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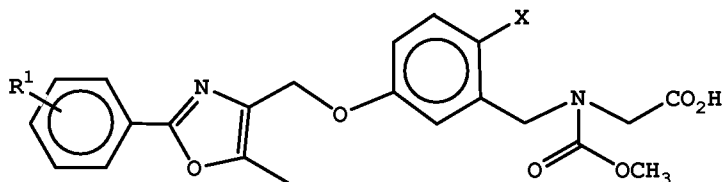
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(54) Title: SUBSTITUTED ACID DERIVATIVES USEFUL AS ANTI-ATHEROSCLEROTIC, ANTI-DYSLIPIDEMIC, ANTI-DIABETIC AND ANTI-OBESITY AGENTS AND METHOD



(I)

(57) Abstract: Compounds are provided which have the structure of Formula (I): wherein R₁ is halogen; and X is hydrogen or halogen, and salts thereof, which compounds are useful as anti-atherosclerotic, anti-dyslipidemic, anti-diabetic, and anti-obesity agents.

WO 2008/006043 A2

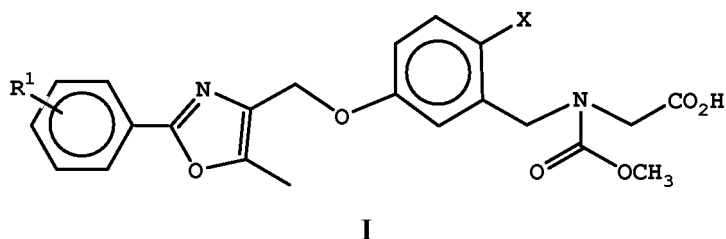
**SUBSTITUTED ACID DERIVATIVES USEFUL AS ANTI-
ATHEROSCLEROTIC, ANTI-DYSLIPIDEMIC, ANTI-DIABETIC AND
ANTI-OBESITY AGENTS AND METHOD**

5 **FIELD OF THE INVENTION**

[0001] The present invention relates to novel substituted acid derivatives which modulate triglyceride levels, lipid levels, blood glucose levels, insulin levels, and non-esterified fatty acid (NEFA) levels, and thus are particularly useful in the treatment of atherosclerosis, dyslipidemia, diabetes, and obesity, and to a method for
10 treating atherosclerosis, dyslipidemia, diabetes, especially Type 2 diabetes, as well as hyperglycemia, hyperinsulinemia, obesity, and related diseases employing such substituted acid derivatives alone or in combination with another anti-diabetic agent and/or an anti-dyslipidemic agent.

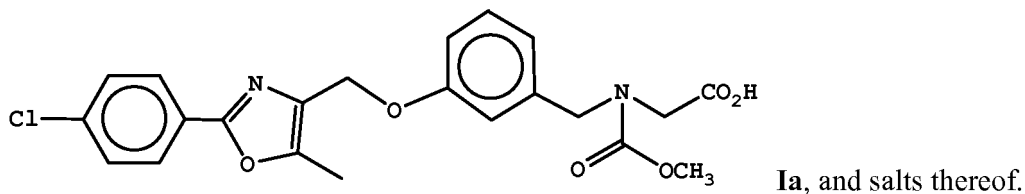
15 **DESCRIPTION OF THE INVENTION**

[0002] In accordance with the present invention, substituted acid derivatives are provided which have the structure of Formula (I):



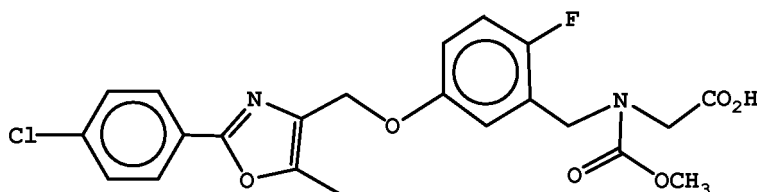
20 wherein R¹ is halogen; and X is hydrogen or halogen, and salts thereof.

[0003] A preferred compound of the present invention has the structure of Formula (Ia):



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[0004] Another preferred compound of the instant invention has the structure of Formula (Ib):



Ib, and salts thereof.

5 [0005] In addition, in accordance with the present invention, a method is provided for treating atherosclerosis, diabetes, especially Type 2 diabetes, and related diseases such as insulin resistance, hyperglycemia, hyperinsulinemia, elevated blood levels of fatty acids or glycerol, dyslipidemia, obesity, hypertriglyceridemia, inflammation, Syndrome X, diabetic complications, dysmetabolic syndrome, and related diseases
10 wherein a therapeutically effective amount of a compound of Formula I is administered to a human patient in need of treatment.

[0006] For ease of reference, when Formula I is mentioned in the description of the invention, it is intended that Formulae Ia and Ib are also included in the scope thereof.

15 [0007] In addition, in accordance with the present invention, a method is provided for treating early malignant lesions (such as ductal carcinoma *in situ* of the breast and lobular carcinoma *in situ* of the breast), premalignant lesions (such as fibroadenoma of the breast and prostatic intraepithelial neoplasia (PIN), liposarcomas and various other epithelial tumors (including breast, prostate, colon, ovarian, gastric and lung),
20 irritable bowel syndrome, Crohn's disease, gastric ulceritis, and osteoporosis and proliferative diseases such as psoriasis, wherein a therapeutically effective amount of a compound of Formula I is administered to a human patient in need of treatment.

[0008] Furthermore, in accordance with the present invention, a method is provided for treating diabetes and related diseases as defined above and hereinafter,
25 wherein a therapeutically effective amount of a combination of a compound of Formula I and another type of anti-diabetic agent and/or a anti-dyslipidemic agent, and/or lipid modulating agent and/or other type of therapeutic agent, is administered to a human patient in need of treatment.

[0009] In the above methods of the invention, the compound of Formula I will be employed in a weight ratio to the antidiabetic agent (depending upon its mode of operation) within the range from about 0.01:1 to about 100:1, preferably from about 0.5:1 to about 10:1.

5 [0010] The conditions, diseases, and maladies collectively referenced to as “Syndrome X” or Dysmetabolic Syndrome are detailed in Johannsson, *J. Clin. Endocrinol. Metab.*, 82:727-734 (1997) and other publications.

[0011] The term “diabetes and related diseases” refers to Type II diabetes, Type I diabetes, impaired glucose tolerance, obesity, hyperglycemia, Syndrome X,
10 dysmetabolic syndrome, diabetic complications and hyperinsulinemia.

[0012] The conditions, diseases and maladies collectively referred to as “diabetic complications” include retinopathy, neuropathy and nephropathy, and other known complications of diabetes.

[0013] The term “other type(s) of therapeutic agents” as employed herein refers to
15 one or more antidiabetic agents (other than compounds of Formula I), one or more anti-obesity agents, and/or one or more lipid-lowering agents, one or more lipid modulating agents (including anti-atherosclerosis agents), and/or one or more antiplatelet agents, one or more agents for treating hypertension, one or more anti-cancer drugs, one or more agents for treating arthritis, one or more anti-osteoporosis
20 agents, one or more anti-obesity agents, one or more agents for treating immunomodulatory diseases, and/or one or more agents for treating anorexia nervosa.

[0014] The term “lipid-modulating” agent as employed herein refers to agents which lower LDL and/or raise HDL and/or lower triglycerides and/or lower total cholesterol and/or other known mechanisms for therapeutically treating lipid
25 disorders.

[0015] Unless otherwise indicated, the term “lower alkyl”, “alkyl” or “alk” as employed herein alone or as part of another group includes both straight and branched chain hydrocarbons, containing 1 to 20 carbons, preferably 1 to 10 carbons, more preferably 1 to 8 carbons, in the normal chain, and may optionally include an oxygen
30 or nitrogen in the normal chain, such as methyl, ethyl, propyl, isopropyl, butyl, t-butyl, isobutyl, pentyl, hexyl, isohexyl, heptyl, 4,4-dimethylpentyl, octyl, 2,2,4-trimethylpentyl, nonyl, decyl, undecyl, dodecyl, the various branched chain isomers

thereof, and the like as well as such groups including 1 to 4 substituents such as halo, for example F, Br, Cl or I or CF₃, alkoxy, aryl, aryloxy, aryl(aryl) or diaryl, arylalkyl, arylalkyloxy, alkenyl, cycloalkyl, cycloalkylalkyl, cycloalkylalkyloxy, amino, hydroxy, hydroxyalkyl, acyl, heteroaryl, heteroaryloxy, cycloheteroalkyl, arylheteroaryl, arylalkoxycarbonyl, heteroarylalkyl, heteroarylalkoxy, aryloxyalkyl, aryloxyaryl, alkylamido, alkanoylamino, arylcarbonylamino, nitro, cyano, thiol, haloalkyl, trihaloalkyl and/or alkylthio and/or any of the R³ groups.

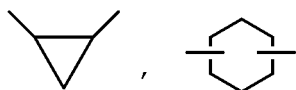
[0016] Unless otherwise indicated, the term “cycloalkyl” as employed herein alone or as part of another group includes saturated or partially unsaturated (containing 1 or 2 double bonds) cyclic hydrocarbon groups containing 1 to 3 rings, including monocyclicalkyl, bicyclicalkyl and tricyclicalkyl, containing a total of 3 to 20 carbons forming the rings, preferably 3 to 10 carbons, forming the ring and which may be fused to 1 or 2 aromatic rings as described for aryl, which include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, cyclodecyl and cyclododecyl, cyclohexenyl,



any of which groups may be optionally substituted with 1 to 4 substituents such as halogen, alkyl, alkoxy, hydroxy, aryl, aryloxy, arylalkyl, cycloalkyl, alkylamido, alkanoylamino, oxo, acyl, arylcarbonylamino, amino, nitro, cyano, thiol and/or alkylthio and/or any of the substituents for alkyl.

[0017] The term “cycloalkenyl” as employed herein alone or as part of another group refers to cyclic hydrocarbons containing 3 to 12 carbons, preferably 5 to 10 carbons and 1 or 2 double bonds. Exemplary cycloalkenyl groups include cyclopentenyl, cyclohexenyl, cycloheptenyl, cyclooctenyl, cyclohexadienyl, and cycloheptadienyl, which may be optionally substituted as defined for cycloalkyl.

[0018] The term “cycloalkylene” as employed herein refers to a “cycloalkyl” group which includes free bonds and thus is a linking group such as



and the like, and may optionally be substituted as defined

above for “cycloalkyl”.

[0019] The term “alkanoyl” as used herein alone or as part of another group refers to alkyl linked to a carbonyl group.

- 5 **[0020]** Unless otherwise indicated, the term “lower alkenyl” or “alkenyl” as used herein by itself or as part of another group refers to straight or branched chain radicals of 2 to 20 carbons, preferably 2 to 12 carbons, and more preferably 1 to 8 carbons in the normal chain, which include one to six double bonds in the normal chain, and may optionally include an oxygen or nitrogen in the normal chain, such as vinyl, 2-
10 propenyl, 3-butenyl, 2-butenyl, 4-pentenyl, 3-pentenyl, 2-hexenyl, 3-hexenyl, 2-heptenyl, 3-heptenyl, 4-heptenyl, 3-octenyl, 3-nonenyl, 4-decenyl, 3-undecenyl, 4-dodecenyl, 4,8,12-tetradecatrienyl, and the like, and which may be optionally substituted with 1 to 4 substituents, namely, halogen, haloalkyl, alkyl, alkoxy, alkenyl, alkynyl, aryl, arylalkyl, cycloalkyl, amino, hydroxy, heteroaryl, cycloheteroalkyl,
15 alkanoylamino, alkylamido, arylcarbonylamino, nitro, cyano, thiol, alkylthio and/or any of the substituents for alkyl set out herein.

- [0021]** Unless otherwise indicated, the term “lower alkynyl” or “alkynyl” as used herein by itself or as part of another group refers to straight or branched chain radicals of 2 to 20 carbons, preferably 2 to 12 carbons and more preferably 2 to 8 carbons in
20 the normal chain, which include one triple bond in the normal chain, and may optionally include an oxygen or nitrogen in the normal chain, such as 2-propynyl, 3-butynyl, 2-butynyl, 4-pentynyl, 3-pentynyl, 2-hexynyl, 3-hexynyl, 2-heptynyl, 3-heptynyl, 4-heptynyl, 3-octynyl, 3-nonynyl, 4-decynyl, 3-undecynyl, 4-dodecynyl and the like, and which may be optionally substituted with 1 to 4 substituents, namely,
25 halogen, haloalkyl, alkyl, alkoxy, alkenyl, alkynyl, aryl, arylalkyl, cycloalkyl, amino, heteroaryl, cycloheteroalkyl, hydroxy, alkanoylamino, alkylamido, arylcarbonylamino, nitro, cyano, thiol, and/or alkylthio, and/or any of the substituents for alkyl set out herein.

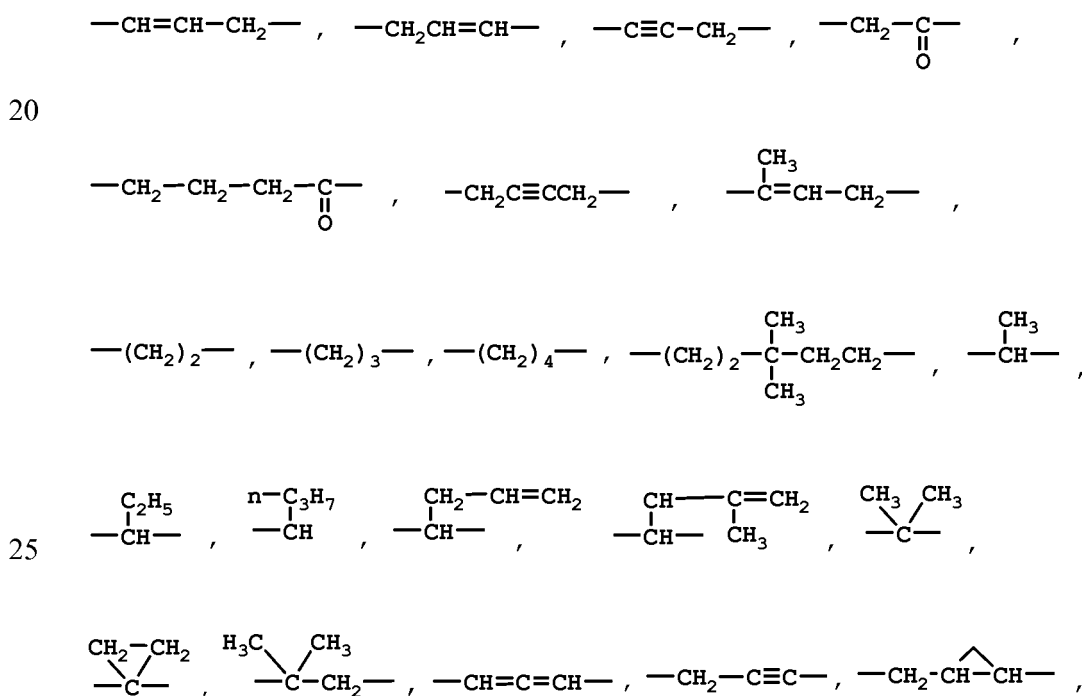
- [0022]** The terms “arylalkenyl” and “arylalkynyl” as used alone or as part of
30 another group refer to alkenyl and alkynyl groups as described above having an aryl substituent.

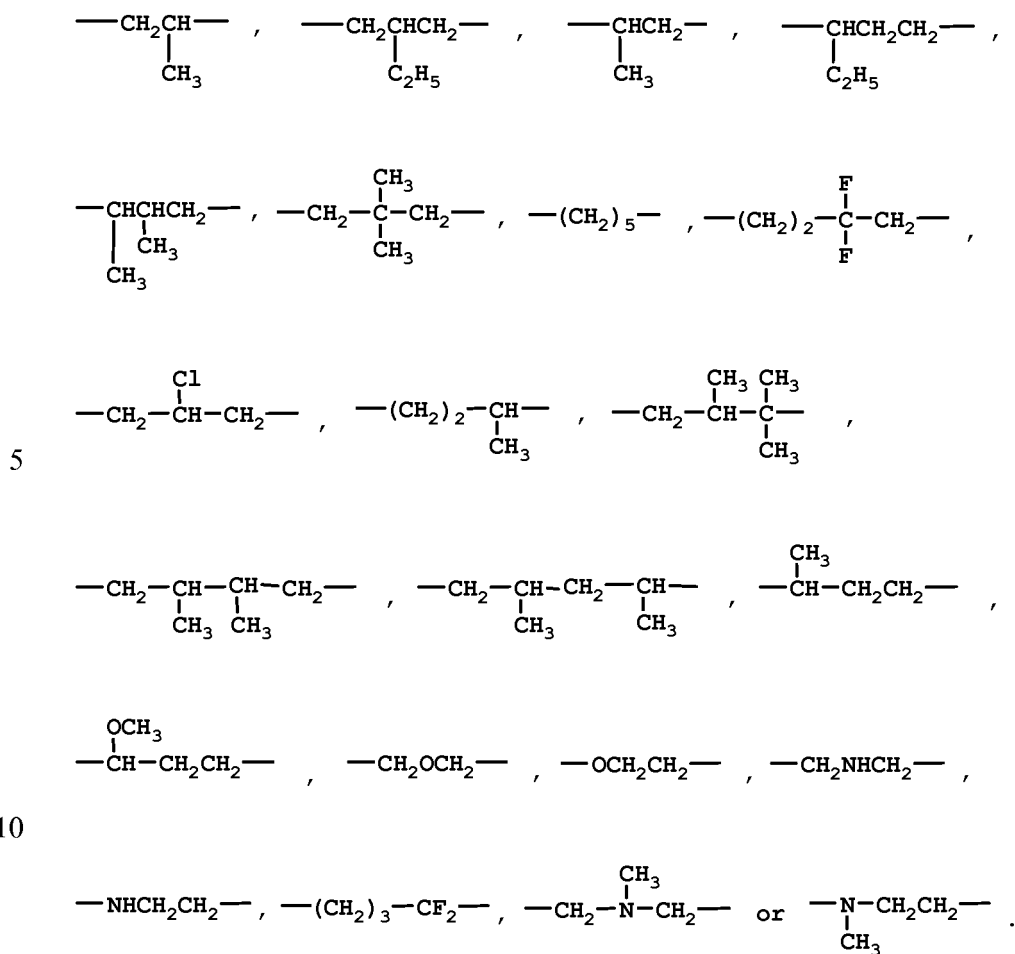
[0023] Where alkyl groups as defined above have single bonds for attachment to other groups at two different carbon atoms, they are termed “alkylene” groups and may optionally be substituted as defined above for “alkyl”.

[0024] Where alkenyl groups as defined above and alkynyl groups as defined above, respectively, have single bonds for attachment at two different carbon atoms, they are termed “alkenylene groups” and “alkynylene groups”, respectively, and may optionally be substituted as defined above for “alkenyl” and “alkynyl”.

[0025] $(\text{CH}_2)_x$, $(\text{CH}_2)_m$, $(\text{CH}_2)_n$ or $(\text{CH}_2)_y$ includes alkylene, allenyl, alkenylene or alkynylene groups, as defined herein, each of which may optionally include an oxygen or nitrogen in the normal chain, which may optionally include 1, 2, or 3 substituents which include alkyl, alkenyl, halogen, cyano, hydroxy, alkoxy, amino, thioalkyl, keto, C_3 - C_6 cycloalkyl, alkylcarbonylamino or alkylcarbonyloxy; the alkyl substituent may be an alkylene moiety of 1 to 4 carbons which may be attached to one or two carbons in the $(\text{CH}_2)_x$ or $(\text{CH}_2)_m$ or $(\text{CH}_2)_n$ group to form a cycloalkyl group therewith.

[0026] Examples of $(\text{CH}_2)_x$, $(\text{CH}_2)_m$, $(\text{CH}_2)_n$, $(\text{CH}_2)_y$, alkylene, alkenylene and alkynylene include

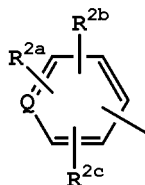




[0027] The term “halogen” or “halo” as used herein alone or as part of another group refers to chlorine, bromine, fluorine, and iodine as well as CF₃, with chlorine or fluorine being preferred.

[0028] The term “metal ion” refers to alkali metal ions such as sodium, potassium or lithium and alkaline earth metal ions such as magnesium and calcium, as well as zinc and aluminum.

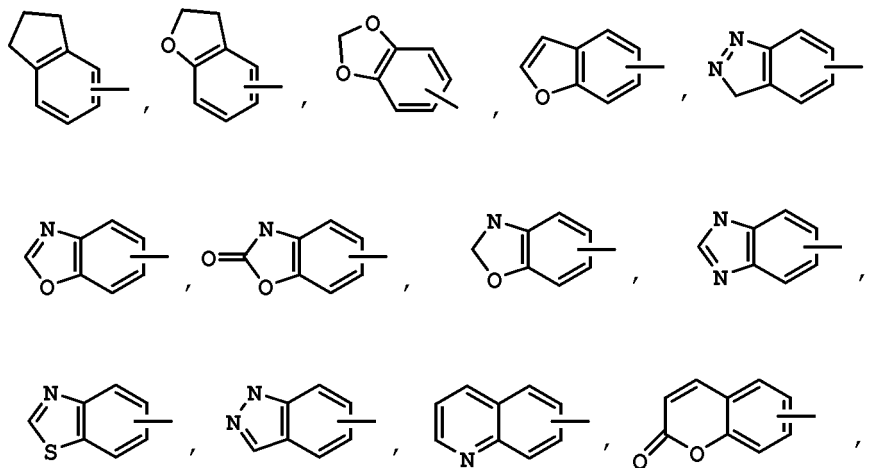
[0029] Unless otherwise indicated, the term “aryl” or the group



20 where Q is C, as employed herein alone or as part of another group refers to monocyclic and bicyclic aromatic groups containing 6 to 10 carbons in the ring

portion (such as phenyl or naphthyl including 1-naphthyl and 2-naphthyl) and may optionally include one to three additional rings fused to a carbocyclic ring or a heterocyclic ring (such as aryl, cycloalkyl, heteroaryl or cycloheteroalkyl rings for example

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and may be optionally substituted through available carbon atoms with 1, 2, or 3 groups selected from hydrogen, halo, haloalkyl, alkyl, haloalkyl, alkoxy, haloalkoxy, alkenyl, trifluoromethyl, trifluoromethoxy, alkynyl, cycloalkyl-alkyl, cycloheteroalkyl, cycloheteroalkylalkyl, aryl, heteroaryl, arylalkyl, aryloxy, arylalkoxy, arylalkoxy, alkoxy, carbonyl, arylalkenyl, aminocarbonyl, arylthio, arylsulfinyl, arylazo, heteroarylalkyl, heteroarylalkenyl, heteroarylheteroaryl, heteroaryloxy, hydroxy, nitro, cyano, amino, substituted amino wherein the amino includes 1 or 2 substituents (which are alkyl, aryl or any of the other aryl compounds mentioned in the definitions), thiol, alkylthio, arylthio, heteroarylthio, arylthioalkyl, alkoxyarylthio, alkylcarbonyl, arylcarbonyl, alkylaminocarbonyl, arylaminocarbonyl, alkoxy, carbonyl, aminocarbonyl, alkylcarbonyloxy, arylcarbonyloxy, alkylcarbonylamino, arylcarbonylamino, arylsulfinyl, arylsulfinylalkyl, arylsulfonylamino or arylsulfonaminocarbonyl and/or any of the substituents for alkyl set out herein.

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[0030] Unless otherwise indicated, the term “lower alkoxy”, “alkoxy”, “aryloxy” or “aralkoxy” as employed herein alone or as part of another group includes any of the above alkyl, aralkyl or aryl groups linked to an oxygen atom.

[0031] Unless otherwise indicated, the term “substituted amino” as employed herein alone or as part of another group refers to amino substituted with one or two substituents, which may be the same or different, such as alkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, cycloheteroalkyl, cycloheteroalkylalkyl, cycloalkyl, cycloalkylalkyl, haloalkyl, hydroxyalkyl, alkoxyalkyl or thioalkyl. These substituents may be further substituted with a carboxylic acid and/or any of the substituents for alkyl as set out above. In addition, the amino substituents may be taken together with the nitrogen atom to which they are attached to form 1-pyrrolidinyl, 1-piperidinyl, 1-azepinyl, 4-morpholinyl, 4-thiamorpholinyl, 1-piperazinyl, 4-alkyl-1-piperazinyl, 4-arylalkyl-1-piperazinyl, 4-diarylalkyl-1-piperazinyl, 1-pyrrolidinyl, 1-piperidinyl, or 1-azepinyl, optionally substituted with alkyl, alkoxy, alkylthio, halo, trifluoromethyl or hydroxy.

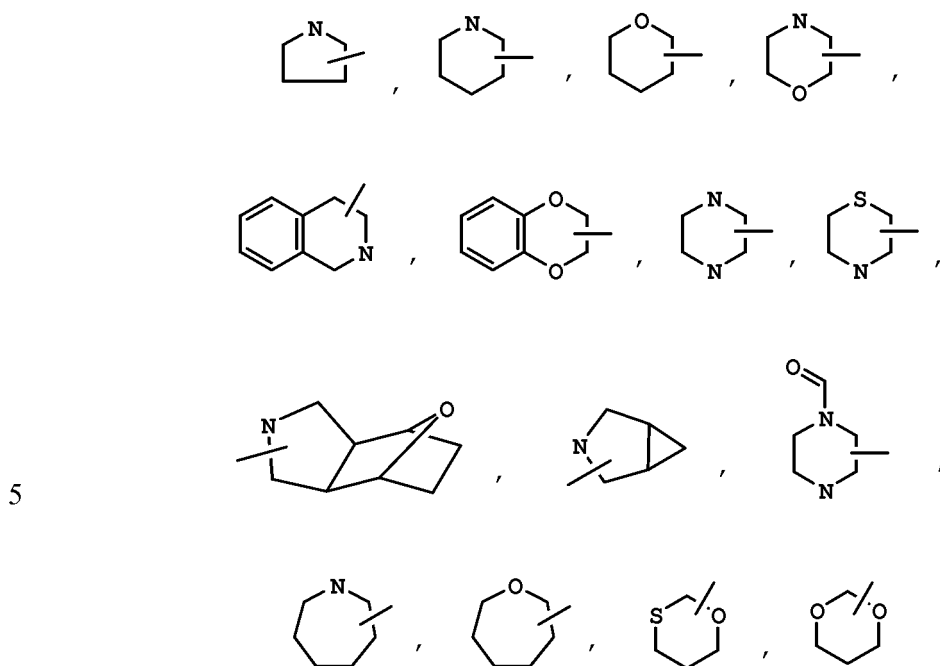
[0032] Unless otherwise indicated, the term “lower alkylthio”, “alkylthio”, “arylthio” or “aralkylthio” as employed herein alone or as part of another group includes any of the above alkyl, aralkyl or aryl groups linked to a sulfur atom.

[0033] Unless otherwise indicated, the term “lower alkylamino”, “alkylamino”, “arylamino”, or “arylalkylamino” as employed herein alone or as part of another group includes any of the above alkyl, aryl or arylalkyl groups linked to a nitrogen atom.

[0034] Unless otherwise indicated, the term “acyl” as employed herein by itself or part of another group, as defined herein, refers to an organic radical linked to a carbonyl $\left(\begin{array}{c} \text{O} \\ \parallel \\ \text{C} \end{array} \right)$ group; examples of acyl groups include any of the R³ groups attached to a carbonyl, such as alkanoyl, alkenoyl, aroyl, aralkanoyl, heteroaroyl, cycloalkanoyl, cycloheteroalkanoyl and the like.

[0035] Unless otherwise indicated, the term “cycloheteroalkyl” as used herein alone or as part of another group refers to a 5-, 6- or 7-membered saturated or partially unsaturated ring which includes 1 to 2 hetero atoms such as nitrogen, oxygen and/or sulfur, linked through a carbon atom or a heteroatom, where possible, optionally via the linker (CH₂)_p (where p is 1, 2 or 3), such as

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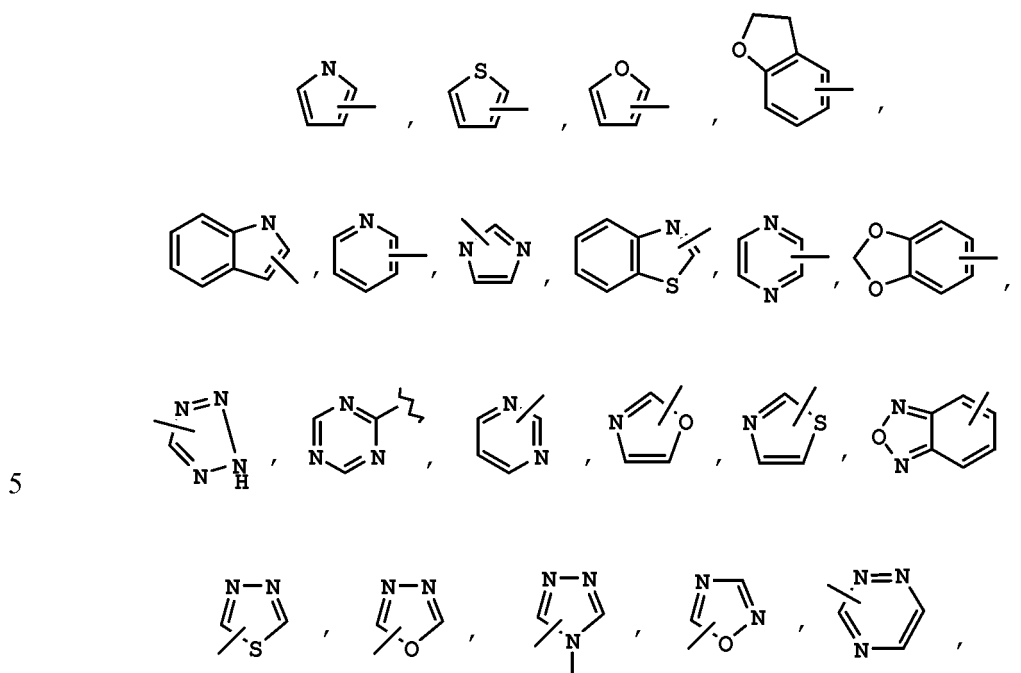


and the like. The above groups may include 1 to 4 substituents such as alkyl, halo,
 10 oxo and/or any of the substituents for alkyl or aryl set out herein. In addition, any of
 the cycloheteroalkyl rings can be fused to a cycloalkyl, aryl, heteroaryl or
 cycloheteroalkyl ring.

[0036] Unless otherwise indicated, the term “heteroaryl” as used herein alone or
 as part of another group refers to a 5- or 6- membered aromatic ring including



where Q is N, which includes 1, 2, 3 or 4 hetero atoms such as nitrogen, oxygen or
 sulfur, and such rings fused to an aryl, cycloalkyl, heteroaryl or cycloheteroalkyl ring
 (e.g. benzothiophenyl, indolyl), and includes possible N-oxides. The heteroaryl
 group may optionally include 1 to 4 substituents such as any of the substituents for
 20 alkyl or aryl set out above. Examples of heteroaryl groups include the following:



and the like.

10 **[0037]** The term “cycloheteroalkylalkyl” as used herein alone or as part of another group refers to cycloheteroalkyl groups as defined above linked through a C atom or heteroatom to a $(\text{CH}_2)_p$ chain.

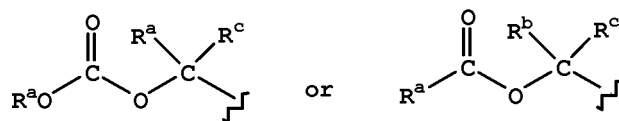
[0038] The term “heteroarylalkyl” or “heteroarylalkenyl” as used herein alone or as part of another group refers to a heteroaryl group as defined above linked through a
15 C atom or heteroatom to a $-(\text{CH}_2)_p-$ chain, alkylene or alkenylene as defined above.

[0039] The term “polyhaloalkyl” as used herein refers to an “alkyl” group as defined above which includes from 2 to 9, preferably from 2 to 5, halo substituents, such as F or Cl, preferably F, such as CF_3CH_2 , CF_3 or $\text{CF}_3\text{CF}_2\text{CH}_2$.

[0040] The term “polyhaloalkyloxy” as used herein refers to an “alkoxy” or
20 “alkyloxy” group as defined above which includes from 2 to 9, preferably from 2 to 5, halo substituents, such as F or Cl, preferably F, such as $\text{CF}_3\text{CH}_2\text{O}$, CF_3O or $\text{CF}_3\text{CF}_2\text{CH}_2\text{O}$.

[0041] The term “prodrug esters” as employed herein includes prodrug esters which are known in the art for carboxylic and phosphorus acid esters such as methyl,
25 ethyl, benzyl and the like. Other prodrug ester examples of R^4 include the following groups:

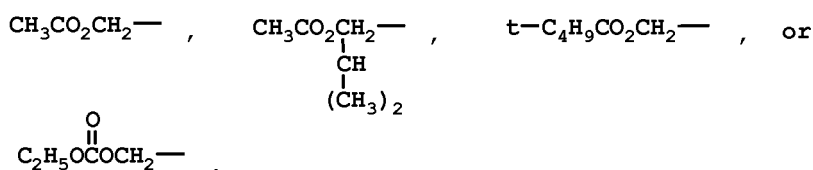
(1-alkanoyloxy)alkyl such as,



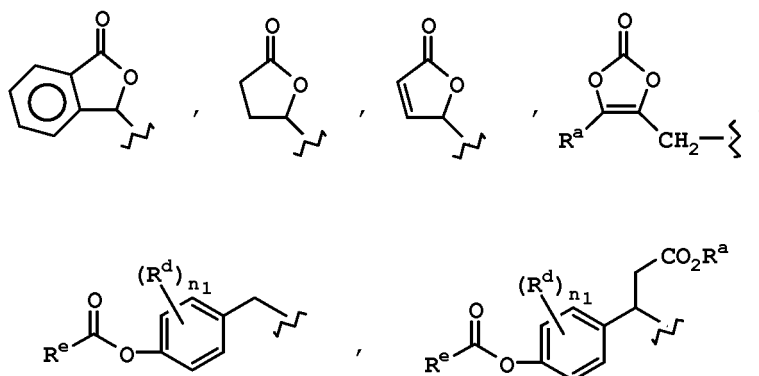
wherein R^a, R^b and R^c are H, alkyl, aryl or arylalkyl; however, R^aO cannot be HO.

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[0042] Examples of such prodrug esters R⁴ include



10 [0043] Other examples of suitable prodrug esters R⁴ include



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wherein R^a can be H, alkyl (such as methyl or t-butyl), arylalkyl (such as benzyl) or aryl (such as phenyl); R^d is H, alkyl, halogen or alkoxy, R^c is alkyl, aryl, arylalkyl or alkoxy, and n₁ is 0, 1 or 2.

[0044] Where the compounds of Formula I are in acid form they may form a
 20 pharmaceutically acceptable salt such as alkali metal salts such as lithium, sodium or potassium, alkaline earth metal salts such as calcium or magnesium as well as zinc or aluminum and other cations such as ammonium, choline, diethanolamine, lysine (D or

L), ethylenediamine, t-butylamine, t-octylamine, tris- (hydroxymethyl)aminomethane (TRIS), N-methyl glucosamine (NMG), triethanolamine and dehydroabietylamine.

[0045] The invention may be embodied in other specific forms without departing from the spirit or essential attributes thereof. This invention also encompasses all combinations of alternative aspects of the invention noted herein. It is understood that any and all embodiments of the present invention may be taken in conjunction with any other embodiment to describe additional embodiments of the present invention. Furthermore, any elements of an embodiment may be combined with any and all other elements from any of the embodiments to describe additional
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embodiments.

UTILITIES AND COMBINATIONS

[0046] Where desired, the compounds of Formula I may be used in combination with one or more anti-dyslipidemic agents or lipid-lowering agents and/or one or more other types of therapeutic agents including antidiabetic agents, anti-obesity agents, antihypertensive agents, platelet aggregation inhibitors, and/or anti-osteoporosis agents, which may be administered orally in the same dosage form, in a separate oral dosage form or by injection.

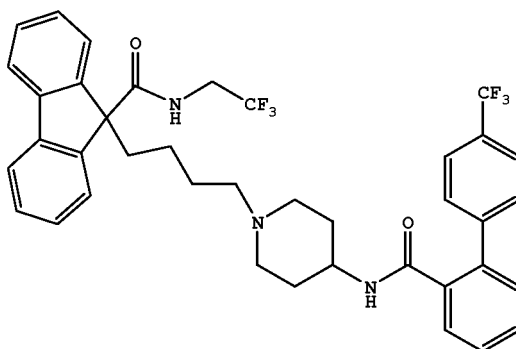
[0047] The anti-dyslipidemic agent or lipid-lowering agent which may be optionally employed in combination with the compounds of Formula I of the invention may include 1, 2, 3 or more MTP inhibitors, HMG CoA reductase inhibitors, squalene synthetase inhibitors, ACAT inhibitors, lipoxygenase inhibitors, cholesterol absorption inhibitors, ileal Na⁺/bile acid cotransporter inhibitors, upregulators of LDL receptor activity, bile acid sequestrants, cholesterol ester transfer protein (CETP) inhibitors [e.g., torcetrapib (Pfizer) and JTT-302 (Japan Tobacco)], and/or nicotinic acid and derivatives thereof.

[0048] MTP inhibitors employed herein include MTP inhibitors disclosed in U.S. Patent No. 5,595,872, U.S. Patent No. 5,739,135, U.S. Patent No. 5,712,279, U.S. Patent No. 5,760,246, U.S. Patent No. 5,827,875, U.S. Patent No. 5,885,983 and U.S. Application Serial No. 09/175,180 filed October 20, 1998, now U.S. Patent No. 5,962,440. Preferred are each of the preferred MTP inhibitors disclosed in each of the above patents and applications.

[0049] All of the above U.S. Patents and applications are incorporated herein by reference.

[0050] Most preferred MTP inhibitors to be employed in accordance with the present invention include preferred MTP inhibitors as set out in U.S. Patent Nos. 5,739,135 and 5,712,279, and U.S. Patent No. 5,760,246.

[0051] The most preferred MTP inhibitor is 9-[4-[4-[[2-(2,2,2-Trifluoroethoxy)benzoyl]amino]-1-piperidinyl]butyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide



10 [0052] The anti-dyslipidemic agent may be an HMG CoA reductase inhibitor which includes, but is not limited to, mevastatin and related compounds as disclosed in U.S. Patent No. 3,983,140, lovastatin (mevinolin) and related compounds as disclosed in U.S. Patent No. 4,231,938, pravastatin and related compounds such as disclosed in U.S. Patent No. 4,346,227, simvastatin and related compounds as
 15 disclosed in U.S. Patent Nos. 4,448,784 and 4,450,171. Other HMG CoA reductase inhibitors which may be employed herein include, but are not limited to, fluvastatin, disclosed in U.S. Patent No. 5,354,772, atorvastatin disclosed in U.S. Patent Nos. 4,681,893, 5,273,995, 5,385,929 and 5,686,104, itavastatin (Nissan/Sankyo's nisvastatin (NK-104)) disclosed in U.S. Patent No. 5,011,930, Shionogi-Astra/Zeneca
 20 visastatin (ZD-4522) disclosed in U.S. Patent No. 5,260,440, and related statin compounds disclosed in U.S. Patent No. 5,753,675, pyrazole analogs of mevalonolactone derivatives as disclosed in U.S. Patent No. 4,613,610, indene analogs of mevalonolactone derivatives as disclosed in PCT application WO 86/03488, 6-[2-(substituted-pyrrol-1-yl)-alkyl]pyran-2-ones and derivatives thereof as
 25 disclosed in U.S. Patent No. 4,647,576, Searle's SC-45355 (a 3-substituted pentanedioic acid derivative) dichloroacetate, imidazole analogs of mevalonolactone

as disclosed in PCT application WO 86/07054, 3-carboxy-2-hydroxy-propane-phosphonic acid derivatives as disclosed in French Patent No. 2,596,393, 2,3-disubstituted pyrrole, furan and thiophene derivatives as disclosed in European Patent Application No. 0221025, naphthyl analogs of mevalonolactone as disclosed in U.S. Patent No. 4,686,237, octahydronaphthalenes such as disclosed in U.S. Patent No. 4,499,289, keto analogs of mevinolin (lovastatin) as disclosed in European Patent Application No.0,142,146 A2, and quinoline and pyridine derivatives disclosed in U.S. Patent No. 5,506,219 and 5,691,322.

[0053] In addition, phosphinic acid compounds useful in inhibiting HMG CoA reductase suitable for use herein are disclosed in GB 2205837.

[0054] The squalene synthetase inhibitors suitable for use herein include, but are not limited to, α -phosphono-sulfonates disclosed in U.S. Patent No. 5,712,396, those disclosed by Biller et al, J. Med. Chem., 1988, Vol. 31, No. 10, pp. 1869-1871, including isoprenoid (phosphinyl-methyl)phosphonates as well as other known squalene synthetase inhibitors, for example, as disclosed in U.S. Patent No. 4,871,721 and 4,924,024 and in Biller, S.A., Neuenschwander, K., Ponpipom, M.M., and Poulter, C.D., Current Pharmaceutical Design, 2, 1-40 (1996).

[0055] In addition, other squalene synthetase inhibitors suitable for use herein include the terpenoid pyrophosphates disclosed by P. Ortiz de Montellano et al, J. Med. Chem., 1977, 20:243-249, the farnesyl diphosphate analog A and presqualene pyrophosphate (PSQ-PP) analogs as disclosed by Corey and Volante, J. Am. Chem. Soc., 1976, 98, 1291-1293, phosphinylphosphonates reported by McClard, R.W. et al, J.A.C.S., 1987, 109:5544 and cyclopropanes reported by Capson, T.L., PhD dissertation, June, 1987, Dept. Med. Chem. U of Utah, Abstract, Table of Contents, pp 16, 17, 40-43, 48-51, Summary.

[0056] Other anti-dyslipidemic agents suitable for use herein include, but are not limited to, probucol, and related compounds as disclosed in U.S. Patent No. 3,674,836, probucol being preferred; bile acid sequestrants such as cholestyramine, colestipol and DEAE-Sephadex (Secholex[®], Policexide[®]) and cholestagel (Sankyo/Geltex), as well as lipostabil (Rhone-Poulenc), Eisai E-5050 (an N-substituted ethanolamine derivative), imanixil (HOE-402), tetrahydrolipstatin (THL), istigmastanylphos-phorylcholine (SPC, Roche), aminocyclodextrin (Tanabe Seiyoku),

Ajinomoto AJ-814 (azulene derivative), melinamide (Sumitomo), Sandoz 58-035, American Cyanamid CL-277,082 and CL-283,546 (disubstituted urea derivatives); nicotinic acid (niacin), acipimox, acifran, neomycin, p-aminosalicylic acid, aspirin; poly(diallylmethylamine) derivatives such as disclosed in U.S. Patent No. 4,759,923; 5 quaternary amine poly(diallyldimethylammonium chloride) and ionenes such as disclosed in U.S. Patent No. 4,027,009, and other known serum cholesterol lowering agents.

[0057] The anti-dyslipidemic agent may be an ACAT inhibitor such as disclosed in, *Drugs of the Future* 24, 9-15 (1999), (Avasimibe); “The ACAT inhibitor, CI-1011 10 is effective in the prevention and regression of aortic fatty streak area in hamsters”, Nicolosi et al, *Atherosclerosis* (Shannon, Irel). (1998), 137(1), 77-85; “The pharmacological profile of FCE 27677: a novel ACAT inhibitor with potent dyslipidemic activity mediated by selective suppression of the hepatic secretion of ApoB100-containing lipoprotein”, Ghiselli, Giancarlo, *Cardiovasc. Drug Rev.* (1998), 15 16(1), 16-30; “RP 73163: a bioavailable alkylsulfinyl-diphenylimidazole ACAT inhibitor”, Smith, C., et al, *Bioorg. Med. Chem. Lett.* (1996), 6(1), 47-50; “ACAT inhibitors: physiologic mechanisms for dyslipidemic and anti-atherosclerotic activities in experimental animals”, Krause et al, Editor(s): Ruffolo, Robert R., Jr.; Hollinger, Manfred A., *Inflammation: Mediators Pathways* (1995), 173-98, 20 Publisher: CRC, Boca Raton, Fla.; “ACAT inhibitors: potential anti-atherosclerotic agents”, Sliskovic et al, *Curr. Med. Chem.* (1994), 1(3), 204-25; “Inhibitors of acyl-CoA:cholesterol O-acyl transferase (ACAT) as hypocholesterolemic agents. 6. The first water-soluble ACAT inhibitor with lipid-regulating activity. Inhibitors of acyl-CoA:cholesterol acyltransferase (ACAT). 7. Development of a series of substituted 25 N-phenyl-N'-[(1-phenylcyclopentyl)methyl]ureas with enhanced hypocholesterolemic activity”, Stout et al, *Chemtracts: Org. Chem.* (1995), 8(6), 359-62, or TS-962 (Taisho Pharmaceutical Co. Ltd).

[0058] The anti-dyslipidemic agent may be an upregulator of LD2 receptor activity such as MD-700 (Taisho Pharmaceutical Co. Ltd) and LY295427 (Eli Lilly).

30 **[0059]** The anti-dyslipidemic agent may be a cholesterol absorption inhibitor preferably Schering-Plough's SCH48461 as well as those disclosed in *Atherosclerosis* 115, 45-63 (1995) and *J. Med. Chem.* 41, 973 (1998).

[0060] The anti-dyslipidemic agent may be an ileal Na⁺/bile acid cotransporter inhibitor such as disclosed in Drugs of the Future, 24, 425-430 (1999).

[0061] The lipid-modulating agent may be a cholesteryl ester transfer protein (CETP) inhibitor such as Pfizer's CP 529,414 (WO/0038722 and EP 818448) and
5 Pharmacia's SC-744 and SC-795.

[0062] The ATP citrate lyase inhibitor which may be employed in the combination of the invention may include, for example, those disclosed in U.S. Patent No. 5,447,954.

[0063] Preferred anti-dyslipidemic agents are pravastatin, lovastatin, simvastatin,
10 atorvastatin, fluvastatin, itavastatin and visastatin and ZD-4522.

[0064] The above-mentioned U.S. patents are incorporated herein by reference. The amounts and dosages employed will be as indicated in the Physician's Desk Reference and/or in the patents set out above.

[0065] The compounds of Formula I of the invention will be employed in a
15 weight ratio to the anti-dyslipidemic agent (where present), within the range from about 500:1 to about 1:500, preferably from about 100:1 to about 1:100.

[0066] The dose administered must be carefully adjusted according to age, weight and condition of the patient, as well as the route of administration, dosage form and regimen and the desired result.

20 [0067] The dosages and formulations for the anti-dyslipidemic agent will be as disclosed in the various patents and applications discussed above.

[0068] The dosages and formulations for the other anti-dyslipidemic agent to be employed, where applicable, will be as set out in the latest edition of the Physicians' Desk Reference.

25 [0069] For oral administration, a satisfactory result may be obtained employing the MTP inhibitor in an amount within the range of from about 0.01 mg to about 500 mg and preferably from about 0.1 mg to about 100 mg, one to four times daily.

[0070] A preferred oral dosage form, such as tablets or capsules, will contain the MTP inhibitor in an amount of from about 1 to about 500 mg, preferably from about 2
30 to about 400 mg, and more preferably from about 5 to about 250 mg, one to four times daily.

[0071] For oral administration, a satisfactory result may be obtained employing an HMG CoA reductase inhibitor, for example, pravastatin, lovastatin, simvastatin, atorvastatin, fluvastatin or rosuvastatin in dosages employed as indicated in the Physician's Desk Reference, such as in an amount within the range of from about 1 to
5 2000 mg, and preferably from about 4 to about 200 mg.

[0072] The squalene synthetase inhibitor may be employed in dosages in an amount within the range of from about 10 mg to about 2000 mg and preferably from about 25 mg to about 200 mg.

[0073] A preferred oral dosage form, such as tablets or capsules, will contain the
10 HMG CoA reductase inhibitor in an amount from about 0.1 to about 100 mg, preferably from about 0.5 to about 80 mg, and more preferably from about 1 to about 40 mg.

[0074] A preferred oral dosage form, such as tablets or capsules will contain the squalene synthetase inhibitor in an amount of from about 10 to about 500 mg,
15 preferably from about 25 to about 200 mg.

[0075] The anti-dyslipidemic agent may also be a lipoxygenase inhibitor including a 15-lipoxygenase (15-LO) inhibitor such as benzimidazole derivatives as disclosed in WO 97/12615, 15-LO inhibitors as disclosed in WO 97/12613, isothiazolones as disclosed in WO 96/38144, and 15-LO inhibitors as disclosed by
20 Sendobry et al "Attenuation of diet-induced atherosclerosis in rabbits with a highly selective 15-lipoxygenase inhibitor lacking significant antioxidant properties", Brit. J. Pharmacology (1997) 120, 1199-1206, and Cornicelli et al, "15-Lipoxygenase and its Inhibition: A Novel Therapeutic Target for Vascular Disease", Current Pharmaceutical Design, 1999, 5, 11-20.

[0076] The compounds of Formula I and the anti-dyslipidemic agent may be
25 employed together in the same oral dosage form or in separate oral dosage forms taken at the same time.

[0077] The compositions described above may be administered in the dosage forms as described above in single or divided doses of one to four times daily. It may
30 be advisable to start a patient on a low dose combination and work up gradually to a high dose combination.

[0078] The preferred anti-dyslipidemic agent is pravastatin, simvastatin, lovastatin, atorvastatin, fluvastatin or rosuvastatin as well as niacin and/or cholestagel.

[0079] The other antidiabetic agent which may be optionally employed in
5 combination with the compound of Formula I may be 1, 2, 3 or more antidiabetic agents or antihyperglycemic agents including insulin secretagogues or insulin sensitizers, or other antidiabetic agents preferably having a mechanism of action different from the compounds of Formula I of the invention, which may include
10 biguanides, sulfonyl ureas, glucosidase inhibitors, PPAR γ agonists, such as thiazolidinediones, dipeptidyl peptidase IV (DP4) inhibitors, SGLT2 inhibitors, and/or meglitinides, as well as insulin, and/or glucagon-like peptide-1 (GLP-1).

[0080] The other antidiabetic agent may be an oral antihyperglycemic agent preferably a biguanide such as metformin or phenformin or salts thereof, preferably metformin HCl.

15 [0081] Where the antidiabetic agent is a biguanide, the compounds of Formula I will be employed in a weight ratio to biguanide within the range from about 0.001:1 to about 10:1, preferably from about 0.01:1 to about 5:1.

[0082] The other antidiabetic agent may also preferably be a sulfonyl urea such as glyburide (also known as glibenclamide), glimepiride (disclosed in U.S. Patent No.
20 4,379,785), glipizide, gliclazide or chlorpropamide, other known sulfonylureas or other antihyperglycemic agents which act on the ATP-dependent channel of the β -cells, with glyburide and glipizide being preferred, which may be administered in the same or in separate oral dosage forms.

[0083] The compounds of Formula I will be employed in a weight ratio to the
25 sulfonyl urea in the range from about 0.01:1 to about 100:1, preferably from about 0.02:1 to about 5:1.

[0084] The oral antidiabetic agent may also be a glucosidase inhibitor such as acarbose (disclosed in U.S. Patent No. 4,904,769) or miglitol (disclosed in U.S.
Patent No. 4,639,436), which may be administered in the same or in a separate oral
30 dosage forms.

[0085] The compounds of Formula I will be employed in a weight ratio to the glucosidase inhibitor within the range from about 0.01:1 to about 100:1, preferably from about 0.05:1 to about 10:1.

[0086] The compounds of Formula I may be employed in combination with a
5 PPAR γ agonist such as a thiazolidinedione oral anti-diabetic agent or other insulin sensitizers (which has an insulin sensitivity effect in NIDDM patients) such as rosiglitazone (SKB), pioglitazone (Takeda), Mitsubishi's MCC-555 (disclosed in U.S. Patent No. 5,594,016), R-119702 (Sankyo/WL), or YM-440 (Yamanouchi), preferably rosiglitazone and pioglitazone.

10 [0087] The compounds of Formula I will be employed in a weight ratio to the thiazolidinedione in an amount within the range from about 0.01:1 to about 100:1, preferably from about 0.05 to about 10:1.

[0088] The sulfonyl urea and thiazolidinedione in amounts of less than about 150 mg oral antidiabetic agent may be incorporated in a single tablet with the compounds
15 of Formula I.

[0089] The compounds of Formula I may also be employed in combination with a antihyperglycemic agent such as insulin or with glucagon-like peptide-1 (GLP-1) such as GLP-1(1-36) amide, GLP-1(7-36) amide, GLP-1(7-37) (as disclosed in U.S. Patent No. 5,614,492 to Habener, the disclosure of which is incorporated herein by
20 reference), as well as AC2993 (Amylin) and LY-315902 (Lilly), which may be administered via injection, intranasal, inhalation or by transdermal or buccal devices.

[0090] Where present, metformin, the sulfonyl ureas, such as glyburide, glimepiride, glipyrider, glipizide, chlorpropamide and gliclazide and the glucosidase inhibitors acarbose or miglitol or insulin (injectable, pulmonary, buccal, or oral) may
25 be employed in formulations as described above and in amounts and dosing as indicated in the Physician's Desk Reference (PDR).

[0091] Where present, metformin or salt thereof may be employed in amounts within the range from about 500 to about 2000 mg per day which may be administered in single or divided doses one to four times daily.

30 [0092] Where present, the thiazolidinedione anti-diabetic agent may be employed in amounts within the range from about 0.01 to about 2000 mg/day which may be administered in single or divided doses one to four times per day.

[0093] Where present insulin may be employed in formulations, amounts and dosing as indicated by the Physician's Desk Reference.

[0094] Where present GLP-1 peptides may be administered in oral buccal formulations, by nasal administration or parenterally as described in U.S. Patent Nos. 5,346,701 (TheraTech), 5,614,492 and 5,631,224 which are incorporated herein by reference.

[0095] The other antidiabetic agent may also be a PPAR α/γ dual agonist such as Muraglitazar (Bristol-Myers Squibb).

[0096] The antidiabetic agent may be an SGLT2 inhibitor such as disclosed in U.S. Patent No. 6,414,126, employing dosages as set out therein. Preferred are the compounds designated as preferred in the above patent. Other suitable SGLT2 inhibitors include T-1095, phlorizin, WAY-123783, and those described in WO 01/27128, US 6515117 and US6414126.

[0097] The antidiabetic agent may be a DPP4 inhibitor. These include saxagliptin (Bristol-Myers Squibb), vildagliptin (Novartis), sitagliptin (Merck) and alogliptin (Takeda) as well as those such as disclosed in WO99/38501, WO99/46272, WO99/67279 (PROBIODRUG), WO99/67278 (PROBIODRUG), WO99/61431 (PROBIODRUG), NVP-DPP728A (1-[[[2-[(5-cyanopyridin-2-yl)amino]ethyl]amino]acetyl]-2-cyano-(S)-pyrrolidine) (Novartis) as disclosed by Hughes et al, Biochemistry, 38(36), 11597-11603, 1999, TSL-225 (tryptophyl-1,2,3,4-tetrahydro-isoquinoline-3-carboxylic acid) disclosed by Yamada et al, Bioorg. & Med. Chem. Lett. 8 (1998) 1537-1540, 2-cyanopyrrolidides and 4-cyanopyrrolidides as disclosed by Ashworth et al, Bioorg. & Med. Chem. Lett., Vol. 6, No. 22, pp 1163-1166 and 2745-2748 (1996) employing dosages as set out in the above references.

[0098] The meglitinide which may optionally be employed in combination with the compound of Formula I of the invention may be repaglinide, nateglinide (Novartis) or KAD1229 (PF/Kissei), with repaglinide being preferred.

[0099] The compound of Formula I will be employed in a weight ratio to the meglitinide, PPAR- α/γ dual agonist, DP4 inhibitor or SGLT2 inhibitor within the range from about 0.01:1 to about 100:1, preferably from about 0.05 to about 10:1.

[00100] The other type of therapeutic agent which may be optionally employed with a compound of Formula I may be 1, 2, 3 or more of an anti-obesity agent including a beta 3 adrenergic agonist, a lipase inhibitor, a serotonin (and dopamine) reuptake inhibitor, a thyroid receptor agonist, a cannabinoid receptor 1 (CB-1) antagonist and/or an anorectic agent.

[00101] The beta 3 adrenergic agonist which may be optionally employed in combination with a compound of Formula I may be AJ9677 (Takeda/Dainippon), L750355 (Merck), or CP331648 (Pfizer) or other known beta 3 agonists as disclosed in U.S. Patent Nos. 5,541,204, 5,770,615, 5,491,134, 5,776,983 and 5,488,064, with AJ9677, L750,355 and CP331648 being preferred.

[00102] The lipase inhibitor which may be optionally employed in combination with a compound of Formula I may be orlistat or ATL-962 (Alizyme), with orlistat being preferred.

[00103] The serotonin (and dopamine) reuptake inhibitor which may be optionally employed in combination with a compound of Formula I may be sibutramine, topiramate (Johnson & Johnson) or axokine (Regeneron), with sibutramine and topiramate being preferred.

[00104] The thyroid receptor agonist which may be optionally employed in combination with a compound of Formula I may be a thyroid receptor ligand as disclosed in WO97/21993 (U. Cal SF), WO99/00353 (KaroBio), WO 00/039077 (KaroBio), and U.S. Patent No. 6,800,605, with compounds of the KaroBio applications and the above patent being preferred.

[00105] Cannabinoid receptor 1 antagonists and inverse agonists which may be optionally employed in combination with compounds of the present invention include rimonabant, SLV 319, and those discussed in D. L. Hertzog, Expert Opin. Ther. Patents 2004, 14, 1435-1452.

[00106] The anorectic agent which may be optionally employed in combination with a compound of Formula I may be dexamphetamine, phentermine, phenylpropanolamine or mazindol, with dexamphetamine being preferred.

[00107] The various anti-obesity agents described above may be employed in the same dosage form with the compound of Formula I or in different dosage forms, in dosages and regimens as generally known in the art or in the PDR.

[00108] The antihypertensive agents which may be employed in combination with the compound of Formula I of the invention include ACE inhibitors, angiotensin II receptor antagonists, NEP/ACE inhibitors, as well as calcium channel blockers, β -adrenergic blockers and other types of antihypertensive agents, including diuretics.

5 [00109] The angiotensin converting enzyme inhibitor which may be employed herein includes those containing a mercapto (-S-) moiety such as substituted proline derivatives, such as any of those disclosed in U.S. Pat. No. 4,046,889 to Ondetti et al mentioned above, with captopril, that is, 1-[(2S)-3-mercapto-2-methylpropionyl]-L-proline, being preferred, and mercaptoacyl derivatives of substituted prolines such as
10 any of those disclosed in U.S. Pat. No. 4,316,906 with zofenopril being preferred.

[00110] Other examples of mercapto containing ACE inhibitors that may be employed herein include rentiapril (fentiapril, Santen) disclosed in Clin. Exp. Pharmacol. Physiol. 10:131 (1983); as well as pivopril and YS980.

[00111] Other examples of angiotensin converting enzyme inhibitors which may
15 be employed herein include any of those disclosed in U.S. Pat. No. 4,374,829 mentioned above, with N-(1-ethoxycarbonyl-3-phenylpropyl)-L-alanyl-L-proline, that is, enalapril, being preferred; any of the phosphonate substituted amino or imino acids or salts disclosed in U.S. Pat. No. 4,452,790, with (S)-1-[6-amino-2-[[hydroxy-(4-phenylbutyl)phosphinyl]oxy]-1-oxohexyl]-L-proline or (ceronapril) being preferred;
20 phosphinylalkanoyl prolines disclosed in U.S. Pat. No. 4,168,267 mentioned above with fosinopril being preferred; any of the phosphinylalkanoyl substituted prolines disclosed in U.S. Pat. No. 4,337,201; and the phosphonamidates disclosed in U.S. Pat. No. 4,432,971 discussed above.

[00112] Other examples of ACE inhibitors that may be employed herein include
25 Beecham's BRL 36,378 as disclosed in European Patent Application Nos. 80822 and 60668; Chugai's MC-838 disclosed in C.A. 102:72588v and Jap. J. Pharmacol. 40:373 (1986); Ciba-Geigy's CGS 14824 (3-([1-ethoxycarbonyl-3-phenyl-(1S)-propyl]amino)-2,3,4,5-tetrahydro-2-oxo-1-(3S)-benzazepine-1 acetic acid HCl) disclosed in U.K. Patent No. 2103614 and CGS 16,617 (3(S)-[[[(1S)-5-amino-1-
30 carboxypentyl]amino]-2,3,4,5-tetrahydro-2-oxo-1H-1-benzazepine-1-ethanoic acid) disclosed in U.S. Pat. No. 4,473,575; cetapril (alacepril, Dainippon) disclosed in Eur. Therap. Res. 39:671 (1986); ramipril (Hoechst) disclosed in Euro. Patent No. 79-022

and Curr. Ther. Res. 40:74 (1986); Ru 44570 (Hoechst) disclosed in
Arzneimittelforschung 34:1254 (1985); cilazapril (Hoffman-LaRoche) disclosed in J.
Cardiovasc. Pharmacol. 9:39 (1987); R 31-2201 (Hoffman-LaRoche) disclosed in
FEBS Lett. 165:201 (1984); lisinopril (Merck); indalapril (delapril) disclosed in U.S.
5 Pat. No. 4,385,051; indolapril (Schering) disclosed in J. Cardiovasc. Pharmacol.
5:643, 655 (1983); spirapril (Schering) disclosed in Acta. Pharmacol. Toxicol. 59
(Supp. 5):173 (1986); perindopril (Servier) disclosed in Eur. J. Clin. Pharmacol.
31:519 (1987); quinapril (Warner-Lambert) disclosed in U.S. Pat. No. 4,344,949 and
CI925 (Warner-Lambert) ([3S-[2[R(*)R(*)]]3R(*)]-2-[2-[[1-(ethoxy-carbonyl)-3-
10 phenylpropyl]amino]-1-oxopropyl]-1,2,3,4-tetrahydro-6,7-dimethoxy-3-
isoquinolinecarboxylic acid HCl) disclosed in Pharmacologist 26:243, 266 (1984),
WY-44221 (Wyeth) disclosed in J. Med. Chem. 26:394 (1983).

[00113] Preferred ACE inhibitors are captopril, fosinopril, enalapril, lisinopril,
quinapril, benazepril, fentiapril, ramipril and moexipril.

15 **[00114]** NEP/ACE inhibitors may also be employed herein in that they possess
neutral endopeptidase (NEP) inhibitory activity and angiotensin converting enzyme
(ACE) inhibitory activity. Examples of NEP/ACE inhibitors suitable for use herein
include those disclosed in U.S. Pat. Nos. 5,362,727, 5,366,973, 5,225,401, 4,722,810,
5,223,516, 4,749,688, 5,552,397, 5,504,080, 5,612,359, and 5,525,723, European
20 Patent Applications 0599,444, 0481,522, 0599,444, 0595,610, 0534363A2, 534,396,
534,492, and 0629627A2.

[00115] Preferred are those NEP/ACE inhibitors and dosages thereof which are
designated as preferred in the above patents/applications which U.S. patents are
incorporated herein by reference; most preferred are omapatrilat, BMS 189,921 ([S-
25 (R*,R*)]-hexahydro-6-[(2-mercapto-1-oxo-3-phenylpropyl)amino]-2,2-dimethyl-7-
oxo-1H-azepine-1-acetic acid (gemopatrilat)) and CGS 30440.

[00116] The angiotensin II receptor antagonist (also referred to herein as
angiotensin II antagonist or AII antagonist) suitable for use herein includes, but is not
limited to, irbesartan, losartan, valsartan, candesartan, telmisartan, tасosartan or
30 eprosartan, with irbesartan, losartan or valsartan being preferred.

[00117] A preferred oral dosage form, such as tablets or capsules, will contain the
ACE inhibitor or AII antagonist in an amount within the range from about 0.1 to about

500 mg, preferably from about 5 to about 200 mg and more preferably from about 10 to about 150 mg.

[00118] For parenteral administration, the ACE inhibitor, angiotensin II antagonist or NEP/ACE inhibitor will be employed in an amount within the range from about 5 0.005 mg/kg to about 10 mg/kg and preferably from about 0.01 mg/kg to about 1 mg/kg.

[00119] Where a drug is to be administered intravenously, it will be formulated in conventional vehicles, such as distilled water, saline, Ringer's solution or other conventional carriers.

10 **[00120]** It will be appreciated that preferred dosages of ACE inhibitor and AII antagonist as well as other antihypertensives disclosed herein will be as set out in the latest edition of the Physician's Desk Reference (PDR).

[00121] Other examples of preferred antihypertensive agents suitable for use herein include omapatrilat (Vanlev[®]), amlodipine besylate (Norvasc[®]), prazosin HCl 15 (Minipress[®]), verapamil, nifedipine, nadolol, diltiazem, felodipine, nisoldipine, isradipine, nicardipine, atenolol, carvedilol, sotalol, terazosin, doxazosin, propranolol, and clonidine HCl (Catapres[®]).

[00122] Diuretics which may be employed in combination with compounds of Formula I include hydrochlorothiazide, torasemide, furosemide, spironolactone, and 20 indapamide.

[00123] Antiplatelet agents which may be employed in combination with compounds of Formula I of the invention include aspirin, clopidogrel, ticlopidine, dipyridamole, abciximab, tirofiban, eptifibatide, anagrelide, and ifetroban, with clopidogrel and aspirin being preferred.

25 **[00124]** The antiplatelet drugs may be employed in amounts as indicated in the PDR. Ifetroban may be employed in amounts as set out in U.S. Patent No. 5,100,889.

[00125] Antiosteoporosis agents suitable for use herein in combination with the compounds of Formula I of the invention include parathyroid hormone or bisphosphonates, such as MK-217 (alendronate) (Fosamax[®]). Dosages employed will 30 be as set out in the PDR.

[00126] In carrying out the method of the invention, a pharmaceutical composition will be employed containing the compounds of Formula I, with or without another

therapeutic agent, in association with a pharmaceutical vehicle or diluent. The pharmaceutical composition can be formulated employing conventional solid or liquid vehicles or diluents and pharmaceutical additives of a type appropriate to the mode of desired administration. The compounds can be administered to mammalian species including humans, monkeys, dogs, etc. by an oral route, for example, in the form of tablets, capsules, granules or powders, or they can be administered by a parenteral route in the form of injectable preparations. The dose for adults is preferably between 0.1 and 2,000 mg per day, which can be administered in a single dose or in the form of individual doses from 1-4 times per day. Alternatively, another preferred mode of administration may be intermittent dosing (i.e., a single dose of drug administered at intervals, ranging from once every 2 days to once every 7 days).

[00127] A typical capsule for oral administration contains compounds of Formula I (25 mg), lactose (7.5 mg) and magnesium stearate (1.5 mg). The mixture is passed through a 60 mesh sieve and packed into a No. 1 gelatin capsule.

[00128] The following Examples represent preferred embodiments of the invention.

ABBREVIATIONS

[00129] For ease of reference, the following abbreviations are employed herein, including the methods of preparation and in the Examples that follow:

aq. = aqueous
Ar = argon
Bn = benzyl
Boc = tert-butoxycarbonyl
BBr₃ = boron tribromide
Cbz = carbobenzyloxy or carbobenzoxy or benzyloxycarbonyl
Cbz-Cl = benzyl chloroformate
CH₂Cl₂ = dichloromethane
DCE = 1,2 dichloroethane
DIBALH = diisobutyl aluminum hydride
DMAP = 4-dimethylaminopyridine
DME = 1,2 dimethoxyethane

- DMF = dimethyl formamide
DMSO = dimethyl sulfoxide
EDC (or EDC.HCl) or EDCI (or EDCI.HCl) or EDAC = 3-ethyl-3'-
(dimethylamino)propyl- carbodiimide hydrochloride (or 1-(3-
5 dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride)
Et = ethyl
Et₂O = diethyl ether
Et₃N = triethylamine
EtOAc = ethyl acetate
10 EtOH = ethanol
Fmoc = fluorenylmethoxycarbonyl
g = gram(s)
h or hr = hour(s)
hex = hexanes
15 HMPA = hexamethyl phosphoric triamide
HOAc or AcOH = acetic acid
HPLC = high performance liquid chromatography
HRMS = high resolution mass spectrometry
i-Pr₂NEt = diisopropylethylamine
20 i-PrOH = isopropanol
ISCO = The Teledyne Isco Chromatography instrument is used for purification of
organic compounds using silica gel and organic solvents under medium pressure
with automatic fraction collectors using UV detection.
K₂CO₃ = potassium carbonate
25 Kg = kilogram(s)
KOH = potassium hydroxide
L = liter
LC/MS = high performance liquid chromatography/mass spectrometry
LiAlH₄ = lithium aluminum hydride
30 LiOH = lithium hydroxide
LRMS = low resolution mass spectrometry
Me = methyl

- MeCN = acetonitrile
MeOH = methanol
meq = milliequivalent
mg = milligram(s)
- 5 MgSO₄ = magnesium sulfate
min = minute(s)
mL = milliliter
mmol = millimole(s)
mol = moles
- 10 mp = melting point
MS or Mass Spec = mass spectrometry
N₂ = nitrogen
NaBH(OAc)₃ = sodium triacetoxyborohydride
NaBH₄ = sodium borohydride
- 15 NaHCO₃ = sodium bicarbonate
NaN(TMS)₂ = sodium hexamethyldisilazide or sodium bis(trimethylsilyl)amide
NaOH = sodium hydroxide
NMM = N-methyl morpholine
NMR = nuclear magnetic resonance
- 20 NMR spectral data: s = singlet; d = doublet; m = multiplet; br = broad; t = triplet
Pd/C = palladium on carbon
Ph = phenyl
Ph₃P = triphenylphosphine
RT = room temperature
- 25 sat or sat'd = saturated
SiO₂ = silica gel
TBS = tert-butyl dimethylsilyl
t-Bu = tertiary butyl
TFA = trifluoroacetic acid
- 30 THF = tetrahydrofuran
TLC = thin layer chromatography
TMS = trimethylsilyl

μL = microliter

EXAMPLES

METHODS OF PREPARATION

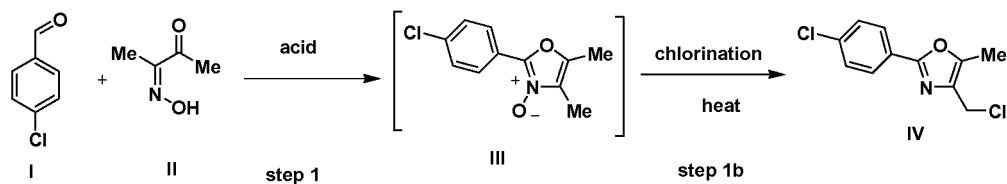
- 5 **[00130]** The compounds of Formula (I) may generally be prepared according to the following general synthetic reaction schemes as well as relevant published literature procedures that may be used by one skilled in the art. Exemplary reagents, procedures and conditions for these reactions appear hereinafter and in the working examples. Starting materials are commercially available or can be readily prepared
- 10 by one of ordinary skill in the art using known methods. Unless otherwise specified the various substituents of the compounds are defined in the same manner as the Formula I.

SCHEMES

- 15 **[00131]** Schemes 1-3 describe a general synthetic sequence for the preparation of the compounds of Formula I. During the preparation of compounds of Formula I, one or more protecting groups might be used; reaction conditions for protection and deprotection may be found in the "Protective Groups in Organic Synthesis", 3rd Edition, T. W. Greene and P. G. M. Wuts, John Wiley and Sons Inc, 1999, or other
- 20 methods used by one of ordinary skill in the art.

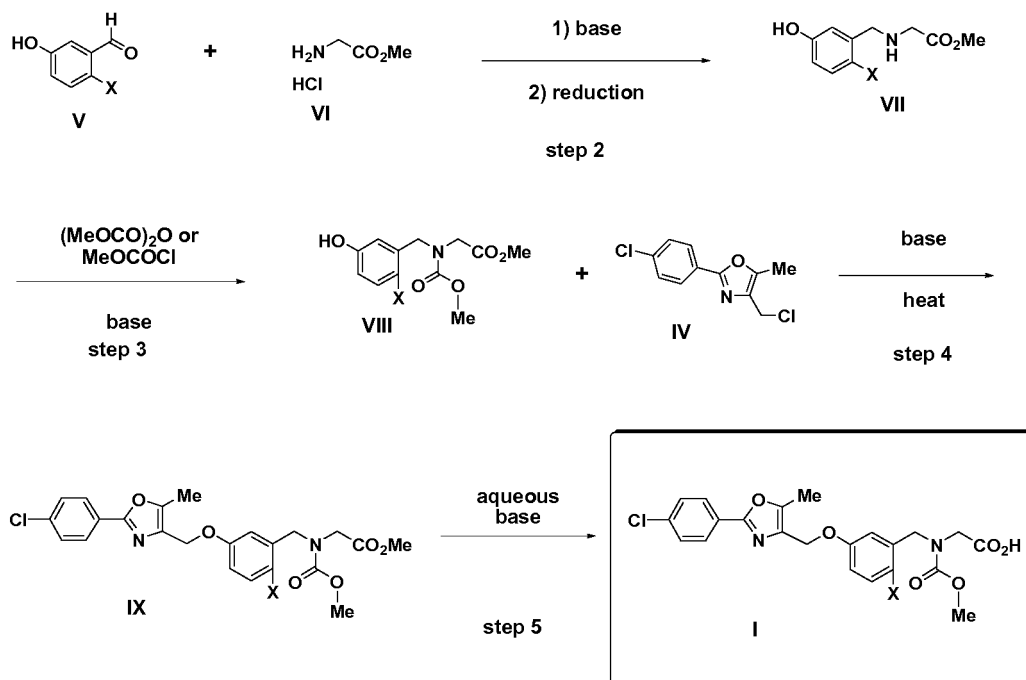
- [00132]** The syntheses of compounds of Formula I (including Ia and Ib) can be accomplished via the convergent route outlined in Schemes 1 and 2. The synthesis of the key intermediate, the 4-chloromethyl 2-para-chloro-phenyloxazole **IV**, is optimally achieved in a one-pot, two step procedure from 2,3-butanedione mono-
- 25 oxime and p-chlorobenzaldehyde involving HCl-mediated condensation, followed by dehydrative chlorination with acetyl chloride (Scheme 1). An alternative synthesis utilizes POCl_3 to perform the dehydrative chlorination of **III** to **IV**.

SCHEME 1



[00133] Intermediate IV is then used as shown in Scheme 2 below. Starting from 3-hydroxybenzaldehydes V and glycine methyl ester hydrochloride VI, the corresponding imines are formed by condensation in the presence of base. These imines can then be reduced *in situ* to the secondary amines VII. Amines VII give the methyl carbamates VIII after treatment with dimethyl dicarbonate and base. Alternatively, treatment of amines VII with methyl chloroformate under Schotten-Baumann conditions also proceed in comparable yield. Phenols VIII can be reacted with the chloromethyl-oxazole IV in the presence of base to give the methyl esters IX. Hydrolysis of esters IX with aqueous base gives compounds of Formula I.

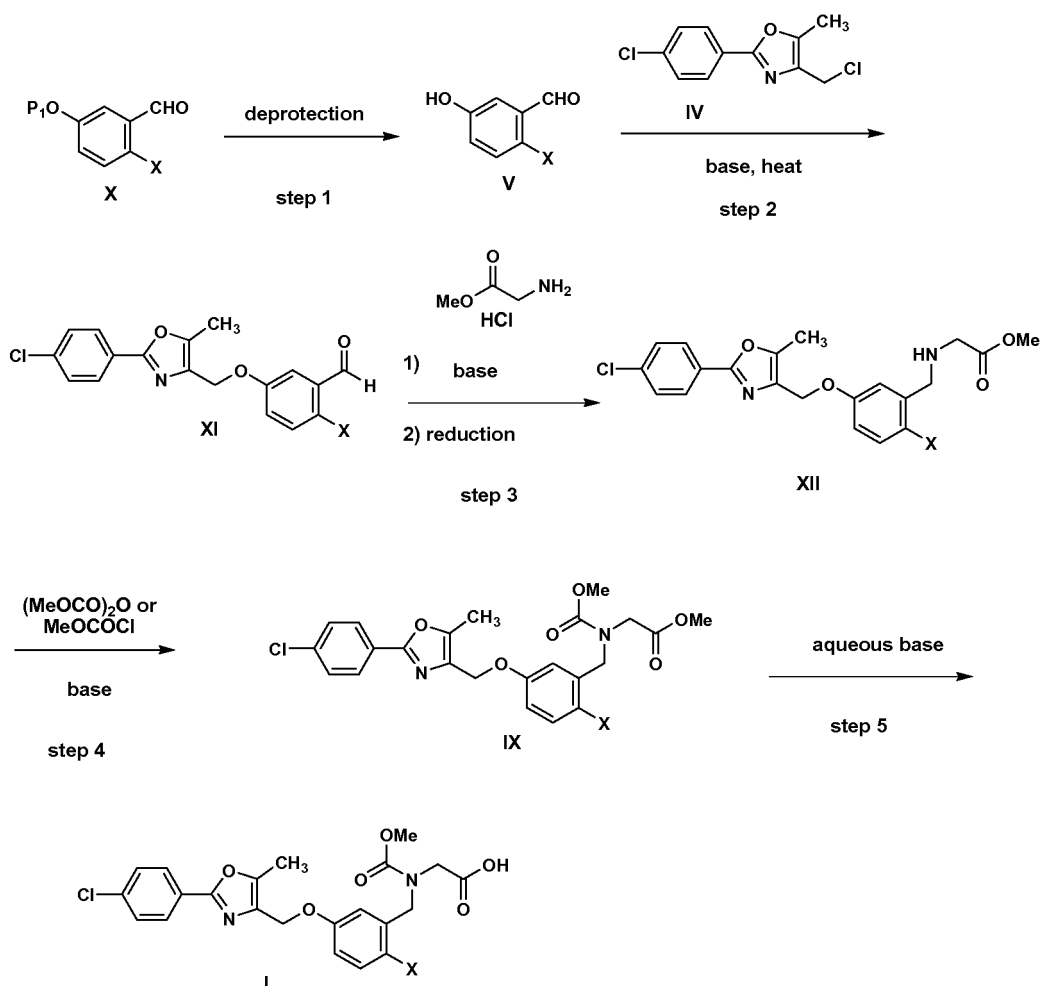
SCHEME 2



[00134] The synthesis of compounds of Formula I can alternatively be accomplished via the route outlined in Scheme 3. The 3-hydroxybenzaldehydes **V** can be alternatively derived from substituted ethers **X** by deprotection methods known in the art. The phenols **V** can be treated first with the chloromethyl-oxazole intermediate **IV** and base to give the phenyloxazole benzaldehydes **XI**. Imine formation from benzaldehydes **XI** and glycine methyl ester hydrochloride **VI**, followed by *in situ* reduction gives the secondary amines **XII**. Methyl carbamate formation from amines **XII** as described in Scheme 2 provides the methyl esters **IX**. Hydrolysis of esters **IX** with aqueous base gives compounds of Formula I.

10

SCHEME 3



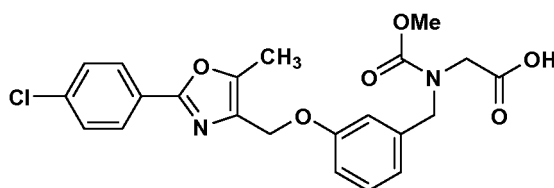
Detailed Description of Procedures

[00135] The experimental procedures are described below. Where indicated, detailed spectroscopic and physical characterization of intermediates was performed on purified samples from previous syntheses of the Examples.

5

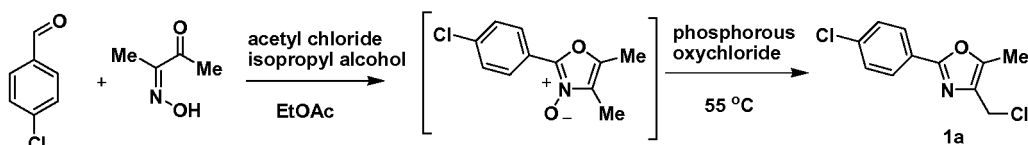
EXAMPLE 1

Glycine, *N*-[[3-[[2-(4-chlorophenyl)-5-methyl-4-oxazolyl]methoxy]phenyl]methyl]-*N*-(methoxycarbonyl)-



10

Synthesis of 1a: 4-(Chloromethyl)-5-methyl-2-[4-chlorophenyl]oxazole:



15

[00136] To a white slurry of 4-chlorobenzaldehyde (150.0 g, 1070 mmol) and 2,3-butanedione monoxime (102.5 g, 1010 mmol) in EtOAc (600 mL) at 0°C under N₂ was bubbled gaseous HCl for 20 min. The reaction mixture was stirred at RT under N₂ for 40 h, then was concentrated *in vacuo* to a volume of ~400 mL, and stirred at 20 0°C for 45 min. The resulting slurry was filtered and the filtrate was washed with cold EtOAc (5 x 100 mL) to give the intermediate N-oxide (228.5 g) as a solid. This material was dissolved in CHCl₃ (900 mL), and POCl₃ (128 mL, 1378 mmol) was slowly added over 25 min. The mixture was heated at 55°C for 2.5 h, then was cooled to RT and concentrated *in vacuo*. The syrup was dissolved in EtOAc (1 L) and cooled with an ice water bath. Saturated aqueous NaHCO₃ (750 mL) was slowly 25 added over 5 min to the reaction solution while the temperature was kept at <15°C. The pH was then adjusted to ~6 by adding solid Na₂CO₃ (191 g). The aqueous layer

was extracted with EtOAc (300 mL). The combined organic layers were dried (Na₂SO₄) and concentrated *in vacuo* to give the crude oxazole chloride **1a** (212 g) which was dissolved in 4:1 CH₂Cl₂ / heptane (375 mL), and filtered through a pad of silica gel (400 mL). After volatiles were removed *in vacuo*, the residue was

5 crystallized from CH₂Cl₂ / heptane (600 mL, 3/2) to afford the desired oxazole chloride **1a** (189.7 g, 77.3 %) as a white solid. : ¹H NMR (CDCl₃) δ 7.91 (d, 2H, J = 8.8 Hz), 7.38 (d, 2H, J = 8.7 Hz), 4.52 (s, 2H), 2.39 (s, 3H) ppm; ¹³C NMR (CDCl₃) δ 159.0, 146.8, 136.3, 133.0, 129.0 (2C), 127.4 (2C), 125.6, 37.1, 10.3; HRMS for C₁₁H₉Cl₂NO, Calcd for (M+H)⁺: 242.0139, Found: 242.0135.

10

Alternative synthesis of **1a**:

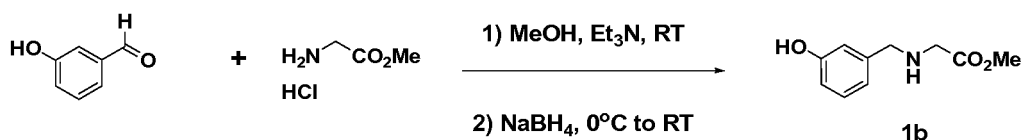
[00137] To a stirred mixture of 4-chlorobenzaldehyde (7.0 g, 49.7 mmol), 2,3-butanedione monoxime (5.05 g, 49.9 mmol) in EtOAc (35 mL) and iPrOH (18 mL) was added acetyl chloride (21.3 mL) dropwise over 15 min at 0°C under N₂. The

15 reaction mixture was stirred at 0°C for 30 min, then was warmed to RT and stirred at RT for an additional 2 h. More acetyl chloride (10 mL) was added dropwise over 5 min at RT, after which the mixture was heated to 55°C for 45 min. The reaction was cooled to RT, and quenched into saturated aqueous K₂CO₃ (50 mL). The organic layer was separated and the aqueous layer was extracted with EtOAc (2 x 30 mL).

20 The combined organic extracts were dried (Na₂SO₄) and concentrated *in vacuo* to give the crude product (12.5 g) which was recrystallized from i-PrOH to give the desired oxazole chloride **1a** (11.8 g, 97%) as a white solid. HRMS *m/e* 242.0132 (M⁺); Elemental analysis calculated for C₁₁H₉Cl₂NO: C, 54.57%; H, 3.74%; N, 5.78%. Found: C, 54.66%; H, 3.59%; N, 5.70%.

25

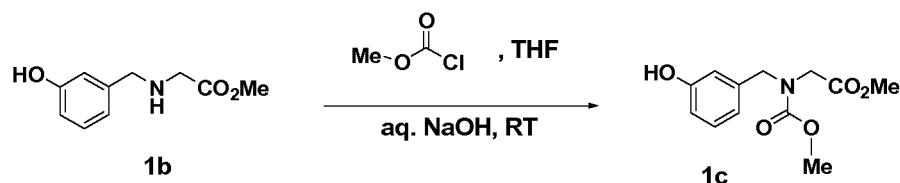
Synthesis of **1b**:



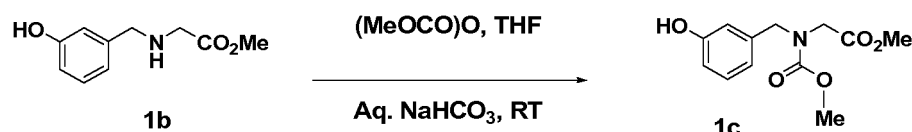
[00138] To a RT solution of glycine methyl ester hydrochloride (84.86 g, 0.67 mol) in MeOH (900 mL) was added Et₃N (68.29 g, 0.675 mol). After 15 min, a solution of 3-hydroxybenzaldehyde (75 g, 0.614 mol) in MeOH (500 mL) was added. After stirring for 1 h at RT, the reaction mixture was cooled to 0°C, and NaBH₄ (5.7 g, 150 mmol) was then added portion-wise over 20 min (temperature maintained at ≤25°C). After stirring 1 h, volatiles were removed *in vacuo* at 45-50°C from the reaction mixture. The resulting residue was partitioned between EtOAc (500 mL) and water (500 mL). The aqueous layer was extracted with EtOAc (200 mL). The combined organic extracts were washed with brine, dried (Na₂SO₄), then concentrated *in vacuo* to afford the desired amino-ester **7** as a pale yellow solid (113.9 g, 95%), which was used in the next step without further purification.

[00139] Material purified from a previous batch: ¹H-NMR (CDCl₃, 400 MHz) δ7.16 (m, 1H), 6.82 (m, 1H), 6.78 (s, 1H), 6.72 (m, 1H), 3.73 (m, 4H), 3.43 (s, 3H);

15 **Synthesis of 1c: [(3-Hydroxy-benzyl)-methoxycarbonyl-amino]-acetic acid methyl ester:**

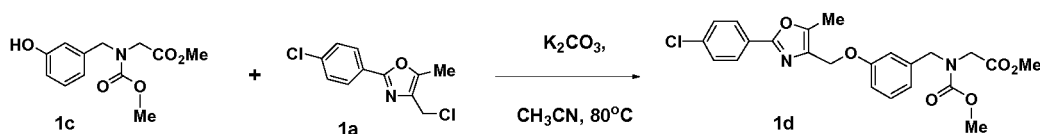


20 [00140] To a stirred 0°C solution of compound **1b** (65.0 g, 333 mmol) in THF (325 mL) and saturated aqueous NaHCO₃ (260 mL) was added dropwise methyl chloroformate (25.7 mL, 333 mmol) over 20 min under N₂. The mixture was stirred at 0°C for 45 min, then was extracted with EtOAc (2 X 260 mL). The combined organic extracts were dried (Na₂SO₄) and concentrated *in vacuo* to give the crude carbamate-ester **8** (83.8 g, 99.4%) as a yellow oil. This material was used directly in the next step without further purification. ¹H-NMR (CDCl₃, 400 MHz) δ7.19 (m, 1H), 6.78 (m, 3H), 6.14 (br. s, 1H), 4.54 (d, 2H, *J* = 5.6 Hz), 3.98 (s, 1H), 3.90 (s, 1H), 3.80 (d, 3H, *J* = 13.2 Hz), 3.73 (d, 3H, *J* = 4.8 Hz).

Alternate synthesis of **1c**:

[00141] To a solution of Example **1b** compound (9.76 g, 50.0 mmol) in THF (100 mL) was added 1 M aqueous NaHCO₃ (105 mL, 105 mmol). With vigorous stirring, dimethyl dicarbonate (5.63 mL, 52.5 mmol) was added dropwise over ~2 min at RT. After 20 min, the reaction mixture was extracted with twice with EtOAc. The combined organic extracts were dried (Na₂SO₄), then concentrated *in vacuo*. The resulting pale-yellow residue was chromatographed (SiO₂; 330g column, continuous gradient from 0-100% EtOAc in hexanes over 20 min, flow rate = 80mL/min, ISCO chromatography system), to provide Example **1c** as a clear, colorless viscous oil (9.0 g, 71%).

15 **Synthesis of 1d: Methyl ({3-[2-(4-chloro-phenyl)-5-methyl-oxazol-4-ylmethoxy]-benzyl}-methoxycarbonyl-amino)-acetic acid methyl ester:**



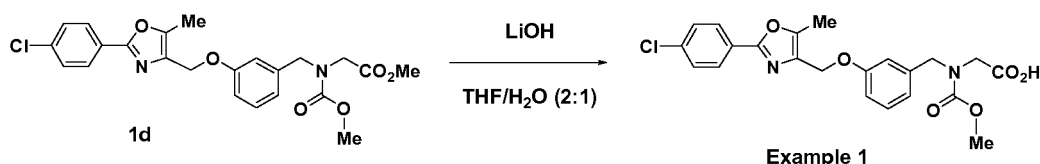
[00142] To a solution of example **1c** (83.8 g, 331 mmol) in MeCN (700 mL) was added example **1a** (80.1 g, 331 mmol) and anhydrous K₂CO₃ (137 g, 993 mmol). The mixture was heated at 70°C for 21 h under N₂, then was cooled to 5°C and poured into saturated aqueous NH₄Cl (1 L), and extracted with EtOAc (400 mL). The organic layer was dried (Na₂SO₄), and concentrated *in vacuo* to yield the carbamate ester (155.8 g) as a yellow syrup, which was chromatographed (2.5 kg SiO₂, elution with a gradient from 20 to 50% EtOAc in heptane) to give the desired carbamate-ester **1d** (108.1 g, 70.7%) as a colorless solid. mp 83.4°C. ¹H-NMR (CDCl₃, 400 MHz) δ 7.97 (m, 2H), 7.42 (d, 2H, *J* = 8.4 Hz), 7.28 (m, 1H), 6.89 (m, 3H), 4.98 (s, 2H), 4.56 (d, 2H, *J* = 12.0 Hz), 3.97 (s, 1H), (3.88 (s, 1H), 3.76 (d, 3H, *J* = 15.2 Hz), 3.73

(d, 3H, $J = 1.2$ Hz), 2.45 (s, 3H); ^{13}C -NMR (CDCl_3 , 100 MHz) δ 170.5, 170.4, 159.5, 159.3, 159.2, 157.5, 157.3, 147.8, 138.9, 136.6, 136.6, 132.5, 130.2, 130.1, 129.4, 127.8, 126.3, 126.3, 121.4, 120.7, 114.9, 114.6, 114.3, 114.1, 62.5, 53.6 (2 signals; rotamers), 52.5, 51.7, 51.4, 48.1, 47.6, 10.9; HRMS m/e 459.1323 (M^+); Elemental analysis calculated for $\text{C}_{23}\text{H}_{23}\text{ClN}_2\text{O}_6$: C, 60.20%; H, 5.05%; N, 6.10%. Found: C, 60.41%; H, 5.08%; N, 6.00%.

[00143]

Synthesis of Example 1: Glycine, *N*-[[3-[[2-(4-chlorophenyl)-5-methyl-4-oxazolyl]methoxy] phenyl]methyl]-*N*-(methoxycarbonyl)-:

10



[00144] To a stirred solution of methyl ester **1d** (108 g, 235 mmol) in THF (732 mL) and water (366 mL) was added LiOH.H₂O (24.6 g, 585.9 mmol). The mixture was stirred at RT under N₂ for 2 h and diluted with EtOAc (200 mL). The solution was acidified to pH = 2 by the addition of aqueous 1N HCl. The organic layer was separated and the aqueous layer was extracted with EtOAc (2 X 250 mL). The combined organic extracts were washed with water (2 X 150 mL), dried (Na₂SO₄), and concentrated *in vacuo* to give crude acid Example **1** (97 g, 93%). HPLC analysis showed that the purity of this batch was 98.5%.

[00145] Recrystallization: Crude acid Example **1** (210 g, material combined from several batches) was dissolved in hot EtOAc (1.2 L) at 78°C, then was cooled to RT over 60 min, then further cooled to 5°C. The slurry was stirred at 5°C for 40 min and filtered. The solid filter cake was washed with cold EtOAc (2 x 100 mL). The colorless solid was dried *in vacuo* at 55°C for 8 h until a constant weight was obtained. The weight of the purified Example **1** compound was 191 g (91% recovered yield). The chemical purity was determined to be 99.9% by analytical HPLC.

[00146] ^1H NMR (DMSO-*d*₆; 500 MHz, 19.8°C) δ 12.72 (s, 1 H), 7.93 (d, *J*=8.8 Hz, 2 H), 7.57 (d, *J*=8.8 Hz, 2 H), 7.26 (m, 1 H), 6.94 (m, 2 H), 6.86 (m, 1 H), 4.98 (s, 2H), 4.42 (d, *J*=4.4 Hz, 2 H), 3.84 (d, *J*=4.9 Hz, 2 H), 3.60 (d, *J*=7.4 Hz, 3 H), 2.43 (s, 3 H).

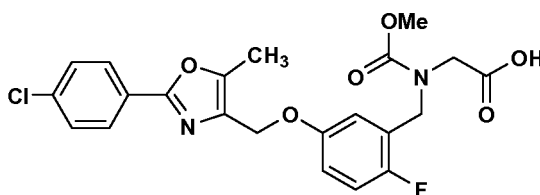
5 [00147] ^1H NMR (DMSO-*d*₆; 500 MHz, 65°C) δ 12.47 (s, 1 H), 7.93 (d, *J* = 8.79 Hz, 2 H), 7.56 (d, *J* = 8.35 Hz, 2 H), 7.25 (t, *J* = 8.13 Hz, 13 H), 6.91 - 6.98 (m, 2 H), 6.86 (d, *J* = 7.47 Hz, 2 H), 4.44 (s, 2 H), 3.85 (s, 2 H), 3.62 (s, 3 H), 2.43 (s, 3 H).

[00148] ^{13}C NMR (DMSO-*d*₆; 126 MHz, 19.8°C) δ 170.7, 170.6, 158.2, 157.9, 156.4, 147.8, 139.2, 135.0, 132.1, 129.2, 127.3, 125.6, 120.1, 119.7, 114.0, 113.4,
10 61.1, 52.6, 51.0, 50.6, 48.4, 47.9, 39.5, 9.9 (note: extra peaks due to rotamers as the spectrum was run at 19.8°C).

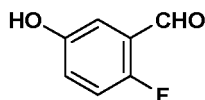
[00149] HRMS(M+H)⁺ = 445.1173 (Δ = 1.4 ppm).

EXAMPLE 2

15 **Glycine, *N*-[[3-[[2-(4-chlorophenyl)-5-methyl-4-oxazolyl]methoxy] 5-fluorophenyl]methyl]-*N*-(methoxycarbonyl)-**



a.



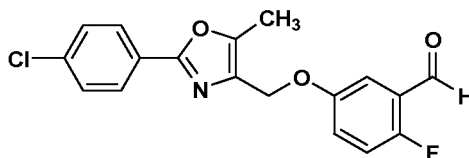
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[00150] To a -78°C solution of 2-fluoro-5-methoxybenzaldehyde (16.2 g, 105.2 mmol) in dry CH₂Cl₂ (60 mL) was added BBr₃ (126.2 mL of a 1.0 M solution in CH₂Cl₂, 126.2 mmol) dropwise over 5 min. The reaction was allowed to warm to 0°C
25 and stirred at 0°C for 4 h, (at this point HPLC/LCMS indicated that starting material had been completely consumed), then was cooled to -78°C. CH₂Cl₂ (200 mL) and water (100 mL) were added cautiously to quench the reaction, which was then

warmed to RT. The organic layer was separated, and the aqueous layer was extracted with CH₂Cl₂ (3 x 200 mL). The combined organic extracts were dried (MgSO₄) and concentrated in vacuo to afford a brown residue, which was chromatographed (120 g SiO₂ ISCO column; continuous gradient from 1:99 to 40:60 EtOAc:hexanes) to give compound **2a** (14 g) as a brown solid. Spectra data for **2a**: ¹H NMR (CDCl₃) δ 10.22 (s, 1H), 7.27-7.45 (m, 2H), 7.11-7.15 (m, 1H), 7.02 (t, 1H, J = 9.4 Hz) ppm; ¹⁹F NMR (CDCl₃) δ -131.95 ppm; ¹³C NMR (CDCl₃) δ 188.66 (d, J = 5.1 Hz), 159.43 (d, J = 251.8 Hz), 152.55, 124.44 (d, J = 10.2 Hz), 123.90 (d, J = 7.6 Hz), 117.65 (d, J = 12.9 Hz), 113.15 ppm; LRMS for C₇H₅FO₂: (M+H)⁺ = 141

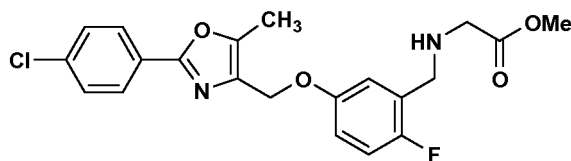
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b. 5-((2-(4-Chlorophenyl)-5-methyloxazol-4-yl)methoxy)-2-fluorobenzaldehyde 3



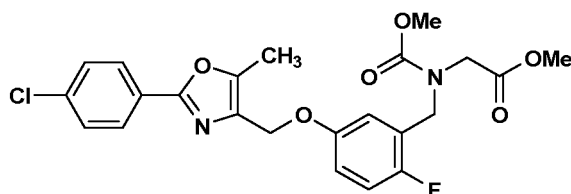
15 **[00151]** A solution of Example **2a** compound (4.0 g, 28.6 mmol), Example **1a** compound (6.89 g, 28.6 mmol) and K₂CO₃ (11.84 g, 85.8 mmol) in MeCN (50 mL) was heated at 80°C under N₂ for 6 h, at which point HPLC analysis indicated that the reaction was complete. The reaction was cooled to RT. CH₂Cl₂ (50 mL) was added and the mixture was stirred for 5 min, then was filtered. The solid was washed with
20 CH₂Cl₂ (20 mL). The combined filtrates were concentrated in vacuo; the residue was chromatographed (SiO₂; 120 g ISCO column; continuous gradient from 1-40% EtOAc in hexanes) to give Example **2b** compound (9.76 g; 99%) as a white solid. ¹H NMR (CDCl₃) δ 10.29 (s, 1H), 7.89 (d, 2H, J = 8.8 Hz), 7.42 (dd, 1H, J = 5.3, 3.6 Hz), 7.35 (d, 2H, J = 8.3 Hz), 7.19-7.22 (m, 1H), 7.06 (t, 1H, J = 9.3 Hz), 4.94 (s, 2H),
25 2.41 (s, 3H) ppm; ¹⁹F NMR (CDCl₃) δ -131.71 ppm; ¹³C NMR (CDCl₃) δ 186.7 (d, J = 7.6 Hz), 159.6 (d, J = 254.3 Hz), 159.1, 154.7, 147.5, 136.1, 131.5, 128.9 (2C), 127.3 (2C), 125.7, 124.5 (d, J = 10.2 Hz), 124.0 (d, J = 10.2 Hz), 117.5 (d, J = 22.9 Hz), 111.0, 62.5, 10.4; LRMS for C₁₈H₁₃ClFNO₃: (M+H)⁺ = 346.

c. **Methyl 2-(5-((2-(4-chlorophenyl)-5-methyloxazol-4-yl)methoxy)-2-fluorobenzylamino)acetate**



[00152] To the above **2b** compound (9.76 g; 28.3 mmol) in dry MeOH (50 mL)
 5 was added glycine methyl ester hydrochloride (4.31 g, 34.3 mmol) and Et₃N (5.17 ml, 37.2 mmol), and the mixture was stirred under N₂ at RT overnight. The reaction was then cooled to -5°C and NaBH₄ (1.41 g, 37.3 mmol) was added portionwise. The reaction was stirred at 0°C for 30 min, then was warmed to RT over 30 min. MeOH (5 mL) was then added dropwise at 0°C to quench the reaction. The mixture was
 10 concentrated in vacuo. The residue was partitioned between EtOAc (100 mL) and water (20 mL). The organic phase was washed with brine (20 mL), dried (MgSO₄), and concentrated in vacuo. The residue was chromatographed (SiO₂; 120 g ISCO column; continuous gradient from 0 to 100% EtOAc in hexanes) to afford Example **2c** compound (8.5 g; 72% yield from Example **2a** compound). ¹H NMR (CDCl₃, N-H
 15 proton not located) δ 7.95 (d, 2H, J = 8.8 Hz), 7.42 (d, 2H, J = 8.8 Hz), 7.03 (dd, 1H, J = 5.7, 2.8 Hz), 6.97 (t, 1H, J = 9.4 Hz), 6.84-6.87 (m, 1H), 4.94 (s, 2H), 3.84 (s, 2H), 3.72 (s, 3H), 3.43 (s, 2H), 2.43 (s, 3H) ppm; ¹⁹F NMR (CDCl₃) δ -128.92 ppm; ¹³C NMR (CDCl₃) δ 172.6, 159.1, 155.8 (d, J = 239.1 Hz), 154.6, 147.4, 136.2, 132.1, 129.01 (2C), 127.4 (2C), 127.1 (d, J = 15.3 Hz), 125.9, 116.2, 115.9 (d, J = 22.9 Hz),
 20 114.8 (d, J = 7.6 Hz), 62.7, 51.80, 49.8, 46.6, 10.5; HRMS for C₂₁H₂₀ClFN₂O₄, Calcd for (M+H)⁺: 419.1174, Found: 419.1170.

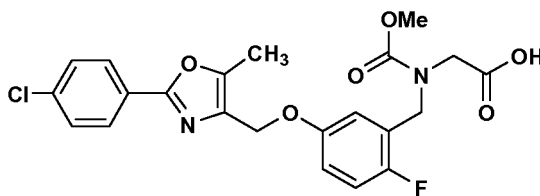
d. **Methyl 2-((5-((2-(4-chlorophenyl)-5-methyloxazol-4-yl)methoxy)-2-fluorobenzyl)(methoxycarbonyl)amino)acetate**



25

[00153] To a THF solution (15 mL) of Example **2c** compound (3.9 g, 9.33 mmol) was added saturated aqueous Na₂CO₃ (10 mL) and methyl chloroformate (2.16 ml, 28 mmol). The reaction was stirred at RT for 20 min; at this time analytical HPLC indicated that the reaction was complete. The reaction was extracted with EtOAc (3 x 40 mL). The combined organic extracts were dried (MgSO₄) and concentrated in vacuo. The residue was chromatographed (SiO₂; 40 g ISCO column; continuous gradient from 0 to 60% EtOAc in hexanes) to afford Example **2d** compound (4.2 g; 95%) as an oil. ¹H NMR (CDCl₃) δ 7.91 (d, 2H, J = 8.3 Hz), 7.38 (d, 2H, J = 8.8 Hz), 6.98-7.0 (m, 1H), 6.94 (dd, 1H, J = 14.8, 8.8 Hz), 6.85-6.90 (m, 1H), 4.90 (s, 2H), 4.55 (d, 2H, J = 7.6 Hz), 3.95 (d, 2H, J = 15.7 Hz), 3.73 (s, 2H, one of carbamate's methoxy group rotamer), 3.69 (s, 4H, contains another carbamate's methoxy group rotamer and the ester methoxy group), 2.40 (s, 3H) ppm; ¹⁹F NMR (CDCl₃) δ -128.31 and -128.63 ppm (rotamers); ¹³C NMR (CDCl₃) δ 169.9, 159.1, 156.9 and 156.7 (1C; rotamers), [156.6 and 154.7 (d, C-F, J = 241.6 Hz), 156.4 and 154.5 (d, C-F, J = 241.6 Hz)] (rotamers), 154.6, 147.4, 136.2 and 136.1 (1C; rotamers), 131.9, 128.9 (2C), 127.3 (2C), 125.8 and 125.7 (1C; rotamers), 124.8 - 124.5 (1C; rotamers), 115.7 - 116.2 (1C; rotamers), 115.4 and 115.3 (1C; rotamers), 114.8 (1C; 2 peaks; rotamers), 62.6, 53.2 and 53.1 (1C; rotamers), 52.1, 48.2 and 47.9 (1C; rotamers), 45.4 and 45.2 (1C; rotamers), 10.4; HRMS for C₂₃H₂₂ClFN₂O₆, Calcd for (M+H)⁺: 477.1229, Found: 477.1225.

Synthesis of Example 2: Glycine, N-[[3-[[2-(4-chlorophenyl)-5-methyl-4-oxazolyl]methoxy] 5-fluorophenyl]methyl]-N-(methoxycarbonyl)-:



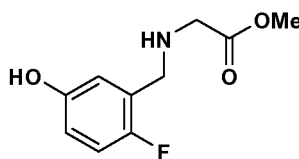
25

[00154] To a solution of Example **2d** compound (4.2 g, 8.8 mmol) in THF (40 mL) was added aqueous NaOH (46 mL of a 1 N solution; 46 mmol). The reaction was stirred for 2 h at RT, after which HPLC indicated that the reaction was complete. The

reaction was acidified with aqueous 1 N HCl to pH ~ 2-3 and extracted with EtOAc (3 x 50 mL). The combined organic extracts were dried (MgSO₄) and concentrated *in vacuo* to ~10 mL volume. MeCN (50 mL) was added, and the mixture was concentrated at 40°C to ~30 mL volume, then was stored at 0°C overnight. The resulting white solid was filtered off, washed with MeCN (10 mL) and dried in *vacuo* for 72 h to afford the title compound **Example 2** (3.2 g). An additional 0.19 g of the title compound was obtained from the mother liquor by further recrystallization from MeCN. ¹H NMR (DMSO-d₆) δ 7.93 (d, 2H, J = 8.4 Hz), 7.58 (d, 2H, J = 8.4 Hz), 7.09 - 7.15 (m, 1H), 6.94 - 6.99 (m, 1H), 6.85-6.90 (m, 1H), 4.97 and 4.96 (s, 2H, rotamers), 4.47 and 4.46 (s, 2H, rotamers), 3.91 (s, 2H), 3.60 and 3.58 (s, 3H, methoxy group rotamers), 2.43 (s, 3H) ppm; ¹⁹F NMR (DMSO-d₆) δ -129.04 and -129.15 ppm (rotamers); ¹³C NMR (DMSO-d₆) δ 170.8 and 170.7 (1C; rotamers), 158.0, 156.2, [155.7 and 153.8; 1C; d C-F, J = 238.0 Hz), 155.6 and 153.7 (1C; d, C-F, J = 236.5 Hz)] (rotamers), 154.3 (1C; 2 peaks; rotamers), 147.9, 135.0, 132.0, 129.3 (2C), 127.4 (2C), 125.6, 125.0-125.5 (1C; rotamers), 115.8-116.1 (1C; rotamers), 115.4-115.8 (1C; rotamers), 114.56-114.93 (rotamers), 61.7, 52.7, 48.8 and 47.4 (1C; rotamers), 45.6 and 45.3 (1C; rotamers), 10.0 ; HRMS for C₂₂H₂₀ClFN₂O₆, Calcd for (M+H)⁺: 463.1072, Found: 463.1076; Anal. Calcd For C₂₂H₂₀ClFN₂O₆: C 57.08; H 4.35; Cl 7.66; F 4.10; N 6.05. Found: C 57.09; H 4.37; Cl 7.62; F 4.08; N 6.19.

Alternative synthesis of Example 2d:

Synthesis of 2e:

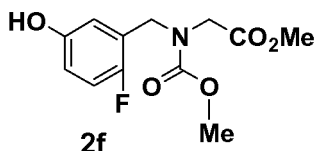


2e

[00155] To glycine methyl ester hydrochloride (0.45 g, 3.6 mmol) in dry MeOH (5 ml) was added Et₃N (0.5 ml, 3.6 mmol). After 5 min, Example **2a** compound (0.25 g, 1.8 mmol) was added and the reaction was stirred at RT for 30 min, followed by the addition of NaBH₄ (0.13 g, 3.6 mmol) over 2 h in four portions. HPLC analysis showed complete reaction. MeOH (5 mL) was then added to the reaction mixture,

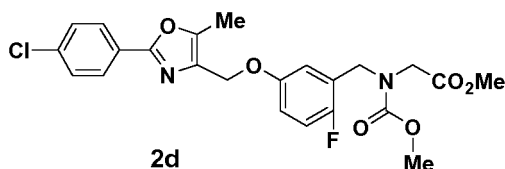
which was then concentrated *in vacuo*. The residue was partitioned between EtOAc and water. The organic phase was washed with brine (10 mL), dried (MgSO₄), and concentrated *in vacuo*. The residue was chromatographed (SiO₂, eluting with 50% EtOAc/heptane; 2x 20 mL) to afford 0.27 g of compound **2e** (71% yield).

5

Synthesis of 2f:

[00156] To a THF (1.3 ml) solution of Example **2e** compound (0.25 g, 1.2 mmol) was added saturated aqueous NaHCO₃ (1 mL). After cooling to 5°C, methyl chloroformate (0.09 ml, 1.2 mmol) was added with stirring. After 10 min, HPLC showed that the reaction was complete. The organic layer (pale clear yellow) was dried (Na₂SO₄), and concentrated *in vacuo* to give crude **2f** compound as a pale yellow oil (0.40 g), which was used in the next reaction without further purification.

15

Alternate synthesis of 2d:

[00157] A cloudy white slurry of crude Example **2f** compound (0.32 g, ≤ 1.2 mmol), Example **1a** compound (0.29 g, 1.2 mmol), and K₂CO₃ (0.5 g, 3.6 mmol) in MeCN (5 mL) was heated at 55°C for 4 h. At this point, HPLC showed <2 % of unreacted compound **2f** remained. The reaction was cooled to RT and saturated aqueous NH₄Cl (5 mL) was added; the aqueous layer was extracted with EtOAc (2 x 10 mL). The combined organic extracts were dried (Na₂SO₄) and concentrated *in vacuo*. The crude product was purified by silica gel chromatography as previously described for **2d** to give 0.44 g of Example **2d** compound as a clear oil. The ¹H-NMR

25

spectrum is consistent with the sample of Example **2d** compound prepared using the previous synthetic route.

Biological Data

5 **[00158]** In vitro PPAR agonist functional assays were performed by transiently transfecting GAL4-hPPAR α -LBD or GAL4-hPPAR γ -LBD constructs respectively into HEK293 (human embryonic kidney) cells stably expressing 5 x GAL4RE-Luciferase. Agonist binding results in an increase in luciferase enzyme activity which can be monitored by measuring luminescence upon cell lysing and the addition
10 of luciferin substrate. EC₅₀ values (μ M) for PPAR α or γ agonist activity were calculated as the concentration of the test ligand (μ M) required for the half-maximal activity in HEK293 cells. The efficacy of a test ligand is defined as its maximum activity as compared to the maximal activity of the primary standards, 100 μ M fenofibric acid for PPAR α and 1 μ M rosiglitazone for PPAR γ , reported as % efficacy.
15 Compounds of formula I are functional agonists with activities in the range of EC₅₀ = 1-10 nM against the human PPAR α receptor and EC₅₀ > 4000 nM against the human PPAR γ receptor. The ratios of the PPAR γ :PPAR α EC₅₀ values of compounds of formula I are between 400 and 1100 in this functional assay.

20

Table 1

In vitro functional data for Compounds 1 - 2

Compound	PPAR α EC ₅₀ (nM) (% efficacy)	PPAR γ EC ₅₀ (nM) (% efficacy)
1	10 \pm 3 (81 \pm 14%)	4090 \pm 1741 (83 \pm 8%)
2	4 \pm 1 (81 \pm 10%)	4511 \pm 1314 (67 \pm 13%)

[00159] The present PPAR α selective agonists/activators of Formula I are more potent in a GAL4 functional transactivation assay in a HEK (human embryonic
25 kidney) cell line than the current marketed PPAR α selective agonists (fibrates). The

current fibrates are weak PPAR α ligands, and have modest efficacy in modulating serum lipids.

[00160] It is known by one skilled in the art that the compounds of the present invention decrease plasma triglycerides and cholesterol levels at doses ≥ 10 mg/kg in rodent models of atherosclerosis and dyslipidemia (e. g. the high fat-fed hamster model). The typical administration of said compounds is expected to be between 0.1 to 2,000 mg/day in the clinical setting, and is preferably between 0.5 to 100 mg/day. (Reference for high fat-fed hamster model as an in vivo rodent model for anti-atherosclerosis efficacy: P-R Wang et al., *Eur. Journ. of Pharm.*, **2001**, 427, 285-293).

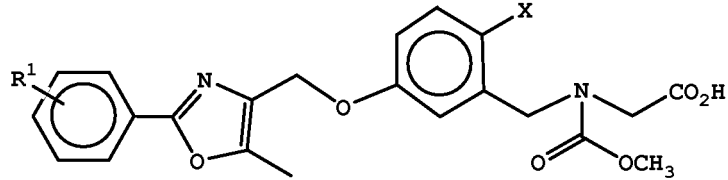
[00161] Male Golden Syrian Hamster (*Mesocricetus auratus*), 7-10 weeks of age and weighing 110-120 grams, were put on a high fat diet (D11953) for two weeks. The high fat diet was formulated by Research Diets, Inc, New Brunswick, NJ using Purina 5001 as the base diet. Final composition (% by weight) of the diet is: 11.5% coconut oil, 11.5% corn oil, 0.5% cholesterol and 5% fructose. Hamsters were then dosed orally once daily with the Example 1 or 2 compounds using a vehicle comprised of 5% Cremaphore, 5% ethanol, 10% 1-methyl-pyrrolidinone, and 80% water. Plasma samples were obtained from hamsters fasted overnight (18 hours after last administration of compound) on day 22. The plasma triglyceride and cholesterol levels were determined and the percentage reductions in both parameters of drug-treated animals relative to vehicle-treated animals are shown in Table 2 below.

Table 2.

Compound (10 mg/kg orally dosed once daily for 14 days)	% Reduction in Plasma Total Cholesterol vs Vehicle-control group	% Reduction in Plasma Triglycerides vs Vehicle-control group
1	-38%	-77%
2	-60%	-85%

WHAT IS CLAIMED IS:

1. A compound having the structure of Formula (I):

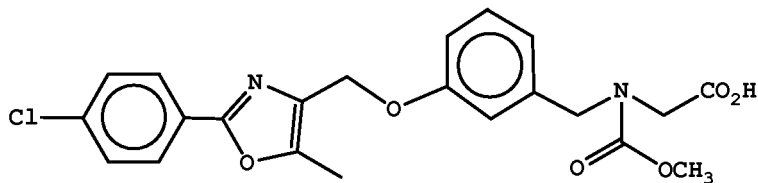


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(I) ,

wherein R¹ is halogen; and X is hydrogen or halogen, and salts thereof.

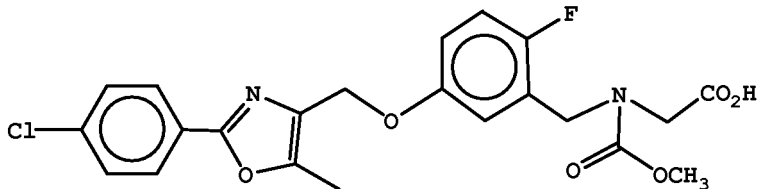
2. A compound having the structure of Formula (Ia):



Ia, and salts thereof.

10

3. A compound having the structure of Formula (Ib):



Ib, and salts thereof.

4. A pharmaceutical composition comprising a compound as defined in Claim 1 and a pharmaceutically acceptable carrier thereof.

15

5. A method for treating atherosclerosis which comprises administering to a patient in need of treatment a therapeutically effective amount of a compound as defined in Claim 1.

20

6. A method for lowering blood glucose levels which comprises administering to a patient in need of treatment a therapeutically effective amount of a compound as defined in Claim 1.

7. A method for treating diabetes which comprises administering to a patient in need of treatment a therapeutically effective amount of a compound as defined in Claim 1.

5

8. A method for treating dyslipidemia which comprises administering to a patient in need of treatment a therapeutically effective amount of a compound as defined in Claim 1.

9. A pharmaceutical combination comprising a compound as defined in Claim 1 and a anti-dyslipidemic agent, a lipid modulating agent, an anti-diabetic agent, an anti-obesity agent, an anti-hypertensive agent, a platelet aggregation inhibitor or an anti-osteoporosis agent, or a combination thereof.

10. The pharmaceutical combination as defined in Claim 9, comprising said compound and an anti-diabetic agent.

11. The pharmaceutical combination as defined in Claim 10, wherein the anti-diabetic agent is 1, 2, 3 or more of a biguanide, a sulfonyl urea, a glucosidase inhibitor, a PPAR γ agonist, a PPAR α/γ dual agonist, an SGLT2 inhibitor, a DP4 inhibitor, an insulin sensitizer, a glucagon-like peptide-1 (GLP-1) or one of its analogs, a cannabinoid receptor 1 (CB-1) antagonist, insulin or a meglitinide, or a combination thereof.

12. The pharmaceutical combination as defined in Claim 11, wherein the anti-diabetic agent is 1, 2, 3 or more of metformin, glyburide, glimepiride, glipyrice, glipizide, chlorpropamide, gliclazide, acarbose, miglitol, pioglitazone, rosiglitazone, insulin, exenatide, sitagliptin, saxagliptin, vildagliptin, alogliptin, NN-2344, L895645, YM-440, R-119702, AJ9677, repaglinide, nateglinide, KAD1129, AC2993, LY315902, P32/98 or NVP-DPP-728A, or a combination thereof.

13. The pharmaceutical combination as defined in Claim 10, wherein said compound is present in a weight ratio to the anti-diabetic agent within the range from about 0.001 to about 100:1.

5 14. The pharmaceutical combination as defined in Claim 9, wherein the anti-obesity agent is a beta 3 adrenergic agonist, a lipase inhibitor, a serotonin (and dopamine) reuptake inhibitor, a thyroid receptor agonist, a cannabinoid receptor 1 (CB-1) antagonist, and aP2 inhibitor or an anorectic agent or a combination thereof.

10 15. The pharmaceutical combination as defined in Claim 14, wherein the anti-obesity agent is orlistat, ATL-962, AJ9677, L750355, CP331648, sibutramine, topiramate, axokine, dexamphetamine, phentermine, phenylpropanolamine, rimonabant, SLV-319, or mazindol or a combination thereof.

15 16. A method for treating insulin resistance, hyperglycemia, hyperinsulinemia, elevated blood levels of free fatty acids or glycerol, dyslipidemia, obesity, Syndrome X, dysmetabolic syndrome, inflammation, diabetic complications, impaired glucose homeostasis, impaired glucose tolerance, hypertriglyceridemia or atherosclerosis, which comprises administering to a mammalian species in need of
20 treatment thereof a therapeutically effective amount of a pharmaceutical combination as defined in Claim 9.

17. A method for treating irritable bowel syndrome, Crohn's disease, gastric ulceritis, osteoporosis, or psoriasis, which comprises administering to a
25 mammalian species in need of treatment thereof a therapeutically effective amount of a compound as defined in Claim 1.

18. A method for treating irritable bowel syndrome, Crohn's disease, gastric ulceritis, osteoporosis, or psoriasis, which comprises administering to a
30 mammalian species in need of treatment thereof a therapeutically effective amount of a pharmaceutical combination as defined in Claim 9.