SUBSTITUTED ACID DERIVATIVES USEFUL AS ANTIDIABETIC AND ANTIOBESITY AGENTS AND METHOD

Compounds are provided which have the structure of Formula (I): wherein R is hydrogen or C1-C4 alkyl, and each of R1 and R2 is independently hydrogen, C1-C4 alkyl, halo or C1-C4 alkoxy, and salts thereof, which compounds are useful as antidiabetic, hypolipidemic, and antiobesity agents.
The present invention relates to novel substituted acid derivatives which modulate blood glucose levels, triglyceride levels, insulin levels and non-esterified fatty acid (NEFA) levels, and thus are particularly useful in the treatment of diabetes and obesity, and to a method for treating diabetes, especially Type 2 diabetes, as well as hyperglycemia, hyperinsulinemia, dyslipidemia, obesity, atherosclerosis and related diseases employing such substituted acid derivatives alone or in combination with another antidiabetic agent and/or an anti-dyslipidemic agent.

In accordance with the present invention, substituted acid derivatives are provided which have the Formula (I):

wherein R is hydrogen or C₁-C₄ alkyl; and each of R¹ and R² is independently hydrogen, C₁-C₄ alkyl, halo or C₁-C₄ alkoxy, and salts thereof.

A preferred compound of the present invention has the structure of Formula (Ia):
Another preferred compound of the instant invention has the structure of Formula (Ib):

Yet another preferred compound of the instant invention has the structure of Formula (Ic):

In addition, in accordance with the present invention, a method is provided for treating 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, atherosclerosis, and related diseases wherein a therapeutically effective amount of a compound of Formula I is administered to a human patient in need of treatment.

[0007] For ease of reference, when Formula I is mentioned in the description of the invention, it is intended that Formulae Ia, Ib and Ic are also included in the scope thereof.

[0008] 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), 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.

[0009] Furthermore, in accordance with the present invention, a method is provided for treating diabetes and related diseases as defined above and hereinafter, wherein a therapeutically effective amount of a combination of a compound of Formula I and another type anti-diabetic agent and/or a hypolipidemic agent, and/or lipid modulating agent and/or other type of therapeutic agent, is administered to a human patient in need of treatment.

[0010] In the above methods of the invention, the compound of Formula I will be employed in a weight ratio to the anti-diabetic 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.


[0012] The term “diabetes and related diseases” refers to Type II diabetes, Type I diabetes, impaired glucose tolerance, obesity, hyperglycemia, Syndrome X, dysmetabolic syndrome, diabetic complications and hyperinsulinemia.
The conditions, diseases and maladies collectively referred to as “diabetic complications” include retinopathy, neuropathy and nephropathy, and other known complications of diabetes.

The term “other type(s) of therapeutic agents” as employed herein refers to one or more anti-diabetic 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 anti-platelet 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 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.

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 disorders.

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 or nitrogen in the normal chain, such as methyl, ethyl, propyl, isopropyl, butyl, t-butyl, isobutyl, pentyl, hexyl, isoamyl, 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, arylxoy, aryl(aryl) or diaryl, arylalkyl, arylalkyloxy, alkenyl, cycloalkyl, cycloalkylalkyl, cycloalkylalkyloxy, amino, hydroxy, hydroxyalkyl, acyl, heteroaryl, heteroaryloxy, cycloheteroalkyl, arylheteroaryl, arylalkoxycarbonyl, heteroarylalkyl, heteroarylalkoxy, arylxoyalkyl, aryloxyaryl, alkylamido, alkanoylamino, arylcarbonylamino, nitro, cyano, thiol, haloalkyl, trihaloalkyl and/or alkylthio and/or any of the R³ groups.

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.

[0018] 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.

[0019] 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”.

[0020] The term “alkanoyl” as used herein alone or as part of another group refers to alkyl linked to a carbonyl group.

[0021] 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-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, alkanoylamino, alkylamido, arylcarbonylamino, nitro, cyano, thiol, alkylthio and/or any of the substituents for alkyl set out herein.

5 [0022] 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 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-butylnyl, 2-butylnyl, 4-pentylnyl, 3-pentylnyl, 2-hexynyl, 3-hexynyl, 2-heptynyln, 3-heptynyln, 4-heptynyln, 3-octynyl, 3-nonylnyl, 4-decynyl, 3-undecynyl, 4-dodecynyl 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, heteroaryl, cycloheteroalkyl, hydroxy, alkanoylamino, alkylamido, arylcarbonylamino, nitro, cyano, thiol, and/or alkylthio, and/or any of the substituents for alkyl set out herein.

10 [0023] The terms “aryalkenyl” and “arylalkynyl” as used alone or as part of another group refer to alkenyl and alkynyl groups as described above having an aryl substituent.

[0024] 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”.

[0025] 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 “alkylene groups” and “alkynylene groups”, respectively, and may optionally be substituted as defined above for “alkenyl” and “alkynyl”.

25 [0026] \((\text{CH}_2)_n, (\text{CH}_3)_n, (\text{CH}_2)_n\) or \((\text{CH}_2)_n\) 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 \((\text{CH}_2)_n\) or \((\text{CH}_3)_n\) or \((\text{CH}_2)_n\) group to form a cycloalkyl group therewith.
Examples of \((\text{CH}_2)_n\), \((\text{CH}_2)_m\), \((\text{CH}_2)_m\), \((\text{CH}_2)_n\), alkyne, alkenylene and alkynylene include

\[
\begin{align*}
\text{-CH=CH-CH-}, & \quad \text{-CH}_2\text{CH=CH-}, & \quad \text{-C=C-CH-}, & \quad \text{-CH}_2\text{C-}, \\
\text{-CH}_2\text{-CH}_2\text{-CH-}, & \quad \text{-CH}_2\text{C=CHCH}_2, & \quad \text{CH}_3, & \quad \text{-CH=CH-CH-}, \\
\text{(CH}_2\text{)}_2, & \quad \text{(CH}_2\text{)}_3, & \quad \text{(CH}_2\text{)}_4, & \quad \text{(CH}_2\text{)}_2\text{CH=CH}-\text{CH}_3, & \quad \text{-CH-}, \\
\text{C}_2\text{H}_5, & \quad \text{n-C}_3\text{H}_7, & \quad \text{CH}_2\text{CH=CH}_2, & \quad \text{CH}_3, & \quad \text{CH}_3, \\
\text{-CH-}, & \quad \text{-CH-}, & \quad \text{-CH-}, & \quad \text{-CH-CH}_3, & \quad \text{C}, \\
\text{CH}=\text{CH-CH}_2, & \quad \text{H}_3\text{C}, & \quad \text{C-CH}_2, & \quad \text{-CH=C=CH-}, & \quad \text{-CH}_2\text{C=C-}, & \quad \text{-CH}_2\text{CH=CH-}, \\
\text{CH}_3, & \quad \text{CH}_2\text{CHCH}_2, & \quad \text{CHCH}_2, & \quad \text{CHCHCH}_2, \\
\text{(CHCHCH}_2, & \quad \text{CH}_2\text{C-CH}_2, & \quad \text{(CH}_2\text{)}_5, & \quad \text{(CH}_2\text{)}_2\text{C-CH}_2, \\
\text{CH}_3, & \quad \text{CH}_3, & \quad \text{F}, & \quad \text{F}, \\
\text{-CH}_2\text{-CH-CH}_2, & \quad \text{(CH}_2\text{)}_2\text{-CH-}, & \quad \text{-CH}_2\text{-CH-CH}_3, & \quad \text{CH}_3, \\
\text{CH}_3, & \quad \text{CH}_3, & \quad \text{CH}_3, & \quad \text{CH}_3, \\
\text{-CH}_2\text{-CH-CH-CH}_2, & \quad \text{-CH}_2\text{-CH-CH}_2\text{-CH-}, & \quad \text{-CH-CH}_2\text{CH-}, & \quad \text{-CH}_2\text{CH=CH-CH}_2. \\
\end{align*}
\]
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.

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.

Unless otherwise indicated, the term “aryl” or the group

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
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, aryloxalkyl, arylalkoxy, alkoxy carbonyl, arylcarboxyl, arylalkenyl, aminocarbonylaryl, arylthio, arylsulfanyl, arylazo, heteroarylalkyl, heteroarylcycloalkyl, heteroarylthio, 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, arylthio alkyl, alkoxy alkyl, alkylsulfanyl, alkylsulfinylland/or any of the substituents for alkyl set out herein.

[0031] 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.

[0032] 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, heteroarylcycloalkyl, 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-pyrroolidinyl, 1-piperidinyl, 1-azepinyl, 4-morpholinyl, 4-thiomorpholinyl, 1-piperazinyl, 4-alkyl-1-piperazinyl, 4-aryalkyl-1-piperazinyl, 4-diarylalkyl-1-piperazinyl, 1-pyrroolidinyl, 1-piperidinyl, or 1-azepinyl, optionally substituted with alkyl, alkoxy, alkylthio, halo, trifluoromethyl or hydroxy.
Unless otherwise indicated, the term “lower alkylthio”, alkythio”, “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.

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.

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 group; examples of acyl groups include any of the $R^3$ groups attached to a carbonyl, such as alkanoyl, alkenoyl, aroyl, aralkanoyl, heteroaroyl, cycloalkanoyl, cycloheteroalkanoyl and the like.

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 (CH$_2$)$_p$ (where $p$ is 1, 2 or 3), such as

![Diagram of various acyl and cycloheteroalkyl groups]

and the like. The above groups may include 1 to 4 substituents such as alkyl, halo, 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.

[0037] 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 the substituents for alkyl or aryl
set out above. Examples of heteroaryl groups include the following:

and the like.

[0038] 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 (CH₂)ₚ chain.
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 C atom or heteroatom to a -(CH₂)ₚ- chain, alkenylene or alkenylene as defined above.

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 CF₃CH₂, CF₂, or CF₃CF₂CH₂.

The term “polyhaloalkyloxy” as used herein refers to an “alkoxy” or “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 CF₃CH₂O, CF₂O or CF₃CF₂CH₂O.

The term “prodrug esters” as employed herein includes prodrug esters which are known in the art for carboxylic acid and phosphorus acid esters such as methyl, ethyl, benzyl and the like. Other prodrug ester examples of R⁴ include the following groups:

(1-alkanoyloxy)alkyl such as,

\[
\text{R}^a \quad \text{R}^b \quad \text{R}^c
\]

wherein R⁴, R⁴ and R⁵ are H, alkyl, aryl or arylalkyl; however, R⁴O cannot be HO.

Examples of such prodrug esters R⁴ include

\[
\text{CH}_3\text{CO}_2\text{CH}_2, \quad \text{CH}_3\text{CO}_2\text{CH}_2, \quad \text{t-C}_4\text{H}_9\text{CO}_2\text{CH}_2 \quad \text{or}
\]

\[
\text{CH}_3\text{CO}_2\text{CH}_2
\]

Other examples of suitable prodrug esters R⁴ include
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^e is alkyl, aryl, arylalkyl or alkoxy, and n_1 is 0, 1 or 2.

[0045] Where the compounds of Formula I are in acid form they may form a 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.

[0046] All stereoisomers of the compounds of the instant invention are contemplated, either in admixture or in pure or substantially pure form. The compounds of the present invention can have chiral centers at any of the carbon atoms including any one of the R substituents. Consequently, compounds of Formula I can exist in enantiomeric or diastereomeric forms or in mixtures thereof. The processes for preparation can utilize racemates, enantiomers or diastereomers as starting materials. When diastereomeric or enantiomeric products are prepared, they can be separated by conventional methods for example, chromatographic or fractional crystallization.

[0047] 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 embodiments.

**UTILITIES AND COMBINATIONS**
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.

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, lipooxygenase 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.


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

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.

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
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 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 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 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.

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


[0058] Other anti-dyslipidemic agents suitable for use herein include, but are not limited to, propbucol, and related compounds as disclosed in U.S. Patent No. 3,674,836, propbucol 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-aminoaclyclic acid, aspirin; poly(diallylmethylamine) derivatives such as disclosed in U.S. Patent No. 4,759,923; 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.

[0059] 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, Cl-1011 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

[0060] The anti-dyslipidemic agent may be an upregulator of LD2 receptor activity such as MD-700 (Taisho Pharmaceutical Co. Ltd) and LY295427 (Eli Lilly).


[0062] 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).

[0063] 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 Pharmacia’s SC-744 and SC-795.

[0064] 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.

[0065] Preferred anti-dyslipidemic agents are pravastatin, lovastatin, simvastatin, atorvastatin, fluvastatin, itavastatin and visastatin and ZD-4522.

[0066] 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.
[0067] The compounds of Formula I of the invention will be employed in a 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.

[0068] 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.

[0069] The dosages and formulations for the anti-dyslipidemic agent will be as disclosed in the various patents and applications discussed above.

[0070] 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.

[0071] 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.

[0072] 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 to about 400 mg, and more preferably from about 5 to about 250 mg, one to four times daily.

[0073] 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 2000 mg, and preferably from about 4 to about 200 mg.

[0074] 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.

[0075] A preferred oral dosage form, such as tablets or capsules, will contain the 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.

[0076] 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, preferably from about 25 to about 200 mg.

[0078] The compounds of Formula I and the anti-dyslipidemic agent may be employed together in the same oral dosage form or in separate oral dosage forms taken at the same time.

[0079] 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 be advisable to start a patient on a low dose combination and work up gradually to a high dose combination.

[0080] The preferred anti-dyslipidemic agent is pravastatin, simvastatin, lovastatin, atorvastatin, fluvastatin or rosuvastatin as well as niacin and/or cholestagel.

[0081] The other antidiabetic agent which may be optionally employed in 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 biguanides, sulfonyl ureas, glucosidase inhibitors, PPAR \( \gamma \) 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).

[0082] The other antidiabetic agent may be an oral antihyperglycemic agent preferably a biguanide such as metformin or phenformin or salts thereof, preferably metformin HCl.

[0083] 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.
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. 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.

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

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 dosage forms.

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.

The compounds of Formula I may be employed in combination with a 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.

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.

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 of Formula I.

The compounds of Formula I may also be employed in combination with an 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 reference), as
well as AC2993 (Amylin) and LY-315902 (Lilly), which may be administered via injection, intranasal, inhalation or by transdermal or buccal devices.

[0092] Where present, metformin, the sulfonyl ureas, such as glyburide, glimepiride, glipizide, chlorpropamide and gliclazide and the glucosidase inhibitors acarbose or miglitol or insulin (injectable, pulmonary, buccal, or oral) may be employed in formulations as described above and in amounts and dosing as indicated in the Physician’s Desk Reference (PDR).

[0093] 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.

[0094] 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.

[0095] Where present insulin may be employed in formulations, amounts and dosing as indicated by the Physician’s Desk Reference.

[0096] 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.

[0097] The other antidiabetic agent may also be a PPAR α/γ dual agonist such as Muraglitazar (Bristol-Myers Squibb).

[0098] 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 US614126.

[0099] 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 (PROBIDRUG), WO99/67278 (PROBIDRUG), WO99/61431 (PROBIDRUG), NVP-DPP728A (1-[[2-[[5-cyanopyridin-2-yl]amino]ethyl]amino]acyl]-2-cyano-(S)-pyrrolidine) (Novartis) as disclosed by Hughes et al, Biochemistry, 38(36), 11597-11603,

[00100] 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.

[00101] 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.

[00102] 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.

[00103] 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.

[00104] 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.

[00105] 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.

[00106] 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.

[00107] 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.

[00108] The anorectic agent which may be optionally employed in combination with a compound of Formula I may be dexamphetamine, phenetermine, phenylpropanolamine or mazindol, with dexamphetamine being preferred.

[00109] 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.

[00110] 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.

[00111] 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-mercaptop-2-methylpropionyl]-L-proline, being preferred, and mercaptooeyl derivatives of substituted prolines such as any of those disclosed in U.S. Pat. No. 4,316,906 with zofenopril being preferred.

[00112] Other examples of mercapto containing ACE inhibitors that may be employed herein include reniapril (fentiapril, Santen) disclosed in Clin. Exp. Pharmacol. Physiol. 10:131 (1983); as well as pivopril and YS980.

[00113] Other examples of angiotensin converting enzyme inhibitors which may 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-pherylbutyl)phosphinyl]oxy]-1-oxohexyl]-L-proline or (ceronapril) being preferred; phosphinylalkanoyl prolines disclosed in U.S. Pat. No. 4,168,267 mentioned above with
fosinopril being preferred; any of the phosphinyalkanoyl 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.


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

[00117] 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-
(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.

[00118] 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, tasosartan or eprosartan, with
irbesartan, losartan or valsartan being preferred.

[00119] 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.

[00120] For parenteral administration, the ACE inhibitor, angiotensin II antagonist or
NEP/ACE inhibitor will be employed in an amount within the range from about 0.005
mg/kg to about 10 mg/kg and preferably from about 0.01 mg/kg to about 1 mg/kg.

[00121] 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.

[00122] 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).

[00123] Other examples of preferred antihypertensive agents suitable for use herein
include omapatrilat (Vanlev\(^\text{®}\)), amlodipine besylate (Norvasc\(^\text{®}\)), prazosin HCl
(Minipress\(^\text{®}\), verapamil, nifedipine, nadolol, diltiazem, felodipine, nisoldipine,
isradipine, nicardipine, atenolol, carvedilol, sotalol, terazosin, doxazosin, propranolol,
and clonidine HCl (Catapres\(^\text{®}\)).

[00124] Diuretics which may be employed in combination with compounds of
Formula I include hydrochlorothiazide, torasemide, furosemide, spironolactone, and
indapamide.

[00125] 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.

[00126] 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.

5 [00127] 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 be as set out in the PDR.

[00128] 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).

[00129] 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.

[00130] The following Examples represent preferred embodiments of the invention.

ABBREVIATIONS

[00131] For ease of reference, the following abbreviations are employed herein, including the methods of preparation and Examples that follow:

30 aq. = aqueous
Ar = argon
Bn = benzyl
Boc = tert-butoxycarbonyl
BOP reagent = benzotriazol-1-ylxy-tris (dimethylamino) phosphonium hexafluorophosphate
CAN = ceric ammonium nitrate

5 Cbz = carboxyloxy or carbobenzoxy or benzoyloxycarbonyl
Cbz-Cl = benzyl chloroformate
DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene
DCE = 1,2-dichloroethane
DEAD = diethyl azodicarboxylate

10 DIAD = diisopropyl azodicarboxylate
DIBALH = diisobutyl aluminum hydride
DMAP = 4-dimethylaminopyridine
DME = 1,2-dimethoxyethane
DMF = dimethyl formamide

15 DMSO = dimethyl sulfoxide
EDC (or EDC.HCl) or EDCI (or EDCI.HCl) or EDAC = 3-ethyl-3’-(dimethylamino)propyl carbodiimide hydrochloride (or 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride)
Et = ethyl

20 Et₂O = diethyl ether
Et₃N = triethylamine
EtOAc = ethyl acetate
EtOH = ethanol
FMOC = fluorenylmethoxycarbonyl

g = gram(s)
h or hr = hour(s)
hex = hexanes
HMPA = hexamethyl phosphoric triamide
HOAc or AcOH = acetic acid

30 HOAT = 1-Hydroxy-7-azabenzotriazole
HOBT or HOBT.H₂O = 1-hydroxybenzotriazole hydrate
HPLC = high performance liquid chromatography
i-Pr$_2$NEt = diisopropylethylamine
i-PrOH = IPA = isopropanol
K$_2$CO$_3$ = potassium carbonate
KOH = potassium hydroxide

5 L = liter
LC/MS = high performance liquid chromatography/mass spectrometry
LiAlH$_4$ = lithium aluminum hydride
LiOH = lithium hydroxide
LRMS = low resolution mass spectrometry

10 Me = methyl
MeOH = methanol
meq = milliequivalent
mg = milligram(s)
min = minute(s)

15 mL = milliliter
mmol = millimole(s)
mol = moles
mp = melting point
MS or Mass Spec = mass spectrometry

20 N$_2$ = nitrogen
NaBH(OAc)$_3$ = sodium triacetoxyborohydride
NaBH$_4$ = sodium borohydride
NaHCO$_3$ = sodium bicarbonate
NaN(TMS)$_2$ = sodium hexamethyldisilazide or sodium bis(trimethylsilyl)amide

25 NaOH = sodium hydroxide
n-BuLi = n-butyllithium
NMM = N-methyl morpholine
NMR = nuclear magnetic resonance
NMR spectral data: s = singlet; d = doublet; m = multiplet; br = broad; t = triplet

30 Pd(OAc)$_2$ = Palladium acetate
Pd/C = palladium on carbon
Ph = phenyl
Ph₃P = triphenylphosphine
(Ph₃P)₄Pd⁰ = tetrakis triphenylphosphine palladium
PtO₂ = platinum oxide
RT = room temperature
5 sat or sat’d = saturated
SAX = Strong Anion Exchanger
SCX = Strong Cation Exchanger
TBS = tert-butyldimethylsilyl
t-Bu = tertiary butyl
10 TFA = trifluoroacetic acid
THF = tetrahydrofuran
TLC = thin layer chromatography
TMS = trimethylsilyl
TMSN₃ = trimethylsilyl azide
15 μL = microliter

METHODS OF PREPARATION

[00132] Schemes 1-2 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 methods used by one of ordinary skill in the art.

[00133] The compounds of Formula (I) may generally be prepared according to the following schemes and the knowledge of one skilled in the art.

SCHEMES
The synthesis of Compound I (including Compounds Ia, Ib and Ic) can be accomplished via the general route shown above in Scheme 1 which adapted the key steps from the previous synthesis of Example 498 in U.S. Patent No. 6,414,002 B1, incorporated by reference herein. The synthesis of the key chiral secondary amine VI...
was accomplished using the 5-step sequence shown in the scheme below, starting from (S)-(-)-1-(4-methoxyphenyl)ethylamine II. Demethylation of II with HBr in acetic acid with heating furnished the crude phenol-amine hydrobromide III, which was immediately reacted with benzyl chloroformate in aqueous base/THF to give the phenol-benzyl carbamate IV. Phenol IV was protected (e.g. as a tert-butyl dimethylsilyl ether) and the benzyl carbamate was subsequently hydrogenolyzed to provide the protected benzylamine V. Alkylation of amine V with methyl bromoacetate in the presence of base (e.g. triethylamine) furnished the key secondary amine intermediate VI. Acylation of secondary amine VI with an appropriately substituted aryl chloroformate VII under Schotten-Baumann conditions provided the carbamate-ester VIII, which was then deprotected to provide the aryl carbamate phenol IX. Alkylation of phenol IX with the chlorophenylloxazole X under basic conditions with heating gave the penultimate intermediate phenyloxazole carbamate ester XI. Hydrolysis of XI in aqueous lithium hydroxide/THF furnished Compounds Ia-Ic.
An alternative synthetic route to Compounds Ia-Ic is shown in Scheme 2 above. 4-hydroxybenzaldehyde XII is alkylated with chlorophenyl oxazole X in the presence of base and sodium iodide to give the alkylated phenyloxazole-benzaldehyde XIII. Condensation of the chiral tert-butyl sulfonamide XIV furnishes the chiral imine XV. Highly diastereoselective addition of methyl magnesium bromide to the chiral imine XV provides the methylated sulfonamide XVI. The tert-butyl sulfonamide is deprotected to give the chiral α-methyl benzylamine XVII, which is alkylated with ethyl bromoacetate in the presence of base (e.g. triethylamine) to furnish the key secondary amine XVIII. Amine XVIII is acylated with an appropriate aryl chloroformate VII in the presence of aqueous base (e.g. Schotten-Baumann conditions) to give the carbamate esters XIX. Base-mediated hydrolysis of the esters XIX provides the desired compound Ia-Ic.
EXAMPLES

Example 1
Preparation of Compound 1a (Procedure 1).

Synthesis of 3-fluoro-4-methylphenyl carbonochloridate (2):

[00136] A 1L 3-necked round bottom flask equipped with a mechanic stirrer was charged with 3-fluoro-4-methylphenol 1 (50 g, 446 mmol), triphosgene (43.67g, 147 mmol) and CH$_2$Cl$_2$ (400 mL). Pyridine (35.2 g, 446 mmol) was added dropwise at 0°C under N$_2$ over a period of 30 minutes. The reaction mixture was allowed to warm to room temperature over 45 minutes, and then stirred at reflux for an additional 2 hours. The reaction was cooled to room temperature, and the solvents were removed in vacuo.

Anhydrous Et$_2$O (200 mL) was added to the residue, and the resulting slurry was filtered. The filtrate was concentrated in vacuo to afford crude 3-fluoro-4-methylphenyl chloroformate (83.5g, 99% yield) as a thick oil, which was immediately used in the next step without further purification.

Synthesis of 4-(chloromethyl)-5-methyl-2-phenyloxazole (3):
Gaseous HCl was bubbled through a mixture of benzaldehyde (110 g; 1.04 mol) and 2,3-butanedione monoxime (100 g, 0.990 mol) in EtOAc (500 mL) at 0°C for ~10 minutes. The reaction mixture was stirred overnight at room temperature and concentrated in vacuo (to 100 mL). A precipitate formed, which was filtered and washed with cold EtOAc. The crude N-oxide was dissolved in CHCl₃ (800 mL), and POCl₃ (101 mL, 1.09 mol) was added at room temperature in one portion. The reaction was heated to 60°C and stirred at 60°C for 12 hours, then cooled to room temperature and concentrated in vacuo. The residue was taken up in EtOAc and neutralized/basified with saturated aqueous NaHCO₃ and solid Na₂CO₃. The mixture was stirred vigorously for 15 min at room temperature and partitioned. The organic phase was dried (MgSO₄) and concentrated in vacuo to give the crude product (162 g) as a gray solid. This material was recrystallized from EtOAc/hexane to give 3 (109 g; 54%; HPLC purity = 98.1%) as an off-white crystalline solid. An additional 47 g of crude product in the mother liquor was not further purified. A purified sample was characterized:

1H NMR (CDCl₃, 400 MHz): δ 2.41 (s, 3H, CH₃), 4.56 (s, 2H, CH₂), 7.43 (m, 3H, Ar-H), 8.00 (m, 2H, Ar-H).

13C NMR (400 MHz, CDCl₃): δ 10.2 (CH₃), 37.2 (CH₂), 126.1 (CH), 127.1 (C), 128.6 (CH), 130.1 (CH), 132.8 (C), 146.5 (C), 159.9 (C).

LC/MS m/z 207 (M⁺); HPLC (continuous gradient from 50:50 Solvent A:B to 100% Solvent B over 8 min at 2.5 mL/min, where solvent A = 90:10:0.2 H₂O:MeOH:H₃PO₄, and solvent B = 90:10:0.2 MeOH:H₂O:H₃PO₄; Zorbax SB-C18 4.6 x 75 mm column, retention time = 2.69 min.

Synthesis of (S)-(−)-1-(4-hydroxyphenyl)ethylamine hydrobromide (6)
[00138] A solution of (S)-(−)-1-(4-methoxyphenyl)ethylamine (5, 75 g, 496.7 mmol) in 30% hydrogen bromide in acetic acid (350 mL, Aldrich) in a 1 liter sealed tube was heated at 100-110°C in an oil bath for 6 hours. The reaction was cooled to room temperature, and nitrogen gas was bubbled into the solution to purge the excess HBr (the HBr was purged into aqueous NaOH). Volatiles were then removed in vacuo to afford the crude phenol amine HBr salt 9 (110 g) as a brown oil, which was used in the next reaction without further purification.

Synthesis of (S)-(−)-1-(4-methoxyphenyl)ethylamine benzyl carbamate (7):

[00139] To a stirred room temperature solution of crude amine hydrobromide 6 (320 g) in 50% aqueous THF (400 mL) was slowly added solid NaHCO₃ (740 g; 6 equivalents) until the pH = 8. Benzyl chloroformate (325 g, 1.9 mol) was added dropwise to the mixture, and the reaction was stirred at room temperature for 2 hours (until TLC indicated that the reaction was complete). The mixture was extracted with EtOAc (5 x 1 L), and the combined organic extracts were dried (Na₂SO₄) and concentrated in vacuo to afford crude compound 7 (520 g) as a brown oil, which was taken on to the next step without further purification.

A purified sample was characterized:

1H NMR (400 MHz, CDCl₃): δ 1.07 (d, J = 4.0 Hz, 3H, -CH₂CH₂-), 4.79 (m, 1H), 5.10 (m, 2H), 5.28 (d, J = 8.0 Hz, 1H), 6.75 (d, J = 4.0 Hz, 2H), 7.11 (d, J = 4 Hz, 2H), 7.25-7.34 (m, 5H).

13C NMR (100 MHz, CDCl₃): δ 22.34, 50.21, 66.89, 115.44, 127.05, 127.59, 128.06, 128.42, 134.79, 136.07, 155.34, 155.86.

CHN: Calculated for C₁₆H₁₇NO₃: C 70.83, H 6.31, N 5.16; Found: C 70.78, H 6.31, N 5.07.

IR (KBr): 3316 (s, br), 1700 (s), 1686 (s), 1676 (s), 1530 (s), 1515 (s), 1259 (s), 1237 (s) cm⁻¹.
UV (MeOH; 16.4 mg/L): $\lambda_{\text{max}} = 283, 277$ nm

$[\alpha]_D = -57.57^\circ$ (c = 10.1 mg/mL, MeOH, temperature = 25°C)

5 LRMS (M + Na$^+$): 294.1; HRMS: Calculated for C$_{16}$H$_{17}$NO$_3$Na: 294.1106, found: 294.1118.

Synthesis of (S)-benzyl 1-(4-(tert-butyldimethylsilyloxy)phenyl) ethylcarbamate (7a):

[00140] Imidazole (255 g, 3.75 mol) was added to a 0°C solution of crude phenol carbamate 7 (510 g, 1.87 mol) in DMF (1.1 L). The mixture was stirred for 15 min, after which t-butyldimethylsilyl chloride (340 g, 2.7 mol) was added. The reaction was allowed to warm to RT and stirred for 1 h at RT, at which point TLC indicated that the reaction was complete. The solution was concentrated in vacuo, and the residue was partitioned between EtOAc (3 L) and aqueous 1.5 N aqueous HCl (1 L). The organic phase was washed with aqueous 1.5 N HCl (1 L), brine, dried (MgSO$_4$) and concentrated in vacuo. The crude product was chromatographed (SiO$_2$; 60-120 mesh, 9:1 hexane:EtOAc) to afford 7a (250 g of product which was 75% pure by $^1$HNMR; the major impurity was TBSCI).

A purified sample was characterized:

Chiral HPLC (Daicel Chiralcel AD 4.6 X 250 mm column, isocratic 2% iPrOH/Heptane system, 30 min run) showed an ee of 100% (the retention time of the desired product is 13.9 min, while its enantiomer has a retention time of 11.6 min).

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.26 - 7.42 (m, 5 H), 7.15 (d, J=7.83 Hz, 2 H), 6.78 (d, J=8.31 Hz, 2 H), 5.01 - 5.16 (m, 2 H), 4.94 (br. s., 1 H), 4.81 (br. s., 1 H), 1.46 (d, J=6.60 Hz, 3 H), 0.98 (s, 9 H), 0.18 (s, 6 H)

$^{13}$C NMR (101 MHz, CDCl$_3$): $\delta$ 155.50, 154.88, 136.57, 136.09, 128.47, 128.05, 127.05, 120.05, 66.66, 50.17, 25.67, 22.30, 18.18, -4.42
\([\alpha]_D = -36.89^\circ \) (c = 3.79 mg/mL, CH\(_2\)Cl\(_2\), temperature = 25.1°C)

LRMS (M+Na\(^+\)): 408.1

Synthesis of (S)-1-(4-(tert-butyldimethylsilyloxy)phenyl)ethanamine (8):

5 [00141] To a solution of partially purified 7a (250 g, 0.64 mol) in methanol (2.5 L) was cautiously added 10% palladium on carbon (25 g) under an atmosphere of nitrogen. The reaction mixture was subjected to hydrogenation under pressure (3.5 kG). After the reaction was complete, the mixture was filtered through Celite\(^\circledR\) and volatiles were removed in vacuo to give a semi-solid. This material was dissolved in CH\(_2\)Cl\(_2\) (1.0 L), dried (anhydrous K\(_2\)CO\(_3\)) and concentrated in vacuo to give amine 8 as a yellow oil (175 g, 70%) which was sufficiently pure (95%) to be used in the next step without further purification.

\(^1\)H NMR (300 MHz; CDCl\(_3\)): \(\delta \) 0.19 (s, 6H, Si-CH\(_3\)), 0.98 (s, 9H, Si - tBu), 1.40 (d, 3H, J = 6.0 Hz, CH\(_3\)), 3.08 (s, 2H, NH\(_2\)), 4.04 - 4.10 (q, 1H, J = 6 Hz, CH), 6.80 - 6.72 (d, 2H, J = 9 Hz, Ar), 7.27 - 7.15 (d, 2H, J = 9 Hz, Ar).

Synthesis of (S)-methyl 2-(1-(4-(tert-butyldimethylsilyloxy)phenyl)ethylamino) acetate (4):

20 [00142] To a stirred solution of crude 8 (200 g, 0.79 m) in THF (1.2 L) at room temperature were successively added triethylamine (120 g, 1.19 mol) and methyl bromoacetate (158 g, 1.03 mol). The reaction mixture was stirred at RT for a further 12 h. The mixture was filtered and the residue was washed with excess THF. The combined filtrates were concentrated in vacuo and the residue was partitioned between EtOAc (2.5
L) and water. The organic phase was washed with brine, dried (Na₂SO₄) and concentrated \textit{in vacuo}. The residue was chromatographed (SiO₂; 60 – 120 mesh, 4:1 hexane/EtOAc) to afford amine 4 (125 g; 49% yield) which was 98% pure by HPLC.

A purified sample was characterized:

5 Chiral HPLC (Daicel Chiralcel AD 4.6 X 250 mm column, 0.8% isopropanol/heptane isocratic, 30 min run) showed 100% e.e. (the retention time of the desired product is 7.00 min, while its enantiomer has a retention time of 5.20 min).

$^1$H NMR (400 MHz, CDCl₃) δ 7.12 (d, J=8.79 Hz, 2 H), 6.76 (d, J=8.35 Hz, 2 H), 3.70 (q, J=6.59 Hz, 1 H), 3.66 (s, 3 H), 3.17 - 3.29 (m, 2 H), 1.91 (br. s, 1 H), 1.32 (d, J=6.15 Hz, 3 H), 0.95 (s, 9 H), 0.17 (s, 6 H)

$^{13}$C NMR (126 MHz, CDCl₃) δ 173.01, 154.61, 137.08, 127.61, 119.87, 57.02, 51.60, 48.55, 25.60, 24.06, 18.10, -4.49

$[\alpha]_D$ = -57.65° (c = 8.4 mg/mL, MeOH, temperature = 25.2 °C)

15 LRMS (M-glycine methyl ester + H)$^+$: 235.3

**Synthesis of (S)-methyl N-((3-fluoro-4-methylphenoxy)carbonyl)-N-(1-(4-(tert-butyldimethylsilyloxy)phenyl)ethylamino)acetate (9):**

[00143] A 2L 3 neck round bottom flask equipped with a mechanical stirrer was charged with amine 4 (120g, 370 mmol), THF (600 mL) and saturated aqueous NaHCO₃ (500 mL). A solution of crude chloroformate 2 (86 g, 440 mmol) in THF (200 mL) was added dropwise over a period of 30 minutes to the mixture at 0°C under an atmosphere of N₂. After the addition was complete, the mixture was allowed to warm up to room temperature and stirred at room temperature for an additional 30 min. Et₂O (600 mL)
and H₂O (150 mL) were then added. The organic layer was washed with aqueous NaOH (1 N, 3 X 100 mL), H₂O (2 X 100 mL), and brine (2 X 100 mL). The organic layer was dried (Na₂SO₄) and concentrated in vacuo to afford the carbamate 9 (170 g, 97%) as a light yellow oil.

A purified sample was characterized:

^1H NMR (500 MHz, DMSO-d6) δ 7.22 - 7.34 (m, 3 H), 6.78 - 6.95 (m, 4 H), 5.33 - 5.44 (m, 1 H), 3.83 - 4.09 (m, 2 H), 3.59 (s, 3 H), 2.20 (s, 3 H), 1.57 and 1.49 (d, J=7.15 Hz 1:2 rotamers, 3 H), 0.94 (s, 9 H), 0.18 (s, 6 H)

^13C NMR (126 MHz, DMSO-d6, 75°C) δ 169.56, 160.08 (d, J = 244.14 Hz, 1 C), 154.46, 153.39, 149.81 (d, J = 10.19 Hz, 1 C), 132.82, 131.20, 128.37, 120.90 (d, J = 17.84 Hz, 1 C), 119.47, 117.09, 108.68 (d, J = 25.49 Hz, 1 C), 53.98, 51.51, 44.68, 25.39, 17.72, 16.71, 13.29, -4.70

^19F NMR (376 MHz, DMSO-d6) δ -114.82 (s, 1 F)

[α]D = -84.6° (c = 12.4 mg/mL, MeOH, temperature = 24.2°C)

LRMS (M+Na)^+: 498.3

HPLC Method: Gradient solvent system: from 50% A: 50% B to 0% A: 100% B(A = 90% H₂O/10% MeOH + 0.2% H₃PO₄; B = 90% MeOH/10% H₂O + 0.2% H₃PO₄) for 8 min; detection at 220 nm; Flow rate = 2.5 mL/min; Zorbax SB C18 4.6 x 50 mm column; Retention time = 9.39 min

Synthesis of N-((3-fluoro-4-methylphenoxy)carbonyl)-N-(1-(4-hydroxyphenyl) ethyl amino)acetate (10):

|00144| To a 1L 3 neck round bottom flask equipped with a mechanical stirrer containing compound 9 (133 g, 0.28 mol) in THF (300 mL) at 0°C was slowly added Bu₄NF (280 mL of a 1 M solution in THF; 280 mmol) over 30 minutes. After the
addition was complete, the reaction mixture was allowed to warm up to room
temperature and stirred for an additional 30 minutes. By the end of the addition, HPLC
showed that the reaction was complete. Solvent was removed in vacuo, and the residue
was partitioned between EtOAc (500 mL) and aqueous HCl (3 X 150 mL of a 1 N
solution). The organic phase was washed with H$_2$O (150 mL) and brine (150 mL), then
dried (MgSO$_4$) and concentrated in vacuo to afford the crude product, which was purified
by flash column chromatography (25% to 40% EtOAc/Hexane) to afford the desired
phenol 10 (91.98 g, 91% yield) as a light yellow oil.

A purified sample was characterized:

HPLC Method: Gradient solvent system: from 50% A: 50% B to 0% A: 100% B(A =
90%H$_2$O/10% MeOH + 0.2% H$_3$PO$_4$; B = 90% MeOH/10% H$_2$O + 0.2 % H$_3$PO$_4$) for 8
min; detection at 220 nm. Flow rate = 2.5ml/min. Zorbax SB C18 4.6 x 50 mm column;
Retention time = 4.43 min

$^1$H NMR (500 MHz, DMSO-d6) $\delta$ 9.43 (s, 1 H), 7.12 - 7.34 (m, 3 H), 6.70 - 7.01 (m, 4
H), 5.28 - 5.42 (m, 1 H), 3.78 - 3.93 (m, 2 H), 3.60 (s, 3 H), 2.21 (s, 3 H), 1.54, 1.47 (d,
J=7.15 Hz, 1:2 rotamers, 3 H)

$^{13}$C NMR (126 MHz, DMSO-d6, 75°C) $\delta$ 169.56, 159.94 (d, J = 244.14 Hz, 1 C), 156.60,
153.26, 149.70 (d, J=12.71 Hz, 1 C), 130.84, 130.07, 128.11, 120.78 (d, J=17.80 Hz, 1
C), 117.01, 114.97, 108.58 (d, J=25.43 Hz, 1 C), 53.82, 51.43, 44.43, 16.53, 12.61

$^{19}$F NMR (376 MHz, DMSO-d6) $\delta$ -114.76 (s, 1 F)

$[\alpha]_D$ = -102.43 ° (c = 12.2 mg/mL, MeOH, temperature = 24.7°C)

LRMS (M+Na)$^+$: 384.1

Synthesis of Glycine, N-[(3-fluoro-4-methylphenoxy)carbonyl]-N-[(1S)-1-[4-[(5-

![Chemical Structure](attachment:chemical.png)
A 2 L 3 neck round bottom flask equipped with a mechanical stirrer was charged with compound 10 (100 g, 277 mmol), CH3CN (500 mL), compound 3 (58.5 g, 282 mmol) and K2CO3 (76.5 g, 540 mmol). After the reaction mixture was stirred at 80°C for 8 hours, it was cooled down to room temperature, then to 5°C. Saturated aqueous NH4Cl (300 mL) was added via an additional funnel. The organic layer was separated and the aqueous layer was extracted with EtOAc (2 x 200 mL). The combined organic layers were washed with brine(150 mL), dried over anhydrous Na2SO4 and concentrated in vacuo. The crude product was purified by flash column chromatography (SiO2; from 30% to 35% EtOAc/Hexane) to afford 11 (118 g, 80% yield) as a light yellow oil.

A purified sample was characterized:

\[ ^1H \text{NMR (400 MHz, DMSO-d6, 80 ^\circ\text{C}}) \delta 7.93 (d, J = 5.27 \text{ Hz, 2 H}), 7.45 - 7.55 (m, 3 H), 7.33 (d, J=8.35 \text{ Hz, 2 H}), 7.26 (t, J = 8.57 \text{ Hz, 1 H}), 7.04 (d, J = 8.35 \text{ Hz, 2 H}), 6.90 (d, J=10.55 \text{ Hz, 1 H}), 6.83 (d, J=7.91 \text{ Hz, 1 H}), 5.37 (q, J = 6.74 \text{ Hz, 1 H}), 3.95 - 4.07 (m, 1 \text{ H}) 5.02 (s, 2 \text{ H}), 3.84 - 3.94 (m, 1 \text{ H}), 3.60 (s, 3 \text{ H}), 2.43 (s, 3 \text{ H}), 2.21 (s, 3 \text{ H}), 1.54 (d, J=4.83 \text{ Hz, 3 H}) \]

\[ ^13C \text{NMR (101 MHz, DMSO-d6, 80 ^\circ\text{C}}) \delta 169.4, 169.2, 159.8 (d, J = 245.3 \text{ Hz, 1 C}), 157.4, 153.1, 149.5 (d, J = 10.1 \text{ Hz, 1 C}), 146.9, 131.8, 131.0, 131.0, 129.9, 128.6, 128.0, 126.7, 125.3, 120.7 (d, J = 18.2 \text{ Hz, 1 C}), 116.9, 114.6, 108.4 (d, J = 26.3 Hz, 1 C), 61.59, 53.9, 51.3, 44.7, 16.7, 13.1, 9.6 \]

\[ ^19F \text{NMR (376 MHz, DMSO-d6, 80^\circ\text{C})} \delta 115.3 (s, 1 \text{ F}) \]

[\( \alpha \)_D] = -98.3 ° (c = 3.2 mg/mL, CH2Cl2, temperature = 25.2°C)

LRMS (M+H)^+: 533.2

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Synthesis of Compound Ia
A 2L 3-neck round bottom flask was charged ester 11 (115 g, 216 mmol), THF (800 mL), H₂O (400 mL) and LiOH·H₂O (22.67 g, 540 mmol). After the reaction mixture was stirred at room temperature overnight under N₂, the reaction was judged to be complete by HPLC. The reaction mixture was diluted with EtOAc (200 mL), and the pH was adjusted with aqueous 1N HCl to pH = 2. The organic layer was separated, and the aqueous layer was extracted with EtOAc (2 X 250 mL). The organic layer was washed with water (2 X 150 mL), dried (Na₂SO₄) and concentrated in vacuo to afford crude Compound la (110 g, 99% yield). HPLC analysis showed that the purity of this batch was 98.1%.

Recrystallization:

Crude Compound la (180g) was dissolved in hot EtOH (700 mL) at 85°C. The mixture temperature was cooled to room temperature, then to 5°C. The slurry was filtered and the cake was washed with cold EtOH (2 x 100 mL). The white solid was dried under vacuum at 55°C for 8 hours until a constant weight was obtained. The weight of the solid was 144 g (80% recovered yield). The chemical purity was determined by DAS to be 99.5% with 99.2% ee

¹H NMR (500 MHz, DMSO-d₆; 24°C) δ 12.71 (s, 1 H), 7.89 - 7.99 (m, 2 H), 7.45 - 7.59 (m, 3 H), 7.22 - 7.41 (m, 3 H), 6.99 - 7.10 (m, 2 H), 6.88 - 6.99 (m, 1 H), 6.78 - 6.88 (m, 1 H), 5.28 - 5.46 (m, 1 H), 4.99 (s, 2H), 3.80 - 4.03 (m, 1 H), 3.68 - 3.80 (m, 1 H), 2.44 (s, 3 H), 2.20 (s, 3 H), 1.56, 1.49 (d, J = 7.15 Hz, rotamers, 3 H)

¹³C NMR (126 MHz, DMSO-d₆; 24°C) δ 171.2, 170.7, 161.3, 159.4, 159.1, 157.8, 157.7, 154.0, 153.7, 150.2, 147.7, 133.4, 132.8, 132.2, 131.6, 130.6, 129.4, 128.7, 128.49, 127.1, 125.8, 121.4, 121.3, 117.8, 117.7, 114.8, 109.4, 109.2, 61.6, 54.6, 53.8, 45.5, 44.8, 18.0, 16.9, 13.9, 10.3 (note: extra peaks are due to rotamers as the spectrum was run at 24°C)

¹⁹F NMR (471 MHz, DMSO-d₆; 24°C) δ -115.2 (s, 1 F)
HRMS(M+H)$^+$ = 519.1945 ($\Delta$ = 2.5 ppm);

$[\alpha]_D = -89.6^\circ$ (c = 9.100 mg/mL, CHCl$_3$, temperature = 25°C)

Example 2

Preparation of Compound 1a (Procedure 2)

Preparation of Compound 13

[00148] Into a 1000 mL 3-neck round bottom flask equipped with a mechanical stirrer, a thermal couple, a heating mantle, and a condenser was charged Compound 3 (30.2 grams, 145.4 mmol, 1.00 equiv.), Compound 12 (4-hydroxybenzaldehyde, 19.2 grams, 1.08 equiv.), potassium carbonate (26.3 grams, 1.31 equiv.), sodium iodide (2.40 grams, 0.11 equiv.), and 181.0 mL CH$_2$CN (6.0 vol./g input of Compound 3). The resulting slurry was stirred at ambient temperature for 15-30 min. The slurry was then heated to 65.5°C and continually stirred at 65.5°C for ~ 2.0 h. Thereafter, the batch was cooled to 2-10°C. Then 420 mL (~ 14.0 vol./g input of Compound 3) of water was added into the reaction mixture in < 1 min. An off-white slurry was formed uniformly. The slurry was heated back to ~55-60°C and held at that temperature for ~ 1 h. The batch was cooled to ambient temp. in 2-3 h. and continuously stirred at ambient temperature for 18 h. The slurry was filtered through a Buchner funnel with a #1 Whatman® filter paper to collect the crystalline solid. The wet cake was washed with water (90 mL x 3). The wet cake
was de-liquored with vacuum for 30 min at ambient temp. The estimated weight of the product was ~ 42.6 (g) with an isolated yield of 96.8%. The product (Compound 13) can be further purified by re-crystallization from acetone. mp 117.2 °C. 1H NMR (CDCl3): δ 2.46 (s, 3H), 5.08 (s, 2H), 7.13-7.15 (m, 2H), 7.44-7.46 (m, 3H), 7.85-7.87 (m, 2H), 8.01-8.04 (m, 2H), 9.90 (s, 1H). 13C NMR (CDCl3): δ 10.4, 62.4, 115.0, 126.1, 127.2, 128.7, 130.1, 130.2, 131.2, 131.9, 147.4, 160.1, 163.4, 190.7. IR (KBr): 2919.4, 2794.3, 2725.2, 1691.8, 1643.8, 1600.4, 1575.2, 1556.1, 1508.0, 1484.4, 1302.1, 1245.3, 1212.3, 1159.2, 998.2, 869.6, 776.3, 715.0, 698.8, 692.6 cm⁻¹. HRMS calec for C18H16NO3 [M+H]^+: 294.1130, found, 294.1131. Anal. Calec for C18H16NO3: C, 73.70; H, 5.15; N, 4.77. Found: C, 73.49; H, 4.97; N, 4.60.

**Preparation of Compound 15**

![Chemical Structure of Compounds 13, 14, and 15]

To a 1000 mL jacketed reactor equipped with a temperature probe, a mechanic agitator, and a condenser, and a bath circulator was charged Compound 13 (50.0 g, 170.5 mmol, 1.0 equiv.), Compound 14 (25.0 g, 206.3 mmol, 1.21 equiv.), copper sulfate (CuSO₄) (81.6 g, 511.4 mmol, 3.0 equiv.), pyridinium p-toluenesulfonate (PPTS) (2.14 g, 8.5 mmol, 0.05 equiv.) and 300 mL methylene chloride. The resulting slurry was heated to reflux and was held at reflux for ~4-6 hours. The reaction mixture was then allowed to cool down to ambient temperature. The insoluble inorganic salts were then filtered off. The inorganic salt cake was washed with 100 mL x 2 of methylene chloride. The filtrate and washes were combined as a methylene chloride solution. The organic solution was washed with aqueous 5%wt ammonium acetate (aq, 250 mL x 2) and water (250 mL). After the phases were separated, the organic layer was concentrated to ~175-200 mL via distillation under atmospheric pressure. Heptane (1200 mL) was charged to the concentrated methylene chloride solution in 1.5 hours while maintaining the batch temperature at ~33°C. After charging heptane, the resulting slurry was allowed to cool down to ~5°C in > 1 hr and stirred at ~5°C for 20 min. The solids
were then collected by filtration, followed by washing with 160 mL of heptane. The wet cake was dried at 45°C under reduced pressure to give ~56 g of Compound 15 as a bright yellow solid. The isolated yield is 85.8%. The product can be further purified by recrystallization from methylene chloride and heptane. mp 160.0°C. 1H NMR (CDCl3): δ 1.09 (s, 9H), 2.29 (s, 3H), 4.9 (s, 2H), 6.92-6.94 (m, 2H), 7.27-7.30 (m, 3H), 7.64-7.66 (m, 2H), 7.84-7.87 (m, 2H), 8.35 (s, 1H). 13C NMR (CDCl3): δ 10.2, 22.2, 57.2, 62.0, 114.8, 125.8, 127.0, 127.2, 128.4, 129.9, 130.9, 131.2, 147.0, 159.7, 161.3, 161.6. IR (KBr): 2972.6, 2922.4, 2868.5, 1639.8, 1597.8, 1563.7, 1508.4, 1467.8, 1401.2, 1302.3, 1248.4, 1240.6, 1168.7, 1076.3, 987.1, 876.9, 837.2, 775.2, 716.2, 698.0, 650.4, 593.0, 521.9 cm⁻¹. Anal. Calcd for C22H24N2O3S: C, 66.64; H, 6.10; N, 7.06. Found: C, 66.51; H, 5.88; N, 6.99. [α]D = +0.589° (c 0.89, MeOH).

**Preparation of Compound 16**

![Chemical Structure]

15 [00150] To a 500 mL 3-neck jacketed flask equipped with a temperature probe, a mechanic agitator, and a condenser, and a bath circulator was charged Compound 15 (15 g, 37.8 mmol, 1.0 equiv.), and 225 mL (15 vol. of each g of Compound 15 input) of methylene chloride to form a light yellow solution at ambient temp. The resulting solution was cooled to ~ -15°C. Methyl magnesium chloride (3 N in THF, 32.0 mL, 2.54 equiv.) was charged to the solution over 20 min while maintaining the batch temperature below -7°C. The reaction was stirred at ~ -10°C for 5 h. Then the reaction mixture was allowed to warm up to ~ 0°C and held for 30 min at 0°C. 5.6 mL of acetone was charged to the reaction mixture over 20 min while maintaining the batch temperature < 20°C. The resulting solution was stirred at room temperature for 30 min. 72 mL of aqueous 10% wt. NH4OAc was charged to the reaction mixture. Subsequently, the pH of the reaction mixture was adjusted to 4.0-5.0 (top aq layer) with 1 N HCl (aq) solution in 15 min. The bi-phasic system was stirred for ~ 20 min at ambient temp. After the phases were
separated, the bottom organic layer was retained followed by washing with aqueous 5\%wt. NaHCO₃ (60 mL) and water (60 mL).

[00151] The isolated organic solution was concentrated to 45-60 mL volume through distillation at atmospheric pressure. 150 mL of ethyl acetate was charged to the concentrated solution at ambient temp. The solution was distilled to concentrate to 75 mL through vacuum distillation while maintaining the batch temp. at 50-55°C. Another 150 mL ethyl acetate was charged to the residual solution followed by vacuum distillation to reduce the volume to ~75 mL. When necessary, the ethyl acetate charge-distillation sequence was repeated until % (v/v) contents of methylene chloride and THF were both <1% relative to EtOAc by GC analysis. The solution was cooled down to ~40°C followed by adding 1.5 mL of water. 45 mL of heptane was added while maintaining the batch temp at 35–40°C. The resulting solution was seeded with 225 mg of Compound 16 seed crystals, then was stirred at 35–40°C for 30 min. To the resulting white slurry, 225 mL of heptane was added over a period of 1 h while maintaining the batch temp at 35-40°C. The slurry was cooled to ambient temp over 1 h, and stirring was continued at ambient temp for 14 h. The solids were collected through filtration. The product was washed with heptane (80 mL x 2). The wet product cake was de-liquored for 1 h at ambient temp, followed by drying at ambient temp under vacuum for >12 h. 15.2 g of Compound 16 was obtained as a white solid, with an isolated yield of 88%.

The product can be further purified by re-crystallized from EtOAc, heptane, and water. mp 124.0 °C. ¹H NMR (CDCl₃): δ 1.17 (s, 9H), 1.50 (d, J = 6.5 Hz, 3H), 2.40 (s, 3H), 2.53 (m, 1H), 3.40 (s, 1H), 4.52 (m, 1H), 4.96 (s, 3H), 6.97 (d, J = 8.3 Hz, 2H), 7.25 (d, J = 8.6 Hz, 2H), 7.40 (m, 3H), 7.99-8.00 (m, 2H). ¹³C NMR (CDCl₃): δ 10.3, 22.4, 24.8, 53.9, 55.3, 62.1, 114.6, 125.9, 127.2, 127.9, 128.5, 129.9, 131.8, 135.7, 146.9, 157.7, 159.7. IR (KBr): 3391.5, 3150.6, 2975.6, 2930.9, 1695.6, 1643.9, 1610.0, 1583.6, 1557.0, 1512.2, 1492.6, 1460.2, 1448.2, 1366.0, 1231.5, 1180.9, 1069.7, 1024.9, 1002.8, 949.0, 867.0, 832.2, 775.1, 713.9, 690.8, 647.1, 551.2 cm⁻¹. Anal. Caled for C₂₃H₃₉Na₂O₆S: C, 64.16; H, 7.02; N, 6.50; S, 7.44. Found: C, 64.22; H, 7.19; N, 6.41, S, 7.33. [α]D = -60.68° (c 2.03, MeOH).
Preparation of Compound 17

[00152] Into a 1000 mL jacketed reactor equipped with a overhead stirrer, a thermal couple, a condenser, a heating mantle, and a bath circulator was charged Compound 16 (40.0 grams, 92.9 mmol, 1.0 equiv.), isopropanol (IPA, 280 ml, 7.0 ml per g input of Compound 16). The resulting slurry was stirred at ambient temperature for 5-10 min. The slurry was then heated to 40°C to achieve full dissolution. It was then distilled under vacuum at ~ 40°C until the KF of the IPA solution was < 0.1%wt. while maintaining the volume of the solution by adding fresh isopropanol. TMSCl (18.1 mL, 1.5 equiv.) was charged slowly into the solution at ~ 40°C for ~1-1.5 h. White solids precipitated out to form a slurry. The slurry was stirred at ~ 40°C for 30 min, after which 600 mL of n-heptane was added at ~ 40°C in 3 h followed by holding at ~ 40°C for ~1 h. The white slurry was cooled to ambient temp (~20°C) and held at ambient temperature for > 6 h.

The slurry was filtered through a Buchner funnel with a #1 Whatman® filter paper to collect the crystalline solid. The wet product cake was washed with a mixture of isopropanol (40 mL) and n-heptane (160 mL), followed by additional n-heptane (200 mL x 3). The wet cake was de-liquored under nitrogen under vacuum for 30 min at ambient temp. The product was dried at 50°C in a vacuum oven overnight to give 29.2 g of Compound 17 as a white solid. Yield = 91.7%. The product can be further purified by re-crystallization from EtOH and MTBE (methyl t-butyl ether). mp 200.0°C. \(^1\)H NMR (CD\(_3\)OD): \(\delta\) 1.61 (d, \(J = 6.8\) Hz, 3H), 2.45 (s, 3H), 4.41 (m, 1H), 5.03 (s, 2H), 7.10-7.13 (m, 2H), 7.40-7.42 (m, 2H), 7.47-7.51 (m, 3H), 7.96-8.00 (m, 2H). \(^{13}\)C NMR (CD\(_3\)OD): \(\delta\) 10.7, 21.0, 52.3, 63.3, 117.0, 127.5, 128.6, 129.7, 130.5, 132.2, 132.5, 133.4, 149.5, 160.8, 161.9. IR (KBr): 3257.5, 2945.1, 2899.0, 2806.8, 1603.4, 1506.1, 1465.1, 1219.3, 1147.7, 999.1, 819.9 cm\(^{-1}\). Anal. Caled for C\(_{19}\)H\(_{21}\)ClN\(_2\)O\(_2\): C, 66.17; H, 6.13; N, 8.12; Cl, 10.28. Found: C, 65.88; H, 5.91; N, 8.04, Cl, 10.48. [\(\alpha\)]\(_D\) = -60.68° (c 2.03, MeOH).
Preparation of Compound 18

Compound 17 (25.0 g, 72.6 mmol, 1.0 equiv.) was charged to a round bottom flask, followed by EtOAc (10 mL/g) and water (4 mL/g). At ambient temperature, the mixture was allowed to agitate for ~15 minutes until full dissolution was reached. 20 wt% aqueous K₂PO₄ (124.0 g) was then charged in one portion, bringing the pH to ~10. Subsequently, ethyl bromoacetate (12.7 g, 76.0 mmol, 1.05 equiv.) was charged in one portion. The biphasic reaction mixture was agitated at ambient temperature for 1.5-2 hours. 20 wt% aqueous K₂PO₄ (30.0 g) was then charged into the reaction. The reaction mixture was then heated to 40-45°C and held at 40-45°C for 5-7 h. If the reaction was not complete by HPLC (< 4 AP of Compound 17) monitoring at this point, the reaction mixture was cooled to ambient temperature and held overnight with agitation. When the reaction was complete, the agitation was stopped and the phases were allowed to settle at ambient temperature. The bottom aqueous layer was then removed. The upper organic layer was washed first with phosphate buffer (250 mL, pH 5-5.5), followed by water (250 mL). From the retained top organic layer, water was removed by azeotropic distillation under vacuum to ≤ 1500 ppm, and EtOAc was added to bring the volume to the original volume after distillation. Next, MeOH (4.64 g, 145.0 mmol) was added to the EtOAc solution and the mixture was heated to 45°C. TMSCl (9.45 g, 87.0 mmol, 1.2 equiv.) was slowly added over 45-60 minutes; a slurry formed when 15-40% of the TMSCl had been added. After addition was complete, the slurry was allowed to stir at 45-50°C for 1 h, then cooled to ambient temperature over 1 h, and allowed to stir for an additional 1-2 h before filtration and EtOAc wash (75 mL). The wet cake was dried under vacuum at ambient temperature for 72 h to give Compound 18 as a white powder (26.4 g). Yield = 84.6%. The product can be further purified by re-slurrying in EtOA followed by filtration. mp 182.3°C. ¹H NMR (400 MHz, CDCl₃): δ 1.19 (t, J = 7.14 Hz, 3H), 1.91 (d, J = 6.81 Hz, 3H), 2.39 (s, 3H), 3.41 (d, J = 16.92 Hz, 1H), 3.64 (d, J = 16.92 Hz, 1H), 4.14 (dd, J = 7.18 Hz, 2H), 4.58 (m, 1H), 4.94 (s, 2H), 7.02 (d, J = 8.79 Hz, 2H), 7.37-
7.41 (m, 3H), 7.55 (d, J = 8.79 Hz, 2H), 7.97 (dd, J = 4.61, 3.30 Hz, 2H), 10.18 (s, 1H), 10.39 (s, 1H). 13C NMR (CDCl₃, 100 MHz): δ 10.4, 13.9, 20.0, 44.6, 58.1, 62.1, 115.5, 126.0, 127.3, 127.5, 128.6, 129.7, 130.0, 131.6, 147.1, 159.3, 160.0, 165.7. IR (KBr): 3416.8, 2934.3, 2711.6, 2610.9, 2462.4, 1757.3, 1630.1, 1614.1, 1584.4, 1554.5, 1485.7, 1430.0, 1449.2, 1412.9, 1395.4, 1329.5, 1309.9, 1269.9, 1024.4, 979.2, 713.9, 705.8, 693.0, 687.2 cm⁻¹. Anal. Calc’d for C33H27ClN2O4: C, 64.01; H, 6.31; N, 6.50; Cl, 8.22. Found: C, 64.00; H, 6.36; N, 6.44; Cl, 8.26. [α]D = -27.56° (c 1.04, MeOH).

[00154] In the first step (above), another base, triethylamine, can be used in place of K₂PO₄ under anhydrous conditions.

**Preparation of Compound 1a**

![Chemical Structure](image)

[00155] To a 250mL glass reactor equipped with an agitator, a temperature probe and a condenser, was added 25.0 g of Compound 18 (58.01 mmol), 150 mL THF, and 10.0 mL water. After the reaction mixture was stirred to obtain a homogenous solution and cooled to 0-5°C, 10 N NaOH (aq., 14.5 mL, 145 mmol, 2.5 equiv.) was added over ~10-15 minutes. Chloroformate 2 (11.5 g, 60.98 mmol, 1.05 equiv.) was then added in ~ 20 minutes while maintaining the batch temperature at ≤ 5°C. After the addition was complete, the reaction mixture was allowed to warm up to ambient temperature and the reaction was monitored by HPLC for completion. After the acylation reaction was complete, additional 10.0 N NaOH (aq., ~ 40.6 mL, 406 mmol, 7.0 equiv.) was added within 5-10 minutes. The reaction mixture was stirred at ~35°C for ~4-6 h before
cooling to ambient temperature and was held overnight at ambient temperature. HPLC indicated that the reaction was completed (Compound 19). The bottom aqueous layer was removed upon phase separation. About 375.0 mL deionized water was then added to the organic layer to form a solution. The pH of the resulting solution was adjusted to ~6.5-7.5 using 1 N HCl (aq). Seed crystals (~0.25 g) of Compound 1a were added. The pH adjustment was continued slowly over 2-4 h using 1 N HCl (aq) to the final pH of 2.2. The slurry was stirred at ambient temperature overnight. The solid was filtered via a Buchner funnel and was washed with 125 mL x 4 water. The wet cake was dried in a vacuum oven at ~40-50°C under house vacuum for 22 h to provide 28.35 g of Compound 1a. Yield: 92.8%. The product can be further crystallized from EtOH to improve the purity and enantiomeric purity to 100.0%. \(^1\)H NMR (DMSO-\(d_6\), 95.0 °C): \(\delta\ 1.55\ (d, J=6.37\ Hz, 3\ H), 2.21\ (s, 3H), 2.43\ (s, 3\ H), 3.77\ (br\ d, J=17.8\ Hz, 1H), 3.95\ (br\ d, J=18.0\ Hz, 1H), 5.02\ (s, 2H), 5.37\ (q, J=6.96\ Hz, 1H), 6.85-6.92\ (m, 2H), 7.04\ (d, J=8.35\ Hz, 2H), 7.25\ (t, J=8.57\ Hz, 1H), 7.34\ (d, J=8.35\ Hz, 2H), 7.47-7.52\ (m, 3H), 7.94\ (d, J=7.69\ Hz, 2H). \(^{13}\)C NMR (DMSO-\(d_6\), 22.8 °C): \(\delta\ 9.99, 13.64, 16.69, 17.71, 44.52, 45.29, 53.58, 54.39, 61.37, 108.91, 109.15, 114.58, 117.42, 117.54, 120.99, 121.15, 125.59, 126.82, 128.25, 128.50, 129.10, 130.35, 131.36, 131.42, 131.93, 132.59, 133.16, 147.48, 149.74, 149.84, 149.96, 153.45, 153.79, 157.48, 157.56, 158.83, 161.30, 170.43, 170.96. Extra peaks in \(^{13}\)C NMR spectra are due to the presence of rotamers. Anal. Calcd for C\(_{29}\)H\(_{27}\)FN\(_2\)O\(_6\): C, 62.17; H, 5.24; N, 5.40; F, 3.66. Found: C, 67.18; H, 5.25; N, 5.34, F, 3.86. \([\alpha]_D = -92.80°\) (c 0.912, CHCl\(_3\)).

Example 3

Preparation of Compound 1b
Synthesis of 4-fluoro-3-methylphenyl carbonochloridate (21):

To a 0°C solution of 4-fluoro-3-methylphenol 20 (10 g, 89.2 mmol) and triphosgene (8.7 g, 29.4 mmol) in CH₂Cl₂ (80 mL) was added pyridine (7.2 mL, 89.2 mmol) dropwise over 10 min. The reaction mixture was allowed to warm to RT, then was heated to 45°C and stirred at 45°C for an additional 2 h. The reaction was then cooled to RT, and volatiles were removed in vacuo. Anhydrous Et₂O (300 mL) was added to the residue, and the resulting slurry was filtered. The filtrate was concentrated in vacuo to afford crude 4-fluoro-3-methylphenyl chloroformate (17 g, >100% yield) as an oil, which was immediately used in the next step without further purification.

Synthesis of (S)-methyl 2-((1-(4-(tert-butyldimethylsilyloxy)phenyl)ethyl)((4-fluoro-3-methylphenoxy)carbonyl)amino)acetate (22):

To a 5°C mixture of amine 4 (24.0 g, 248 mmol), THF (120 mL), and saturated aqueous NaHCO₃ (100 mL) in a 500 mL round bottom flask (equipped with a mechanical stirrer) was added dropwise over 10 min a solution of crude chloroformate 21 (16.8 g, 89.2 mmol) in THF (10 mL) under an atmosphere of N₂. After the addition was complete, the mixture was allowed to warm to RT. The organic layer was separated, and the aqueous layer was extracted with EtOAc (200 mL). The combined organic extracts were concentrated in vacuo, and the residue was taken up in hexanes and washed with 1N aqueous NaOH (2 x 40 mL) and H₂O (2 x 40 mL). The organic layer was dried.
(Na$_2$SO$_4$), filtered, and concentrated in vacuo to afford the desired carbamate product 22 (35 g, 99% yield) as an oil.

**Synthesis of (S)-methyl 2-(((4-fluoro-3-methylphenoxy)carbonyl)(1-(4-hydroxyphenyl)ethyl)amino)acetate (23):**

![Chemical Structure of 22 and 23](image)

[00158] Multiple lots of compound 22 were synthesized, combined and used in the next reaction as follows. To a 10°C solution of compound 22 (135 g, 0.28 mol) in THF (300 mL) was slowly added Bu$_3$NF (280 mL of a 1 M solution in THF; 280 mmol) over 30 min. After addition was complete, the reaction mixture was allowed to warm up to RT and stirred at RT for an additional 30 min. Volatiles were removed in vacuo, and the residue was taken up in hexanes and washed with H$_2$O (2 x 400 mL). The organic phase was dried (Na$_2$SO$_4$) and concentrated in vacuo. The residue was triturated with Et$_2$O to afford the product phenol 23 (100 g, 98% yield) as a white solid.

**Synthesis of Glycine, N-[(4-fluoro-3-methylphenoxy)carbonyl]-N-[(1S)-1-[4-2-(5-methyl-2-phenyl-4-oxazolyl) methoxy] phenyl]ethyl] methyl ester (24):**

![Chemical Structure of 23 and 24](image)

[00159] A mixture of phenol 23 (100 g, 277 mmol), chloride 3 (57.4 g, 277 mmol), and K$_2$CO$_3$ (76 g, 554 mmol) in CH$_3$CN (500 mL) was stirred at 85°C for 3 h, then was cooled to RT. The reaction was diluted with toluene (200 mL) and filtered through a pad of Celite®. The filtrate was concentrated in vacuo to afford the crude product, which was
chromatographed (SiO₂; 20% EtOAc/Hexane) to afford compound 24 (138 g, 93% yield) as a light yellow oil.

**Synthesis of Compound 1b**

![Chemical Structure of 24 and Compound 1b]

5

**00160** A mixture of ester 24 (135 g, 253 mmol), THF (800 mL), H₂O (400 mL) and LiOH·H₂O (26.5 g, 632 mmol) was stirred at RT overnight and then diluted with EtOAc (500 mL). The pH was adjusted with aqueous 1N HCl to ~2. The organic layer was separated, dried (Na₂SO₄), and concentrated *in vacuo* to afford crude Compound 1b (125 g, 95% yield). HPLC analysis showed that the purity of this batch was 98.1%.

**Recrystallization:**

**00161** Crude Compound 1b (240 g, from multiple batches) was dissolved in hot EtOH (3 L) at 85°C. The mixture was cooled to RT, then to 5°C. The slurry was filtered, and the filter cake was washed with cold EtOH (2 x 100 mL). The white solid was dried in vacuo at 55°C for 6 h. The weight of the solid was 192 g (80% recovered yield). The chemical purity was determined to be 98.6%. This batch of partially purified Compound 1b (192 g) was dissolved in hot EtOH (2 L) and hot MeOH (500 mL). EtOAc (500 mL) was added dropwise until a precipitate was formed. The mixture was cooled to RT, then to 0°C for 30 min. The solid was collected by filtration and was dried in vacuo at 60°C for 5 h until a constant weight was obtained. The weight of the solid was 188 g (98% recovered yield). The chemical purity was determined to be 99.6%, with >99.9% ee.

**1H NMR** (500 MHz, DMSO-d₆; 24°C) δ 12.70 (br. s., 1 H), 7.89 - 8.00 (m, 2 H), 7.45 - 7.57 (m, 3 H), 7.28 - 7.41 (m, 2 H), 7.10 - 7.20 (m, 1 H), 6.98 - 7.08 (m, 3 H), 6.87 - 6.96
(m, 1 H), 5.31 - 5.47 (m, 1 H), 5.01 (s, 2 H), 3.67 - 4.03 (m, 2 H), 2.46 (s, 3 H), 2.22 (s, 3 H), 1.43 - 1.63 (m, 3 H).

$^{13}$C NMR (126 MHz, DMSO-d6; 24°C) δ 171.0, 170.5, 158.8, 158.7, 157.5, 156.8, 154.0, 153.8, 147.5, 146.8, 133.3, 132.7, 131.9, 130.4, 129.1, 128.4, 128.2, 126.8, 125.6, 125.2, 125.0, 124.4, 120.6, 115.4, 115.2, 114.6, 61.3, 54.3, 53.5, 45.3, 44.5, 17.7, 16.7, 14.0, 10.0 (note: extra peaks are due to rotamers as the spectrum was run at 24°C).

$^{19}$F NMR (471 MHz, DMSO-d6; 24°C) δ -122.0 (s, 1 F).

HRMS (M+H)$^+$ = 519

$[\alpha]_D = -87.44^\circ$ (CHCl$_3$, temperature = 25°C, 589 nm).

Theoretical elemental analysis calculation for C$_{29}$H$_{37}$FN$_2$O$_6$: C 67.17%, H 5.24%, N 5.40%, F 3.66%. Average values found from two separate elemental analysis tests:

(C$_{29}$H$_{37}$FN$_2$O$_6$): C 67.08%, H 5.49%, N 5.33%, F 3.57%

**Example 4**

**Preparation of Compound 1c**

![Chemical structure of Compound 1c]

**Synthesis of 3-methoxyphenyl carbonochloridate (26):**

![Synthesis reaction of 3-methoxyphenyl carbonochloridate (26)]
To a 0°C solution of 3-methoxyphenol 25 (60 g, 483 mmol) and triphosgene (48 g, 161 mmol) in CH₂Cl₂ (500 mL) was added pyridine (39.1 mL, 483 mmol) dropwise over 1 h. The reaction mixture was then heated at 50°C for an additional 1 h, then was cooled to RT, and volatiles were removed in vacuo. Anhydrous Et₂O (200 mL) was added to the residue, and the resulting slurry was filtered. The filtrate was concentrated in vacuo to afford crude 3-methoxyphenyl carbonochloridate 26 (89 g, 98.7% yield) as an oil, which was immediately used in the next step without further purification.

Synthesis of (S)-methyl 2-((1-(4-(tert-butyldimethylsilyloxy)phenyl)ethyl)((3-methoxyphenoxo)carbonyl)amino)acetate (27):

To a RT solution of amine 4 (60 g, 186 mmol) in THF (200 mL), saturated aqueous NaHCO₃ (200 mL), and H₂O (100 ml) was added the crude chloroformate 26 (26 g, 139 mmol) dropwise over 30 min. After the addition was complete, the mixture was stirred at RT for an additional 30 min, then was diluted with Et₂O (200 mL). The organic phase was washed with H₂O (200 mL), 1N aqueous NaOH (7 x 150 mL), 1N aqueous HCl (200 mL), H₂O (2 x 200 mL), then dried (Na₂SO₄) and concentrated in vacuo to provide the crude carbamate 27 (80 g, >100 %) as a yellow oil.

Synthesis of (S)-methyl 2-((1-(4-hydroxyphenyl)ethyl)((3-methoxyphenoxo)carbonyl)amino)acetate (28):
To a 0°C solution of carbamate 27 (80 g, 222 mmol) in THF (200 mL) was slowly added Bu$_3$NF (200 mL of a 1 N solution in THF; 200 mmol) over 30 min. After the addition was complete, the reaction mixture was stirred at 0°C for an additional 15 min. Volatiles were removed in vacuo, and the residue was taken up in Et$_2$O (300 mL). The organic phase was washed with H$_2$O (200 mL), 1N aqueous HCl (4 x 100 mL), and H$_2$O (2 x 100 mL), then was dried (Na$_2$SO$_4$), and concentrated in vacuo to provide the crude phenol 28 as a yellow oil. This material was chromatographed (SiO$_2$, 330 g ISCO column, continuous gradient from 0-50% EtOAc in hexane over 50 min, held at 1:1 EtOAc:hexane for 30 min) to afford phenol 28 (62 g, 92.8% yield) as a light yellow oil.

**Synthesis of 4-(chloromethyl)-5-methyl-2-p-tolyloxazole (29):**

![Chemical structure of 4-(chloromethyl)-5-methyl-2-p-tolyloxazole (29)](image)

To a solution of p-tolualdehyde (100.0 g, 0.832 mol) in EtOAc (400 mL) was added 2,3-butanedione monoxime (80.0 g, 0.791 mol). The resulting solution was cooled to 0°C and HCl (g) was bubbled through the solution for 10 min. The reaction mixture was stirred overnight at RT, then was concentrated to half the original volume and cooled to 0°C. The solids were filtered off and rinsed with cold EtOAc (100mL) to afford a white solid. This crude N-oxide was dissolved in CHCl$_3$ (500 mL), and POCl$_3$ (81.0 mL, 0.870 mol) was added at RT in one portion. The reaction mixture was heated to 60°C with stirring for 24 h, then was cooled to RT and concentrated in vacuo. The residue was taken up in EtOAc (750 mL) and cooled to 0°C; H$_2$O (500 mL) was added, and the pH of the mixture was carefully adjusted to >8 by portionwise addition of solid NaHCO$_3$. The organic phase was washed with brine (100mL), dried (MgSO$_4$) and concentrated in vacuo. The crude product was dissolved in EtOAc (700mL) and filtered through a 2 inch plug of silica gel, which was rinsed with EtOAc (75 mL). The filtrate was concentrated in vacuo to give provide the oxazole chloride 29 (107 g, 61%) as a white solid.

M.P. 91-92°C
H NMR (400 MHz, CDCl₃) δ 2.39 (s, 3H, CH₃), 2.41 (s, 3H, CH₃), 4.55 (s, 2H, CH₂), 7.24 (d, 2H, Ar-H), 7.88 (d, 2H, Ar-H)

¹³C NMR (400 MHz, CDCl₃) δ 10.29, 21.43, 37.32, 124.50, 126.12, 129.37, 132.69, 140.46, 146.15, 160.23

LC/MS m/e 221 (M+)

Calcd for C₁₂H₁₂ClNO: C, 65.01; H, 5.45; N, 6.31; Cl, 15.99. Found: C, 64.96; H, 5.71; N, 6.19; Cl, 16.04.

Synthesis of Glycine, N-[(4-fluoro-3-methylphenoxy)carbonyl]-N-[(1S)-1-[4-[2-(5-methyl-2-phenyl-4-oxazolyl) methoxy] phenyl]ethyl] methyl ester (30):

[00166] To a solution of phenol 28 (62 g, 172 mmol) in CH₃CN (800 mL), were successively added K₂CO₃ (124 g, 900 mmol) and chloride 29 (42 g, 189 mmol). The reaction mixture was stirred at reflux (oil bath temperature = 94°C) for 5.5 h, then was cooled to RT and filtered. The solids were thoroughly washed with EtOAc (3 x 50 mL). The combined filtrates were concentrated in vacuo. The residue was chromatographed (SiO₂, 330 g ISCO column (x2), continuous gradient from 0-35% EtOAc in hexanes over 50 min, then held at 35% EtOAc in hexane for 30 min) to provide the phenol ether 30 (90 g, 96%) as a colorless oil.

Synthesis of Compound 1c
To a solution of carbamate ester 30 (90 g, 165 mmol) in THF (200 mL) was added a solution of LiOH•H$_2$O (13.9 g, 330 mmol) in H$_2$O (200 mL). The mixture was warmed to 40°C and stirred at 40°C for 3 h, then was cooled to 0°C. The pH of the mixture was adjusted to 1 by addition of concentrated HCl (~30 mL) at 0°C. The mixture was diluted with EtOAc (500 mL), and the organic phase was washed with H$_2$O (8 x 200 mL) and concentrated to half the original volume, during which a white solid formed. This solid was dried in vacuo to give crude carbamate-acid Ic (62 g, 117 mmol) with purity >99%. The mother liquor was collected and concentrated to half the original volume, then was left at RT overnight, after which a white solid was formed. This material was collected, dried under vacuum, and combined with the previous 62 g batch. The combined batches of crude carbamate-acid Ic (75.5 g, 86.3%) had a purity of >99%.

Recrystallization:

Crude carbamate-acid Ic (168.4 g, multiple lots) was dissolved in hot EtOAc (2 L) at reflux, then was concentrated to ~75% of the original volume. This EtOAc solution was filtered, then was stirred at 60°C for a further 7 h, cooled to RT and kept at RT for 2 days. A white solid formed, was collected and the solid was washed with EtOAc/hexanes (1:1, 400 mL), followed by hexanes (3 x 300 mL). The white solid was dried in vacuo at 60°C for 24 h to give carbamate-acid Ic (157 g, 93% recovered yield) with >99.5% purity and 99.6% ee.

1H NMR (500 MHz, DMSO-d$_6$; 24°C) δ 12.70 (br. s., 1 H), 7.83 (d, $J$=8.25 Hz, 2 H), 7.22 - 7.42 (m, 5 H), 6.96 - 7.10 (m, 2 H), 6.80 (d, $J$=7.15 Hz, 1 H), 6.59 - 6.71 (m, 2 H), 5.31 - 5.46 (m, 1 H), 4.98 (s, 2 H), 3.72 - 4.00 (m, 5 H), 2.43 (s, 3 H), 2.36 (s, 3 H), 1.44 - 1.62 (m, 3 H)
$^{13}$C NMR (126 MHz, DMSO-d6; 24°C) δ 170.5, 159.9, 159.0, 157.5, 153.9, 153.6, 152.2, 147.1, 140.2, 133.3, 132.7, 131.8, 129.7, 128.4, 128.2, 125.6, 124.2, 114.6, 113.9, 113.7, 111.0, 110.9, 107.7, 107.5, 61.4, 55.3, 54.4, 53.5, 45.3, 44.5, 21.0, 17.8, 16.7, 10.0 (note: extra peaks are due to rotamers as the spectrum was run at 24°C)

HRMS (M+H)$^+$ = 531.2122 ($\Delta$ = -1.8 ppm)

$[\alpha]_D$ = -90.07° (c = 7.366 mg/mL, CH$_3$OH, temperature = 25°C, λ = 589 nm)

Theoretical for (C$_{36}$H$_{30}$N$_2$O$_7$): C 67.91%, H 5.69%, N 5.28%
Average found from two tests (C$_{36}$H$_{30}$N$_2$O$_7$): C 67.92%, H 5.76%, N 5.22%

**Biological Data**

[00169] In vitro PPAR agonist functional assays were performed by transiently transfecting GAL4-hPPARα-LBD or GAL4-hPPARγ-LBD constructs respectively into HEK293 (human embryonic kidney) cells stably expressing 5 x GAL4RE-Luciferase. Data were normalized for efficacy at 1 μM to known agonists (BRL-49653 for hPPARγ and GW-2331 for hPPARα). Agonist binding results in an increase in luciferase enzyme activity which can be monitored by measuring luminescence upon cell lysing and the addition of luciferin substrate. EC$_{50}$ values (μM) for PPARα or γ agonist activity were calculated as the concentration of the test ligand (μM) required for the half-maximal fold induction of HEK293 cells. The “intrinsic activity” of a test ligand is defined as its activity at 1 μM (expressed as a percentage) relative to the activity of the primary standards (GW2331 for PPARα and BRL-49653/rosiglitazone for PPARγ respectively, both tested at 1 μM). Compounds of formula I are functional agonists with activities in the range of EC$_{50}$ = 1-10 nM against the human PPARγ receptor and EC$_{50}$ = 1-10 nM against the human PPARα receptor. The ratios of the PPARα:PPARγ EC$_{50}$ values of compounds of formula I are between 1:2 and 2:1 in this functional assay.

*In vitro* functional data for Compounds 1a-1c are shown in the table below.
Table 1

<table>
<thead>
<tr>
<th>Compound</th>
<th>PPARα EC₅₀ (nM) (% efficacy)</th>
<th>PPARγ EC₅₀ (nM) (% efficacy)</th>
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</thead>
<tbody>
<tr>
<td>la</td>
<td>6 ± 1 (92 ± 16%)</td>
<td>3 ± 1 (128 ± 19%)</td>
</tr>
<tr>
<td>lb</td>
<td>8 ± 2 (95 ± 9%)</td>
<td>4 ± 2 (126 ± 23%)</td>
</tr>
<tr>
<td>lc</td>
<td>6 ± 2 (82 ± 10%)</td>
<td>5 ± 2 (124 ± 19%)</td>
</tr>
</tbody>
</table>

[00170] It is typically known in the art that PPARγ agonists cause edema both in animals and in the clinic. The present PPAR α/γ dual agonists/activators, which have equivalent human PPARα vs. human PPARγ functional activity in a Gal4 transactivation assay in a HEK (human embryonic kidney) cell line, may be advantageous over other PPARα/γ dual agonists with increased potency at PPARγ than at PPARα (i.e., EC₅₀ PPARγ << EC₅₀ PPARα) in that the anti-dyslipidemic effects (from activation of PPARα) may be manifested at a sufficiently low dose before the edemagenic effects from activation of PPARγ become unmanageable.

[00171] 8 week old female db/db mice were dosed orally once daily for 14 days at 10 mg/kg with the Example 1a-1c compounds using a vehicle comprised of 5% 1-methylpyrrolidinone, 20% polyethylene glycol (PEG400) and 75% 20 mM dibasic sodium phosphate. Plasma samples were obtained from mice fasted overnight (18 hours after last administration of compound) on day 15. The plasma glucose and triglycerides levels were determined and the percentage reductions in both parameters of drug-treated animal relative to vehicle-treated animals are shown in the table below.
## Table 2

<table>
<thead>
<tr>
<th>Compound</th>
<th>% Reduction in Plasma Glucose vs Vehicle-control group</th>
<th>% Reduction in Plasma Triglycerides vs Vehicle-control group</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a</td>
<td>-45%</td>
<td>-45%</td>
</tr>
<tr>
<td>1b</td>
<td>-34%</td>
<td>-50%</td>
</tr>
<tr>
<td>1c</td>
<td>-34%</td>
<td>-61%</td>
</tr>
</tbody>
</table>

[00172] It is known by one skilled in the art that the compounds of the present invention normalize plasma glucose levels and decrease plasma triglycerides at doses ≥ 10 mg/kg in rodent models of type 2 diabetes (e.g. the db/db mouse). 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 db/db mouse as an in vivo rodent model for antidiabetic efficacy: T. Harrity et al, *Diabetes*, 2006, 55, 240-248).
WHAT IS CLAIMED IS:

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

   \[ \text{I,} \]

   wherein R is hydrogen or C₁-C₄ alkyl; and each of R¹ and R² is independently hydrogen, C₁-C₄ alkyl, halo or C₁-C₄ alkoxy, and salts thereof.

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

   \[ \text{Ia, and salts thereof.} \]

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

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

6. 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.

7. 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.

8. 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.
9. 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.

10. A pharmaceutical combination comprising a compound as defined in Claim 9 and an 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.

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

12. The pharmaceutical combination as defined in Claim 11, wherein the anti-diabetic agent is 1, 2, 3 or more of a biguanide, a sulfonyl urea, a glucosidase inhibitor, a PPARγ agonist, a PPARα/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.

13. The pharmaceutical combination as defined in Claim 12, wherein the anti-diabetic agent is 1, 2, 3 or more of metformin, glyburide, glimepiride, glipryide, glipizide, chloropropamide, 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.

14. The pharmaceutical combination as defined in Claim 11, 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.

15. The pharmaceutical combination as defined in Claim 14, 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.

16. The pharmaceutical combination as defined in Claim 15, 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.

17. 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 treatment thereof a therapeutically effective amount of a pharmaceutical combination as defined in Claim 10.

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

19. A compound having the structure of Formula (II), and salts thereof:

\[
\begin{align*}
\text{II,} \\
\text{wherein } R^3 \text{ is selected from the group consisting of } -\text{COH, } -\text{CH=N-(R)-S(O)C(CH}_3)_3, -
\end{align*}
\]

\[
\begin{align*}
(S)-\text{CH(CH}_3)(\cdot \text{H}_2 \text{O})\text{NH-(R)-S(O)C(CH}_3)_3, -(S)-\text{CH(CH}_3)\text{NH-(R)-S(O)C(CH}_3)_3, -(S)-
\end{align*}
\]

\[
\begin{align*}
\text{CH(CH}_3)\text{NH}_2 \cdot \text{HCl, (S)-CH(CH}_3)\text{NH}_2, -(S)-\text{CH(CH}_3)\text{NH-CH}_2 \text{CO}_2 \text{Et, and (S)-}
\end{align*}
\]

\[
\begin{align*}
\text{CH(CH}_3)\text{NH(\cdot HCl)-CH}_2 \text{CO}_2 \text{Et.}
\end{align*}
\]
20. A compound having the structure of Formula (IV):

![Chemical Structure Image]

IV, and salts thereof.