH), 4.15 (t, J = 4.8 Hz, 2H), 3.85 (m, 2H), 3.68 (s, 2H). MS calculated for C ₂₅ H ₁₉ Cl ₃ N ₃ O ₅ (M+H ⁺) 546.0, found 546.0.

Compound Number	Compound Structure	Physical Data ¹ H NMR 400 MHz (DMSO- <i>d</i> ₆) and/or MS (m/z)
G18		¹ H-NMR (400 MHz, CDCl ₃) δ = 7.64-7.22 (m, 7H), 6.83 (d, J = 8.8 Hz, 1H), 6.72 (t, J = 5.5 Hz, NH), 6.65 (m, 1H), 4.08 (t, J = 4.8 Hz, 2H), 3.84 (q, J = 5.2 Hz, 2H), 3.61 (s, 2H). MS calculated for C ₂₄ H ₁₈ Cl ₃ N ₂ O ₆ (M+H ⁺) 535.0, found 535.0.
G19		¹ H-NMR (400 MHz, CDCl ₃) δ = 8.60 (s, 1H), 7.55-7.06 (m, 7H), 6.75 (d, J = 8.8 Hz, 1H), 5.94 (t, J = 5.5 Hz, NH), 3.96 (t, J = 4.8 Hz, 2H), 3.75 (q, J = 5.2 Hz, 2H), 3.49 (s, 2H). MS calculated for C ₂₄ H ₁₈ Cl ₃ N ₂ O ₆ (M+H ⁺) 535.0, found 535.0.

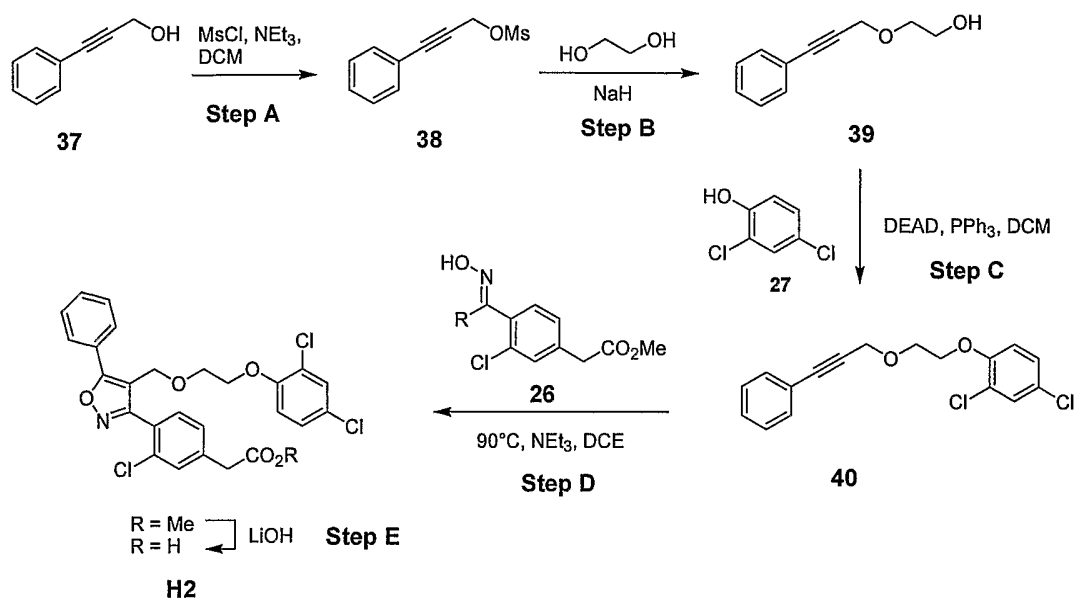
[00145] Example H1: [3-Chloro-4-(4-{[2-(2,4-dichloro-phenoxy)-ethyl]-methyl-carbamoyl}-5-phenyl-isoxazol-3-yl)-phenyl]-acetic acid.



[00146] Step A: To a solution of example **G1** (50 mg, 0.092 mmol) in DMF (1.5 mL) is added NaH (60% dispersion, 7.4 mg, 0.18 mmol) at 0°C. The mixture is stirred at 0°C for 10 minutes, then MeI (10uL, 0.14 mmol) is added and the mixture is stirred at room temperature for 30 minutes. The resulting mixture is concentrated and purified on reverse phase HPLC (H₂O/MeCN gradient) to afford [3-Chloro-4-(4-{[2-(2,4-dichloro-phenoxy)-

ethyl]-methyl-carbamoyl}-5-phenyl-isoxazol-3-yl)-phenyl]-acetic acid **H1** as a white solid:
 $^1\text{H-NMR}$ (400 MHz, CDCl_3) δ = 7.69 (d, J = 7.5 Hz, 2H), 7.45-7.10 (m, 8H), 6.73 (d, J = 8.8 Hz, 1H), 4.11 (m, 2H), 3.61 (m, 2H), 3.49 (s, 2H), 2.95 (s, 3H). MS calculated for $\text{C}_{27}\text{H}_{22}\text{Cl}_3\text{N}_2\text{O}_5$ ($\text{M}+\text{H}^+$) 559.1, found 559.1.

[00147] **Example H2:** (3-Chloro-4-{4-[2-(2,4-dichloro-phenoxy)-ethoxymethyl]-5-phenyl-isoxazol-3-yl}-phenyl)-acetic acid.



[00148] **Step A:** 3-Phenyl-prop-2-yn-1-ol **37** (3.0 g, 22.7 mmol) is dissolved in DCM (50 mL). The solution is cooled to 0°C , then methanesulfonyl chloride (4.5 mL, 34.1 mmol) and triethyl amine (4.7 mL, 34.1 mmol) is added. The mixture is allowed to warm to room temperature and stirred overnight at room temperature. The mixture is washed with H_2O (2x30 mL). The organic layer is dried (MgSO_4), filtered, and concentrated to afford crude methanesulfonic acid 3-phenyl-prop-2-ynyl ester **38** as a clear oil: $^1\text{H-NMR}$ (400 MHz, CDCl_3) δ = 7.47-7.32 (m, 5H), 4.38 (s, 2H), 3.67 (s, 3H).

[00149] **Step B:** Sodium hydride (60% dispersion, 250 mg, 17.4 mmol) is suspended in ethylene glycol (10 mL) and stirred for 20 minutes at room temperature. To the resulting solution is added mesylate **38** (1.0 g, 4.8 mmol) and the mixture is heated to 100°C overnight. The mixture is diluted with DCM (120 mL) and washed with H_2O (2x60 mL).

The organic layer is dried (MgSO_4), filtered, concentrated and purified by column chromatography using a DCM/MeOH gradient to afford intermediate **39** as a yellow oil: $^1\text{H-NMR}$ (400 MHz, CDCl_3) δ = 7.46-7.30 (m, 5H), 4.43 (s, 2H), 3.80 (t, J = 4.5 Hz, 2H), 3.72 (t, J = 4.5 Hz, 2H), 2.12 (s, OH). MS calculated for $\text{C}_{11}\text{H}_{13}\text{O}_2$ ($\text{M}+\text{H}^+$) 177.1, found 177.1.

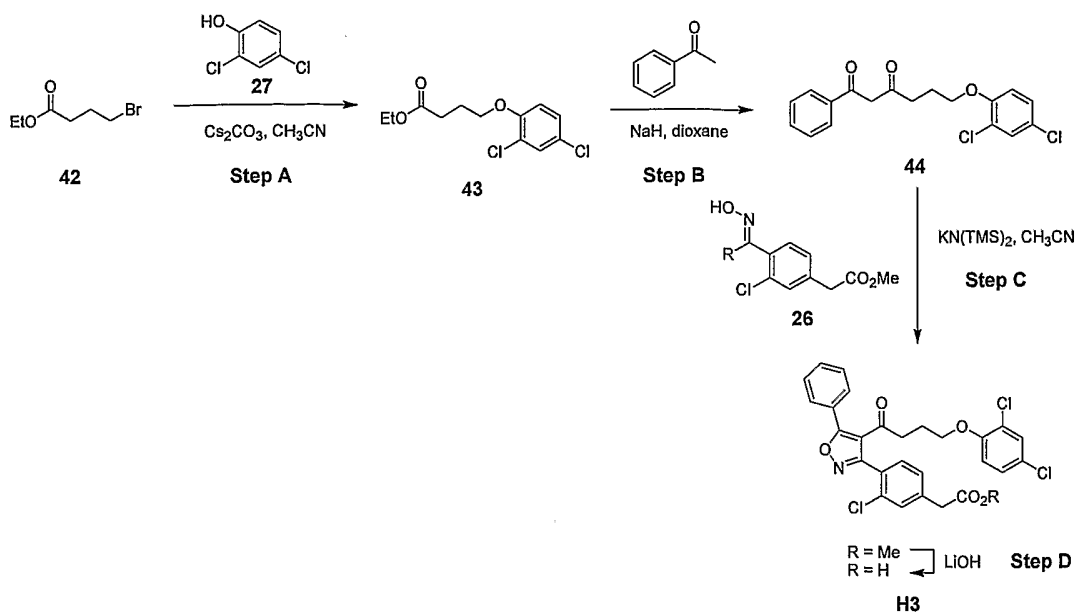
[00150] **Step C:** Intermediate **39** (0.30 g, 1.7 mmol), 2,4-dichlorophenol **27** (0.33 g, 2.0 mmol) and triphenyl phosphine (0.89 g, 3.4 mmol) is dissolved in DCM (25 mL).

Diethyl azodicarboxylate (0.61 mL, 2.6 mmol) is added and the solution is stirred at room temperature for 4 hours. The crude mixture is purified by column chromatography using a DCM/MeOH gradient to afford intermediate **40** as an oil: $^1\text{H-NMR}$ (400 MHz, CDCl_3) δ = 7.46-6.88 (m, 8H), 4.53 (s, 2H), 4.23 (t, J = 4.8 Hz, 2H), 4.01 (t, J = 4.8 Hz, 2H). MS calculated for $\text{C}_{17}\text{H}_{15}\text{Cl}_2\text{O}_2$ ($\text{M}+\text{H}^+$) 321.0, found 321.0.

[00151] **Step D:** Intermediate **26** (0.20 g, 0.75 mmol) is dissolved in DCE (5 mL). Triethylamine (125 μL , 0.9 mmol) is added and a precipitate forms. Intermediate **40** (0.24 g, 0.75 mmol) is added and the mixture is stirred at 90°C for 16 hours. The solvent is removed in vacuo and the remainder (crude intermediate **41** as a mixture of regioisomers) is used in the next step without further purification.

[00152] **Step E:** (3-Chloro-4-{4-[2-(2,4-dichloro-phenoxy)-ethoxymethyl]-5-phenyl-isoxazol-3-yl}-phenyl)-acetic acid methyl ester **41** (0.75 mmol) is dissolved in THF (5 mL). A solution of 1 M LiOH in H_2O (3.5 mL) is added and the mixture is stirred for 6 hours at room temperature. The mixture is acidified with 1 M HCl (3 mL), DCM (50 mL) is added and the organic layer washed with H_2O (2x30 mL). The organic layer is dried (MgSO_4), filtered, concentrated and purified on reverse phase HPLC ($\text{H}_2\text{O}/\text{MeCN}$ gradient) to afford the title compound **H2** as a white solid: $^1\text{H-NMR}$ (400 MHz, CDCl_3) δ = 7.84 (m, 2H), 7.44-7.19 (m, 7H), 7.06 (dd, J = 8.8 Hz, J = 2.5 Hz, 1H), 6.70 (d, J = 8.8 Hz, 1H), 4.45 (s, 2H), 4.00 (t, J = 4.5 Hz, 2H), 3.71 (t, J = 4.5 Hz, 2H), 3.62 (s, 2H). MS calculated for $\text{C}_{26}\text{H}_{21}\text{Cl}_3\text{NO}_5$ ($\text{M}+\text{H}^+$) 532.0, found 532.1.

[00153] **Example H3:** (3-Chloro-4-{4-[4-(2,4-dichloro-phenoxy)-butyryl]-5-phenyl-isoxazol-3-yl}-phenyl)-acetic acid.



[00154] Step A: Ethyl-4-bromobutyrate **42** (1.0 g, 5.1 mmol) and 2,4-dichlorophenol **27** (0.84 g, 5.1 mmol) is dissolved in MeCN (50 mL). Cs_2CO_3 is added and the suspension is stirred at 50°C for 7 hours. The mixture is then filtered, concentrated in vacuo, diluted with H_2O and extracted three times with EtOAc. The organic layers are combined, dried (MgSO_4), filtered, and concentrated to afford intermediate **43** as an oil: $^1\text{H-NMR}$ (400 MHz, CDCl_3) $\delta = 7.27$ (d, $J = 2.5$ Hz, 1H), 7.08 (dd, $J = 2.5$ Hz, $J = 8.8$ Hz, 1H), 6.76 (d, $J = 8.8$ Hz, 1H), 4.07 (q, $J = 7.1$ Hz, 2H), 3.98 (t, $J = 6.1$ Hz, 2H), 2.48 (t, $J = 7.2$ Hz, 2H), 2.07 (m, 2H), 1.18 (t, $J = 7.1$ Hz, 3H). MS calculated for $\text{C}_{12}\text{H}_{15}\text{Cl}_2\text{O}_3$ ($\text{M}+\text{H}^+$) 277.0, found 277.1.

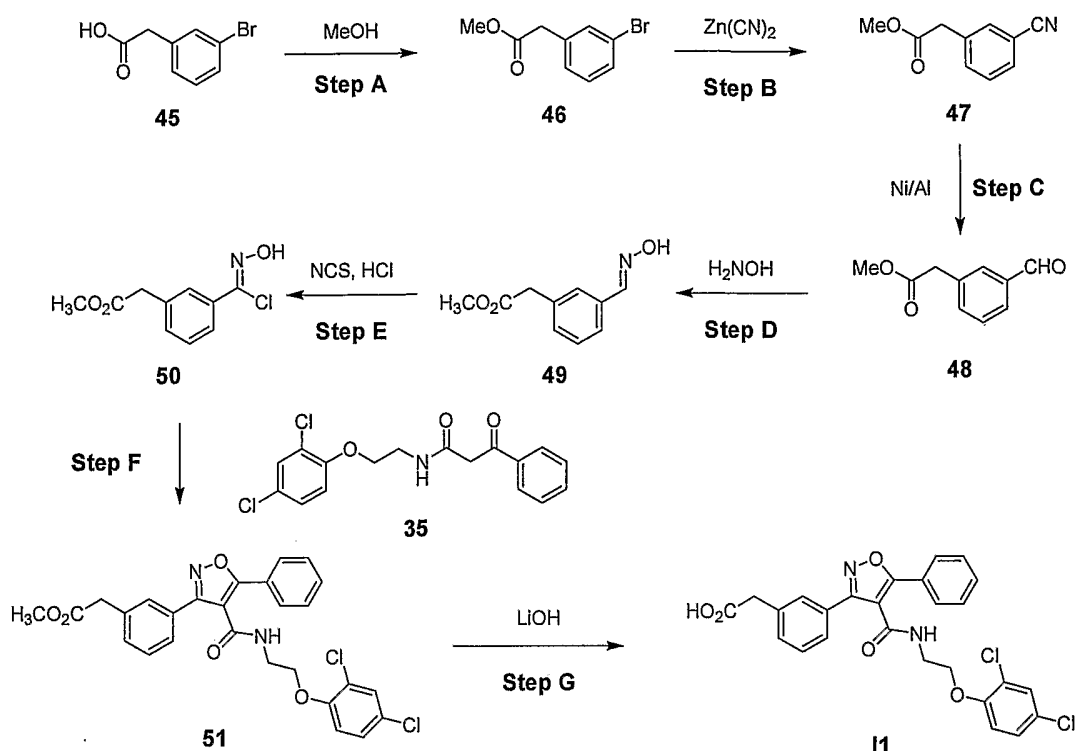
[00155] Step B: Sodium hydride (60% dispersion, 560 mg, 14 mmol) is dissolved in dioxane (30 mL) and stirred vigorously for 10 min at room temperature. To the vigorously stirring solution is added acetophenone (dropwise) (0.54 mL, 4.7 mmol) and intermediate **43** (1.29 g, 4.7 mmol) dissolved in dioxane (10 mL). The mixture is heated to reflux for 3 hours, then cooled to room temperature and poured into a cold solution of 0.5 M HCl (100 mL). EtOAc (200 mL) is added and the organic layer is washed with H_2O and brine (2x100 mL). The organic layer is dried (MgSO_4), filtered, concentrated and purified by column chromatography using a hexanes/EtOAc gradient to afford intermediate **44** as an oil: MS calculated for $\text{C}_{18}\text{H}_{17}\text{Cl}_2\text{O}_3$ ($\text{M}+\text{H}^+$) 351.0, found 351.1.

[00156] Step C: Intermediate **44** (0.20 g, 0.57 mmol) is dissolved in MeCN (5 mL). Potassium bis(trimethylsilyl)amide (270 mg, 1.36 mmol) is added slowly while stirring at

room temperature. Then the mixture is cooled to 0°C, and a solution of intermediate **16** (0.71 mmol) in CH₃CN (4 mL) is added dropwise. The mixture is stirred at room temperature for 3 hours, then concentrated to afford crude (3-Chloro-4-{4-[2-(2,4-dichloro-phenoxy)-ethyl-carbamoyl]-5-phenyl-isoxazol-3-yl}-phenyl)-acetic acid methyl ester **45** as a mixture of regioisomers. MS calculated for C₂₈H₂₃Cl₃NO₅ (M+H⁺) 558.1, found 558.1.

[00157] **Step D:** Crude (3-Chloro-4-{4-[2-(2,4-dichloro-phenoxy)-ethyl-carbamoyl]-5-phenyl-isoxazol-3-yl}-phenyl)-acetic acid methyl ester **45** is dissolved in THF (5 mL). A solution of 1 M LiOH in H₂O (3.5 mL) is added and the mixture is stirred for 6h at room temperature. The mixture is acidified with 1 M HCl (3 mL), DCM (50 mL) is added and the organic layer washed with H₂O (2x30 mL). The organic layer is dried (MgSO₄), filtered, concentrated and purified on reverse phase HPLC (H₂O/MeCN gradient) to afford the title compound **H2** as a white solid (minor isomer!): ¹H-NMR (400 MHz, CDCl₃) δ = 7.65 (d, J = 7.0 Hz, 2H), 7.39-6.93 (m, 8H), 6.54 (d, J = 8.8 Hz, 1H), 3.72 (t, J = 5.9 Hz, 2H), 3.53 (s, 2H), 2.50 (t, J = 6.8 Hz, 2H), 1.88 (m, 2H). MS calculated for C₂₇H₂₁Cl₃NO₅ (M+H⁺) 544.0, found 544.1.

[00158] **Example II:** (5-{4-[2-(2,4-Dichloro-phenoxy)-ethyl-carbamoyl]-5-phenyl-isoxazol-3-yl}-phenyl)-acetic acid.



[00159] Step A: 3-Bromophenyl acetic acid 45 (1.17 g, 5.44 mmol) is dissolved in MeOH (15 mL) containing catalytic amounts of conc. H₂SO₄ (0.2 mL). The solution is heated to reflux overnight. The solvent is evaporated, the remainder is dissolved in DCM and washed with water and saturated aqueous NaHCO₃. The organic layer is dried (MgSO₄), filtered and concentrated to afford the methyl ester 46 as an oil: ¹H-NMR (400MHz, CDCl₃) δ = 7.44 (s, 1H), 7.40 (ddd, J = 2.0, 2.4, 6.8 Hz, 1H), 7.20 (m, 2H), 3.70 (s, 3H), 3.59 (s, 2H). MS calculated for C₉H₁₀BrO₂ (M+H⁺) 229.1, found 229.0.

[00160] Step B: To a solution of (3-bromophenyl)-acetic acid methyl ester 46 (1.20 g, 5.28 mmol) in dry dimethyl-acetamide (5 mL) is added under argon zinc cyanide (0.78 g, 6.64 mmol) and tetrakis(triphenylphosphine) palladium (0.63 g, 0.55 mmol). The mixture is stirred for 24 hours at 80°C. After cooling to room temperature, the mixture is diluted with EtOAc (15 mL) and water (20 mL). The resulting precipitate is removed by vacuum filtration. The organic layer of the filtrate is separated and washed with H₂O, then dried over MgSO₄, filtered and concentrated. Purification by silica gel chromatography (0 to 20% EtOAc/hexane) to give (3-cyano-phenyl) acetic acid methyl ester 47 as an oil: ¹H-NMR (400MHz, CDCl₃) δ = 7.63 (d, J = 8.0 Hz, 1H), 7.47 (d, J = 1.2 Hz, 1H), 7.30 (dd, J = 1.2 Hz,

J= 8.0 Hz, 1H), 3.72 (s, 3H), 3.69 (s, 2H). MS calculated for C₁₀H₉O₂CIN (M+H⁺) 210.0, found 210.0.

[00161] Step C: A solution of (3-cyanophenyl) acetic acid methyl ester **47** (0.86 g, 4.9 mmol) in 88% formic acid (6 mL) is combined with Raney nickel alloy (0.48 g) and heated to reflux for 24 hours at 110°C. After cooling to room temperature, the alloy is removed by filtration over Celite. The filtrate is concentrated to ~10% of the original volume and diluted with EtOAc (50 mL) and washed three times with water (20 mL). The organic layer is dried (MgSO₄), filtered and concentrated to afford crude product, which is purified by silica gel chromatography using an EtOAc/hexane gradient to give (3-formylphenyl)-acetic acid methyl ester **48** as an oil: ¹H-NMR (400MHz, CDCl₃) δ = 9.97 (s, 1H), 7.40-7.52 (m, 4H), 3.68 (s, 3H), 3.67 (s, 2H). MS calculated for C₁₀H₁₁O₃ (M+H⁺) 179.1, found 179.1.

[00162] Step D: (3-Formylphenyl)-acetic acid methyl ester **48** (0.28 g, 1.6 mmol) is dissolved in dimethoxy-ethane (5 mL). Hydroxy-amine hydrochloride (0.11 g, 1.58 mmol) is added, followed by ethyl-diisopropylamine (0.3 mL, 1.7 mmol). The mixture is stirred at room temperature for 2 hours. The solvent is removed in vacuo and the residue is extracted three times with dichloromethane. The organic layers are combined, dried over MgSO₄, filtered, and concentrated to afford the oxime **49** as a white solid: ¹H-NMR (400MHz, CDCl₃) δ = 8.12 (s, 1H), 7.65-7.70 (m, 4H), 3.70 (s, 3H), 3.64 (s, 2H). MS calculated for C₁₀H₁₂NO₃ (M+H⁺) 194.1, found 104.1.

[00163] Step E: [3-(Hydroxyimino-methyl)-phenyl]-acetic acid methyl ester **49** (0.3 g, 1.6 mmol) and N-chlorosuccinimide (0.27 g, 2.0 mmol) are dissolved in DME (4 mL). After adding catalytic amounts of HCl (4M solution in dioxane) to the solution, an exothermic reaction occurred. After stirring for 2 hours at room temperature, the mixture is diluted with H₂O and extracted three times with ethyl acetate to afford intermediate **50** as a semi-solid; a stock solution is made in DME; MS calculated for C₁₀H₁₁CINO₃ (M+H⁺) 228.1, found 228.0.

[00164] Step F: A solution of N-[2-(2,4-Dichloro-phenoxy)-ethyl]-3-oxo-3-phenyl-propionamide **35** (0.11 g, 0.3 mmol) in DME (4 mL) is cooled to -20 °C. Potassium t-butoxide (0.6 mL of a 1.0 M solution in THF) is added and the solution is stirred for 20 minutes at -20°C. Intermediate **50** (0.07 g, 0.3 mmol) is added as a solution in 1mL DME. The mixture is stirred for 30 minutes at -20°C, then it is warmed to room temperature. After stirring at room temperature for 1 hour the mixture is poured into H₂O and extracted three

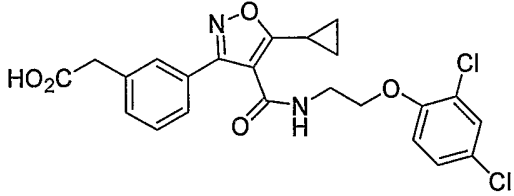
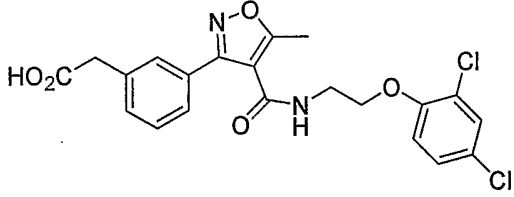
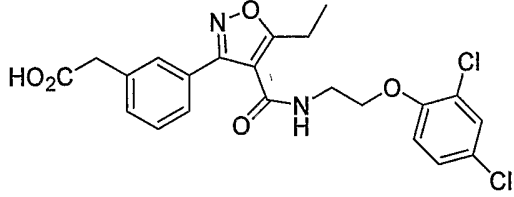
times with EtOAc. The organic layers are combined, dried (MgSO₄), filtered, and concentrated to afford crude (3-{4-[2-(2,4-dichloro-phenoxy)-ethyl-carbamoyl]-5-phenyl-isoxazol-3-yl}-phenyl)-acetic acid methyl ester **51**.

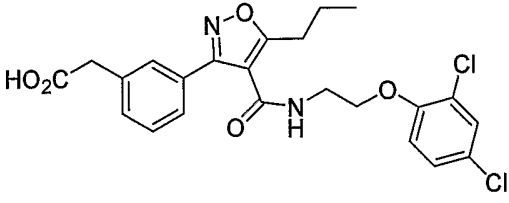
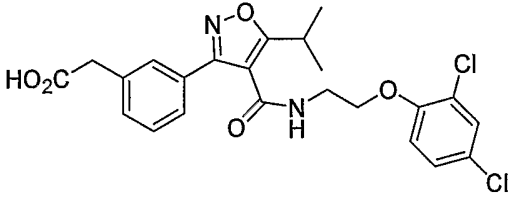
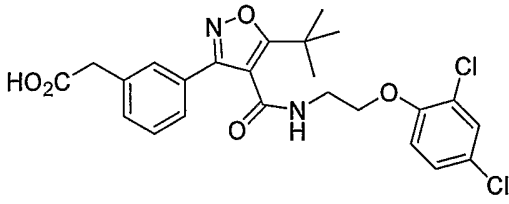
[00165] Step G: The crude (3-{4-[2-(2,4-dichloro-phenoxy)-ethyl-carbamoyl]-5-phenyl-isoxazol-3-yl}-phenyl)-acetic acid methyl ester **51** is dissolved in DME (2 mL). A solution of 1 M LiOH in H₂O (0.2 mL) and is added and the mixture is stirred overnight at room temperature. The mixture is concentrated, then acidified with 1 M HCl, extracted with EtOAc (10 mL), dried over MgSO₄, filtered, concentrated and purified on reverse phase HPLC (H₂O/MeCN gradient) to afford the title compound **I1** as an off-white solid: ¹H-NMR (400 MHz, CD₃CN) δ = 7.61 (s, 1H), 7.57 (m, 1H), 7.38 (m, 5H), 7.33 (d, J = 2.4 Hz, 1H), 7.28 (m, 2H), 7.20 (dd, J = 9.2, 2.8 Hz, 1H), 7.16 (t, J = 5.2 Hz, NH), 6.90 (d, J = 8.8 Hz, 1H), 4.04 (t, J = 5.2 Hz, 2H), 3.63 (q, J = 5.2 Hz, 2H), 3.59 (s, 2H). MS calculated for C₂₆H₂₁Cl₂N₂O₅ (M+H⁺) 511.0, found 511.0.

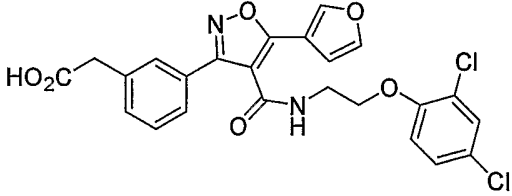
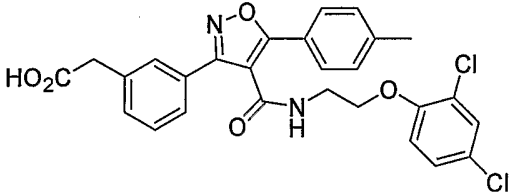
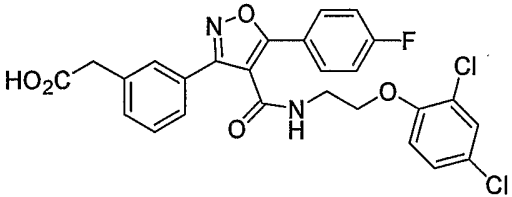
[00166] By repeating the procedure described in the above examples, using appropriate starting materials, the following compounds of Formula I are obtained as identified in Table 2.

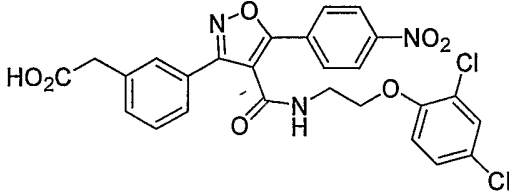
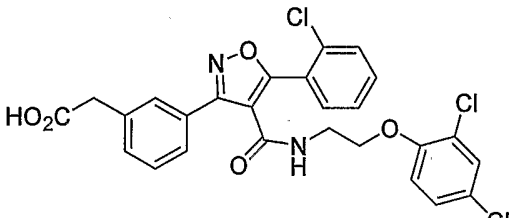
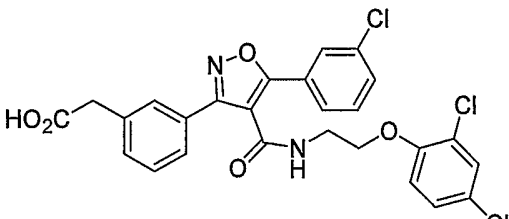
Table 2

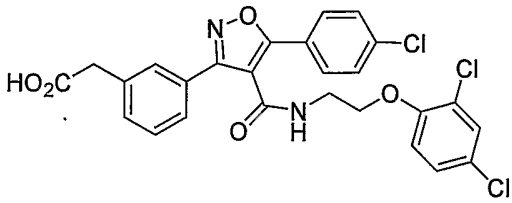
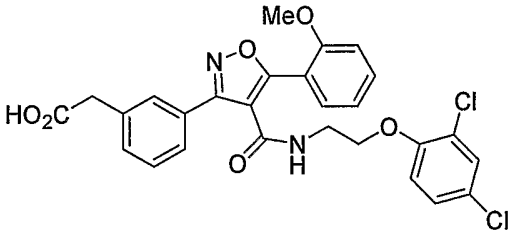
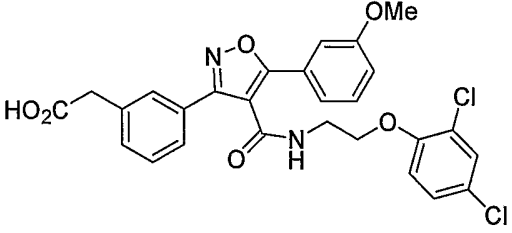
Compound Number	Compound Structure	Physical Data ¹ H NMR 400 MHz and/or MS (m/z)
I2		¹ H-NMR (400 MHz, d ⁶ -DMSO) δ = 9.06 (1H), 7.92 (1H), 7.66-7.16 (m, 7H), 6.68 (1H), 4.20 (2H), 3.63 (2H), 3.62 (2H). MS calculated for C ₂₄ H ₁₉ Cl ₂ N ₂ O ₆ (M+H ⁺) 501.1, found 501.0.

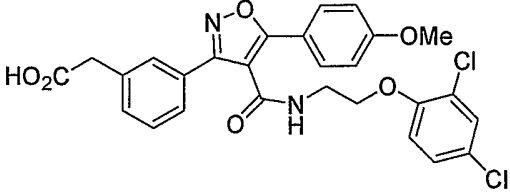
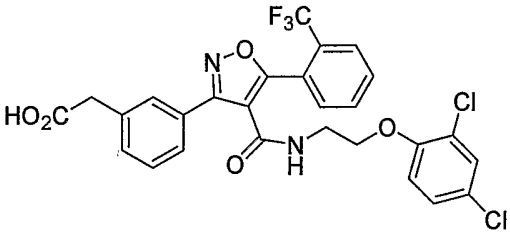
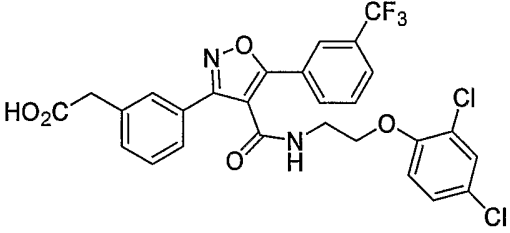
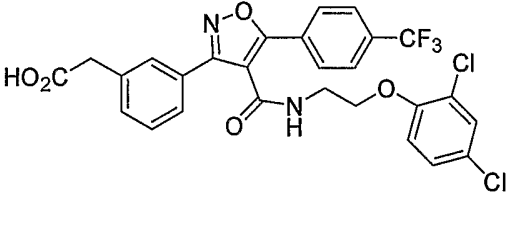
Compound Number	Compound Structure	Physical Data ¹ H NMR 400 MHz and/or MS (m/z)
I3		¹ H-NMR (400 MHz, d ⁶ -DMSO) δ = 8.63 (1H), 7.65-7.19 (m, 6H), 4.17 (2H), 3.60 (2H), 3.60 (2H), 2.32 (1H), 1.07 (4H). MS calculated for C ₂₃ H ₂₁ Cl ₂ N ₂ O ₅ (M+H ⁺) 475.1, found 475.0.
I4		MS calculated for C ₂₁ H ₁₉ Cl ₂ N ₂ O ₅ (M+H ⁺) 449.1, found 449.1.
I5		¹ H-NMR (400 MHz, CDCl ₃) δ = 7.53 (s, 1H), 7.49 (m, 1H), 7.33-7.25 (m, 3H), 7.14 (dd, J = 2.5 Hz, J = 8.8 Hz, 1H), 6.73 (d, J = 8.8 Hz, 1H), 5.95 (t, NH), 3.97 (t, J = 5.2 Hz, 2H), 3.70 (q, J = 5.2 Hz, 2H), 3.63 (s, 2H), 3.12 (q, J = 7.6 Hz, 2H), 1.36 (t, J = 7.6 Hz, 3H). MS calculated for C ₂₂ H ₂₁ Cl ₂ N ₂ O ₅ (M+H ⁺) 463.1, found 463.1.

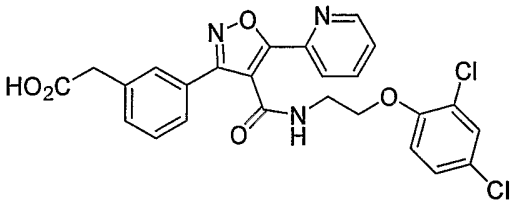
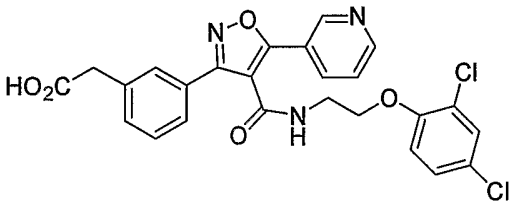
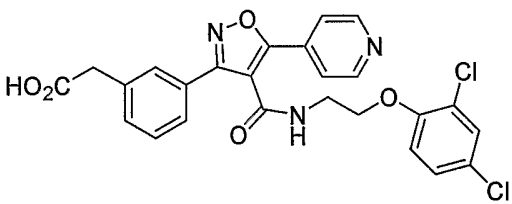
Compound Number	Compound Structure	Physical Data ¹ H NMR 400 MHz and/or MS (m/z)
I6		¹ H-NMR (400 MHz, CDCl ₃) δ = 7.53 (s, 1H), 7.49 (m, 1H), 7.33-7.25 (m, 3H), 7.14 (dd, J = 2.5 Hz, J = 8.8 Hz, 1H), 6.73 (d, J = 8.8 Hz, 1H), 5.96 (t, NH), 3.97 (t, J = 5.2 Hz, 2H), 3.70 (q, J = 5.2 Hz, 2H), 3.63 (s, 2H), 3.06 (t, J = 7.6 Hz, 2H), 1.81 (m, 2H), 1.56 (t, J = 7.4 Hz, 3H). MS calculated for C ₂₃ H ₂₃ Cl ₂ N ₂ O ₅ (M+H ⁺) 477.1, found 477.1.
I7		¹ H-NMR (400 MHz, CDCl ₃) δ = 7.51 (s, 1H), 7.47 (m, 1H), 7.30-7.23 (m, 3H), 7.13 (dd, J = 2.5 Hz, J = 8.8 Hz, 1H), 6.71 (d, J = 8.8 Hz, 1H), 5.97 (t, NH), 3.95 (t, J = 5.2 Hz, 2H), 3.76-3.67 (m, 3H), 3.60 (s, 2H), 1.37 (d, J = 7.0 Hz, 6H). MS calculated for C ₂₃ H ₂₃ Cl ₂ N ₂ O ₅ (M+H ⁺) 477.1, found 477.1.
I8		¹ H-NMR (400 MHz, CDCl ₃) δ = 7.54 (s, 1H), 7.50 (m, 1H), 7.36-7.17 (m, 3H), 7.13 (dd, J = 2.5 Hz, J = 8.8 Hz, 1H), 6.69 (d, J = 8.8 Hz, 1H), 6.20 (t, NH), 3.95 (t, J = 4.7 Hz, 2H), 3.70 (q, J = 4.7 Hz, 2H), 3.59 (s, 2H), 1.41 (s, 9H). MS calculated for C ₂₄ H ₂₅ Cl ₂ N ₂ O ₅ (M+H ⁺) 491.1, found 491.2.

Compound Number	Compound Structure	Physical Data ¹ H NMR 400 MHz and/or MS (m/z)
I9		¹ H-NMR (400 MHz, CDCl ₃) δ = 8.44 (s, 1H), 7.58-7.49 (m, 3H), 7.31-7.25 (m, 3H), 7.13 (dd, J = 2.5 Hz, J = 8.8 Hz, 1H), 6.96 (d, J = 1.5 Hz, 1H), 6.71 (d, J = 8.8 Hz, 1H), 5.95 (t, NH), 3.96 (t, J = 5.2 Hz, 2H), 3.73 (q, J = 5.2 Hz, 2H), 3.64 (s, 2H). MS calculated for C ₂₄ H ₁₉ Cl ₂ N ₂ O ₆ (M+H ⁺) 501.1, found 501.1.
I10		¹ H-NMR (400 MHz, CDCl ₃) δ = 7.71 (s, 1H), 7.69 (s, 1H), 7.67 (s, 1H), 7.63 (d, J = 6.6 Hz, 1H), 7.31-7.24 (m, 4H), 7.13 (m, 3H), 6.68 (d, J = 8.8 Hz, 1H), 6.26 (t, NH), 3.97 (t, J = 5.2 Hz, 2H), 3.74 (q, J = 5.2 Hz, 2H), 3.65 (s, 2H), 2.32 (s, 3H). MS calculated for C ₂₇ H ₂₃ Cl ₂ N ₂ O ₅ (M+H ⁺) 525.1, found 525.2.
I11		¹ H-NMR (400 MHz, CDCl ₃) δ = 7.92-7.89 (m, 2H), 7.67 (s, 1H), 7.60 (d, J = 6.6 Hz, 1H), 7.29-7.24 (m, 3H), 7.14 (dd, J = 2.5 Hz, J = 8.8 Hz, 1H), 7.08 (m, 2H), 6.70 (d, J = 8.8 Hz, 1H), 6.15 (t, NH), 3.98 (t, J = 5.2 Hz, 2H), 3.76 (q, J = 5.2 Hz, 2H), 3.66 (s, 2H). MS calculated for C ₂₆ H ₂₀ Cl ₂ FN ₂ O ₅ (M+H ⁺) 529.1, found 529.2.

Compound Number	Compound Structure	Physical Data ¹ H NMR 400 MHz and/or MS (m/z)
I12		¹ H-NMR (400 MHz, CDCl ₃) δ = 8.24 (d, J = 8.8 Hz, 1H), 8.10 (d, J = 8.8 Hz, 1H), 7.66 (s, 1H), 7.61 (d, J = 6.6 Hz, 1H), 7.30-7.24 (m, 3H), 7.15 (dd, J = 2.5 Hz, J = 8.8 Hz, 1H), 6.70 (d, J = 8.8 Hz, 1H), 6.23 (t, NH), 3.99 (t, J = 4.9 Hz, 2H), 3.76 (q, J = 4.9 Hz, 2H), 3.66 (s, 2H). MS calculated for C ₂₆ H ₂₀ Cl ₂ N ₃ O ₇ (M+H ⁺) 556.1, found 556.1.
I13		¹ H-NMR (400 MHz, CDCl ₃) δ = 7.66 (s, 1H), 7.63 (d, J = 6.7 Hz, 1H), 7.52 (m, 1H), 7.31-7.21 (m, 6H), 7.09 (dd, J = 2.5 Hz, J = 8.8 Hz, 1H), 6.62 (d, J = 8.8 Hz, 1H), 6.13 (t, NH), 3.84 (t, J = 4.8 Hz, 2H), 3.62 (q, J = 4.8 Hz, 2H), 3.61 (s, 2H). MS calculated for C ₂₆ H ₂₀ Cl ₃ N ₂ O ₅ (M+H ⁺) 545.0, found 545.1.
I14		¹ H-NMR (400 MHz, CDCl ₃) δ = 7.87 (s, 1H), 7.76 (d, J = 7.7 Hz, 1H), 7.68 (s, 1H), 7.62 (m, 1H), 7.38-7.23 (m, 5H), 7.14 (dd, J = 2.5 Hz, J = 8.8 Hz, 1H), 6.70 (d, J = 8.8 Hz, 1H), 6.20 (t, NH), 3.99 (t, J = 5.2 Hz, 2H), 3.77 (q, J = 5.2 Hz, 2H), 3.67 (s, 2H). MS calculated for C ₂₆ H ₂₀ Cl ₃ N ₂ O ₅ (M+H ⁺) 545.0, found 545.1.

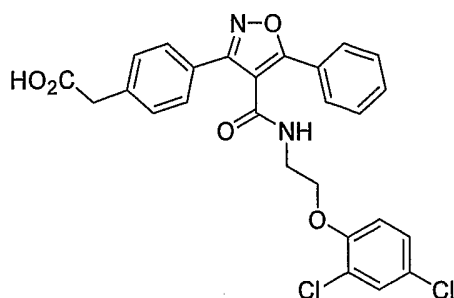
Compound Number	Compound Structure	Physical Data ¹ H NMR 400 MHz and/or MS (m/z)
I15		¹ H-NMR (400 MHz, CDCl ₃) δ = 7.79 (d, J = 8.6 Hz, 2H), 7.64 (s, 1H), 7.59 (m, 1H), 7.32 (d, J = 8.6 Hz, 2H), 7.27-7.25 (m, 3H), 7.14 (dd, J = 2.5 Hz, J = 8.8 Hz, 1H), 6.67 (d, J = 8.8 Hz, 1H), 6.27 (t, NH), 3.95 (t, J = 5.2 Hz, 2H), 3.73 (q, J = 5.2 Hz, 2H), 3.64 (s, 2H). MS calculated for C ₂₆ H ₂₀ Cl ₃ N ₂ O ₅ (M+H ⁺) 545.0, found 545.1.
I16		MS calculated for C ₂₇ H ₂₃ Cl ₂ N ₂ O ₆ (M+H ⁺) 541.1, found 541.1.
I17		¹ H-NMR (400 MHz, CDCl ₃) δ = 7.69 (s, 1H), 7.64 (m, 1H), 7.41 (m, 2H), 7.30-7.24 (m, 4H), 7.13 (dd, J = 2.5 Hz, J = 8.8 Hz, 1H), 6.93 (m, 1H), 6.69 (d, J = 8.8 Hz, 1H), 6.28 (t, NH), 3.97 (t, J = 5.0 Hz, 2H), 3.81 (s, 3H), 3.76 (q, J = 5.0 Hz, 2H), 3.66 (s, 2H). MS calculated for C ₂₇ H ₂₃ Cl ₂ N ₂ O ₆ (M+H ⁺) 541.1, found 541.2.

Compound Number	Compound Structure	Physical Data ¹ H NMR 400 MHz and/or MS (m/z)
118		MS calculated for C ₂₇ H ₂₃ Cl ₂ N ₂ O ₆ (M+H ⁺) 541.1, found 541.2.
119		¹ H-NMR (400 MHz, CDCl ₃) δ = 7.75-7.33 (m, 7H), 7.32-7.29 (m, 3H), 7.12 (dd, J = 2.5 Hz, J = 8.8 Hz, 1H), 6.62 (d, J = 8.8 Hz, 1H), 6.05 (t, NH), 3.81 (t, J = 5.1 Hz, 2H), 3.66 (s, 2H), 3.62 (q, J = 5.1 Hz, 2H). MS calculated for C ₂₇ H ₂₀ Cl ₂ F ₃ N ₂ O ₆ (M+H ⁺) 579.1, found 579.1.
120		MS calculated for C ₂₇ H ₂₀ Cl ₂ F ₃ N ₂ O ₆ (M+H ⁺) 579.1, found 579.1.
121		MS calculated for C ₂₇ H ₂₀ Cl ₂ F ₃ N ₂ O ₆ (M+H ⁺) 579.1, found 579.1.

Compound Number	Compound Structure	Physical Data ¹ H NMR 400 MHz and/or MS (m/z)
I22		¹ H-NMR (400 MHz, CDCl ₃) δ = 8.60 (d, J = 4.3 Hz, 1H), 8.09 (d, J = 7.9 Hz, 1H), 7.94 (m, 1H), 7.94 (m, 1H), 7.58 (m, NH), 7.41 (m, 3H), 7.30 (d, J = 2.5 Hz, 1H), 7.13 (dd, J = 2.5 Hz, J = 8.8 Hz, 1H), 6.81 (d, J = 8.8 Hz, 1H), 4.15 (t, J = 4.8 Hz, 2H), 3.84 (q, J = 4.8 Hz, 2H), 3.69 (s, 2H). MS calculated for C ₂₅ H ₂₀ Cl ₂ N ₃ O ₅ (M+H ⁺) 512.1, found 512.1.
I23		MS calculated for C ₂₅ H ₂₀ Cl ₂ N ₃ O ₅ (M+H ⁺) 512.1, found 512.1.
I24		MS calculated for C ₂₅ H ₂₀ Cl ₂ N ₃ O ₅ (M+H ⁺) 512.1, found 512.1.

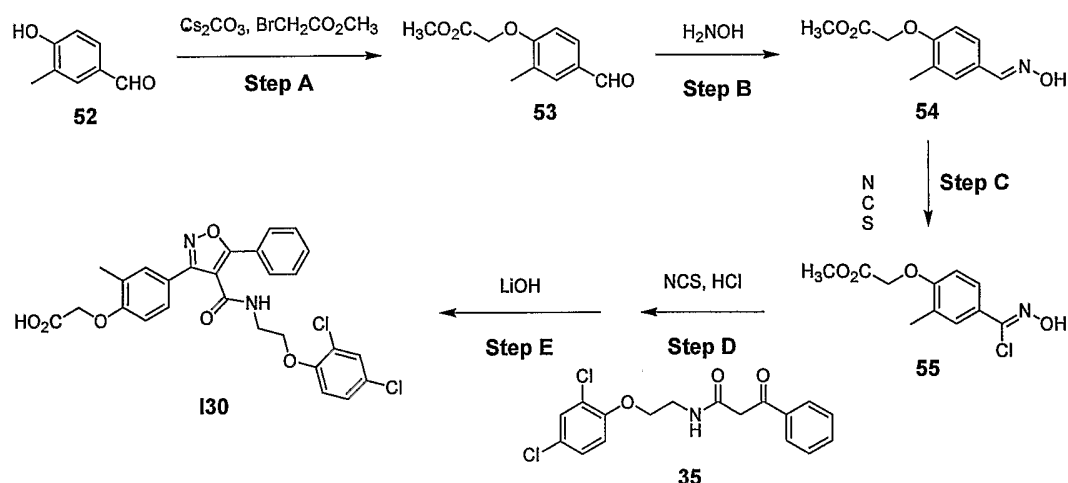
Compound Number	Compound Structure	Physical Data ¹ H NMR 400 MHz and/or MS (m/z)
I25		¹ H-NMR (400 MHz, CDCl ₃) δ = 7.91 (m, 1H), 7.61 (s, 1H), 7.57 (m, 1H), 7.52 (m, 1H), 7.31-7.25 (m, 3H), 7.14-7.09 (m, 2H), 6.70 (d, J = 2.5 Hz, 1H), 6.16 (m, NH), 3.99 (t, J = 5.2 Hz, 2H), 3.84 (q, J = 5.2 Hz, 2H), 3.64 (s, 2H). MS calculated for C ₂₄ H ₁₉ Cl ₂ N ₂ O ₅ S (M+H ⁺) 517.0, found 517.1.
I26		¹ H-NMR (400 MHz, CDCl ₃) δ = 7.71 (s, 1H), 7.68 (d, J = 7.0 Hz, 1H), 7.43-7.11 (m, 8H), 6.63 (d, J = 8.8 Hz, 1H), 6.10 (t, NH), 3.83 (t, J = 5.2 Hz, 2H), 3.66 (m, 4H), 2.35 (s, 3H). MS calculated for C ₂₇ H ₂₃ Cl ₂ N ₂ O ₅ (M+H ⁺) 525.1, found 525.2.
I27		¹ H-NMR (400 MHz, CDCl ₃) δ = 7.67-7.59 (m, 3H), 7.28-7.10 (m, 6H), 6.68 (d, J = 8.8 Hz, 1H), 6.32 (t, NH), 3.96 (t, J = 5.2 Hz, 2H), 3.74 (q, J = 5.2 Hz, 2H), 3.64 (s, 3H), 2.35 (s, 3H). MS calculated for C ₂₇ H ₂₃ Cl ₂ N ₂ O ₅ (M+H ⁺) 525.1, found 525.2.

[00167] **Example I29:** (4-{4-[2-(2,4-Dichloro-phenoxy)-ethyl-carbamoyl]-5-phenyl-isoxazol-3-yl}-phenyl)-acetic acid.



[00168] Following the procedure of **Example I1** above, using 4-bromophenyl acetic acid instead of intermediate **45**, the title compound **I29** is prepared as a white solid: $^1\text{H-NMR}$ (400 MHz, CD_3CN) δ = 8.00 (m, 1H), 7.86 (d, J = 8.4 Hz, 2H), 7.62 (m, 5H), 7.55 (m, 2H), 7.44 (m, 2H), 7.12 (d, J = 8.8 Hz, 1H), 4.26 (t, J = 4.8 Hz, 2H), 3.87 (q, J = 5.2 Hz, 2H), 3.76 (s, 2H). MS calculated for $\text{C}_{26}\text{H}_{21}\text{Cl}_2\text{N}_2\text{O}_5$ ($\text{M}+\text{H}^+$) 511.0, found 511.1.

[00169] **Example I30**: (4-{4-[2-(2,4-Dichloro-phenoxy)-ethyl-carbamoyl]-5-phenyl-isoxazol-3-yl}-2-methyl-phenoxy)-acetic acid.



[00170] **Step A**: 4-Hydroxy-3-methyl-benzaldehyde **52** (0.50 g, 3.67 mmol) is dissolved in 10 mL acetonitrile. Cesium carbonate (2.07 g, 6.35 mmol) and methyl bromoacetate (0.40 mL, 4.35 mmol) are added and the suspension is vigorously stirred at room temperature overnight. The suspension is poured into 1N aqueous HCl and extracted with EtOAc. Drying over MgSO_4 , filtration and concentration yielded (4-formyl-2-methyl-phenoxy)-acetic acid methyl ester **53**: $^1\text{H-NMR}$ (400MHz, CDCl_3) δ = 9.86 (s, 1H), 7.71 (d,

J = 1.6 Hz, 1H), 7.68 (dd, J = 8.4, 1.6 Hz, 1H), 6.77 (d, J = 8.4 Hz, 1H), 4.75 (s, 2H), 3.81 (s, 3H), 2.34 (s, 3H). MS calculated for C₁₁H₁₃O₄ (M+H⁺) 209.0, found 209.0.

[00171] Step B: (4-Formyl-2-methyl-phenoxy)-acetic acid methyl ester **53** (0.8 g, 3.6 mmol) is dissolved in dimethoxy-ethane (5 mL). Hydroxy-amine hydrochloride (0.47 g, 6.8 mmol) is added, followed by ethyl-diisopropylamine (1.4 mL, 8.5 mmol). The mixture is stirred at room temperature for 6 hours. The solvent is removed in vacuo and the residue is extracted three times with ethyl acetate. The organic layers are combined, dried over MgSO₄, filtered, and concentrated to afford the oxime **54** as a white solid: ¹H-NMR (400MHz, CDCl₃) δ = 8.06 (s, 1H), 7.42 (d, J = 1.6 Hz, 1H), 7.32 (dd, J = 8.4, 1.6 Hz, 1H), 6.68 (d, J = 8.4 Hz, 1H), 4.69 (s, 2H), 3.81 (s, 3H), 2.30 (s, 3H). MS calculated for C₁₁H₁₄NO₄ (M+H⁺) 224.1, found 224.1.

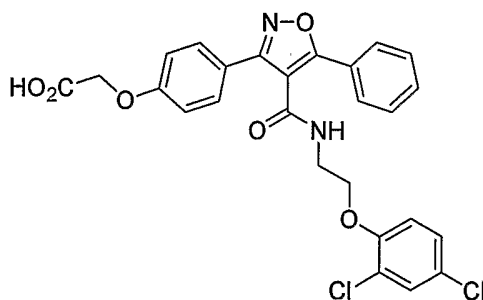
[00172] Step C: [4-(Hydroxyimino-methyl)-2-methyl-phenoxy]-acetic acid methyl ester **54** (0.05 g, 0.22 mmol) and N-chlorosuccinimide (0.025 g, 0.19 mmol) are dissolved in DME (2 mL). After adding catalytic amounts of HCl (4M solution in dioxane) to the solution, an exothermic reaction occurred. After stirring for 2 hours at room temperature, the mixture is diluted with H₂O and extracted three times with ethyl acetate to afford intermediate **55**; the crude material is dissolved in 1 mL DME and used as such; MS calculated for C₁₁H₁₂ClNO₄ (M+H⁺) 258.1, found 258.0.

[00173] Step D: A solution of N-[2-(2,4-Dichloro-phenoxy)-ethyl]-3-oxo-3-phenyl-propionamide **35** (0.04 g, 0.12 mmol) in DME (1 mL) is cooled to -20 °C. Potassium t-butoxide (0.2 mL of a 1.0 M solution in THF) is added and the solution is stirred for 10 min at -20 °C. Intermediate **55** prepared in **Step C** is added as a solution in 1 mL DME. The mixture is stirred for 30 min at -20 °C, and then it is warmed to room temperature. After stirring at room temperature for 1 hour the mixture is poured into water and extracted three times with EtOAc. The organic layers are combined, dried (MgSO₄), filtered, and concentrated to afford crude (4-{4-[2-(2,4-dichloro-phenoxy)-ethyl-carbamoyl]-5-phenyl-isoxazol-3-yl}-2-methyl-phenoxy)-acetic acid methyl ester. MS calculated for C₂₈H₂₅Cl₂N₂O₆ (M+H⁺) 555.0, found 555.0.

[00174] Step E: The crude (4-{4-[2-(2,4-dichloro-phenoxy)-ethyl-carbamoyl]-5-phenyl-isoxazol-3-yl}-2-methyl-phenoxy)-acetic acid methyl ester is dissolved in DME (1 mL). A solution of 1 M LiOH in H₂O (0.2 mL) and is added and the mixture is stirred overnight at room temperature. The mixture is concentrated, then acidified with 1 M HCl,

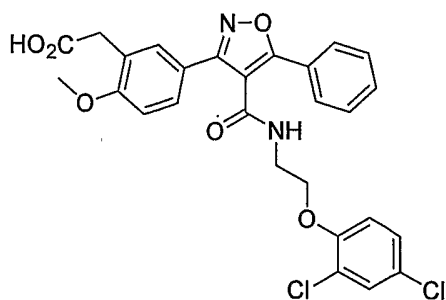
extracted with EtOAc (10 mL), dried over MgSO₄, filtered, concentrated and purified on reverse phase HPLC (H₂O/MeCN gradient) to afford the title compound **I30** as a white solid: ¹H-NMR (400 MHz, CD₃CN) δ = 7.56 (d, J = 1.6, 1H), 7.49 (dd, J = 8.4, 2.4 Hz, 1H), 7.45 (m, 5H), 7.39 (d, J = 2.4 Hz, 1H), 7.27 (dd, J = 8.8, 2.8 Hz, 1H), 7.20 (t, J = 5.6 Hz, NH), 6.96 (d, J = 8.8 Hz, 1H), 6.73 (d, J = 8.8 Hz, 1H), 4.64 (s, 2H), 4.08 (t, J = 5.2 Hz, 2H), 3.70 (q, J = 5.3 Hz, 2H), 2.23 (s, 3H). MS calculated for C₂₇H₂₃Cl₂N₂O₆ (M+H⁺) 541.0, found 541.0.

[00175] **Example I31:** (4-{4-[2-(2,4-Dichloro-phenoxy)-ethyl-carbamoyl]-5-phenyl-isoxazol-3-yl}-phenoxy)-acetic acid.



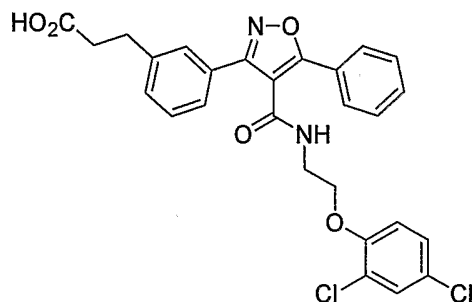
[00176] Following an analogous procedure to the one for **Example I29** above, the title compound **I31** is prepared as a white solid: ¹H-NMR (400 MHz, CDCl₃) δ = 7.86 (m, 2H), 7.70 (d, J = 8.8 Hz, 2H), 7.40 (m, 3H), 7.28 (d, J = 2.4 Hz, 1H), 7.17 (dd, J = 8.8, 2.4 Hz, 1H), 6.87 (d, J = 8.8 Hz, 2H), 6.72 (d, J = 8.8 Hz, 2H), 6.21 (t, J = 5.6 Hz, NH), 4.60 (s, 2H), 4.01 (t, J = 5.2 Hz, 2H), 3.81 (td, J = 5.6, 5.2 Hz, 2H). MS calculated for C₂₆H₂₁Cl₂N₂O₆ (M+H⁺) 527.0, found 526.9.

[00177] **Example I32:** (5-{4-[2-(2,4-Dichloro-phenoxy)-ethyl-carbamoyl]-5-phenyl-isoxazol-3-yl}-2-methoxy-phenyl)-acetic acid.



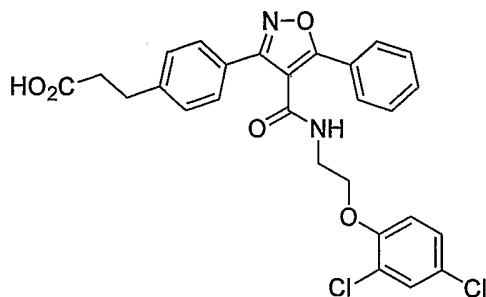
[00178] Following the procedure of **Example I30** above, using the appropriate bromide in **Step A**, the title compound **I32** is prepared as a white solid: MS calculated for $C_{27}H_{23}Cl_2N_2O_6$ ($M+H^+$) 541.0, found 541.0.

[00179] **Example I33:** 3-(3-{4-[2-(2,4-Dichloro-phenoxy)-ethyl-carbamoyl]-5-phenyl-isoxazol-3-yl}-phenyl)-propionic acid.



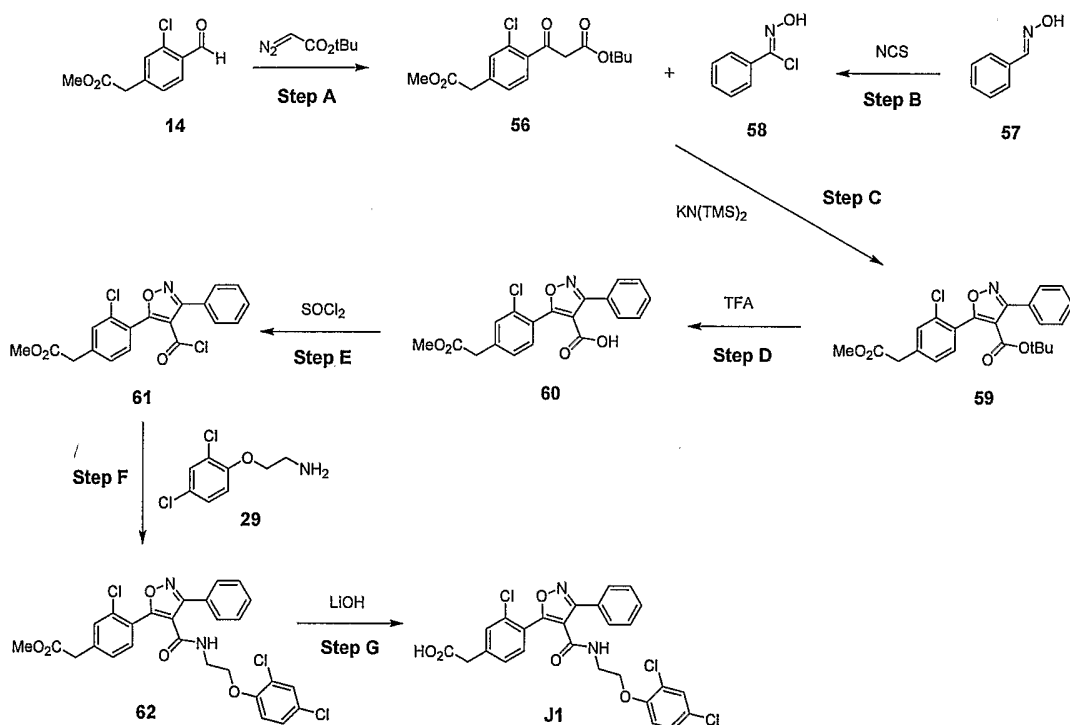
[00180] Following the procedure of **Example I1** above, using the appropriate bromide in **Step A**, the title compound **I33** is prepared as a white solid: MS calculated for $C_{27}H_{23}Cl_2N_2O_5$ ($M+H^+$) 525.0, found 525.0.

[00181] **Example I34:** 3-(4-{4-[2-(2,4-Dichloro-phenoxy)-ethyl-carbamoyl]-5-phenyl-isoxazol-3-yl}-phenyl)-propionic acid.



[00182] Following the procedure of **Example I1** above, using the appropriate bromide in **Step A**, the title compound **I34** is prepared as a white solid: MS calculated for $C_{27}H_{23}Cl_2N_2O_5$ ($M+H^+$) 525.0, found 525.0.

[00183] **Example J1:** (3-Chloro-4-{4-[2-(2,4-dichloro-phenoxy)-ethylcarbamoyl]-3-phenyl-isoxazol-5-yl}-phenyl)-acetic acid.



[00184] **Step A:** A flame-dried flask is charged with tert-butyl-diazoacetate (0.62 mL, 4.48 mmol) and anhydrous tin(II) chloride (168 mg, 0.88 mmol) in dry DCM (10 mL). (3-Chloro-4-formyl-phenyl)-acetic acid methyl ester **14** (500 mg, 2.35 mmol) is dissolved in

DCM (5 mL) and added dropwise to the reaction mixture. After stirring for 6 h at room temperature the reaction mixture is poured into brine (50 mL) and extracted with ether (3x50 mL). The combined organic layers are dried (MgSO_4), filtered, concentrated and purified on reverse phase HPLC ($\text{H}_2\text{O}/\text{MeCN}$ gradient) to afford 3-(2-Chloro-4-methoxycarbonylmethyl-phenyl)-3-oxo-propionic acid tert-butyl ester **56** as a white solid: MS calculated for $\text{C}_{16}\text{H}_{19}\text{Cl}_2\text{NaO}_5$ ($\text{M}+\text{Na}^+$) 349.1, found 349.1.

[00185] Step B: Benzaldoxime **57** (0.50 g, 4.1 mmol) and N-chlorosuccinimide (0.55 g, 4.1 mmol) are dissolved in MeCN (10 mL). After stirring for 3 hours at room temperature the solvent is removed in vacuo to afford benzyl chloroxime **58** (0.64 g, 4.1 mmol, quant.) as a wax-like solid, which is used immediately without further purification: MS calculated for $\text{C}_7\text{H}_7\text{ClNO}$ ($\text{M}+\text{H}^+$) 156.0, found 156.0.

[00186] Step C: Intermediate **56** (115 mg, 0.35 mmol) is dissolved in MeCN (3 mL). Potassium bis(trimethylsilyl)amide (106 mg, 0.53 mmol) is added slowly while stirring at room temperature. Then the mixture is cooled to 0°C , and a solution of intermediate **58** (55 mg, 0.35 mmol) in CH_3CN (1 mL) is added. The mixture is stirred at room temperature overnight, then H_2O (5 mL) is added and the mixture is extracted with DCM (3x10 mL). After concentration the crude product is purified on reverse phase HPLC ($\text{H}_2\text{O}/\text{MeCN}$ gradient) to afford 5-(2-chloro-4-methoxycarbonylmethyl-phenyl)-3-phenyl-isoxazole-4-carboxylic acid tert-butyl ester **59** as a white solid: $^1\text{H-NMR}$ (400 MHz, CDCl_3) $\delta = 7.73$ (m, 2H), 7.47 (m, 5H), 7.33 (m, 1H), 3.72 (s, 3H), 3.68 (s, 2H), 1.23 (s, 9H). MS calculated for $\text{C}_{23}\text{H}_{23}\text{ClNO}_5$ ($\text{M}+\text{H}^+$) 428.1, found 428.1.

[00187] Step D: 5-(2-Chloro-4-methoxycarbonylmethyl-phenyl)-3-phenyl-isoxazole-4-carboxylic acid tert-butyl ester **59** (25 mg, 0.06 mmol) is dissolved in trifluoroacetic acid (1 mL) and stirred at room temperature for 2 hours. Then the solvent is evaporated and the remainder is dried on high vacuum to afford 5-(2-Chloro-4-methoxycarbonylmethyl-phenyl)-3-phenyl-isoxazole-4-carboxylic acid **60** as a white solid: $^1\text{H-NMR}$ (400 MHz, CDCl_3) $\delta = 7.62$ (m, 2H), 7.38 (m, 5H), 7.24 (m, 1H), 3.64 (s, 3H), 3.59 (s, 2H). MS calculated for $\text{C}_{19}\text{H}_{15}\text{ClNO}_5$ ($\text{M}+\text{H}^+$) 372.1, found 372.1.

[00188] Step E: 5-(2-Chloro-4-methoxycarbonylmethyl-phenyl)-3-phenyl-isoxazole-4-carboxylic acid **60** (22 mg, 0.06 mmol) and thionyl chloride (5 μL , 0.07 mmol) are dissolved in toluene (0.8 mL). The mixture is stirred at 120°C for 3 hours. Then the reaction mixture is cooled down to 0°C and triethylamine (35 μL , 0.25 mmol) are added dropwise.

The resulting solution containing crude [3-chloro-4-(4-chlorocarbonyl-3-phenyl-isoxazol-5-yl)-phenyl]-acetic acid methyl ester **61** is used without further purification: MS calculated for $C_{19}H_{14}Cl_2NO_4$ ($M+H^+$) 390.0, found 390.1.

[00189] Step F: A solution of 2-(2,4-Dichloro-phenoxy)-ethylamine **29** (19 mg, 0.09 mmol) in toluene (0.2 mL) is cooled to 0°C. The above solution of intermediate **61** (0.06 mmol) is added and the solution is warmed to room temperature. After stirring at room temperature for 1 hour the mixture is poured into H₂O and extracted three times with DCM. The organic layers are combined, dried (MgSO₄), filtered, and concentrated to afford crude (3-Chloro-4-{4-[2-(2,4-dichloro-phenoxy)-ethyl-carbamoyl]-3-phenyl-isoxazol-5-yl}-phenyl)-acetic acid methyl ester **62**.

[00190] Step G: The crude (3-Chloro-4-{4-[2-(2,4-dichloro-phenoxy)-ethyl-carbamoyl]-3-phenyl-isoxazol-5-yl}-phenyl)-acetic acid methyl ester **62** is dissolved in THF (2 mL). A solution of 1 M LiOH in H₂O (0.6 mL) is added and the mixture is stirred overnight at room temperature. The mixture is acidified with 1 M HCl, DCM (10 mL) is added and the organic layer washed with H₂O (3x5 mL). The organic layer is dried (MgSO₄), filtered, concentrated and purified on reverse phase HPLC (H₂O/MeCN gradient) to afford the title compound **J1** as a white solid: ¹H-NMR (400 MHz, CDCl₃) δ = 7.66 (m, 2H), 7.51 (d, J = 7.9 Hz, 1H), 7.34-7.19 (m, 6H), 7.09 (dd, J = 8.8 Hz, J = 2.5 Hz, 1H), 6.62 (d, J = 8.8 Hz, 1H), 6.04 (t, J = 5.6 Hz, NH), 3.86 (t, J = 4.9 Hz, 2H), 3.63 (q, J = 5.2 Hz, 2H), 3.51 (s, 2H). MS calculated for $C_{26}H_{20}Cl_3N_2O_5$ ($M+H^+$) 545.0, found 545.0.

Transcriptional Assay

[00191] 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 PPAR δ , PPAR α or PPAR γ 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.

[00192] 293T human embryonic kidney cells (8×10^6) are seeded in a 175cm^2 flask a day prior to the start of the experiment in 10% FBS, 1% Penicillin/Streptomycin/Fungizome, DMEM Media. The cells are harvested by washing with PBS (30ml) and then dissociating using trypsin (0.05%; 3ml). The trypsin is inactivated by the addition of assay media (DMEM, CA-dextran fetal bovine serum (5%). The cells are spun down and resuspended to 170,000 cells/ml. A Transfection mixture of GAL4-PPAR LBD expression plasmid ($1 \mu\text{g}$), UAS-luciferase reporter plasmid ($1 \mu\text{g}$), Fugene (3:1 ratio; $6 \mu\text{L}$) and serum-free media ($200 \mu\text{L}$) 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 ($50 \mu\text{l/well}$) are then plated into 384 white, solid-bottom, TC-treated plates. The cells are further incubated at 37°C , 5.0% CO_2 for 5-7 hours. A 12-point series of dilutions (3 fold serial dilutions) are prepared for each test compound in DMSO with a starting compound concentration of $10 \mu\text{M}$. Test compound (500nl) is added to each well of cells in the assay plate and the cells are incubated at 37°C , 5.0% CO_2 for 18-24 hours. The cell lysis/luciferase assay buffer, Bright-Glo™ (25%; $25 \mu\text{l}$; Promega), is added to each well. After a further incubation for 5 minutes at room temperature, the luciferase activity is measured.

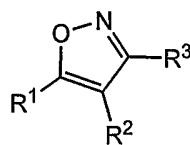
[00193] Raw luminescence values are normalized by dividing them by the value of the DMSO control present on each plate. Normalized data is analyzed and dose-response curves are fitted using Prism graph fitting program. EC50 is defined as the concentration at which the compound elicits a response that is half way between the maximum and minimum values. Relative efficacy (or percent efficacy) is calculated by comparison of the response elicited by the compound with the maximum value obtained for a reference PPAR modulator.

[00194] 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 PPAR δ of less than $1 \mu\text{M}$, more preferably less than 500nm , more preferably less than 100nM . Compounds of the invention are at least 100-fold selective for PPAR δ over PPAR γ .

[00195] It is understood that the examples and embodiments described herein are for illustrative purposes only and that various modifications or changes in light thereof will be suggested to persons skilled in the art and are to be included within the spirit and purview of this application and scope of the appended claims. All publications, patents, and patent applications cited herein are hereby incorporated by reference for all purposes.

WE CLAIM:

1. A compound of Formula I:



I

in which

R^1 is selected from C_{1-6} alkyl, C_{3-12} cycloalkyl, C_{3-8} heterocycloalkyl, C_{6-10} aryl and C_{5-10} heteroaryl; wherein any alkyl, aryl, heteroaryl, cycloalkyl and heterocycloalkyl of R^1 is optionally substituted with 1 to 3 radicals independently selected from halo, nitro, cyano, C_{1-6} alkyl, C_{1-6} alkoxy, halo-substituted- C_{1-6} alkyl, halo-substituted- C_{1-6} alkoxy, - $XC(O)YR^5$ and $-XYC(O)R^5$; wherein X is a bond or C_{1-4} alkylene and Y is selected from a bond, O, S, and NR^6 ; and R^5 is selected from C_{1-6} alkyl, C_{3-12} cycloalkyl, C_{3-8} heterocycloalkyl, C_{6-10} aryl and C_{5-10} heteroaryl; and R^6 is selected from hydrogen, C_{1-6} alkyl, C_{3-12} cycloalkyl, C_{3-8} heterocycloalkyl, C_{6-10} aryl and C_{5-10} heteroaryl;

R^2 is selected from $-XOXOR^5$, $-XOR^5$, $-C(O)OR^5$, $-C(O)NR^4R^4$, $-C(O)NR^4XOR^4$, $-C(O)OXOR^5$, $-C(O)XOR^5$, $-C(O)NR^4XOR^5$, $-C(O)NR^4R^5$ and $-C(O)NR^4XR^5$; wherein X is a bond or C_{1-4} alkylene; R^4 is selected from hydrogen and C_{1-6} alkyl; R^5 is selected from C_{1-6} alkyl, C_{3-12} cycloalkyl, C_{3-8} heterocycloalkyl, C_{6-10} aryl and C_{5-10} heteroaryl; or R^4 and R^5 together with the nitrogen atom to which R^4 and R^5 are attached form C_{3-8} heterocycloalkyl or C_{5-10} heteroaryl;

wherein any alkylene group of R^2 is optionally substituted by halo, C_{1-6} alkyl and phenyl; wherein any aryl, heteroaryl, cycloalkyl and heterocycloalkyl of R^2 is optionally substituted with 1 to 3 radicals independently selected from halo, nitro, cyano, C_{1-6} alkyl, C_{1-6} alkoxy, halo-substituted- C_{1-6} alkyl and halo-substituted- C_{1-6} alkoxy;

R^3 is selected from C_{3-12} cycloalkyl, C_{3-8} heterocycloalkyl, C_{6-10} aryl and C_{5-10} heteroaryl; wherein any aryl, heteroaryl, cycloalkyl and heterocycloalkyl of R^3 is optionally substituted with 1 to 3 radicals independently selected from halo, nitro, cyano, C_{1-6} alkyl, C_{1-6} alkoxy, halo-substituted- C_{1-6} alkyl, halo-substituted- C_{1-6} alkoxy, $-XOXC(O)OR^5$, $-XC(O)OR^5$ wherein X is independently selected from a bond and C_{1-4} alkylene; and R^5 is

selected from hydrogen and C₁₋₆alkyl; and the pharmaceutically acceptable salts, hydrates, solvates, isomers and prodrugs thereof.

2. The compound of claim 1 in which:

R¹ is selected from C₁₋₆alkyl, C₃₋₁₂cycloalkyl, C₅₋₁₀heteroaryl and C₆₋₁₀aryl; wherein any aryl or heteroaryl of R₁ is optionally substituted by 1 to 3 radicals independently selected from halo, nitro, C₁₋₆alkyl, C₁₋₆alkoxy, halo-substituted-C₁₋₆alkyl and -XC(O)OR⁵; wherein X is a bond or C₁₋₄alkylene; and R⁵ is selected from hydrogen and C₁₋₆alkyl;

R² is selected from -XOXOR⁵, -XOR⁵, -C(O)NR⁴XOR⁴, -C(O)NR⁴XOR⁵, -C(O)OXOR⁵, -C(O)XOR⁵, -C(O)NR⁴R⁴, -C(O)NR⁴R⁵ and -C(O)NR⁴XR⁵; wherein X is a bond or C₁₋₄alkylene; R⁴ is selected from hydrogen and C₁₋₆alkyl; R⁵ is C₃₋₁₂cycloalkyl, C₃₋₈heterocycloalkyl, C₆₋₁₀aryl and C₅₋₁₀heteroaryl; or R⁴ and R⁵ together with the nitrogen atom to which R⁴ and R⁵ are attached form C₃₋₈heterocycloalkyl or C₅₋₁₀heteroaryl; wherein any alkylene group of R² is optionally substituted by C₁₋₆alkyl and phenyl; wherein any aryl, heteroaryl, cycloalkyl and heterocycloalkyl of R² is optionally substituted with 1 to 3 radicals independently selected from halo, nitro, C₁₋₆alkyl, C₁₋₆alkoxy, halo-substituted-C₁₋₆alkyl and halo-substituted-C₁₋₆alkoxy; and

R³ is C₆₋₁₀aryl optionally substituted with 1 to 3 radicals independently selected from halo, C₁₋₆alkyl, C₁₋₆alkoxy, -OXC(O)OR⁵ and -XC(O)OR⁵ wherein X is a bond or C₁₋₄alkylene; and R⁵ is selected from hydrogen and C₁₋₆alkyl.

3. The compound of claim 1 in which:

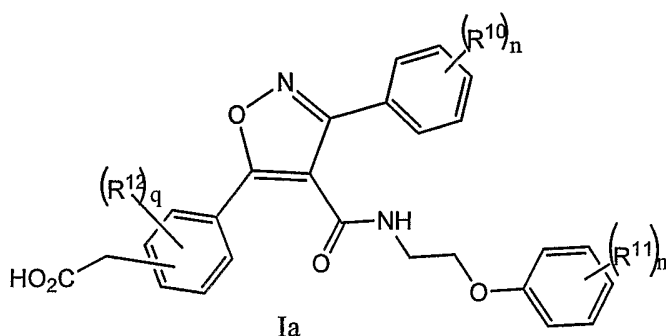
R¹ is selected from methyl, ethyl, t-butyl, propyl, cyclopropyl, isopropyl, pyridinyl, furanyl, thienyl and phenyl optionally substituted with 1 to 2 radicals independently selected from halo, methyl, nitro, methoxy, carboxymethyl and trifluoromethyl;

R² is selected from -C(O)NHR⁴, -C(O)NHR⁵, -C(O)N(CH₃)CH₂R⁵, -CH₂O(CH₂)₂OR⁵, -CH₂OR⁵, -C(O)NH(CH₂)₂OR⁵, -C(O)O(CH₂)₂OR⁵, -C(O)(CH₂)₃OR⁵, -C(O)NH(CH₂)₁₋₃R⁵, -C(O)NH(CH₂)₂OR⁴ and -C(O)N(CH₃)(CH₂)₂OR⁵; wherein R⁴ is selected from methyl and butyl; R⁵ is selected from phenyl, cyclopentyl, furanyl, pyridinyl and naphthyl; or R⁴ and R⁵ together with the nitrogen atom to which R⁴ and R⁵ are attached

form 3,4-dihydro-1H-isoquinolin-2-yl; wherein any alkylene group of R^2 is optionally substituted by a radical selected from methyl and phenyl; wherein any aryl, heteroaryl, cycloalkyl and heterocycloalkyl of R^2 is optionally substituted with 1 to 3 radicals independently selected from halo, nitro, methyl, trifluoromethyl, trifluoromethoxy and methoxy; and

R^3 is phenyl optionally substituted with 1 to 3 radicals independently selected from halo, methyl, methoxy, $-\text{OCH}_2\text{C}(\text{O})\text{OH}$, $-(\text{CH}_2)_2\text{C}(\text{O})\text{OH}$ and $-\text{CH}_2\text{C}(\text{O})\text{OH}$.

4. The compound of claim 1 of Formula Ia:



in which: q, m and n are independently selected from 0, 1 and 2; and R^{10} , R^{11} and R^{12} are each independently selected from halo, C_{1-6} alkyl, nitro, C_{1-6} alkoxy and halo-substituted- C_{1-6} alkyl.

5. The compound of claim 4 selected from: (5-{4-[2-(2,4-Dichloro-phenoxy)-ethyl-carbamoyl]-5-phenyl-isoxazol-3-yl}-phenyl)-acetic acid; (3-Chloro-4-{4-[2-(2,4-dichloro-phenoxy)-ethylcarbamoyl]-5-phenyl-isoxazol-3-yl}-phenyl)-acetic acid; (3-Chloro-4-{4-[2-(2,4-dichloro-phenoxy)-ethylcarbamoyl]-5-p-tolyl-isoxazol-3-yl}-phenyl)-acetic acid; {3-Chloro-4-[4-[2-(2,4-dichloro-phenoxy)-ethylcarbamoyl]-5-(4-fluoro-phenyl)-isoxazol-3-yl]-phenyl}-acetic acid; {3-Chloro-4-[4-[2-(2,4-dichloro-phenoxy)-ethylcarbamoyl]-5-(4-nitro-phenyl)-isoxazol-3-yl]-phenyl}-acetic acid; (3-Chloro-4-{5-(2-chloro-phenyl)-4-[2-(2,4-dichloro-phenoxy)-ethylcarbamoyl]-isoxazol-3-yl}-phenyl)-acetic acid; (3-Chloro-4-{5-(4-chloro-phenyl)-4-[2-(2,4-dichloro-phenoxy)-ethylcarbamoyl]-isoxazol-3-yl}-phenyl)-acetic acid; {3-Chloro-4-[4-[2-(2,4-dichloro-phenoxy)-

ethylcarbamoyl]-5-(2-methoxy-phenyl)-isoxazol-3-yl]-phenyl}-acetic acid; {3-Chloro-4-[4-[2-(2,4-dichloro-phenoxy)-ethylcarbamoyl]-5-(3-methoxy-phenyl)-isoxazol-3-yl]-phenyl}-acetic acid; {3-Chloro-4-[4-[2-(2,4-dichloro-phenoxy)-ethylcarbamoyl]-5-(4-methoxy-phenyl)-isoxazol-3-yl]-phenyl}-acetic acid; {3-Chloro-4-[4-[2-(2,4-dichloro-phenoxy)-ethylcarbamoyl]-5-(2-trifluoromethyl-phenyl)-isoxazol-3-yl]-phenyl}-acetic acid; {3-Chloro-4-[4-[2-(2,4-dichloro-phenoxy)-ethylcarbamoyl]-5-(3-trifluoromethyl-phenyl)-isoxazol-3-yl]-phenyl}-acetic acid; {3-Chloro-4-[4-[2-(2,4-dichloro-phenoxy)-ethylcarbamoyl]-5-(4-trifluoromethyl-phenyl)-isoxazol-3-yl]-phenyl}-acetic acid; (3-{4-[2-(2,4-Dichloro-phenoxy)-ethylcarbamoyl]-5-p-tolyl-isoxazol-3-yl}-phenyl)-acetic acid; {3-[4-[2-(2,4-Dichloro-phenoxy)-ethylcarbamoyl]-5-(4-fluoro-phenyl)-isoxazol-3-yl]-phenyl}-acetic acid; {3-[4-[2-(2,4-Dichloro-phenoxy)-ethylcarbamoyl]-5-(4-nitro-phenyl)-isoxazol-3-yl]-phenyl}-acetic acid; (3-{5-(2-Chloro-phenyl)-4-[2-(2,4-dichloro-phenoxy)-ethylcarbamoyl]-isoxazol-3-yl}-phenyl)-acetic acid; (3-{5-(3-Chloro-phenyl)-4-[2-(2,4-dichloro-phenoxy)-ethylcarbamoyl]-isoxazol-3-yl}-phenyl)-acetic acid; (3-{5-(4-Chloro-phenyl)-4-[2-(2,4-dichloro-phenoxy)-ethylcarbamoyl]-isoxazol-3-yl}-phenyl)-acetic acid; {3-[4-[2-(2,4-Dichloro-phenoxy)-ethylcarbamoyl]-5-(2-methoxy-phenyl)-isoxazol-3-yl]-phenyl}-acetic acid; {3-[4-[2-(2,4-Dichloro-phenoxy)-ethylcarbamoyl]-5-(3-methoxy-phenyl)-isoxazol-3-yl]-phenyl}-acetic acid; {3-[4-[2-(2,4-Dichloro-phenoxy)-ethylcarbamoyl]-5-(4-methoxy-phenyl)-isoxazol-3-yl]-phenyl}-acetic acid; {3-[4-[2-(2,4-Dichloro-phenoxy)-ethylcarbamoyl]-5-(2-trifluoromethyl-phenyl)-isoxazol-3-yl]-phenyl}-acetic acid; {3-[4-[2-(2,4-Dichloro-phenoxy)-ethylcarbamoyl]-5-(3-trifluoromethyl-phenyl)-isoxazol-3-yl]-phenyl}-acetic acid; {3-[4-[2-(2,4-Dichloro-phenoxy)-ethylcarbamoyl]-5-(4-trifluoromethyl-phenyl)-isoxazol-3-yl]-phenyl}-acetic acid; (3-{4-[2-(2,4-Dichloro-phenoxy)-ethylcarbamoyl]-5-o-tolyl-isoxazol-3-yl}-phenyl)-acetic acid; and (3-{4-[2-(2,4-Dichloro-phenoxy)-ethylcarbamoyl]-5-m-tolyl-isoxazol-3-yl}-phenyl)-acetic acid.

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

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

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

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

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

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

a) anti-diabetic agents such as insulin, insulin derivatives and mimetics; insulin secretagogues such as the sulfonylureas, e.g., Glipizide, glyburide and Amaryl; insulinotropic sulfonylurea receptor ligands such as meglitinides, e.g., nateglinide and repaglinide; insulin sensitizer such as protein tyrosine phosphatase-1B (PTP-1B) inhibitors such as PTP-112; GSK3 (glycogen synthase kinase-3) inhibitors such as SB-517955, SB-4195052, SB-216763, NN-57-05441 and NN-57-05445; RXR ligands such as GW-0791 and AGN-194204; sodium-dependent glucose co-transporter inhibitors such as T-1095; glycogen

phosphorylase A inhibitors such as BAY R3401; biguanides such as metformin; alpha-glucosidase inhibitors such as acarbose; GLP-1 (glucagon like peptide-1), GLP-1 analogs such as Exendin-4 and GLP-1 mimetics; dipeptidyl peptidase IV inhibitors such as DPP728, vildagliptin, MK-0431, saxagliptin, GSK23A ; an AGE breaker; a thiazolidone derivative (glitazone) such as pioglitazone, rosiglitazone, or (*R*)-1-{4-[5-methyl-2-(4-trifluoromethyl-phenyl)-oxazol-4-ylmethoxy]-benzenesulfonyl}-2,3-dihydro-1*H*-indole-2-carboxylic acid, a non-glitazone type PPAR γ agonist e.g. GI-262570;

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

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

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

- e) a HDL increasing compound;
- f) a cholesterol absorption modulator such as Zetia® and KT6-971;
- g) Apo-A1 analogues and mimetics;
- h) thrombin inhibitors such as Ximelagatran;
- i) aldosterone inhibitors such as anastrozole, fadrazole, eplerenone;
- j) Inhibitors of platelet aggregation such as aspirin, clopidogrel bisulfate;
- k) estrogen, testosterone, a selective estrogen receptor modulator, a selective androgen receptor modulator;
- l) a chemotherapeutic agent such as aromatase inhibitors e.g. femara, anti-estrogens, topoisomerase I inhibitors, topoisomerase II inhibitors, microtubule active agents, alkylating agents, antineoplastic antimetabolites, platin compounds, compounds decreasing the protein kinase activity such as a PDGF receptor tyrosine kinase inhibitor preferably Imatinib or 4-Methyl-N-[3-(4-methyl-imidazol-1-yl)-5-trifluoromethyl-phenyl]-3-(4-pyridin-3-yl-pyrimidin-2-ylamino)-benzamide; and
- m) an agent interacting with a 5-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.

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

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

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

INTERNATIONAL SEARCH REPORT

I
PCT/US05/16672

A. CLASSIFICATION OF SUBJECT MATTER
 IPC(7) : C07D 261/14
 US CL : 548/248
 According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
 U.S. : 548/248

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

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
 Please See Continuation Sheet

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 3,562,286 (HOYLE et al) 9 February 1971 (09.02.1971), column 1, lines 30-45.	5

Further documents are listed in the continuation of Box C. See patent family annex.

* Special categories of cited documents:		
"A" document defining the general state of the art which is not considered to be of particular relevance	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"E" earlier application or patent published on or after the international filing date	"X"	document of particular relevance, the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"O" document referring to an oral disclosure, use, exhibition or other means		
"P" document published prior to the international filing date but later than the priority date claimed	"&"	document member of the same patent family

Date of the actual completion of the international search
 13 October 2005 (13.10.2005)

Date of mailing of the international search report
07 NOV 2005

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INTERNATIONAL SEARCH REPORT

PCT/US05/16672

Box No. 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. Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. Claims Nos.: 1-4 and 6-14
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:
Please See Continuation Sheet

3. Claims Nos.: 9-14
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. 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. As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of any additional fees.
3. 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. 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**
- The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
- The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application
PCT/US05/16872

Continuation of Box II Reason 2:

The numerous variables, e.g. (R1, R2, R3, R4, R5, R6, X, Y, R10, R12, R11, m, n, q, etc.) and their voluminous, complex meanings and their virtual incomprehensible permutations and combinations make it impossible to determine the full scope and complete meaning of the claimed subject matter. As presented the claimed subject matter cannot be regarded as being a clear and concise description for which protection is sought and as such the listed claims do not comply with the requirements of PCT Article 6. Thus it is impossible to carry out a meaningful search on same. A search will be carried out on the first discernable invention which is claim 5.

Continuation of B. FIELDS SEARCHED Item 3:

CAS ONLINE
STN structure search