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(54) Title: INDOLINE COMPOUNDS AND THEIR USE IN THE TREATMENT OF ARTERIOSCLEROSIS

(57) Abstract: Indoline compounds, pharmaceutical compositions containing such compounds and the use of such compounds to elevate certain plasma lipid levels, including high density lipoprotein-cholesterol and to lower certain other plasma lipid levels, such as LDL-cholesterol and triglycerides and accordingly to treat diseases which are exacerbated by low levels of HDL cholesterol and/or high levels of LDL-cholesterol and triglycerides, such as atherosclerosis and cardiovascular diseases in some mammals, including humans.



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INDOLINE COMPOUNDS AND THEIR USE IN THE TREATMENT OF ARTERIOSCLEROSIS

BACKGROUND OF INVENTION

This invention relates to indoline compounds, pharmaceutical compositions containing such inhibitors and the use of such inhibitors to elevate certain plasma lipid levels, including high density lipoprotein (HDL)-cholesterol and to lower certain other plasma lipid levels, such as low density lipoprotein (LDL)-cholesterol and triglycerides and accordingly to treat diseases which are affected by low levels of HDL cholesterol and/or high levels of LDL-cholesterol and triglycerides, such as atherosclerosis and cardiovascular diseases in certain mammals (i.e., those which have CETP in their plasma), including humans.

Atherosclerosis and its associated coronary artery disease (CAD) is the leading cause of mortality in the industrialized world. Despite attempts to modify secondary risk factors (smoking, obesity, lack of exercise) and treatment of dyslipidemia with dietary modification and drug therapy, coronary heart disease (CHD) remains the most common cause of death in the U.S., where cardiovascular disease accounts for 44% of all deaths, with 53% of these associated with atherosclerotic coronary heart disease.

Risk for development of this condition has been shown to be strongly correlated with certain plasma lipid levels. While elevated LDL-C may be the most recognized form of dyslipidemia, it is by no means the only significant lipid associated contributor to CHD. Low HDL-C is also a known risk factor for CHD (Gordon, D.J., et al., "High-density Lipoprotein Cholesterol and Cardiovascular Disease", *Circulation*, (1989), 79: 8-15).

High LDL-cholesterol and triglyceride levels are positively correlated, while high levels of HDL-cholesterol are negatively correlated with the risk for developing cardiovascular diseases. Thus, dyslipidemia is not a unitary risk profile for CHD but may be comprised of one or more lipid aberrations.

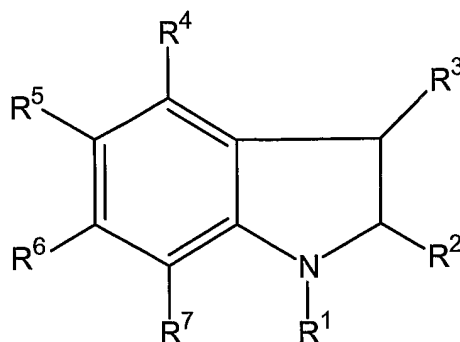
Among the many factors controlling plasma levels of these disease dependent principles, cholesteryl ester transfer protein (CETP) activity affects all three. The role of this 70,000 dalton plasma glycoprotein found in a number of animal species, including humans, is to transfer cholesteryl ester and triglyceride between lipoprotein particles, including high density lipoproteins (HDL), low density lipoproteins (LDL), very low density lipoproteins (VLDL), and chylomicrons. The net result of CETP activity is a lowering of HDL cholesterol and an increase in LDL cholesterol. This effect on lipoprotein profile is believed to be pro-atherogenic, especially in subjects whose lipid profile constitutes an increased risk for CHD.

No wholly satisfactory HDL-elevating therapies are on the market today. Niacin can significantly increase HDL, but has serious toleration issues which reduce compliance. Fibrates and the HMG CoA reductase inhibitors raise HDL-C, but in some patients, the result is an increase of modest proportions (~10-12%). As a result, there is an unmet medical need for an approved therapeutic agent that elevates plasma HDL levels, thereby reversing or slowing the progression of atherosclerosis.

Thus, although there are a variety of anti-atherosclerosis therapies, there is a continuing need and a continuing search in this field of art for alternative therapies.

SUMMARY OF THE INVENTION

This invention is directed to compounds according to Formula I



Formula I

a prodrug thereof, or a pharmaceutically acceptable salt of said compound or of said prodrug;

R^1 is Y, W-X or W- Y^1 ; wherein W is a carbonyl, thiocarbonyl, sulfinyl or sulfonyl; X is -O-Y, -S-Y, -N(H)-Y or -N-(Y^1)₂; Y for each occurrence is independently Z or a fully saturated, partially unsaturated or fully unsaturated one to ten membered straight or branched carbon chain wherein each carbon, other than the connecting carbon, may optionally be replaced with one or two heteroatoms selected independently from oxygen, sulfur and nitrogen and said carbon is optionally mono-, di- or tri-substituted independently with halo, said carbon is optionally mono-substituted with hydroxy, said carbon is optionally mono-substituted with oxo, said sulfur is optionally mono- or di-substituted with oxo, said nitrogen is optionally mono-, or di-substituted with oxo, and said carbon chain is optionally mono-substituted with Z; and Y^1 for each occurrence is independently Z or a fully saturated, partially unsaturated or fully unsaturated one to ten membered straight or branched carbon chain wherein each carbon, other than the connecting carbon, may optionally be replaced with one or two heteroatoms selected independently from oxygen, sulfur and nitrogen and said carbon is optionally mono-, di- or tri-substituted independently with halo, said carbon is optionally mono-substituted with hydroxy, said carbon is optionally mono-substituted with oxo, said sulfur is optionally mono- or di-substituted with oxo, said nitrogen is optionally mono-, or di-substituted with oxo, and said carbon chain is optionally mono-substituted with Z; wherein Z is a partially saturated, fully saturated or fully unsaturated three to eight membered ring optionally having one to four heteroatoms selected independently from oxygen, sulfur and nitrogen, or a bicyclic ring consisting of two fused partially saturated, fully saturated or fully unsaturated three to six membered rings, taken independently, optionally having one to four heteroatoms selected independently from nitrogen, sulfur and oxygen; and said Z substituent is optionally mono-, di- or tri-substituted independently with halo, (C₂-C₆)alkenyl, (C₁-C₆) alkyl, hydroxy, (C₁-C₆)alkoxy, (C₁-C₄)alkylthio, amino, nitro, cyano, oxo, carboxy, (C₁-C₆)alkyloxycarbonyl, mono-N- or di-N,N-(C₁-C₆)alkylamino wherein said (C₁-C₆)alkyl substituent is optionally mono-, di- or tri-substituted independently with halo, hydroxy, (C₁-C₆)alkoxy, (C₁-C₄)alkylthio, amino, nitro, cyano, oxo, carboxy, (C₁-C₆)alkyloxycarbonyl, mono-N- or di-N,N-(C₁-C₆)alkylamino, said (C₁-C₆)alkyl or (C₁-C₆)alkoxy substituent is also optionally substituted with from one to nine fluorines;

R^2 is a partially saturated, fully saturated or fully unsaturated one to six membered straight or branched carbon chain wherein each carbon, other than the connecting carbon, may optionally be replaced with one or two heteroatoms selected independently from oxygen and sulfur, and said carbon is optionally mono-, di- or tri-substituted independently with halo, said carbon chain is optionally mono-substituted with oxo, said carbon is optionally mono-substituted with hydroxy, said sulfur is optionally

mono- or di-substituted with oxo,; or said R^2 is a partially saturated, fully saturated or fully unsaturated three to seven membered ring optionally having one to two heteroatoms selected independently from oxygen and sulfur, wherein said R^2 ring is optionally attached through (C₁-C₄)alkyl; wherein said R^2 ring is optionally mono-, di- or tri-substituted independently with halo, (C₂-C₆)alkenyl, (C₁-C₆) alkyl, hydroxy, (C₁-C₆)alkoxy, (C₁-C₄)alkylthio, amino, nitro, cyano, oxo, carboxy, (C₁-C₆)alkyloxycarbonyl, mono-N- or di-N,N-(C₁-C₆)alkylamino wherein said (C₁-C₆)alkyl substituent is optionally mono-, di- or tri-substituted independently with halo, hydroxy, (C₁-C₆)alkoxy, (C₁-C₄)alkylthio, oxo or (C₁-C₆)alkyloxycarbonyl;

R^3 is a fully saturated, partially unsaturated or fully unsaturated one to six membered straight or branched carbon chain wherein each carbon in the carbon chain may optionally be replaced with one heteroatom selected from oxygen and nitrogen, and said carbon is optionally mono-, di- or tri-substituted with halo, said carbon is optionally mono-substituted with hydroxy, oxo, cyano, carbonyl, or amino, said carbon is optionally mono-substituted with oxo or nitrogen, said nitrogen is optionally mono- or di-substituted with hydrogen or oxo, and said carbon chain is mono, di-, or tri-substituted with V;

wherein V is a partially saturated, fully saturated or fully unsaturated three to eight membered ring optionally having one to four heteroatoms selected independently from oxygen, sulfur and nitrogen; a bicyclic ring consisting of two fused partially saturated, fully saturated or fully unsaturated three to six membered rings, taken independently, optionally having one to four heteroatoms selected independently from nitrogen, sulfur and oxygen; or a tricyclic ring consisting of three fused partially saturated, fully saturated or fully unsaturated three to six membered rings, taken independently, optionally having one to

four heteroatoms selected independently from nitrogen, sulfur and oxygen; and said V substituent is optionally mono-, di-, tri-, tetra- or penta-substituted independently with (R^0)_n, V^1 , (C₁-C₆)alkyl- V^1 , C(O)- V^1 , O-(C₀-C₆)alkyl- V^1 , (C₁-C₆)alkyl-O- V^1 , C(O)-mono-N- or di-N,N-(C₁-C₆)alkyl- V^1 , halo, (C₁-C₆)alkyl, (C₂-C₆)alkenyl, hydroxy, (C₁-C₆)alkoxy, (C₁-C₄)alkylthio, (C₁-C₄)alkylsulfinyl, (C₁-C₄)alkylsulfonyl, mono-N- or di-N,N-(C₁-C₆)alkylsulfonyl, amino, nitro, cyano, oxo, carboxamoyl, mono-N- or di-N,N-(C₁-C₆)

alkylcarboxamoyl, carboxy, (C₁-C₆)alkyloxycarbonyl, mono-N- or di-N,N-(C₁-C₆)alkylamino, wherein said (C₁-C₆)alkyl or (C₂-C₆)alkenyl substituent is optionally mono-, di- or tri-substituted independently with hydroxy, (C₁-C₆)alkoxy, (C₁-C₄)alkylthio, amino, nitro, cyano, oxo, carboxy, (C₁-C₆)alkyloxycarbonyl, mono-N- or di-N,N-(C₁-C₆)alkylamino, wherein each (C₁-C₆)alkyl, (C₁-C₆)alkoxy, (C₁-C₄)alkylthio, (C₁-C₄)alkylsulfonyl or (C₂-C₆)alkenyl substituents are also optionally substituted with from one to nine fluorines, and wherein n is 1, 2, 3 or 4 and each R^0 is independently halo, (C₁-C₆)alkyl, (C₂-C₆)alkenyl, hydroxy, (C₁-C₆)alkoxy, (C₁-C₄)alkylthio, amino, nitro, cyano, oxo, carboxamoyl, carboxy, (C₁-C₆)alkyloxycarbonyl, mono-N- or di-N,N-(C₁-C₆)alkylamino, (C₁-C₆)alkyloxycarbonyl, mono-N- or di-N,N-(C₁-C₆)alkylamino wherein said (C₁-C₆)alkyl substituent is optionally mono-substituted with oxo, said (C₁-C₆)alkyl substituent is also optionally substituted with from one to nine fluorines;

wherein V^1 is a partially saturated, fully saturated or fully unsaturated three to six membered ring optionally having one to two heteroatoms selected independently from oxygen, sulfur and nitrogen, or a bicyclic ring consisting of two fused partially saturated, fully saturated or fully unsaturated three to six membered rings, taken independently, optionally having one to four heteroatoms selected independently from nitrogen, sulfur and oxygen; and said V^1 substituent is optionally mono-, di-, tri-, tetra- or penta-substituted independently with halo, (C₁-C₆)alkyl, (C₁-C₆)alkoxy, hydroxy, oxo, amino, nitro, cyano, (C₁-C₆)alkyloxycarbonyl, mono-N- or di-N,N-(C₁-C₆)alkylamino wherein said (C₁-C₆)alkyl substituent is

optionally mono-substituted with oxo, said (C₁-C₆)alkyl or (C₁-C₆)alkoxy substituent is also optionally substituted with from one to nine fluorines; and

each of R⁴, R⁵, R⁶ and R⁷ are independently hydrogen, a bond, nitro or halo wherein said bond is substituted with T or a partially saturated, fully saturated or fully unsaturated (C₁-C₁₂) straight or

5 branched carbon chain wherein each carbon may optionally be replaced with one or two heteroatoms per carbon chain wherein the heteroatoms are selected independently from oxygen, sulfur and nitrogen, wherein said carbon is optionally mono-, di- or tri-substituted independently with halo, said carbon is optionally mono-substituted with hydroxy, said carbon is optionally mono-substituted with oxo or nitrogen, said sulfur is optionally mono- or di-substituted with oxo, said nitrogen is optionally mono- or di-

10 substituted with hydrogen or oxo, and said carbon chain is optionally mono-substituted with T; wherein T is a partially saturated, fully saturated or fully unsaturated three to twelve membered ring optionally having one to four heteroatoms selected independently from oxygen, sulfur and nitrogen, or a bicyclic ring consisting of two fused partially saturated, fully saturated or fully unsaturated three to six membered rings, taken independently, optionally having one to four heteroatoms selected independently from

15 nitrogen, sulfur and oxygen; and said T substituent is optionally mono-, di- or tri-substituted independently with halo, (C₁-C₆)alkyl, (C₂-C₆)alkenyl, hydroxy, (C₁-C₆)alkoxy, (C₁-C₄)alkylthio, amino, nitro, cyano, oxo, carboxy, (C₁-C₆)alkyloxycarbonyl, mono-N- or di-N,N-(C₁-C₆)alkylamino wherein said (C₁-C₆)alkyl substituent is optionally mono-, di- or tri-substituted independently with hydroxy, (C₁-C₆)alkoxy, (C₁-C₄)alkylthio, amino, nitro, cyano, oxo, carboxy, (C₁-C₆)alkyloxycarbonyl, mono-N- or di-

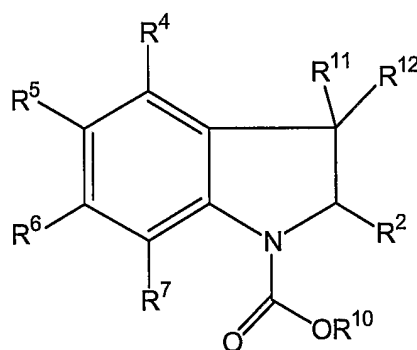
20 N,N-(C₁-C₆)alkylamino, said (C₁-C₆)alkyl or (C₁-C₆)alkoxy substituent also optionally has from one to nine fluorines;

R⁴ and R⁵, R⁵ and R⁶, and/or R⁶ and R⁷ may optionally be taken together and can form at least one ring that is a partially saturated or fully unsaturated four to eight membered ring optionally having one to three heteroatoms independently selected from nitrogen, sulfur and oxygen; wherein each ring

25 formed by R⁴ and R⁵, or R⁵ and R⁶, and/or R⁶ and R⁷ is optionally mono-, di- or tri-substituted independently with halo, (C₁-C₆)alkyl, (C₁-C₄)alkylsulfonyl, (C₂-C₆)alkenyl, hydroxy, (C₁-C₆)alkoxy, (C₁-C₄)alkylthio, amino, nitro, cyano, oxo, carboxy, (C₁-C₆)alkyloxycarbonyl, mono-N- or di-N,N-(C₁-C₆)alkylamino wherein said (C₁-C₆)alkyl substituent is optionally mono-, di- or tri-substituted independently with hydroxy, (C₁-C₆)alkoxy, (C₁-C₄)alkylthio, amino, nitro, cyano, oxo, carboxy, (C₁-

30 C₆)alkyloxycarbonyl, mono-N- or di-N,N-(C₁-C₆)alkylamino, said (C₁-C₆)alkyl substituent also optionally has from one to nine fluorines.

Furthermore, the present invention is directed to compounds according to Formula II



Formula II

wherein

R^2 is (C₁-C₄)alkyl, cyclopropyl or cyclobutyl;

R^5 is CF₃;

R^6 is hydrogen;

5 R^{10} is a fully saturated (C₁-C₄) straight or branched carbon chain;

R^{11} is -C(O)NH((C₁-C₄)alkyl), -C(O)N((C₁-C₄)alkyl)((C₁-C₄)alkyl); -C(O)NH(O(C₁-C₄)alkyl) or -C(O)N((C₁-C₄)alkyl)(O(C₁-C₄)alkyl);

R^{12} is hydrogen or halo;

or R^{11} and R^{12} are taken together to form oxo or N₂;

10 or a pharmaceutically acceptable salt or prodrug thereof.

In addition, the present invention provides methods for treating atherosclerosis, coronary artery disease, coronary heart disease, coronary vascular disease, peripheral vascular disease, dyslipidemia, hyperbetalipoproteinemia, hypoalphalipoproteinemia, hypercholesterolemia, hypertriglyceridemia, familial-hypercholesterolemia or myocardial infarction in a mammal by administering to a mammal in
15 need of such treatment an atherosclerosis, coronary artery disease, coronary heart disease, coronary vascular disease, peripheral vascular disease, dyslipidemia, hyperbetalipoproteinemia, hypoalphalipoproteinemia, hypercholesterolemia, hypertriglyceridemia, familial-hypercholesterolemia or myocardial infarction treating amount of a compound of the present invention, or a pharmaceutically acceptable form of said compound.

20 In addition, the present invention provides pharmaceutical compositions which comprise a therapeutically effective amount of a compound of the present invention, or a pharmaceutically acceptable form of said compound and a pharmaceutically acceptable vehicle, diluent or carrier.

In addition, the present invention provides pharmaceutical compositions for the treatment of atherosclerosis, coronary artery disease, coronary heart disease, coronary vascular disease, peripheral
25 vascular disease, dyslipidemia, hyperbetalipoproteinemia, hypoalphalipoproteinemia, hypercholesterolemia, hypertriglyceridemia, familial-hypercholesterolemia or myocardial infarction in a mammal which comprise a therapeutically effective amount of a compound of the present invention, or a pharmaceutically acceptable form of said compound and a pharmaceutically acceptable vehicle, diluent or carrier.

30 Moreover, the present invention provides pharmaceutical combination compositions comprising: a therapeutically effective amount of a composition comprising

a first compound, said first compound being a compound of the present invention, or a pharmaceutically acceptable form of said compound;

a second compound, said second compound being an HMG CoA reductase inhibitor, an
35 MTP/Apo B secretion inhibitor, a PPAR modulator, a bile acid reuptake inhibitor, a cholesterol absorption inhibitor, a cholesterol synthesis inhibitor, a fibrate, niacin, slow-release niacin, a combination of niacin and lovastatin, an ion-exchange resin, an antioxidant, an ACAT inhibitor or a bile acid sequestrant (preferably an HMG-CoA reductase inhibitor, a PPAR modulator, lovastatin, simvastatin, pravastatin, fluvastatin, atorvastatin, rivastatin, rosuvastatin or pitavastatin); and

40 a pharmaceutical vehicle, diluent or carrier. This composition may be used to treat the aforementioned diseases, including atherosclerosis.

Also, the present invention provides a kit for achieving a therapeutic effect in a mammal comprising packaged in association a first therapeutic agent comprising a therapeutically effective amount of a compound of the present invention, a prodrug thereof, or a pharmaceutically acceptable salt of said compound or of said prodrug and a pharmaceutically acceptable carrier, a second therapeutic agent comprising a therapeutically effective amount of an HMG CoA reductase inhibitor, a PPAR modulator, a cholesterol absorption inhibitor, a cholesterol synthesis inhibitor, a fibrate, niacin, slow-release niacin, a combination of niacin and lovastatin, an ion-exchange resin, an antioxidant, an ACAT inhibitor or a bile acid sequestrant and a pharmaceutically acceptable carrier and directions for administration of said first and second agents to achieve the therapeutic effect.

It is to be understood that both the foregoing general description and the following detailed description are exemplary and explanatory only and are not restrictive of the invention, as claimed.

DETAILED DESCRIPTION OF THE INVENTION

The present invention may be understood more readily by reference to the following detailed description of exemplary embodiments of the invention and the examples included therein.

Before the present compounds, compositions and methods are disclosed and described, it is to be understood that this invention is not limited to specific synthetic methods of making that may of course vary. It is also to be understood that the terminology used herein is for the purpose of describing particular embodiments only and is not intended to be limiting.

The present invention also relates to the pharmaceutically acceptable acid addition salts of compounds of the present invention. The acids which are used to prepare the pharmaceutically acceptable acid addition salts of the aforementioned base compounds of this invention are those which form non-toxic acid addition salts, (*i.e.*, salts containing pharmacologically acceptable anions, such as the hydrochloride, hydrobromide, hydroiodide, nitrate, sulfate, bisulfate, phosphate, acid phosphate, acetate, lactate, citrate, acid citrate, tartrate, bitartrate, succinate, maleate, fumarate, gluconate, saccharate, benzoate, methanesulfonate, ethanesulfonate, benzenesulfonate, p-toluenesulfonate and pamoate (*i.e.*, 1,1'-methylene-bis-(2-hydroxy-3-naphthoate)) salts.

The invention also relates to base addition salts of the compounds of the present invention. The chemical bases that may be used as reagents to prepare pharmaceutically acceptable base salts of those compounds of the present invention that are acidic in nature are those that form non-toxic base salts with such compounds. Such non-toxic base salts include, but are not limited to those derived from such pharmacologically acceptable cations such as alkali metal cations (*e.g.*, potassium and sodium) and alkaline earth metal cations (*e.g.*, calcium and magnesium), ammonium or water-soluble amine addition salts such as N-methylglucamine-(meglumine), and the lower alkanolammonium and other base salts of pharmaceutically acceptable organic amines.

The chemist of ordinary skill will recognize that certain compounds of this invention will contain one or more atoms which may be in a particular stereochemical or geometric configuration, giving rise to stereoisomers and configurational isomers. All such isomers and mixtures thereof are included in this invention. Hydrates and solvates of the compounds of this invention are also included.

Where the compounds of the present invention possess two or more stereogenic centers and the absolute or relative stereochemistry is given in the name, the designations R and S refer respectively to

each stereogenic center in ascending numerical order (1, 2, 3, etc.) according to the conventional IUPAC number schemes for each molecule. Where the compounds of the present invention possess one or more stereogenic centers and no stereochemistry is given in the name or structure, it is understood that the name or structure is intended to encompass all forms of the compound, including the racemic form.

5 The compounds of this invention may contain olefin-like double bonds. When such bonds are present, the compounds of the invention exist as cis and trans configurations and as mixtures thereof. The term "cis" refers to the orientation of two substituents with reference to each other and the plane of the ring (either both "up" or both "down"). Analogously, the term "trans" refers to the orientation of two substituents with reference to each other and the plane of the ring (the substituents being on opposite
10 sides of the ring).

Alpha and Beta refer to the orientation of a substituent with reference to the plane of the ring. Beta is above the plane of the ring and Alpha is below the plane of the ring.

This invention also includes isotopically-labeled compounds, which are identical to those described by formulas I and II, except for the fact that one or more atoms are replaced by one or more
15 atoms having specific atomic mass or mass numbers. Examples of isotopes that can be incorporated into compounds of the invention include isotopes of hydrogen, carbon, nitrogen, oxygen, sulfur, fluorine, and chlorine such as ^2H , ^3H , ^{13}C , ^{14}C , ^{15}N , ^{18}O , ^{17}O , ^{18}F , and ^{36}Cl respectively. Compounds of the present invention, prodrugs thereof, and pharmaceutically acceptable salts of the compounds or of the prodrugs which contain the aforementioned isotopes and/or other isotopes of other atoms are within the
20 scope of this invention. Certain isotopically-labeled compounds of the present invention, for example those into which radioactive isotopes such as ^3H and ^{14}C are incorporated, are useful in drug and/or substrate tissue distribution assays. Tritiated (*i.e.*, ^3H), and carbon-14 (*i.e.*, ^{14}C), isotopes are particularly preferred for their ease of preparation and detectability. Further, substitution with heavier isotopes such as deuterium (*i.e.*, ^2H), can afford certain therapeutic advantages resulting from greater metabolic
25 stability, for example increased *in vivo* half-life or reduced dosage requirements and, hence, may be preferred in some circumstances. Isotopically labeled compounds of this invention and prodrugs thereof can generally be prepared by carrying out the procedures disclosed in the schemes and/or in the Examples below, by substituting a readily available isotopically labeled reagent for a non-isotopically labeled reagent.

30 In this specification and in the claims that follow, reference will be made to a number of terms that shall be defined to have the following meanings:

As used herein, the term mammals is meant to refer to all mammals which contain CETP in their plasma, for example, rabbits and primates such as monkeys and humans, including males and females. Certain other mammals *e.g.*, dogs, cats, cattle, goats, sheep and horses do not contain CETP in their
35 plasma and so are not included herein.

The term "treating", "treat" or "treatment" as used herein includes preventative (*e.g.*, prophylactic) and palliative treatment.

By "pharmaceutically acceptable" is meant the carrier, diluent, excipients, and/or salt must be compatible with the other ingredients of the formulation, and not deleterious to the recipient thereof.

40 "Compounds" when used herein includes any pharmaceutically acceptable derivative or variation, including conformational isomers (*e.g.*, cis and trans isomers) and all optical isomers (*e.g.*,

enantiomers and diastereomers), racemic, diastereomeric and other mixtures of such isomers, as well as solvates, hydrates, isomorphs, polymorphs, tautomers, esters, salt forms, and prodrugs. By "tautomers" is meant chemical compounds that may exist in two or more forms of different structure (isomers) in equilibrium, the forms differing, usually, in the position of a hydrogen atom. Various types of tautomerism can occur, including keto-enol, ring-chain and ring-ring tautomerism. The expression "prodrug" refers to compounds that are drug precursors which following administration, release the drug *in vivo* via some chemical or physiological process (e.g., a prodrug on being brought to the physiological pH or through enzyme action is converted to the desired drug form). Exemplary prodrugs upon cleavage release the corresponding free acid, and such hydrolyzable ester-forming residues of the compounds of the present invention include but are not limited to those having a carboxyl moiety wherein the free hydrogen is replaced by (C₁-C₄)alkyl, (C₂-C₇)alkanoyloxymethyl, 1-(alkanoyloxy)ethyl having from 4 to 9 carbon atoms, 1-methyl-1-(alkanoyloxy)-ethyl having from 5 to 10 carbon atoms, alkoxycarbonyloxymethyl having from 3 to 6 carbon atoms, 1-(alkoxycarbonyloxy)ethyl having from 4 to 7 carbon atoms, 1-methyl-1-(alkoxycarbonyloxy)ethyl having from 5 to 8 carbon atoms, N-(alkoxycarbonyl)aminomethyl having from 3 to 9 carbon atoms, 1-(N-(alkoxycarbonyl)amino)ethyl having from 4 to 10 carbon atoms, 3-phthalidyl, 4-crotonolactonyl, gamma-butyrolacton-4-yl, di-N,N-(C₁-C₂)alkylamino(C₂-C₃)alkyl (such as β-dimethylaminoethyl), carbamoyl-(C₁-C₂)alkyl, N,N-di(C₁-C₂)alkylcarbamoyl-(C₁-C₂)alkyl and piperidino-, pyrrolidino- or morpholino(C₂-C₃)alkyl.

The following paragraphs describe exemplary ring(s) for the generic ring descriptions contained herein.

Exemplary partially saturated, fully saturated or fully unsaturated three to eight membered rings optionally having one to four heteroatoms selected independently from oxygen, sulfur and nitrogen include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl and phenyl. Further exemplary five membered rings include tetrazolyl, triazolyl, 2H-pyrrolyl, 3H-pyrrolyl, 2-pyrrolinyl, 3-pyrrolinyl, pyrrolidinyl, 1,3-dioxolanyl, oxazolyl, thiazolyl, imidazolyl, 2H-imidazolyl, 2-imidazolyl, imidazolidinyl, pyrazolyl, 2-pyrazolinyl, pyrazolidinyl, isoxazolyl, isothiazolyl, 1,2-dithiolyl, 1,3-dithiolyl, 3H-1,2-oxathiolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, 1,3,4-thiadiazolyl, 1,2,3,4-oxatriazolyl, 1,2,3,5-oxatriazolyl, 3H-1,2,3-dioxazolyl, 1,2,4-dioxazolyl, 1,3,2-dioxazolyl, 1,3,4-dioxazolyl, 5H-1,2,5-oxathiazolyl and 1,3-oxathiolyl.

Further exemplary six membered rings include 2H-pyranyl, 4H-pyranyl, pyridinyl, piperidinyl, 1,2-dioxinyl, 1,3-dioxinyl, 1,4-dioxanyl, morpholinyl, 1,4-dithianyl, thiomorpholinyl, pyridazinyl, pyrimidinyl, pyrazinyl, piperazinyl, 1,3,5-triazinyl, 1,2,4-triazinyl, 1,2,3-triazinyl, 1,3,5-trithianyl, 4H-1,2-oxazinyl, 2H-1,3-oxazinyl, 6H-1,3-oxazinyl, 6H-1,2-oxazinyl, 1,4-oxazinyl, 2H-1,2-oxazinyl, 4H-1,4-oxazinyl, 1,2,5-oxathiazinyl, 1,4-oxazinyl, o-isoxazinyl, p-isoxazinyl, 1,2,5-oxathiazinyl, 1,2,6-oxathiazinyl, 1,4,2-oxadiazinyl and 1,3,5,2-oxadiazinyl.

Further exemplary seven membered rings include azepinyl, oxepinyl, and thiepinyl.

Further exemplary eight membered rings include cyclooctyl, cyclooctenyl and cyclooctadienyl.

Exemplary bicyclic rings consisting of two fused partially saturated, fully saturated or fully unsaturated five or six membered rings, taken independently, optionally having one to four heteroatoms selected independently from nitrogen, sulfur and oxygen include indolizinyl, indolyl, isoindolyl, 3H-indolyl, 1H-isoindolyl, indolinyl, cyclopenta(b)pyridinyl, pyrano(3,4-b)pyrrolyl, benzofuryl, isobenzofuryl,

benzo(b)thienyl, benzo(c)thienyl, 1H-indazolyl, indoxazolyl, benzoxazolyl, benzimidazolyl, benzthiazolyl, purinyl, 4H-quinoliziny, quinoliny, isoquinoliny, cinnoliny, phthalazinyl, quinazolinyl, quinoxaliny, 1,8-naphthyridiny, pteridiny, indenyl, isoindenyl, naphthyl, tetraliny, decaliny, 2H-1-benzopyrany, pyrido(3,4-b)-pyridiny, pyrido(3,2-b)-pyridiny, pyrido(4,3-b)-pyridiny, 2H-1,3-benzoxazinyl, 2H-1,4-benzoxazinyl, 1H-2,3-benzoxazinyl, 4H-3,1-benzoxazinyl, 2H-1,2-benzoxazinyl and 4H-1,4-benzoxazinyl.

By "halo" or "halogen" is meant chloro, bromo, iodo, or fluoro.

By "alkyl" is meant straight chain saturated hydrocarbon or branched chain saturated hydrocarbon. Exemplary of such alkyl groups (assuming the designated length encompasses the particular example) are methyl, ethyl, propyl, isopropyl, butyl, sec-butyl, tertiary butyl, isobutyl, pentyl, isopentyl, neopentyl, tertiary pentyl, 1-methylbutyl, 2-methylbutyl, 3-methylbutyl, hexyl, isohexyl, heptyl and octyl.

"Alkenyl" referred to herein may be linear or branched, and they may also be cyclic (e.g. cyclobutenyl, cyclopentenyl, cyclohexenyl) or bicyclic or contain cyclic groups. They contain 1-3 carbon-carbon double bonds, which can be cis or trans.

By "alkoxy" is meant straight chain saturated alkyl or branched chain saturated alkyl bonded through an oxy. Exemplary of such alkoxy groups (assuming the designated length encompasses the particular example) are methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, tertiary butoxy, pentoxy, isopentoxy, neopentoxy, tertiary pentoxy, hexoxy, isohexoxy, heptoxy and octoxy.

As used herein the term "mono-N-" or "di-N,N-(C₁-C_x)alkylamino" refers to the (C₁-C_x)alkyl moiety taken independently when it is di-N,N-(C₁-C_x)alkyl (x refers to integers).

References (e.g., claim 1) to "said carbon" in the phrase "said carbon is optionally mono-, di- or tri-substituted independently with halo, said carbon is optionally mono-substituted with hydroxy, said carbon is optionally mono-substituted with oxo" refers to each of the carbons in the carbon chain including the connecting carbon.

References to a "nitrogen is optionally mono-, or di-substituted with oxo" herein (e.g., claim 1) refer to a terminal nitrogen which constitutes a nitro functionality.

It is to be understood that if a carbocyclic or heterocyclic moiety may be bonded or otherwise attached to a designated substrate through differing ring atoms without denoting a specific point of attachment, then all possible points are intended, whether through a carbon atom or, for example, a trivalent nitrogen atom. For example, the term "pyridyl" means 2-, 3- or 4-pyridyl, the term "thienyl" means 2- or 3-thienyl, and so forth.

As used herein, the expressions "reaction-inert solvent" and "inert solvent" refer to a solvent or a mixture thereof which does not interact with starting materials, reagents, intermediates or products in a manner which adversely affects the yield of the desired product.

In one embodiment of the compounds of the present invention,

R¹ is W-X;

W is carbonyl;

X is -O-Y;

Y for each occurrence is independently (C₁-C₆)alkyl, said (C₁-C₆)alkyl optionally having one to nine fluorines or said (C₁-C₆)alkyl optionally mono-substituted with Z;

wherein Z is a partially saturated, fully saturated or fully unsaturated three to six membered ring optionally having one to two heteroatoms selected independently from oxygen, sulfur and nitrogen;

wherein said Z substituent is optionally mono-, di- or tri-substituted independently with halo, nitro, amino, hydroxy, cyano, carboxy, acyl, (C₁-C₆)alkoxy, (C₁-C₄)alkylthio, oxo, (C₁-C₆)alkyloxycarbonyl or (C₁-C₆)alkyl, said (C₁-C₄)alkyl is optionally substituted with from one to nine halo, carboxy, oxo, (C₁-C₆)alkoxy, carboxy, and (C₁-C₆)alkyloxycarbonyl;

R² is beta and is a partially saturated, fully saturated or fully unsaturated (C₁-C₄) straight or branched carbon chain wherein one carbon, other than the connecting carbon, may optionally be replaced with oxygen or sulfur and wherein said carbon is optionally mono-, di- or tri-substituted independently with halo, said carbon chain is optionally mono-substituted with oxo or hydroxy, said sulfur is optionally mono- or di-substituted with oxo,; or said R² is a partially saturated, fully saturated or fully unsaturated three to five membered ring optionally having one heteroatom selected independently from oxygen and sulfur;

wherein said R² ring is optionally mono-, di- or tri-substituted independently with halo, hydroxy, (C₁-C₆)alkoxy, amino, nitro, (C₁-C₄)alkyloxycarbonyl or carboxy;

R³ is mono-substituted or di-substituted with V;

R⁴ is hydrogen;

R⁵ and R⁶ are each independently hydrogen, halo, T, (C₁-C₆)alkoxy or (C₁-C₆)alkyl, said (C₁-C₆)alkoxy or (C₁-C₆)alkyl substituent optionally having from one to nine fluorines or said (C₁-C₆)alkoxy or (C₁-C₆)alkyl substituent optionally mono-substituted with T;

wherein T is a partially saturated, fully saturated or fully unsaturated five to six membered ring optionally having one to two heteroatoms selected independently from oxygen, sulfur and nitrogen;

wherein said T substituent is optionally mono-, di- or tri-substituted independently with halo, (C₁-C₆)alkyl, hydroxy, (C₁-C₆)alkoxy, (C₁-C₄)alkylthio, amino, oxo, carboxy, (C₁-C₆)alkyloxycarbonyl, mono-N- or di-N,N-(C₁-C₆)alkylamino wherein said (C₁-C₆)alkyl or (C₁-C₆)alkoxy substituent optionally has from one to nine fluorines;

R⁷ is hydrogen;

or a pharmaceutically acceptable salt thereof.

In another embodiment of the compounds of the present invention,

Y is (C₁-C₄)alkyl, wherein said (C₁-C₄)alkyl substituent optionally has one to nine fluorines;

R² is (C₁-C₄)alkyl, cyclopropyl or cyclobutyl;

R³ is -CH₂-N(C(O)-(C₁-C₂)alkyl)CH₂(V), -CH₂N(C(O)OCH₃)CH₂(V), -C(O)N(H)-(C₁-C₃)alkyl-(V), -C(O)(V), -(C₁-C₃)alkyl-(OH)(V), -(C₁-C₂)alkyl-C(O)(V), -(C₁-C₂)alkyl-N(V)-(C₁-C₂)alkyl-(V), -C(O)N(V)-(C₁-C₃)alkyl-(V), -(C₁-C₃)alkoxy-(V)₂, -(C₁-C₃)alkyl-(OH)(V)₂, or -(C₁-C₃)alkyl-(V)₂;

V is tetrazole, triazole, imidazole, pyrazole, oxadiazole, isoxazole, oxazole, furan, thiadiazole, isothiazole, thiazole, thiophene, phenyl, pyrimidine, or pyridine wherein V is optionally mono-, di- or tri-substituted independently with halo, (C₁-C₆)alkyl, hydroxy, (C₁-C₆)alkoxy, nitro, cyano or oxo wherein said (C₁-C₆)alkyl or (C₁-C₆)alkoxy substituent optionally has from one to nine fluorines;

R⁵ and R⁶ are each independently hydrogen, halo, (C₁-C₃)alkoxy or (C₁-C₆)alkyl, said (C₁-C₃)alkoxy optionally having from one to seven halo, said (C₁-C₆)alkyl optionally having from one to nine halo;

or a pharmaceutically acceptable salt thereof.

In another embodiment of the compounds of the present invention,

R¹ is W-Y¹ or Y;

W is carbonyl;

5 Y and Y¹ are each independently Z or (C₁-C₄)alkyl, said (C₁-C₄)alkyl substituted with Z

and optionally substituted with from one to nine fluorines, or hydroxy;

wherein Z is a partially saturated, fully saturated or fully unsaturated three to six membered ring optionally having one to two heteroatoms selected independently from oxygen, sulfur and nitrogen;

wherein said Z substituent is optionally mono-, di- or tri-substituted independently with

10 halo, nitro, amino, hydroxy, cyano, carboxy, acyl, (C₁-C₆)alkoxy, (C₁-C₄)alkylthio, oxo, (C₁-C₆)alkyloxycarbonyl or (C₁-C₆)alkyl, said (C₁-C₄)alkyl is optionally substituted with from one to nine halo, carboxy, oxo, (C₁-C₆)alkoxy, carboxy, and (C₁-C₆)alkyloxycarbonyl;

R² is beta and is a partially saturated, fully saturated or fully unsaturated (C₁-C₄) straight or branched carbon chain wherein one carbon, other than the connecting carbon, may optionally

15 be replaced with oxygen or sulfur and wherein said carbon is optionally mono-, di- or tri-substituted independently with halo, said carbon chain is optionally mono-substituted with oxo or hydroxy, said sulfur is optionally mono- or di-substituted with oxo,; or said R² is a partially saturated, fully saturated or fully unsaturated three to five membered ring optionally having one heteroatom selected independently from oxygen and sulfur;

20 wherein said R² ring is optionally mono-, di- or tri-substituted independently with halo, hydroxy, (C₁-C₆)alkoxy, amino, nitro, (C₁-C₄)alkyloxycarbonyl or carboxy;

R³ is mono-substituted or di-substituted with V;

R⁴ is hydrogen;

25 R⁵ and R⁶ are each independently hydrogen, halo, T, (C₁-C₆)alkoxy or (C₁-C₆)alkyl, said (C₁-C₆)alkoxy or (C₁-C₆)alkyl substituent optionally having from one to nine fluorines or said (C₁-C₆)alkoxy or (C₁-C₆)alkyl substituent optionally mono-substituted with T;

wherein T is a partially saturated, fully saturated or fully unsaturated five to six membered ring optionally having one to two heteroatoms selected independently from oxygen, sulfur and nitrogen;

30 wherein said T substituent is optionally mono-, di- or tri-substituted independently with halo, (C₁-C₆)alkyl, hydroxy, (C₁-C₆)alkoxy, (C₁-C₄)alkylthio, amino, oxo, carboxy, (C₁-C₆)alkyloxycarbonyl, mono-N- or di-N,N-(C₁-C₆)alkylamino wherein said (C₁-C₆)alkyl or (C₁-C₆)alkoxy substituent optionally has from one to nine fluorines;

R⁷ is hydrogen;

or a pharmaceutically acceptable salt thereof.

35 In another embodiment of the compounds of the present invention,

R¹ is W-Y¹;

Z is (C₃-C₆)cycloalkyl optionally substituted with one, two or three halo, nitro, amino, hydroxy, cyano, carboxy, acyl, (C₁-C₆)alkoxy, or (C₁-C₆)alkyl, wherein said (C₁-C₄)alkyl is optionally substituted with one to three substituents selected from the group consisting of: halo, 40 carboxy, oxo, (C₁-C₆)alkoxy, carboxy, and (C₁-C₆)alkyloxycarbonyl;

R² is (C₁-C₄)alkyl, cyclopropyl or cyclobutyl;

R^3 is $-C(F)(V)_2$, $-C(OCH_3)(V)_2$, $-C(OH)(V)_2$, $-CH(V)_2$,

V is tetrazole, triazole, imidazole, pyrazole, oxadiazole, isoxazole, oxazole, furan, thiadiazole, isothiazole, thiazole, thiophene, phenyl, pyrimidine, or pyridine wherein V is optionally mono-, di- or tri-substituted independently with halo, (C_1-C_6) alkyl, hydroxy, (C_1-C_6) alkoxy, nitro, cyano or oxo wherein

5 said (C_1-C_6) alkyl or (C_1-C_6) alkoxy substituent optionally has from one to nine fluorines;

R^5 and R^6 are each independently hydrogen, halo, (C_1-C_3) alkoxy or (C_1-C_6) alkyl, said (C_1-C_3) alkoxy optionally having from one to seven halo, said (C_1-C_6) alkyl optionally having from one to nine halo;

or a pharmaceutically acceptable salt thereof.

10 In another embodiment of the compounds of the present invention,

R^1 is $W-Y^1$ or Y ;

W is carbonyl;

Y and Y^1 are each independently Z or (C_1-C_4) alkyl, said (C_1-C_4) alkyl substituted with Z and optionally substituted with from one to nine fluorines or hydroxy;

15 wherein Z is a partially saturated, fully saturated or fully unsaturated three to six membered ring optionally having one to two heteroatoms selected independently from oxygen, sulfur and nitrogen;

wherein said Z substituent is optionally mono-, di- or tri-substituted independently with halo, nitro, amino, hydroxy, cyano, carboxy, acyl, (C_1-C_6) alkoxy, (C_1-C_4) alkylthio, oxo, (C_1-C_6) alkyloxycarbonyl or (C_1-C_6) alkyl, said (C_1-C_4) alkyl is optionally substituted with from one to

20 nine halo, carboxy, oxo, (C_1-C_6) alkoxy, carboxy, and (C_1-C_6) alkyloxycarbonyl;

R^2 is beta and is a partially saturated, fully saturated or fully unsaturated (C_1-C_4) straight or branched carbon chain wherein one carbon, other than the connecting carbon, may optionally be replaced with oxygen or sulfur and wherein said carbon is optionally mono-, di- or tri-substituted independently with halo, said carbon chain is optionally mono-substituted with oxo or hydroxy, said sulfur

25 is optionally mono- or di-substituted with oxo,; or said R^2 is a partially saturated, fully saturated or fully unsaturated three to five membered ring optionally having one heteroatom selected independently from oxygen and sulfur;

wherein said R^2 ring is optionally mono-, di- or tri-substituted independently with halo, hydroxy, (C_1-C_6) alkoxy, amino, nitro, (C_1-C_4) alkyloxycarbonyl or carboxy;

30 R^3 is mono-substituted or di-substituted with V;

R^4 is hydrogen;

R^5 and R^6 are each independently hydrogen, halo, T, (C_1-C_6) alkoxy or (C_1-C_6) alkyl, said (C_1-C_6) alkoxy or (C_1-C_6) alkyl substituent optionally having from one to nine fluorines or said (C_1-C_6) alkoxy or (C_1-C_6) alkyl substituent optionally mono-substituted with T;

35 wherein T is a partially saturated, fully saturated or fully unsaturated five to six membered ring optionally having one to two heteroatoms selected independently from oxygen, sulfur and nitrogen;

wherein said T substituent is optionally mono-, di- or tri-substituted independently with halo, (C_1-C_6) alkyl, hydroxy, (C_1-C_6) alkoxy, (C_1-C_4) alkylthio, amino, oxo, carboxy, (C_1-C_6) alkyloxycarbonyl, mono-N- or di-N,N- (C_1-C_6) alkylamino wherein said (C_1-C_6) alkyl or (C_1-C_6) alkoxy substituent optionally has from

40 one to nine fluorines;

R^7 is hydrogen;

or a pharmaceutically acceptable salt thereof.

In another embodiment of the compounds of the present invention,

R¹ is W-Y;

Z is (C₃-C₆)cycloalkyl optionally substituted with one, two or three halo, nitro, amino,

5 hydroxy, cyano, carboxy, acyl, (C₁-C₆)alkoxy, or (C₁-C₆)alkyl, wherein said (C₁-C₄)alkyl is optionally substituted with one to three substituents selected from the group consisting of: halo, carboxy, oxo, (C₁-C₆)alkoxy, carboxy, and (C₁-C₆)alkyloxycarbonyl;

R² is (C₁-C₄)alkyl, cyclopropyl or cyclobutyl;

10 R³ is -((C₁-C₄)alkyl)(NH₂)(V), -((C₁-C₃)alkyl)(NH(C₁-C₂)alkyl)(V), -((C₁-C₄)alkyl)(OH)(V), -((C₁-C₄)alkyl)(F)(V), -((C₁-C₂)alkyl)(O-C(O)(C₁-C₂)alkyl)(V), -C(O)-V, -C(OH)(C(O)O(C₁-C₃)alkyl)(V), -CF₂(V), -((C₁-C₂)alkyl)(NHC(O)(C₁-C₂)alkyl)(V), -CH₂(V), -((C₁-C₂)alkyl)(C(O)O(C₁-C₂)alkyl)(V), -((C₁-C₄)alkyl)(C(O)NH₂)(V), -((C₁-C₄)alkyl)(CN)(V), or -((C₁-C₃)alkyl)((C₁-C₃)alkoxy)(V),

V is phenyl optionally mono-, di- or tri-substituted independently with halo, (C₁-C₆)alkyl, hydroxy, (C₁-C₆)alkoxy, nitro, cyano or oxo wherein said (C₁-C₆)alkyl or (C₁-C₆)alkoxy substituent optionally has

15 from one to nine fluorines;

R⁵ and R⁶ are each independently hydrogen, halo, (C₁-C₃)alkoxy or (C₁-C₆)alkyl, said (C₁-C₃)alkoxy optionally having from one to seven halo, said (C₁-C₆)alkyl optionally having from one to nine halo;

or a pharmaceutically acceptable salt thereof.

20 In another embodiment of the compounds of the present invention,

Y is methyl, ethyl, 1-propyl, 2-propyl or tert-butyl;

R² is methyl, ethyl, 2-propyl, cyclopropyl or cyclobutyl;

25 R³ is -C(O)-V, -C(OH)(C(O)OCH₃)(V), -CH(F)(V), -CF₂(V), -CH(OCH₃)(V), -CH(C(O)OCH₃)(V), -CH(CN)(V), -CH(OH)(V), -CH₂(V), -CH(NH₂)(V), -CH(NH(CH₃))(V), -CH(C(O)NH₂)(V), -CH(CH₂OH)V, -CH(CH₂OCH₃)V, -CH(CH₂OC(O)CH₃)V, -CH(CH₂F)V, or -CH(CH₂NH₂)V; and

V is phenyl optionally mono-, di- or tri-substituted independently with halo, nitro, or (C₁-C₂)alkyl, wherein said (C₁-C₂)alkyl optionally has from one to five fluorines;

R⁵ and R⁶ are each independently hydrogen, methyl, methoxy or chloro; said methoxy optionally having from one to three fluorines, said methyl optionally having from one to three fluorines;

30 or a pharmaceutically acceptable salt thereof.

In another embodiment of the compounds of the present invention,

Z is cyclobutyl, cyclopentyl, or cyclohexyl, and Z is optionally substituted with one or two carboxy, (C₁-C₆)alkoxy, or (C₁-C₆)alkyl, wherein said (C₁-C₆)alkyl substituent is optionally substituted with one, two or three substituents selected from halo, (C₁-C₆)alkoxy, carboxy, and (C₁-C₆)alkyloxycarbonyl;

35 R² is ethyl or methyl;

40 R³ is (3,5-bis-(trifluoromethyl)-phenyl)-hydroxy-methoxycarbonyl-methyl; (3,5-bis-trifluoromethyl-phenyl)-methoxycarbonyl-methyl; (3,5-bis-trifluoromethyl-phenyl)-cyano-methyl, 3,5-bis-trifluoromethyl-benzoyl; (3,5-bis-trifluoromethyl-phenyl)-hydroxy-methyl; (3,5-bis-trifluoromethyl-phenyl)-fluoro-methyl; (3,5-bis-trifluoromethyl-phenyl)-difluoro-methyl; (3,5-bis-(trifluoromethyl)-benzyl); (3,5-bis-trifluoromethyl-phenylcarbamoyl)-methyl; amino-(3,5-bis-(trifluoromethyl)-phenyl)-methyl; (3,5-bis-(trifluoromethyl)-phenyl)-methylamine-methyl; 1-(3,5-bis-(trifluoromethyl)-phenyl)-2-amino-ethyl; 1-(3,5-bis-

(trifluoromethyl)-phenyl)-2-fluoro-ethyl; 1-(3,5-bis-(trifluoromethyl)-phenyl)-2-methoxy-ethyl; 1-(3,5-bis-(trifluoromethyl)-phenyl)-2-hydroxy-ethyl; or 2-acetoxy-1-(3,5-bis-(trifluoromethyl)-phenyl)-ethyl;

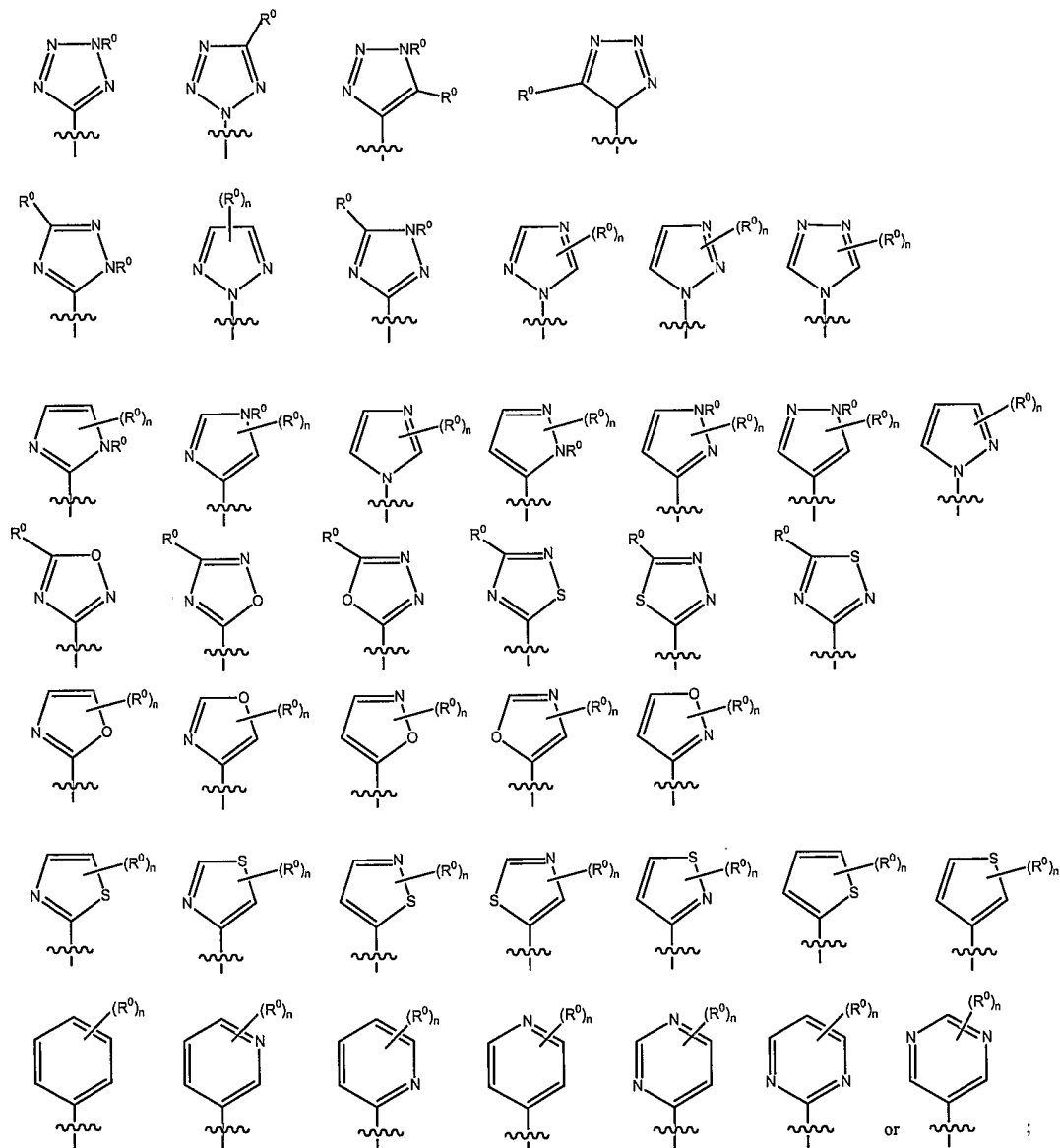
R⁵ is methoxy or trifluoromethyl; and

R⁶ is hydrogen or methoxy;

5 or a pharmaceutically acceptable salt thereof.

In another embodiment of the compounds of the present invention,

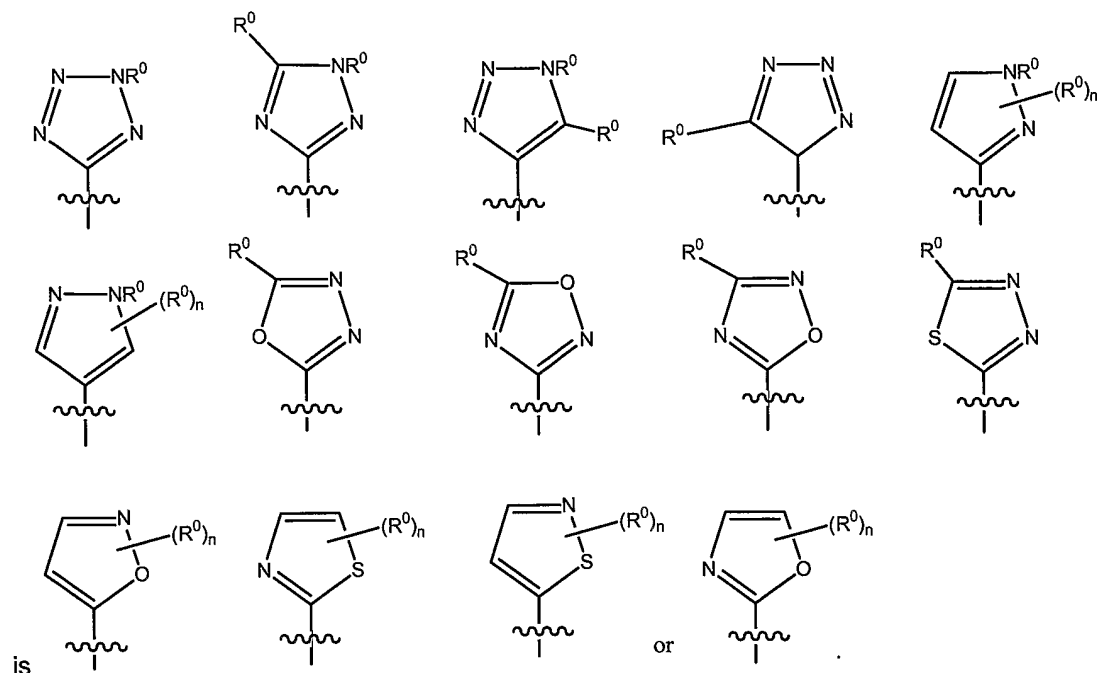
V is



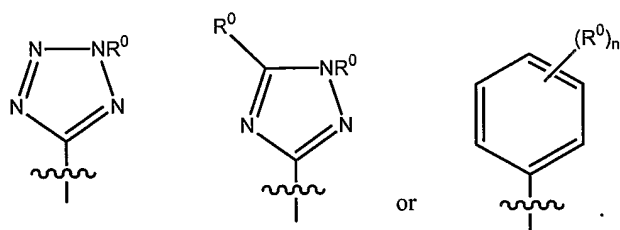
wherein each R⁰ is independently hydrogen, (C₁-C₃)alkyl, (C₁-C₃)alkoxy, hydroxy, or halo,

10 wherein the alkyl or alkoxy is optionally substituted with 1 to nine halo or hydroxy.

In another embodiment of the compounds of the present invention, V



In another embodiment of the compounds of the present invention, V is



5

In another embodiment of the compounds of the present invention, the compound is

3-[[[(3,5-Bis-trifluoromethyl-benzyl)-methoxycarbonyl-amino]-methyl]-2-methyl-6-trifluoromethyl-indoline-1-carboxylic acid ethyl ester;

10 (R,R) -3-[[[(3,5-Bis-trifluoromethyl-benzyl)-methoxycarbonyl-amino]-methyl]-2-methyl-6-trifluoromethyl-indoline-1-carboxylic acid ethyl ester;

(R,S) -3-[[[(3,5-Bis-trifluoromethyl-benzyl)-methoxycarbonyl-amino]-methyl]-2-methyl-6-trifluoromethyl-indoline-1-carboxylic acid ethyl ester;

3-[[[Acetyl-(3,5-bis-trifluoromethyl-benzyl)-amino]-methyl]-2-methyl-6-trifluoromethyl-indoline-1-carboxylic acid ethyl ester;

15 (R,R) -3-[[[Acetyl-(3,5-bis-trifluoromethyl-benzyl)-amino]-methyl]-2-methyl-6-trifluoromethyl-indoline-1-carboxylic acid ethyl ester;

(R,S) -3-[[[Acetyl-(3,5-bis-trifluoromethyl-benzyl)-amino]-methyl]-2-methyl-6-trifluoromethyl-indoline-1-carboxylic acid ethyl ester;

20 3-[[[(3,5-Bis-trifluoromethyl-benzyl)-methoxycarbonyl-amino]-methyl]-2-methyl-5-trifluoromethyl-indoline-1-carboxylic acid ethyl ester;

(R,R) -3-[[[(3,5-Bis-trifluoromethyl-benzyl)-methoxycarbonyl-amino]-methyl]-2-methyl-5-trifluoromethyl-indoline-1-carboxylic acid ethyl ester;

(*R,S*)-3-[[[(3,5-Bis-trifluoromethyl-benzyl)-methoxycarbonyl-amino]-methyl]-2-methyl-5-trifluoromethyl-indoline-1-carboxylic acid ethyl ester;

3-[[Acetyl-(3,5-bis-trifluoromethyl-benzyl)-amino]-methyl]-2-methyl-5-trifluoromethyl-indoline-1-carboxylic acid ethyl ester;

5 (*R,R*)-3-[[Acetyl-(3,5-bis-trifluoromethyl-benzyl)-amino]-methyl]-2-methyl-5-trifluoromethyl-indoline-1-carboxylic acid ethyl ester;

(*R,S*)-3-[[Acetyl-(3,5-bis-trifluoromethyl-benzyl)-amino]-methyl]-2-methyl-5-trifluoromethyl-indoline-1-carboxylic acid ethyl ester;

10 3-[[Acetyl-(3,5-bis-trifluoromethyl-benzyl)-amino]-methyl]-2-ethyl-6-trifluoromethyl-indoline-1-carboxylic acid tert-butyl ester;

(*R,R*)-3-[[Acetyl-(3,5-bis-trifluoromethyl-benzyl)-amino]-methyl]-2-ethyl-6-trifluoromethyl-indoline-1-carboxylic acid tert-butyl ester;

(*R,S*)-3-[[Acetyl-(3,5-bis-trifluoromethyl-benzyl)-amino]-methyl]-2-ethyl-6-trifluoromethyl-indoline-1-carboxylic acid tert-butyl ester;

15 3-[[[(3,5-Bis-trifluoromethyl-benzyl)-methoxycarbonyl-amino]-methyl]-2-ethyl-6-trifluoromethyl-indoline-1-carboxylic acid tert-butyl ester;

(*R,R*)-3-[[[(3,5-Bis-trifluoromethyl-benzyl)-methoxycarbonyl-amino]-methyl]-2-ethyl-6-trifluoromethyl-indoline-1-carboxylic acid tert-butyl ester;

20 (*R,S*)-3-[[[(3,5-Bis-trifluoromethyl-benzyl)-methoxycarbonyl-amino]-methyl]-2-ethyl-6-trifluoromethyl-indoline-1-carboxylic acid tert-butyl ester;

3-(3,5-Bis-trifluoromethyl-benzylcarbamoyl)-2-ethyl-6-trifluoromethyl-indoline-1-carboxylic acid tert-butyl ester;

(*R,R*)-3-(3,5-Bis-trifluoromethyl-benzylcarbamoyl)-2-ethyl-6-trifluoromethyl-indoline-1-carboxylic acid tert-butyl ester;

25 (*R,S*)-3-(3,5-Bis-trifluoromethyl-benzylcarbamoyl)-2-ethyl-6-trifluoromethyl-indoline-1-carboxylic acid tert-butyl ester;

3-(3,5-Bis-trifluoromethyl-benzoyl)-2-ethyl-6-trifluoromethyl-indoline-1-carboxylic acid tert-butyl ester;

30 (*R,R*)-3-(3,5-Bis-trifluoromethyl-benzoyl)-2-ethyl-6-trifluoromethyl-indoline-1-carboxylic acid tert-butyl ester;

(*R,S*)-3-(3,5-Bis-trifluoromethyl-benzoyl)-2-ethyl-6-trifluoromethyl-indoline-1-carboxylic acid tert-butyl ester;

3-[(3,5-Bis-trifluoromethyl-phenyl)-hydroxy-methyl]-2-ethyl-6-trifluoromethyl-indoline-1-carboxylic acid tert-butyl ester;

35 (*R,R*)-3-[(3,5-Bis-trifluoromethyl-phenyl)-hydroxy-methyl]-2-ethyl-6-trifluoromethyl-indoline-1-carboxylic acid tert-butyl ester;

(*R,S*)-3-[(3,5-Bis-trifluoromethyl-phenyl)-hydroxy-methyl]-2-ethyl-6-trifluoromethyl-indoline-1-carboxylic acid tert-butyl ester;

40 3-[2-(3,5-Bis-trifluoromethyl-phenyl)-2-oxo-ethyl]-2-ethyl-6-trifluoromethyl-indoline-1-carboxylic acid ethyl ester;

(*R,R*)-3-[2-(3,5-Bis-trifluoromethyl-phenyl)-2-oxo-ethyl]-2-ethyl-6-trifluoromethyl-indoline-1-carboxylic acid ethyl ester;

(*R,S*)-3-[2-(3,5-Bis-trifluoromethyl-phenyl)-2-oxo-ethyl]-2-ethyl-6-trifluoromethyl-indoline-1-carboxylic acid ethyl ester;

5 3-[2-(3,5-Bis-trifluoromethyl-phenyl)-2-hydroxy-ethyl]-2-ethyl-6-trifluoromethyl-indoline-1-carboxylic acid ethyl ester;

(*R,R*)-3-[2-(3,5-Bis-trifluoromethyl-phenyl)-2-hydroxy-ethyl]-2-ethyl-6-trifluoromethyl-indoline-1-carboxylic acid ethyl ester;

10 (*R,S*)-3-[2-(3,5-Bis-trifluoromethyl-phenyl)-2-hydroxy-ethyl]-2-ethyl-6-trifluoromethyl-indoline-1-carboxylic acid ethyl ester;

Ethyl 3-((N-(3,5-bis(trifluoromethyl)benzyl)acetamido)methyl)-2-ethyl-5-(trifluoromethyl)indoline-1-carboxylate;

(*R,R*)-Ethyl 3-((N-(3,5-bis(trifluoromethyl)benzyl)acetamido)methyl)-2-ethyl-5-(trifluoromethyl)indoline-1-carboxylate;

15 (*R,S*)-Ethyl 3-((N-(3,5-bis(trifluoromethyl)benzyl)acetamido)methyl)-2-ethyl-5-(trifluoromethyl)indoline-1-carboxylate;

Methyl (1-(ethoxycarbonyl)-2-ethyl-5-(trifluoromethyl)indolin-3-yl)methyl 3,5-bis(trifluoromethyl)benzylcarbamate;

20 (*R,R*)-Methyl (1-(ethoxycarbonyl)-2-ethyl-5-(trifluoromethyl)indolin-3-yl)methyl 3,5-bis(trifluoromethyl)benzylcarbamate;

(*R,S*)-Methyl (1-(ethoxycarbonyl)-2-ethyl-5-(trifluoromethyl)indolin-3-yl)methyl 3,5-bis(trifluoromethyl)benzylcarbamate;

Ethyl 3-((N-(3,5-bis(trifluoromethyl)benzyl)acetamido)methyl)-2-cyclopropyl-5-(trifluoromethyl)indoline-1-carboxylate;

25 (*R,R*)-Ethyl 3-((N-(3,5-bis(trifluoromethyl)benzyl)acetamido)methyl)-2-cyclopropyl-5-(trifluoromethyl)indoline-1-carboxylate;

(*R,S*)-Ethyl 3-((N-(3,5-bis(trifluoromethyl)benzyl)acetamido)methyl)-2-cyclopropyl-5-(trifluoromethyl)indoline-1-carboxylate;

30 Methyl (1-(ethoxycarbonyl)-2-cyclopropyl-5-(trifluoromethyl)indolin-3-yl)methyl 3,5-bis(trifluoromethyl)benzylcarbamate;

(*R,R*)-Methyl (1-(ethoxycarbonyl)-2-cyclopropyl-5-(trifluoromethyl)indolin-3-yl)methyl 3,5-bis(trifluoromethyl)benzylcarbamate;

(*R,S*)-Methyl (1-(ethoxycarbonyl)-2-cyclopropyl-5-(trifluoromethyl)indolin-3-yl)methyl 3,5-bis(trifluoromethyl)benzylcarbamate;

35 Tert-butyl 3-((N-(3,5-bis(trifluoromethyl)benzyl)acetamido)methyl)-2-ethyl-5-(trifluoromethyl)indoline-1-carboxylate;

(*R,R*)-Tert-butyl 3-((N-(3,5-bis(trifluoromethyl)benzyl)acetamido)methyl)-2-ethyl-5-(trifluoromethyl)indoline-1-carboxylate;

40 (*R,S*)-Tert-butyl 3-((N-(3,5-bis(trifluoromethyl)benzyl)acetamido)methyl)-2-ethyl-5-(trifluoromethyl)indoline-1-carboxylate;

a prodrug thereof, or a pharmaceutically acceptable salt of said compound or of said prodrug.

In one embodiment, the compound of formula II is

2-Ethyl-3-(methoxycarbonylamino-methyl)-6-trifluoromethyl-indoline-1-carboxylic acid tert-butyl ester;

2-Ethyl-3-(methoxycarbonylamino-methyl)-6-trifluoromethyl-indoline-1-carboxylic acid ethyl ester;

3-(Acetylamino-methyl)-2-ethyl-6-trifluoromethyl-indoline-1-carboxylic acid tert-butyl ester; or

5 3-(Acetylamino-methyl)-2-ethyl-6-trifluoromethyl-indoline-1-carboxylic acid ethyl ester.

In one embodiment of the method of the present invention, atherosclerosis is treated.

In another embodiment of the method of the present invention, peripheral vascular disease is treated.

In another embodiment of the method of the present invention, dyslipidemia is treated.

10 In another embodiment of the method of the present invention, hyperbetalipoproteinemia is treated.

In another embodiment of the method of the present invention, hypoalphalipoproteinemia is treated.

15 In another embodiment of the method of the present invention, familial-hypercholesterolemia is treated.

In another embodiment of the method of the present invention, coronary artery disease is treated.

In another embodiment of the method of the present invention, myocardial infarction is treated.

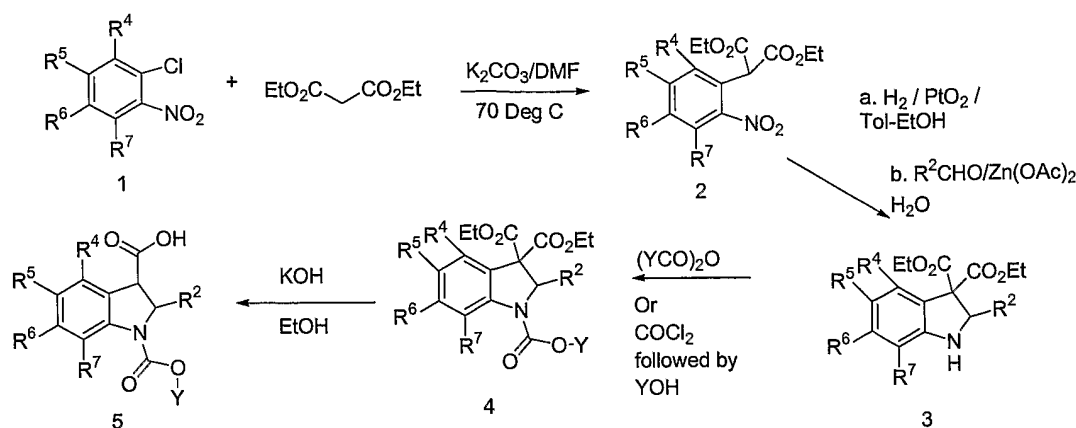
20 In one embodiment of the combination or kit of the present invention, the second compound is an HMG-CoA reductase inhibitor or a PPAR modulator.

In another embodiment of the combination or kit of the present invention, the second compound is lovastatin, simvastatin, pravastatin, fluvastatin, atorvastatin, rivastatin, rosuvastatin or pitavastatin.

25 In another embodiment of the combination or kit of the present invention, the combination further comprising a cholesterol absorption inhibitor, wherein the cholesterol absorption inhibitor may be ezetimibe.

In general, the compounds of this invention can be made by processes which include processes analogous to those known in the chemical arts, particularly in light of the description contained herein. Certain processes for the manufacture of the compounds of this invention are provided as further features of the invention and are illustrated by the following reaction schemes. Other processes may be
30 described in the experimental section.

SCHEME 1



According to Scheme 1 the desired compounds wherein R^2 , R^4 , R^5 , R^6 , R^7 and Y are as described

5 above.

The desired Formula 2 compounds of Scheme 1 may be prepared from the corresponding 2-nitrochlorobenzene by reaction with dialkyl malonate, in polar aprotic solvents such as DMF or DMSO etc., at high temperature, in the presence of an appropriate base such as K_2CO_3 , Cs_2CO_3 , NaH etc. The resulting reaction mixture is concentrated to dryness and the compounds of Formula 2 can be usually crystallized or

10 alternatively can be purified by flash chromatography on silica gel.

The desired Formula 3 compounds of Scheme 1 may be prepared from the corresponding compounds of Formula 2 by catalytic hydrogenation in the presence of standard catalysts well known to those skilled in the art, for example as described in L.A. Paquette (Ed), Encyclopedia of Reagents for Organic Synthesis, John Wiley and Sons, Chichester, England, 1995. Typically the compound is

15 dissolved in an organic solvent. Additives such as sodium acetate are usually added to improve the reaction rate. An appropriate catalyst is chosen, such as Platinum oxide. Hydrogenation is carried out at elevated pressures in appropriate apparatus, preferably for about 6 hours. The catalyst is filtered off to yield the corresponding aniline, which is typically isolated after chromatography on silica gel. The crude aniline is taken up in a alcoholic solvent such as ethanol and an appropriate aldehyde (R_1CHO). This

20 crude mixture is treated with $\text{Zn}(\text{OAc})_2$ Dihydrate and the mixture is reacted until the desired product 3 is formed. After a standard aqueous work-up the product 3 is isolated by flash chromatography on silica gel.

The desired Formula 4 compounds of Scheme 1 may be prepared from the corresponding Formula 3 compounds by reaction with carbamoylating agent such as boc-anhydride as described in the

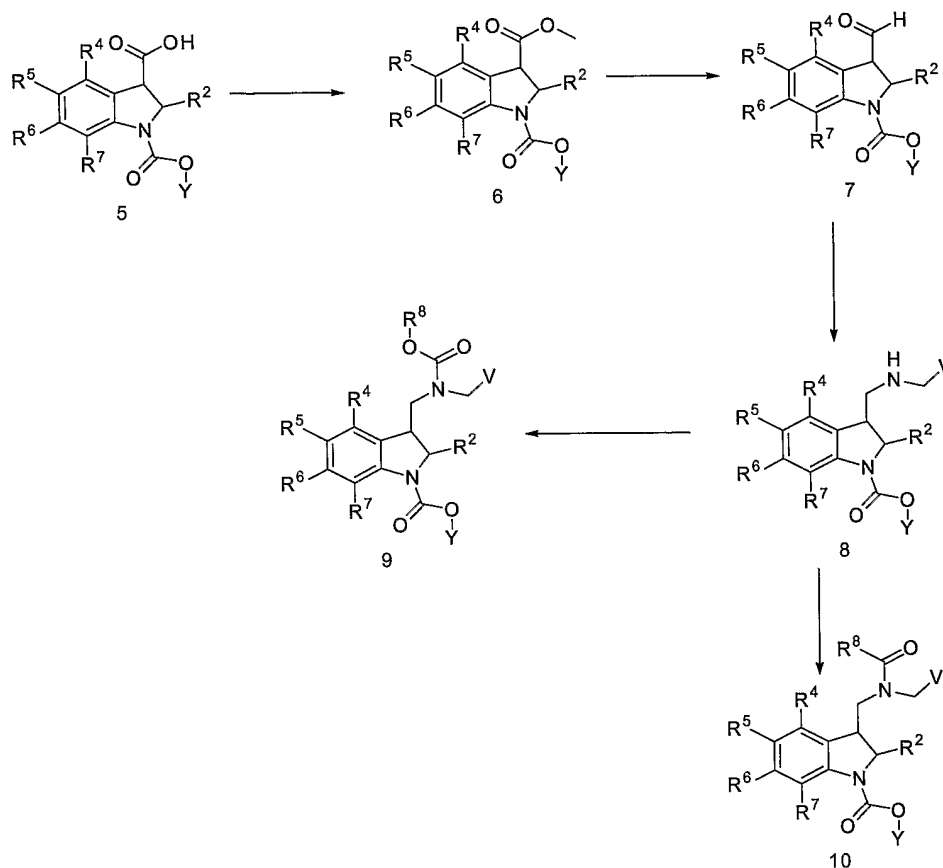
25 Grenne, T. W. and Wuts, G. M., Protective groups in Organic Synthesis, Wiley Interscience, 1991. Typically the reaction is carried out in solvent a such as methylene chloride. An alternative procedure is to convert the Formula 3 compounds to the corresponding carbamoyl chlorides by treatment with phosgene in a suitable solvent such as toluene and subsequent reaction with an alcohol (methanol, ethanol etc.) to afford the compounds of Formula 4. The compounds of Formula 4 can be purified by standard silica gel

30 chromatography, if needed.

The desired Formula 5 compounds of Scheme 1 may be prepared from the corresponding compounds of Formula 4 under standard saponification conditions well known to those skilled in the art,

for example as described in L.A. Paquette (Ed), Encyclopedia of Reagents for Organic Synthesis, John Wiley and Sons, Chichester, England, 1995.

SCHEME 2



5

According to Scheme 2 the desired compounds wherein R^2 , R^4 , R^5 , R^6 , R^7 , Y and V are as described above.

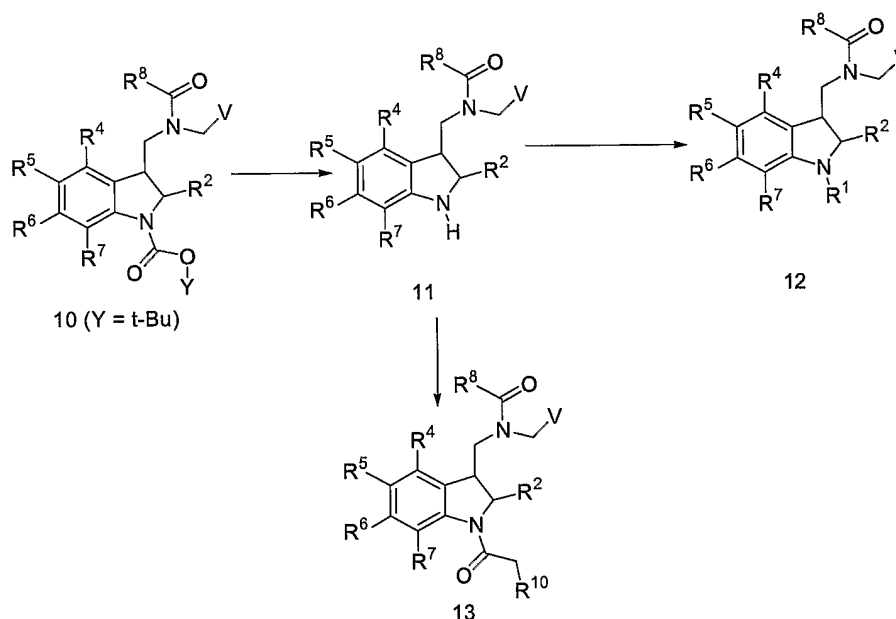
The desired Formula 7 compounds of Scheme 2 may be prepared from the corresponding Formula 5 compounds by conversion of the hydroxy group to the corresponding methyl or ethyl ester to produce compounds of Formula 6 and subsequent conversion of the ester under standard esterification conditions well known to those skilled in the art, for example as described in L.A. Paquette (Ed), Encyclopedia of Reagents for Organic Synthesis, John Wiley and Sons, Chichester, England, 1995. The resulting ester can be reduced to the corresponding aldehyde either directly or via the corresponding alcohol using reaction conditions well known to those skilled in the art, for example as described in L.A. Paquette (Ed), Encyclopedia of Reagents for Organic Synthesis, John Wiley and Sons, Chichester, England, 1995.

The desired Formula 8 compounds of Scheme 2 may be prepared from the corresponding Formula 7 compounds under reductive amination conditions well known to those skilled in the art, for example as described in L.A. Paquette (Ed), Encyclopedia of Reagents for Organic Synthesis, John Wiley and Sons, Chichester, England, 1995. The compounds of Formula 7 can be treated with an aryl aldehyde ($V = \text{aryl}$) in a solvent such as methylene chloride. Addition of a dehydrating agent can expedite the reaction. The intermediate imine is then reduced with an appropriate hydride source such as sodium triacetoxy borohydride in a protic solvent such as ethanol or methanol.

Compounds of Formula 9 wherein R^8 is a (C_1-C_6) alkyl may be prepared from the corresponding Formula 8 compounds, by reaction with an alkylchloroformate, in a solvent such as methylene chloride or chloroform optionally containing a base such as pyridine, diisopropylethylamine, DMAP, 2,6-di-tert-butylpyridine at a temperature between 0°C to 60°C , typically ambient, for a period of 1 to 24 hours. The compounds can be isolated by silica gel chromatography.

Compounds of Formula 10 wherein R^8 is a (C_1-C_6) alkyl may be prepared from the corresponding compounds of Formula 8, by reaction with an acid chloride, in a solvent such as methylene chloride or chloroform optionally containing a base such as pyridine, diisopropylethylamine, DMAP, 2,6-di-tert-butylpyridine at a temperature between 0°C to 60°C , typically ambient, for a period of 1 to 24 hours. The compounds can be isolated by silica gel chromatography.

SCHEME 3



According to Scheme 3 the desired Formula 11 compounds wherein R^2 , R^4 , R^5 , R^6 , R^7 , Y and V and are as described above and R^8 is a (C_1-C_6) alkyl may be prepared from the boc-derivative of Formula 10 ($Y = t\text{-Bu}$) by treatment with acid as described in the Grenne, T. W. and Wuts, G. M., Protective groups in Organic Synthesis, Wiley Interscience, 1991. In a typical procedure the bis-carbamate is treated with trifluoroacetic acid. The reaction is typically complete in an hour or so. Upon completion, the acid is removed by evaporation and the residue is partitioned between an organic solvent (preferably methylene chloride) & NaHCO_3 . Evaporation of the organic solvent affords compounds of Formula 11.

The desired Formula 13 compounds wherein R^{10} is X as defined above may be prepared from the corresponding compounds of Formula 11 by reaction with an acid chloride, in a solvent such as methylene chloride or chloroform optionally containing a base such as pyridine, diisopropylethylamine, DMAP, 2,6-di-tert-butylpyridine at a temperature between 0°C to 60°C , typically ambient, for a period of 1 to 24 hours. Upon completion of the reaction, the mixture is washed with aqueous acid and brine to afford the compounds of Formula 13 after silicagel chromatography. Often times when an acid chloride is not commercially available it can be generated *in situ*, from the corresponding carboxylic acid and triphenyl phosphine in conjunction with agents such as carbon tetrachloride, hexachloroethane, trichloroacetonitrile etc. This later procedure can be carried out with resin bound triphenylphosphine which makes it

amenable to automated chemistry. Filtration of the resin followed by evaporation and purification on silica gel yields the required product.

The desired compounds of Formula 12, wherein R¹ is described above may be prepared from the corresponding compounds of Formula 11 by alkylation with the appropriate alkyl bromides. These alkylations are classically carried out in a polar solvent such as DMF, DMSO, NMP etc. in the presence of a base (K₂CO₃, Et₃N, Pyridine, DMAP, lutidine etc.). These reactions are usually carried out from ambient temperatures to about 150°C. Often times because of the unreactivity of quinoxalines heating in the microwave at an appropriate temperature is preferred. Alkylations can be performed with a variety of alkyl bromides such as arylmethyl bromides, alpha-substituted arylmethyl bromides. The alkylation reactions proceed in a better yield if they are substituted with an alpha electron withdrawing group (such as compounds of Formula 11). Use of suitable microwave equipment such as facilitates these reactions Emrys Optimizer, Milestone microwave etc.

As an initial note, in the preparation of compounds, it is noted that some of the preparation methods useful for the preparation of the compounds described herein may require protection of remote functionality (e.g., primary amine, secondary amine, carboxyl in intermediates). The need for such protection will vary depending on the nature of the remote functionality and the conditions of the preparation methods. The need for such protection is readily determined by one skilled in the art. The use of such protection/deprotection methods is also within the skill in the art. For a general description of protecting groups and their use, see T.W. Greene, Protective Groups in Organic Synthesis, John Wiley & Sons, New York, 1991.

For example, in the reaction schemes, certain compounds contain primary amines or carboxylic acid functionalities which may interfere with reactions at other sites of the molecule if left unprotected. Accordingly, such functionalities may be protected by an appropriate protecting group which may be removed in a subsequent step. Suitable protecting groups for amine and carboxylic acid protection include those protecting groups commonly used in peptide synthesis (such as N-t-butoxycarbonyl, benzyloxycarbonyl, and 9-fluorenylmethylenoxycarbonyl for amines and lower alkyl or benzyl esters for carboxylic acids) which are generally not chemically reactive under the reaction conditions described and can typically be removed without chemically altering other functionality in the compound.

Prodrugs of the compounds of the present invention may be prepared according to methods known to those skilled in the art. Exemplary processes are described below.

Prodrugs of this invention where a carboxyl group in a carboxylic acid of the compounds is replaced by an ester may be prepared by combining the carboxylic acid with the appropriate alkyl halide in the presence of a base such as potassium carbonate in an inert solvent such as dimethylformamide at a temperature of about 0 to 100°C for about 1 to about 24 hours. Alternatively the acid is combined with an appropriate alcohol as solvent in the presence of a catalytic amount of acid such as concentrated sulfuric acid at a temperature of about 20 to 100°C, preferably at a reflux, for about 1 hour to about 24 hours. Another method is the reaction of the acid with a stoichiometric amount of the alcohol in the presence of a catalytic amount of acid in an inert solvent such as toluene or tetrahydrofuran, with concomitant removal of the water being produced by physical (e.g., Dean-Stark trap) or chemical (e.g., molecular sieves) means.

Prodrugs of this invention where an alcohol function has been derivatized as an ether may be prepared by combining the alcohol with the appropriate alkyl bromide or iodide in the presence of a base such as potassium carbonate in an inert solvent such as dimethylformamide at a temperature of about 0 to 100°C for about 1 to about 24 hours. Alkanoylaminoethyl ethers may be obtained by reaction of the alcohol with a bis-(alkanoylamino)methane in the presence of a catalytic amount of acid in an inert solvent such as tetrahydrofuran, according to a method described in US 4,997,984. Alternatively, these compounds may be prepared by the methods described by Hoffman et al. in J. Org. Chem. 1994, 59, 3530.

Glycosides are prepared by reaction of the alcohol and a carbohydrate in an inert solvent such as toluene in the presence of acid. Typically the water formed in the reaction is removed as it is being formed as described above. An alternate procedure is the reaction of the alcohol with a suitably protected glycosyl halide in the presence of base followed by deprotection.

N-(1-hydroxyalkyl) amides, N-(1-hydroxy-1-(alkoxycarbonyl)methyl) amides may be prepared by the reaction of the parent amide with the appropriate aldehyde under neutral or basic conditions (e.g., sodium ethoxide in ethanol) at temperatures between 25 and 70°C. N-alkoxymethyl or N-1-(alkoxy)alkyl derivatives can be obtained by reaction of the N-unsubstituted compound with the necessary alkyl halide in the presence of a base in an inert solvent.

The compounds of this invention may also be used in conjunction with other pharmaceutical agents (e.g., LDL-cholesterol lowering agents, triglyceride lowering agents) for the treatment of the disease/conditions described herein. For example, they may be used in combination with a HMG-CoA reductase inhibitor, a cholesterol synthesis inhibitor, a cholesterol absorption inhibitor, another CETP inhibitor, a MTP/Apo B secretion inhibitor, a PPAR modulator and other cholesterol lowering agents such as a fibrate, niacin, an ion-exchange resin, an antioxidant, an ACAT inhibitor, and a bile acid sequestrant. Other pharmaceutical agents would also include the following: a bile acid reuptake inhibitor, an ileal bile acid transporter inhibitor, an ACC inhibitor, an antihypertensive (such as NORVASC®), a selective estrogen receptor modulator, a selective androgen receptor modulator, an antibiotic, an antidiabetic (such as metformin, a PPAR γ activator, a sulfonylurea, insulin, an aldose reductase inhibitor (ARI) and a sorbitol dehydrogenase inhibitor (SDI)), and aspirin (acetylsalicylic acid or a nitric oxide releasing aspirin). A slow-release form of niacin is available and is known as Niaspan. Niacin may also be combined with other therapeutic agents such as statins, i.e. lovastatin, which is an HMG-CoA reductase inhibitor and described further below. This combination therapy is known as ADVICOR® (Kos Pharmaceuticals Inc.) In combination therapy treatment, both the compounds of this invention and the other drug therapies are administered to mammals (e.g., humans, male or female) by conventional methods.

Any HMG-CoA reductase inhibitor may be used in the combination aspect of this invention. The term HMG-CoA reductase inhibitor refers to compounds which inhibit the bioconversion of hydroxymethylglutaryl-coenzyme A to mevalonic acid catalyzed by the enzyme HMG-CoA reductase. Such inhibition is readily determined by those skilled in the art according to standard assays (e.g., Meth. Enzymol. 1981; 71:455-509 and references cited therein). A variety of these compounds are described and referenced below however other HMG-CoA reductase inhibitors will be known to those skilled in the art. U.S. Pat. No. 4,231,938 (the disclosure of which is hereby incorporated by reference) discloses certain compounds isolated after cultivation of a microorganism belonging to the genus *Aspergillus*, such

as lovastatin. Also, U.S. Pat. No. 4,444,784 (the disclosure of which is hereby incorporated by reference) discloses synthetic derivatives of the aforementioned compounds, such as simvastatin. Also, U.S. Pat. No. 4,739,073 (the disclosure of which is incorporated by reference) discloses certain substituted indoles, such as fluvastatin. Also, U.S. Pat. No. 4,346,227 (the disclosure of which is incorporated by reference) discloses ML-236B derivatives, such as pravastatin. Also, EP-491226A (the disclosure of which is incorporated by reference) discloses certain pyridyldihydroxyheptenoic acids, such as cerivastatin. In addition, U.S. Pat. No. 5,273,995 (the disclosure of which is incorporated by reference) discloses certain 6-[2-(substituted-pyrrol-1-yl)alkyl]pyran-2-ones such as atorvastatin and any pharmaceutically acceptable form thereof (i.e. LIPITOR®). Additional HMG-CoA reductase inhibitors include rosuvastatin and pitavastatin. Statins also include such compounds as rosuvastatin disclosed in U.S. RE37,314 E, pitivastatin disclosed in EP 304063 B1 and US 5,011,930; mevastatin, disclosed in U.S. 3,983,140, which is incorporated herein by reference; velostatin, disclosed in U.S. 4,448,784 and U.S. 4,450,171, both of which are incorporated herein by reference; compactin, disclosed in U.S. 4,804,770, which is incorporated herein by reference; dalvastatin, disclosed in European Patent Application Publication No. 738510 A2; fluindostatin, disclosed in European Patent Application Publication No. 363934 A1; and dihydrocompactin, disclosed in U.S. 4,450,171, which is incorporated herein by reference.

Any PPAR modulator may be used in the combination aspect of this invention. The term PPAR modulator refers to compounds which modulate peroxisome proliferator activator receptor (PPAR) activity in mammals, particularly humans. Such modulation is readily determined by those skilled in the art according to standard assays known in the literature. It is believed that such compounds, by modulating the PPAR receptor, regulate transcription of key genes involved in lipid and glucose metabolism such as those in fatty acid oxidation and also those involved in high density lipoprotein (HDL) assembly (for example, apolipoprotein AI gene transcription), accordingly reducing whole body fat and increasing HDL cholesterol. By virtue of their activity, these compounds also reduce plasma levels of triglycerides, VLDL cholesterol, LDL cholesterol and their associated components such as apolipoprotein B in mammals, particularly humans, as well as increasing HDL cholesterol and apolipoprotein AI. Hence, these compounds are useful for the treatment and correction of the various dyslipidemias observed to be associated with the development and incidence of atherosclerosis and cardiovascular disease, including hypoalphalipoproteinemia and hypertriglyceridemia. A variety of these compounds are described and referenced below, however, others will be known to those skilled in the art. International Publication Nos. WO 02/064549 and 02/064130 and U.S. patent application 10/720942, filed November 24, 2003 and U.S. patent application 60/552114 filed March 10, 2004 (the disclosures of which are hereby incorporated by reference) disclose certain compounds which are PPAR α activators.

Any other PPAR modulator may be used in the combination aspect of this invention. In particular, modulators of PPAR β and/or PPAR γ may be useful in combination with compounds of the present invention. An example PPAR inhibitor is described in US2003/0225158 as {5-Methoxy-2-methyl-4-[4-(4-trifluoromethyl-benzyloxy)-benzylsulfany]-phenoxy}-acetic acid.

Any MTP/Apo B (microsomal triglyceride transfer protein and or apolipoprotein B) secretion inhibitor may be used in the combination aspect of this invention. The term MTP/Apo B secretion inhibitor refers to compounds which inhibit the secretion of triglycerides, cholesteryl ester, and phospholipids. Such inhibition is readily determined by those skilled in the art according to standard assays (e.g.,

Wetterau, J. R. 1992; Science 258:999). A variety of these compounds are described and referenced below however other MTP/Apo B secretion inhibitors will be known to those skilled in the art, including imipridone (Bayer) and additional compounds such as those disclosed in WO 96/40640 and WO 98/23593, (two exemplary publications).

5 For example, the following MTP/Apo B secretion inhibitors are particularly useful:

4'-trifluoromethyl-biphenyl-2-carboxylic acid [2-(1H-[1,2,4,]triazol-3-ylmethyl)-1,2,3,4-tetrahydro-isoquinolin-6-yl]-amide;

4'-trifluoromethyl-biphenyl-2-carboxylic acid [2-(2-acetylamino-ethyl)-1,2,3,4-tetrahydro-isoquinolin-6-yl]-amide;

10 (2-{6-[(4'-trifluoromethyl-biphenyl-2-carbonyl)-amino]-3,4-dihydro-1H-isoquinolin-2-yl}-ethyl)-carbamic acid methyl ester;

4'-trifluoromethyl-biphenyl-2-carboxylic acid [2-(1H-imidazol-2-ylmethyl)-1,2,3,4-tetrahydro-isoquinolin-6-yl]-amide;

15 4'-trifluoromethyl-biphenyl-2-carboxylic acid [2-(2,2-diphenyl-ethyl)-1,2,3,4-tetrahydro-isoquinolin-6-yl]-amide;

4'-trifluoromethyl-biphenyl-2-carboxylic acid [2-(2-ethoxy-ethyl)-1,2,3,4-tetrahydro-isoquinolin-6-yl]-amide;

(S)-N-{2-[benzyl(methyl)amino]-2-oxo-1-phenylethyl}-1-methyl-5-[4'-(trifluoromethyl)[1,1'-biphenyl]-2-carboxamido]-1H-indole-2-carboxamide;

20 (S)-2-[(4'-Trifluoromethyl-biphenyl-2-carbonyl)-amino]-quinoline-6-carboxylic acid (pentylcarbamoil-phenyl-methyl)-amide;

1H-indole-2-carboxamide, 1-methyl-N-[(1S)-2-[methyl(phenylmethyl)amino]-2-oxo-1-phenylethyl]-5-[[[4'-(trifluoromethyl)[1,1'-biphenyl]-2-yl]carbonyl]amino]; and

25 N-[(1S)-2-(benzylmethylamino)-2-oxo-1-phenylethyl]-1-methyl-5-[[[4'-(trifluoromethyl)biphenyl-2-yl]carbonyl]amino]-1H-indole-2-carboxamide.

Any HMG-CoA synthase inhibitor may be used in the combination aspect of this invention. The term HMG-CoA synthase inhibitor refers to compounds which inhibit the biosynthesis of hydroxymethylglutaryl-coenzyme A from acetyl-coenzyme A and acetoacetyl-coenzyme A, catalyzed by the enzyme HMG-CoA synthase. Such inhibition is readily determined by those skilled in the art according to standard assays (Meth Enzymol. 1975; 35:155-160; Meth. Enzymol. 1985; 110:19-26 and references cited therein). A variety of these compounds are described and referenced below, however other HMG-CoA synthase inhibitors will be known to those skilled in the art. U.S. Pat. No. 5,120,729 (the disclosure of which is hereby incorporated by reference) discloses certain beta-lactam derivatives. U.S. Pat. No. 5,064,856 (the disclosure of which is hereby incorporated by reference) discloses certain spiro-lactone derivatives prepared by culturing a microorganism (MF5253). U.S. Pat. No. 4,847,271 (the disclosure of which is hereby incorporated by reference) discloses certain oxetane compounds such as 11-(3-hydroxymethyl-4-oxo-2-oxetanyl)-3,5,7-trimethyl-2,4-undeca-dienoic acid derivatives.

Any compound that decreases HMG-CoA reductase gene expression may be used in the combination aspect of this invention. These agents may be HMG-CoA reductase transcription inhibitors that block the transcription of DNA or translation inhibitors that prevent or decrease translation of mRNA coding for HMG-CoA reductase into protein. Such compounds may either affect transcription or

translation directly, or may be biotransformed to compounds that have the aforementioned activities by one or more enzymes in the cholesterol biosynthetic cascade or may lead to the accumulation of an isoprene metabolite that has the aforementioned activities. Such compounds may cause this effect by decreasing levels of SREBP (sterol receptor binding protein) by inhibiting the activity of site-1 protease (S1P) or agonizing the oxzgenal receptor or SCAP. Such regulation is readily determined by those skilled in the art according to standard assays (Meth. Enzymol. 1985; 110:9-19). Several compounds are described and referenced below, however other inhibitors of HMG-CoA reductase gene expression will be known to those skilled in the art. U.S. Pat. No. 5,041,432 (the disclosure of which is incorporated by reference) discloses certain 15-substituted lanosterol derivatives. Other oxygenated sterols that suppress synthesis of HMG-CoA reductase are discussed by E.I. Mercer (Prog.Lip. Res. 1993;32:357-416).

Any compound having activity as a CETP inhibitor can serve as the second compound in the combination therapy aspect of the present invention. The term CETP inhibitor refers to compounds that inhibit the cholesteryl ester transfer protein (CETP) mediated transport of various cholesteryl esters and triglycerides from HDL to LDL and VLDL. Such CETP inhibition activity is readily determined by those skilled in the art according to standard assays (e.g., U.S. Pat. No. 6,140,343). A variety of CETP inhibitors will be known to those skilled in the art, for example, those disclosed in commonly assigned U.S. Patent Number 6,140,343 and commonly assigned U.S. Patent Number 6,197,786. CETP inhibitors disclosed in these patents include compounds, such as [2R,4S] 4-[(3,5-bis-trifluoromethyl-benzyl)-methoxycarbonyl-amino]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester, which is also known as torcetrapib. CETP inhibitors are also described in U.S. Patent Number 6,723,752, which includes a number of CETP inhibitors including (2R)-3-[[3-(4-Chloro-3-ethyl-phenoxy)-phenyl]-[[3-(1,1,2,2-tetrafluoro-ethoxy)-phenyl]-methyl]-amino]-1,1,1-trifluoro-2-propanol. Moreover, CETP inhibitors included herein are also described in U.S. Patent Application Number 10/807838 filed March 23, 2004. U.S. Patent Number 5,512,548 discloses certain polypeptide derivatives having activity as CETP inhibitors, while certain CETP-inhibitory rosenonolactone derivatives and phosphate-containing analogs of cholesteryl ester are disclosed in *J. Antibiot.*, 49(8): 815-816 (1996), and *Bioorg. Med. Chem. Lett.*; 6:1951-1954 (1996), respectively.

Any squalene synthetase inhibitor may be used in the combination aspect of this invention. The term squalene synthetase inhibitor refers to compounds which inhibit the condensation of 2 molecules of farnesylpyrophosphate to form squalene, catalyzed by the enzyme squalene synthetase. Such inhibition is readily determined by those skilled in the art according to standard assays (Meth. Enzymol. 1969; 15: 393-454 and Meth. Enzymol. 1985; 110:359-373 and references contained therein). A variety of these compounds are described in and referenced below however other squalene synthetase inhibitors will be known to those skilled in the art. U.S. Pat. No. 5,026,554 (the disclosure of which is incorporated by reference) discloses fermentation products of the microorganism MF5465 (ATCC 74011) including zaragozic acid. A summary of other patented squalene synthetase inhibitors has been compiled (Curr. Op. Ther. Patents (1993) 861-4).

Any squalene epoxidase inhibitor may be used in the combination aspect of this invention. The term squalene epoxidase inhibitor refers to compounds which inhibit the bioconversion of squalene and molecular oxygen into squalene-2,3-epoxide, catalyzed by the enzyme squalene epoxidase. Such inhibition is readily determined by those skilled in the art according to standard assays (Biochim. Biophys.

Acta 1984; 794:466-471). A variety of these compounds are described and referenced below, however other squalene epoxidase inhibitors will be known to those skilled in the art. U.S. Pat. Nos. 5,011,859 and 5,064,864 (the disclosures of which are incorporated by reference) disclose certain fluoro analogs of squalene. EP publication 395,768 A (the disclosure of which is incorporated by reference) discloses
5 certain substituted allylamine derivatives. PCT publication WO 9312069 A (the disclosure of which is hereby incorporated by reference) discloses certain amino alcohol derivatives. U.S. Pat. No. 5,051,534 (the disclosure of which is hereby incorporated by reference) discloses certain cyclopropyloxy-squalene derivatives.

Any squalene cyclase inhibitor may be used as the second component in the combination aspect
10 of this invention. The term squalene cyclase inhibitor refers to compounds which inhibit the bioconversion of squalene-2,3-epoxide to lanosterol, catalyzed by the enzyme squalene cyclase. Such inhibition is readily determined by those skilled in the art according to standard assays (FEBS Lett. 1989;244:347-350.). In addition, the compounds described and referenced below are squalene cyclase inhibitors, however other squalene cyclase inhibitors will also be known to those skilled in the art. PCT publication
15 WO9410150 (the disclosure of which is hereby incorporated by reference) discloses certain 1,2,3,5,6,7,8,8a-octahydro-5,5,8(beta)-trimethyl-6-isoquinolineamine derivatives, such as N-trifluoroacetyl-1,2,3,5,6,7,8,8a-octahydro-2-allyl-5,5,8(beta)-trimethyl-6(beta)-isoquinolineamine. French patent publication 2697250 (the disclosure of which is hereby incorporated by reference) discloses certain beta, beta-dimethyl-4-piperidine ethanol derivatives such as 1-(1,5,9-trimethyldecyl)-beta,beta-dimethyl-4-
20 piperidineethanol

Any combined squalene epoxidase/squalene cyclase inhibitor may be used as the second component in the combination aspect of this invention. The term combined squalene epoxidase/squalene cyclase inhibitor refers to compounds that inhibit the bioconversion of squalene to lanosterol via a squalene-2,3-epoxide intermediate. In some assays it is not possible to distinguish between squalene
25 epoxidase inhibitors and squalene cyclase inhibitors, however, these assays are recognized by those skilled in the art. Thus, inhibition by combined squalene epoxidase/squalene cyclase inhibitors is readily determined by those skilled in art according to the aforementioned standard assays for squalene cyclase or squalene epoxidase inhibitors. A variety of these compounds are described and referenced below, however other squalene epoxidase/squalene cyclase inhibitors will be known to those skilled in the art.
30 U.S. Pat. Nos. 5,084,461 and 5,278,171 (the disclosures of which are incorporated by reference) disclose certain azadecalin derivatives. EP publication 468,434 (the disclosure of which is incorporated by reference) discloses certain piperidyl ether and thio-ether derivatives such as 2-(1-piperidyl)pentyl isopentyl sulfoxide and 2-(1-piperidyl)ethyl ethyl sulfide. PCT publication WO 9401404 (the disclosure of which is hereby incorporated by reference) discloses certain acyl-piperidines such as 1-(1-oxopentyl-5-
35 phenylthio)-4-(2-hydroxy-1-methyl)-ethyl)piperidine. U.S. Pat. No. 5,102,915 (the disclosure of which is hereby incorporated by reference) discloses certain cyclopropyloxy-squalene derivatives.

The compounds of the present invention can also be administered in combination with naturally occurring compounds that act to lower plasma cholesterol levels. These naturally occurring compounds are commonly called nutraceuticals and include, for example, garlic extract and niacin. A slow-release
40 form of niacin is available and is known as Niaspan. Niacin may also be combined with other therapeutic

agents such as lovastatin, or another is an HMG-CoA reductase inhibitor. This combination therapy with lovastatin is known as ADVICOR™ (Kos Pharmaceuticals Inc.).

Any cholesterol absorption inhibitor can be used as an additional in the combination aspect of the present invention. The term cholesterol absorption inhibition refers to the ability of a compound to prevent cholesterol contained within the lumen of the intestine from entering into the intestinal cells and/or passing from within the intestinal cells into the lymph system and/or into the blood stream. Such cholesterol absorption inhibition activity is readily determined by those skilled in the art according to standard assays (e.g., J. Lipid Res. (1993) 34: 377-395). Cholesterol absorption inhibitors are known to those skilled in the art and are described, for example, in PCT WO 94/00480. An example of a recently approved cholesterol absorption inhibitor is ZETIA™ (ezetimibe) (Schering-Plough/Merck).

Any ACAT inhibitor may be used in the combination therapy aspect of the present invention. The term ACAT inhibitor refers to compounds that inhibit the intracellular esterification of dietary cholesterol by the enzyme acyl CoA: cholesterol acyltransferase. Such inhibition may be determined readily by one of skill in the art according to standard assays, such as the method of Heider et al. described in *Journal of Lipid Research.*, 24:1127 (1983). A variety of these compounds are known to those skilled in the art, for example, U.S. Patent No. 5,510,379 discloses certain carboxysulfonates, while WO 96/26948 and WO 96/10559 both disclose urea derivatives having ACAT inhibitory activity. Examples of ACAT inhibitors include compounds such as Avasimibe (Pfizer), CS-505 (Sankyo) and Eflucimibe (Eli Lilly and Pierre Fabre).

A lipase inhibitor may be used in the combination therapy aspect of the present invention. A lipase inhibitor is a compound that inhibits the metabolic cleavage of dietary triglycerides or plasma phospholipids into free fatty acids and the corresponding glycerides (e.g. EL, HL, etc.). Under normal physiological conditions, lipolysis occurs via a two-step process that involves acylation of an activated serine moiety of the lipase enzyme. This leads to the production of a fatty acid-lipase hemiacetal intermediate, which is then cleaved to release a diglyceride. Following further deacylation, the lipase-fatty acid intermediate is cleaved, resulting in free lipase, a glyceride and fatty acid. In the intestine, the resultant free fatty acids and monoglycerides are incorporated into bile acid-phospholipid micelles, which are subsequently absorbed at the level of the brush border of the small intestine. The micelles eventually enter the peripheral circulation as chylomicrons. Such lipase inhibition activity is readily determined by those skilled in the art according to standard assays (e.g., Methods Enzymol. 286: 190-231).

Pancreatic lipase mediates the metabolic cleavage of fatty acids from triglycerides at the 1- and 3-carbon positions. The primary site of the metabolism of ingested fats is in the duodenum and proximal jejunum by pancreatic lipase, which is usually secreted in vast excess of the amounts necessary for the breakdown of fats in the upper small intestine. Because pancreatic lipase is the primary enzyme required for the absorption of dietary triglycerides, inhibitors have utility in the treatment of obesity and the other related conditions. Such pancreatic lipase inhibition activity is readily determined by those skilled in the art according to standard assays (e.g., Methods Enzymol. 286: 190-231).

Gastric lipase is an immunologically distinct lipase that is responsible for approximately 10 to 40% of the digestion of dietary fats. Gastric lipase is secreted in response to mechanical stimulation, ingestion of food, the presence of a fatty meal or by sympathetic agents. Gastric lipolysis of ingested fats is of physiological importance in the provision of fatty acids needed to trigger pancreatic lipase activity in the

intestine and is also of importance for fat absorption in a variety of physiological and pathological conditions associated with pancreatic insufficiency. See, for example, C.K. Abrams, et al., *Gastroenterology*, 92,125 (1987). Such gastric lipase inhibition activity is readily determined by those skilled in the art according to standard assays (e.g., *Methods Enzymol.* 286: 190-231).

5 A variety of gastric and/or pancreatic lipase inhibitors are known to one of ordinary skill in the art. Preferred lipase inhibitors are those inhibitors that are selected from the group consisting of lipstatin, tetrahydrolipstatin (orlistat), valilactone, esterastin, ebelactone A, and ebelactone B. The compound tetrahydrolipstatin is especially preferred. The lipase inhibitor, N-3-trifluoromethylphenyl-N'-3-chloro-4'-trifluoromethylphenylurea, and the various urea derivatives related thereto, are disclosed in U.S. Patent
10 No. 4,405,644. The lipase inhibitor, esteracin, is disclosed in U.S. Patent Nos. 4,189,438 and 4,242,453. The lipase inhibitor, cyclo-O,O'-[(1,6-hexanediyl)-bis-(iminocarbonyl)]dioxime, and the various bis(iminocarbonyl)dioximes related thereto may be prepared as described in Petersen et al., *Liebig's Annalen*, 562, 205-229 (1949).

A variety of pancreatic lipase inhibitors are described herein below. The pancreatic lipase
15 inhibitors lipstatin, (2S, 3S, 5S, 7Z, 10Z)-5-[(S)-2-formamido-4-methyl-valeryloxy]-2-hexyl-3-hydroxy-7,10-hexadecanoic acid lactone, and tetrahydrolipstatin (orlistat), (2S, 3S, 5S)-5-[(S)-2-formamido-4-methyl-valeryloxy]-2-hexyl-3-hydroxy-hexadecanoic 1,3 acid lactone, and the variously substituted N-formylleucine derivatives and stereoisomers thereof, are disclosed in U.S. Patent No. 4,598,089. For example, tetrahydrolipstatin is prepared as described in, e.g., U.S. Patent Nos. 5,274,143; 5,420,305;
20 5,540,917; and 5,643,874. The pancreatic lipase inhibitor, FL-386, 1-[4-(2-methylpropyl)cyclohexyl]-2-[(phenylsulfonyl)oxy]-ethanone, and the variously substituted sulfonate derivatives related thereto, are disclosed in U.S. Patent No. 4,452,813. The pancreatic lipase inhibitor, WAY-121898, 4-phenoxyphenyl-4-methylpiperidin-1-yl-carboxylate, and the various carbamate esters and pharmaceutically acceptable salts related thereto, are disclosed in U.S. Patent Nos. 5,512,565; 5,391,571 and 5,602,151. The
25 pancreatic lipase inhibitor, valilactone, and a process for the preparation thereof by the microbial cultivation of *Actinomyces* strain MG147-CF2, are disclosed in Kitahara, et al., *J. Antibiotics*, 40 (11), 1647-1650 (1987). The pancreatic lipase inhibitors, ebelactone A and ebelactone B, and a process for the preparation thereof by the microbial cultivation of *Actinomyces* strain MG7-G1, are disclosed in Umezawa, et al., *J. Antibiotics*, 33, 1594-1596 (1980). The use of ebelactones A and B in the suppression
30 of monoglyceride formation is disclosed in Japanese Kokai 08-143457, published June 4, 1996.

Other compounds that are marketed for hyperlipidemia, including hypercholesterolemia and which are intended to help prevent or treat atherosclerosis include bile acid sequestrants, such as Welchol®, Colestid®, LoCholest® and Questran®; and fibric acid derivatives, such as Atromid®, Lopid® and Tricor®.

35 Diabetes can be treated by administering to a patient having diabetes (especially Type II), insulin resistance, impaired glucose tolerance, metabolic syndrome, or the like, or any of the diabetic complications such as neuropathy, nephropathy, retinopathy or cataracts, a therapeutically effective amount of a compound of the present invention in combination with other agents (e.g., insulin) that can be used to treat diabetes. This includes the classes of anti-diabetic agents (and specific agents) described
40 herein.

Any glycogen phosphorylase inhibitor can be used as the second agent in combination with a compound of the present invention. The term glycogen phosphorylase inhibitor refers to compounds that inhibit the bioconversion of glycogen to glucose-1-phosphate which is catalyzed by the enzyme glycogen phosphorylase. Such glycogen phosphorylase inhibition activity is readily determined by those skilled in the art according to standard assays (e.g., J. Med. Chem. 41 (1998) 2934-2938). A variety of glycogen phosphorylase inhibitors are known to those skilled in the art including those described in WO 96/39384 and WO 96/39385.

Any aldose reductase inhibitor can be used in combination with a compound of the present invention. The term aldose reductase inhibitor refers to compounds that inhibit the bioconversion of glucose to sorbitol, which is catalyzed by the enzyme aldose reductase. Aldose reductase inhibition is readily determined by those skilled in the art according to standard assays (e.g., J. Malone, *Diabetes*, 29:861-864 (1980). "Red Cell Sorbitol, an Indicator of Diabetic Control"). A variety of aldose reductase inhibitors are known to those skilled in the art.

Any sorbitol dehydrogenase inhibitor can be used in combination with a compound of the present invention. The term sorbitol dehydrogenase inhibitor refers to compounds that inhibit the bioconversion of sorbitol to fructose which is catalyzed by the enzyme sorbitol dehydrogenase. Such sorbitol dehydrogenase inhibitor activity is readily determined by those skilled in the art according to standard assays (e.g., *Analyt. Biochem* (2000) 280: 329-331). A variety of sorbitol dehydrogenase inhibitors are known, for example, U.S. Patent Nos. 5,728,704 and 5,866,578 disclose compounds and a method for treating or preventing diabetic complications by inhibiting the enzyme sorbitol dehydrogenase.

Any glucosidase inhibitor can be used in combination with a compound of the present invention. A glucosidase inhibitor inhibits the enzymatic hydrolysis of complex carbohydrates by glycoside hydrolases, for example amylase or maltase, into bioavailable simple sugars, for example, glucose. The rapid metabolic action of glucosidases, particularly following the intake of high levels of carbohydrates, results in a state of alimentary hyperglycemia which, in adipose or diabetic subjects, leads to enhanced secretion of insulin, increased fat synthesis and a reduction in fat degradation. Following such hyperglycemias, hypoglycemia frequently occurs, due to the augmented levels of insulin present. Additionally, it is known chyme remaining in the stomach promotes the production of gastric juice, which initiates or favors the development of gastritis or duodenal ulcers. Accordingly, glucosidase inhibitors are known to have utility in accelerating the passage of carbohydrates through the stomach and inhibiting the absorption of glucose from the intestine. Furthermore, the conversion of carbohydrates into lipids of the fatty tissue and the subsequent incorporation of alimentary fat into fatty tissue deposits is accordingly reduced or delayed, with the concomitant benefit of reducing or preventing the deleterious abnormalities resulting therefrom. Such glucosidase inhibition activity is readily determined by those skilled in the art according to standard assays (e.g., *Biochemistry* (1969) 8: 4214).

A generally preferred glucosidase inhibitor includes an amylase inhibitor. An amylase inhibitor is a glucosidase inhibitor that inhibits the enzymatic degradation of starch or glycogen into maltose. Such amylase inhibition activity is readily determined by those skilled in the art according to standard assays (e.g., *Methods Enzymol.* (1955) 1: 149). The inhibition of such enzymatic degradation is beneficial in reducing amounts of bioavailable sugars, including glucose and maltose, and the concomitant deleterious conditions resulting therefrom.

A variety of glucosidase inhibitors are known to one of ordinary skill in the art and examples are provided below. Preferred glucosidase inhibitors are those inhibitors that are selected from the group consisting of acarbose, adiposine, voglibose, miglitol, emiglitate, camiglibose, tendamistat, trestatin, pradimicin-Q and salbostatin. The glucosidase inhibitor, acarbose, and the various amino sugar derivatives related thereto are disclosed in U.S. Patent Nos. 4,062,950 and 4,174,439 respectively. The glucosidase inhibitor, adiposine, is disclosed in U.S. Patent No. 4,254,256. The glucosidase inhibitor, voglibose, 3,4-dideoxy-4-[[2-hydroxy-1-(hydroxymethyl)ethyl]amino]-2-C-(hydroxymethyl)-D-epi-inositol, and the various N-substituted pseudo-aminosugars related thereto, are disclosed in U.S. Patent No. 4,701,559. The glucosidase inhibitor, miglitol, (2*R*,3*R*,4*R*,5*S*)-1-(2-hydroxyethyl)-2-(hydroxymethyl)-3,4,5-piperidinetriol, and the various 3,4,5-trihydroxypiperidines related thereto, are disclosed in U.S. Patent No. 4,639,436. The glucosidase inhibitor, emiglitate, ethyl *p*-[2-[(2*R*,3*R*,4*R*,5*S*)-3,4,5-trihydroxy-2-(hydroxymethyl)piperidino]ethoxy]-benzoate, the various derivatives related thereto and pharmaceutically acceptable acid addition salts thereof, are disclosed in U.S. Patent No. 5,192,772. The glucosidase inhibitor, MDL-25637, 2,6-dideoxy-7-*O*- β -D-glucopyrano-syl-2,6-imino-D-glycero-L-gluco-heptitol, the various homodisaccharides related thereto and the pharmaceutically acceptable acid addition salts thereof, are disclosed in U.S. Patent No. 4,634,765. The glucosidase inhibitor, camiglibose, methyl 6-deoxy-6-[(2*R*,3*R*,4*R*,5*S*)-3,4,5-trihydroxy-2-(hydroxymethyl)piperidino]- α -D-glucopyranoside sesquihydrate, the deoxy-nojirimycin derivatives related thereto, the various pharmaceutically acceptable salts thereof and synthetic methods for the preparation thereof, are disclosed in U.S. Patent Nos. 5,157,116 and 5,504,078. The glycosidase inhibitor, salbostatin and the various pseudosaccharides related thereto, are disclosed in U.S. Patent No. 5,091,524.

A variety of amylase inhibitors are known to one of ordinary skill in the art. The amylase inhibitor, tendamistat and the various cyclic peptides related thereto, are disclosed in U.S. Patent No. 4,451,455. The amylase inhibitor AI-3688 and the various cyclic polypeptides related thereto are disclosed in U.S. Patent No. 4,623,714. The amylase inhibitor, trestatin, consisting of a mixture of trestatin A, trestatin B and trestatin C and the various trehalose-containing aminosugars related thereto are disclosed in U.S. Patent No. 4,273,765.

Additional anti-diabetic compounds, which can be used as the second agent in combination with a compound of the present invention, include, for example, the following: biguanides (e.g., metformin), insulin secretagogues (e.g., sulfonylureas and glinides), glitazones, non-glitazone PPAR γ agonists, PPAR β agonists, inhibitors of DPP-IV, inhibitors of PDE5, inhibitors of GSK-3, glucagon antagonists, inhibitors of f-1,6-BPase (Metabasis/Sankyo), GLP-1/analogues (AC 2993, also known as exendin-4), insulin and insulin mimetics (Merck natural products). Other examples would include PKC- β inhibitors and AGE breakers.

The compounds of the present invention can be used in combination with anti-obesity agents. Any anti-obesity agent can be used as the second agent in such combinations and examples are provided herein. Such anti-obesity activity is readily determined by those skilled in the art according to standard assays known in the art.

Suitable anti-obesity agents include phenylpropanolamine, ephedrine, pseudoephedrine, phentermine, β_3 adrenergic receptor agonists, apolipoprotein-B secretion/microsomal triglyceride transfer protein (apo-B/MTP) inhibitors, MCR-4 agonists, cholecystokinin-A (CCK-A) agonists, monoamine

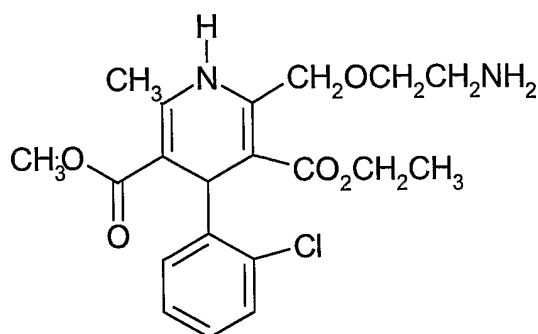
reuptake inhibitors (e.g., sibutramine), sympathomimetic agents, serotonergic agents, cannabinoid receptor (CB-1) antagonists (e.g., rimonabant described in U.S. Pat. No. 5,624,941 (SR-141,716A), purine compounds, such as those described in US Patent Publication No. 2004/0092520; pyrazolo[1,5-a][1,3,5]triazine compounds, such as those described in US Non-Provisional Patent Application No.10/763105 filed on January 21, 2004; and bicyclic pyrazolyl and imidazolyl compounds, such as those described in U.S. Provisional Application No. 60/518280 filed on November 7, 2003), dopamine agonists (e.g., bromocriptine), melanocyte-stimulating hormone receptor analogs, 5HT_{2c} agonists, melanin concentrating hormone antagonists, leptin (the OB protein), leptin analogs, leptin receptor agonists, galanin antagonists, lipase inhibitors (e.g., tetrahydrolipstatin, i.e. orlistat), bombesin agonists, anorectic agents (e.g., a bombesin agonist), Neuropeptide-Y antagonists, thyroxine, thyromimetic agents, dehydroepiandrosterones or analogs thereof, glucocorticoid receptor agonists or antagonists, orexin receptor antagonists, urocortin binding protein antagonists, glucagon-like peptide-1 receptor agonists, ciliary neurotrophic factors (e.g., Axokine™), human agouti-related proteins (AGRP), ghrelin receptor antagonists, histamine 3 receptor antagonists or inverse agonists, neuromedin U receptor agonists, and the like.

Any thyromimetic can be used as the second agent in combination with a compound of the present invention. Such thyromimetic activity is readily determined by those skilled in the art according to standard assays (e.g., Atherosclerosis (1996) 126: 53-63). A variety of thyromimetic agents are known to those skilled in the art, for example those disclosed in U.S. Patent Nos. 4,766,121; 4,826,876; 4,910,305; 5,061,798; 5,284,971; 5,401,772; 5,654,468; and 5,569,674. Other antiobesity agents include sibutramine which can be prepared as described in U.S. Patent No. 4,929,629. and bromocriptine which can be prepared as described in U.S. Patent Nos. 3,752,814 and 3,752,888.

The compounds of the present invention can also be used in combination with other antihypertensive agents. Any anti-hypertensive agent can be used as the second agent in such combinations and examples are provided herein. Such antihypertensive activity is readily determined by those skilled in the art according to standard assays (e.g., blood pressure measurements).

Examples of presently marketed products containing antihypertensive agents include calcium channel blockers, such as Cardizem®, Adalat®, Calan®, Cardene®, Covera®, Dilacor®, DynaCirc®, Procardia XL®, Sular®, Tiazac®, Vascor®, Verelan®, Isoptin®, Nimotop®, Norvasc®, and Plendil®; angiotensin converting enzyme (ACE) inhibitors, such as Accupril®, Altace®, Captopril®, Lotensin®, Mavik®, Monopril®, Prinivil®, Univasc®, Vasotec® and Zestril®.

Amlodipine and related dihydropyridine compounds are disclosed in U.S. Patent No. 4,572,909, which is incorporated herein by reference, as potent anti-ischemic and antihypertensive agents. U.S. Patent No.4,879,303, which is incorporated herein by reference, discloses amlodipine benzenesulfonate salt (also termed amlodipine besylate). Amlodipine and amlodipine besylate are potent and long lasting calcium channel blockers. As such, amlodipine, amlodipine besylate, amlodipine maleate and other pharmaceutically acceptable acid addition salts of amlodipine have utility as antihypertensive agents and as antiischemic agents. Amlodipine besylate is currently sold as Norvasc®. Amlodipine has the formula



Calcium channel blockers which are within the scope of this invention include, but are not limited to: bepridil, which may be prepared as disclosed in U.S. Patent No. 3,962, 238 or U.S. Reissue No. 30,577; clentiazem, which may be prepared as disclosed in U.S. Patent No. 4,567,175; diltiazem, which may be prepared as disclosed in U.S. Patent No. 3,562, fendiline, which may be prepared as disclosed in U.S. Patent No. 3,262,977; gallopamil, which may be prepared as disclosed in U.S. Patent No. 3,261,859; mibefradil, which may be prepared as disclosed in U.S. Patent No. 4,808,605; prenylamine, which may be prepared as disclosed in U.S. Patent No. 3,152,173; semotiadil, which may be prepared as disclosed in U.S. Patent No. 4,786,635; terodiline, which may be prepared as disclosed in U.S. Patent No. 3,371,014; verapamil, which may be prepared as disclosed in U.S. Patent No. 3,261,859; aranipine, which may be prepared as disclosed in U.S. Patent No. 4,572,909; barnidipine, which may be prepared as disclosed in U.S. Patent No. 4,220,649; benidipine, which may be prepared as disclosed in European Patent Application Publication No. 106,275; cilnidipine, which may be prepared as disclosed in U.S. Patent No. 4,672,068; efonidipine, which may be prepared as disclosed in U.S. Patent No. 4,885,284; elgodipine, which may be prepared as disclosed in U.S. Patent No. 4,952,592; felodipine, which may be prepared as disclosed in U.S. Patent No. 4,264,611; isradipine, which may be prepared as disclosed in U.S. Patent No. 4,466,972; lacidipine, which may be prepared as disclosed in U.S. Patent No. 4,801,599; lercanidipine, which may be prepared as disclosed in U.S. Patent No. 4,705,797; manidipine, which may be prepared as disclosed in U.S. Patent No. 4,892,875; nicardipine, which may be prepared as disclosed in U.S. Patent No. 3,985,758; nifedipine, which may be prepared as disclosed in U.S. Patent No. 3,485,847; nilvadipine, which may be prepared as disclosed in U.S. Patent No. 4,338,322; nimodipine, which may be prepared as disclosed in U.S. Patent No. 3,799,934; nisoldipine, which may be prepared as disclosed in U.S. Patent No. 4,154,839; nitrendipine, which may be prepared as disclosed in U.S. Patent No. 3,799,934; cinnarizine, which may be prepared as disclosed in U.S. Patent No. 2,882,271; flunarizine, which may be prepared as disclosed in U.S. Patent No. 3,773,939; lidoflazine, which may be prepared as disclosed in U.S. Patent No. 3,267,104; lomerizine, which may be prepared as disclosed in U.S. Patent No. 4,663,325; bencyclane, which may be prepared as disclosed in Hungarian Patent No. 151,865; etafenone, which may be prepared as disclosed in German Patent No. 1,265,758; and perhexiline, which may be prepared as disclosed in British Patent No. 1,025,578. The disclosures of all such U.S. Patents are incorporated herein by reference.

Angiotensin Converting Enzyme Inhibitors (ACE-Inhibitors) which are within the scope of this invention include, but are not limited to: alacepril, which may be prepared as disclosed in U.S. Patent No. 4,248,883; benazepril, which may be prepared as disclosed in U.S. Patent No. 4,410,520; captopril, which may be prepared as disclosed in U.S. Patent Nos. 4,046,889 and 4,105,776; ceronapril, which may

be prepared as disclosed in U.S. Patent No. 4,452,790; delapril, which may be prepared as disclosed in U.S. Patent No. 4,385,051; enalapril, which may be prepared as disclosed in U.S. Patent No. 4,374,829; fosinopril, which may be prepared as disclosed in U.S. Patent No. 4,337,201; imadapril, which may be prepared as disclosed in U.S. Patent No. 4,508,727; lisinopril, which may be prepared as disclosed in U.S. Patent No. 4,555,502; moveltopril, which may be prepared as disclosed in Belgian Patent No. 893,553; perindopril, which may be prepared as disclosed in U.S. Patent No. 4,508,729; quinapril, which may be prepared as disclosed in U.S. Patent No. 4,344,949; ramipril, which may be prepared as disclosed in U.S. Patent No. 4,587,258; spirapril, which may be prepared as disclosed in U.S. Patent No. 4,470,972; temocapril, which may be prepared as disclosed in U.S. Patent No. 4,699,905; and trandolapril, which may be prepared as disclosed in U.S. Patent No. 4,933,361. The disclosures of all such U.S. patents are incorporated herein by reference.

Angiotensin-II receptor antagonists (A-II antagonists) which are within the scope of this invention include, but are not limited to: candesartan, which may be prepared as disclosed in U.S. Patent No. 5,196,444; eprosartan, which may be prepared as disclosed in U.S. Patent No. 5,185,351; irbesartan, which may be prepared as disclosed in U.S. Patent No. 5,270,317; losartan, which may be prepared as disclosed in U.S. Patent No. 5,138,069; and valsartan, which may be prepared as disclosed in U.S. Patent No. 5,399,578. The disclosures of all such U.S. patents are incorporated herein by reference.

Beta-adrenergic receptor blockers (beta- or β -blockers) which are within the scope of this invention include, but are not limited to: acebutolol, which may be prepared as disclosed in U.S. Patent No. 3,857,952; alprenolol, which may be prepared as disclosed in Netherlands Patent Application No. 6,605,692; amosulalol, which may be prepared as disclosed in U.S. Patent No. 4,217,305; arotinolol, which may be prepared as disclosed in U.S. Patent No. 3,932,400; atenolol, which may be prepared as disclosed in U.S. Patent No. 3,663,607 or 3,836,671; befunolol, which may be prepared as disclosed in U.S. Patent No. 3,853,923; betaxolol, which may be prepared as disclosed in U.S. Patent No. 4,252,984; bevantolol, which may be prepared as disclosed in U.S. Patent No. 3,857,981; bisoprolol, which may be prepared as disclosed in U.S. Patent No. 4,171,370; bopindolol, which may be prepared as disclosed in U.S. Patent No. 4,340,541; bucumolol, which may be prepared as disclosed in U.S. Patent No. 3,663,570; bufetolol, which may be prepared as disclosed in U.S. Patent No. 3,723,476; bufuralol, which may be prepared as disclosed in U.S. Patent No. 3,929,836; bunitrolol, which may be prepared as disclosed in U.S. Patent Nos. 3,940,489 and 3,961,071; buprandolol, which may be prepared as disclosed in U.S. Patent No. 3,309,406; butiridine hydrochloride, which may be prepared as disclosed in French Patent No. 1,390,056; butofilolol, which may be prepared as disclosed in U.S. Patent No. 4,252,825; carazolol, which may be prepared as disclosed in German Patent No. 2,240,599; carteolol, which may be prepared as disclosed in U.S. Patent No. 3,910,924; carvedilol, which may be prepared as disclosed in U.S. Patent No. 4,503,067; celiprolol, which may be prepared as disclosed in U.S. Patent No. 4,034,009; cetamolol, which may be prepared as disclosed in U.S. Patent No. 4,059,622; cloranolol, which may be prepared as disclosed in German Patent No. 2,213,044; dilevalol, which may be prepared as disclosed in Clifton et al., Journal of Medicinal Chemistry, 1982, 25, 670; epanolol, which may be prepared as disclosed in European Patent Publication Application No. 41,491; indenolol, which may be prepared as disclosed in U.S. Patent No. 4,045,482; labetalol, which may be prepared as disclosed in U.S. Patent No. 4,012,444; levobunolol, which may be prepared as disclosed in U.S. Patent No.

4,463,176; mepindolol, which may be prepared as disclosed in Seeman et al., *Helv. Chim. Acta*, 1971, 54, 241; metipranolol, which may be prepared as disclosed in Czechoslovakian Patent Application No. 128,471; metoprolol, which may be prepared as disclosed in U.S. Patent No. 3,873,600; moprolol, which may be prepared as disclosed in U.S. Patent No. 3,501,769; nadolol, which may be prepared as disclosed in U.S. Patent No. 3,935, 267; nadoxolol, which may be prepared as disclosed in U.S. Patent No. 3,819,702; nebivalol, which may be prepared as disclosed in U.S. Patent No. 4,654,362; nipradilol, which may be prepared as disclosed in U.S. Patent No. 4,394,382; oxprenolol, which may be prepared as disclosed in British Patent No. 1,077,603; perbutolol, which may be prepared as disclosed in U.S. Patent No. 3,551,493; pindolol, which may be prepared as disclosed in Swiss Patent Nos. 469,002 and 472,404; practolol, which may be prepared as disclosed in U.S. Patent No. 3,408,387; pronethalol, which may be prepared as disclosed in British Patent No. 909,357; propranolol, which may be prepared as disclosed in U.S. Patent Nos. 3,337,628 and 3,520,919; sotalol, which may be prepared as disclosed in Uloth et al., *Journal of Medicinal Chemistry*, 1966, 9, 88; sufinalol, which may be prepared as disclosed in German Patent No. 2,728,641; talindol, which may be prepared as disclosed in U.S. Patent Nos. 3,935,259 and 4,038,313; tertatolol, which may be prepared as disclosed in U.S. Patent No. 3,960,891; tilisolol, which may be prepared as disclosed in U.S. Patent No. 4,129,565; timolol, which may be prepared as disclosed in U.S. Patent No. 3,655,663; toliprolol, which may be prepared as disclosed in U.S. Patent No. 3,432,545; and xibenolol, which may be prepared as disclosed in U.S. Patent No. 4,018,824. The disclosures of all such U.S. patents are incorporated herein by reference.

Alpha-adrenergic receptor blockers (alpha- or α -blockers) which are within the scope of this invention include, but are not limited to: amosulalol, which may be prepared as disclosed in U.S. Patent No. 4,217,307; arotinolol, which may be prepared as disclosed in U.S. Patent No. 3,932,400; dapiprazole, which may be prepared as disclosed in U.S. Patent No. 4,252,721; doxazosin, which may be prepared as disclosed in U.S. Patent No. 4,188,390; fenspiride, which may be prepared as disclosed in U.S. Patent No. 3,399,192; indoramin, which may be prepared as disclosed in U.S. Patent No. 3,527,761; labetalol; naftopidil, which may be prepared as disclosed in U.S. Patent No. 3,997,666; nicergoline, which may be prepared as disclosed in U.S. Patent No. 3,228,943; prazosin, which may be prepared as disclosed in U.S. Patent No. 3,511,836; tamsulosin, which may be prepared as disclosed in U.S. Patent No. 4,703,063; tolazoline, which may be prepared as disclosed in U.S. Patent No. 2,161,938; trimazosin, which may be prepared as disclosed in U.S. Patent No. 3,669,968; and yohimbine, which may be isolated from natural sources according to methods well known to those skilled in the art. The disclosures of all such U.S. patents are incorporated herein by reference.

The term "vasodilator," where used herein, is meant to include cerebral vasodilators, coronary vasodilators and peripheral vasodilators. Cerebral vasodilators within the scope of this invention include, but are not limited to: bencyclane; cinnarizine; citicoline, which may be isolated from natural sources as disclosed in Kennedy et al., *Journal of the American Chemical Society*, 1955, 77, 250 or synthesized as disclosed in Kennedy, *Journal of Biological Chemistry*, 1956, 222, 185; cyclandelate, which may be prepared as disclosed in U.S. Patent No. 3,663,597; ciclonicate, which may be prepared as disclosed in German Patent No. 1,910,481; diisopropylamine dichloroacetate, which may be prepared as disclosed in British Patent No. 862,248; eburnamonine, which may be prepared as disclosed in Hermann et al., *Journal of the American Chemical Society*, 1979, 101, 1540; fasudil, which may be prepared as disclosed

in U.S. Patent No. 4,678,783; fenoxedil, which may be prepared as disclosed in U.S. Patent No. 3,818,021; flunarizine, which may be prepared as disclosed in U.S. Patent No. 3,773,939; ibudilast, which may be prepared as disclosed in U.S. Patent No. 3,850,941; ifenprodil, which may be prepared as disclosed in U.S. Patent No. 3,509,164; lomerizine, which may be prepared as disclosed in U.S. Patent No. 4,663,325; nafronyl, which may be prepared as disclosed in U.S. Patent No. 3,334,096; nicametate, which may be prepared as disclosed in Blicke et al., Journal of the American Chemical Society, 1942, 64, 1722; nicergoline, which may be prepared as disclosed above; nimodipine, which may be prepared as disclosed in U.S. Patent No. 3,799,934; papaverine, which may be prepared as reviewed in Goldberg, Chem. Prod. Chem. News, 1954, 17, 371; pentifylline, which may be prepared as disclosed in German Patent No. 860,217; tinofedrine, which may be prepared as disclosed in U.S. Patent No. 3,563,997; vincamine, which may be prepared as disclosed in U.S. Patent No. 3,770,724; vinpocetine, which may be prepared as disclosed in U.S. Patent No. 4,035,750; and viquidil, which may be prepared as disclosed in U.S. Patent No. 2,500,444. The disclosures of all such U.S. patents are incorporated herein by reference.

Coronary vasodilators within the scope of this invention include, but are not limited to:

amotriphene, which may be prepared as disclosed in U.S. Patent No. 3,010,965; bendazol, which may be prepared as disclosed in J. Chem. Soc. 1958, 2426; benfurodil hemisuccinate, which may be prepared as disclosed in U.S. Patent No. 3,355,463; benziodarone, which may be prepared as disclosed in U.S. Patent No. 3,012,042; chloracizine, which may be prepared as disclosed in British Patent No. 740,932; chromonar, which may be prepared as disclosed in U.S. Patent No. 3,282,938; clobenfural, which may be prepared as disclosed in British Patent No. 1,160,925; clonitrate, which may be prepared from propanediol according to methods well known to those skilled in the art, e.g., see *Annalen*, 1870, 155, 165; cloricromen, which may be prepared as disclosed in U.S. Patent No. 4,452,811; dilazep, which may be prepared as disclosed in U.S. Patent No. 3,532,685; dipyridamole, which may be prepared as disclosed in British Patent No. 807,826; droprenilamine, which may be prepared as disclosed in German Patent No. 2,521,113; efloxate, which may be prepared as disclosed in British Patent Nos. 803,372 and 824,547; erythrityl tetranitrate, which may be prepared by nitration of erythritol according to methods well-known to those skilled in the art; etafenone, which may be prepared as disclosed in German Patent No. 1,265,758; fendiline, which may be prepared as disclosed in U.S. Patent No. 3,262,977; floredil, which may be prepared as disclosed in German Patent No. 2,020,464; ganglefene, which may be prepared as disclosed in U.S.S.R. Patent No. 115,905; hexestrol, which may be prepared as disclosed in U.S. Patent No. 2,357,985; hexobendine, which may be prepared as disclosed in U.S. Patent No. 3,267,103; itramin tosylate, which may be prepared as disclosed in Swedish Patent No. 168,308; khellin, which may be prepared as disclosed in Baxter et al., Journal of the Chemical Society, 1949, S 30; lidoflazine, which may be prepared as disclosed in U.S. Patent No. 3,267,104; mannitol hexanitrate, which may be prepared by the nitration of mannitol according to methods well-known to those skilled in the art; medibazine, which may be prepared as disclosed in U.S. Patent No. 3,119,826; nitroglycerin; pentaerythritol tetranitrate, which may be prepared by the nitration of pentaerythritol according to methods well-known to those skilled in the art; pentrinitrol, which may be prepared as disclosed in German Patent No. 638,422-3; perhexilline, which may be prepared as disclosed above; pimefylline, which may be prepared as disclosed in U.S. Patent No. 3,350,400; prenylamine, which may be prepared as disclosed in U.S. Patent No. 3,152,173; propatyl nitrate, which may be prepared as disclosed in French Patent No. 1,103,113;

trapidil, which may be prepared as disclosed in East German Patent No. 55,956; tricromyl, which may be prepared as disclosed in U.S. Patent No. 2,769,015; trimetazidine, which may be prepared as disclosed in U.S. Patent No. 3,262,852; trolnitrate phosphate, which may be prepared by nitration of triethanolamine followed by precipitation with phosphoric acid according to methods well-known to those skilled in the art; 5 visnadine, which may be prepared as disclosed in U.S. Patent Nos. 2,816,118 and 2,980,699. The disclosures of all such U.S. patents are incorporated herein by reference.

Peripheral vasodilators within the scope of this invention include, but are not limited to: aluminum nicotinate, which may be prepared as disclosed in U.S. Patent No. 2,970,082; bamethan, which may be prepared as disclosed in Corrigan et al., *Journal of the American Chemical Society*, 1945, 67, 1894; 10 bencyclane, which may be prepared as disclosed above; betahistine, which may be prepared as disclosed in Walter et al.; *Journal of the American Chemical Society*, 1941, 63, 2771; bradykinin, which may be prepared as disclosed in Hamburg et al., *Arch. Biochem. Biophys.*, 1958, 76, 252; brovincamine, which may be prepared as disclosed in U.S. Patent No. 4,146,643; bufeniode, which may be prepared as disclosed in U.S. Patent No. 3,542,870; buflomedil, which may be prepared as disclosed in U.S. Patent 15 No. 3,895,030; butalamine, which may be prepared as disclosed in U.S. Patent No. 3,338,899; cetiedil, which may be prepared as disclosed in French Patent Nos. 1,460,571; ciclonicate, which may be prepared as disclosed in German Patent No. 1,910,481; cinepazide, which may be prepared as disclosed in Belgian Patent No. 730,345; cinnarizine, which may be prepared as disclosed above; cyclandelate, which may be prepared as disclosed above; diisopropylamine dichloroacetate, which may be prepared as 20 disclosed above; eledoisin, which may be prepared as disclosed in British Patent No. 984,810; fenoxedil, which may be prepared as disclosed above; flunarizine, which may be prepared as disclosed above; hepronicate, which may be prepared as disclosed in U.S. Patent No. 3,384,642; ifenprodil, which may be prepared as disclosed above; iloprost, which may be prepared as disclosed in U.S. Patent No. 4,692,464; inositol niacinate, which may be prepared as disclosed in Badgett et al., *Journal of the American* 25 *Chemical Society*, 1947, 69, 2907; isoxsuprine, which may be prepared as disclosed in U.S. Patent No. 3,056,836; kallidin, which may be prepared as disclosed in *Biochem. Biophys. Res. Commun.*, 1961, 6, 210; kallikrein, which may be prepared as disclosed in German Patent No. 1,102,973; moxislyte, which may be prepared as disclosed in German Patent No. 905,738; nafronyl, which may be prepared as disclosed above; nicametate, which may be prepared as disclosed above; nicergoline, which may be 30 prepared as disclosed above; nicofuranose, which may be prepared as disclosed in Swiss Patent No. 366,523; nylidrin, which may be prepared as disclosed in U.S. Patent Nos. 2,661,372 and 2,661,373; pentifylline, which may be prepared as disclosed above; pentoxifylline, which may be prepared as disclosed in U.S. Patent No. 3,422,107; piribedil, which may be prepared as disclosed in U.S. Patent No. 3,299,067; prostaglandin E₁, which may be prepared by any of the methods referenced in the Merck 35 Index, Twelfth Edition, Budaveri, Ed., New Jersey, 1996, p. 1353; suloctidil, which may be prepared as disclosed in German Patent No. 2,334,404; tolazoline, which may be prepared as disclosed in U.S. Patent No. 2,161,938; and xanthinol niacinate, which may be prepared as disclosed in German Patent No. 1,102,750 or Korbonits et al., *Acta. Pharm. Hung.*, 1968, 38, 98. The disclosures of all such U.S. patents are incorporated herein by reference.

40 The term "diuretic," within the scope of this invention, is meant to include diuretic benzothiadiazine derivatives, diuretic organomercurials, diuretic purines, diuretic steroids, diuretic

sulfonamide derivatives, diuretic uracils and other diuretics such as amanozine, which may be prepared as disclosed in Austrian Patent No. 168,063; amiloride, which may be prepared as disclosed in Belgian Patent No. 639,386; arbutin, which may be prepared as disclosed in Tschitschibabin, *Annalen*, 1930, 479, 303; chlorazanyl, which may be prepared as disclosed in Austrian Patent No. 168,063; ethacrynic acid, which may be prepared as disclosed in U.S. Patent No. 3,255,241; etozolin, which may be prepared as disclosed in U.S. Patent No. 3,072,653; hydracarbazine, which may be prepared as disclosed in British Patent No. 856,409; isosorbide, which may be prepared as disclosed in U.S. Patent No. 3,160,641; mannitol; metochalcone, which may be prepared as disclosed in Freudenberg et al., *Ber.*, 1957, 90, 957; muzolimine, which may be prepared as disclosed in U.S. Patent No. 4,018,890; perhexiline, which may be prepared as disclosed above; ticrynafen, which may be prepared as disclosed in U.S. Patent No. 3,758,506; triamterene which may be prepared as disclosed in U.S. Patent No. 3,081,230; and urea. The disclosures of all such U.S. patents are incorporated herein by reference.

Diuretic benzothiadiazine derivatives within the scope of this invention include, but are not limited to: althiazide, which may be prepared as disclosed in British Patent No. 902,658; bendroflumethiazide, which may be prepared as disclosed in U.S. Patent No. 3,265,573; benzthiazide, McManus et al., 136th Am. Soc. Meeting (Atlantic City, September 1959), Abstract of papers, pp 13-O; benzylhydrochlorothiazide, which may be prepared as disclosed in U.S. Patent No. 3,108,097; buthiazide, which may be prepared as disclosed in British Patent Nos. 861,367 and 885,078; chlorothiazide, which may be prepared as disclosed in U.S. Patent Nos. 2,809,194 and 2,937,169; chlorthalidone, which may be prepared as disclosed in U.S. Patent No. 3,055,904; cyclopenthiazide, which may be prepared as disclosed in Belgian Patent No. 587,225; cyclothiazide, which may be prepared as disclosed in Whitehead et al., *Journal of Organic Chemistry*, 1961, 26, 2814; epithiazide, which may be prepared as disclosed in U.S. Patent No. 3,009,911; ethiazide, which may be prepared as disclosed in British Patent No. 861,367; fenquizone, which may be prepared as disclosed in U.S. Patent No. 3,870,720; indapamide, which may be prepared as disclosed in U.S. Patent No. 3,565,911; hydrochlorothiazide, which may be prepared as disclosed in U.S. Patent No. 3,164,588; hydroflumethiazide, which may be prepared as disclosed in U.S. Patent No. 3,254,076; methyclothiazide, which may be prepared as disclosed in Close et al., *Journal of the American Chemical Society*, 1960, 82, 1132; meticrane, which may be prepared as disclosed in French Patent Nos. M2790 and 1,365,504; metolazone, which may be prepared as disclosed in U.S. Patent No. 3,360,518; paraflutizide, which may be prepared as disclosed in Belgian Patent No. 620,829; polythiazide, which may be prepared as disclosed in U.S. Patent No. 3,009,911; quinethazone, which may be prepared as disclosed in U.S. Patent No. 2,976,289; teclothiazide, which may be prepared as disclosed in Close et al., *Journal of the American Chemical Society*, 1960, 82, 1132; and trichlormethiazide, which may be prepared as disclosed in deStevens et al., *Experientia*, 1960, 16, 113. The disclosures of all such U.S. patents are incorporated herein by reference.

Diuretic sulfonamide derivatives within the scope of this invention include, but are not limited to: acetazolamide, which may be prepared as disclosed in U.S. Patent No. 2,980,679; ambuside, which may be prepared as disclosed in U.S. Patent No. 3,188,329; azosemide, which may be prepared as disclosed in U.S. Patent No. 3,665,002; bumetanide, which may be prepared as disclosed in U.S. Patent No. 3,634,583; butazolamide, which may be prepared as disclosed in British Patent No. 769,757; chloraminophenamide, which may be prepared as disclosed in U.S. Patent Nos. 2,809,194, 2,965,655

and 2,965,656; clofenamide, which may be prepared as disclosed in Olivier, Rec. Trav. Chim., 1918, 37, 307; clopamide, which may be prepared as disclosed in U.S. Patent No. 3,459,756; clorexolone, which may be prepared as disclosed in U.S. Patent No. 3,183,243; disulfamide, which may be prepared as disclosed in British Patent No. 851,287; ethoxolamide, which may be prepared as disclosed in British Patent No. 795,174; furosemide, which may be prepared as disclosed in U.S. Patent No. 3,058,882; mefruside, which may be prepared as disclosed in U.S. Patent No. 3,356,692; methazolamide, which may be prepared as disclosed in U.S. Patent No. 2,783,241; piretanide, which may be prepared as disclosed in U.S. Patent No. 4,010,273; torasemide, which may be prepared as disclosed in U.S. Patent No. 4,018,929; tripamide, which may be prepared as disclosed in Japanese Patent No. 73 05,585; and xipamide, which may be prepared as disclosed in U.S. Patent No. 3,567,777. The disclosures of all such U.S. patents are incorporated herein by reference.

Osteoporosis is a systemic skeletal disease, characterized by low bone mass and deterioration of bone tissue, with a consequent increase in bone fragility and susceptibility to fracture. In the U.S., the condition affects more than 25 million people and causes more than 1.3 million fractures each year, including 500,000 spine, 250,000 hip and 240,000 wrist fractures annually. Hip fractures are the most serious consequence of osteoporosis, with 5-20% of patients dying within one year, and over 50% of survivors being incapacitated.

The elderly are at greatest risk of osteoporosis, and the problem is therefore predicted to increase significantly with the aging of the population. Worldwide fracture incidence is forecasted to increase three-fold over the next 60 years, and one study has estimated that there will be 4.5 million hip fractures worldwide in 2050.

Women are at greater risk of osteoporosis than men. Women experience a sharp acceleration of bone loss during the five years following menopause. Other factors that increase the risk include smoking, alcohol abuse, a sedentary lifestyle and low calcium intake.

Those skilled in the art will recognize that anti-resorptive agents (for example progestins, polyphosphonates, bisphosphonate(s), estrogen agonists/antagonists, estrogen, estrogen/progestin combinations, Premarin®, estrone, estriol or 17 α - or 17 β -ethynyl estradiol) may be used in conjunction with the compounds of the present invention.

Exemplary progestins are available from commercial sources and include: algestone acetophenide, altrenogest, amadinone acetate, anagestone acetate, chlormadinone acetate, cingestol, clogestone acetate, clomegestone acetate, delmadinone acetate, desogestrel, dimethisterone, dydrogesterone, ethynerone, ethynodiol diacetate, etonogestrel, flurogestone acetate, gestaclone, gestodene, gestonorone caproate, gestrinone, haloprogestosterone, hydroxyprogesterone caproate, levonorgestrel, lynestrenol, medrogestone, medroxyprogesterone acetate, melengestrol acetate, methynodiol diacetate, norethindrone, norethindrone acetate, norethynodrel, norgestimate, norgestomet, norgestrel, oxogestone phenpropionate, progesterone, quingestanol acetate, quingestrone, and tigestol.

Preferred progestins are medroxyprogesterone, norethindrone and norethynodrel.

Exemplary bone resorption inhibiting polyphosphonates include polyphosphonates of the type disclosed in U.S. Patent 3,683,080, the disclosure of which is incorporated herein by reference. Preferred polyphosphonates are geminal diphosphonates (also referred to as bis-phosphonates). Tiludronate disodium is an especially preferred polyphosphonate. Ibandronic acid is an especially preferred

polyphosphonate. Alendronate and resindronate are especially preferred polyphosphonates. Zoledronic acid is an especially preferred polyphosphonate. Other preferred polyphosphonates are 6-amino-1-hydroxy-hexylidene-bisphosphonic acid and 1-hydroxy-3(methylpentylamino)-propylidene-bisphosphonic acid. The polyphosphonates may be administered in the form of the acid, or of a soluble alkali metal salt or alkaline earth metal salt. Hydrolyzable esters of the polyphosphonates are likewise included. Specific examples include ethane-1-hydroxy 1,1-diphosphonic acid, methane diphosphonic acid, pentane-1-hydroxy-1,1-diphosphonic acid, methane dichloro diphosphonic acid, methane hydroxy diphosphonic acid, ethane-1-amino-1,1-diphosphonic acid, ethane-2-amino-1,1-diphosphonic acid, propane-3-amino-1-hydroxy-1,1-diphosphonic acid, propane-N,N-dimethyl-3-amino-1-hydroxy-1,1-diphosphonic acid, propane-3,3-dimethyl-3-amino-1-hydroxy-1,1-diphosphonic acid, phenyl amino methane diphosphonic acid, N,N-dimethylamino methane diphosphonic acid, N(2-hydroxyethyl) amino methane diphosphonic acid, butane-4-amino-1-hydroxy-1,1-diphosphonic acid, pentane-5-amino-1-hydroxy-1,1-diphosphonic acid, hexane-6-amino-1-hydroxy-1,1-diphosphonic acid and pharmaceutically acceptable esters and salts thereof.

In particular, the compounds of this invention may be combined with a mammalian estrogen agonist/antagonist. Any estrogen agonist/antagonist may be used in the combination aspect of this invention. The term estrogen agonist/antagonist refers to compounds which bind with the estrogen receptor, inhibit bone turnover and/or prevent bone loss. In particular, estrogen agonists are herein defined as chemical compounds capable of binding to the estrogen receptor sites in mammalian tissue, and mimicking the actions of estrogen in one or more tissue. Estrogen antagonists are herein defined as chemical compounds capable of binding to the estrogen receptor sites in mammalian tissue, and blocking the actions of estrogen in one or more tissues. Such activities are readily determined by those skilled in the art of standard assays including estrogen receptor binding assays, standard bone histomorphometric and densitometer methods, and Eriksen E.F. et al., Bone Histomorphometry, Raven Press, New York, 1994, pages 1-74; Grier S.J. et. al., The Use of Dual-Energy X-Ray Absorptiometry In Animals, Inv. Radiol., 1996, 31(1):50-62; Wahner H.W. and Fogelman I., The Evaluation of Osteoporosis: Dual Energy X-Ray Absorptiometry in Clinical Practice., Martin Dunitz Ltd., London 1994, pages 1-296). A variety of these compounds are described and referenced below.

Another preferred estrogen agonist/antagonist is 3-(4-(1,2-diphenyl-but-1-enyl)-phenyl)-acrylic acid, which is disclosed in Willson et al., Endocrinology, 1997, 138, 3901-3911.

Another preferred estrogen agonist/antagonist is tamoxifen: (ethanamine, 2-(-4-(1,2-diphenyl-1-butenyl)phenoxy)-N,N-dimethyl, (Z)-2-, 2-hydroxy-1,2,3-propanetricarboxylate(1:1)) and related compounds which are disclosed in U.S. patent 4,536,516, the disclosure of which is incorporated herein by reference.

Another related compound is 4-hydroxy tamoxifen, which is disclosed in U.S. patent 4,623,660, the disclosure of which is incorporated herein by reference.

A preferred estrogen agonist/antagonist is raloxifene: (methanone, (6-hydroxy-2-(4-hydroxyphenyl)benzo[b]thien-3-yl)(4-(2-(1-piperidinyl)ethoxy)phenyl)-hydrochloride) which is disclosed in U.S. patent 4,418,068, the disclosure of which is incorporated herein by reference.

Another preferred estrogen agonist/antagonist is toremifene: (ethanamine, 2-(4-(4-chloro-1,2-diphenyl-1-butenyl)phenoxy)-N,N-dimethyl-, (Z)-, 2-hydroxy-1,2,3-propanetricarboxylate (1:1) which is disclosed in U.S. patent 4,996,225, the disclosure of which is incorporated herein by reference.

Another preferred estrogen agonist/antagonist is centchroman: 1-(2-((4-(4-methoxy-2,2, dimethyl-3-phenyl-chroman-4-yl)-phenoxy)-ethyl)-pyrrolidine, which is disclosed in U.S. patent 3,822,287, the disclosure of which is incorporated herein by reference. Also preferred is levormeloxifene.

Another preferred estrogen agonist/antagonist is idoxifene: (E)-1-(2-(4-(1-(4-iodo-phenyl)-2-phenyl-but-1-enyl)-phenoxy)-ethyl)-pyrrolidinone, which is disclosed in U.S. patent 4,839,155, the disclosure of which is incorporated herein by reference.

Another preferred estrogen agonist/antagonist is 2-(4-methoxy-phenyl)-3-[4-(2-piperidin-1-yl-ethoxy)-phenoxy]- benzo[b]thiophen-6-ol which is disclosed in U.S. Patent No. 5,488,058, the disclosure of which is incorporated herein by reference.

Another preferred estrogen agonist/antagonist is 6-(4-hydroxy-phenyl)-5-(4-(2-piperidin-1-yl-ethoxy)-benzyl)-naphthalen-2-ol, which is disclosed in U.S. patent 5,484,795, the disclosure of which is incorporated herein by reference.

Another preferred estrogen agonist/antagonist is (4-(2-(2-aza-bicyclo[2.2.1]hept-2-yl)-ethoxy)-phenyl)-(6-hydroxy-2-(4-hydroxy-phenyl)-benzo[b]thiophen-3-yl)-methanone which is disclosed, along with methods of preparation, in PCT publication no. WO 95/10513 assigned to Pfizer Inc.

Other preferred estrogen agonist/antagonists include the compounds, TSE-424 (Wyeth-Ayerst Laboratories) and arazoxifene.

Other preferred estrogen agonist/antagonists include compounds as described in commonly assigned U.S. patent 5,552,412, the disclosure of which is incorporated herein by reference. Especially preferred compounds described therein are:

cis-6-(4-fluoro-phenyl)-5-(4-(2-piperidin-1-yl-ethoxy)-phenyl)-5,6,7,8-tetrahydro-naphthalene-2-ol; (-)-*cis*-6-phenyl-5-(4-(2-pyrrolidin-1-yl-ethoxy)-phenyl)-5,6,7,8-tetrahydro-naphthalene-2-ol (also known as lasofoxifene);

cis-6-phenyl-5-(4-(2-pyrrolidin-1-yl-ethoxy)-phenyl)-5,6,7,8-tetrahydro-naphthalene-2-ol; *cis*-1-(6'-pyrrolidinoethoxy-3'-pyridyl)-2-phenyl-6-hydroxy-1,2,3,4-tetrahydronaphthalene; 1-(4'-pyrrolidinoethoxyphenyl)-2-(4"-fluorophenyl)-6-hydroxy-1,2,3,4-tetrahydroisoquinoline; *cis*-6-(4-hydroxyphenyl)-5-(4-(2-piperidin-1-yl-ethoxy)-phenyl)-5,6,7,8-tetrahydro-naphthalene-2-ol; and

1-(4'-pyrrolidinoethoxyphenyl)-2-phenyl-6-hydroxy-1,2,3,4-tetrahydroisoquinoline.

Other estrogen agonist/antagonists are described in U.S. patent 4,133,814 (the disclosure of which is incorporated herein by reference). U.S. patent 4,133,814 discloses derivatives of 2-phenyl-3-aro-yl-benzothiophene and 2-phenyl-3-aro-ylbenzothiophene-1-oxide.

Other anti-osteoporosis agents, which can be used as the second agent in combination with a compound of the present invention, include, for example, the following: parathyroid hormone (PTH) (a bone anabolic agent); parathyroid hormone (PTH) secretagogues (see, e.g., U.S. Patent No. 6,132,774), particularly calcium receptor antagonists; calcitonin; and vitamin D and vitamin D analogs.

Any selective androgen receptor modulator (SARM) can be used in combination with a compound of the present invention. A selective androgen receptor modulator (SARM) is a compound that possesses androgenic activity and which exerts tissue-selective effects. SARM compounds can function as androgen receptor agonists, partial agonists, partial antagonists or antagonists. Examples of suitable SARMS include compounds such as cyproterone acetate, chlormadinone, flutamide, hydroxyflutamide, bicalutamide,

nilutamide, spironolactone, 4-(trifluoromethyl)-2(1H)-pyrrolidino[3,2-g] quinoline derivatives, 1,2-dihydropyridino [5,6-g]quinoline derivatives and piperidino[3,2-g]quinolinone derivatives.

Cyterone, also known as (1b,2b)-6-chloro-1,2-dihydro-17-hydroxy-3'H-cyclopropa[1,2]pregna-1,4,6-triene-3,20-dione is disclosed in U.S. Patent 3,234,093. Chlormadinone, also known as 17-

(acetyloxy)-6-chloropregna-4,6-diene-3,20-dione, in its acetate form, acts as an anti-androgen and is disclosed in U.S. Patent 3,485,852. Nilutamide, also known as 5,5-dimethyl-3-[4-nitro-3-

(trifluoromethyl)phenyl]-2,4-imidazolidinedione and by the trade name Nilandron® is disclosed in U.S.

Patent 4,097,578. Flutamide, also known as 2-methyl-N-[4-nitro-3-(trifluoromethyl)phenyl] propanamide and the trade name Eulexin® is disclosed in U.S. Patent 3,847,988. Bicalutamide, also known as 4'-

cyano-a',a',a'-trifluoro-3-(4-fluorophenylsulfonyl)-2-hydroxy-2-methylpropiono-m-toluidide and the trade name Casodex® is disclosed in EP-100172. The enantiomers of bicalutamide are discussed by Tucker and Chesterton, *J. Med. Chem.* 1988, 31, 885-887. Hydroxyflutamide, a known androgen receptor antagonist in most tissues, has been suggested to function as a SARM for effects on IL-6 production by osteoblasts as disclosed in Hofbauer et al. *J. Bone Miner. Res.* 1999, 14, 1330-1337. Additional SARMS

have been disclosed in U.S. Patent 6,017,924; WO 01/16108, WO 01/16133, WO 01/16139, WO 02/00617, WO 02/16310, U.S. Patent Application Publication No. US 2002/0099096, U.S. Patent Application Publication No. US 2003/0022868, WO 03/011302 and WO 03/011824. All of the above references are hereby incorporated by reference herein.

The starting materials and reagents for the above described compounds, are also readily available or can be easily synthesized by those skilled in the art using conventional methods of organic synthesis. For example, many of the compounds used herein, are related to, or are derived from compounds in which there is a large scientific interest and commercial need, and accordingly many such compounds are commercially available or are reported in the literature or are easily prepared from other commonly available substances by methods which are reported in the literature.

Some of the compounds of this invention or intermediates in their synthesis have asymmetric carbon atoms and therefore are enantiomers or diastereomers. Diastereomeric mixtures can be separated into their individual diastereomers on the basis of their physical chemical differences by methods known per se, for example, by chromatography and/or fractional crystallization. Enantiomers can be separated by, for example, chiral HPLC methods or converting the enantiomeric mixture into a diastereomeric mixture by reaction with an appropriate optically active compound (e.g., alcohol), separating the diastereomers and converting (e.g., hydrolyzing) the individual diastereomers to the corresponding pure enantiomers. Also, an enantiomeric mixture of the compounds or an intermediate in their synthesis which contain an acidic or basic moiety may be separated into their corresponding pure enantiomers by forming a diastereomeric salt with an optically pure chiral base or acid (e.g., 1-phenyl-ethyl amine, dibenzyl tartrate or tartaric acid) and separating the diastereomers by fractional crystallization followed by neutralization to break the salt, thus providing the corresponding pure enantiomers. All such isomers, including diastereomers, enantiomers and mixtures thereof are considered as part of this invention for all of the compounds of the present invention, including the compounds of the present invention. Also, some of the compounds of this invention are atropisomers (e.g., substituted biaryls) and are considered as part of this invention.

More specifically, the compounds of this invention may be obtained in enantiomerically enriched form by resolving the racemate of the final compound or an intermediate in its synthesis, employing chromatography (preferably high pressure liquid chromatography [HPLC]) on an asymmetric resin (preferably Chiralcel™ AD or OD (obtained from Chiral Technologies, Exton, Pennsylvania)) with a mobile phase consisting of a hydrocarbon (preferably heptane or hexane) containing between 0 and 50% isopropanol (preferably between 2 and 20 %) and between 0 and 5% of an alkyl amine (preferably 0.1% of diethylamine). Concentration of the product containing fractions affords the desired materials.

Some of the compounds of this invention are acidic and they form a salt with a pharmaceutically acceptable cation. Some of the compounds of this invention are basic and they form a salt with a pharmaceutically acceptable anion. All such salts are within the scope of this invention and they can be prepared by conventional methods such as combining the acidic and basic entities, usually in a stoichiometric ratio, in either an aqueous, non-aqueous or partially aqueous medium, as appropriate. The salts are recovered either by filtration, by precipitation with a non-solvent followed by filtration, by evaporation of the solvent, or, in the case of aqueous solutions, by lyophilization, as appropriate. The compounds can be obtained in crystalline form by dissolution in an appropriate solvent(s) such as ethanol, hexanes or water/ethanol mixtures.

In addition, when the compounds of this invention form hydrates or solvates they are also within the scope of the invention.

The compounds of this invention, their prodrugs and the salts of such compounds and prodrugs are all adapted to therapeutic use as agents that inhibit cholesterol ester transfer protein activity in mammals, particularly humans. Thus, the compounds of this invention elevate plasma HDL cholesterol, its associated components, and the functions performed by them in mammals, particularly humans. By virtue of their activity, these agents also reduce plasma levels of triglycerides, VLDL cholesterol, Apo-B, LDL cholesterol and their associated components in mammals, particularly humans. Moreover, these compounds are useful in equalizing LDL cholesterol and HDL cholesterol. Hence, these compounds are useful for the treatment and correction of the various dyslipidemias observed to be associated with the development and incidence of atherosclerosis and cardiovascular disease, including coronary artery disease, coronary heart disease, coronary vascular disease, peripheral vascular disease, hypoalphalipoproteinemia, hyperbetalipoproteinemia, hypertriglyceridemia, hypercholesterolemia, familial-hypercholesterolemia, low HDL and associated components, elevated LDL and associated components, elevated Lp(a), elevated small-dense LDL, elevated VLDL and associated components and post-prandial lipemia.

Further, introduction of a functional CETP gene into an animal lacking CETP (mouse) results in reduced HDL levels (Agellon, L.B., et al: *J. Biol. Chem.* (1991) 266: 10796-10801.) and increased susceptibility to atherosclerosis. (Marotti, K.R., et al: *Nature* (1993) 364: 73-75.). Also, inhibition of CETP activity with an inhibitory antibody raises HDL-cholesterol in hamster (Evans, G.F., et al: *J. of Lipid Research* (1994) 35: 1634-1645.) and rabbit (Whitlock, M.E., et al: *J. Clin. Invest.* (1989) 84: 129-137). Suppression of increased plasma CETP by intravenous injection with antisense oligodeoxynucleotides against CETP mRNA reduced atherosclerosis in cholesterol-fed rabbits (Sugano, M., et al: *J. of Biol. Chem.* (1998) 273: 5033-5036.) Importantly, human subjects deficient in plasma CETP, due to a genetic mutation possess markedly elevated plasma HDL-cholesterol levels and apolipoprotein A-I, the major

apoprotein component of HDL. In addition, most demonstrate markedly decreased plasma LDL cholesterol and apolipoprotein B (the major apolipoprotein component of LDL. (Inazu, A., Brown, M.L., Hesler, C.B., et al.: *N. Engl. J. Med.* (1990) 323: 1234-1238.)

Given the negative correlation between the levels of HDL cholesterol and HDL associated lipoproteins, and the positive correlation between triglycerides, LDL cholesterol, and their associated apolipoproteins in blood with the development of cardiovascular, cerebral vascular and peripheral vascular diseases, the compounds of this invention, their prodrugs and the salts of such compounds and prodrugs, by virtue of their pharmacologic action, are useful for the prevention, arrestment and/or regression of atherosclerosis and its associated disease states. These include cardiovascular disorders (e.g., angina, ischemia, cardiac ischemia and myocardial infarction), complications due to cardiovascular disease therapies (e.g., reperfusion injury and angioplastic restenosis), hypertension, elevated cardiovascular risk associated with hypertension, stroke, atherosclerosis associated with organ transplantation, cerebrovascular disease, cognitive dysfunction (including, but not limited to, dementia secondary to atherosclerosis, transient cerebral ischemic attacks, neurodegeneration, neuronal deficient, and delayed onset or procession of Alzheimer's disease), elevated levels of oxidative stress, elevated levels of C-Reactive Protein, Metabolic Syndrome and elevated levels of HbA1C.

Because of the beneficial effects widely associated with elevated HDL levels, an agent which inhibits CETP activity in humans, by virtue of its HDL increasing ability, also provides valuable avenues for therapy in a number of other disease areas as well.

Thus, given the ability of the compounds of this invention, their prodrugs and the salts of such compounds and prodrugs to alter lipoprotein composition via inhibition of cholesterol ester transfer, they are of use in the treatment of vascular complications associated with diabetes, lipoprotein abnormalities associated with diabetes and sexual dysfunction associated with diabetes and vascular disease. Hyperlipidemia is present in most subjects with diabetes mellitus (Howard, B.V. 1987. *J. Lipid Res.* 28, 613). Even in the presence of normal lipid levels, diabetic subjects experience a greater risk of cardiovascular disease (Kannel, W.B. and McGee, D.L. 1979. *Diabetes Care* 2, 120). CETP-mediated cholesteryl ester transfer is known to be abnormally increased in both insulin-dependent (Bagdade, J.D., Subbaiah, P.V. and Ritter, M.C. 1991. *Eur. J. Clin. Invest.* 21, 161) and non-insulin dependent diabetes (Bagdade, J.D., Ritter, M.C., Lane, J. and Subbaiah. 1993. *Atherosclerosis* 104, 69). It has been suggested that the abnormal increase in cholesterol transfer results in changes in lipoprotein composition, particularly for VLDL and LDL, that are more atherogenic (Bagdade, J.D., Wagner, J.D., Rudel, L.L., and Clarkson, T.B. 1995. *J. Lipid Res.* 36, 759). These changes would not necessarily be observed during routine lipid screening. Thus the present invention will be useful in reducing the risk of vascular complications as a result of the diabetic condition.

The described agents are useful in the treatment of obesity and elevated cardiovascular risk associated with obesity. In both humans (Radeau, T., Lau, P., Robb, M., McDonnell, M., Ailhaud, G. and McPherson, R., 1995. *Journal of Lipid Research.* 36 (12):2552-61) and nonhuman primates (Quinet, E., Tall, A., Ramakrishnan, R. and Rudel, L., 1991. *Journal of Clinical Investigation.* 87 (5):1559-66) mRNA for CETP is expressed at high levels in adipose tissue. The adipose message increases with fat feeding (Martin, L. J., Connelly, P. W., Nanchoo, D., Wood, N., Zhang, Z. J., Maguire, G., Quinet, E., Tall, A. R., Marcel, Y. L. and McPherson, R., 1993. *Journal of Lipid Research.* 34 (3):437-46), and is translated into

functional transfer protein and through secretion contributes significantly to plasma CETP levels. In human adipocytes the bulk of cholesterol is provided by plasma LDL and HDL (Fong, B. S., and Angel, A., 1989. *Biochimica et Biophysica Acta*. 1004 (1):53-60). The uptake of HDL cholesteryl ester is dependent in large part on CETP (Benoist, F., Lau, P., McDonnell, M., Doelle, H., Milne, R. and McPherson, R., 1997. *Journal of Biological Chemistry*. 272 (38):23572-7). This ability of CETP to stimulate HDL cholesteryl uptake, coupled with the enhanced binding of HDL to adipocytes in obese subjects (Jimenez, J. G., Fong, B., Julien, P., Despres, J. P., Rotstein, L., and Angel, A., 1989. *International Journal of Obesity*. 13 (5):699-709), suggests a role for CETP, not only in generating the low HDL phenotype for these subjects, but in the development of obesity itself by promoting cholesterol accumulation. Inhibitors of CETP activity that block this process therefore serve as useful adjuvants to dietary therapy in causing weight reduction.

CETP inhibitors are useful in the treatment of inflammation due to Gram-negative sepsis and septic shock. For example, the systemic toxicity of Gram-negative sepsis is in large part due to endotoxin, a lipopolysaccharide (LPS) released from the outer surface of the bacteria, which causes an extensive inflammatory response. Lipopolysaccharide can form complexes with lipoproteins (Ulevitch, R.J., Johnston, A.R., and Weinstein, D.B., 1981. *J. Clin. Invest.* 67, 827-37). In vitro studies have demonstrated that binding of LPS to HDL substantially reduces the production and release of mediators of inflammation (Ulevitch, R.J., Johnston, A.R., 1978. *J. Clin. Invest.* 62, 1313-24). In vivo studies show that transgenic mice expressing human apo-AI and elevated HDL levels are protected from septic shock (Levine, D.M., Parker, T.S., Donnelly, T.M., Walsh, A.M., and Rubin, A.L. 1993. *Proc. Natl. Acad. Sci.* 90, 12040-44). Importantly, administration of reconstituted HDL to humans challenged with endotoxin resulted in a decreased inflammatory response (Pajkrt, D., Doran, J.E., Koster, F., Lerch, P.G., Arnet, B., van der Poll, T., ten Cate, J.W., and van Deventer, S.J.H. 1996. *J. Exp. Med.* 184, 1601-08). The CETP inhibitors, by virtue of the fact that they raise HDL levels, attenuate the development of inflammation and septic shock. These compounds would also be useful in the treatment of endotoxemia, autoimmune diseases and other systemic disease indications, organ or tissue transplant rejection and cancer.

The utility of the compounds of the invention, their prodrugs and the salts of such compounds and prodrugs as medical agents in the treatment of the above described disease/conditions in mammals (e.g. humans, male or female) is demonstrated by the activity of the compounds of this invention in conventional assays and the *in vivo* assay described below. The *in vivo* assay (with appropriate modifications within the skill in the art) may be used to determine the activity of other lipid or triglyceride controlling agents as well as the compounds of this invention. Such assays also provide a means whereby the activities of the compounds of this invention, their prodrugs and the salts of such compounds and prodrugs (or the other agents described herein) can be compared to each other and with the activities of other known compounds. The results of these comparisons are useful for determining dosage levels in mammals, including humans, for the treatment of such diseases.

The following protocols can of course be varied by those skilled in the art.

The hyperalphacholesterolemic activity of the compounds can be determined by assessing the effect of these compounds on the action of cholesteryl ester transfer protein by measuring the relative transfer ratio of radiolabeled lipids between lipoprotein fractions, essentially as previously described by Morton in *J. Biol. Chem.* 256, 11992, 1981 and by Dias in *Clin. Chem.* 34, 2322, 1988.

CETP IN VITRO ASSAY

The following is a brief description of assays of cholesteryl ester transfer in 97% (whole) or diluted human plasma (*in vitro*) and animal plasma (*ex vivo*): CETP activity in the presence or absence of drug is assayed by determining the transfer of ^3H -labeled cholesteryl oleate (CO) from exogenous tracer HDL or LDL to the nonHDL or HDL lipoprotein fraction in human plasma, respectively, or from ^3H -labeled LDL to the HDL fraction in animal plasma. Labeled human lipoprotein substrates are prepared similarly to the method described by Morton in which the endogenous CETP activity in plasma is employed to transfer ^3H -CO from phospholipid liposomes to all the lipoprotein fractions in plasma. ^3H -labeled LDL and HDL are subsequently isolated by sequential ultracentrifugation at the density cuts of 1.019-1.063 and 1.10-1.21 g/ml, respectively.

For the 97% or whole plasma activity assay, ^3H -labeled HDL is added to plasma at 10-25 nmoles CO/ml and the samples incubated at 37° C for 2.5-3 hrs. Non-HDL lipoproteins are then precipitated by the addition of an equal volume of 20% (wt/vol) polyethylene glycol 8000 (Dias). The samples are centrifuged 750 g x 20 minutes and the radioactivity contained in the HDL-containing supernatant determined by liquid scintillation counting. Introducing varying quantities of the compounds of this invention as a solution in dimethylsulfoxide into human plasma, before addition of the radiolabeled cholesteryl oleate, and comparing the amounts of radiolabel transferred compared to incubations containing no inhibitor compounds allows the cholesteryl ester transfer inhibitory activities to be determined.

When a more sensitive assay is desirable, an *in vitro* assay using diluted human plasma is utilized. For this assay, ^3H -labeled LDL is added to plasma at 50 nmoles CO/ml and the samples incubated at 37° C for 7 hrs. Non-HDL lipoproteins are then precipitated by the addition of potassium phosphate to 100 mM final concentration followed by manganese chloride to 20 mM final concentration. After vortexing, the samples are centrifuged 750 g x 20 minutes and the radioactivity contained in the HDL-containing supernatant determined by liquid scintillation counting. Introducing varying quantities of the compounds of this invention as a solution in dimethylsulfoxide into diluted human plasma, before addition of the radiolabeled cholesteryl oleate, and comparing the amounts of radiolabel transferred compared to incubations containing no inhibitor compounds allows the cholesteryl ester transfer inhibitory activities to be determined. This assay has been adapted to run in microtiter plate format with liquid scintillation counting accomplished using a Wallac plate reader.

CETP IN VIVO ASSAY

Activity of these compounds *in vivo* can be determined by the amount of agent required to be administered, relative to control, to inhibit cholesteryl ester transfer activity by 50% at various time points *ex vivo* or to elevate HDL cholesterol by a given percentage in a CETP-containing animal species.

Transgenic mice expressing both human CETP and human apolipoprotein AI (Charles River, Boston, MA) may be used to assess compounds *in vivo*. The compounds to be examined are administered by oral gavage in an emulsion vehicle containing 20% (v:v) olive oil and 80% sodium taurocholate (0.5%). Blood is taken from mice retroorbitally before dosing, if a predose blood sample is desirable. At various times after dosing, ranging from 4h to 24h, the animals are sacrificed, blood obtained by heart puncture, and lipid parameters measured, including total cholesterol, HDL and LDL cholesterol, and triglycerides. CETP activity is determined by a method similar to that described above except that ^3H -cholesteryl

oleate-containing LDL is used as the donor source as opposed to HDL. The values obtained for lipids and transfer activity are compared to those obtained prior to dosing and/or to those from mice receiving vehicle alone.

PLASMA LIPIDS ASSAY

5 The activity of these compounds may also be demonstrated by determining the amount of agent required to alter plasma lipid levels, for example HDL cholesterol levels, LDL cholesterol levels, VLDL cholesterol levels or triglycerides, in the plasma of certain mammals, for example marmosets that possess CETP activity and a plasma lipoprotein profile similar to that of humans (Crook et al. Arteriosclerosis 10, 625, 1990). Adult marmosets are assigned to treatment groups so that each group
10 has a similar mean $\pm$ SD for total, HDL, and/or LDL plasma cholesterol concentrations. After group assignment, marmosets are dosed daily with compound as a dietary admix or by intragastric intubation for from one to eight days. Control marmosets receive only the dosing vehicle. Plasma total, LDL VLDL and HDL cholesterol values can be determined at any point during the study by obtaining blood from an antecubital vein and separating plasma lipoproteins into their individual subclasses by density gradient
15 centrifugation, and by measuring cholesterol concentration as previously described (Crook et al. Arteriosclerosis 10, 625, 1990).

IN VIVO ATHEROSCLEROSIS ASSAY

Anti-atherosclerotic effects of the compounds can be determined by the amount of compound required to reduce the lipid deposition in rabbit aorta. Male New Zealand White rabbits are fed a diet
20 containing 0.2% cholesterol and 10% coconut oil for 4 days (meal-fed once per day). Rabbits are bled from the marginal ear vein and total plasma cholesterol values are determined from these samples. The rabbits are then assigned to treatment groups so that each group has a similar mean $\pm$ SD for total plasma cholesterol concentration, HDL cholesterol concentration, triglyceride concentration and/or cholesteryl ester transfer protein activity. After group assignment, rabbits are dosed daily with compound
25 given as a dietary admix or on a small piece of gelatin based confection. Control rabbits receive only the dosing vehicle, be it the food or the gelatin confection. The cholesterol/coconut oil diet is continued along with the compound administration throughout the study. Plasma cholesterol values and cholesteryl ester transfer protein activity can be determined at any point during the study by obtaining blood from the marginal ear vein. After 3-5 months, the rabbits are sacrificed and the aortae are removed from the
30 thoracic arch to the branch of the iliac arteries. The aortae are cleaned of adventitia, opened longitudinally and then analyzed unstained or stained with Sudan IV as described by Holman et. al. (Lab. Invest. 1958, 7, 42-47). The percent of the lesioned surface area is quantitated by densitometry using an Optimas Image Analyzing System (Image Processing Systems). Reduced lipid deposition is indicated by a reduction in the percent of lesioned surface area in the compound-receiving group in comparison with
35 the control rabbits.

ANTI-OBESITY PROTOCOL

The ability of CETP inhibitors to cause weight loss can be assessed in obese human subjects with body mass index (BMI) ≥ 30 kg/m². Doses of inhibitor are administered sufficient to result in an increase of $\geq 25\%$ in HDL cholesterol levels. BMI and body fat distribution, defined as waist (W) to hip
40 (H) ratio (WHR), are monitored during the course of the 3-6 month studies, and the results for treatment groups compared to those receiving placebo.

IN VIVO SEPSIS ASSAY

In vivo studies show that transgenic mice expressing human apo-AI and elevated HDL levels are protected from septic shock. Thus the ability of CETP inhibitors to protect from septic shock can be demonstrated in transgenic mice expressing both human apo-AI and human CETP transgenes (Levine, D. M., Parker, T.S., Donnelly, T. M., Walsh, A. M. and Rubin, A.L., 1993. Proc. Natl. Acad. Sci. 90, 12040-44). LPS derived from *E. coli* is administered at 30mg/kg by i.p. injection to animals which have been administered a CETP inhibitor at an appropriate dose to result in elevation of HDL. The number of surviving mice is determined at times up to 48h after LPS injection and compared to those mice administered vehicle (minus CETP inhibitor) only.

Administration of the compounds of this invention can be via any method which delivers a compound of this invention systemically and/or locally. These methods include oral routes, parenteral, intraduodenal routes, etc. Generally, the compounds of this invention are administered orally, but parenteral administration (e.g., intravenous, intramuscular, subcutaneous or intramedullary) may be utilized, for example, where oral administration is inappropriate for the target or where the patient is unable to ingest the drug.

In general an amount of a compound of this invention is used that is sufficient to achieve the therapeutic effect desired (e.g., HDL elevation).

In general an effective dosage for the compounds of this invention is about 0.001 to 100 mg/kg/day of the compound, a prodrug thereof, or a pharmaceutically acceptable salt of said compound or of said prodrug. An especially preferred dosage is about 0.01 to 10 mg/kg/day of the compound, a prodrug thereof, or a pharmaceutically acceptable salt of said compound or of said prodrug.

A dosage of the combination pharmaceutical agents to be used in conjunction with the CETP inhibitors is used that is effective for the indication being treated.

For example, typically an effective dosage for HMG-CoA reductase inhibitors is in the range of 0.01 to 100 mg/kg/day. In general an effect dosage for a PPAR modulator is in the range of 0.01 to 100 mg/kg/day.

The compounds of the present invention are generally administered in the form of a pharmaceutical composition comprising at least one of the compounds of this invention together with a pharmaceutically acceptable vehicle, diluent or carrier as described below. Thus, the compounds of this invention can be administered individually or together in any conventional oral, parenteral, rectal or transdermal dosage form.

For oral administration a pharmaceutical composition can take the form of solutions, suspensions, tablets, pills, capsules, powders, and the like. Tablets containing various excipients such as sodium citrate, calcium carbonate and calcium phosphate are employed along with various disintegrants such as starch and preferably potato or tapioca starch and certain complex silicates, together with binding agents such as polyvinylpyrrolidone, sucrose, gelatin and acacia. Additionally, lubricating agents such as magnesium stearate, sodium lauryl sulfate and talc are often very useful for tableting purposes. Solid compositions of a similar type are also employed as fillers in soft and hard-filled gelatin capsules; preferred materials in this connection also include lactose or milk sugar as well as high molecular weight polyethylene glycols. A preferred formulation is a solution or suspension in an oil, for example, a vegetable oil, such as olive oil; triglycerides such as those marketed under the name, Miglyol™; or

mono- or diglycerides such as those marketed under the name, Capmul™, for example, in a soft gelatin capsule. Antioxidants may be added to prevent long-term degradation as appropriate. When aqueous suspensions and/or elixirs are desired for oral administration, the compounds of this invention can be combined with various sweetening agents, flavoring agents, coloring agents, emulsifying agents and/or suspending agents, as well as such diluents as water, ethanol, propylene glycol, glycerin and various like combinations thereof.

Pharmaceutical compositions comprising a solid amorphous dispersion of a cholesteryl ester transfer protein (CETP) inhibitor and a concentration-enhancing polymer are described in International Publication No. WO 02/11710, which is hereby incorporated by reference herein. Self-emulsifying formulations of cholesteryl ester transfer protein (CETP) inhibitors are described in International Publication No. WO 03/000295, which is hereby incorporated by reference herein. Methods for depositing small drug crystals on excipients are set forth in the literature, such as in J. Pharm. Pharmacol. 1987, 39:769-773, which is hereby incorporated by reference herein.

For purposes of parenteral administration, solutions in sesame or peanut oil or in aqueous propylene glycol can be employed, as well as sterile aqueous solutions of the corresponding water-soluble salts. Such aqueous solutions may be suitably buffered, if necessary, and the liquid diluent first rendered isotonic with sufficient saline or glucose. These aqueous solutions are especially suitable for intravenous, intramuscular, subcutaneous and intraperitoneal injection purposes. In this connection, the sterile aqueous media employed are all readily obtainable by standard techniques well-known to those skilled in the art.

For purposes of transdermal (e.g., topical) administration, dilute sterile, aqueous or partially aqueous solutions (usually in about 0.1% to 5% concentration), otherwise similar to the above parenteral solutions, are prepared.

Methods of preparing various pharmaceutical compositions with a certain amount of active ingredient are known, or will be apparent in light of this disclosure, to those skilled in this art. For examples of methods of preparing pharmaceutical compositions, see Remington's Pharmaceutical Sciences, Mack Publishing Company, Easter, Pa., 15th Edition (1975).

Pharmaceutical compositions according to the invention may contain 0.1%-95% of the compound(s) of this invention, preferably 1%-70%. In any event, the composition or formulation to be administered will contain a quantity of a compound(s) according to the invention in an amount effective to treat the disease/condition of the subject being treated, e.g., atherosclerosis.

Since the present invention has an aspect that relates to the treatment of the disease/conditions described herein with a combination of active ingredients which may be administered separately, the invention also relates to combining separate pharmaceutical compositions in kit form. The kit comprises two separate pharmaceutical compositions: a compound of the present invention, a prodrug thereof or a salt of such compound or prodrug and a second compound as described above. The kit comprises means for containing the separate compositions such as a container, a divided bottle or a divided foil packet. Typically the kit comprises directions for the administration of the separate components. The kit form is particularly advantageous when the separate components are preferably administered in different dosage forms (e.g., oral and parenteral), are administered at different dosage intervals, or when titration of the individual components of the combination is desired by the prescribing physician.

An example of such a kit is a so-called blister pack. Blister packs are well known in the packaging industry and are being widely used for the packaging of pharmaceutical unit dosage forms (tablets, capsules, and the like). Blister packs generally consist of a sheet of relatively stiff material covered with a foil of a preferably transparent plastic material. During the packaging process recesses are formed in the plastic foil. The recesses have the size and shape of the tablets or capsules to be packed. Next, the tablets or capsules are placed in the recesses and the sheet of relatively stiff material is sealed against the plastic foil at the face of the foil which is opposite from the direction in which the recesses were formed. As a result, the tablets or capsules are sealed in the recesses between the plastic foil and the sheet. Preferably the strength of the sheet is such that the tablets or capsules can be removed from the blister pack by manually applying pressure on the recesses whereby an opening is formed in the sheet at the place of the recess. The tablet or capsule can then be removed via said opening.

It may be desirable to provide a memory aid on the kit, e.g., in the form of numbers next to the tablets or capsules whereby the numbers correspond with the days of the regimen which the tablets or capsules so specified should be ingested. Another example of such a memory aid is a calendar printed on the card, e.g., as follows "First Week, Monday, Tuesday, ...etc.... Second Week, Monday, Tuesday,..." etc. Other variations of memory aids will be readily apparent. A "daily dose" can be a single tablet or capsule or several pills or capsules to be taken on a given day. Also, a daily dose of compounds of the present invention can consist of one tablet or capsule while a daily dose of the second compound can consist of several tablets or capsules and vice versa. The memory aid should reflect this.

In another specific embodiment of the invention, a dispenser designed to dispense the daily doses one at a time in the order of their intended use is provided. Preferably, the dispenser is equipped with a memory-aid, so as to further facilitate compliance with the regimen. An example of such a memory-aid is a mechanical counter which indicates the number of daily doses that has been dispensed. Another example of such a memory-aid is a battery-powered micro-chip memory coupled with a liquid crystal readout, or audible reminder signal which, for example, reads out the date that the last daily dose has been taken and/or reminds one when the next dose is to be taken.

The compounds of this invention either alone or in combination with each other or other compounds generally will be administered in a convenient formulation. The following formulation examples only are illustrative and are not intended to limit the scope of the present invention.

In the formulations which follow, "active ingredient" means a compound of this invention.

Formulation 1: Gelatin Capsules

Hard gelatin capsules are prepared using the following:

Ingredient	Quantity (mg/capsule)
Active ingredient	0.25-100
Starch, NF	0-650
Starch flowable powder	0-50
Silicone fluid 350 centistokes	0-15

A tablet formulation is prepared using the ingredients below:

Formulation 2: Tablets

Ingredient	Quantity (mg/tablet)
Active ingredient	0.25-100
Cellulose, microcrystalline	200-650
Silicon dioxide, fumed	10-650
Stearate acid	5-15

The components are blended and compressed to form tablets.

Alternatively, tablets each containing 0.25-100 mg of active ingredients are made up as follows:

Formulation 3: Tablets

Ingredient	Quantity (mg/tablet)
Active ingredient	0.25-100
Starch	45
Cellulose, microcrystalline	35
Polyvinylpyrrolidone (as 10% solution in water)	4
Sodium carboxymethyl cellulose	4.5
Magnesium stearate	0.5
Talc	1

- 5 The active ingredients, starch, and cellulose are passed through a No. 45 mesh U.S. sieve and mixed thoroughly. The solution of polyvinylpyrrolidone is mixed with the resultant powders which are then passed through a No. 14 mesh U.S. sieve. The granules so produced are dried at 50° - 60°C and passed through a No. 18 mesh U.S. sieve. The sodium carboxymethyl starch, magnesium stearate, and talc, previously passed through a No. 60 U.S. sieve, are then added to the granules which, after mixing, are
- 10 compressed on a tablet machine to yield tablets.

Suspensions each containing 0.25-100 mg of active ingredient per 5 ml dose are made as follows:

Formulation 4: Suspensions

Ingredient	Quantity (mg/5 ml)
Active ingredient	0.25-100 mg
Sodium carboxymethyl cellulose	50 mg
Syrup	1.25 mg
Benzoic acid solution	0.10 mL
Flavor	q.v.
Color	q.v.
Purified Water to	5 mL

- 15 The active ingredient is passed through a No. 45 mesh U.S. sieve and mixed with the sodium carboxymethyl cellulose and syrup to form smooth paste. The benzoic acid solution, flavor, and color are diluted with some of the water and added, with stirring. Sufficient water is then added to produce the required volume.

An aerosol solution is prepared containing the following ingredients:

Formulation 5: Aerosol

Ingredient	Quantity (% by weight)
Active ingredient	0.25
Ethanol	25.75
Propellant 22 (Chlorodifluoromethane)	70.00

The active ingredient is mixed with ethanol and the mixture added to a portion of the propellant 22, cooled to 30°C, and transferred to a filling device. The required amount is then fed to a stainless steel container and diluted with the remaining propellant. The valve units are then fitted to the container.

5 Suppositories are prepared as follows:

Formulation 6: Suppositories

Ingredient	Quantity (mg/suppository)
Active ingredient	250
Saturated fatty acid glycerides	2,000

The active ingredient is passed through a No. 60 mesh U.S. sieve and suspended in the saturated fatty acid glycerides previously melted using the minimal necessary heat. The mixture is then poured into a suppository mold of nominal 2 g capacity and allowed to cool.

10 An intravenous formulation is prepared as follows:

Formulation 7: Intravenous Solution

Ingredient	Quantity
Active ingredient dissolved in ethanol 1%	20 mg
Intralipid™ emulsion	1,000 mL

The solution of the above ingredients is intravenously administered to a patient at a rate of about 1 mL per minute.

Soft gelatin capsules are prepared using the following:

15 Formulation 8: Soft Gelatin Capsule with Oil Formulation

Ingredient	Quantity (mg/capsule)
Active ingredient	10-500
Olive Oil or Miglyol™ Oil	500-1000

The active ingredient above may also be a combination of agents.

GENERAL EXPERIMENTAL PROCEDURES

20 The following examples are put forth so as to provide those of ordinary skill in the art with a disclosure and description of how the compounds, compositions, and methods claimed herein are made and evaluated, and are intended to be purely exemplary of the invention and are not intended to limit the scope of what the inventors regard as their invention. Unless indicated otherwise, percent is percent by weight given the component and the total weight of the composition, temperature is in °C or is at ambient temperature, and pressure is at or near atmospheric. Commercial reagents were utilized without further purification. Room or ambient temperature refers to 20-25 °C. All non-aqueous reactions were run under

25 a nitrogen atmosphere for convenience and to maximize yields. Concentration in vacuo means that a

rotary evaporator was used. The names for the compounds of the invention were created by the Autonom 2.0 PC-batch version from Beilstein Informationssysteme GmbH (ISBN 3-89536-976-4). The chemical structures depicted may be only exemplary of the general structure or of limited isomers, and not include specific stereochemistry as recited in the chemical name.

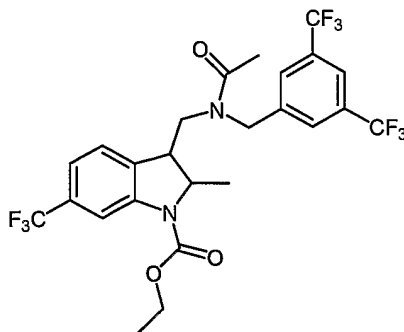
5 NMR spectra were recorded on a Varian Unity 400 (Varian Co., Palo Alto, CA) NMR spectrometer at ambient temperature. Chemical shifts are expressed in parts per million (δ) relative to an external standard (tetramethylsilane). The peak shapes are denoted as follows: s, singlet; d, doublet, t, triplet, q, quartet, m, multiplet with the prefix br indicating a broadened signal. The coupling constant (J) data given have a maximum error of ± 0.41 Hz due to the digitization of the spectra that are acquired. Mass
10 spectra were obtained by (1) atmospheric pressure chemical ionization (APCI) in alternating positive and negative ion mode using a Fisons Platform II Spectrometer or a Micromass MZD Spectrometer (Micromass, Manchester, UK) or (2) electrospray ionization in alternating positive and negative ion mode using a Micromass MZD Spectrometer (Micromass, Manchester, UK) with a Gilson LC-MS interface (Gilson Instruments, Middleton, WI) or (3) a QP-8000 mass spectrometer (Shimadzu Corporation, Kyoto,
15 Japan) operating in positive or negative single ion monitoring mode, utilizing electrospray ionization or atmospheric pressure chemical ionization. Where the intensity of chlorine- or bromine-containing ions are described, the expected intensity ratio was observed (approximately 3:1 for $^{35}\text{Cl}/^{37}\text{Cl}$ -containing ions and 1:1 for $^{79}\text{Br}/^{81}\text{Br}$ -containing ions) and the position of only the lower mass ion is given.

Column chromatography was performed with either Baker Silica Gel (40 μm) (J.T. Baker,
20 Phillipsburg, N.J.) or Silica Gel 60 (40-63 μm) (EM Sciences, Gibbstown, N.J.). Flash chromatography was performed using a Flash 12 or Flash 40 column (Biotage, Dyar Corp., Charlottesville, VA). Radial chromatography was performed using a chromatotron Model 7924T (Harrison Research, Palo Alto, CA). Preparative HPLC purification was performed on a Shimadzu 10A preparative HPLC system (Shimadzu Corporation, Kyoto, Japan) using a model SIL-10A autosampler and model 8A HPLC pumps. Preparative
25 HPLC-MS was performed on an identical system, modified with a QP-8000 mass spectrometer operating in positive or negative single ion monitoring mode, utilizing electrospray ionization or atmospheric pressure chemical ionization. Elution was carried out using water/acetonitrile gradients containing either 0.1% formic acid or ammonium hydroxide as a modifier. In acidic mode, typical columns used include Waters Symmetry C8, 5 μm , 19x50mm or 30x50mm, Waters XTerra C18, 5 μm , 50x50 (Waters Corp,
30 Milford, MA) or Phenomenex Synergi Max-RP 4 μm , 50x50mm (Phenomenex Inc., Torrance, CA). In basic mode, the Phenomenex Synergi Max-RP 4 μm , 21.2x50mm or 30x50mm columns (Phenomenex Inc., Torrance, CA) were used.

Optical rotations were determined using a Jasco P-1020 Polarimeter Jasco Inc., Easton, MD)

Dimethylformamide ("DMF"), tetrahydrofuran ("THF"), toluene and dichloromethane ("DCM") were
35 the anhydrous grade supplied by Aldrich Chemical Company (Milwaukee, WI). Unless otherwise specified, reagents were used as obtained from commercial sources. The terms "concentrated" and "evaporated" refer to removal of solvent at 1-200 mm of mercury pressure on a rotary evaporator with a bath temperature of less than 45°C. The abbreviation "min" stand for "minutes" and "h" or "hr" stand for "hours." The abbreviation "gm" or "g" stand for grams. The abbreviation " μl " or " μL " stand for microliters.

Example 1: Ethyl 3-((N-(3,5-bis(trifluoromethyl)benzyl)acetamido)methyl)-6-(trifluoromethyl)-2-methylindoline-1-carboxylate



Step 1: Preparation of Intermediate diethyl 2-(2-amino-4-(trifluoromethyl)phenyl)malonate

- 5 To diethyl 2-(4-(trifluoromethyl)-2-nitrophenyl)malonate (5.0 g) in ethanol (100 mL) was added PtO_2 (0.5 g). The mixture was hydrogenated on a Parr shaker at 45 psi for 1 hour and filtered through diatomaceous earth. The filtrate was concentrated in vacuo to yield the title compound as a liquid (4.4 g).

^1H NMR (400 MHz, CHCl_3 - d_3) δ ppm 1.3 (m, 6 H) 4.2 (m, 4 H) 4.6 (s, 1 H) 6.9 (s, 1 H) 7.0 (d, $J=7.9$ Hz, 1 H) 7.3 (d, $J=4.6$ Hz, 1 H); MS (ES^+) Calc: 168.03, Found: (M+1).

10 Step 2: Preparation of Intermediate diethyl 6-(trifluoromethyl)-2-methylindoline-3,3-dicarboxylate

- To a solution of diethyl 2-(2-amino-4-(trifluoromethyl)phenyl)malonate (4.4 g, 13.78 mmol) in methanol (30 mL) was added acetaldehyde (0.759 g, 17.23 mmol). The mixture was stirred at room temperature for 20 minutes, zinc acetate (1 g, 5.2 mmol) was added and the mixture was stirred at room temperature for 1 hour. Solvent was removed in vacuo. The residue was diluted with water, and ethyl acetate was added. The precipitate was filtered and the filtrate was extracted with ethyl acetate. The organic layer was washed with water, brine, dried (MgSO_4), filtered and concentrated in vacuo to yield the title compound as an oil (3.6 g, 76%).

^1H NMR (400 MHz, CHCl_3 - d_3) δ ppm 1.3 (m, 9 H) 4.2 (m, 4 H) 4.7 (q, $J=6.6$ Hz, 1 H) 6.9 (s, 1 H) 7.0 (d, $J=7.9$ Hz, 1 H) 7.5 (d, $J=7.9$ Hz, 1 H); MS (ES^+) Calc: 345.12, Found: 346.4 (M+1).

20 Step 3: Preparation of Intermediate triethyl 6-(trifluoromethyl)-2-methylindoline-1,3,3-tricarboxylate

- A mixture of diethyl 6-(trifluoromethyl)-2-methylindoline-3,3-dicarboxylate (1.8 g, 5.21 mmol) and 20 % phosgene in toluene (6.6 g, 10.42 mmol) in toluene (35 mL) was heated at reflux overnight. Solvent was removed in vacuo. The residue was dissolved in ethanol (30 mL) and heated at reflux for 2 days. The mixture was concentrated in vacuo and the residue was purified by flash chromatography (eluted with 5% acetone in hexane) to afford the title compound as a pale yellow oil (1.28 g, 59%).

^1H NMR (400 MHz, CHCl_3 - d_3) δ ppm 1.2 (t, $J=7.1$ Hz, 3 H) 1.2 (d, $J=6.6$ Hz, 3 H) 1.3 (t, $J=7.1$ Hz, 3 H) 1.4 (t, $J=7.1$ Hz, 3 H) 4.2 (m, 6 H) 5.3 (q, $J=7.1$ Hz, 1 H) 7.3 (s, 1 H) 7.3 (d, $J=7.9$ Hz, 1 H) 7.6 (d, $J=7.9$ Hz, 1 H); MS (ES^+) Calc: 417.14, Found: (M+1).

Step 4: Preparation of 1-(ethoxycarbonyl)-6-(trifluoromethyl)-2-methylindoline-3-carboxylic acid

- 30 To a solution of triethyl 6-(trifluoromethyl)-2-methylindoline-1,3,3-tricarboxylate (1.28 g, 3.07 mmol) in ethanol (50 mL) at 0°C and was added 10% aq. KOH solution (8 mL). The mixture was stirred at 0°C for 5 minutes, room temperature for 1 hour, acidified with 1N HCl, diluted with water and extracted with ethyl acetate. The organic layer was extracted with water, brine, dried (MgSO_4), filtered and concentrated in vacuo to yield the title compound as an oil (1.03 g).

¹H NMR (400 MHz, CHLOROFORM-D) δ ppm 1.4 (t, J=7.1 Hz, 3 H) 1.4 (d, J=6.6 Hz, 3 H) 3.7 (s, 1 H) 4.3 (m, 2 H) 4.9 (m, 1 H) 7.3 (s, 1 H) 7.3 (d, J=7.9 Hz, 1 H) 7.5 (d, J=7.9 Hz, 1 H) 8.1 (bs, 1 H); MS (ES⁺) Calc: 317.19, Found: 316.2 (M-1).

Step 5: Preparation of Intermediate ethyl 6-(trifluoromethyl)-3-(hydroxymethyl)-2-methylindoline-1-carboxylate

To a solution of 1-(ethoxycarbonyl)-6-(trifluoromethyl)-2-methylindoline-3-carboxylic acid (0.577 g, 1.82 mmol) in THF (5 mL) at 0°C was added 1.0 M borane in THF (3.64 mL, 3.64 mmol). The resulting mixture was stirred at 0°C for 15 minutes, at room temperature overnight and quenched with 10% CH₃CO₂H/methanol (2 mL). Solvent was removed in vacuo and the residue was purified by flash chromatography (eluted with 10% acetone in hexanes) to afford the title compound as a pale yellow oil (510 mg).

¹H NMR (400 MHz, CHLOROFORM-D) δ ppm 1.3 (d, J=6.2 Hz, 3 H) 1.4 (t, J=6.2 Hz, 3 H) 3.0 (t, J=6.2 Hz, 1 H) 3.7 (m, 2 H) 4.3 (m, 2 H) 4.4 (q, J=5.9 Hz, 1 H) 7.3 (d, J=5.8 Hz, 1 H) 7.3 (s, 1 H) 7.3 (d, J=7.5 Hz, 1 H); MS (ES⁺) Calc: 303.11, Found: 304.4 (M+1).

Step 6 : Preparation of Intermediate ethyl 6-(trifluoromethyl)-3-formyl-2-methylindoline-1-carboxylate

A mixture of ethyl 6-(trifluoromethyl)-3-(hydroxymethyl)-2-methylindoline-1-carboxylate (0.128 g, 0.422 mmol) and Dess-Martin periodinane (0.268 g, 0.633 mmol) in methylene chloride (5 mL) was stirred at room temperature for 2.5 hours. The mixture was extracted with methylene chloride, washed with 1N NaOH, water, brine, dried (MgSO₄) and concentrated in vacuo to yield the title compound as an oil (150 mg).

¹H NMR (400 MHz, CHLOROFORM-D) δ ppm 1.39 (t, J=7.1 Hz, 3 H) 1.41 (d, J=6.6 Hz, 3 H) 3.6 (m, 1 H) 4.3 (q, J=7.5 Hz, 2 H) 5.0 (m, 1 H) 7.26 (s, 1 H) 7.32 (d, J=6.6 Hz, 1 H) 7.4 (d, J=7.9 Hz, 1 H) 9.6 (s, 1 H); MS (ES⁺) Calc: 301.09, Found: (M+1).

Step 7: Preparation of Intermediate ethyl 3-((3,5-bis(trifluoromethyl)benzylamino)methyl)-6-(trifluoromethyl)-2-methylindoline-1-carboxylate

To a solution of ethyl 6-(trifluoromethyl)-3-formyl-2-methylindoline-1-carboxylate (0.150 g, 0.498 mmol) in 95:5 THF/AcOH was added 3,5-Bis(trifluoromethyl)benzylamine (0.167 g, 0.548 mmol) followed by sodium cyanoborohydride (0.078 g, 1.25 mmol). The mixture was stirred at room temperature overnight, diluted with water, basified with 1N NaOH and extracted with ethyl acetate. The organic layer was washed with water, brine, dried (MgSO₄), filtered and concentrated in vacuo. The residue was purified by flash chromatography (eluted with 5-10% acetone in hexanes) to afford the title compound as a colorless oil (72.2 mg).

¹H NMR (400 MHz, CHLOROFORM-D) δ ppm 1.3 (d, J=6.2 Hz, 3 H) 1.4 (t, J=6.8 Hz, 3 H) 2.7 (d, J=6.6 Hz, 2 H) 3.0 (t, J=6.2 Hz, 1 H) 3.9 (s, 2 H) 4.3 (m, 2 H) 4.4 (m, 1 H) 7.3 (m, 2 H) 7.8 (m, 3 H) 8.2 (s, 1 H); MS (ES⁺) Calc: 528.15, Found: 529.4 (M+1).

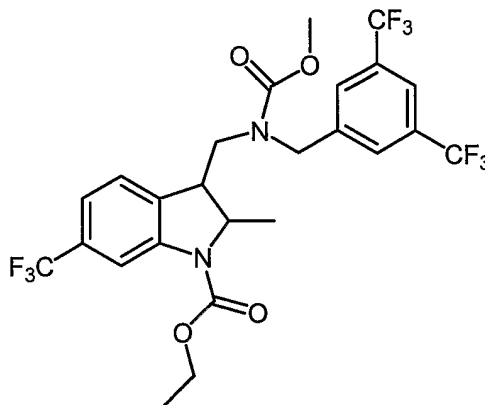
Step 8: Preparation of ethyl 3-((N-(3,5-bis(trifluoromethyl)benzyl)acetamido)methyl)-6-(trifluoromethyl)-2-methylindoline-1-carboxylate

To a solution of ethyl 3-((3,5-bis(trifluoromethyl)benzylamino)methyl)-6-(trifluoromethyl)-2-methylindoline-1-carboxylate (36 mg, 0.068 mmol) and pyridine (16 mg, 0.204 mmol) in methylene chloride was added acetyl chloride (8 mg, 0.102 mmol). The mixture was stirred at room temperature

overnight, diluted with methylene chloride, washed with 1N HCl, brine, dried (MgSO₄), filtered and concentrated in vacuo. The residue was purified by flash chromatography (eluted with 10% acetone in hexanes) to afford the title compound as a colorless oil (27.5 mg).

¹H NMR (400 MHz, CHLOROFORM-D) δ ppm 1.3 (d, J=6.6 Hz, 3 H) 1.4 (m, 3 H) 1.82, 2.16 (s, 3 H) 3.1, 3.47 (t, J=6.6 Hz, 1 H) 4.33 (m, 3 H) 4.6, 4.9 (d, J=15.4 Hz, 1 H) 7.1 (d, J=7.5 Hz, 1 H) 7.3 (m, 1 H) 7.5 (s, 1 H) 7.7 (s, 1 H) 7.8 (s, 1 H) 8.2 (s, 1 H); MS (ES⁺) Calc: 570.16, Found: 571.4 (M+1).

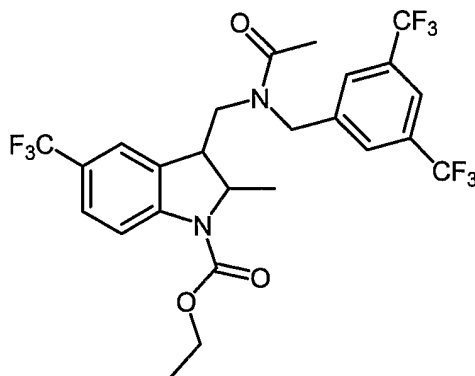
Example 2: Methyl (1-(ethoxycarbonyl)-6-(trifluoromethyl)-2-methylindolin-3-yl)methyl-3,5-bis(trifluoromethyl)benzylcarbamate



To a solution of ethyl 3-((3,5-bis(trifluoromethyl)benzylamino)methyl)-6-(trifluoromethyl)-2-methylindoline-1-carboxylate from example 1 (36 mg, 0.068 mmol) and pyridine (16 mg, 0.204 mmol) in methylene chloride was added methylchloroformate (9.7 mg, 0.102 mmol). The mixture was stirred at room temperature overnight, diluted with methylene chloride, washed with 1N HCl, water, brine, dried (MgSO₄), and concentrated in vacuo. The residue was purified by flash chromatography (eluted with 10% acetone in hexanes) to afford the title compound (29.2 mg).

¹H NMR (400 MHz, CHLOROFORM-D) δ ppm 1.2 (m, 3 H) 1.4 (m, 3 H) 3.19-3.45 (m, 3 H) 3.7 (s, 3 H) 4.24-4.36 (m, 4 H) 4.6 (m, 1 H) 7.19 (s, 1 H) 7.24 (s, 1 H) 7.6 (m, 2 H) 7.8 (s, 1 H) 8.2 (s, 1 H) MS (ES⁺) Calc: 586.15, Found: 587.4 (M+1).

Example 3: Ethyl 3-((N-(3,5-bis(trifluoromethyl)benzyl)acetamido)methyl)-5-(trifluoromethyl)-2-methylindoline-1-carboxylate



Step 1: Preparation of intermediate diethyl 2-(5-(trifluoromethyl)-2-nitrophenyl)malonate

A mixture of 2-chloro-4-(trifluoromethyl)-1-nitrobenzene (10 g, 44.33 mmol), diethylmalonate (9.94 mmol, 62.06 mmol) and potassium carbonate (13.5 g, 97.53 mmol) in DMF (25 mL) was heated at reflux for 2 days. The reaction mixture was cooled and slowly poured into water. The mixture was then acidified with 2N HCl, and extracted with ether. The combined organic layers were washed with water, brine, dried (MgSO₄), filtered and concentrated in vacuo. The residue was chromatographed over silica gel (eluted with 5% ethyl acetate in hexanes) to afford the title compound as a pale yellow liquid (13.8 g, 89%).

¹H NMR (400 MHz, CHLOROFORM-D) δ ppm 1.3 (t, J=7.5 Hz, 6 H) 4.3 (q, J=7.2 Hz, 4 H) 5.3 (s, 1 H) 7.8 (d, J=8.7 Hz, 1 H) 7.8 (s, 1 H) 8.1 (d, J=8.3 Hz, 1 H); MS (ES⁺) Calc: 349.08, Found: 350.4 (M+1).

Step 2: Preparation of intermediate diethyl 2-(2-amino-5-(trifluoromethyl)phenyl)malonate

To a solution of diethyl 2-(5-(trifluoromethyl)-2-nitrophenyl)malonate (6.8 g) in ethanol (100 mL) was added PtO₂ (0.6 g). The mixture was hydrogenated on a Parr shaker at 45 psi for 1 hour. The mixture was filtered through Celite. The filtrate was concentrated in vacuo to yield the title compound as a colorless oil (6.0g).

¹H NMR (400 MHz, CHLOROFORM-D) δ ppm 1.3 (t, J=7.1 Hz, 6 H) 4.3 (m, 4 H) 4.6 (s, 1 H) 6.7 (d, J=8.3 Hz, 1 H) 7.37 (d, J=8.3 Hz, 1 H) 7.39 (s, 1 H); MS (ES⁺) Calc: 319.1, Found: 320.4 (M+1).

Step 3: Preparation of intermediate diethyl 5-(trifluoromethyl)-2-methylindoline-3,3-dicarboxylate

To a solution of diethyl 2-(2-amino-5-(trifluoromethyl)phenyl)malonate (6.0 g, 18.79 mmol) in methanol was added acetaldehyde (1.03 g, 23.49 mmol). The mixture was stirred at room temperature for 20 minutes, and zinc acetate (1.38 g, 7.52 mmol) was added. The resulting mixture was stirred at room temperature for 1 hour. Solvent was removed in vacuo. The residue was extracted into ethyl acetate and washed with water, brine, dried (MgSO₄), filtered and concentrated in vacuo to give the title compound as a dark oil (6.5 g).

¹H NMR (400 MHz, CHLOROFORM-D) δ ppm 1.3 (m, 9H) 4.3 (m, 4 H) 4.7 (q, J=6.5 Hz, 1 H) 6.6 (d, J=8.3 Hz, 1 H) 7.4 (d, J=7.1 Hz, 1 H) 7.7 (s, 1 H); MS (ES⁺) Calc: 345.12, Found: 346.6 (M+1).

Step 4: Preparation of intermediate diethyl 1-(chlorocarbonyl)-5-(trifluoromethyl)-2-methylindoline-3,3-dicarboxylate

To a solution of diethyl 5-(trifluoromethyl)-2-methylindoline-3,3-dicarboxylate (6.5 g, 18.54 mmol) in toluene (125 mL) was added 20% phosgene in toluene (25 mL, 37.08 mmol). The mixture was heated at 110°C overnight. The mixture was concentrated in vacuo to yield the title compound as a dark oil (7.06 g, 94%).

¹H NMR (400 MHz, CHLOROFORM-D) δ ppm 1.3 (m, 9 H) 4.3 (m, 4 H) 5.6 (q, J=6.6 Hz, 1 H) 7.6 (d, J=8.7 Hz, 1 H) 7.9 (s, 1 H) 7.9 (d, J=8.7 Hz, 1 H)

Step 5: Preparation of intermediate triethyl 5-(trifluoromethyl)-2-methylindoline-1,3,3-tricarboxylate

Diethyl 1-(chlorocarbonyl)-5-(trifluoromethyl)-2-methylindoline-3,3-dicarboxylate (3.46 g) in ethanol (50 mL) was heated at reflux for 48 hours. Solvent was removed in vacuo and the residue was purified by flash chromatography (eluted with 5% acetone in hexanes) to afford the title compound as a pale yellow oil (1.83 g, 52%).

¹H NMR (400 MHz, CHLOROFORM-D) δ ppm 1.2 (d, J=5.4 Hz, 3 H) 1.3 (t, J=6.2 Hz, 3 H) 1.3 (t, J=7.1 Hz, 3 H) 1.4 (t, J=7.3 Hz, 3 H) 4.2 (m, 6 H) 5.3 (q, J=6.6 Hz, 1 H) 7.6 (d, J=8.7 Hz, 1 H) 7.77 (s, 1 H) 7.8 (s, 1 H); MS (ES⁺) Calc: 417.14, Found: 418.14 (M+1).

Step 6: Preparation of intermediate 1-(ethoxycarbonyl)-5-(trifluoromethyl)-2-methylindoline-3-carboxylic acid

To a solution of triethyl 5-(trifluoromethyl)-2-methylindoline-1,3,3-tricarboxylate (1.83 g, 4.39 mmol) in ethanol (50 mL) at 0°C was added 10% KOH (10 mL). The mixture was stirred at 0°C for 5 minutes and then at room temperature for 1.5 hours. Solvent was removed in vacuo. The residue was acidified with 1N HCl, diluted with water and extracted with ethyl acetate. The organic layer was washed with water, brine, dried (MgSO₄), filtered and concentrated in vacuo to yield the title compound as an oil (0.93 g, 67%).

¹H NMR (400 MHz, CHLOROFORM-D) δ ppm 1.38 (t, J=7.1 Hz, 3 H) 1.4 (d, J=6.6 Hz, 3 H) 3.7 (d, J=2.5 Hz, 1 H) 4.3 (m, 2 H) 5.0 (m, 1 H) 7.55 (d, J=8.7 Hz, 1 H) 7.64 (s, 1 H) 7.8 (m, 1 H)

Step 7: Preparation of intermediate ethyl 5-(trifluoromethyl)-3-(hydroxymethyl)-2-methylindoline-1-carboxylate

To a solution of 1-(ethoxycarbonyl)-5-(trifluoromethyl)-2-methylindoline-3-carboxylic acid (0.5 g, 1.58 mmol) in THF (4 mL) at 0°C was added BH₃·THF complex (3.15 mL of 1M solution in THF, 3.15 mmol). The mixture was stirred at 0°C for 5 minutes and then at room temperature overnight. The reaction was then quenched with 10% acetic acid in methanol (3 mL) and concentrated in vacuo. The residue was purified by flash chromatography (eluted with 10% acetone in hexanes) to yield the title compound as a colorless oil (283 mg).

¹H NMR (400 MHz, CHLOROFORM-D) δ ppm 1.3 (d, J=6.2 Hz, 3 H) 1.4 (t, J=7.1 Hz, 3 H) 3.0 (t, J=6.0 Hz, 1 H) 3.7 (m, 2 H) 4.3 (m, 2 H) 4.5 (m, 1 H) 7.5 (s, 1 H) 7.5 (d, J=8.3 Hz, 1 H) 7.9 (s, 1 H)

Step 8: Preparation of intermediate ethyl 5-(trifluoromethyl)-3-formyl-2-methylindoline-1-carboxylate

A mixture of ethyl 5-(trifluoromethyl)-3-(hydroxymethyl)-2-methylindoline-1-carboxylate (0.273 g, 0.9 mmol) and Dess-Martin periodane (0.573 g, 1.35 mmol) in methylene chloride (7 mL) at room temperature was stirred for 2.5 hours. The reaction mixture was then extracted into methylene chloride, washed with 1N NaOH, water, brine, dried (MgSO₄), filtered and concentrated in vacuo to yield the title compound as a colorless oil (268 mg).

¹H NMR (400 MHz, CHLOROFORM-D) δ ppm 1.39 (t, J=7.1 Hz, 3 H) 1.41 (d, J=6.2 Hz, 3 H) 3.6 (s, 1 H) 4.4 (m, 2 H) 5.0 (m, 1 H) 7.6 (m, 2 H) 7.9 (s, 1 H) 9.6 (s, 1 H)

Step 9: Preparation of intermediate ethyl 3-((3,5-bis(trifluoromethyl)benzylamino)methyl)-5-(trifluoromethyl)-2-methylindoline-1-carboxylate

To a solution of ethyl 5-(trifluoromethyl)-3-formyl-2-methylindoline-1-carboxylate (0.134 g, 0.445 mmol) in 95:5 THF/AcOH (7 mL) at room temperature was added 3,5-bis(trifluoromethyl)benzylamine (0.149 g, 0.489 mmol) followed by sodium cyanoborohydride (0.07 g, 1.13 mmol). The mixture was stirred at room temperature overnight, then diluted with water, basified with 1N NaOH and extracted with ethyl acetate. The organic layer was washed with water, brine, dried (MgSO₄), filtered and concentrated in vacuo. The residue was purified by flash chromatography (eluted with 5-10% acetone in hexanes) to give the title compound as a colorless oil (98 mg).

¹H NMR (400 MHz, CHLOROFORM-D) δ ppm 1.3 (d, J=6.2 Hz, 3 H) 1.4 (t, J=7.1 Hz, 3 H) 2.8 (d, J=6.6 Hz, 2 H) 3.0 (s, 1 H) 3.9 (s, 2 H) 4.3 (m, 2 H) 4.4 (m, 1 H) 7.4 (s, 1 H) 7.5 (d, J=8.7 Hz, 1 H) 7.8 (m, 3 H) 7.9 (m, 1 H); MS (ES⁺) Calc: 528.15, Found: 529.4 (M+1).

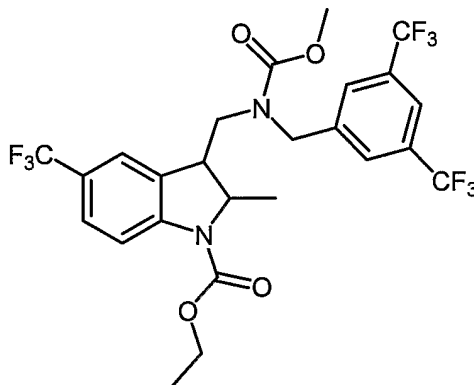
Step 10: Preparation of ethyl 3-((N-(3,5-bis(trifluoromethyl)benzyl)acetamido)methyl)-5-(trifluoromethyl)-

5 2-methylindoline-1-carboxylate

To a solution of ethyl 3-((3,5-bis(trifluoromethyl)benzylamino)methyl)-5-(trifluoromethyl)-2-methylindoline-1-carboxylate (49 mg, 0.093 mmol) and pyridine (22 mg, 0.278 mmol) in methylene chloride (1 mL) at room temperature was added acetyl chloride (11 mg, 0.139 mmol). The mixture was stirred at room temperature overnight, diluted with methylene chloride, washed with 1N HCl, water, brine, dried (MgSO₄), filtered and concentrated in vacuo. The residue was purified by flash chromatography (eluted with 10% acetone in hexanes) to give the title compound as a colorless oil (37.7 mg).

¹H NMR (400 MHz, CHLOROFORM-D) δ ppm 1.18, 1.28 (d, J=6.2 Hz, 3 H) 1.4 (m, 3 H) 1.91, 2.15 (s, 3 H) 3.0 (t, J=8.3 Hz, 1 H) 3.3 (m, 2 H) 4.4 (m, 4 H) 4.7, 4.8 (d, J=15.8 Hz, 1 H) 7.28, 7.34 (s, 1 H) 7.5 (s, 1 H) 7.6 (d, J=7.9 Hz, 1 H) 7.7 (s, 1 H) 7.8 (s, 1 H) 8.0 (s, 1 H); MS (ES⁺) Calc: 570.16, Found: 571.4 (M+1).

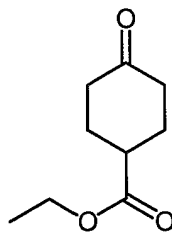
Example 4: Methyl (1-(ethoxycarbonyl)-5-(trifluoromethyl)-2-methylindolin-3-yl)methyl-3,5-bis(trifluoromethyl)benzyl-carbamate



To a solution of ethyl 3-((3,5-bis(trifluoromethyl)benzylamino)methyl)-5-(trifluoromethyl)-2-methylindoline-1-carboxylate (49 mg, 0.093 mmol) and pyridine (22 mg, 0.278 mmol) in methylene chloride (1 mL) at room temperature was added methylchloroformate (13 mg, 0.139 mmol). The mixture was stirred at room temperature overnight, diluted with methylene chloride, washed with 1N HCl, water, brine, dried (MgSO₄), filtered and concentrated in vacuo. The residue was purified by flash chromatography (eluted with 10% acetone in hexanes) to give the title compound as a colorless oil (41.8 mg).

¹H NMR (400 MHz, CHLOROFORM-D) δ ppm 1.2 (m, 3 H) 1.3 (m, 3 H) 3.3 (m, 3 H) 3.7 (s, 3 H) 4.3 (m, 4 H) 4.6 (m, 1 H) 7.3 (s, 1 H) 7.6 (m, 3 H) 7.8 (s, 1 H) 8.0 (s, 1 H); MS (ES⁺) Calc: 586.15, Found: 587.4 (M+1).

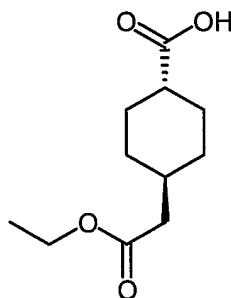
Preparation 1: Ethyl 4-oxocyclohexanecarboxylate



In a 5 L 3-neck flask, fitted with a mechanical stirrer and gas outlet was added ethyl 4-hydroxycyclohexanecarboxylate (167.3 g, 0.971 mol) and methylene chloride (2 L) followed by Celite (275 g). The resulting mixture was cooled in an ice bath and pyridium chlorochromate (272.3 g, 1.26 mol) was added in portions over 20 min. The mixture was stirred at room temperature for 1.5 hours, filtered through a plug of Celite, and rinsed with methylene chloride (2 L). The filtrate was concentrated in vacuo and the residue was chromatographed over a Biotage 75L column (eluted with 20% ethyl acetate in hexanes) to afford the title compound as a colorless liquid (165.5 g).

¹H NMR (400 MHz, CHLOROFORM-D) δ ppm 1.3 (t, J=7.3 Hz, 3 H) 2.0 (m, 2 H) 2.2 (m, 2 H) 2.3 (m, 2 H) 2.5 (m, 2 H) 2.7 (m, 1 H) 4.2 (q, J=7.1 Hz, 2 H)

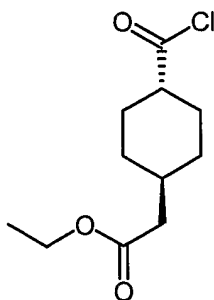
Preparation 2: (1R,4R)-4-((ethoxycarbonyl)methyl)cyclohexanecarboxylic acid



In a 3 L 3-neck flask fitted with addition funnel, thermometer and reflux condenser was added ethyl 4-oxocyclohexanecarboxylate (166 g, 0.975 mol) and ethanol (680 mL). To this solution was added sodium hydroxide (43 g, 1.07 mol) and the mixture was stirred for 1 hour. Triethylphosphonoacetate (218.6 g, 0.975 mol) was added via addition funnel over 10 minutes. The mixture was cooled to 0°C and 21% NaOEt/ethanol was added over 20 minutes. The resulting mixture was stirred at room temperature for 1 h, and ammonium formate (110.7 g, 1.76 mol) was added followed by 10% Pd/C (16.6 g). The mixture was heated at 65°C for 6 hours, and cooled to room temperature. Acetic acid (143 mL) was added over 20 min., and the mixture was stirred overnight. The reaction mixture was filtered through Celite, and rinsed with ethyl acetate. The filtrate was concentrated in vacuo to ¼ volume. The residue was extracted into ethyl acetate (3 L), washed twice with 2 N HCl (500 mL), brine, dried (Na₂SO₄), filtered and concentrated in vacuo. The residue was purified by flash chromatography (eluted with 5%-15% ethyl acetate in hexanes) to yield the title compound as a colorless oil (59 g).

¹H NMR (400 MHz, CHLOROFORM-D) δ ppm 1.0 (dq, J=11.6, 3.3 Hz, 2 H) 1.2 (t, J=7.1 Hz, 3 H) 1.5 (dq, J=12.9, 3.1 Hz, 2 H) 1.79 (m, 1 H) 1.84 (m, 2 H) 2.0 (m, 2 H) 2.2 (d, J=6.6 Hz, 2 H) 2.2 (m, 1 H) 4.1 (q, J=7.1 Hz, 2 H)

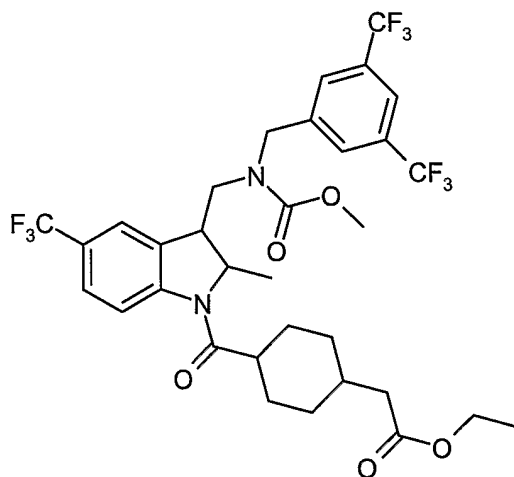
Preparation 3: Ethyl 2-((1R,4R)-4-(chlorocarbonyl)cyclohexyl)acetate



To a solution of (1R,4R)-4-((ethoxycarbonyl)methyl)cyclohexanecarboxylic acid (0.1 g, 0.467 mmol) in THF (0.11 mL) was added thionyl chloride (100 μ L, 1.4 mmol). The mixture was stirred at room temperature for 4 hours, and concentrated in vacuo to give the title compound.

^1H NMR (400 MHz, CHLOROFORM-D) δ ppm 1.0 (dq, $J=12.0, 3.7$ Hz, 2 H) 1.3 (t, $J=7.1$ Hz, 3 H) 1.5 (dq, $J=12.0, 3.3$ Hz, 2 H) 1.8 (m, 1 H) 1.9 (m, 2 H) 2.17-2.23 (m, 2H) 2.2 (d, $J=7.1$ Hz, 2 H) 2.7 (tt, $J=12.1, 3.7$ Hz, 1 H) 4.1 (q, $J=7.1$ Hz, 2 H)

10 Example 5: [4-(3-[(3,5-Bis-trifluoromethyl-benzyl)-methoxycarbonyl-amino]-methyl)-2-methyl-5-trifluoromethyl-indoline-1-carbonyl]-cyclohexyl]-acetic acid ethyl ester



Step 1: Preparation of methyl 3,5-bis(trifluoromethyl)benzyl(5-(trifluoromethyl)-2-methylindolin-3-yl)methylcarbamate

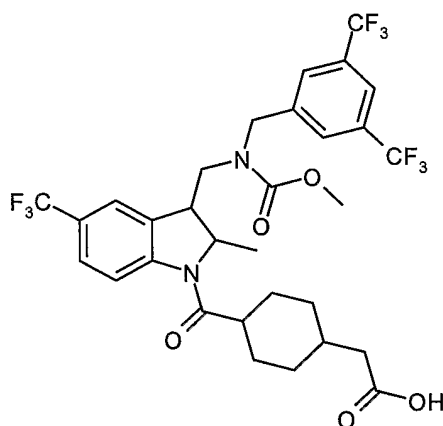
A solution of methyl (1-(tert-butoxycarbonyl)-5-(trifluoromethyl)-2-methylindolin-3-yl)methyl 3,5-bis(trifluoromethyl)benzylcarbamate (100 mg) in 4N HCl in dioxane (2 mL) was stirred at room temperature for 2.5 hours. The mixture was poured into sat. NaHCO_3 , and extracted with ethyl acetate. The organic layer was washed with water, brine, dried (MgSO_4), filtered and concentrated in vacuo to give the title compound (78 mg).

^1H NMR (400 MHz, METHANOL-D4) δ ppm 1.1 (d, $J=6.2$ Hz, 3 H) 3.2 (s, 1 H) 3.6 (m, 6 H) 4.7 (s, 2 H) 6.6 (d, $J=8.3$ Hz, 1 H) 7.2 (m, 2 H) 7.8 (m, $J=30.7$ Hz, 3 H); MS (ES^+) Calc: 514.13, Found: 515.4 ($\text{M}+1$).

Step 2: Preparation of [4-(3-[(3,5-Bis-trifluoromethyl-benzyl)-methoxycarbonyl-amino]-methyl)-2-methyl-5-trifluoromethyl-indoline-1-carbonyl]-cyclohexyl]-acetic acid ethyl ester

To a solution of the indoline (78 mg, 0.152 mmol) and pyridine (72 mg, 0.912 mmol) in methylene chloride (0.5 mL) was added a solution of the acid chloride (109 mg, 0.467 mmol) in methylene chloride (0.5 mL). The mixture was stirred at room temperature overnight, and then extracted with methylene chloride. The organic layer was washed with 1N HCl, water, brine, dried (MgSO₄), filtered and concentrated. The residue was purified by flash chromatography (eluted with 10% acetone in hexanes) to give the title compound as a colorless foam (72 mg, 67%). ¹H NMR (400 MHz, METHANOL-D₄) δ ppm 1.2 (m, 5 H) 1.3 (t, J=7.1 Hz, 3 H) 1.8 (m, 6 H) 2.2 (d, J=6.6 Hz, 2 H) 2.5 (m, 1 H) 3.3 (m, 4 H) 3.7 (m, 4 H) 4.1 (q, J=7.1 Hz, 2 H) 4.7 (m, 2 H) 7.5 (m, 2 H) 7.9 (m, 3 H) 8.3 (d, J=8.7 Hz, 1 H); MS (ES⁺) Calc: 710.24, Found: 711.5 (M+1).

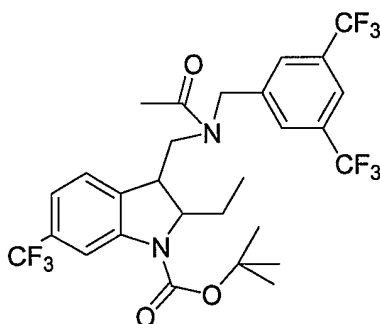
Example 6: [4-(3-[(3,5-Bis-trifluoromethyl-benzyl)-methoxycarbonyl-aminol-methyl]-2-methyl-5-trifluoromethyl-indoline-1-carbonyl)-cyclohexyl]-acetic acid



To a solution of the ethyl ester (72 mg, 0.101 mmol) in 3:1:1 THF/methanol/H₂O (1.6 mL) was added lithium hydroxide (7.3 mg, 0.303 mmol). The resulting mixture was stirred at room temperature overnight, and then diluted with water, acidified with 1N HCl, and extracted with ethyl acetate. The organic layer was washed with water, brine, dried (MgSO₄), filtered and concentrated in vacuo to yield the title compound (56mg).

¹H NMR (400 MHz, METHANOL-D₄) δ ppm 1.2 (m, 5 H) 1.9 (m, 7 H) 2.2 (d, J=7.1 Hz, 2 H) 2.5 (m, 1 H) 3.3 (m, 3 H) 3.7 (m, 4 H) 4.6 (m, 2 H) 7.5 (m, 2 H) 7.9 (m, 3 H) 8.3 (d, J=9.1 Hz, 1 H); MS (ES⁺) Calc: 682.21, Found: 683.5 (M+1).

Example 7: Tert-butyl-3-((N-(3,5-bis(trifluoromethyl)benzyl)acetamido)methyl)-2-ethyl-6-(trifluoromethyl)indoline-1-carboxylate



Step 1: Preparation of 1-tert-butyl 3,3-diethyl 2-ethyl-6-(trifluoromethyl)indoline-1,3,3-tricarboxylate

Diethyl 2-ethyl-6-(trifluoromethyl)indoline-3,3-dicarboxylate (2.9 gm, 8.07 mmol) was dissolved in 50 ml of anhydrous methylene chloride. To this solution was added DMAP (1.0 gm, 8.18 mmol), followed by (BOC)₂O (1.76 gm, 8.07 mmol). The reaction was stirred at room temperature for 6.5 hours. TLC showed starting material and product present. An additional 1.76 gm of (BOC)₂O was added and the reaction was stirred overnight. TLC still showed unreacted starting material. The reaction was treated with an additional 1.0 gm of DMAP and 1.76 gm of (BOC)₂O. The reaction continued to stir at room temperature overnight. The reaction was concentrated in vacuo and the residue partitioned between ethyl acetate and water. The organic layer was separated and combined with a second ethyl acetate extract. The organics were washed with brine and dried over Na₂SO₄. Removal of the solvent afforded 5.9 gm of a liquid. The product was taken up in methylene chloride and chromatographed on a Biotage 90 gm silica column. The column was eluted with 2.5% ethyl acetate/heptane (1L) followed by 5 % ethyl acetate/heptane (1L) and 10% ethyl acetate/heptane (1L). Pure fractions were found by TLC analysis, combined and concentrated to afford 2.10 gm of the title compound as a liquid (56.6%).

¹H NMR (400 MHz, CHLOROFORM-D) δ ppm 0.9 (t, J=7.5 Hz, 3 H) 1.2 (t, J=7.1 Hz, 3 H) 1.3 (t, J=7.1 Hz, 3 H) 1.5 (m, 1 H) 1.6 (s, 9 H) 1.7 (m, 1 H) 4.2 (m, 4 H) 5.2 (m, 1 H) 7.3 (d, J=7.1 Hz, 1 H) 7.6 (d, J=8.3 Hz, 1 H) 8.0 (s, 1 H)

Step 2: Preparation of 1-(tert-butoxycarbonyl)-2-ethyl-6-(trifluoromethyl)indoline-3-carboxylic acid

In 100 ml of absolute ethanol was dissolved 1-tert-butyl 3,3-diethyl 2-ethyl-6-(trifluoromethyl)indoline-1,3,3-tricarboxylate (2.1 gm, 4.57 mmol). The solution was cooled in an ice salt bath to -5°C. To this solution was added 16 ml of 10% w/w KOH solution which had been cooled to 0°C. The reaction was stirred at -5°C for 4 hr and it slowly came to ambient temperature overnight. The reaction was poured onto 400 mL of ice water. The solution was washed with diethyl ether. The aqueous phase was separated and acidified with 6N HCL to a pH = 2. The acidic solution was extracted with chloroform. The extracts were dried through Na₂SO₄ and concentrated to afford 1.16 gm of the title compound as a solid foam (70.6%).

¹H NMR (400 MHz, DMSO-D₆) δ ppm 0.8 (t, J=7.5 Hz, 3 H) 1.5 (s, 9 H) 1.6 (m, 1 H) 1.7 (m, 1 H) 4.0 (s, 1 H) 4.6 (m, 1 H) 7.3 (d, J=6.6 Hz, 1 H) 7.5 (d, J=7.9 Hz, 1 H) 7.9 (s, 1 H) 13.0 (s, 1 H) MS (ES⁺) Calc: 359.13, Found: 358.2 (M-1).

Step 3: Preparation of tert-butyl 3-(3,5-bis(trifluoromethyl)benzylcarbamoyl)-2-ethyl-6-(trifluoromethyl)indoline-1-carboxylate

In a 1 dram (4 ml) vial were combined 1-(tert-butoxycarbonyl)-2-ethyl-6-(trifluoromethyl)indoline-3-carboxylic acid (38 mg, 0.105 mmol), 0.5 ml of anhydrous methylene chloride and PS-DCC (108 mg, 1.3 mmol/g, 0.14 mmol, 2 eq.). The vial was agitated for 5 minutes at room temperature and then a solution containing 17 mg (0.07 mmol) of 3,5-bis(trifluoromethyl)benzylamine in 0.5 ml of methylene chloride was added. The reaction was agitated at room temperature on a shaker overnight. After sitting overnight again at room temperature, the reaction was filtered and the filtrate combined with some methylene chloride washes of the resin. The filtrate was concentrated under a stream of N₂, then dried under high-vacuum to afford 44.3 mg of a white solid. The material was dissolved in 0.5 ml of DMSO and chromatographed using the Shimadzu Prep HPLC/MS. The pure product obtained after concentration amounted to 18.1 mg of the title compound as a white crystalline solid (44%).

¹H NMR (400 MHz, CHLOROFORM-D) δ ppm 0.9 (t, J=7.5 Hz, 3 H) 1.6 (m, 9 H) 1.7 (m, 1 H) 1.9 (m, 1 H) 3.8 (s, 1 H) 4.4 (dd, J=15.8, 5.8 Hz, 1 H) 4.6 (m, 2 H) 5.9 (t, J=6.0 Hz, 1 H) 7.3 (m, 2 H) 7.6 (s, 2 H) 7.8 (s, 1 H) 8.2 (s, 1 H)

Step 4: Preparation of tert-butyl 2-ethyl-6-(trifluoromethyl)-3-(hydroxymethyl)indoline-1-carboxylate

5 In an oven dried 50 ml 3-neck round-bottom flask was placed 4.8 ml of 1M THF/Borane complex in THF. The solution was cooled in an ice bath and was treated with 1-(tert-butoxycarbonyl)-2-ethyl-6-(trifluoromethyl)indoline-3-carboxylic acid (870 mg, 2.42 mmol) in 5 ml of anhydrous THF. The reaction was stirred at 0°C for 4.5 hours. The reaction was carefully quenched with 10 ml of 10% HOAc/methanol. The solution was concentrated and the residue taken up in ethyl acetate. The solution was washed with
10 1N HCl, water, 1N NH₄HCO₃ and brine. After drying through MgSO₄ the solvent was removed in vacuo to afford 0.86 g of a clear oil. The material was taken up in methylene chloride and chromatographed on a Biotage 40 gm silica column. The column was eluted with 5% ethyl acetate/Heptane (1 L) followed by 10% ethyl acetate/Heptane (1 L) and 20% ethyl acetate/Heptane (1 L). Pure fractions were found by TLC, combined and concentrated to afford 450 mg of the title compound as an oil (53.8%).

15 ¹H NMR (400 MHz, CHLOROFORM-D) δ ppm 1.2 (t, J=7.1 Hz, 3 H) 1.4 (m, 1 H) 1.6 (s, 9 H) 1.7 (m, 1 H) 3.1 (t, J=6.6 Hz, 1 H) 3.6 (d, J=6.6 Hz, 1 H) 3.7 (d, J=6.6 Hz, 1 H) 4.2 (m, 1 H) 7.2 (d, J=7.5 Hz, 1 H) 7.3 (d, J=7.5 Hz, 1 H) 8.1 (s, 1 H) MS (ES⁺) Calc: 345.16, Found: 331.4 (M-14).

Step 5: Preparation of tert-butyl 2-ethyl-6-(trifluoromethyl)-3-formylindoline-1-carboxylate

In a dry 25 ml 3-neck round-bottom flask under N₂ was dissolved 31 μL of oxalyl chloride in 0.5 ml
20 of anhydrous methylene chloride. The solution was cooled in a dry ice/acetone bath and was treated with 50 μL of DMSO. After stirring at -78°C for 10 minutes, tert-butyl 2-ethyl-6-(trifluoromethyl)-3-(hydroxymethyl)indoline-1-carboxylate (81.4 mg) in 1 ml of methylene chloride was added via syringe. The reaction was stirred for 15 min at -78°C and then 0.25 ml of di-isopropylethylamine was added. The reaction was stirred for an additional 5 min at -78°C then was allowed to warm to room temperature. The
25 reaction was quenched with 5 ml of water. The mixture was extracted with methylene chloride three times. The organics were washed with 1N HCl, brine, and dried (MgSO₄). The solvent was removed in vacuo to afford 73 mg of an oil (90%). The material was used without additional purification.

¹H NMR (400 MHz, CHLOROFORM-D) δ ppm 0.9 (t, J=7.5 Hz, 3 H) 1.5 (m, 9 H) 1.7 (m, 1 H) 1.9 (m, 1 H) 3.7 (s, 1 H) 4.8 (m, 1 H) 7.3 (d, J=7.9 Hz, 1 H) 7.4 (d, J=7.5 Hz, 1 H) 8.1 (s, 1 H) 9.6 (s, 1 H) MS
30 (ES⁺) Calc: 343.14, Found: 342.2 (M-1).

Step 6: Preparation of tert-butyl 3-((3,5-bis(trifluoromethyl)benzylamino)methyl)-2-ethyl-6-(trifluoromethyl)indoline-1-carboxylate

Tert-butyl 2-ethyl-6-(trifluoromethyl)-3-formylindoline-1-carboxylate (73 mg, 0.212 mmol) was dissolved in 10 ml of 95:5 THF/HOAc. To this solution was added 3,5-Bis(trifluoromethyl)benzylamine (62
35 mg, 0.255 mmol) followed by Si-CN₃BH₃ (0.450 g, 1.18 mmol/g, 0.53 mmol). The reaction was stirred at room temperature overnight. The reaction was filtered and the Silica support was rinsed well with ethyl acetate. The filtrate was concentrated in vacuo and the residue partitioned between ethyl acetate/saturated NaHCO₃. The organic layer was separated and combined with a second extract. The extracts were washed with brine and dried over MgSO₄. Removal of the solvent afforded 106.7 mg of an
40 oil. The material was taken up in methylene chloride and chromatographed on a Biotage 12 gm silica

column. The column was eluted with 10% ethyl acetate/heptane (500 ml) followed by 20% ethyl acetate/heptane (500 ml). Pure fractions were found by TLC, combined and concentrated to afford 53 mg of the title compound as an oil (43.7%).

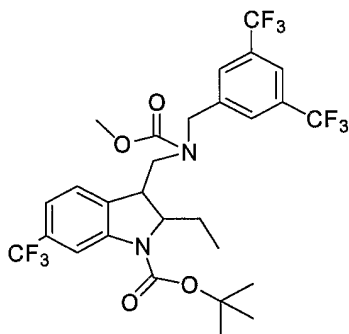
¹H NMR (400 MHz, CHLOROFORM-D) δ ppm 0.9 (t, J=7.5 Hz, 3 H) 1.3 (m, 1 H) 1.6 (s, 9 H) 1.7 (m, 1 H) 2.73 (d, J=2.5 Hz, 1 H) 2.75 (d, J=2.5 Hz, 1 H) 3.0 (t, J=6.8 Hz, 1 H) 3.9 (s, 2 H) 4.2 (m, 1 H) 7.2 (d, J=7.9 Hz, 1 H) 7.3 (d, J=7.5 Hz, 1 H) 7.8 (m, 3 H) 8.1 (s, 1 H) MS (ES⁺) Calc: 570.19, Found: 571.4 (M+1).

Step 7: Preparation of tert-butyl 3-((N-(3,5-bis(trifluoromethyl)benzyl)acetamido)methyl)-2-ethyl-6-(trifluoromethyl)indoline-1-carboxylate

In a 1 dram (4 ml) vial were combined tert-butyl 3-((3,5-bis(trifluoromethyl)benzylamino)methyl)-2-ethyl-6-(trifluoromethyl)indoline-1-carboxylate, pyridine, and acetyl chloride in 1 ml of methylene chloride. The reaction was agitated at room temperature for 4 hours. TLC showed complete loss of the starting material with a single more polar product formed. To this reaction was then added 42 mg of PS-Trisamine resin (3.85 mmol/gm, 0.16 mmol). The reaction was agitated overnight. The reaction was filtered through a Baker bezen sulfonic acid SPE tube (100 mg of sorbent) which was conditioned with methanol. The SPE tube was washed with methanol. The filtrate was concentrated to afford 39 mg of the title compound as an oil.

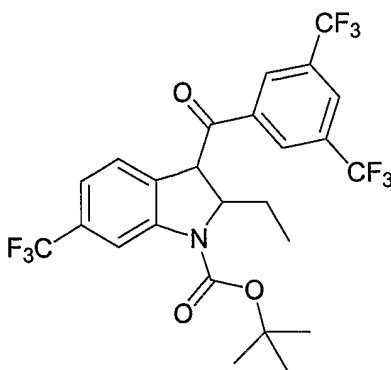
¹H NMR (400 MHz, CHLOROFORM-D) δ ppm 0.88, 0.85 (t, J=7.5 Hz, 3 H) 1.5 (m, 11 H) 2.06, 1.85 (s, 3 H) 3.2 (t, J=8.1 Hz, 1 H) 3.3 (d, J=7.9 Hz, 1 H) 3.5 (s, 2 H) 3.9 (m, 1 H) 4.9, 4.66 (d, J=15.4 Hz, 1 H) 7.2 (d, J=7.1 Hz, 1 H) 7.7 (s, 1 H) 7.8 (m, 2 H) 8.8 (d, J=4.6 Hz, 2 H) MS (ES⁺) Calc: 612.2, Found: 613.4 (M+1).

Example 8: Methyl (1-(tert-butoxycarbonyl)-2-ethyl-6-(trifluoromethyl)indolin-3-yl)methyl-3,5-bis(trifluoromethyl)benzylcarbamate



Tert-butyl 3-((3,5-bis(trifluoromethyl)benzylamino)methyl)-2-ethyl-6-(trifluoromethyl)indoline-1-carboxylate, pyridine, and methyl chloroformate were combined in 1 ml of methylene chloride contained in a 1 Dram (4-ml) vial and agitated for 4 hours at room temperature. At this time, TLC showed complete reaction with the formation of a less polar product. The reaction was treated with 31 mg of PS-Trisamine (3.85 mmol/g, 0.12 mmol) and agitated overnight. The reaction was filtered through a methanol-conditioned Baker Benzene sulfonic acid SPE tube (100 mg) and the column washed well with methanol. The filtrate was evaporated to afford 23 mg of the title compound as an oil.

¹H NMR (400 MHz, CHLOROFORM-D) δ ppm 0.9 (t, J=7.1 Hz, 3 H) 1.6 (s, 9 H) 1.7 (m, 2 H) 3.2 (m, 2 H) 3.4 (m, 1 H) 3.7 (s, 3 H) 3.9 (m, 1 H) 4.5 (m, 2 H) 7.2 (s, 2 H) 7.5 (m, 2 H) 7.8 (s, 1 H) 8.1, 8.66 (s, 1 H) MS (ES⁺) Calc: 628.2, Found: 629.4 (M+1).

Example 9: Tert-butyl 3-(3,5 bis-trifluoromethylbenzoyl)-2-ethyl-6-(trifluoromethyl)indoline-1-carboxylateStep 1: Preparation of tert-butyl 3-(N-methoxy-N-methylcarbamoyl)-2-ethyl-6-(trifluoromethyl)indoline-1-carboxylate

5 In 10 ml of anhydrous methylene chloride under N₂ were combined 1-(tert-butoxycarbonyl)-2-ethyl-6-(trifluoromethyl)indoline-3-carboxylic acid (590 mg, 1.64 mmol), N,O-dimethylhydroxylamine hydrochloride (200 mg, 2.05 mmol), DMAP (12 mg, 0.10 mmol) and diisopropylethylamine (0.23 ml, 1.3 mmol). To this solution was added EDCI (210 mg, 1.10 mmol). The reaction was stirred overnight at room temperature. TLC (1:1 ethyl acetate/heptane) still showed starting material. To the reaction was then
 10 added an additional 210 mg of the hydroxylamine, 0.23 ml of diisopropylethylamine, some DMAP and 200 mg of the EDCI. The reaction was stirred at RT for 6 hours. The reaction was diluted with methylene chloride, washed with 0.5 N HCl, water and brine. After drying through MgSO₄ removal of the solvent afforded 0.500 gm of the title compound as a sticky gum.

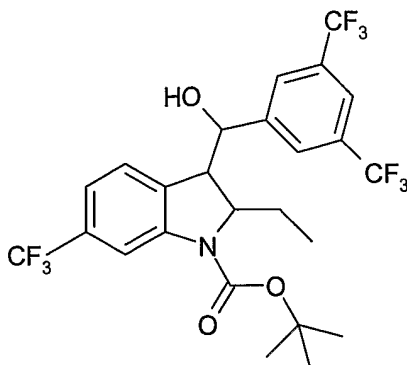
¹H NMR (400 MHz, CHLOROFORM-D) δ ppm 0.9 (t, J=7.5 Hz, 3 H) 1.6 (s, 9 H) 1.7 (m, 1 H) 1.9 (m, 1 H) 3.2 (d, J=5.4 Hz, 3 H) 3.7 (s, 3 H) 4.2 (s, 1 H) 4.6 (m, 1 H) 7.2 (d, J=7.9 Hz, 1 H) 7.3 (d, J=7.9 Hz, 1 H) 8.1 (s, 1 H) MS (ES⁺) Calc: 402.18, Found: 420.5 (M+18).

Step 2: Preparation of tert-butyl 3-(3,5 bis-trifluoromethylbenzoyl)-2-ethyl-6-(trifluoromethyl)indoline-1-carboxylate

In a dry 50 ml 3-neck round-bottom flask were combined bis-3,5-(trifluoromethyl)bromobenzene
 20 (0.21 ml, 1.21 mmol) and 10 ml of anhydrous THF under N₂. The solution was cooled in an ice bath and was treated with 2M iPrMgCl/THF solution (0.65 ml, 1.31 mmol). The Grignard solution was stirred for 1 hr at 0°C. To this solution at 0°C was then added the Weinreb amide (195 mg, 0.485 mmol) in 5 ml of THF. The reaction was stirred for 1 hr at 0°C then warmed to room temperature. After stirring overnight, the reaction was refluxed for 4 hours. The reaction was quenched with saturated NH₄Cl and the THF was
 25 removed in vacuo. The aqueous residue was extracted with ethyl acetate. The extracts were washed with brine and dried over MgSO₄. Removal of the solvent afforded 410 mg of a yellow oil. The material was taken up in methylene chloride and chromatographed on a Biotage Flash 45 S column. The column was eluted with heptane (400 ml) followed by 5% ethyl acetate/heptane (1L) and 10% ethyl acetate/heptane (1L). Pure fractions were found by TLC analysis, combined and concentrated to afford
 30 62.4 mg of the title compound as a gum (23%).

¹H NMR (400 MHz, CHLOROFORM-D) δ ppm 1.0 (t, J=7.5 Hz, 3 H) 1.6 (m, 9 H) 1.8 (m, 1 H) 1.9 (m, 1 H) 4.7 (s, 1 H) 4.8 (m, 1 H) 7.0 (d, J=7.5 Hz, 1 H) 7.1 (d, J=7.9 Hz, 1 H) 8.1 (s, 2 H) 8.4 (s, 2 H) MS (ES⁺) Calc: 555.15, Found: 554.4 (M-1).

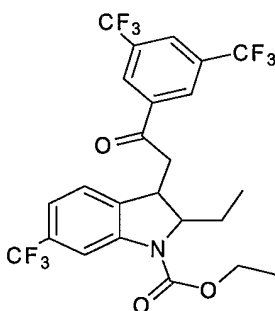
Example 10: Tert-butyl 3-((3,5-bis(trifluoromethyl)phenyl)(hydroxymethyl)-2-ethyl-6-(trifluoromethyl)indoline-1-carboxylate



- 5 Tert-butyl 3-(3,5 bis-trifluoromethylbenzoyl)-2-ethyl-6-(trifluoromethyl)indoline-1-carboxylate (62.4 mg) was dissolved in 5 ml of anhydrous methanol and cooled in an ice bath. To this solution was added NaBH₄ (28 mg). The reaction was stirred for 1 hr at 0°C. HPLC/MS indicated complete reaction with the formation of the desired alcohol. The reaction was concentrated in vacuo and the residue partitioned between 1N HCl/ethyl acetate. The ethyl acetate was separated and combined with a second extract.
- 10 The extracts were washed with brine and dried through MgSO₄. Removal of the solvent afforded a waxy solid. The product was taken up in methylene chloride and chromatographed on a Biotage Flash 12S column. The column was eluted with 5% ethyl acetate/heptane (250 ml) followed by 10% ethyl acetate/heptane (250 ml) and ethyl acetate (250 ml). Pure fractions were found by TLC, combined and concentrated to afford the title compound. Two diastereomers were isolated. The less polar material
- 15 amounted to 18 mg of a gum. The more polar isomer amounted to 27 mg of a white crystalline solid.

¹H NMR (400 MHz, CHLOROFORM-D) δ ppm 0.7 (m, 3 H) 1.5 (m, 9 H) 1.6 (m, 2 H) 2.3 (s, 1 H) 3.3 (m, 1 H) 4.2 (m, 1 H) 4.9 (m, 1 H) 7.3 (m, 2 H) 7.5 (m, 2 H) 7.8 (m, 1 H) 8.0 (s, 1 H) MS (ES⁺) Calc: 557.16, Found: 602.4 (M+43).

20 Example 11: Ethyl-3-(2-(3,5-bistrifluoromethyl)phenyl-2-oxo-ethyl)-2-ethyl-6-(trifluoromethyl)indoline-1-carboxylate



Step 1: Preparation of Ethyl-3-(2-diazo-1-oxo ethyl)-2-ethyl-6-(trifluoromethyl)indoline-1-carboxylate

- 1-(ethoxycarbonyl)-2-ethyl-6-(trifluoromethyl)indoline-3-carboxylic acid was dissolved in 30 ml of anhydrous THF and cooled in an ice salt bath. To this solution was added 0.87 ml of triethylamine followed by 6.4 ml of ethyl chloroformate. The reaction was stirred for 2 hours at 0°C. The reaction was filtered to remove the triethylamine hydrochloride and the filtrate diluted with 30 ml of anhydrous
- 25

acetonitrile. The reaction was cooled in an ice bath and was treated with 6.0 ml of 2M TMS-diazomethane/hexane solution. The reaction was stirred overnight at 0°C, slowly brought to ambient temperature. The reaction was diluted with 100 ml of Et₂O and was washed with 10% aqueous citric acid, saturated NaHCO₃ and brine. After drying through Na₂SO₄ the solvent was removed in vacuo.

5 HPLC/MS showed three UV peaks, the major one having a consistent ion for the desired diazoketone.

¹H NMR (400 MHz, CHLOROFORM-D) δ ppm 0.9 (t, J=7.5 Hz, 3 H) 1.4 (t, J=6.8 Hz, 3 H) 1.6 (m, 1 H) 1.9 (m, 1 H) 3.8 (s, 1 H) 4.3 (m, 2 H) 4.8 (m, 1 H) 7.3 (d, J=6.6 Hz, 1 H) 7.5 (d, J=7.9 Hz, 1 H) 8.1 (s, 1 H); MS (ES⁺) Calc: 358.14, Found: 360.4 (M+2).

10 Step 2: Preparation of Ethyl 3-((N-methoxy-N-methylcarbamoyl)methyl)-2-ethyl-6-(trifluoromethyl)indoline-1-carboxylate

A solution containing of N,O-dimethylhydroxylamine (210 mg, 2.15 mmol), and triethylamine (0.40 ml, 2.87 mmol) in 5 ml of anhydrous THF was prepared. The solution was stirred overnight and was filtered into a solution of the diazoketone (510 mg, 1.44 mmol) in 5 ml of anhydrous THF. The solution
15 was cooled to -40°C and treated with a solution containing silver benzoate (49 mg, 0.22 mmol), and triethylamine (0.6 ml, 4.3 mmol) in 5 ml of anhydrous THF. The reaction was stirred at -35°C and slowly was allowed to reach room temperature. After 1 hr at room temperature, TLC showed complete loss of the diazo ketone with the formation of a single more polar product. The reaction was concentrated in vacuo and the residue partitioned between ethyl acetate/1N HCl. The ethyl acetate layer was separated
20 and combined with a second extract. The organics were then washed with saturated NaHCO₃ and brine. After drying through MgSO₄, the solvent was removed in vacuo to afford 538 mg of an oil. The material was chromatographed on a Biotage Flash 40S column (eluted with 20% ethyl acetate/heptane (1L) followed by 50% ethyl acetate/heptane (1L)). Pure fractions were found by TLC, combined and concentrated to afford 435 mg of the title compound as an oil (78%).

25 ¹H NMR (400 MHz, CHLOROFORM-D) δ ppm 0.9 (t, J=7.3 Hz, 3 H) 1.4 (m, 3 H) 1.7 (m, 1 H) 1.7 (m, 1 H) 2.7 (d, J=6.2 Hz, 2 H) 3.2 (s, 3 H) 3.5 (t, J=7.5 Hz, 1 H) 3.6 (s, 3 H) 4.1 (m, 1 H) 4.3 (m, 2 H) 7.2 (d, J=7.9 Hz, 1 H) 7.3 (d, J=7.9 Hz, 1 H) 8.1 (s, 1 H) MS (ES⁺) Calc: 388.16, Found: 406.5 (M+18).

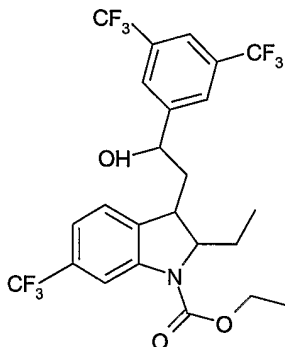
Step 3: Preparation of Ethyl-3-(2-(3,5-bistrifluoromethyl)phenyl-2-oxo-ethyl)-2-ethyl-6-(trifluoromethyl)indoline-1-carboxylate

30 In a dry, 75-ml 3-neck round-bottom flask were combined 3,5-bis(trifluoromethyl)bromobenzene (0.476 ml, 2.76 mmol) and 5 ml of anhydrous THF. The solution was cooled in an ice bath and was treated with 1.5 ml of 2M iPrMgCl/THF (2.98 mmol). After stirring for 1h at 0°C, the solution was cooled to -78°C and was treated with the Weinreb amide (429 mg, 1.10 mmol) in 4 ml of THF. The reaction was warmed to room temperature, stirred for 1 hour, quenched with saturated NH₄Cl and the THF was
35 removed in vacuo. The aqueous residue was extracted with ethyl acetate. The extracts were washed with brine and dried over MgSO₄ to afford 604 mg of an oil. The material was chromatographed on a Biotage Flash 45S column (eluted with 10% ethyl acetate/heptane (1L) followed by 20% (1L) ethyl acetate/heptane). Pure fractions were found by TLC, combined and concentrated to afford 456 mg of the title compound as a sticky foam (76%).

40 ¹H NMR (400 MHz, CHLOROFORM-D) δ ppm 1.0 (t, J=7.3 Hz, 3 H) 1.4 (m, 3 H) 1.7 (m, 1 H) 1.8

(m, 1 H) 3.3 (m, 2 H) 3.7 (t, J=6.6 Hz, 1 H) 4.3 (m, 3 H) 7.2 (d, J=8.7 Hz, 1 H) 7.3 (d, J=7.9 Hz, 1 H) 8.1 (s, 1 H) 8.2 (m, 1 H) 8.3 (s, 2 H) MS (ES⁺) Calc: 541.13, Found: (M-1).

Example 12: Ethyl 3-(2-(3,5-bis(trifluoromethyl)phenyl)-2-hydroxyethyl)-2-ethyl-6-(trifluoromethyl)indoline-1-carboxylate

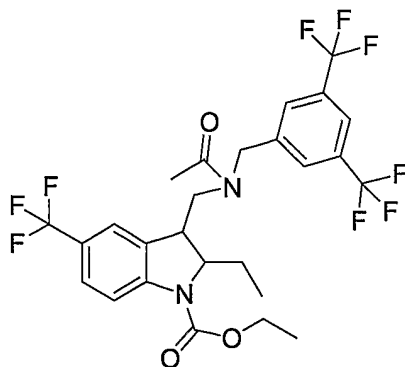


Ethyl-3-(2-(3,5-bistrifluoromethyl)phenyl)-2-oxo-ethyl)-2-ethyl-6-(trifluoromethyl)indoline-1-carboxylate (431 mg, 0.796 mmol) was dissolved in 10 ml of anhydrous methanol and was cooled in an ice bath. To this solution was added NaBH₄ (210mg, 5.57 mmol). After stirring for 1 hour at 0°C, the reaction was concentrated to remove the methanol, and the residue was partitioned between ethyl acetate/1N HCl. The ethyl acetate layer was separated and combined with a second extract. The extracts were washed with brine and dried through MgSO₄. Removal of the solvent afforded 420 mg of a solid foam. The material was taken up in methylene chloride and chromatographed on a Biotage Flash 40S column (eluted with 5% ethyl acetate/Heptane (1L) followed by 10% ethyl acetate/Heptane (1L)). Pure fractions were found by TLC analysis, combined and concentrated. The less polar diastereomer amounted to 179 mg of an oil. The more polar diastereomer amounted to 99 mg of an oil. (64% total yield).

For less polar isomer: ¹H NMR (400 MHz, CHLOROFORM-D) δ ppm 0.9 (t, J=7.5 Hz, 3 H) 1.3 (m, 3 H) 1.8 (m, 2 H) 2.0 (m, 1 H) 2.2 (m, 1 H) 3.3 (s, 1 H) 4.3 (m, 3 H) 4.9 (dd, J=10.0, 2.5 Hz, 1 H) 7.3 (d, 1 H) 7.4 (d, J=7.5 Hz, 1 H) 7.8 (s, 3 H) 8.2 (s, 1 H) MS (ES⁺) Calc: 543.15, Found: 544.4 (M+1).

For more polar isomer: ¹H NMR (400 MHz, CHLOROFORM-D) □ ppm 1.0 (t, J=7.3 Hz, 3 H) 1.4 (m, 3 H) 1.6 (m, 1 H) 1.9 (m, 3 H) 3.4 (d, J=8.3 Hz, 1 H) 4.3 (m, 3 H) 4.9 (s, 1 H) 7.2 (m, 2 H) 7.8 (m, 3 H) 8.1 (s, 1 H); MS (ES⁺) Calc: 543.15, Found: 544.4 (M+1).

Example 13: Ethyl 3-((N-(3,5-bis(trifluoromethyl)benzyl)acetamido)methyl)-2-ethyl-5-(trifluoromethyl)indoline-1-carboxylate



Step 1: Preparation of triethyl 2-ethyl-5-(trifluoromethyl)indoline-1,3,3-tricarboxylate

In 10 ml of anhydrous toluene was dissolved diethyl 2-ethyl-5-(trifluoromethyl)indoline-3,3-dicarboxylate (2.28 gm, 6.34 mmol). To this solution was added 6.7 ml of 20% phosgene/toluene solution (63.42 mmol). The reaction was brought to reflux for 1.5 hours. TLC showed complete loss of the starting material and the formation of a single, less polar product. The reaction was cooled and concentrated in vacuo to a syrup. The light amber syrup was then dissolved in 20 ml of anhydrous ethanol and refluxed for 48 hours. The ethanol was removed in vacuo to afford 2.81 gm of an amber liquid. The material was taken up in methylene chloride and chromatographed on a Biotage Flash 40 M column (eluted with 10% ethyl acetate/Heptane (2L)). Pure fractions were combined and concentrated to afford 2.34 g of the title compound as a colorless oil (85%).

^1H NMR (400 MHz, CHLOROFORM-D) δ ppm 0.8 (t, J=7.5 Hz, 3 H) 1.2 (t, J=7.1 Hz, 3 H) 1.3 (t, J=7.3 Hz, 3 H) 1.4 (t, J=7.1 Hz, 3 H) 1.5 (m, 1 H) 1.7 (m, 1 H) 4.2 (m, 7 H) 5.3 (dd, J=7.1, 4.6 Hz, 1 H) 7.5 (d, J=8.7 Hz, 1 H) 7.8 (s, 2 H) MS (ES⁺) Calc: 431.16, Found: 432.2 (M+1).

Step 2: Preparation of 1-(ethoxycarbonyl)-2-ethyl-5-(trifluoromethyl)indoline-3-carboxylic acid

Triethyl 2-ethyl-5-(trifluoromethyl)indoline-1,3,3-tricarboxylate (2.34 gm, 5.42 mmol) was dissolved in 25 ml of absolute ethanol and cooled in an ice bath. To this solution was added 25 ml of 10% (w/w) aqueous KOH. The reaction was stirred at ice bath temperature. After 2.5 hours, the reaction was complete by TLC. The solution was poured into 400 ml of ice and the melted solution was extracted with Et₂O. The aqueous solution was then acidified with 6N HCl and extracted with chloroform. The extracts were washed with brine and dried over MgSO₄. Removal of the solvent afforded 1.65 gm of the title compound as a sticky gum.

^1H NMR (400 MHz, CHLOROFORM-D) δ ppm 0.9 (t, J=7.5 Hz, 3 H) 1.4 (t, J=7.1 Hz, 3 H) 1.7 (m, 1 H) 1.9 (m, 1 H) 3.8 (d, J=2.1 Hz, 1 H) 4.3 (m, 2 H) 4.8 (m, 1 H) 7.5 (d, J=8.3 Hz, 1 H) 7.6 (s, 1 H) 7.9 (s, 1 H); MS (ES⁺) Calc: 331.1, Found: 330.3 (M-1).

Step 3: Preparation of Ethyl 2-ethyl-5-(trifluoromethyl)-3-(hydroxymethyl)indoline-1-carboxylate

In a dry 100 ml 3-neck round-bottom flask was placed 10 ml of 1M BH₃·THF complex in THF. The solution was cooled in an ice bath and was treated with 1-(ethoxycarbonyl)-2-ethyl-5-(trifluoromethyl)indoline-3-carboxylic acid (1.65 gm, 4.98 mmol) in 8 ml of anhydrous THF. The reaction was stirred for 20 min at 0°C, then warmed to room temperature. After 1 hour at room temperature, TLC showed starting material and two, less polar products. An additional 5 ml of 1M Borane·THF was added. The reaction was stirred for an additional 1.5 hr, and then carefully quenched with 20 ml of 10%HOAc/methanol. The solvents were removed in vacuo and the concentrate partitioned between ethyl

acetate and 1N HCl. The ethyl acetate layer was separated and combined with a second extract. The organics were washed with water, 1M NH_4CO_3 and brine. After drying through MgSO_4 , the solvent was removed in vacuo to afford 1.2 gm of a clear colorless gum. The material was taken up in methylene chloride and chromatographed on a Biotage Flash 40S column (eluted with 10% ethyl acetate/heptane (1L) followed by 20% ethyl acetate/heptane (1L)). Pure fractions were found by TLC, combined and concentrated to afford 872 mg of the title compound as a gum (55%).

Step 4: Preparation of Ethyl 2-ethyl-5-(trifluoromethyl)-3-formylindoline-1-carboxylate

In 5 ml of anhydrous methylene chloride under N_2 was dissolved Ethyl 2-ethyl-5-(trifluoromethyl)-3-(hydroxymethyl)indoline-1-carboxylate (140 mg, 0.44 mmol). To this solution was added the Dess-Martin reagent (224 mg, 0.53 mmol). The reaction was stirred for 30 min at which time TLC showed complete reaction. The reaction was diluted with methylene chloride and washed with 1N NaOH, water and brine. After drying through MgSO_4 removal of the solvent afforded 102 mg of the title compound as an oil (73%).

^1H NMR (400 MHz, CHCl_3 - d_3) δ ppm 0.9 (t, $J=7.1$ Hz, 3 H) 1.4 (t, $J=7.1$ Hz, 3 H) 1.7 (m, 1 H) 1.9 (m, 1 H) 3.7 (s, 1 H) 4.3 (m, 2 H) 4.9 (m, 1 H) 7.6 (m, 2 H) 7.9 (s, 1 H) 9.6 (d, $J=1.7$ Hz, 1 H) MS (ES^+) Calc: 315.11, Found: 314.2 (M-1).

Step 5: Preparation of Ethyl 3-((3,5-bis(trifluoromethyl)benzylamino)methyl)-2-ethyl-5-(trifluoromethyl)indoline-1-carboxylate

In 5 ml of 95:5 THF/HOAc was dissolved Ethyl 2-ethyl-5-(trifluoromethyl)-3-formylindoline-1-carboxylate (102 mg, 0.323 mmol). To this solution was added the amine (94 mg, 0.388 mmol) followed by 0.55 gm of the $\text{Si-CN}(\text{BH}_3)$ (1.18 mmol/g, 0.647 mmol). The reaction was stirred overnight under N_2 . The reaction was filtered and the solid support washed well with ethyl acetate. The filtrate and washings were concentrated and the residue partitioned between ethyl acetate/saturated NaHCO_3 . The ethyl acetate layer was separated and combined with a second extract. The extracts were washed with brine and dried through MgSO_4 . Removal of the solvent afforded 174 mg of an oil. The material was chromatographed on a Biotage Flash 40S column, eluting with 1L of 10% ethyl acetate/Heptane to afford 101mg of the title compound as an oil (57.5%).

^1H NMR (400 MHz, CHCl_3 - d_3) δ ppm 0.9 (t, $J=7.5$ Hz, 3 H) 1.4 (t, $J=6.8$ Hz, 3 H) 1.6 (m, 1 H) 1.8 (m, 1 H) 2.7 (d, $J=5.8$ Hz, 2 H) 3.1 (t, $J=6.0$ Hz, 1 H) 3.9 (s, 2 H) 4.3 (m, 3 H) 7.4 (s, 1 H) 7.5 (d, $J=8.3$ Hz, 1 H) 7.8 (m, 3 H) 7.9 (s, 1 H) MS (ES^+) Calc: 542.16, Found: 543.4 (M+1).

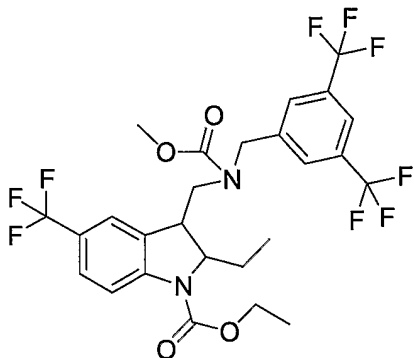
Step 6: Preparation of ethyl 3-((N-(3,5-bis(trifluoromethyl)benzyl)acetamido)methyl)-2-ethyl-5-(trifluoromethyl)indoline-1-carboxylate

Ethyl 3-((3,5-bis(trifluoromethyl)benzylamino)methyl)-2-ethyl-5-(trifluoromethyl)indoline-1-carboxylate (101 mg, 0.186 mmol) was dissolved in 5 ml of anhydrous methylene chloride and cooled in an ice bath. To this solution was added pyridine (45 μL , 0.558 mmol) followed by acetyl chloride (20 μL , 0.279 mmol). The reaction was stirred overnight. The reaction was diluted with methylene chloride and washed with 1N HCl, saturated NaHCO_3 and brine. After drying through MgSO_4 the solvent was removed in vacuo to afford 84 mg of the title compound as an oil (77%).

^1H NMR (400 MHz, CHCl_3 - d_3) δ ppm 0.85, 0.9 (t, $J=7.5$ Hz, 3 H) 1.4 (m, 3 H) 1.5 (m, 1 H) 1.7 (m, $J=5.0$ Hz, 1 H) 3.0 (none, 1 H) 3.3 (m, 1 H) 3.6 (t, $J=7.5$ Hz, 1 H) 4.2 (m, 3 H) 4.5 (s, 1 H) 4.8

(m, 1 H) 7.3 (s, 1 H) 7.5 (s, 1 H) 7.5 (t, J=7.7 Hz, 1 H) 7.7 (s, 1 H) 7.8 (s, 1 H) 8.0 (s, 1 H) MS (ES⁺) Calc: 584.17, Found: 585.4 (M+1).

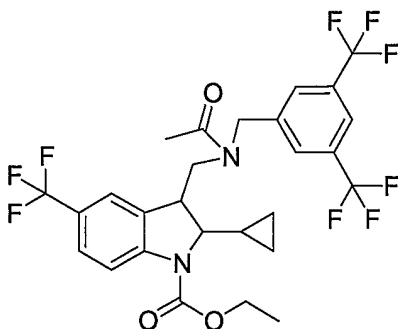
Example 14: Methyl (1-(ethoxycarbonyl)-2-ethyl-5-(trifluoromethyl)indolin-3-yl)methyl-3,5-bis(trifluoromethyl)benzylcarbamate



The substrate (76 mg, 0.141 mmol) was dissolved in 3 ml of anhydrous methylene chloride and cooled in an ice bath. To this solution was added pyridine (34 μ L, 0.420 mmol) followed by methyl chloroformate (16 μ L, 0.210 mmol). The reaction was stirred at ice bath temperatures for 2.5 hours. The reaction was diluted with methylene chloride and washed with 1N HCl, saturated NaHCO₃ and brine. After drying through MgSO₄ the solvent was removed in vacuo to afford 64 mg of a sticky foam. The material was chromatographed on a Biotage Flash 40S column eluting with 1.5 L of 10% ethyl acetate/Heptane to afford 56 mg of the title compound as an oil (66.6 %).

¹H NMR (400 MHz, CHLOROFORM-D) δ ppm 0.9 (t, J=7.3 Hz, 3 H) 1.4 (m, 3 H) 1.5 (m, 1 H) 1.7 (m, 1 H) 3.25-3.48 (m, 3 H) 3.7 (s, 3 H) 4.1 (m, 1 H) 4.3 (m, 2 H) 4.36-4.65 (m, 2 H) 7.3 (s, 1 H) 7.5 (s, 1 H) 7.5 (s, 1 H) 7.6 (s, 1 H) 7.8 (s, 1 H) 7.9 (s, 1 H); MS (ES⁺) Calc: 600.17, Found: 601.4 (M+1).

Example 15: Ethyl 3-((N-(3,5-bis(trifluoromethyl)benzyl)acetamido)methyl)-2-cyclopropyl-5-(trifluoromethyl)indoline-1-carboxylate



Step 1: Preparation of Diethyl 2-cyclopropyl-5-(trifluoromethyl)indoline-3,3-dicarboxylate

In 50 ml of methanol under N₂ were carefully combined 260 mg of PtO₂ and diethyl 2-(5-(trifluoromethyl)-2-nitrophenyl)malonate (3.32 gm, 9.5 mmol). The mixture was hydrogenated at an initial pressure of 42 psi of H₂ until no further uptake of H₂ was observed, approximately 30 min. TLC showed complete loss of the starting material. The reaction mixture was filtered through Celite into a solution containing cyclopropane carboxaldehyde (0.85 ml, 11.4 mmol) in 20 ml of methanol. The resulting

"purple" solution was stirred for 15 minutes at room temperature, and was then treated with 0.67 gm (3.04 mmol) of zinc acetate dehydrate. The reaction was stirred over the weekend. The reaction was concentrated in vacuo and the residue partitioned between ethyl acetate/1N HCl. The ethyl acetate layer was separated and combined with a second extract. The extracts were washed with saturated NaHCO₃,
5 brine and then dried through MgSO₄. Removal of the solvent afforded 3.09 gm of a grey oil. The material was taken up in methylene chloride and chromatographed on a Biotage Flash 40L column. The column was eluted with 5% ethyl acetate/heptane (1L) followed by 10% ethyl acetate/heptane (3L). Pure fractions were combined and concentrated to afford 1.21 gm of the title compound as a reddish solid (34%).

10 ¹H NMR (400 MHz, CHLOROFORM-D) □ ppm 0.4 (m, 1 H) 0.5 (m, 1 H) 0.5 (m, 2 H) 1.0 (m, 1 H) 1.2 (t, J=7.1 Hz, 3 H) 1.3 (t, J=7.3 Hz, 3 H) 3.9 (d, J=9.5 Hz, 1 H) 4.2 (m, 4 H) 6.7 (d, J=8.3 Hz, 1 H) 7.4 (d, J=8.3 Hz, 1 H) 7.6 (s, 1 H); MS (ES⁺) Calc: 371.13, Found: 372.4 (M+1).

Step 2: Preparation of Triethyl 2-cyclopropyl-5-(trifluoromethyl)indoline-1,3,3-tricarboxylate

Diethyl 2-cyclopropyl-5-(trifluoromethyl)indoline-3,3-dicarboxylate (1.21 gm, 3.26 mmol) was
15 dissolved in 15 ml of toluene and treated with 20% phosgene in toluene (17.24 ml, 163 mmol). The solution was heated to reflux and was refluxed for 5 hours. TLC showed complete reaction. The reaction was concentrated to a dry solid, and was then dissolved in 30 ml of anhydrous ethanol. The solution was refluxed for 40 hr. The solvent was removed in vacuo to afford 2.13 g of a yellow solid. The material was taken up in methylene chloride and chromatographed on a Biotage Flash 40M column, eluting with 2L of
20 10% ethyl acetate/heptane. Pure fractions were found by TLC analysis, combined and concentrated to afford 1.17 g of the title compound as a white solid (81%).

¹H NMR (400 MHz, CHLOROFORM-D) □ ppm 0.4 (m, 1 H) 0.5 (m, 2 H) 0.8 (m, 1 H) 0.9 (m, 1 H) 1.2 (t, J=7.1 Hz, 3 H) 1.3 (t, J=7.1 Hz, 3 H) 1.4 (t, J=7.3 Hz, 3 H) 4.1 (m, 1 H) 4.2 (m, 2 H) 4.4 (m, 3 H) 4.7 (d, J=10.0 Hz, 1 H) 7.6 (d, J=8.3 Hz, 1 H) 7.7 (s, 1 H) 7.8 (s, 1 H); MS (ES⁺) Calc: 443.16, Found: 444.4
25 (M+1).

Step 3: Preparation of 1-(ethoxycarbonyl)-2-cyclopropyl-5-(trifluoromethyl)indoline-3-carboxylic acid

In 25 ml of absolute ethanol was dissolved Triethyl 2-cyclopropyl-5-(trifluoromethyl)indoline-1,3,3-tricarboxylate (1.17 gm, 2.64 mmol). The solution was cooled in an ice bath. To this solution was added 15 ml of 10% (w/w) aqueous KOH. The reaction turned dark red and was stirred overnight, slowly coming
30 to room temperature. The reaction was concentrated to remove some of the ethanol. The concentrate was poured onto 300 ml of ice water. The mixture was extracted with Et₂O. The aqueous phase was separated and made acidic with 6N HCl. The acidic solution was extracted with chloroform. The chloroform extracts were washed with brine and dried through MgSO₄. Removal of the solvent afforded 0.75 gm of the title compound as a white solid foam (83%).

35 ¹H NMR (400 MHz, CHLOROFORM-D) □ ppm 0.3 (m, 1 H) 0.5 (m, 1 H) 0.6 (m, 1 H) 0.8 (m, 1 H) 1.0 (m, 1 H) 1.4 (t, J=7.3 Hz, 3 H) 4.0 (s, 1 H) 4.3 (m, 3 H) 7.5 (d, J=7.9 Hz, 1 H) 7.6 (s, 1 H) 7.9 (s, 1 H); MS (ES⁺) Calc: 343.1, Found: 344.4 (M+1).

Step 4: Preparation of Ethyl 2-cyclopropyl-5-(trifluoromethyl)-3-(hydroxymethyl)indoline-1-carboxylate

1-(Ethoxycarbonyl)-2-cyclopropyl-5-(trifluoromethyl)indoline-3-carboxylic acid (750 mg, 2.18
40 mmol) was dissolved in 5 ml of anhydrous THF and cooled in an ice bath. To this solution was added 4.4

ml of a 1M BH₃.THF solution. The reaction was stirred over night, slowly coming to ambient temperature. The reaction was quenched with 10 ml of 20% HOAc/methanol. The solvents were removed in vacuo and the concentrate partitioned between ethyl acetate/1N HCl. The ethyl acetate was separated and combined with a second extract. The organics were then washed with water, 1M NH₄CO₃ and brined.

5 After drying through MgSO₄, the solvent was removed in vacuo to afford 0.71 gm of a clear colorless oil. The material was taken up in methylene chloride and chromatographed on a Biotage Flash 40S column. The column was eluted with 10% ethyl acetate/heptane (1L) followed by 20% ethyl acetate/heptane (1L). Pure fractions were found by TLC, combined and concentrated to afford 641 mg of the title compound as an oil (89%).

10 ¹H NMR (400 MHz, CHLOROFORM-D) □ ppm 0.3 (m, 1 H) 0.5 (m, 1 H) 0.6 (m, 1 H) 0.7 (m, 1 H) 1.0 (m, 1 H) 1.4 (t, J=7.1 Hz, 3 H) 3.2 (t, J=6.6 Hz, 1 H) 3.6 (dd, J=10.8, 7.9 Hz, 1 H) 3.7 (dd, J=10.4, 6.2 Hz, 1 H) 3.8 (d, J=8.7 Hz, 1 H) 4.3 (m, 2 H) 7.4 (s, 1 H) 7.5 (d, J=8.7 Hz, 1 H) 7.9 (s, 1 H); MS (ES⁺) Calc: 329.12, Found: 330.4 (M+1).

Step 5: Preparation of ethyl 2-cyclopropyl-5-(trifluoromethyl)-3-formylindoline-1-carboxylate

15 Ethyl 2-cyclopropyl-5-(trifluoromethyl)-3-(hydroxymethyl)indoline-1-carboxylate (640 mg, 1.94 mmol) was dissolved in 20 ml of anhydrous methylene chloride and treated with the Dess-Martin Reagent (0.99 gm, 2.33 mmol). The reaction was stirred at room temperature overnight. The reaction was diluted with methylene chloride, washed with 1N NaOH, water and brine. After drying over MgSO₄, removal of the solvent afforded 498 mg of the title compounds as an oil (78%).

20 ¹H NMR (400 MHz, CHLOROFORM-D) □ ppm 0.3 (m, 1 H) 0.5 (m, 1 H) 0.7 (m, 1 H) 0.8 (m, 1 H) 1.1 (m, 1 H) 1.4 (t, J=7.3 Hz, 3 H) 3.9 (s, 1 H) 4.3 (m, 3 H) 7.6 (m, 2 H) 7.9 (s, 1 H) 9.6 (s, 1 H); MS (ES⁺) Calc: 327.11, Found: 326.2 (M-1).

Step 6: Preparation of Ethyl 3-((3,5-bis(trifluoromethyl)benzylamino)methyl)-2-cyclopropyl-5-(trifluoromethyl)indoline-1-carboxylate

25 In 20 ml of 95:5 THF/HOAc were combined ethyl 2-cyclopropyl-5-(trifluoromethyl)-3-formylindoline-1-carboxylate (487 mg, 1.48 mmol), 3,5-bis(trifluoromethyl)benzylamine (434 mg, 1.78 mmol) and silica supported cyanoborohydride (2.52 g, 1.18 mmol/gm, 2.97 mmol). The reaction was stirred overnight. The reaction was filtered and the solid support rinsed well with ethyl acetate. The filtrate was concentrated in vacuo and the concentrate then partitioned between ethyl acetate and
30 saturated NaHCO₃. The organic layer was separated and combined with a second extract. The organics were washed with brine and dried through MgSO₄. Removal of the solvent afforded 899 mg of a light yellow oil. The product was taken up in methylene chloride and chromatographed on a Biotage Flash 40S column. The column was eluted with 1L of 10% ethyl acetate/Heptane to afford 519 mg of the title compound as an oil (63%).

35 ¹H NMR (400 MHz, CHLOROFORM-D) □ ppm 0.2 (m, 1 H) 0.4 (m, 1 H) 0.6 (m, 1 H) 0.7 (m, 1 H) 1.0 (m, 1 H) 1.4 (t, J=7.1 Hz, 3 H) 2.7 (m, 2 H) 3.2 (t, J=6.2 Hz, 1 H) 3.8 (d, J=8.7 Hz, 1 H) 3.9 (d, J=2.9 Hz, 2 H) 4.2 (m, 1 H) 4.3 (m, 1 H) 7.4 (s, 1 H) 7.5 (d, J=8.3 Hz, 1 H) 7.8 (m, 3 H) 7.8 (s, 1 H); MS (ES⁺) Calc: 554.16, Found: 555.4 (M+1).

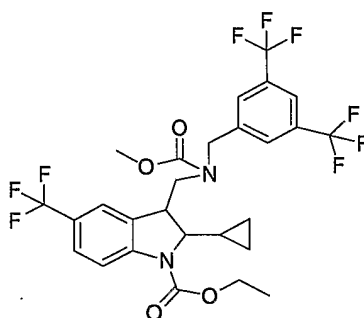
Step 7: Preparation of ethyl 3-((N-(3,5-bis(trifluoromethyl)benzyl)acetamido)methyl)-2-cyclopropyl-5-(trifluoromethyl)indoline-1-carboxylate

40

In 3 ml of anhydrous methylene chloride under N₂ was combined with ethyl 3-((3,5-bis(trifluoromethyl)benzylamino)methyl)-2-cyclopropyl-5-(trifluoromethyl)indoline-1-carboxylate (92 mg, 0.166 mmol) and pyridine (40 μ L, 0.49 mmol). The solution was cooled in an ice bath and was treated with acetyl chloride (18 μ L, 0.25 mmol). The reaction was stirred for 1 hr at which time TLC showed complete reaction to form a more polar product. The reaction was diluted with methylene chloride and washed with 1N HCl, saturated NaHCO₃ and brine. After drying through MgSO₄, the solvent was removed in vacuo to afford 82 mg of the title compound as an oil (83%).

¹H NMR (400 MHz, CHLOROFORM-D) δ ppm 0.1, 0.2 (m, 1 H) 0.5 (m, 1 H) 0.6 (m, 2 H) 1.0 (m, 1 H) 1.4 (t, J=6.6 Hz, 3 H) 1.89, 2.13 (s, 3 H) 3.1, 3.3 (m, 1 H) 3.3 (d, J=8.3 Hz, 1 H) 3.4, 3.57 (t, J=7.9 Hz, 1 H) 3.6, 3.7 (t, J=7.7 Hz, 1 H) 4.3 (m, 2 H) 4.2, 4.7 (d, J=15.4 Hz, 1 H) 4.5, 4.9 (d, J=15.4 Hz, 1 H) 7.27, 7.34 (s, 1 H) 7.4 (s, 1 H) 7.6 (t, J=7.7 Hz, 1 H) 7.7 (s, 1 H) 7.8 (s, 1 H) 8.0 (s, 1 H); MS (ES⁺) Calc: 596.17, Found: 597.4 (M+1).

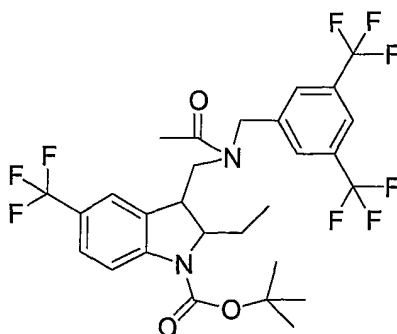
Example 16: Methyl (1-(ethoxycarbonyl)-2-cyclopropyl-5-(trifluoromethyl)indolin-3-yl)methyl 3,5-bis(trifluoromethyl)benzylcarbamate



In 3 ml of anhydrous methylene chloride under N₂ were combined ethyl 3-((3,5-bis(trifluoromethyl)benzylamino)methyl)-2-cyclopropyl-5-(trifluoromethyl)indoline-1-carboxylate (98 mg, 0.177 mmol) and pyridine (43 μ L, 0.53 mmol). The solution was cooled in an ice bath and was treated with methyl chloroformate (20 μ L, 0.265 mmol). The reaction was stirred for 1 hr at which time TLC showed complete reaction to form a slightly more polar product. The reaction was diluted with methylene chloride and washed with 1N HCl, saturated NaHCO₃ and brine. After drying through MgSO₄, the solvent was removed in vacuo to afford 79 mg of the title compound as an oil (73%).

¹H NMR (400 MHz, CHLOROFORM-D) δ ppm 0.1 (m, 1 H) 0.5 (m, 1 H) 0.6 (m, 2 H) 1.0 (m, 1 H) 1.4 (t, J=7.1 Hz, 3 H) 3.2 (m, 1 H) 3.3-3.6 (m, 3 H) 3.7 (s, 3 H) 4.3 (m, 2 H) 4.5 (m, 1 H) 4.7 (m, 1 H) 7.3 (s, 1 H) 7.5 (s, 1 H) 7.5 (s, 1 H) 7.6 (s, 1 H) 7.8 (s, 1 H) 7.9 (s, 1 H); MS (ES⁺) Calc: 612.17, Found: 613.4 (M+1).

Example 17: tert-butyl 3-((N-(3,5-bis(trifluoromethyl)benzyl)acetamido)methyl)-2-ethyl-5-(trifluoromethyl)indoline-1-carboxylate



Step 1: Preparation of tert-butyl 3-((3,5-bis(trifluoromethyl)benzylamino)methyl)-2-ethyl-5-(trifluoromethyl)indoline-1-carboxylate

In 10 ml of 95:5 THF/HOAc was dissolved tert-butyl 2-ethyl-5-(trifluoromethyl)-3-formylindoline-1-carboxylate (122 mg 0.355 mmol). To this solution was added the amine (103 mg, 0.426 mmol) followed by 0.602 g (1.18 mmol/g, 0.711 mmol) of the Si-CN₃BH₃. The reaction was stirred overnight under N₂. The reaction was filtered and the silica washed well with ethyl acetate. The filtrate was concentrated and the residue partitioned between ethyl acetate and saturated NaHCO₃. The organic layer was separated and combined with a second extract. The organics were washed with brine and dried over MgSO₄.

Removal of the solvent afforded 199 mg of an oil. The product was taken up in methylene chloride and chromatographed on a Biotage Flash 40S column. The column was eluted with 10% ethyl acetate/heptane. (1L) to afford 107 mg of the title compound as an oil (52.8%).

¹H NMR (400 MHz, CHLOROFORM-D) δ ppm 0.9 (t, J=7.5 Hz, 3 H) 1.6 (s, 9 H) 1.6 (m, 1 H) 1.7 (m, 1 H) 2.7 (m, 2 H) 3.0 (t, J=6.2 Hz, 1 H) 3.9 (s, 2 H) 4.2 (m, 1 H) 7.4 (s, 1 H) 7.5 (d, J=8.3 Hz, 1 H) 7.8 (m, 4 H); MS (ES⁺) Calc: 570.19, Found: 571.5 (M+1).

Step 2: Preparation of tert-butyl 3-((N-(3,5-bis(trifluoromethyl)benzyl)acetamido)methyl)-2-ethyl-5-(trifluoromethyl)indoline-1-carboxylate

Tert-butyl 3-((3,5-bis(trifluoromethyl)benzylamino)methyl)-2-ethyl-5-(trifluoromethyl)indoline-1-carboxylate (107 mg, 0.187 mmol) was dissolved in 5 ml of anhydrous methylene chloride and cooled in an ice bath. To this solution was added pyridine (46 μL, 0.563 mmol) followed by acetyl chloride (20 μL, 0.281 mmol). The reaction was stirred at ice bath temperatures starting for 3.5 hr. The reaction was diluted with methylene chloride and washed with 1N HCl, saturated NaHCO₃ and brine. After drying through MgSO₄, removal of the solvent afforded 89 mg of an oil. The product was chromatographed on a Biotage Flash 40S column, eluting with 1.5 L of 20% ethyl acetate/heptane to afford 81 mg of the title compound as an oil (70.5%).

¹H NMR (400 MHz, CHLOROFORM-D) δ ppm 0.85, 0.89 (t, J=7.7 Hz, 3 H) 1.5 (m, 1 H) 1.6 (s, 9 H) 1.7 (m, 1 H) 1.93, 2.1 (s, 3 H) 3.0, 3.1 (t, J=7.9 Hz, 1 H) 3.3 (m, 1 H) 3.5, 3.8 (t, J=7.5 Hz, 1 H) 4.0 (m, 1 H) 4.1, 4.5 (s, 1 H) 4.8 (s, 1 H) 7.23, 7.31 (s, 1 H) 7.5 (s, 1 H) 7.5 (t, J=7.5 Hz, 1 H) 7.7 (s, 1 H) 7.8 (s, 1 H) 7.9 (s, 1 H); MS (ES⁺) Calc: 612.2, Found: 613.5 (M+1).

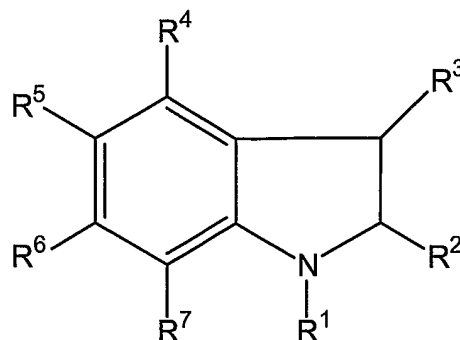
Throughout this application, various publications are referenced. The disclosures of these publications in their entireties are hereby incorporated by reference into this application for all purposes.

It will be apparent to those skilled in the art that various modifications and variations can be made in the present invention without departing from the scope or spirit of the invention. Other embodiments of the invention will be apparent to those skilled in the art from consideration of the specification and

practice of the invention disclosed herein. It is intended that the specification and examples be considered as exemplary only, with a true scope and spirit of the invention being indicated by the following claims.

What is claimed is:

1. A compound according to Formula I



Formula I

5 or a pharmaceutically acceptable salt of said compound;

R¹ is Y, W-X or W-Y¹; wherein W is a carbonyl, thiocarbonyl, sulfinyl or sulfonyl; X is -O-Y, -S-Y, -N(H)-Y or -N-(Y)₂; Y for each occurrence is independently Z or a fully saturated, partially unsaturated or fully unsaturated one to ten membered straight or branched carbon chain wherein each carbon, other than the connecting carbon, may optionally be replaced with one or two heteroatoms selected

10 independently from oxygen, sulfur and nitrogen and said carbon is optionally mono-, di- or tri-substituted independently with halo, said carbon is optionally mono-substituted with hydroxy, said carbon is optionally mono-substituted with oxo, said sulfur is optionally mono- or di-substituted with oxo, said nitrogen is optionally mono-, or di-substituted with oxo, and said carbon chain is optionally mono-

substituted with Z; and Y¹ for each occurrence is independently Z or a fully saturated, partially

15 unsaturated or fully unsaturated one to ten membered straight or branched carbon chain wherein each carbon, other than the connecting carbon, may optionally be replaced with one or two heteroatoms selected independently from oxygen, sulfur and nitrogen and said carbon is optionally mono-, di- or tri-substituted independently with halo, said carbon is optionally mono-substituted with hydroxy, said carbon is optionally mono-substituted with oxo, said sulfur is optionally mono- or di-substituted with oxo, said

20 nitrogen is optionally mono-, or di-substituted with oxo, and said carbon chain is optionally mono-substituted with Z; wherein Z is a partially saturated, fully saturated or fully unsaturated three to eight membered ring optionally having one to four heteroatoms selected independently from oxygen, sulfur and nitrogen, or a bicyclic ring consisting of two fused partially saturated, fully saturated or fully unsaturated three to six membered rings, taken independently, optionally having one to four heteroatoms

25 selected independently from nitrogen, sulfur and oxygen; and said Z substituent is optionally mono-, di- or tri-substituted independently with halo, (C₂-C₆)alkenyl, (C₁-C₆) alkyl, hydroxy, (C₁-C₆)alkoxy, (C₁-C₄)alkylthio, amino, nitro, cyano, oxo, carboxy, (C₁-C₆)alkyloxycarbonyl, mono-N- or di-N,N-(C₁-C₆)alkylamino wherein said (C₁-C₆)alkyl substituent is optionally mono-, di- or tri-substituted

30 independently with halo, hydroxy, (C₁-C₆)alkoxy, (C₁-C₄)alkylthio, amino, nitro, cyano, oxo, carboxy, (C₁-C₆)alkyloxycarbonyl, mono-N- or di-N,N-(C₁-C₆)alkylamino, said (C₁-C₆)alkyl or (C₁-C₆)alkoxy substituent is also optionally substituted with from one to nine fluorines;

R² is a partially saturated, fully saturated or fully unsaturated one to six membered straight or branched carbon chain wherein each carbon, other than the connecting carbon, may optionally be replaced with one or two heteroatoms selected independently from oxygen and sulfur, and said carbon is

optionally mono-, di- or tri-substituted independently with halo, said carbon chain is optionally mono-substituted with oxo, said carbon is optionally mono-substituted with hydroxy, said sulfur is optionally mono- or di-substituted with oxo,; or said R² is a partially saturated, fully saturated or fully unsaturated three to seven membered ring optionally having one to two heteroatoms selected independently from oxygen and sulfur, wherein said R² ring is optionally attached through (C₁-C₄)alkyl; wherein said R² ring is optionally mono-, di- or tri-substituted independently with halo, (C₂-C₆)alkenyl, (C₁-C₆) alkyl, hydroxy, (C₁-C₆)alkoxy, (C₁-C₄)alkylthio, amino, nitro, cyano, oxo, carboxy, (C₁-C₆)alkyloxycarbonyl, mono-N- or di-N,N-(C₁-C₆)alkylamino wherein said (C₁-C₆)alkyl substituent is optionally mono-, di- or tri-substituted independently with halo, hydroxy, (C₁-C₆)alkoxy, (C₁-C₄)alkylthio, oxo or (C₁-C₆)alkyloxycarbonyl;

R³ is a fully saturated, partially unsaturated or fully unsaturated one to six membered straight or branched carbon chain wherein each carbon in the carbon chain may optionally be replaced with one heteroatom selected from oxygen and nitrogen, and said carbon is optionally mono-, di- or tri-substituted with halo, said carbon is optionally mono-substituted with hydroxy, oxo, cyano, carbonyl, or amino, said carbon is optionally mono-substituted with oxo or nitrogen, said nitrogen is optionally mono- or di-substituted with hydrogen or oxo, and said carbon chain is mono, di-, or tri-substituted with V;

wherein V is a partially saturated, fully saturated or fully unsaturated three to eight membered ring optionally having one to four heteroatoms selected independently from oxygen, sulfur and nitrogen; a bicyclic ring consisting of two fused partially saturated, fully saturated or fully unsaturated three to six membered rings, taken independently, optionally having one to four heteroatoms selected independently from nitrogen, sulfur and oxygen; or a tricyclic ring consisting of three fused partially saturated, fully saturated or fully unsaturated three to six membered rings, taken independently, optionally having one to four heteroatoms selected independently from nitrogen, sulfur and oxygen; and said V substituent is optionally mono-, di-, tri-, tetra- or penta-substituted independently with (R⁰)_n, V¹, (C₁-C₆)alkyl-V¹, C(O)-V¹, O-(C₀-C₆)alkyl-V¹, (C₁-C₆)alkyl-O-V¹, C(O)-mono-N- or di-N,N-(C₁-C₆)alkyl-V¹, halo, (C₁-C₆)alkyl, (C₂-C₆)alkenyl, hydroxy, (C₁-C₆)alkoxy, (C₁-C₄)alkylthio, (C₁-C₄)alkylsulfinyl, (C₁-C₄)alkylsulfonyl, mono-N- or di-N,N-(C₁-C₆)alkylsulfonyl, amino, nitro, cyano, oxo, carboxamoyl, mono-N- or di-N,N-(C₁-C₆)alkylcarboxamoyl, carboxy, (C₁-C₆)alkyloxycarbonyl, mono-N- or di-N,N-(C₁-C₆)alkylamino, wherein said (C₁-C₆)alkyl or (C₂-C₆)alkenyl substituent is optionally mono-, di- or tri-substituted independently with hydroxy, (C₁-C₆)alkoxy, (C₁-C₄)alkylthio, amino, nitro, cyano, oxo, carboxy, (C₁-C₆)alkyloxycarbonyl, mono-N- or di-N,N-(C₁-C₆)alkylamino, wherein each (C₁-C₆)alkyl, (C₁-C₆)alkoxy, (C₁-C₄)alkylthio, (C₁-C₄)alkylsulfonyl or (C₂-C₆)alkenyl substituents are also optionally substituted with from one to nine fluorines, and wherein n is 1, 2, 3 or 4 and each R⁰ is independently halo, (C₁-C₆)alkyl, (C₂-C₆)alkenyl, hydroxy, (C₁-C₆)alkoxy, (C₁-C₄)alkylthio, amino, nitro, cyano, oxo, carboxamoyl, carboxy, (C₁-C₆)alkyloxycarbonyl, mono-N- or di-N,N-(C₁-C₆)alkylamino, (C₁-C₆)alkyloxycarbonyl, mono-N- or di-N,N-(C₁-C₆)alkylamino wherein said (C₁-C₆)alkyl substituent is optionally mono-substituted with oxo, said (C₁-C₆)alkyl substituent is also optionally substituted with from one to nine fluorines;

wherein V¹ is a partially saturated, fully saturated or fully unsaturated three to six membered ring optionally having one to two heteroatoms selected independently from oxygen, sulfur and nitrogen, or a bicyclic ring consisting of two fused partially saturated, fully saturated or fully unsaturated three to six membered rings, taken independently, optionally having one to four heteroatoms selected independently from nitrogen, sulfur and oxygen; and said V¹ substituent is optionally mono-, di-, tri-, tetra- or penta-

substituted independently with halo, (C₁-C₆)alkyl, (C₁-C₆)alkoxy, hydroxy, oxo, amino, nitro, cyano, (C₁-C₆)alkyloxycarbonyl, or mono-N- or di-N,N-(C₁-C₆)alkylamino wherein said (C₁-C₆)alkyl substituent is optionally mono-substituted with oxo, said (C₁-C₆)alkyl or (C₁-C₆)alkoxy substituent is also optionally substituted with from one to nine fluorines; and

- 5 each of R⁴, R⁵, R⁶ and R⁷ are independently hydrogen, a bond, nitro or halo wherein said bond is substituted with T or a partially saturated, fully saturated or fully unsaturated (C₁-C₁₂) straight or branched carbon chain wherein each carbon may optionally be replaced with one or two heteroatoms per carbon chain wherein the heteroatoms are selected independently from oxygen, sulfur and nitrogen, wherein said carbon is optionally mono-, di- or tri-substituted independently with halo, said carbon is
- 10 optionally mono-substituted with hydroxy, said carbon is optionally mono-substituted with oxo or nitrogen, said sulfur is optionally mono- or di-substituted with oxo, said nitrogen is optionally mono- or di-substituted with hydrogen or oxo, and said carbon chain is optionally mono-substituted with T; wherein T is a partially saturated, fully saturated or fully unsaturated three to twelve membered ring optionally having one to four heteroatoms selected independently from oxygen, sulfur and nitrogen, or a bicyclic
- 15 ring consisting of two fused partially saturated, fully saturated or fully unsaturated three to six membered rings, taken independently, optionally having one to four heteroatoms selected independently from nitrogen, sulfur and oxygen; and said T substituent is optionally mono-, di- or tri-substituted independently with halo, (C₁-C₆)alkyl, (C₂-C₆)alkenyl, hydroxy, (C₁-C₆)alkoxy, (C₁-C₄)alkylthio, amino, nitro, cyano, oxo, carboxy, (C₁-C₆)alkyloxycarbonyl, or mono-N- or di-N,N-(C₁-C₆)alkylamino wherein said
- 20 (C₁-C₆)alkyl substituent is optionally mono-, di- or tri-substituted independently with hydroxy, (C₁-C₆)alkoxy, (C₁-C₄)alkylthio, amino, nitro, cyano, oxo, carboxy, (C₁-C₆)alkyloxycarbonyl, mono-N- or di-N,N-(C₁-C₆)alkylamino, said (C₁-C₆)alkyl or (C₁-C₆)alkoxy substituent also optionally has from one to nine fluorines;

- R⁴ and R⁵, R⁵ and R⁶, and/or R⁶ and R⁷ may optionally be taken together and can form at least
- 25 one ring that is a partially saturated or fully unsaturated four to eight membered ring optionally having one to three heteroatoms independently selected from nitrogen, sulfur and oxygen; wherein each ring formed by R⁴ and R⁵, or R⁵ and R⁶, and/or R⁶ and R⁷ is optionally mono-, di- or tri-substituted independently with halo, (C₁-C₆)alkyl, (C₁-C₄)alkylsulfonyl, (C₂-C₆)alkenyl, hydroxy, (C₁-C₆)alkoxy, (C₁-C₄)alkylthio, amino, nitro, cyano, oxo, carboxy, (C₁-C₆)alkyloxycarbonyl, or mono-N- or di-N,N-(C₁-C₆)alkylamino wherein said (C₁-C₆)alkyl substituent is optionally mono-, di- or tri-substituted
- 30 independently with hydroxy, (C₁-C₆)alkoxy, (C₁-C₄)alkylthio, amino, nitro, cyano, oxo, carboxy, (C₁-C₆)alkyloxycarbonyl, or mono-N- or di-N,N-(C₁-C₆)alkylamino, said (C₁-C₆)alkyl substituent also optionally has from one to nine fluorines.

- 35 2. A compound as recited in claim 1 wherein

R¹ is W-X;

W is carbonyl;

X is -O-Y;

- 40 Y for each occurrence is independently (C₁-C₆)alkyl, said (C₁-C₆)alkyl optionally having one to nine fluorines or said (C₁-C₆)alkyl optionally mono-substituted with Z;

wherein Z is a partially saturated, fully saturated or fully unsaturated three to six membered ring optionally having one to two heteroatoms selected independently from oxygen, sulfur and nitrogen;

wherein said Z substituent is optionally mono-, di- or tri-substituted independently with halo, nitro, amino, hydroxy, cyano, carboxy, acyl, (C₁-C₆)alkoxy, (C₁-C₄)alkylthio, oxo, (C₁-

5 C₆)alkyloxycarbonyl or (C₁-C₆)alkyl, said (C₁-C₄)alkyl is optionally substituted with from one to nine halo, carboxy, oxo, (C₁-C₆)alkoxy, carboxy, or (C₁-C₆)alkyloxycarbonyl;

R² is beta and is a partially saturated, fully saturated or fully unsaturated (C₁-C₄) straight or branched carbon chain wherein one carbon, other than the connecting carbon, may optionally be replaced with oxygen or sulfur and wherein said carbon is optionally mono-, di- or tri-substituted

10 independently with halo, said carbon chain is optionally mono-substituted with oxo or hydroxy, said sulfur is optionally mono- or di-substituted with oxo,; or said R² is a partially saturated, fully saturated or fully unsaturated three to five membered ring optionally having one heteroatom selected independently from oxygen and sulfur;

wherein said R² ring is optionally mono-, di- or tri-substituted independently with halo, hydroxy, (C₁-C₆)alkoxy, amino, nitro, (C₁-C₄)alkyloxycarbonyl or carboxy;

R³ is mono-substituted or di-substituted with V;

R⁴ is hydrogen;

R⁵ and R⁶ are each independently hydrogen, halo, T, (C₁-C₆)alkoxy or (C₁-C₆)alkyl, said (C₁-C₆)alkoxy or (C₁-C₆)alkyl substituent optionally having from one to nine fluorines or said (C₁-C₆)alkoxy or (C₁-C₆)alkyl substituent optionally mono-substituted with T;

wherein T is a partially saturated, fully saturated or fully unsaturated five to six membered ring optionally having one to two heteroatoms selected independently from oxygen, sulfur and nitrogen;

wherein said T substituent is optionally mono-, di- or tri-substituted independently with halo, (C₁-C₆)alkyl, hydroxy, (C₁-C₆)alkoxy, (C₁-C₄)alkylthio, amino, oxo, carboxy, (C₁-C₆)alkyloxycarbonyl, or mono-N- or di-N,N-(C₁-C₆)alkylamino wherein said (C₁-C₆)alkyl or (C₁-C₆)alkoxy substituent optionally has from one to nine fluorines;

R⁷ is hydrogen;

or a pharmaceutically acceptable salt thereof.

30 3. A compound as recited in claim 2 wherein

Y is (C₁-C₄)alkyl, wherein said (C₁-C₄)alkyl substituent optionally has one to nine fluorines;

R² is (C₁-C₄)alkyl, cyclopropyl or cyclobutyl;

R³ is -CH₂-N(C(O)-(C₁-C₂)alkyl)CH₂(V), -CH₂N(C(O)OCH₃)CH₂(V), -C(O)N(H)-(C₁-C₃)alkyl-(V), -C(O)(V), -(C₁-C₃)alkyl-(OH)(V), -(C₁-C₂)alkyl-C(O)(V), -(C₁-C₂)alkyl-N(V)-(C₁-C₂)alkyl-(V), -C(O)N(V)-(C₁-C₃)alkyl-(V), -(C₁-C₃)alkoxy-(V)₂, -(C₁-C₃)alkyl-(OH)(V)₂, or -(C₁-C₃)alkyl-(V)₂;

V is tetrazole, triazole, imidazole, pyrazole, oxadiazole, isoxazole, oxazole, furan, thiadiazole, isothiazole, thiazole, thiophene, phenyl, pyrimidine, or pyridine wherein V is optionally mono-, di- or tri-substituted independently with halo, (C₁-C₆)alkyl, hydroxy, (C₁-C₆)alkoxy, nitro, cyano or oxo wherein said (C₁-C₆)alkyl or (C₁-C₆)alkoxy substituent optionally has from one to nine fluorines;

R^5 and R^6 are each independently hydrogen, halo, (C₁-C₃)alkoxy or (C₁-C₆)alkyl, said (C₁-C₃)alkoxy optionally having from one to seven halo, said (C₁-C₆)alkyl optionally having from one to nine halo;

or a pharmaceutically acceptable salt thereof.

5

4. A compound as recited in claim 1 wherein

R^1 is W-Y¹ or Y;

W is carbonyl;

Y and Y¹ are each independently Z or (C₁-C₄)alkyl, said (C₁-C₄)alkyl substituted with Z

10 and optionally substituted with from one to nine fluorines, or hydroxy;

wherein Z is a partially saturated, fully saturated or fully unsaturated three to six membered ring optionally having one to two heteroatoms selected independently from oxygen, sulfur and nitrogen;

wherein said Z substituent is optionally mono-, di- or tri-substituted independently with halo, nitro, amino, hydroxy, cyano, carboxy, acyl, (C₁-C₆)alkoxy, (C₁-C₄)alkylthio, oxo, (C₁-

15 C₆)alkyloxycarbonyl or (C₁-C₆)alkyl, said (C₁-C₄)alkyl is optionally substituted with from one to nine halo, carboxy, oxo, (C₁-C₆)alkoxy, carboxy, and (C₁-C₆)alkyloxycarbonyl;

R^2 is beta and is a partially saturated, fully saturated or fully unsaturated (C₁-C₄) straight or branched carbon chain wherein one carbon, other than the connecting carbon, may optionally be replaced with oxygen or sulfur and wherein said carbon is optionally mono-, di- or tri-

20 substituted independently with halo, said carbon chain is optionally mono-substituted with oxo or hydroxy, said sulfur is optionally mono- or di-substituted with oxo,; or said R^2 is a partially saturated, fully saturated or fully unsaturated three to five membered ring optionally having one heteroatom selected independently from oxygen and sulfur;

wherein said R^2 ring is optionally mono-, di- or tri-substituted independently with halo, hydroxy, (C₁-C₆)alkoxy, amino, nitro, (C₁-C₄)alkyloxycarbonyl or carboxy;

25 R^3 is mono-substituted or di-substituted with V;

R^4 is hydrogen;

R^5 and R^6 are each independently hydrogen, halo, T, (C₁-C₆)alkoxy or (C₁-C₆)alkyl, said (C₁-C₆)alkoxy or (C₁-C₆)alkyl substituent optionally having from one to nine fluorines or said (C₁-C₆)alkoxy or

30 (C₁-C₆)alkyl substituent optionally mono-substituted with T;

wherein T is a partially saturated, fully saturated or fully unsaturated five to six membered ring optionally having one to two heteroatoms selected independently from oxygen, sulfur and nitrogen;

wherein said T substituent is optionally mono-, di- or tri-substituted independently with halo, (C₁-C₆)alkyl, hydroxy, (C₁-C₆)alkoxy, (C₁-C₄)alkylthio, amino, oxo, carboxy, (C₁-C₆)alkyloxycarbonyl, or mono-N- or di-N,N-(C₁-C₆)alkylamino wherein said (C₁-C₆)alkyl or (C₁-C₆)alkoxy substituent optionally has from one to nine fluorines;

35 R^7 is hydrogen;

or a pharmaceutically acceptable salt thereof.

40 5. A compound as recited in claim 4 wherein

R^1 is W-Y¹;

Z is (C₃-C₆)cycloalkyl optionally substituted with independently one, two or three halo, nitro, amino, hydroxy, cyano, carboxy, acyl, (C₁-C₆)alkoxy, or (C₁-C₆)alkyl, wherein said (C₁-C₄)alkyl is optionally substituted with one to three substituents selected from the group consisting of: halo, carboxy, oxo, (C₁-C₆)alkoxy, carboxy, and (C₁-C₆)alkyloxycarbonyl;

5 R² is (C₁-C₄)alkyl, cyclopropyl or cyclobutyl;

R³ is -C(F)(V)₂, -C(OCH₃)(V)₂, -C(OH)(V)₂, -CH(V)₂,

V is tetrazole, triazole, imidazole, pyrazole, oxadiazole, isoxazole, oxazole, furan, thiadiazole, isothiazole, thiazole, thiophene, phenyl, pyrimidine, or pyridine wherein V is optionally mono-, di- or tri-substituted independently with halo, (C₁-C₆)alkyl, hydroxy, (C₁-C₆)alkoxy, nitro, cyano or oxo wherein

10 said (C₁-C₆)alkyl or (C₁-C₆)alkoxy substituent optionally has from one to nine fluorines;

R⁵ and R⁶ are each independently hydrogen, halo, (C₁-C₃)alkoxy or (C₁-C₆)alkyl, said (C₁-C₃)alkoxy optionally having from one to seven halo, said (C₁-C₆)alkyl optionally having from one to nine halo;

or a pharmaceutically acceptable salt thereof.

15

6. A compound as recited in claim 1 wherein

R¹ is W-Y¹ or Y;

W is carbonyl;

Y and Y¹ are each independently Z or (C₁-C₄)alkyl, said (C₁-C₄)alkyl substituted with Z

20 and optionally substituted with from one to nine fluorines or hydroxy;

wherein Z is a partially saturated, fully saturated or fully unsaturated three to six membered ring optionally having one to two heteroatoms selected independently from oxygen, sulfur and nitrogen;

wherein said Z substituent is optionally mono-, di- or tri-substituted independently with halo, nitro, amino, hydroxy, cyano, carboxy, acyl, (C₁-C₆)alkoxy, (C₁-C₄)alkylthio, oxo, (C₁-

25 C₆)alkyloxycarbonyl or (C₁-C₆)alkyl, said (C₁-C₄)alkyl is optionally substituted with from one to nine halo, carboxy, oxo, (C₁-C₆)alkoxy, carboxy, or (C₁-C₆)alkyloxycarbonyl;

R² is beta and is a partially saturated, fully saturated or fully unsaturated (C₁-C₄) straight or branched carbon chain wherein one carbon, other than the connecting carbon, may optionally be replaced with oxygen or sulfur and wherein said carbon is optionally mono-, di- or tri-substituted independently with halo, said carbon chain is optionally mono-substituted with oxo or hydroxy, said sulfur is optionally mono- or di-substituted with oxo,; or said R² is a partially saturated, fully saturated or fully unsaturated three to five membered ring optionally having one heteroatom selected independently from oxygen and sulfur;

30 wherein said R² ring is optionally mono-, di- or tri-substituted independently with halo, hydroxy, (C₁-C₆)alkoxy, amino, nitro, (C₁-C₄)alkyloxycarbonyl or carboxy;

R³ is mono-substituted or di-substituted with V;

R⁴ is hydrogen;

R⁵ and R⁶ are each independently hydrogen, halo, T, (C₁-C₆)alkoxy or (C₁-C₆)alkyl, said (C₁-C₆)alkoxy or (C₁-C₆)alkyl substituent optionally having from one to nine fluorines or said (C₁-C₆)alkoxy or

40 (C₁-C₆)alkyl substituent optionally mono-substituted with T;

wherein T is a partially saturated, fully saturated or fully unsaturated five to six membered ring optionally having one to two heteroatoms selected independently from oxygen, sulfur and nitrogen;

wherein said T substituent is optionally mono-, di- or tri-substituted independently with halo, (C₁-C₆)alkyl, hydroxy, (C₁-C₆)alkoxy, (C₁-C₄)alkylthio, amino, oxo, carboxy, (C₁-C₆)alkyloxycarbonyl, mono-N- or di-N,N-(C₁-C₆)alkylamino wherein said (C₁-C₆)alkyl or (C₁-C₆)alkoxy substituent optionally has from one to nine fluorines;

R⁷ is hydrogen;

or a pharmaceutically acceptable salt thereof.

7. A compound as recited in claim 6 wherein

R¹ is W-Y;

Z is (C₃-C₆)cycloalkyl optionally substituted with one, two or three halo, nitro, amino, hydroxy, cyano, carboxy, acyl, (C₁-C₆)alkoxy, or (C₁-C₆)alkyl, wherein said (C₁-C₄)alkyl is optionally substituted with one to three substituents selected from the group consisting of: halo,

carboxy, oxo, (C₁-C₆)alkoxy, carboxy, and (C₁-C₆)alkyloxycarbonyl;

R² is (C₁-C₄)alkyl, cyclopropyl or cyclobutyl;

R³ is -((C₁-C₄)alkyl)(NH₂)(V), -((C₁-C₃)alkyl)(NH(C₁-C₂)alkyl)(V), -((C₁-C₄)alkyl)(OH)(V), -((C₁-C₄)alkyl)(F)(V), -((C₁-C₂)alkyl)(O-C(O)(C₁-C₂)alkyl)(V), -C(O)-V, -C(OH)(C(O)O(C₁-C₃)alkyl)(V), -CF₂(V), -((C₁-C₂)alkyl)(NHC(O)(C₁-C₂)alkyl)(V), -CH₂(V), -((C₁-C₂)alkyl)(C(O)O(C₁-C₂)alkyl)(V), -((C₁-C₄)alkyl)(C(O)NH₂)(V), -((C₁-C₄)alkyl)(CN)(V), or -((C₁-C₃)alkyl)((C₁-C₃)alkoxy)(V),

V is phenyl optionally mono-, di- or tri-substituted independently with halo, (C₁-C₆)alkyl, hydroxy, (C₁-C₆)alkoxy, nitro, cyano or oxo wherein said (C₁-C₆)alkyl or (C₁-C₆)alkoxy substituent optionally has from one to nine fluorines;

R⁵ and R⁶ are each independently hydrogen, halo, (C₁-C₃)alkoxy or (C₁-C₆)alkyl, said (C₁-C₃)alkoxy optionally having from one to seven halo, said (C₁-C₆)alkyl optionally having from one to nine halo;

or a pharmaceutically acceptable salt thereof.

8. A compound of claim 7 wherein

Y is methyl, ethyl, 1-propyl, 2-propyl or tert-butyl;

R² is methyl, ethyl, 2-propyl, cyclopropyl or cyclobutyl;

R³ is -C(O)-V, -C(OH)(C(O)OCH₃)(V), -CH(F)(V), -CF₂(V), -CH(OCH₃)(V), -CH(C(O)OCH₃)(V), -CH(CN)(V), -CH(OH)(V), -CH₂(V), -CH(NH₂)(V), -CH(NH(CH₃))(V), -CH(C(O)NH₂)(V), -CH(CH₂OH)V, -CH(CH₂OCH₃)V, -CH(CH₂OC(O)CH₃)V, -CH(CH₂F)V, or -CH(CH₂NH₂)V; and

V is phenyl optionally mono-, di- or tri-substituted independently with halo, nitro, or (C₁-C₂)alkyl, wherein said (C₁-C₂)alkyl optionally has from one to five fluorines;

R⁵ and R⁶ are each independently hydrogen, methyl, methoxy or chloro; said methoxy optionally having from one to three fluorines, said methyl optionally having from one to three fluorines;

or a pharmaceutically acceptable salt thereof.

9. A compound of claim 8 wherein

Z is cyclobutyl, cyclopentyl, or cyclohexyl, and Z is optionally substituted with one or two carboxy, (C₁-C₆)alkoxy, or (C₁-C₆)alkyl, wherein said (C₁-C₆)alkyl substituent is optionally substituted with one, two or three substituents selected from halo, (C₁-C₆)alkoxy, carboxy, and (C₁-C₆)alkyloxycarbonyl;

R² is ethyl or methyl;

- 5 R³ is (3,5-bis-(trifluoromethyl)-phenyl)-hydroxy-methoxycarbonyl-methyl; (3,5-bis-trifluoromethyl-phenyl)-methoxycarbonyl-methyl; (3,5-bis-trifluoromethyl-phenyl)-cyano-methyl, 3,5-bis-trifluoromethyl-benzoyl; (3,5-bis-trifluoromethyl-phenyl)-hydroxy-methyl; (3,5-bis-trifluoromethyl-phenyl)-fluoro-methyl; (3,5-bis-trifluoromethyl-phenyl)-difluoro-methyl; (3,5-bis-(trifluoromethyl)-benzyl); (3,5-bis-trifluoromethyl-phenylcarbamoyl)-methyl; amino-(3,5-bis-(trifluoromethyl)-phenyl)-methyl; (3,5-bis-(trifluoromethyl)-phenyl)-methylamine-methyl; 1-(3,5-bis-(trifluoromethyl)-phenyl)-2-amino-ethyl; 1-(3,5-bis-(trifluoromethyl)-phenyl)-2-fluoro-ethyl; 1-(3,5-bis-(trifluoromethyl)-phenyl)-2-methoxy-ethyl; 1-(3,5-bis-(trifluoromethyl)-phenyl)-2-hydroxy-ethyl; or 2-acetoxy-1-(3,5-bis-(trifluoromethyl)-phenyl)-ethyl;

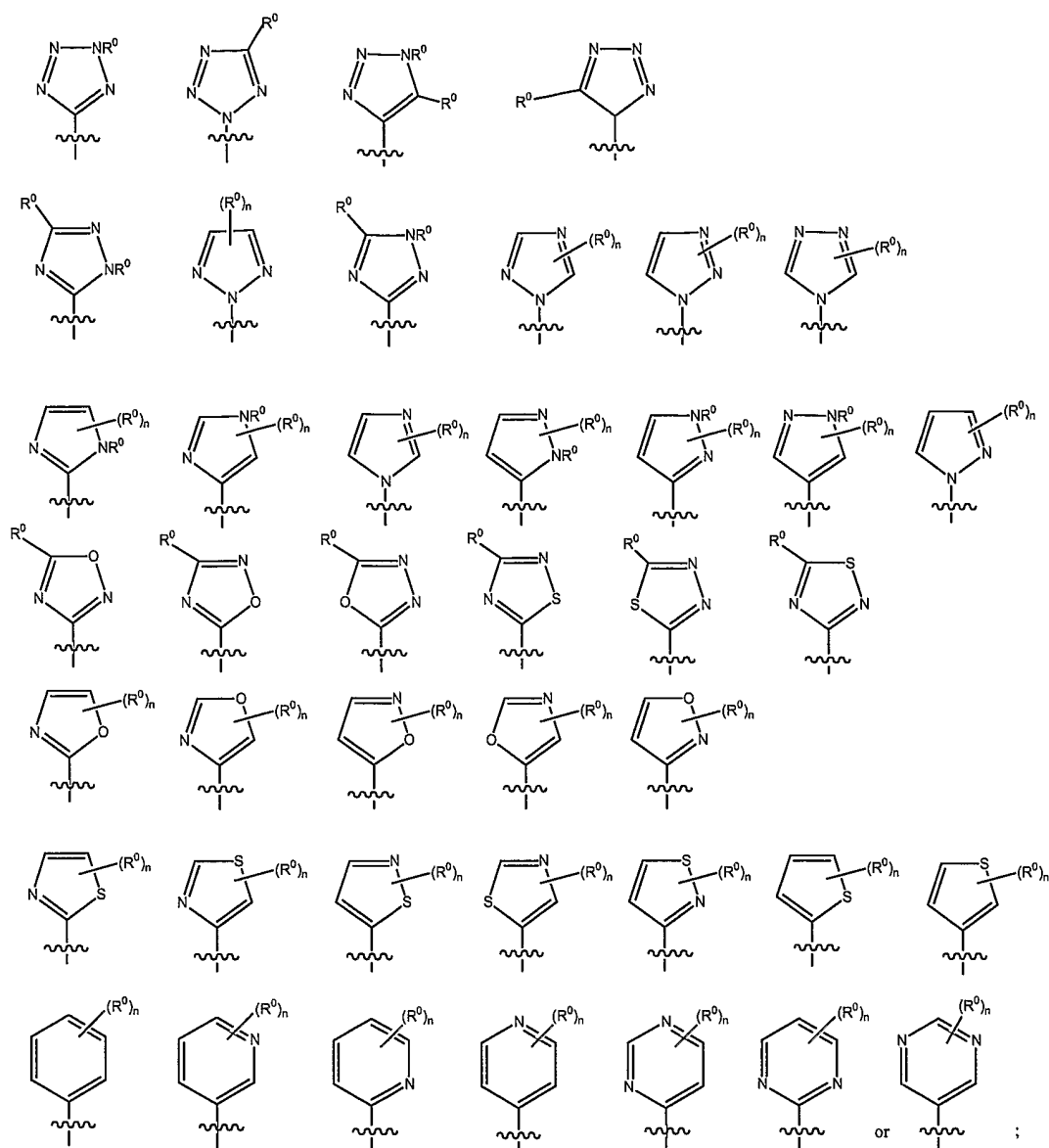
R⁵ is methoxy or trifluoromethyl; and

R⁶ is hydrogen or methoxy;

- 15 or a pharmaceutically acceptable salt thereof.

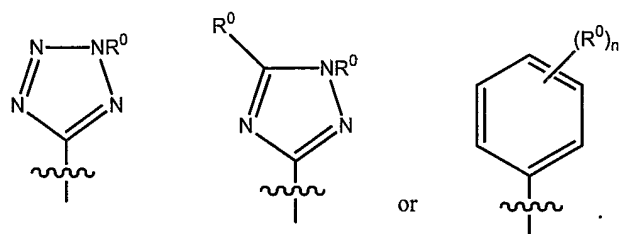
10. A compound as recited in any of claims 1-6 wherein

V is



wherein each R^0 is independently hydrogen, (C_1-C_3) alkyl, (C_1-C_3) alkoxy, hydroxy, or halo, wherein the alkyl or alkoxy is optionally substituted with 1 to nine halo or hydroxy.

- 5 11. A compound according to claim 11, wherein V is



12. A compound selected from the group consisting of:

3-[[[(3,5-Bis-trifluoromethyl-benzyl)-methoxycarbonyl-amino]-methyl]-2-methyl-6-trifluoromethyl-indoline-1-carboxylic acid ethyl ester;

(*R,R*)-3-[[[(3,5-Bis-trifluoromethyl-benzyl)-methoxycarbonyl-amino]-methyl]-2-methyl-6-trifluoromethyl-indoline-1-carboxylic acid ethyl ester;

(*R,S*)-3-[[[(3,5-Bis-trifluoromethyl-benzyl)-methoxycarbonyl-amino]-methyl]-2-methyl-6-trifluoromethyl-indoline-1-carboxylic acid ethyl ester;

5 3-[[Acetyl-(3,5-bis-trifluoromethyl-benzyl)-amino]-methyl]-2-methyl-6-trifluoromethyl-indoline-1-carboxylic acid ethyl ester;

(*R,R*)-3-[[Acetyl-(3,5-bis-trifluoromethyl-benzyl)-amino]-methyl]-2-methyl-6-trifluoromethyl-indoline-1-carboxylic acid ethyl ester;

10 (*R,S*)-3-[[Acetyl-(3,5-bis-trifluoromethyl-benzyl)-amino]-methyl]-2-methyl-6-trifluoromethyl-indoline-1-carboxylic acid ethyl ester;

3-[[[(3,5-Bis-trifluoromethyl-benzyl)-methoxycarbonyl-amino]-methyl]-2-methyl-5-trifluoromethyl-indoline-1-carboxylic acid ethyl ester;

(*R,R*)-3-[[[(3,5-Bis-trifluoromethyl-benzyl)-methoxycarbonyl-amino]-methyl]-2-methyl-5-trifluoromethyl-indoline-1-carboxylic acid ethyl ester;

15 (*R,S*)-3-[[[(3,5-Bis-trifluoromethyl-benzyl)-methoxycarbonyl-amino]-methyl]-2-methyl-5-trifluoromethyl-indoline-1-carboxylic acid ethyl ester;

3-[[Acetyl-(3,5-bis-trifluoromethyl-benzyl)-amino]-methyl]-2-methyl-5-trifluoromethyl-indoline-1-carboxylic acid ethyl ester;

20 (*R,R*)-3-[[Acetyl-(3,5-bis-trifluoromethyl-benzyl)-amino]-methyl]-2-methyl-5-trifluoromethyl-indoline-1-carboxylic acid ethyl ester;

(*R,S*)-3-[[Acetyl-(3,5-bis-trifluoromethyl-benzyl)-amino]-methyl]-2-methyl-5-trifluoromethyl-indoline-1-carboxylic acid ethyl ester;

3-[[Acetyl-(3,5-bis-trifluoromethyl-benzyl)-amino]-methyl]-2-ethyl-6-trifluoromethyl-indoline-1-carboxylic acid tert-butyl ester;

25 (*R,R*)-3-[[Acetyl-(3,5-bis-trifluoromethyl-benzyl)-amino]-methyl]-2-ethyl-6-trifluoromethyl-indoline-1-carboxylic acid tert-butyl ester;

(*R,S*)-3-[[Acetyl-(3,5-bis-trifluoromethyl-benzyl)-amino]-methyl]-2-ethyl-6-trifluoromethyl-indoline-1-carboxylic acid tert-butyl ester;

30 3-[[[(3,5-Bis-trifluoromethyl-benzyl)-methoxycarbonyl-amino]-methyl]-2-ethyl-6-trifluoromethyl-indoline-1-carboxylic acid tert-butyl ester;

(*R,R*)-3-[[[(3,5-Bis-trifluoromethyl-benzyl)-methoxycarbonyl-amino]-methyl]-2-ethyl-6-trifluoromethyl-indoline-1-carboxylic acid tert-butyl ester;

(*R,S*)-3-[[[(3,5-Bis-trifluoromethyl-benzyl)-methoxycarbonyl-amino]-methyl]-2-ethyl-6-trifluoromethyl-indoline-1-carboxylic acid tert-butyl ester;

35 3-(3,5-Bis-trifluoromethyl-benzylcarbamoyl)-2-ethyl-6-trifluoromethyl-indoline-1-carboxylic acid tert-butyl ester;

(*R,R*)-3-(3,5-Bis-trifluoromethyl-benzylcarbamoyl)-2-ethyl-6-trifluoromethyl-indoline-1-carboxylic acid tert-butyl ester;

40 (*R,S*)-3-(3,5-Bis-trifluoromethyl-benzylcarbamoyl)-2-ethyl-6-trifluoromethyl-indoline-1-carboxylic acid tert-butyl ester;

3-(3,5-Bis-trifluoromethyl-benzoyl)-2-ethyl-6-trifluoromethyl-indoline-1-carboxylic acid tert-butyl ester;

(*R,R*)-3-(3,5-Bis-trifluoromethyl-benzoyl)-2-ethyl-6-trifluoromethyl-indoline-1-carboxylic acid tert-butyl ester;

5 (*R,S*)-3-(3,5-Bis-trifluoromethyl-benzoyl)-2-ethyl-6-trifluoromethyl-indoline-1-carboxylic acid tert-butyl ester;

3-[(3,5-Bis-trifluoromethyl-phenyl)-hydroxy-methyl]-2-ethyl-6-trifluoromethyl-indoline-1-carboxylic acid tert-butyl ester;

10 (*R,R*)-3-[(3,5-Bis-trifluoromethyl-phenyl)-hydroxy-methyl]-2-ethyl-6-trifluoromethyl-indoline-1-carboxylic acid tert-butyl ester;

(*R,S*)-3-[(3,5-Bis-trifluoromethyl-phenyl)-hydroxy-methyl]-2-ethyl-6-trifluoromethyl-indoline-1-carboxylic acid tert-butyl ester;

3-[2-(3,5-Bis-trifluoromethyl-phenyl)-2-oxo-ethyl]-2-ethyl-6-trifluoromethyl-indoline-1-carboxylic acid ethyl ester;

15 (*R,R*)-3-[2-(3,5-Bis-trifluoromethyl-phenyl)-2-oxo-ethyl]-2-ethyl-6-trifluoromethyl-indoline-1-carboxylic acid ethyl ester;

(*R,S*)-3-[2-(3,5-Bis-trifluoromethyl-phenyl)-2-oxo-ethyl]-2-ethyl-6-trifluoromethyl-indoline-1-carboxylic acid ethyl ester;

20 3-[2-(3,5-Bis-trifluoromethyl-phenyl)-2-hydroxy-ethyl]-2-ethyl-6-trifluoromethyl-indoline-1-carboxylic acid ethyl ester;

(*R,R*)-3-[2-(3,5-Bis-trifluoromethyl-phenyl)-2-hydroxy-ethyl]-2-ethyl-6-trifluoromethyl-indoline-1-carboxylic acid ethyl ester;

(*R,S*)-3-[2-(3,5-Bis-trifluoromethyl-phenyl)-2-hydroxy-ethyl]-2-ethyl-6-trifluoromethyl-indoline-1-carboxylic acid ethyl ester;

25 Ethyl 3-((N-(3,5-bis(trifluoromethyl)benzyl)acetamido)methyl)-2-ethyl-5-(trifluoromethyl)indoline-1-carboxylate;

(*R,R*)-Ethyl 3-((N-(3,5-bis(trifluoromethyl)benzyl)acetamido)methyl)-2-ethyl-5-(trifluoromethyl)indoline-1-carboxylate;

30 (*R,S*)-Ethyl 3-((N-(3,5-bis(trifluoromethyl)benzyl)acetamido)methyl)-2-ethyl-5-(trifluoromethyl)indoline-1-carboxylate;

Methyl (1-(ethoxycarbonyl)-2-ethyl-5-(trifluoromethyl)indolin-3-yl)methyl-3,5-bis(trifluoromethyl)benzylcarbamate;

(*R,R*)-Methyl (1-(ethoxycarbonyl)-2-ethyl-5-(trifluoromethyl)indolin-3-yl)methyl-3,5-bis(trifluoromethyl)benzylcarbamate;

35 (*R,S*)-Methyl (1-(ethoxycarbonyl)-2-ethyl-5-(trifluoromethyl)indolin-3-yl)methyl-3,5-bis(trifluoromethyl)benzylcarbamate;

Ethyl 3-((N-(3,5-bis(trifluoromethyl)benzyl)acetamido)methyl)-2-cyclopropyl-5-(trifluoromethyl)indoline-1-carboxylate;

40 (*R,R*)-Ethyl 3-((N-(3,5-bis(trifluoromethyl)benzyl)acetamido)methyl)-2-cyclopropyl-5-(trifluoromethyl)indoline-1-carboxylate;

(*R,S*)-Ethyl 3-((*N*-(3,5-bis(trifluoromethyl)benzyl)acetamido)methyl)-2-cyclopropyl-5-(trifluoromethyl)indoline-1-carboxylate;

Methyl (1-(ethoxycarbonyl)-2-cyclopropyl-5-(trifluoromethyl)indolin-3-yl)methyl 3,5-bis(trifluoromethyl)benzylcarbamate;

(*R,R*)-Methyl (1-(ethoxycarbonyl)-2-cyclopropyl-5-(trifluoromethyl)indolin-3-yl)methyl 3,5-bis(trifluoromethyl)benzylcarbamate;

(*R,S*)-Methyl (1-(ethoxycarbonyl)-2-cyclopropyl-5-(trifluoromethyl)indolin-3-yl)methyl 3,5-bis(trifluoromethyl)benzylcarbamate;

Tert-butyl 3-((*N*-(3,5-bis(trifluoromethyl)benzyl)acetamido)methyl)-2-ethyl-5-(trifluoromethyl)indoline-1-carboxylate;

(*R,R*)-Tert-butyl 3-((*N*-(3,5-bis(trifluoromethyl)benzyl)acetamido)methyl)-2-ethyl-5-(trifluoromethyl)indoline-1-carboxylate; and

(*R,S*)-Tert-butyl 3-((*N*-(3,5-bis(trifluoromethyl)benzyl)acetamido)methyl)-2-ethyl-5-(trifluoromethyl)indoline-1-carboxylate;

or a pharmaceutically acceptable salt of said compound.

13. A method for treating atherosclerosis, coronary artery disease, coronary heart disease, coronary vascular disease, peripheral vascular disease, dyslipidemia, hyperbetalipoproteinemia, hypoalphalipoproteinemia, hypercholesterolemia, hypertriglyceridemia, familial-hypercholesterolemia or myocardial infarction in a mammal by administering to a mammal in need of such treatment an atherosclerosis, coronary artery disease, coronary heart disease, coronary vascular disease, peripheral vascular disease, dyslipidemia, hyperbetalipoproteinemia, hypoalphalipoproteinemia, hypercholesterolemia, hypertriglyceridemia, familial-hypercholesterolemia or myocardial infarction treating amount of a compound of claim 1 or a pharmaceutically acceptable salt of said compound.

14. A pharmaceutical composition which comprises a therapeutically effective amount of a compound of claim 1 or a pharmaceutically acceptable salt of said compound and a pharmaceutically acceptable vehicle, diluent or carrier.

15. A pharmaceutical combination composition comprising: a therapeutically effective amount of a composition comprising

a first compound, said first compound being a compound of claim 1 or a pharmaceutically acceptable salt of said compound;

a second compound, said second compound being an HMG CoA reductase inhibitor, an MTP/Apo B secretion inhibitor, a PPAR modulator, a bile acid reuptake inhibitor, a cholesterol absorption inhibitor, a cholesterol synthesis inhibitor, a fibrate, niacin, slow-release niacin, a combination of niacin and lovastatin, an ion-exchange resin, an antioxidant, an ACAT inhibitor or a bile acid sequestrant; and a pharmaceutical vehicle, diluent or carrier.

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2005/002805

A. CLASSIFICATION OF SUBJECT MATTER
C07D209/14 C07D209/12 A61K31/404

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61K C07D

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

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, CHEM ABS Data, WPI Data, BIOSIS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	COLLOT, VALERIE ET AL: "Regiospecific functionalization of indole-2-carboxylates and diastereoselective preparation of the corresponding indolines" HETEROCYCLES, 51(12), 2823-2847 CODEN: HTCYAM; ISSN: 0385-5414, 1999, XP001246429 scheme 6, compound 31, scheme 7 compounds 40, 51	1
X	REIMANN, E. ET AL: "Selective catalytic hydrogenation and hydrogenolysis. Part 7. Stereoselective synthesis of 1-acyl-2,3-dihydro-2-carbalkoxy-1H-indoleacetic acid esters" PHARMAZIE, 54(6), 418-421 CODEN: PHARAT; ISSN: 0031-7144, 1999, XP001246428 compounds 5, 8a, 8b ----- -/--	1

☒ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents:

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- *Z* document member of the same patent family

Date of the actual completion of the international search

26 January 2006

Date of mailing of the international search report

22/02/2006

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INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2005/002805

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 97/06140 A1 (CEMAF, FR.; LABORATOIRES BESINS ISCOVESCO S.A.; FOURTILLAN, JEAN-BERNA) 20 February 1997 (1997-02-20) examples 13,14,22 -----	1
X	COULTON, STEVEN ET AL: "Catalytic hydrogenation of N-(t-butoxycarbonyl)indoles", TETRAHEDRON , 53(2), 791-798 CODEN: TETRAB; ISSN: 0040-4020, 1997, XP002364542 compounds 2d, 2e, 2l, 2m, 2n -----	1
X	ROWLEY, MICHAEL ET AL: "2-Carboxyindolines and -indoles as potential glycine NMDA antagonists: effect of five-membered ring conformation on affinity" BIOORGANIC & MEDICINAL CHEMISTRY LETTERS , 2(12), 1627-30 CODEN: BMCLE8; ISSN: 0960-894X, 1992, XP002364543 compounds 7-8 -----	1
A	WO 98/34920 A1 (BAYER A.-G., GERMANY) 13 August 1998 (1998-08-13) page 25, line 17 - line 25 claim 2 -----	1,13

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB2005/002805

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

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

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 13 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

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

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

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/IB2005/002805

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