(11) Application No. AU 2004242777 B2

(19) AUSTRALIAN PATENT OFFICE

(54) Title

Substituted pyrrole derivatives and their use as HMG-Co inhibitors

(51)[6] International Patent Classification(s)

C07D 207/34 (2006.01)
A61K 31/366 (2006.01)
A61K 31/40 (2006.01)
C07D 207/00 (2006.01)
C07D 401/12 (2006.01)
C07D 405/06 (2006.01)
C07D 405/14 (2006.01)
C07D 207/34 20060101AFI2007072 1BMEP
A61K 31/366 20060101ALI2006112 5BMEP
A61K 31/40 20060101ALI2006112 5BMEP
C07D 207/00 20060101ALI2007022 4BMEP
C07D 401/12 20060101ALI2007072 1BMEP
C07D 405/06 20060101ALI2007072 1BMEP
C07D 405/14 20060101ALI2007072 1BMEP
PCT/IB2004/001761

(21) Application No: 2004242777

(22) Application Date: 2004.05.28

(87) WIPO No: WO04/106299

(30) Priority Data

(31) Number	(32) Date	(33) Country
10/449,418	2003.05.30	US

(43) Publication Date : 2004.12.09

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(56) Related Art

EP 0 247 633 B1, EP 0 680 963 B1, EP 0 409 281 B1

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

CORRECTED VERSION

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
9 December 2004 (09.12.2004)

PCT

(10) International Publication Number
WO 2004/106299 A3

(51) International Patent Classification[7]: C07D 405/06, 207/34, 401/12, 405/14, A61K 31/40, 31/366

(21) International Application Number: PCT/IB2004/001761

(22) International Filing Date: 28 May 2004 (28.05.2004)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
10/449,418 30 May 2003 (30.05.2003) US

(63) Related by continuation (CON) or continuation-in-part (CIP) to earlier application:
US 10/449,418 (CIP)
Filed on 30 May 2003 (30.05.2003)

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(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US (patent), UZ, VC, VN, YU, ZA, ZM, ZW.

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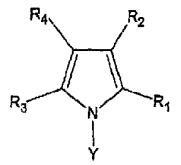
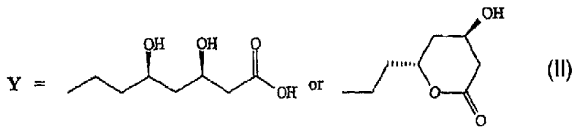
(54) Title: SUBSTITUTED PYRROLE DERIVATIVES AND THEIR USE AS HMG-CO INHIBITORS



(I)



(II)

(57) Abstract: The present invention relates to substituted pyrrole derivatives of formula I, which can be used as 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors. Compounds disclosed herein can function as cholesterol lowering agents and can be used for the treatment of cholesterol-related diseases and related symptoms. Processes for the preparation of disclosed compounds are provided, as well as pharmaceutical compositions containing the disclosed compounds, and methods of treating cholesterol-related diseases and related symptoms. Its pharmaceutically acceptable salts, pharmaceutically acceptable solvates, prodrugs, metabolites, polymorphs, tautomers, racemates, pure enantiomers, diastereoisomers or N-oxides wherein Formula (II).

WO 2004/106299 A3

(84) **Designated States** *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*

(88) **Date of publication of the international search report:**
28 April 2005

(48) **Date of publication of this corrected version:**
29 September 2005

(15) **Information about Correction:**
see PCT Gazette No. 39/2005 of 29 September 2005, Section II

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

SUBSTITUTED PYRROLE DERIVATIVES

Field of the Invention

The present invention relates to substituted pyrrole derivatives, which can be used as 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors.

Compounds disclosed herein can function as cholesterol lowering agents and can be used for the treatment of cholesterol-related diseases and related symptoms. Processes for the preparation of disclosed compounds are provided, as well as pharmaceutical compositions containing the disclosed compounds, and methods of treating cholesterol-related diseases and related symptoms.

Background of the Invention

Cardiovascular disease and its associated maladies, dysfunctions and complications are a principal cause of disability and the chief cause of death. One specific factor significantly contributing to this pathophysiologic process is atherosclerosis, which has been generally recognized as the leading health care problem both with respect to mortality and health care costs.

Atherosclerosis is characterized by the deposition of fatty substances, primarily cholesterol, resulting in plaque formation on the inner surface of the arterial wall and degenerative change to the arteries.

It is now well established that cardiovascular disorders including myocardial infarction, coronary heart disease, hypertension and hypotension, cerebrovascular disorders including stroke, cerebral thrombosis and memory loss due to stroke; peripheral vascular disease and intestinal infarction are caused by blockage of arteries and arterioles by atherosclerotic plaque. Atherosclerotic plaque formation is multi-factorial in its production. Hypercholesterolemia, especially elevated levels of low-density lipoprotein cholesterol (LDL), is an important risk factor for atherosclerosis and arteriosclerosis and associated diseases.

The HMG-CoA reductase inhibitors (statins) have been used in reducing blood levels of LDL cholesterol. Cholesterol is produced via the mevalonic acid pathway. Reducing the formation of mevalonic acid, a precursor to cholesterol, leads to a corresponding decrease in hepatic cholesterol biosynthesis with a reduction in the cellular pool of cholesterol.

U. S. Patent No. 4,681,893 assigned to Warner-Lambert, discloses certain trans-6-[2-(3-,or 4-carbaoxamido-substituted pyrrole-1-yl)alkyl]-4-hydroxypyran-2-ones and the corresponding ring-opened hydroxy acids derived therefrom, including trans(±)-5-(4-fluorophenyl)-2-(1-methylethyl)-N,4-diphenyl-1-[2-tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1H-pyrrole-3-carboxamide, which are inhibitors of 3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMG-CoA), an important coenzyme catalyzing the intracellular synthesis of cholesterol.

U. S. Patent No. 5,273,995 assigned to Warner Lambert, relates to the optically pure (R, R) form of the ring-opened acid of trans-5-(4-fluorophenyl)-2-(1-methylethyl-N,4-diphenyl-1-[2-tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1H-pyrrole-3-carboxamide that is [R-(R*, R*)]-2-(4-fluorophenyl)-β,δ-dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)carbonyl]-1H-pyrrole-1-heptanoic acid, pharmaceutically acceptable salts thereof, specifically its calcium salt (Atorvastatin, Lipitor®), which is currently being used for the treatment of hypercholesterolemia.

U. S. Patent No. 5,385,929 discloses certain phenyl hydroxy derivatives of the compounds disclosed in U. S. 5,273,995, and that such phenyl hydroxy derivatives are also active as the inhibitors of the biosynthesis of cholesterol.

Summary of the Invention

The present invention relates to substituted pyrrole derivatives, which can be used as 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors, and processes for the synthesis of these compounds. These compounds show utility in inhibiting HMG-CoA reductase, among the key rate limiting steps in the biosynthetic pathway of cholesterol formation. Therefore, these compounds hold promise for the treatment of hypercholesterolemia and hyperlipidemia

Pharmaceutically acceptable salts, pharmaceutically acceptable solvates, tautomers, racemates, polymorphs, pure enantiomers, diastereoisomers, metabolites, prodrugs or N-oxides of these compounds having the same type of activity are also provided.

Pharmaceutical composition containing the compounds, and which may also contain pharmaceutically acceptable carriers or diluents, which can be used for the treatment of cholesterol-related disease or related symptoms thereof are also provided.

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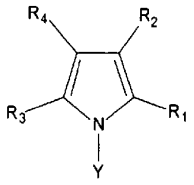
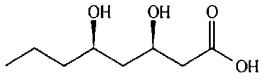
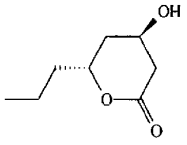
In an embodiment of the invention there is provided a compound of the structure of Formula I,



Formula I

or a pharmaceutically acceptable salt thereof, pharmaceutically acceptable tautomer, racemate, pure enantiomer, diastereoisomer or a lactone form or N-oxide thereof, wherein

Y =  or 

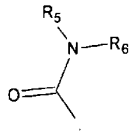
$\mathbf{R_1}$ is C_1-C_6 alkyl, C_3-C_6 cycloalkyl, or optionally substituted phenyl (wherein up to three substituents are independently selected from halogens, C_1-C_6 alkyl, cyano, and C_1-C_3 perfluoroalkyl);

$\mathbf{R_2}$ is optionally substituted phenyl (wherein up to three substituents are independently selected from cyano, acetyl, and optionally substituted amino, wherein up to two amino substituents are independently selected from C_1-C_6 alkyl, C_3-C_6 cycloalkyl, acetyl, and sulfonamide);

$\mathbf{R_3}$ is optionally substituted C_1-C_6 alkyl or C_3-C_6 cycloalkyl (wherein substituents are independently selected from halogens, hydroxyl, C_1-C_3 alkoxy and protected hydroxyl); or

$\mathbf{R_3}$ is $-NR_8R_9$, wherein R_8 and R_9 are optionally substituted C_1-C_6 alkyl (wherein the optional substituent(s) is/are selected from halogens, hydroxy, C_1-C_3 alkoxy and protected hydroxyl);

$\mathbf{R_4}$ is

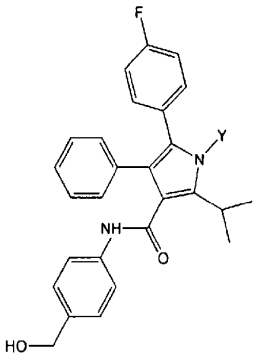


wherein R_5 is hydrogen and R_6 is aryl substituted with C_1-C_6 alkyl substituted with one or two substituents independently selected from hydroxyl and protected hydroxyl

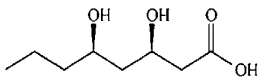
with the provisio that R_2 is phenyl only when:

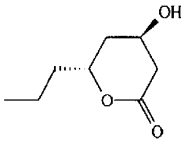
R_6 is phenyl substituted with hydroxyalkyl.

In a further embodiment of the invention there is provided a compound of the chemical formula:



wherein

Y = 

or 

or a pharmaceutically acceptable salt thereof.

In a further embodiment of the invention there is provided use of the above embodiments in the manufacture of a medicament of the treatment of diabetes or a disease selected from the group consisting of arteriosclerosis, atherosclerosis, hyperlipidemia, hyperlipoproteinemia, hypercholesterolemia, hypertriglyceridemia, hypertension, stroke, ischemia, peripheral vascular disease, peripheral arterial disease, coronary heart disease, myocardial infarction, cerebral infarction, myocardial microvascular disease, dementia, Alzheimer's disease, angina and restenosis.

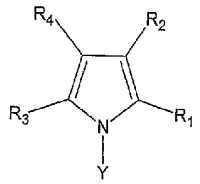
The use of the above embodiments in the treatment of diabetes or a disease selected from the group consisting of arteriosclerosis, atherosclerosis, hyperlipidemia, hyperlipoproteinemia, hypercholesterolemia, hypertriglyceridemia, hypertension, stroke, ischemia, peripheral vascular disease, peripheral arterial disease, coronary heart disease, myocardial infarction, cerebral infarction, myocardial microvascular disease, dementia, Alzheimer's disease, angina and restenosis is also an embodiment of the invention.

Other aspects will be set forth in the accompanying description which follows and in the part will be apparent from the description or may be learnt by the practice of the invention.

In accordance with another aspect, there is provided a method for treating a mammal suffering from cholesterol related disease, diabetes and related disease, cerebrovascular disease or cardiovascular disease, comprising administering to a mammal a therapeutically effective amount of compounds disclosed herein.

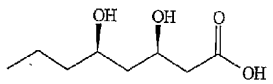
The compounds of the present invention can be used for treating arteriosclerosis, atherosclerosis, hypercholesterolemia, hyperlipidemia, hyperlipoproteinemia, hypertriglyceridemia, hypertension, stroke, ischemia, endothelium dysfunction, peripheral vascular disease, peripheral arterial disease, coronary heart disease, myocardial infarction, cerebral infarction, myocardial microvascular disease, dementia, Alzheimer's disease, osteoporosis and/or osteopenia, angina or resterosis.

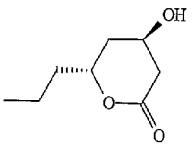
In accordance with one aspect, there is provided a compound having the structure of Formula I,



Formula I

its pharmaceutically acceptable salts, pharmaceutically acceptable solvates, prodrugs, metabolites, polymorphs, tautomers, racemates, pure enantiomers, diastereoisomers or N-oxides wherein

Y = 

or 

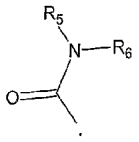
R_1 can be C_1-C_6, C_3-C_6, or optionally substituted phenyl (wherein up to three substituents are independently selected from halogens, C_1-C_6 alkyl, cyano, or C_1-C_3 perfluoroalkyl);

R_2 can be optionally substituted phenyl (wherein up to three substituents are independently selected from cyano, acetyl, or optionally substituted amino, wherein up to two amino substituents are independently selected from C_1-C_6 alkyl, C_3-C_6 cycloalkyl, acetyl, or sulfonamide);

R_3 can be optionally substituted C_1-C_6 alkyl or C_3-C_6 cycloalkyl (wherein substituents are independently selected from halogens, hydroxyl, C_1-C_3 alkoxy and protected hydroxyl);

R_3 can also be $-NR_8R_9$, wherein R_8 and R_9 are optionally substituted C_1-C_6 alkyl (wherein the optional substituent(s) is/are selected from halogens, hydroxy, C_1-C_3 alkoxy and protected hydroxyl);

R_4 can be



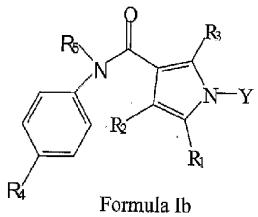
wherein R_5 and R_6 are independently hydrogen, C_1-C_6 alkyl or C_3-C_6 cycloalkyl, optionally substituted aryl or aralkyl, wherein the substituents are selected from halogens, cyano, optionally substituted C_1-C_6 alkyl (wherein up to two substituents are independently selected from hydroxyl, protected hydroxyl, and halogen(s)), optionally substituted amino (wherein up to two substituents are independently selected from SO_2R_7, COR_7, or $CONHR_7$, wherein R_7 is C_1-C_6 alkyl or aryl), or acetyl, trifluoromethyl, or C_1-C_6 alkoxycarbonyl, or R_5 and R_6 together form a 5-7 membered ring with one or more optional heteroatoms wherein the hetero atom(s) are independently selected from nitrogen, oxygen and sulfur,

or R_4 can be an optionally substituted mono-, bi- or tricyclic heterocycle having one or more hetero atom(s) wherein said hereto atom(s) is/are independently selected from oxygen, nitrogen and sulfur, and the optional substituents are independently selected from halogens, hydroxy, protected hydroxyl, C_1-C_3 alkoxy, cyano, C_1-C_3 perfluoroalkyl, C_1-C_6 alkyl or C_3-C_6 cycloalkyl, aryl or optionally substituted aralkyl wherein the substituents are independently selected from halogens, hydroxy, protected hydroxyl, C_1-C_3 alkoxy, cyano, or C_1-C_3 perfluoroalkyl,

and the pharmaceutically acccptable salts, tautomers, racemates, pure enantiomers or diastereoisomers, and solvates of the compounds of Formula I,

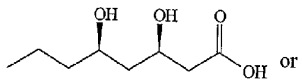
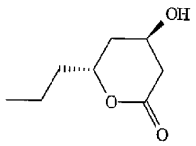
with the proviso that R_2 is phenyl only when (1) R_5 or R_6 is C_3-C_6 cycloalkyl or phenyl substituted with acetyl, alkyl, cycloalkyl, hydroxyalkyl, alkylsulfonamido, acetamido or (2) when R_5 and R_6 together form a 5-7 membered ring with or without one or more heteroatoms wherein the hetero atom(s) are selected from nitrogen, oxygen and sulfur or (3) when R_5 or R_6 is aralkyl optionally substituted with halogens, cyano, C_1-C_6 alkyl, C_1-C_6 halogenated alkyl or (4) when R_4 is optionally substituted mono-, bi- or tricyclic heterocycle having one or more hetero atom(s) (wherein the optional substituents are independently selected from halogens, hydroxy, protected hydroxyl, C_1-C_3 alkoxy, cyano, perfluoroalkyl of one to three carbon atoms, C_1-C_6 alkyl, C_3-C_6 cycloalkyl, aryl, or optionally substituted aralkyl (wherein the aralkyl substituents are independently selected from halogens, hydroxy, protected hydroxyl, C_1-C_3 alkoxy, cyano, or C_1-C_3 perfluoroalkyl)).

In accordance with another aspect, there are provided compounds having the structure of Formula Ib,



Formula Ib

their pharmaceutically acceptable salts, pharmaceutically acceptable solvates, tautomers, racemates, polymorphs, pure enantiomers, diastereoisomers, metabolites, prodrugs or N-oxides wherein

Y =  or 

R_1 can be C_1-C_6 alkyl, C_3-C_6 cycloalkyl, or optionally substituted phenyl (wherein the substituent(s) is/are selected from halogens, C_1-C_6 alkyl, cyano and C_1-C_3 perfluoroalkyl);

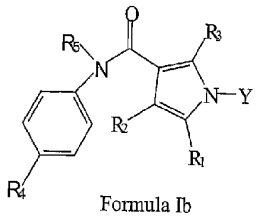
R_2 can be optionally substituted phenyl (wherein the substituent(s) is/are selected from cyano, acetyl and optionally substituted amino);

R_3 can be optionally substituted C_1-C_6 alkyl or C_3-C_6 cycloalkyl (wherein the substituent(s) is/are selected from halogens, hydroxyl, C_1-C_3 alkoxy, and protected hydroxyl); R_3 can also be $-NR_6R_7$ wherein R_6 and R_7 are optionally substituted C_1-C_6 alkyl (wherein the optional substituent(s) is/are selected from halogens, hydroxyl, C_1-C_3 alkoxy, and protected hydroxyl);

R_4 can be acetyl, C_1-C_2 alkoxycarbonyl, optionally substituted C_1-C_6 alkyl (wherein the substituent is hydroxy or protected hydroxyl), NHR_8 [wherein R_8 is selected from alkyl, aralkyl, SO_2R_9, COR_9 or $CONHR_9$, $CSNHR_9$ (wherein R_9 is C_1-C_6 alkyl, aryl or aralkyl)]; R_4 can also be $-COR_{10}$ (wherein R_{10} is selected from hydroxyl and $-NR_{11}R_{12}$ (wherein R_{11} and R_{12} are independently selected from hydrogen, alkyl, aryl, C_3-C_7 cycloalkyl, heterocyclyl, aralkyl and R_{11} and R_{12} together form 5-7 membered ring with one or more optional heteroatom(s) wherein the heteroatom(s) is/are independently selected from nitrogen, oxygen and sulphur);

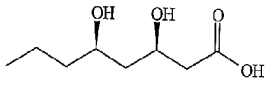
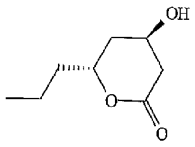
R_5 can be hydrogen, C_1-C_6 alkyl or C_3-C_6 cycloalkyl, optionally substituted aryl or aralkyl [wherein the substituents are selected from halogens, cyano, optionally substituted C_1-C_6 alkyl (wherein the substituents are independently selected from hydroxyl, protected hydroxyl, and halogen(s)], optionally substituted amino, acetyl, trifluoromethyl and C_1-C_6 alkoxycarbonyl.

In one particular embodiment, there are provided compounds of Formula Ib,



Formula Ib

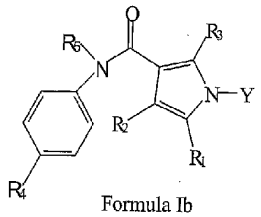
their pharmaceutically acceptable salts, pharmaceutically acceptable solvates, tautomers, racemates, polymorphs, pure enantiomers, diastereoisomers, metabolites, prodrugs or N-oxides wherein

Y =  or 

R_1, R_2, R_3 and R_5 are as defined earlier;

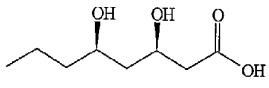
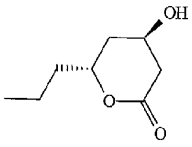
R_4 can be NHR_8 [wherein R_8 is selected from aralkyl, $CONHR_9$ (wherein R_9 is aralkyl); $CSNHR_9$ (wherein R_9 is C_1-C_6 alkyl, aryl or aralkyl)]; $-COR_{10}$ (wherein R_{10} is selected from hydroxyl and $-NR_{11}R_{12}$ (wherein R_{11} and R_{12} are independently selected from hydrogen, alkyl, aryl, C_3-C_7 cycloalkyl, aralkyl and R_{11} and R_{12} together form 5-7 membered ring with one or more optional heteroatom(s) wherein the heteroatom(s) is/are independently selected from nitrogen, oxygen and sulphur);

In yet another particular embodiment, there are provided compounds of Formula Ib,



Formula Ib

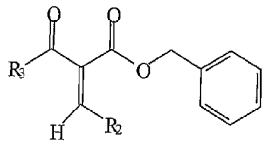
their pharmaceutically acceptable salts, pharmaceutically acceptable solvates, tautomers, racemates, polymorphs, pure enantiomers, diastereoisomers, metabolites, prodrugs or N-oxides wherein

Y =  or 

R_1, R_2, R_3 and R_5 can be 4-fluorophenyl, phenyl, isopropyl and hydrogen, respectively;

R_4 can be C_1-C_2 alkoxycarbonyl, optionally substituted C_1-C_6 alkyl (wherein the substituent is hydroxy or protected hydroxyl), NHR_8 [wherein R_8 is selected from SO_2R_9, COR_9 or $CONHR_9$ (wherein R_9 is methyl or phenyl)]

In accordance with further aspect, there are provided intermediates having the structure of Formula XIX,



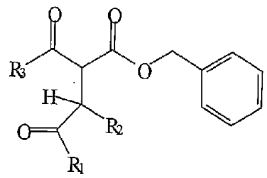
Formula XIX

wherein

R_2 can be optionally substituted phenyl (wherein the substituent(s) is/are selected from cyano, acetyl and optionally substituted amino;

R_3 can be optionally substituted C_1-C_6 alkyl or C_3-C_6 cycloalkyl (wherein the substituent(s) is/are selected from halogens, hydroxyl, C_1-C_3 alkoxy, and protected hydroxyl); **R_3** can also be $-NR_6R_7$ wherein R_6 and R_7 are optionally substituted C_1-C_6 alkyl (wherein the optional substituent(s) is/are selected from halogens, hydroxyl, C_1-C_3 alkoxy, and protected hydroxyl).

In accordance with third aspect, there are provided intermediates having the structure of Formula XX,



Formula XX

wherein

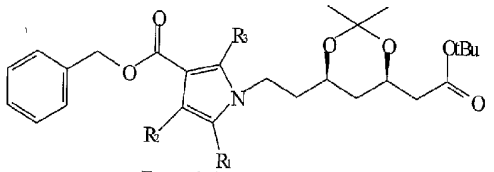
R_1 can be C_1-C_6 alkyl, C_3-C_6 cycloalkyl, or optionally substituted phenyl (wherein the substituent(s) is/are selected from halogens, C_1-C_6 alkyl, cyano and C_1-C_3 perfluoroalkyl);

R_2 can be optionally substituted phenyl (wherein the substituent(s) is/are selected from cyano, acetyl and optionally substituted amino;

R_3 can be optionally substituted C_1-C_6 alkyl or C_3-C_6 cycloalkyl (wherein the substituent(s) is/are selected from halogens, hydroxyl, C_1-C_3 alkoxy, and protected hydroxyl); **R_3** can also be $-NR_6R_7$ wherein R_6 and R_7 are optionally substituted C_1-C_6 alkyl

(wherein the optional substituent(s) is/are selected from halogens, hydroxyl, C_1-C_3 alkoxy, and protected hydroxyl).

In accordance with fourth aspect, there are provided intermediates having the structure of Formula XXI,



Formula XXI

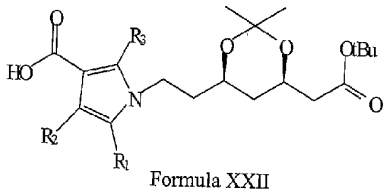
wherein

R_1 can be C_1-C_6 alkyl, C_3-C_6 cycloalkyl, or optionally substituted phenyl (wherein the substituent(s) is/are selected from halogens, C_1-C_6 alkyl, cyano and C_1-C_3 perfluoroalkyl);

R_2 can be optionally substituted phenyl (wherein the substituent(s) is/are selected from cyano, acetyl and optionally substituted amino;

R_3 can be optionally substituted C_1-C_6 alkyl or C_3-C_6 cycloalkyl (wherein the substituent(s) is/are selected from halogens, hydroxyl, C_1-C_3 alkoxy, and protected hydroxyl); R_3 can also be $-NR_6R_7$ wherein R_6 and R_7 are optionally substituted C_1-C_6 alkyl (wherein the optional substituent(s) is/are selected from halogens, hydroxyl, C_1-C_3 alkoxy, and protected hydroxyl).

In accordance with fifth aspect, there are provided intermediates having the structure of Formula XXII,



Formula XXII

wherein

R_1 can be C_1-C_6 alkyl, C_3-C_6 cycloalkyl, or optionally substituted phenyl (wherein the substituent(s) is/are selected from halogens, C_1-C_6 alkyl, cyano and C_1-C_3 perfluoroalkyl);

$\mathbf{R_2}$ can be optionally substituted phenyl (wherein the substituent(s) is/are selected from cyano, acetyl and optionally substituted amino;

$\mathbf{R_3}$ can be optionally substituted C_1-C_6 alkyl or C_3-C_6 cycloalkyl (wherein the substituent(s) is/are selected from halogens, hydroxyl, C_1-C_3 alkoxy, and protected hydroxyl); $\mathbf{R_3}$ can also be $-NR_6R_7$ wherein R_6 and R_7 are optionally substituted C_1-C_6 alkyl (wherein the optional substituent(s) is/are selected from halogens, hydroxyl, C_1-C_3 alkoxy, and protected hydroxyl).

As used herein the term "alkyl", unless otherwise defined, refers to straight or branched chain hydrocarbon of from 1 to 10 carbon atom(s). Examples of alkyl include, but are not limited to, methyl, ethyl, n-propyl, isopropyl, butyl, octyl, and the like.

Alkyl may optionally be substituted with halogen, hydroxy, protected hydroxyl, C_1-C_3 alkoxy, optionally substituted amino and C_1-C_6 alkoxycarbonyl.

As used herein the term "optionally substituted amino", unless otherwise defined, refers to $NR_{14}R_{15}$ wherein R_{14} and R_{15} are independently selected from hydrogen, alkyl, aryl, aralkyl, C_3-C_7 cycloalkyl, SO_2R_{16}, COR_{16}, $CONHR_{16}$ and $CSNHR_{16}$ (wherein R_{16} is C_1-C_6 alkyl, aryl or aralkyl).

As used herein the term "protected hydroxyl" refers to a hydroxy moiety protected by a group R_{17} wherein R_{17} is selected from alkyl, cycloalkyl, aralkyl, aryl, $-(CH_2)_nOR_{18}$ (wherein R_{18} is selected from alkyl, cycloalkyl, aralkyl, aryl and n represents an integer from 1 to 6), COR_{19}, CSR_{19}, $CONHR_{19}$ and $CSNHR_{19}$ (wherein R_{19} is selected from alkyl, aryl, aralkyl and heterocyclyl). Examples of protected hydroxyl include, but are not limited to, $-OCH_3$, $-OC_2H_5$, -O-n-propyl, -O-i-propyl, -O-cyclopropyl, $-O-CH_2OCH_3$, -O-cyclopentyl, -O-cyclohexyl, -O-benzyl, -O-chlorobenzyl, -O-methoxybenzyl, -O-phenyl, -O-chlorophenyl, $-O-COCH_3$, $-O-COC_2H_5$, -O-CObenzyl, -O-COphenyl, -O-COpyridinyl, -O-CONHphenyl, -O-CONHpyridinyl, -O-CONH-octyl, -O-CSNHphenyl, and the like.

As used herein the term "aralkyl" refers to $(CH_2)_n$aryl wherein n is an integer from 1 to 6.

As used herein the term "aryl", unless otherwise defined, refers to an aromatic radical having 6 to 14 carbon atoms. Examples of aryl include, but are not limited to, phenyl, napthyl, anthryl and biphenyl, and the like.

As used herein the term "heterocyclyl" refers to non-aromatic, aromatic or aromatic fused with non-aromatic ring system having one or more heteroatom (s) in either the aromatic or the non-aromatic part wherein the said hetero atom (s) is/ are selected from the group comprising of nitrogen, sulphur and oxygen and the ring system includes mono, bi or tricyclic. Examples of heterocycles include, but not limited to, benzoxazinyl, benzthiazinyl, benzimidazolyl, benzofuranyl, carbazolyl, Indolyl, indolinyl, oxazolyl, phenoxazinyl, pyridyl and phenothiazinyl, and the like.

The said aryl or heterocyclyl may optionally be substituted with one or more substituent(s) independently selected from halogen, hydroxy, nitro, cyano, alkyl, aryl, alkoxy, thioalkyl, cycloalkoxy, optionally substituted amino.

In accordance with yet another aspect, there are provided processes for the preparation of the compounds described herein.

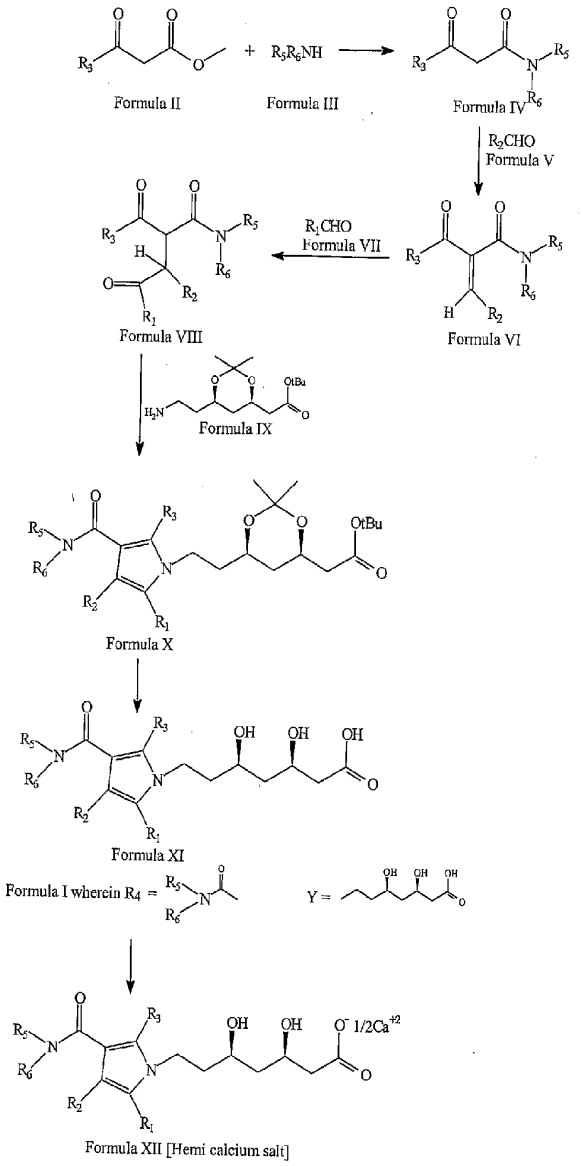
In accordance with another aspect, there is provided a method for treating a mammal suffering from cholesterol related disease, diabetes and related disease, cerebrovascular disease or cardiovascular disease, comprising administering to a mammal a therapeutically effective amount of compounds disclosed herein.

The compounds of the present invention can be used for treating arteriosclerosis, atherosclerosis, hypercholesterolemia, hyperlipidemia, hyperlipoproteinemia, hypertriglyceridemia, hypertension, stroke, ischemia, endothelium dysfunction, peripheral vascular disease, peripheral arterial disease, coronary heart disease, myocardial infarction, cerebral infarction, myocardial microvascular disease, dementia, Alzheimer's disease, osteoporosis and/or osteopenia, angina or resterosis.

Detailed Description of the Invention

The compounds described herein may be prepared by techniques well known in the art and familiar to the average synthetic organic chemist. In addition, the compounds of the present invention may be prepared by the following reaction sequences as depicted in Schemes I, Ia, Ib, II, IIa, III, IIIa, and IV. Further compounds which can be useful for treatment of these diseases, and methods for making such compounds, are disclosed in copending United States Patent Application Serial No. 10/448,770 filed 30 May, 2003, entitled "Substituted Pyrrole Derivatives," and PCT Application No. PCT/IB2004/____ filed _____ entitled "Substituted Pyrrole Derivatives," which applications are incorporated herein in their entirety.

Scheme I


Formula II
Formula III
Formula IV
R2CHO
Formula V
Formula VI
R1CHO
Formula VII
Formula VIII
Formula IX
Formula X
Formula XI
Formula I wherein R4 =
Y =
Formula XII [Hemi calcium salt]

SCHEME I

The compound of Formula XII can be prepared according to Scheme I. Accordingly, a compound of Formula II is reacted with a compound of Formula III, wherein R_3, R_5 and R_6 are as defined earlier, to give a compound of Formula IV which on reaction with a compound of Formula V (wherein R_2 is as defined earlier) gives a compound of Formula VI, which on treatment with a compound of Formula VII (wherein R_1 is as defined earlier) yields a compound of Formula VIII, which on further reaction with a compound of Formula IX gives a compound of Formula X, which on hydrolysis gives a compound of Formula XI, which can then be further converted to hemicalcium salt.

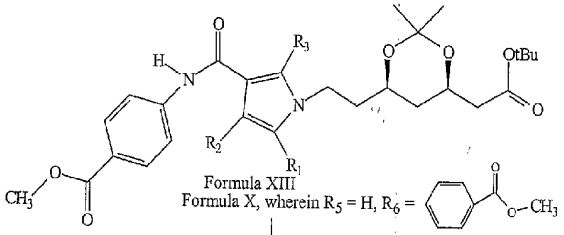
The reaction of a compound of Formula II with a compound of Formula III to give a compound of Formula IV can be carried out in a nonpolar solvent, such as xylene or toluene. The reaction of a compound of Formula II with a compound of Formula III can be carried out in the presence of an organic base, such as triethylamine, pyridine or 1,2-ethylenediamine. The reaction of a compound of Formula IV with an aldehyde of Formula V to give a compound of Formula VI can be carried out in a nonpolar solvent such as hexane, heptane, dichloromethane or toluene or mixture(s) thereof. The reaction of a compound of Formula IV with an aldehyde of Formula V can be carried out in the presence of an organic base such as piperidine, pyridine or β-alanine and an organic acid such as glacial acetic acid or benzoic acid. The reaction of a compound of Formula VI with an aldehyde of Formula VII to give a compound of Formula VIII can be carried out in the presence of a suitable catalyst, such as sodium cyanide, 3-ethyl-5- (2-hydroxyethyl)-4-methyl thiazolium bromide or 3-benzyl-5- (2-hydroxyethyl)-4-methyl thiazolium chloride, in a solvent free condition or in an alcoholic solvent, such as methanol, ethanol, propanol or isopropanol. The reaction of a compound of Formula VI with an aldehyde of Formula VII can be carried out in the presence of an organic base, such as triethylamine or pyridine.

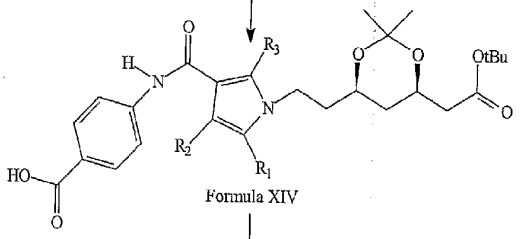
The reaction of a compound of Formula VIII with a compound of Formula IX to give a compound of Formula X can be carried out in a nonpolar solvent, such as xylene, toluene hexane, heptane, tetrahydrofuran, or a mixture thereof in a suitable ratio. The reaction of a compound of Formula VIII with a compound of Formula IX can be carried out in the presence of an organic acid, such as pivalic acid or p-toluene sulfonic acid.

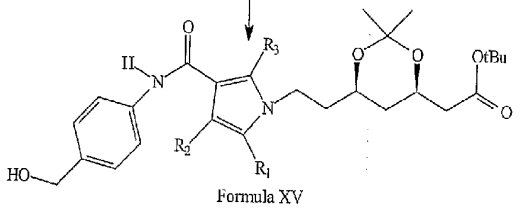
The conversion of a compound of Formula X to a compound of Formula XI can be carried out in a two-step manner, involving an initial acid-catalysed cleavage of ketal, followed by base-catalysed hydrolysis of the tert-butyl ester. The acid can be a mineral acid, such as hydrochloric acid. The cleavage of ketal can be carried out by any other cleavage method known in the prior art. The base can be an organic base, such as lithium hydroxide, sodium hydroxide or potassium hydroxide.

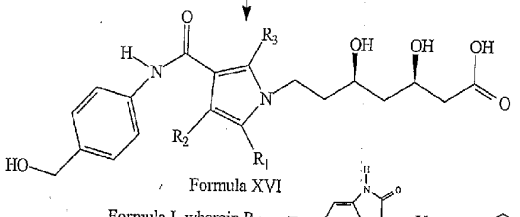
The compound of Formula XI can be converted into its corresponding hemi calcium salt by following procedures well-known to a person ordinary skilled in the art. The hemi calcium salts of compound of Formula XI can also be prepared from the corresponding lactones form of Formula XI by following procedures well-known in the art.

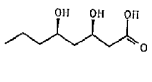
Scheme Ia



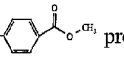






Formula I, wherein R_4 = Y = 

SCHEME Ia

The compound of Formula XVII can be prepared according to Scheme Ia. Accordingly, a compound of Formula XIII (that is, Formula X wherein R_5=H and R_6=  prepared according to Scheme I) is hydrolyzed to give a compound of Formula XIV which, on reduction, gives a compound of Formula XV, which on hydrolysis gives a compound of Formula XVI, which can then be further converted to hemi calcium salt.

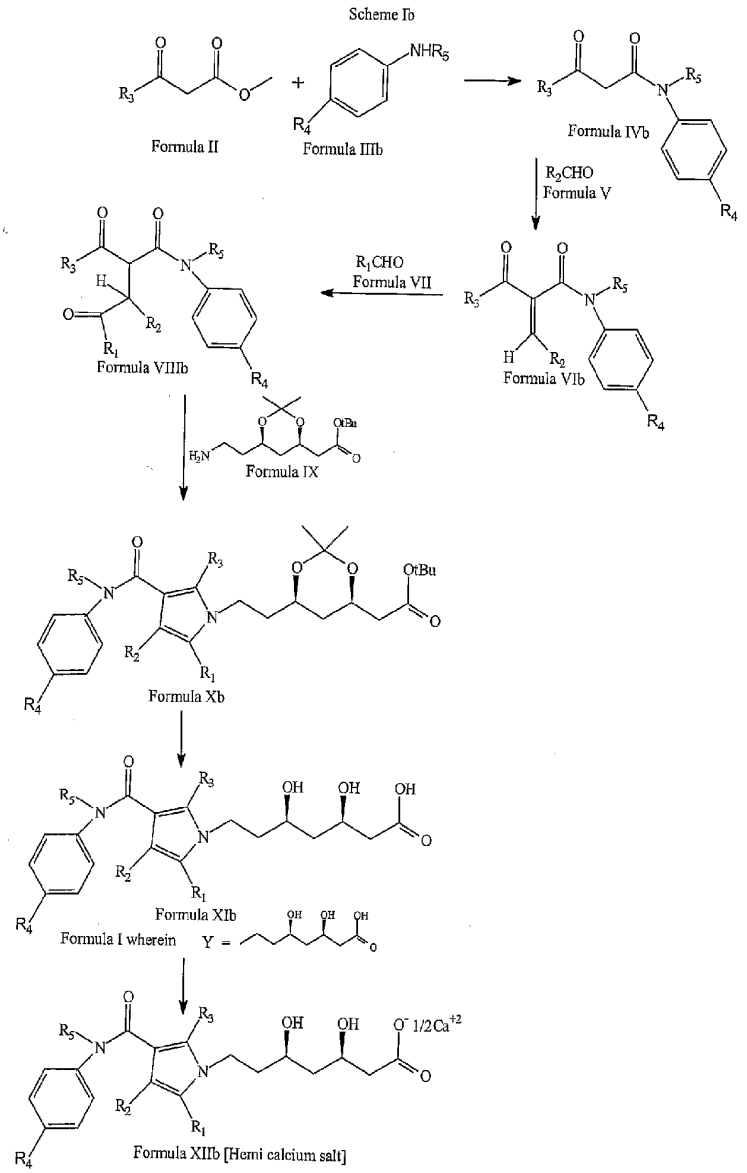
The hydrolysis of a compound of Formula XIII to give a compound of Formula XIV can be carried out in a polar solvent, such as tetrahydrofuran, dioxane, methanol, ethanol or mixture(s) thereof. The hydrolysis of a compound of Formula XIII can be carried out in the presence of an inorganic base such as lithium hydroxide, sodium hydroxide or potassium hydroxide.

The reduction of a compound of Formula XIV to give a compound of Formula XV can be carried out in the presence of iodine and a reducing agent, such as sodium borohydride or borane dimethylsulphide in an organic solvent, such as tetrahydrofuran, dioxane or diethylether.

The conversion of a compound of Formula XV to a compound of Formula XVI is carried out in a two-step manner, involving an initial acid-catalyzed cleavage of ketal, followed by base-catalyzed hydrolysis of the tert-butyl ester. The acid can be a mineral acid, such as hydrochloric acid. The cleavage of ketal can be carried out by any other cleavage method known in the prior art. The base can be an inorganic base, such as lithium hydroxide, sodium hydroxide or potassium hydroxide.

The compound of Formula XVI can be converted into its corresponding hemi calcium salt by following procedures well-known to a person ordinary skilled in the art. The hemi calcium salts of compound of Formula XVI can also be prepared from the corresponding lactone form of Formula XVI by following procedures well-known in the art.

Scheme Ib


Formula II
Formula IIIb
Formula IVb
R2CHO
Formula V
R1CHO
Formula VII
Formula VIb
Formula VIIIb
Formula IX
Formula Xb
Formula XIb
Formula I wherein Y =
Formula XIIb [Hemi calcium salt]

SCHEME Ib

The compound of Formula XIIb can be prepared according to Scheme Ib. Accordingly, a compound of Formula II is reacted with a compound of Formula IIIb, wherein R_3, R_4 and R_5 are as defined earlier, to give a compound of Formula IVb which on reaction with a compound of Formula V (wherein R_2 is as defined earlier) gives a compound of Formula VIb, which on treatment with a compound of Formula VII (wherein R_1 is as defined earlier) yields a compound of Formula VIIIb, which on further reaction with a compound of Formula IX gives a compound of Formula Xb, which on hydrolysis gives a compound of Formula XIb, which can then be further converted to hemicalcium salt.

The reaction of a compound of Formula II with a compound of Formula IIIb to give a compound of Formula IVb can be carried out in an aromatic solvent, such as xylene or toluene. The reaction of a compound of Formula II with a compound of Formula IIIb can be carried out in the presence of an organic base, such as triethylamine, pyridine or 1,2-ethylenediamine.

The reaction of a compound of Formula IVb with an aldehyde of Formula V to give a compound of Formula VIb can be carried out in a hydrocarbon solvent, such as hexane, heptane, or halogenated solvent, such as dichloromethane, or aromatic solvent, such as toluene, or mixture thereof. The reaction of a compound of Formula IVb with an aldehyde of Formula V can be carried out in the presence of an organic base such as piperidine, pyridine or β-alanine and an organic acid such as glacial acetic acid or benzoic acid.

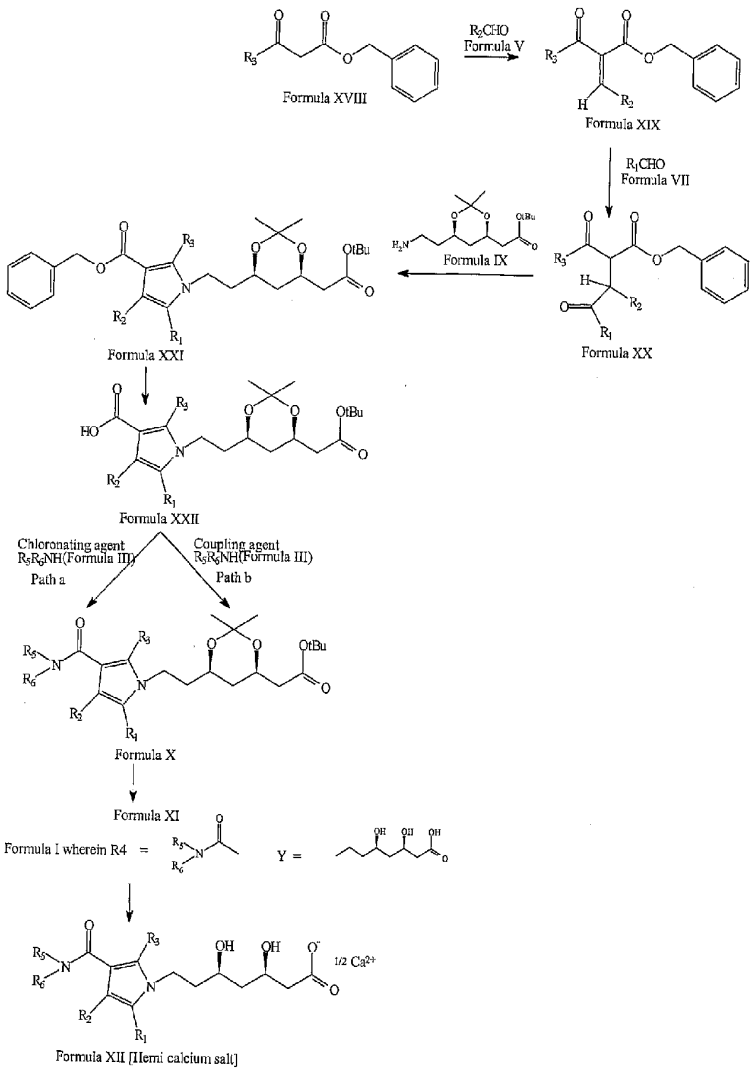
The reaction of a compound of Formula VIb with an aldehyde of Formula VII to give a compound of Formula VIIIb can be carried out in the presence of a suitable catalyst, such as sodium cyanide, 3-ethyl-5- (2-hydroxyethyl)-4-methyl thiazolium bromide or 3-benzyl-5- (2-hydroxyethyl)-4-methyl thiazolium chloride, in a solvent free condition or in an alcoholic solvent, such as methanol, ethanol, propanol or isopropanol or ethers, such as dioxan or tetrahydrofuran. The reaction of a compound of Formula VIb with an aldehyde of Formula VII can be carried out in the presence of an organic base, such as triethylamine or pyridine.

The reaction of a compound of Formula VIIIb with a compound of Formula IX to give a compound of Formula Xb can be carried out in a solvent, such as xylene, toluene, hexane, heptane, tetrahydrofuran, or a mixture thereof in a suitable ratio. The reaction of a compound of Formula VIIIb with a compound of Formula IX can be carried out in the presence of an organic acid, such as pivalic acid or p-toluene sulfonic acid.

The conversion of a compound of Formula Xb to a compound of Formula XIb can be carried out in a two-step manner, involving an initial acid-catalysed cleavage of ketal, followed by base-catalysed hydrolysis of the tert-butyl ester. The acid can be a mineral acid, such as hydrochloric acid. The cleavage of ketal can be carried out by any other cleavage method known in the prior art. The base can be an inorganic base, such as lithium hydroxide, sodium hydroxide or potassium hydroxide.

The compound of Formula XIb can be converted into its corresponding hemi calcium salt by following procedures well-known to a person ordinary skilled in the art. The hemi calcium salts of compound of Formula XIb can also be prepared from the corresponding lactones form of Formula XIb by following procedures well-known in the art.

Scheme II


R3CHO
Formula V
Formula XVIII
Formula XIX
R1CHO
Formula VII
Formula IX
Formula XXI
Formula XX
Formula XXII
Chloronating agent
R5R6NH(Formula III)
Path a
Coupling agent
R5R6NH(Formula III)
Path b
Formula X
Formula XI
Formula I wherein R4 =
Y =
1/2 Ca2+
Formula XII [Hemi calcium salt]

SCHEME II

The compound of Formula XII can also be prepared according to Scheme II. Accordingly, a compound of Formula XVIII is reacted with a compound of Formula V to give a compound of Formula XIX (wherein R_2 and R_3 are as defined earlier in Scheme I) which on reaction with a compound of Formula VII (wherein R_1 is as defined earlier) gives a compound of Formula XX, which on treatment with a compound of Formula IX yields a compound of Formula XXI, which on debenzylation gives a compound of Formula XXII, which on

(a) conversion to corresponding acid chloride followed by reaction with an amine of Formula III (Path a) or

(b) reaction with an amine of Formula III in the presence of a coupling agent (Path b), gives a compound of Formula X, which on hydrolysis gives a compound of Formula XI, which can be further converted to hemicalcium salt of Formula XI by following the procedure well known in the art.

The reaction of a compound of Formula XVIII with an aldehyde of Formula V to give a compound of Formula XIX can be carried out in a nonpolar solvent, such as xylene, toluene, heptane, hexane or dichloromethane or mixture thereof. The reaction of a compound of Formula XVIII with a compound of Formula V can be carried out in the presence of an organic base, such as triethylamine, pyridine, piperidine or β-alanine and an organic acid such as glacial acetic acid or benzoic acid.

The reaction of a compound of Formula XIX with an aldehyde of Formula VII to give a compound of Formula XX can be carried out in a polar solvent, such as an alcoholic solvent, for example, methanol, ethanol, propanol or isopropanol. The reaction of a compound of Formula XIX with an aldehyde of Formula VII can be carried out in the presence of an organic base, such as triethylamine or pyridine. The reaction of a compound of Formula XIX with an aldehyde of Formula VII to give a compound of Formula XX can be carried out in the presence of a catalyst, such as sodium cyanide, 3-ethyl-5- (2-hydroxyethyl)-4-methyl thiazolium bromide or 3-benzyl-5- (2-hydroxyethyl)-4-methyl thiazolium chloride.

The reaction of a compound of Formula XX with an amine of Formula IX to give a compound of Formula XXI can be carried out in the presence of an acid, such as pivalic

acid and p-toluene sulfonic acid in a nonpolar solvent such as hexane, heptane, toluene or tetrahydrofuran.

The debenzylation of a compound of Formula XXI to give a compound of Formula XXII can be carried out in the presence of a catalyst, such as palladium on carbon and hydrogen, in a polar solvent, such as methanol, ethanol, propanol or dioxane.

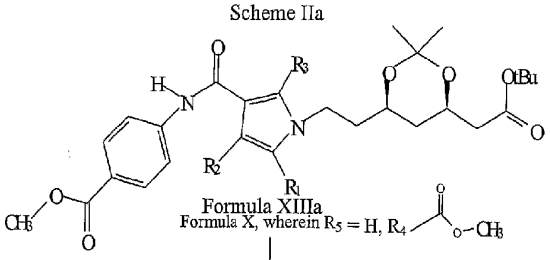
The conversion of compound of Formula XXII to its corresponding acid chloride (Path a) can be carried out with any suitable chlorinating agent, such as oxalyl chloride, in a nonpolar solvent, such as benzene, dichloromethane, tetrahydrofuran, toluene or xylene, followed by reaction with an amine of Formula III to give a compound of Formula X, in a nonpolar solvent, such as benzene, and in the presence of an organic base, such as triethylamine or pyridine.

Reaction of compound of Formula XXII with an amine of Formula III to give a compound of Formula X can be carried out in the presence of a coupling agent (Path b), such as O-benzotriazol-1-yl-N,N,N',N'-tetramethyl uronium hexafluorophosphate (HBTU), bis(2-oxo-3-oxazolidinyl)phosphine (BOP), 1,3-dicyclohexycarbodiimide (DCC), 2-(1H-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate (TBTU), benzotriazole-1-yl-oxy-tris-pyrrolidino-phosphonium hexafluorophosphate (PyBOP) or carbonyldiimidazole (CDI) in a polar solvent, such as dimethylformamide, and an organic base, such as diisopropylethyl amine.

The conversion of a compound of Formula X to a compound of Formula XI can be carried out in a two-step manner, involving an initial acid-catalysed cleavage of ketal, followed by base-catalysed hydrolysis of the tert-butyl ester. The acid can be a mineral acid, such as hydrochloric acid. The cleavage of ketal can be carried out by any other cleavage method known in the prior art. The base can be an inorganic base, for example, lithium hydroxide, sodium hydroxide or potassium hydroxide.

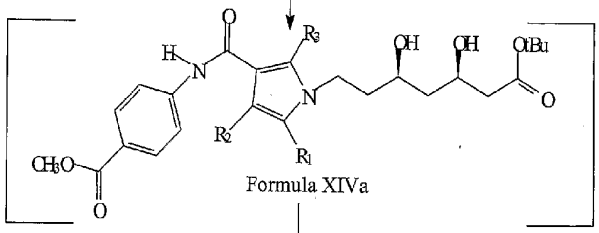
The compound of Formula XI can be converted into its corresponding hemi calcium salt by following procedures well-known to a person ordinary skilled in the art. The hemi calcium salts of compound of Formula XI can also be prepared from the corresponding lactone form of Formula XI by following procedures well-known in the art.

Scheme IIa

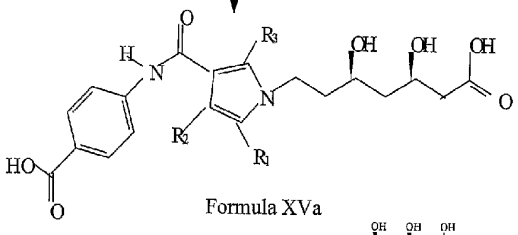


Formula XIIIa

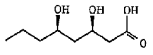
Formula X, wherein R_5 = H, R_4

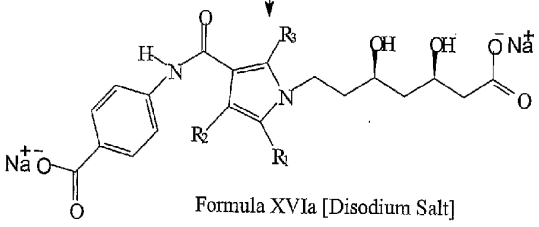


Formula XIVa



Formula XVa

Formula I, wherein R_4 =-COOH, R_5=H , Y = 



Formula XVIa [Disodium Salt]

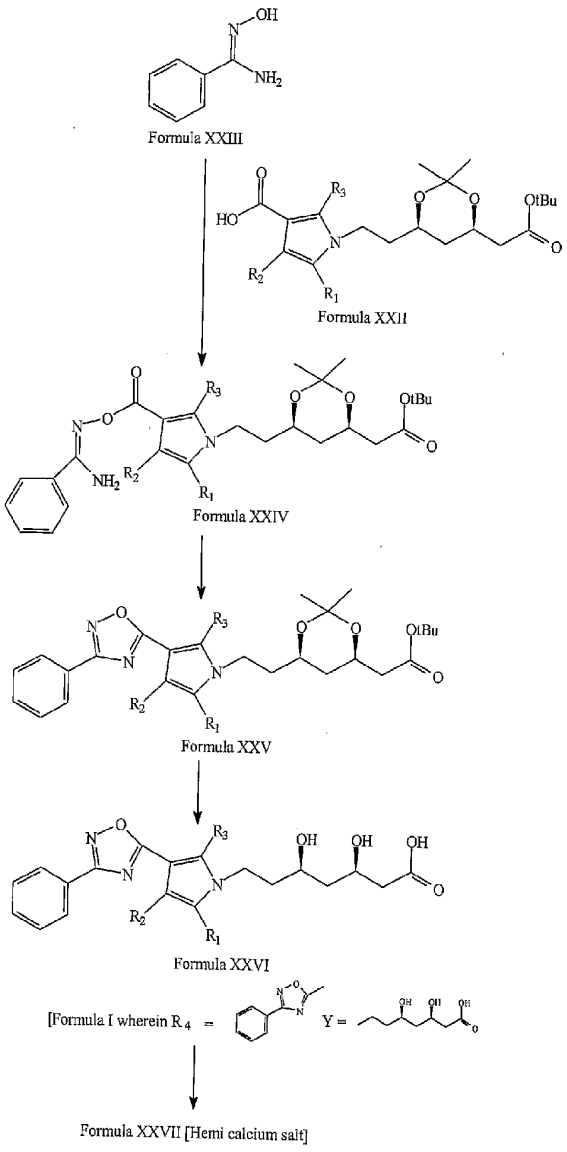
SCHEME IIa

The compound of Formula XVIa can be prepared according to Scheme IIa. Accordingly, a compound of Formula XIIIa (that is, Formula Xa wherein R_5=H and R_4= -$COOCH_3$, prepared according to Scheme I) is hydrolyzed to give a compound of Formula XIVa, which on further hydrolysis gives a compound of Formula XVa, which can then be converted to disodium salt.

The conversion of compounds of Formula XIIIa to compounds of Formula XVa can be carried out in a two-step manner, involving an initial acid-catalyzed cleavage of ketal, followed by base-catalyzed hydrolysis of the methyl and tert-butyl ester. The acid can be a mineral acid, such as hydrochloric acid. The cleavage of ketal can be carried out by any other cleavage method known in the prior art. The base can be an inorganic base, such as lithium hydroxide, sodium hydroxide or potassium hydroxide.

The compound of Formula XVa can be converted into its corresponding disodium salt by following procedures well-known to a person ordinary skilled in the art.

Scheme III


Formula XXIII
Formula XXII
Formula XXIV
Formula XXV
Formula XXVI
[Formula I wherein R4 =
Y =
Formula XXVII [Hemi calcium salt]

SCHEME III

The compound of Formula XXVII can be prepared according to Scheme III. Amidoxime (prepared as per procedure described in *J. Med. Chem.*, 45:944 (2002) and *J. Med. Chem.*, 29:2174 (1986)) of Formula XXIII on coupling with a compound of Formula XXII (prepared following the steps of Scheme II) gives a compound of Formula XXIV, which on cyclisation in diglyme gives a compound of Formula XXV, which on hydrolysis gives a compound of Formula XXVI, which can be further converted to its hemi calcium salt.

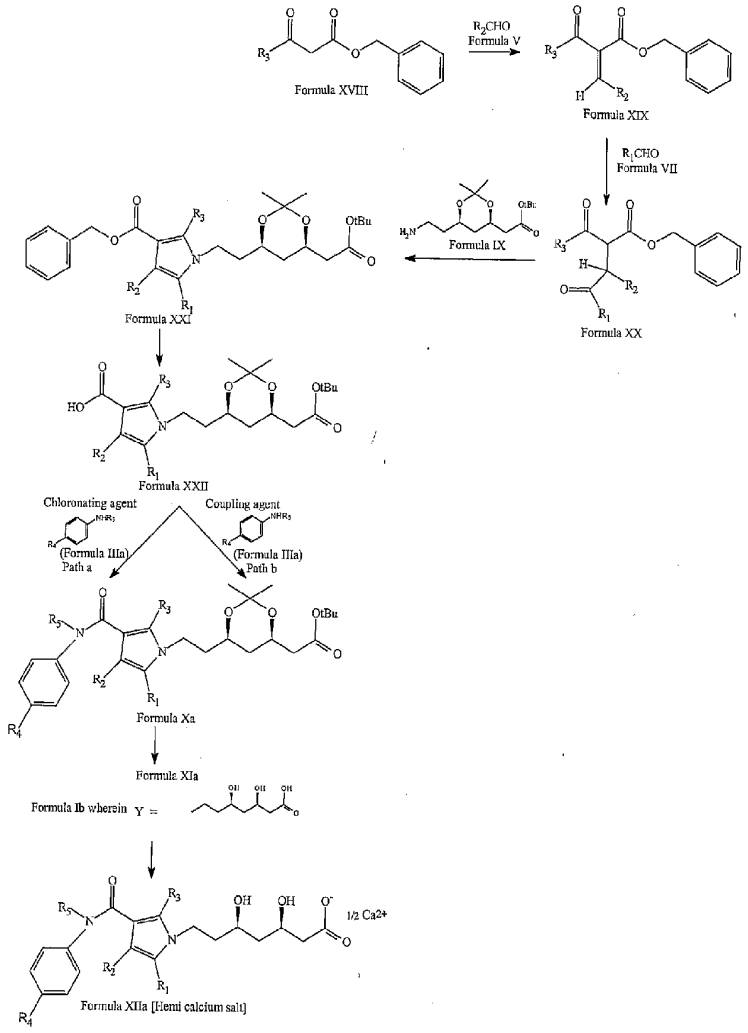
The coupling of compound of Formula XXIII with a compound of Formula XXII can be carried out in the presence of N, N'-carbonyldiimidazole in an organic solvent, such as tetrahydrofuran, dioxane or ether.

The cyclisation of compound of Formula XXIV can be carried out in diglyme to give a compound of Formula XXV.

The conversion of a compound of Formula XXV to a compound of Formula XXVI can be carried out in a two-step manner, involving an initial acid-catalyzed cleavage of ketal, followed by base-catalyzed hydrolysis of the tert-butyl ester. The acid can be a mineral acid, such as hydrochloric acid. The cleavage of ketal can be carried out by any other cleavage method known in the prior art. The base can be an inorganic base, for example, lithium hydroxide, sodium hydroxide or potassium hydroxide.

The compound of Formula XXVI can be converted into its corresponding hemi calcium salt by following procedures well-known to a person ordinary skilled in the art. The hemi calcium salts of compound of Formula XXVI can also be prepared from the corresponding lactone form of Formula XXVI by following procedures well-known in the art.

Scheme IIIa


Formula XVIII
R2CHO
Formula V
Formula XIX
R1CHO
Formula VII
Formula IX
Formula XX
Formula XXI
Formula XXII
Chloronating agent
Coupling agent
(Formula IIIa)
Path a
(Formula IIIa)
Path b
Formula Xa
Formula XIa
Formula Ib wherein Y =
1/2 Ca2+
Formula XIIa [Hemi calcium salt]

SCHEME IIIa

The compound of Formula XIIa can also be prepared according to Scheme IIIa. Accordingly, a compound of Formula XVIII is reacted with a compound of Formula V to give a compound of Formula XIX (wherein R_2 and R_3 are as defined earlier) which on reaction with a compound of Formula VII (wherein R_1 is as defined earlier) gives a compound of Formula XX, which on treatment with a compound of Formula IX yields a compound of Formula XXI, which on debenzylation gives a compound of Formula XXII, which on

(a) conversion to corresponding acid chloride followed by reaction with an amine of Formula IIIa (Path a) or

(b) reaction with an amine of Formula IIIa in the presence of a coupling agent (Path b) gives a compound of Formula Xa, which on hydrolysis gives a compound of Formula XIa, which can be further converted to hemi calcium salt of Formula XIa by following the procedure well known in the art.

The reaction of a compound of Formula XVIII with an aldehyde of Formula V to give a compound of Formula XIX can be carried out in a hydrocarbon solvent, such as hexane or heptane, or halogenated solvent, such as dichloromethane, or aromatic solvent, such as toluene or xylene, or mixture thereof. The reaction of a compound of Formula XVIII with a compound of Formula V can be carried out in the presence of an organic base, such as triethylamine, pyridine, piperidine or β-alanine and an organic acid such as glacial acetic acid or benzoic acid.

The reaction of a compound of Formula XIX with an aldehyde of Formula VII to give a compound of Formula XX can be carried out in a polar solvent, such as an alcoholic solvent, for example, methanol, ethanol, propanol or isopropanol. The reaction of a compound of Formula XIX with an aldehyde of Formula VII can be carried out in the presence of an organic base, such as triethylamine or pyridine. The reaction of a compound of Formula XIX with an aldehyde of Formula VII to give a compound of Formula XX can be carried out in the presence of a catalyst, such as sodium cyanide, 3-ethyl-5- (2-hydroxyethyl)-4-methyl thiazolium bromide or 3-benzyl-5- (2-hydroxyethyl)-4-methyl thiazolium chloride.

The reaction of a compound of Formula XX with an amine of Formula IX to give a compound of Formula XXI can be carried out in the presence of an acid, such as pivalic

acid and p-toluene sulfonic acid in a hydrocarbon solvent, such as hexane or heptane, or aromatic solvent, such as toluene, or ether, such as tetrahydrofuran or mixture thereof.

The debenzylation of a compound of Formula XXI to give a compound of Formula XXII can be carried out in the presence of a catalyst, such as palladium on carbon and hydrogen, in a polar solvent, such as alcoholic solvent, for example, methanol, ethanol or propanol, or ether solvent, for example, dioxane.

The conversion of compound of Formula XXII to its corresponding acid chloride (Path a) can be carried out with any suitable chlorinating agent, such as oxalyl chloride or thionyl chloride, in an aromatic solvent, such as benzene, toluene or xylene, or halogenated solvent, such as dichloromethane, or ether, such as tetrahydrofuran, followed by reaction with an amine of Formula IIIa to give a compound of Formula Xa, in an aromatic solvent, such as benzene, and in the presence of an organic base, such as triethylamine or pyridine.

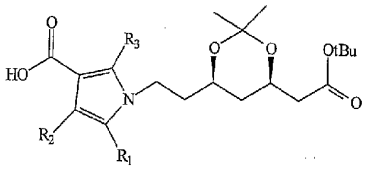
Reaction of compound of Formula XXII with an amine of Formula IIIa to give a compound of Formula Xa (path b) can be carried out in the presence of a coupling agent, such as O-benzotriazol-1-yl-N,N,N',N'-tetramethyl uronium hexafluorophosphate (HBTU), bis(2-oxo-3-oxazolidinyl)phosphine (BOP), 1,3-dicyclohexycarbodiimide (DCC), 2-(1H-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate (TBTU), benzotriazole-1-yl-oxy-tris-pyrrolidino-phosphonium hexafluorophosphate (PyBOP) or carbonyldiimidazole (CDI) in a polar solvent, such as dimethylformamide, and an organic base, such as diisopropylethylamine.

The conversion of a compound of Formula Xa to a compound of Formula XIa can be carried out in a two-step manner, involving an initial acid-catalysed cleavage of ketal, followed by base-catalysed hydrolysis of the tert-butyl ester. The acid can be a mineral acid, such as hydrochloric acid. The cleavage of ketal can be carried out by any other cleavage method known in the prior art. The base can be an inorganic base, for example, lithium hydroxide, sodium hydroxide or potassium hydroxide.

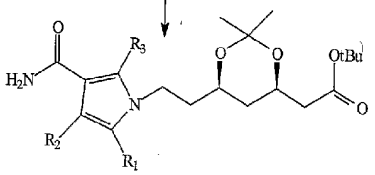
The compound of Formula XIa can be converted into its corresponding hemi calcium salt by following procedures well-known to a person ordinary skilled in the art.

The hemi calcium salts of compound of Formula XIa can also be prepared from the corresponding lactones form of Formula XIa by following procedures well-known in the art.

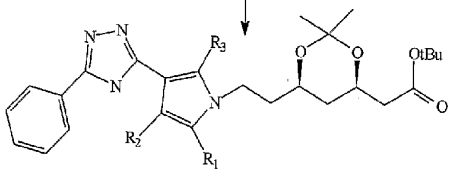
Scheme IV



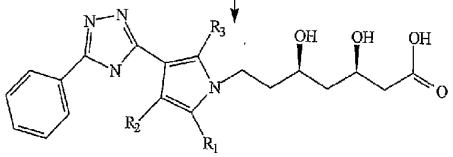
Formula XII



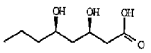
Formula XXVIII



Formula XXIX



Formula XXX

Formula I wherein R_4 =  Y = 

Formula XXXI
[Hemi calcium salt]

SCHEME IV

The compound of Formula XXXI can be prepared according to Scheme IV. Accordingly, treating acid chloride of compound of Formula XXII with ammonia affords a compound of Formula XXVIII, which on condensation with N,N-dimethylbenzamide dimethylketal followed by treatment with hydrazine hydrate gives a compound of Formula XXIX, which on hydrolysis gives a compound of Formula XXX, which can be further converted to its hemi calcium salt.

The reaction of compound of Formula XXII to give compound of Formula XXVIII can be carried out in presence of a chlorinating agent, such as oxalyl chloride or thionyl chloride followed by reaction with ammonia.

The condensation of a compound of Formula XXVIII with N, N-dimethylbenzamide dimethylacetal followed by treatment with hydrazine hydrate affords compound of Formula XXIX.

The conversion of a compound of Formula XXIX to a compound of Formula XXX can be carried out in a two-step manner, involving an initial acid-catalyzed cleavage of ketal, followed by base-catalyzed hydrolysis of the tert-butyl ester. The acid can be a mineral acid, such as hydrochloric acid. The cleavage of ketal can be carried out by any other cleavage method known in the prior art. The base can be an inorganic base, for example, lithium hydroxide, sodium hydroxide or potassium hydroxide.

The compound of Formula XXX can be converted into its corresponding hemi calcium salt by following procedures well-known to a person ordinary skilled in the art. The calcium salts of compound of Formula XXX can also be prepared from the corresponding lactone form of Formula XXX by following procedures well-known in the art.

In the above schemes, where specific reagents, such as particular bases, reducing agents, solvents, etc., are mentioned, it is to be understood that other bases, reducing agents, solvents, etc., known to those skilled in the art may be used. Similarly, the reaction temperature and duration may be adjusted according to the desired needs.

An illustrative list of particular compounds disclosed herein is given below (also shown in Table I):

(3R,5R)-7-[2-(4-fluorophenyl)-5- isopropyl-3-phenyl-4-[(2-acetylphenylamino) carbonyl]-pyrrol-1-yl]-3,5-dihydroxy-heptanoic acid (Compound No. 1)

(3R,5R)-7-[2-(4-fluorophenyl)-5- isopropyl-3-phenyl-4-[(3-acetylphenylamino) carbonyl]-pyrrol-1-yl]-3,5-dihydroxy-heptanoic acid (Compound No. 2)

(3R,5R)-7-[2-(4-fluorophenyl)-5- isopropyl-3-phenyl-4-[(4-acetylphenylamino) carbonyl]-pyrrol-1-yl]-3,5-dihydroxy-heptanoic acid (Compound No. 3)

(3R,5R)-7-[2-(4-fluorophenyl)-5- isopropyl-3-phenyl-4-[(2,4-dimethylphenylamino) carbonyl]-pyrrol-1-yl]-3,5-dihydroxy-heptanoic acid (Compound No. 4)

(3R,5R)-7-[2-(4-fluorophenyl)-5- isopropyl-3-phenyl-4-[(cyclohexylamino) carbonyl)]-pyrrol-1-yl]-3,5-dihydroxy-heptanoic acid (Compound No. 5)

(3R,5R)-7-[2-(4-fluorophenyl)-5- isopropyl-3-phenyl-4-[(4-trifluoromethylbenzylamino) carbonyl)]-pyrrol-1-yl]-3,5-dihydroxy-heptanoic acid (Compound No. 6)

(3R,5R)-7-[2-(4-fluorophenyl)-5- isopropyl-3-phenyl-4-(morpholine-4-carbonyl)-pyrrol-1-yl]-3,5-dihydroxy-heptanoic acid (Compound No. 7)

(3R,5R)-7-[2-(4-fluorophenyl)-5- isopropyl-3-phenyl-4-(piperidine-1-carbonyl)-pyrrol-1-yl]-3,5-dihydroxy-heptanoic acid (Compound No. 8)

(3R,5R)-7-[2-(4-fluorophenyl)-5- isopropyl-3-phenyl-4-[(4-hydroxymethylphenylamino) carbonyl]-pyrrol-1-yl]-3,5-dihydroxy-heptanoic acid (Compound No. 11)

(3R,5R)-7-[2-(4-fluorophenyl)-5- isopropyl-3-phenyl-4-[(4-methanesulfonylaminophenyl amino) carbonyl]-pyrrol-1-yl]-3,5-dihydroxy-heptanoic acid (Compound No. 12)

(3R,5R)-7-[2-(4-fluorophenyl)-5-isopropyl-3-phenyl-4-[(4-acetylaminophenylamino) carbonyl]-pyrrol-1-yl]-3,5-dihydroxy-heptanoic acid (Compound No. 13)

(3R,5R)-7-[2-(4-fluorophenyl)-5- isopropyl-3-(4-cyanophenyl)-4-[(phenylamino) carbonyl)]-pyrrol-1-yl]-3,5-dihydroxy-heptanoic acid (Compound No. 14)

(3R,5R)-7-[2-(4-fluorophenyl)-5- isopropyl-3-phenyl-4-[4-carboxyphenyl)amino) carbonyl]-pyrrol-1-yl]-3,5-dihydroxy-heptanoic acid (Compound No. 1a),

(3R,5R)-7-[2-(4-fluorophenyl)-5- isopropyl-3-phenyl-4-[4-acetoxymethylphenyl) amino) carbonyl]-pyrrol-1-yl]-3,5-dihydroxy-heptanoic acid (Compound No. 2a),

(3R,5R)-7-[2-(4-fluorophenyl)-5-isopropyl-3-phenyl-4-[4-phenylthiocarbamoyl oxymethylphenyl)amino)carbonyl]-pyrrol-1-yl]-3,5-dihydroxy-heptanoic acid (Compound No. 3a),

(3R,5R)-7-[2-(4-fluorophenyl)-5- isopropyl-3-phenyl-4-[4-propionyloxymethyl phenyl)amino) carbonyl]-pyrrol-1-yl]-3,5-dihydroxy-heptanoic acid (Compound No. 4a),

(3R,5R)-7-[2-(4-fluorophenyl)-5- isopropyl-3-phenyl-4-[4-octylcarbamoyloxymethyl phenyl)amino) carbonyl]-pyrrol-1-yl]-3,5-dihydroxy-heptanoic acid (Compound No. 5a),

(3R, 5R)-7-[2-(4-fluorophenyl)-5- isopropyl-3-phenyl-4-[4-phenylacetoxymethyl phenyl)amino) carbonyl]-pyrrol-1-yl]-3,5-dihydroxy-heptanoic acid (Compound No. 6a),

(3R, 5R)-7-[2-(4-fluorophenyl)-5- isopropyl-3-phenyl-4-[4-phenylcarbamoyl oxymethyl phenyl)amino) carbonyl]-pyrrol-1-yl]-3,5-dihydroxy-heptanoic acid (Compound No. 7a),

(3R, 5R)-7-[2-(4-fluorophenyl)-5- isopropyl-3-phenyl-4-[4-benzoyloxymethyl phenyl)amino) carbonyl]-pyrrol-1-yl]-3,5-dihydroxy-heptanoic acid (Compound No. 8a),

(3R, 5R)-7-[2-(4-fluorophenyl)-5- isopropyl-3-phenyl-4-[4-isonicotinoyloxymethyl phenyl)amino) carbonyl]-pyrrol-1-yl]-3,5-dihydroxy-heptanoic acid (Compound No. 9a),

(3R, 5R)-7-[2-(4-fluorophenyl)-5-isopropyl-3-phenyl-4- [4-pyridin-4-ylcarbamoyl oxymethyl phenyl) amino) carbonyl]-pyrrol-1-yl]-3,5-dihydroxy-heptanoic acid (Compound No. 10a),

(3R, 5R)-7-[2-(4-fluorophenyl)-5- isopropyl-3-phenyl-4-[4-phenylcarbamoyl phenyl)
amino) carbonyl]-pyrrol-1-yl]-3,5-dihydroxy-heptanoic acid (Compound No. 11a),

(3R, 5R)-7-[2-(4-fluorophenyl)-5- isopropyl-3-phenyl-4-[4-cyclohexylcarbamoyl-phenyl) amino) carbonyl]-pyrrol-1-yl]-3,5-dihydroxy-heptanoic acid (Compound No. 12a),

(3R, 5R)-7-[2-(4-fluorophenyl)-5- isopropyl-3-phenyl-4-[4-methylcarbamoyl)-phenyl)amino) carbonyl]-pyrrol-1-yl]-3,5-dihydroxy-heptanoic acid (Compound No. 13a),

(3R, 5R)-7-[2-(4-fluorophenyl)-5- isopropyl-3-phenyl-4-[4-benzylcarbamoyl)-phenyl)amino) carbonyl]-pyrrol-1-yl]-3,5-dihydroxy-heptanoic acid (Compound No. 14a),

(3R, 5R)-7-[2-(4-fluorophenyl)-5- isopropyl-3-phenyl-4-[4-(morpholine-4-carbonyl)-phenyl)amino) carbonyl]-pyrrol-1-yl]-3,5-dihydroxy-heptanoic acid (Compound No. 15),

(3R, 5R)-7-[2-(4-fluorophenyl)-5- isopropyl-3-phenyl-4-[4-(piperidine-1-carbonyl)-phenyl)amino) carbonyl]-pyrrol-1-yl]-3,5-dihydroxy-heptanoic acid (Compound No. 16),

(3R, 5R)-7-[2-(4-fluorophenyl)-5- isopropyl-3-phenyl-4-[4-benzylamino phenyl)amino) carbonyl]-pyrrol-1-yl]-3,5-dihydroxy-heptanoic acid (Compound No. 17),

(3R,5R)-7-[2-(4-fluorophenyl)-5- isopropyl-3-phenyl-4-[4-(1-hydroxyethyl)phenylamino) carbonyl]-pyrrol-1-yl]-3,5-dihydroxy-heptanoic acid (Compound No. 18),

(3R,5R)-7-[2-(4-fluorophenyl)-5- isopropyl-3-phenyl-4-[4-(2-hydroxyethyl) phenylamino) carbonyl]-pyrrol-1-yl]-3,5-dihydroxy-heptanoic acid (Compound No. 19),

(3R,5R)-7-[2-(4-fluorophenyl)-5- isopropyl-3-phenyl-4-[4-(3-hydroxypropyl phenylamino) carbonyl]-pyrrol-1-yl]-3,5-dihydroxy-heptanoic acid (Compound No. 20),

(3R,5R)-7-[2-(4-fluorophenyl)-5- isopropyl-3-phenyl-4-[(4-methoxymethyl phenylamino) carbonyl]-pyrrol-1-yl]-3,5-dihydroxy-heptanoic acid (Compound No. 21),

(3R,5R)-7-[2-(4-fluorophenyl)-5- isopropyl-3-phenyl-4-[(4-ethoxymethyl phenylamino) carbonyl]-pyrrol-1-yl]-3,5-dihydroxy-heptanoic acid (Compound No. 22),

(3R,5R)-7-[2-(4-fluorophenyl)-5- isopropyl-3-phenyl-4-[(4-isopropoxymethyl phenylamino) carbonyl]-pyrrol-1-yl]-3,5-dihydroxy-heptanoic acid (Compound No. 23),

(3R,5R)-7-[2-(4-fluorophenyl)-5- isopropyl-3-phenyl-4-[(4-propoxymethyl phenylamino) carbonyl]-pyrrol-1-yl]-3,5-dihydroxy-heptanoic acid (Compound No. 24),

(3R,5R)-7-[2-(4-fluorophenyl)-5- isopropyl-3-phenyl-4-[(4-methoxymethoxymethylphenylamino) carbonyl]-pyrrol-1-yl]-3,5-dihydroxy-heptanoic acid (Compound No. 25),

(3R,5R)-7-[2-(4-fluorophenyl)-5- isopropyl-3-phenyl-4-[(4-cyclohexyloxymethyl phenylamino) carbonyl]-pyrrol-1-yl]-3,5-dihydroxy-heptanoic acid (Compound No. 26),

(3R,5R)-7-[2-(4-fluorophenyl)-5- isopropyl-3-phenyl-4-[(4-cyclopentyloxymethyl phenylamino) carbonyl]-pyrrol-1-yl]-3,5-dihydroxy-heptanoic acid (Compound No. 27),

(3R,5R)-7-[2-(4-fluorophenyl)-5- isopropyl-3-phenyl-4-[(4-benzyloxymethyl phenylamino) carbonyl]-pyrrol-1-yl]-3,5-dihydroxy-heptanoic acid (Compound No. 28)

(3R,5R)-7-[2-(4-fluorophenyl)-5- isopropyl-3-phenyl-4-[(4-chlorobenzyloxymethyl phenylamino) carbonyl]-pyrrol-1-yl]-3,5-dihydroxy-heptanoic acid (Compound No. 29),

(3R,5R)-7-[2-(4-fluorophenyl)-5- isopropyl-3-phenyl-4-[(4-methoxybenzyloxymethyl phenylamino) carbonyl]-pyrrol-1-yl]-3,5-dihydroxy-heptanoic acid (Compound No. 30),

(3R,5R)-7-[2-(4-fluorophenyl)-5- isopropyl-3-phenyl-4-[(4-phenoxymethylphenylamino) carbonyl]-pyrrol-1-yl]-3,5-dihydroxy-heptanoic acid (Compound No. 31),

(3R,5R)-7-[2-(4-fluorophenyl)-5- isopropyl-3-phenyl-4-[(4-chlorophenoxymethyl phenylamino) carbonyl]-pyrrol-1-yl]-3,5-dihydroxy-heptanoic acid (Compound No. 32),

(3R,5R)-7-[2-(4-fluorophenyl)-5- isopropyl-3-phenyl-4-[(4-acetylaminophenylamino) carbonyl]-pyrrol-1-yl]-3,5-dihydroxy-heptanoic acid (Compound No. 33),

(3R,5R)-7-[2-(4-fluorophenyl)-5- isopropyl-3-phenyl-4-[(4-benzoylamino phenylamino) carbonyl]-pyrrol-1-yl]-3,5-dihydroxy-heptanoic acid (Compound No. 34),

(3R,5R)-7-[2-(4-fluorophenyl)-5- isopropyl-3-phenyl-4-[(4-benzenesulfonylamino phenylamino) carbonyl]-pyrrol-1-yl]-3,5-dihydroxy-heptanoic acid (Compound No. 36)

(3R,5R)-7-[2-(4-fluorophenyl)-5- isopropyl-3-phenyl-4-[4-(3-phenyl-ureido)-phenylamino) carbonyl]-pyrrol-1-yl]-3,5-dihydroxy-heptanoic acid (Compound No. 37),

(3R,5R)-7-[2-(4-fluorophenyl)-5- isopropyl-3-phenyl-4-[4-(3-methyl-ureido)-phenylamino) carbonyl]-pyrrol-1-yl]-3,5-dihydroxy-heptanoic acid (Compound No. 38),

(3R,5R)-7-[2-(4-fluorophenyl)-5- isopropyl-3-phenyl-4-[4-(3-benzyll-ureido)-phenylamino) carbonyl]-pyrrol-1-yl]-3,5-dihydroxy-heptanoic acid (Compound No. 39),

(3R,5R)-7-[2-(4-fluorophenyl)-5- isopropyl-3-phenyl-4-[4-(3-benzyl-thioureido)-phenylamino) carbonyl]-pyrrol-1-yl]-3,5-dihydroxy-heptanoic acid (Compound No. 40),

(3R,5R)-7-[2-(4-fluorophenyl)-5- isopropyl-3-phenyl-4-[4-(3-phenyl-thioureido)-phenylamino) carbonyl]-pyrrol-1-yl]-3,5-dihydroxy-heptanoic acid (Compound No. 41),

(3R,5R)-7-[2-(4-fluorophenyl)-5- isopropyl-3-phenyl-4-[4-(3-methyl-thioureido)-phenylamino) carbonyl]-pyrrol-1-yl]-3,5-dihydroxy-heptanoic acid (Compound No. 42),

and their pharmaceutically acceptable salts, pharmaceutically acceptable solvates, tautomers, racemates, polymorphs, pure enantiomers, diastereoisomers, metabolites, prodrugs or N-oxides.

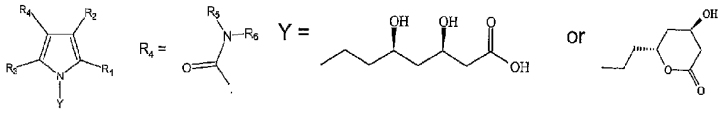
An illustrative list of compounds, which can be prepared by following Schemes III and IV is given below (also shown in Table I):

(3R,5R)-7-[2-(4-Fluorophenyl)-5-isopropyl-3-phenyl-4-(3-phenyl-[1,2,4]oxadiazol-5-yl)-pyrrol-1-yl]-3,5-dihydroxy-heptanoic acid (Compound No. 9)

(3R,5R)-7-[2-(4-Fluorophenyl0-5-isopropyl-3-phenyl-4-(5-phenyl-2H-[1,2,4]triazol-3-yl)-pyrrol-1-yl]-3,5-dihydroxy-heptanoic acid (Compound No. 10)

In Tables I and Ia, R_4 is the indicated structure, unless otherwise noted.

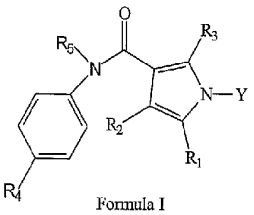
Table I



C. No.	R_1	R_2	R_3	R_4	R_5	R_6
1	4-Fluorophenyl	Phenyl	Isopropyl	-	Hydrogen	2-Acetylphenyl
2	4-Fluorophenyl	Phenyl	Isopropyl	-	Hydrogen	3-Acetylphenyl
3	4-Fluorophenyl	Phenyl	Isopropyl	-	Hydrogen	4-Acetylphenyl
4	4-Fluorophenyl	Phenyl	Isopropyl	-	Hydrogen	2,4-Dimethylphenyl
5	4-Fluorophenyl	Phenyl	Isopropyl	-	Hydrogen	Cyclohexyl
6	4-Fluorophenyl	Phenyl	Isopropyl	-	Hydrogen	4-trifluoromethyl benzyl
7	4-Fluorophenyl	Phenyl	Isopropyl	-	$-(CH2)_2-O-(CH2)_2-$	
8	4-Fluorophenyl	Phenyl	Isopropyl	-	$-(CH2)_5-$	
9*	4-Fluorophenyl	Phenyl	Isopropyl	1,2,4-Oxadiazinylphenyl	--	
10*	4-Fluorophenyl	Phenyl	Isopropyl	1,2,4-Triazolylphenyl	--	
11	4-Fluorophenyl	Phenyl	Isopropyl	-	Hydrogen	4-(Hydroxymethyl)phenyl
12	4-Fluorophenyl	Phenyl	Isopropyl	-	Hydrogen	4-(Methylsulfonamido)-phenyl
13	4-Fluorophenyl	Phenyl	Isopropyl	-	Hydrogen	4-(Acetamido)phenyl
14	4-Fluorophenyl	4-cyanoPhenyl	Isopropyl	-	Hydrogen	Phenyl

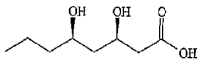
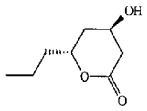
* Hypothetical examples

Table Ia



Formula I

wherein

Y =  or 

R_1=4-fluorophenyl, R_2= phenyl, R_3=isopropyl, R_5=hydrogen

Compound No.	R_4
1a	COOH
2a	acetoxymethyl
3a	phenylthiocarbamoyloxymethyl
4a	propionyloxymethyl
5a	octylcarbamoyloxymethyl
6a	phenylacetoxymethyl
7a	phenylcarbamoyloxymethyl
8a	benzoyloxymethyl
9a	isonicotinoyloxymethyl
10a	pyridin-4-ylcarbamoyloxymethyl
11a	phenylcarbamoyl
12a	cyclohexylcarbamoyl
13a	methylcarbamoyl
14a	benzylcarbamoyl
15	morpholine-4-carbonyl
16	piperidine-1-carbonyl
17	benzylamino
18	(1-hydroxyethyl)
19	(2-hydroxyethyl)
20	(3-hydroxypropyl)
21	methoxymethyl
22	ethoxymethyl
23	isopropoxymethyl
24	propoxymethyl
25	methoxymethoxymethyl
26	cyclohexyloxymethyl
27	cyclopentyloxymethyl
28	benzyloxymethyl

Compound No.	R_4
29	4-chlorobenzyloxymethyl
30	4-methoxybenzyloxymethyl
31	phenoxymethyl
32	4-chlorophenoxymethyl
33	acetylamino
34	Benzoylamino
36	benzenesulfonylamino
37	3-phenyl-ureido
38	3-methyl-ureido
39	3-benzyl-ureido
40	3-benzyl-thioureido
41	3-phenyl-thioureido
42	3-methyl-thioureido

The term "pharmaceutically acceptable" means approved by regulatory agency of the federal or a state government or listed in the U.S. Pharmacopeia or other generally recognized pharmacopeia for use in animals, and more particularly in humans.

The term "pharmaceutically acceptable salts" refer to a salt prepared from pharmaceutically acceptable monovalent, divalent or trivalent non-toxic metal or organic base. Examples of such metal salts include, but are not limited to, lithium, sodium, potassium, calcium, magnesium, zinc, aluminum, and the like. Examples of such organic bases include, but are not limited to, amino acid, ammonia, mono-alkyl ammonium, dialkyl ammonium, trialkyl ammonium and N-methyl glucamine and the like. The free acid forms of compounds of the present invention may be prepared from the salt forms, if desired, by contacting the salt with dilute aqueous solution of an acid such as hydrochloric acid. The base addition salts may differ from the free acid forms of the compounds of this invention in such physical characteristics as solubility and melting point.

The term "pharmaceutically acceptable solvates" refers to solvates with water (i-e hydrates) or pharmaceutically acceptable solvents, for example solvates with ethanol and the like. Such solvates are also encompassed within the scope of the disclosure.

Furthermore, some of the crystalline forms for compounds described herein may exist as polymorphs and as such are intended to be included in the scope of the disclosure.

The present invention also includes within its scope prodrugs of these agents. In general, such prodrugs will be functional derivatives of these compounds, which are readily convertible *in vivo* into the required compound. Conventional procedure for the

selection and preparation of suitable prodrug derivatives are described, for example, in "design of prodrugs", ed. H Bundgaard and, Elsevier, 1985.

The present invention also includes metabolites, which become active upon introduction into the biological system.

The compounds of the invention possess two chiral centers, they may, therefore, exist as enantiomers and diastereomers. It is to be understood that all such isomers and racemic mixtures therefore are encompassed within the scope of the present invention. Preferably, this invention contemplates compounds only with 3R and 5R configuration.

The crystalline or amorphous forms of compounds disclosed herein may exist as polymorphs and as such are intended to be included in the present invention.

Pharmaceutical compositions comprising compounds disclosed herein, their pharmaceutically acceptable salt, pharmaceutically acceptable solvates, or polymorphs, and pharmaceutically acceptable carrier or excipient are also disclosed herein.

The compositions provided herein, both those containing one disclosed compound and those containing two or more compounds, may be suitable for oral or parenteral administration. The compositions may be formulated to provide immediate or sustained release of the therapeutic compounds. The compounds described herein can be administered alone but will generally be administered as an admixture with a suitable pharmaceutically acceptable carrier. The term "pharmaceutically acceptable carrier" is intended to include non-toxic, inert solid, semi-solid, liquid filter, diluent, encapsulating materials or formulation auxiliaries of any type.

Solid form preparations for oral administration may include capsules, tablets, pills, powder, granules or suppositories. For solid form preparations, the active compound is mixed with at least one inert, pharmaceutically acceptable excipient or carrier, for example, sodium citrate, dicalcium phosphate and/or a filler, an extender, for example, starch, lactose, sucrose, glucose, mannitol or silicic acid; binders, for example, carboxymethyl cellulose, alginates, gelatins, polyvinylpyrroledinone, sucrose, or acacia; disintegrating agents, for example, agar-agar, calcium carbonate, potato starch, aliginic acid, certain silicates or sodium carbonate; absorption accelerators, for example, quaternary ammonium compounds; wetting agents, for example, cetyl alcohol, glycerol, or mono stearate adsorbents, for example, Kaolin; lubricants, for example, talc, calcium

stearate, magnesium stearate, solid polyethyleneglycol, or sodium lauryl sulphate, and mixtures thereof.

In case of capsules, tablets, and pills, the dosage form may also comprise buffering agents.

The solid preparation of tablets, capsules, pills, or granules can be accomplished with coatings and/or shells, for example, enteric coatings and other coatings well known in the pharmaceutical formulating art.

Liquid form preparations for oral administration can include pharmaceutically acceptable emulsions, solutions, suspensions, syrups and elixirs. For liquid form preparations, the active compound can be mixed with water or other solvent, solubilizing agents and emulsifiers, for example, ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propylene glycol, 1,3-butylene glycol, dimethyl formamide, oils (for example, cottonseed, ground corn, germ, live, caster and sesamine oil), glycerol and fatty acid ester of sorbitan and mixture thereof.

Besides inert diluents, the oral compositions can also include adjuvants, for example, wetting agents, emulsifying agents, suspending agents, sweetening agents, flavoring agents and perfuming agents.

The formulations as described herein may be formulated so as to provide quick, sustained, or delayed release of the active compound after administration to the patient by employing procedures well-known to the art. The term "patient" as used herein refers to a human or non-human mammal, which is the object of treatment, observation or experiment.

The pharmaceutical preparations can be in unit dosage forms, and in such forms, the preparations are subdivided into unit doses containing appropriate quantities of an active compound.

The amount of a compound disclosed herein that will be effective in the treatment of a particular disorder or condition can be determined by standard clinical techniques. In addition, *in vitro* or *in vivo* assays may optionally be employed to help identify optimal dosage ranges.

Examples set forth below demonstrate general synthetic procedures for preparation of particular representative compounds. The examples are provided to

illustrate particular aspects of the disclosure, and do not constrain the scope of the present invention as defined by the claims.

EXAMPLES

General Procedure

Schemes I and Ib

Step 1: Preparation of β-ketoamide-1 (Formula IV and IVb)

A mixture of β ketoester (Formula II, 1 equiv.), amine (Formula III, 1 equiv) 1,2-ethylene diamine (0.01 equiv) in xylene was refluxed with the azeotropic removal of water. After the completion of reaction, solvent was evaporated & the residue purified on column (silica gel; 100-200 mesh). Compounds of Formula IVb can be prepared analogously. The following intermediates were prepared following above general procedure

4-Methyl-3-oxo-pentanoic acid (3-acetylphenyl)-amide

^{1}H NMR($CDCl_3$):δ 1.19 (d, J=6.9Hz, 6H), 2.61 (s, 3H), 2.75 (sep, J=6.9Hz, 1H), 3.64 (s, 2H), 7.43 (t, J=7.8Hz, 1H), 7.71 (d, J=7.8Hz, 1H), 7.87 (d, J=8.1Hz, 1H), 8.08 (s, 1H), 9.44 (brs, 1H); MS (positive ion mode): m/z 248 [M+1]; Yield: 49%

4-Methyl-3-oxo-pentanoic acid (4-acetylphenyl)-amide

^{1}H NMR($CDCl_3$):δ 1.19 (d, J=6Hz, 6H), 2.58 (s, 3H), 2.75 (sep, J=6Hz, 1H), 3.65 (s, 2H), 7.67 (d, J=6Hz, 2H), 7.95 (d, J=6Hz, 2H), 9.60 (s, 1H), MS (positive ion mode): m/z 248 [M+1]; Yield 54%

4-Methyl-3-oxo-pentanoic acid (2,4-dimethylphenyl)-amide

^{1}H NMR($CDCl_3$):δ 1.18 (d, J=6Hz, 6H), 2.29 (s, 6H), 2.73 (Sep, J=6Hz, 1H), 3.64 (s, 2H), 7.00 (s, 2H), 7.76 (d, J=6Hz, 1H), 9.11 (brs, 1H); MS (positive ion mode): m/z 234 [M+1] Yield 72%

4-Methyl-3-oxo-pentanoic acid 4-trifluoromethylbenzyl amide

^{1}H NMR($CDCl_3$):δ 1.14 (d, J=6Hz, 6H), 2.70 (sept, J=6Hz, 1H), 3.53 (s, 2H), 4.53 (d, J=6Hz, 2H), 7.40 (d, J=6Hz, 2H), 7.59 (d, J=6Hz, 2H); MS (positive ion mode): m/z 287

4-Methyl-1-piperidin-1-yl-pentane-1,3-dione

^{1}H NMR($CDCl_3$, 300MHz):δ 1.14 (d, J=6Hz, 6H), 1.57-1.65 (m, 6H), 2.76 (brs, 1H), 3.20-3.75 (m, 6H);

4-Methyl-3-oxo-pentanoic acid phenylamide

Step 2: Preparation of β-ketoamide-2 (Formula VI and VIb)

To β-ketoamide-1 (Formula IV, 1 equiv) in hexane was added to β-alanine (0.18 equiv), aldehyde (Formula V, 1.1 equiv) and glacial acetic acid (0.16 % w/w of β-ketoamide-1). The resulting suspension was heated under reflux with the azeotropic removal of water. The reaction mixture was cooled and product was isolated by filtration. The product was purified by washing the precipitate with hot hexane, water and dried in vacuo to afford β-ketoamide-2. Compounds of Formula VIb can be prepared analogously. The following intermediates were prepared following above general procedure

2-Benzylidene-4-methyl-3-oxo-pentanoic acid (3-acetylphenyl)-amide; Isomer-1

^{1}H NMR($CDCl_3$):δ 1.1 (d, J=6.9Hz, 6H), 2.50-2.70 (m, 4H), 7.28-7.52 (m, 6H), 7.73 (d, J=7.2Hz, 1H), 7.93 (d, J=8.1Hz, 1H), 8.19 (d, J=9.9Hz, 2H), 9.23 (s, 1H); MS (positive ion mode): m/z 336 [M+1]; Yield: 13%

2-Benzylidene-4-methyl-3-oxo-pentanoic acid (3-acetylphenyl)-amide; Isomer-2

^{1}H NMR($CDCl_3$):δ 1.24 (d, J=9Hz, 6H), 2.60 (s, 3H), 3.39 (sep, J=6Hz, 1H), 7.33-7.98 (m, 11H); MS (positive ion mode): m/z 336 [M+1]; Yield: 32%

2-Benzylidene-4-methyl-3-oxo-pentanoic acid (4-acetylphenyl)-amide

^{1}H NMR($CDCl_3$):δ 1.23 (d, J=6.6Hz, 6H), 2.58 (s, 3H), 3.37 (Sep, J=6.6Hz, 1H), 7.27-7.42 (m, 3H), 7.49-7.73 (m,5H), 7.95 (d, J=8.7Hz, 2H); MS (positive ion mode): m/z 336 [M+1]; Yield 48%

2-Benzylidene-4-methyl-3-oxo-pentanoic acid (2,4-dimethylphenyl)-amide

^{1}H NMR($CDCl_3$):δ 1.23 (d, J=6Hz, 6H), 1.99 (s, 1H), 2.29 (s, 1H), 3.38 (Sep,J=6Hz, 1H), 6.97 (s, 1H), 7.04 (d, J=6Hz, 1H), 7.30 (s, 1H), 7.35-7.45 (m, 3H), 7.53-7.72 (m, 7H) MS (positive ion mode): m/z 323 [M+1]; Yield 50%

2-Benzylidine-4-methyl-3-oxo-pentanoic acid 4-trifluoromethylbenzyl amide
^{1}H NMR($CDCl_3$, 300MHz):δ 1.19 (d, J=6.9Hz, 6H), 3.30 (sept, J=6.9Hz, 1H), 6.16 (brs, 1H), 7.26-7.60 (m, 10H)

2-Benzylidene-4-methyl-1-piperidin-1-yl-pentane-1,3-dione
^{1}H NMR($CDCl_3$, 300 MHz):δ 0.88-0.97 (m, 2H), 1.15-1.35 (m, 8H), 1.43-1.62 (m, 4H), 3.13-3.30 (m, 3H), 3.61 (brs, 1H), 3.78 (brs, 1H), 7.38 (brs, 3H), 7.54 (brs, 3H); MS (positive ion mode): m/z 286 (M^++1)

2-(4-Cyanobenzylidene)-4-methyl-3-oxo-pentanoic acid phenylamide
^{1}H NMR ($CDCl_3$):δ 1.23 (d, J=6Hz, 6H), 3.34 (Sep, J=6Hz, 1H), 7.18 (t, J=6Hz, 1H), 7.36 (t, J=6Hz, 2H), 7.48 (d, J=6Hz, 2H), 7.57 (s, 1H), 7.65 (s, 4H), 7.81 (s, 1H); MS (positive ion mode): m/z 319 [M+1]; Yield: 67%

Step 3: Preparation of Diketone (Formula VIII and VIIIb)

β-ketoamide-2 (Formula VI, 1 equiv), aldehyde (Formula VII, 1.1 equiv), triethylamine (1 equiv) ethanol and 3-ethyl-5- (2-hydroxyethyl)-4-methyl thiazolium bromide (0.2 equiv) were placed in a vial. The contents were flushed with N_2 and the vial was capped immediately and was heated to 78°C. After the completion of reaction, contents were cooled and triturated with ethyl acetate. The organic layer was washed with 6N hydrochloric acid, water, dried over anhydrous sodium sulphate, concentrated on rotary evaporator and residue was purified on a chromatographic column (silica gel, 100-200 mesh). Compounds of Formula VIIIb can be prepared analogously. The following intermediates were prepared following above general procedure

2-[2-(Fluorophenyl)-2-oxo-1-phenyl-ethyl]-4-methyl-3-oxo-pentanoic acid (3-acetylphenyl)-amide
^{1}H NMR($CDCl_3$):δ 1.15 (d, J=6Hz, 3H), 1.20 (d, J=6Hz, 3H), 2.58 (s, 3H), 2.99 (sep, J=6Hz, 1H), 4.61 (d, J=12Hz, 1H), 5.38 (d, J=12Hz, 1H), 7.05 (t, J=9Hz, 2H), 7.15-7.44 (m, 6H), 7.54-7.72 (m, 4H), 7.94-8.05 (m, 2H); MS (positive ion mode): m/z 460 [M+1]; Yield: 55%

2-[2-(4-Fluorophenyl)-2-oxo-1-phenylethyl]-4-methyl-3-oxo-pentanoic acid (4-acetylphenyl)-amide
^{1}H NMR($CDCl_3$):δ 1.16 d, J=6.9Hz, 3H), 1.23 (d, J=6.9Hz, 3H), 2.55 (s, 3H), 2.99 (Sep, J=6.6Hz, 1H), 4.56 (d, J=10.5Hz, 1H), 5.35 (d, J=10.8Hz, 1H), 7.04 (t, J=8.7Hz, 3H), 7.18-7.37 (brm, 6H), 7.48 (s, 1H), 7.86 (d, J=8.4Hz, 2H), 7.87-8.03 (m, 2H); MS (positive ion mode): m/z 460 [M+1]; Yield 64%

2-[2-(4-Fluorophenyl)-2-oxo-1-phenylethyl]-4-methyl-3-oxo-pentanoic acid (2,4-dimethylphenyl)-amide
^{1}H NMR(DMSO-d_6):δ 0.99 (d, J=6.6Hz, 3H), 1.19 (d, J=6.9Hz, 3H), 1.67 (s, 3H), 2.18 (s, 3H), 3.00 (Sep, J=6.9Hz, 1H), 4.94 (d, J=11.1Hz, 1H), 5.36 (d, s=10.8Hz, 1H), 6.68 (d, J=8.1Hz, 1H), 6.82-6.93 (m, 2H), 7.17-7.45 (m, 7H), 8.08-8.24 (m, 2H), 9.60 (brs, 1H) MS (positive ion mode): m/z 446 [M+1]; Yield 66%

2-[2-(4-Fluorophenyl)-2-oxo-1-phenyl-ethyl]-4-methyl-3-oxo-pentanoic acid 4-trifluoromethylbenzyl amide
^{1}H NMR($CDCl_3$, 300MHz):δ 1.10 (d, J=6.6Hz, 3H), 1.16 (d, J=7.2Hz, 3H), 2.88 (sept, J=6.9Hz, 1H0, 4.15 (dd, J=15 & 4.8Hz, 1H), 4.40 (dd, J=15.9 & 6.6Hz, 1H), 4.46 (d, J=11.1Hz, 1H), 5.32 (d, J=10.8Hz, 1H), 5.80 (brs, 1H), 6.89 (d, J=7.8Hz, 2H), 6.97 (t, J=8.4Hz, H), 7.45 (d, J=7.5Hz, 2H), 7.94-7.98 (m, 2H); MS (positive ion mode): m/z 500 (M^++1}

1-(4-Fluorophenyl)-5-methyl-2-pentyl-3-(piperidine-1-carbonyl-hexane-1,4-dione
^{1}H NMR($CDCl_3$, 300MHz):δ 1.05 (d, J=6.9Hz, 3H), 1.19 (d, J=7.1Hz, 4H), 1.45 (brs, 5H), 2.62 (sept, J=6.8Hz, 1H), 2.95-3.15 (m, 1H), 3.20-3.40 (m, 2H), 3.45-3.60 (m, 1H), 4.99 (d, J=10.5Hz, 1H), 5.34 (d, J=10.6Hz, 1H), 7.03 (t, J=8.5Hz, 2H), 7.24 (brs, 5H), 7.97-8.07 (m, 2H); MS (positive ion mode): m/z 493 (M^++1)

2-[1-(4-Cyanophenyl)-2-(4-fluorophenyl)-2-oxo-ethyl]-4-methyl-3-oxo-pentanoic acid phenylamide
MS (positive ion mode): m/z 443 [M+1]

Step 4: Preparation of Pyrrole (Formula X and Xb)

A mixture of diketone (Formula VIII, 1 equiv), amine (Formula IX, 1.00, equiv) and pivalic acid (1.03 equiv) in heptane:toluene:tetrahydrofuran (4:1:1) was refluxed and water was removed using Dean Stark trap. After the completion of reaction, solvents were removed and the residue was dissolved in ethyl acetate. The organic layer was washed in

saturated sodium bicarbonate, water, dried over anhydrous sodium sulphate, concentrated on rotary evaporator and the residue was purified on a chromatographic column (silica gel, 100-200 mesh). Compounds of Formula Xb can be prepared analogously. The following intermediates were prepared following above general procedure

(6-{2-[3-(3-Acetylphenylcarbamoyl)-5-(4-fluorophenyl)-2-isopropyl-4-phenyl-pyrrol-1-yl]-ethyl}-2,2-dimethyl-[1,3]dioxan-4-yl)-acetic acid tert-butyl ester

^{1}H NMR($CDCl_3$):δ 1.30 (s, 3H), 1.36 (s, 3H), 1.43 (s, 9H), 1.53 (d, J=6Hz, 6H), 1.67 (brs, 2H), 2.20-2.43 (m, 2H), 2.52 (s, 3H), 3.52-3.75 (m, 2H), 3.76-3.88 (m, 1H), 4.00-4.22 (m, 2H), 6.85-7.05 (m, 3H), 7.10-7.51 (m, 10H), 7.58 (d, J=9Hz, 1H); MS (positive ion mode): m/z 697 [M+1]; Yield: 23%

(6-{2-[3-(4-Acetylphenylcarbamoyl)-5-(4-fluorophenyl)-2-isopropyl-4-phenyl-pyrrol-1-yl]-ethyl}-2,2-dimethyl-[1,3]dioxan-4-yl)-acetic acid tert-butyl ester

^{1}H NMR($CDCl_3$):δ 1.31 (s, 3H), 1.38 (s, 3H), 1.44 (s, 9H), 1.53 (d, J=9Hz, 6H), 1.66 (brs, 2H), 2.22-2.49 (m, 2H), 2.54 (s, 3H), 3.49-3.75 (m, 2H), 4.00-4.25 (m, 2H), 7.01 (t, J=6Hz, 2H), 7.06-7.26 (m, 10H), 7.81 (d, J=9Hz, zH); MS (positive ion mode): m/z 698 [M+1]; Yield: 14%

(6-{2-[3-(2,4-Dimethylphenylcarbamoyl)-5-(4-fluorophenyl)-2-isopropyl-4-phenyl-pyrrol-1-yl]-ethyl}-2,2-dimethyl-[1,3]dioxan-4-yl)-acetic acid tert-butyl ester

^{1}H NMR($CDCl_3$):δ 1.30 (s, 3H), 1.36 (s, 3H), 1.43 (s, 9H), 1.52 (d, s=6Hz, 6H), 1.65-1.76 (m, 2H), 2.18-2.32 (m, 4H), 2.33-2.47 (m, 1H), 3.48 (Sep, J=6Hz, 1H), 3.63-3.90 (m, 2H), 4.0-4.25 m, 2H), 6.72 (s, 1H), 6.81 (s, 1H), 6.99 (t, S=6Hz, 3H), 7.07-7.25 (m, 7H), 7.88 (d, J=6Hz, 1H); MS (positive ion mode): m/z 684 [M+1]; Yield 21%

(6-{2-[2-(4-Fluorophenyl)-5-isopropyl-3-phenyl-4-(4-trifluoromethylbenzylcarbamoyl)-pyrrol-1-yl]-ethyl}-2,2-dimethyl-[1,3]dioxan-4-yl) acetic acid tert-butyl ester

^{1}H NMR($CDCl_3$, 300MHz):δ 0.8-1.2 (m, 2H), 1.29 (s, 3H), 1.35 (s, 3H), 1.43 (s, 9H), 1.63 (brs, 2H), 2.22-2.27 (m, 1H), 2.38 (dd, J=15.0 & 6.0Hz, 1H), 9.36-3.50 (m, 1H), 3.6-3.7 (m, 1H), 3.71-3.85 (m, 1H), 4.1-4.25 (m, 2H), 4.38 (d, J=6.0Hz, 2H), 7.02-7.16 (m, 12H), 7.41 (d, J=9.0Hz, 2H); MS (positive ion): m/z 737.4 $[M+1]^+$

6-{2-[2-(4-Fluorophenyl)-5-isopropyl-3-phenyl-4-(piperidine-1-carbonyl)-pyrrol-1-yl]-ethyl}-2,2-dimethyl-[1,3]dioxan-4-yl)-acetic acid tert-butyl ester

^{1}H NMR($CDCl_3$, 300MHz):δ 0.99-1.60 (m, 29H), 2.17-2.52 (m, 2H), 2.80-3.25 m, 3H), 3.35-3.50 (m, 1H), 3.65-3.90 (m, 3H), 3.90-4.25 (m, 3H), 6.91-7.19 (m, 9H); MS (positive ion mode): m/z 646 (M^++1)

(6-{2-[3-(4-cyanophenyl)-5-isopropyl-2-(4-fluorophenyl)- 4-(phenylamino) carbonyl-pyrrol-1-yl]-ethyl}-2,2-dimethyl-[1,3]dioxan-4-yl) acetic acid tert-butyl ester

^{1}H NMR ($CDCl_3$):δ 1.30 (s, 3H), 1.36 (s, 3H), 1.44 (s, 9H), 1.50 (d, J=6.9Hz, 6H), 1.67 (brs, 3H), 1.55-1.75 (brm, 3H), 2.20-2.40 (m, 2H), 3.38 (sep, J=6.6Hz, 1H), 3.63-3.88 (m, 2H), 3.97-4.24 (m, 2H), 6.85 (s, 1H), 6.96-7.48 (m, 12H); MS (positive ion mode): m/z 680 [M+1]; Yield: 20%

Step 5: Preparation of hemi calcium salt of compound of Formula XI and XIb

(a) To a solution of a compound of Formula X in methanol and tetrahydrofuran (1:1) was added 1N hydrochloric acid (3 equiv) and the mixture was stirred at ambient temperature. After the complete hydrolysis of the ketal, the reaction mixture was cooled to 0°C and sodium hydroxide pellets (6 equiv) were added. The reaction was then stirred at ambient temperature. At the end of ester hydrolysis, solvents were removed and the residue was dissolved in water; aqueous layer was washed with ether, and was neutralized with 1N hydrochloric acid. The organic phase was extracted into ethyl acetate, and concentrated. The residue was then purified on a chromatographic column (silica gel 100-200 mesh).

(b) To an aqueous solution of sodium salt of acid (is prepared by adding 1 equivalent 1N sodium hydroxide solution) was added dropwise an aqueous solution (1M) of calcium acetate (0.55 equiv). White precipitate was obtained, which was filtered off, washed with copious amount of water, and dried *in vacuo*.

Compounds of Formula XIb and XIIb can be formed analogously. The following compounds were prepared following above general procedure

Hemi calcium salt of (3R,5R)-7-[2-(4-fluorophenyl)-5-isopropyl-3-phenyl-4-[(3-acetylphenylamino) carbonyl]-pyrrol-1-yl]-3,5-dihydroxy-heptanoic acid

^{1}H NMR(DMSO-d_6):δ 1.23 (brs, 2H), 1.38 (d, J=6Hz, 6H), 1.63 (brs, 2H), 1.90-2.15 (m, 2H), 3.52 (brs, 1H), 3.76 (brs, 2H), 3.99 (brs, 1H), 6.95-7.45 (m, 10H), 7.60 (d, J=7.5Hz, 1H), 7.71 (d, J=7.5Hz, 1H), 8.15 (s, 1H), 9.98 (s, 1H, D_2O exchanged); MS (positive ion mode): m/z 601 [Acid+1]; Yield: 21.35; m.pt: 167.5-204°C

Hemi calcium salt of (3R,5R)-7-[2-(4-fluorophenyl)-5-isopropyl-3-phenyl-4-[(4-acetylphenylamino) carbonyl]-pyrrol-1-yl]-3,5-dihydroxy-heptanoic acid

^{1}H NMR(DMSO-d_6):δ 1.24 (brs, 2H), 1.37 (d, 3=6Hz, 6H), 1.58 (brs, 2H), 1.88-1.99 (m, 1H), 2.00-2.12 (m, 1H), 3.53 (brs, 1H), 3.73 (brs, 2H), 3.96 (brs, 1H), 7.09 (brs, 5H), 7.14-7.37 (m, 4H), 7.66 (d, J=9 Hz, 2H), 7.85 (d, J=9 Hz, 2H), 10.21 (s, 1H, D_2O cxchanged); MS (positive ion mode): m/z 601 [Acid+1]; Yield 23%; m.pt 188.9-216.5°C

Hemi calcium salt of (3R,5R)-7-[2-(4-fluorophenyl)-5-isopropyl-3-phenyl-4-[(2,4-dimethylphenylamino) carbonyl]-pyrrol-1-yl]-3,5-dihydroxy-heptanoic acid

^{1}H NMR(DMSO):δ 1.29 (brs, 2H), 1.31-1.76 (m, 11H), 1.87-2.01 (dd, J=15 & 6Hz, 1H), 2.02-2.15 (dd, J=15 & 3Hz, 1H), 2.19 (s, 3H), 3.59 (brs, 1H), 3.76 (brs, 2H), 3.95 (brs, 1H), 6.85-6.95 (m, 2H), 7.05-7.33 (m, 10H), 8.78 (s, 1H, D_2O exchanged); MS (positive ion mode): m/z 587 [Acid+1]; Yield 45%; m.p 172.6-198.9°C

Hemi calcium salt of (3R,5R)-7-[2-(4-fluorophenyl)-5-isopropyl-3-phenyl-4-[(4-trifluoromethylbenzylamino) carbonyl)]-pyrrol-1-yl]-3,5-dihydroxy-heptanoic acid

^{1}H NMR(DMSO-d_6, 300MHz):δ 1.15-1.24 (m, 2H), 1.31 (d, J=6Hz, 6H), 1.48-1.56 (m, 2H), 1.84 (dd, J=158, 7.8Hz, 1H), 2.01 (dd, J=15 &4.2Hz, 1H), 3.15-3.33 (m, 1H), 3.42 (brs, 1H), 3.50 (brs, 1H), 3.68-3.73 (m, 2H), 3.80-4.02 (m, 1H), 4.29 d, J=5.4Hz, 1H), 6.99 (brs, 2H), 7.05 (brs, 3H), 7.12-7.23 (m, 6H), 7.50 (d, J=8.1Hz, 2H), 8.24 (t, J=5.4Hz, 1H); MS (positive ion mode): m/z 641 (acid+1)

Hemi calcium salt of (3R,5R)-7-[2-(4-fluorophenyl)-5-isopropyl-3-phenyl-4-(piperidine-1-carbonyl)-pyrrol-1-yl]-3,5-dihydroxy-heptanoic acid

^{1}H NMR(DMSO-d_6, 300MHz, D_2O exchanged):δ 1.08-1.13 (m, 2H), 1.24 (brs, 7H), 1.27 (d, J=9Hz, 6H), 1.43 (brs, 2H), 2.02 (dd, J=15 & 6Hz, 1H), 2.15-2.19 (m, 1H), 2.88-2.95 (m, 2H), 3.12-3.24 m, 2H), 3.64-3.69 (m, 3H), 6.95 (d, J=6Hz, 2H), 7.05-7.15 (m, 5H), 7.25 (brs, 2H), 8.08 (s, 1H).

Hemi calcium salt of (3R,5R)-7-[2-(4-fluorophenyl)-5-isopropyl-3-(4-cyanophenyl)-4-[(phenylamino) carbonyl)]-pyrrol-1-yl]-3,5-dihydroxy-heptanoic acid

^{1}H NMR (DMSO-d_6):δ 1.24 (brs, 2H), 1.37 (d, J=6Hz, 6H), 1.45-1.73 (m, 2H), 1.87-2.15 (m, 2H), 3.10-3.60 (m, 2H), 3.70-3.90 (brm, 2H), 3.91-4.08 (brm, 1H), 7.01 (t, J=6Hz, 1H), 7.13-7.35 (m, 8H), 7.45-7.63 (m, 4H), 10.02 (s, 1H, D_2O exchanged); MS (positive ion mode): m/z 584 [Acid+1]; Yield: 87%; m.pt. 197.7-222.1°C

SCHEME Ia

Step 1: Preparation of compound of Formula XIV

Compound XIII (prepared following the appropriate steps of Scheme I to produce a compound of Formula X with appropriate substitution) was dissolved in tetrahydrofuran: methanol (1:2) mixture and 1N lithium hydroxide (equiv) was added. The reaction mixture was stirred at 0 ^{0}C for 12 to 15 hours. After completion of reaction, reaction mixture was acidified and the solvent was evaporated under reduced pressure to get crude product. The crude product was purified by column chromatography (silica gel –100-200 mesh) using 50% ethyl acetate in hexane. The following intermediates wee prepared in this fashion.

4-{[1-[2-(6-tert-butoxycarbonylmethyl-2,2-dimethyl-[1,3]dioxan-4-yl)-ethyl]-5-(4-fluorophenyl)-2-isopropyl-4-phenyl-1H-pyrrol-3-carbonyl]-amino}-benzoic acid

^{1}H NMR($CDCl_3$):δ 1.03-1.11 (m, 1H), 1.26 (s, 3H), 1.30 (s, 3H), 1.43 (s, 9H), 1.53 (d, J=7.2Hz, 3H), 1.65-1.69 (m, 2H), 2.23 (dd, J=15.6 & 6.3Hz, 1H), 2.40 (dd, J=15.6 & 6.3Hz, 1H), 3.63-3.71 (m, 2H), 3.75-3.8 (m, 1H), 4.05-4.20 (m, 2H), 6.96-7.20 (m, 12H), 7.90 (d, J=8.4Hz, 2H); MS (positive ion mode): m/z 698 (M^++1); Yield = 51%

Step 2: Preparation of compound of Formula XV

Method A: Compound XIV (1 equiv) was dissolved in dry tetrahydrofuran and sodium borohydride (2 equiv) was added slowly in two to three fractions. The resulting suspension was stirred for 5 minutes at 0 ^{0}C. A solution of iodine (1 equiv) in tetrahydrofuran was added slowly at 0 ^{0}C and reaction mixture was stirred for 24 to 30 hours at an ambient temperature. At the end of reaction, solvent was evaporated to get crude product. The crude product was purified by column chromatography (silica gel, 100-200 mesh) using 25% ethyl acetate in hexane.

^{1}H NMR($CDCl_3$, 300MHz):δ 1.02=1.06 (m, 1H), 1.26 (s, 3H), 1.33 (s, 3H), 1.43 (s, 9H), 1.55 (d, J=6Hz, 6H), 2.21 (dd, J=15 & 6Hz, 1H), 2.38 (dd, J=15 & 6Hz, 1H), 2.40-4.17 (m, 5H), 4.58 (s, 2H), 6.87-7.19 (m, 13H); MS (+ ve ion mode): m/z 685 (M^++1); Yield = 87%

Method B: A mixture of compound of Formula XIV (1 equiv.) and tetrahydrofuran (4 mL, Dry) was placed in a 3 neck round bottom flask equipped with a reflux condenser, nitrogen was purged. The reaction mixture was heated at about 50 °C and borane

dimethylsulphide (2 equiv.) was added dropwise over 1 hour. Water (6 mL) was added to the reaction mixture, solvent was evaporated. Solid residue was dissolved in ethyl acetate, washed with water and the aqueous layer was extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous sodium sulphate, concentrated. The crude product was purified by silica gel column chromatography using ethyl acetate and hexane as eluant.

Yield: 2.16 g (73.72%)

Step 3: Preparation of hemi calcium salt of Formula XVI

(a) To a solution of XV in methanol and tetrahydrofuran (1:1) was added 1N hydrochloric acid (3 equiv) and the mixture stirred at an ambient temperature. After the complete hydrolysis of ketal, the reaction mixture was cooled to 0°C and sodium hydroxide pellets (6 equiv) were added. The reaction was then allowed to stir at ambient temperature. At the end of ester hydrolysis, solvents were removed and the residue was dissolved in water; the aqueous layer was washed with ether, and neutralized with 1N hydrochloric acid. The organic phase was extracted into ethyl acetate, and concentrated. The residue was then purified on column (silica gel 100-200 mesh).

(b) To an aqueous solution of the sodium salt of the acid (prepared by adding 1 equivalent 1N sodium hydroxide solution) was added dropwise an aqueous solution (1M) of calcium acetate (0.55 equiv). White precipitate was obtained, which was filtered off and washed with copious amount of water, and dried in vacuo.

The following compound was prepared similarly.

Hemi calcium salt of (3R,5R)-7-[2-(4-fluorophenyl)-5- isopropyl-3-phenyl-4-[(4-hydroxymethylphenylamino)carbonyl]-pyrrol-1-yl]-3,5-dihydroxy-heptanoic acid

^{1}H NMR(DMSO-d_6):δ 1.22-1.62 (M, 11H), 1.98 (dd, J=15 & 8.1Hz, 1H), 2.06-2.16 (m, 1H), 3.25-3.37 (m, 2H), 3.57 (brs, 2H), 3.80 (brs, 1H), 4.43 (s, 2H), 7.03-7.28 (m, 12H), 7.50 (d, J=6H, 2H), 9.80 (s, 1H); MS (positive ion mode): m/z 589 (Acid+1); Yield = 31%; m.p. = 189-204°C

Scheme IIa

Step I: Preparation of compound of Formula XVa

A compound of Formula XIIIa (1 equiv.) and a mixture of 1N hydrochloric acid:methanol:tetrahydrofuran (2:5:5) were stirred at room temperature for about 7 hours. At the end of reaction, sodium hydroxide pellets (7 equiv.) were added and the reaction mixture was further stirred at room temperature for about 5 hours. Reaction mixture was concentrated and the residue was dissolved in distilled water and acidified to ~1pH with 1N hydrochloric acid. The aqueous layer was extracted with ethyl acetate, washed with water, brine and dried over anhydrous sodium sulphate. Organic layer was concentrated and adsorbed over silica gel (5% methanol-dichloromethane). The following compound was prepared by following above procedures

(3R,5R)-7-[2-(4-fluorophenyl)-5- isopropyl-3-phenyl-4-[4-carboxyphenyl)amino) carbonyl]-pyrrol-1-yl]-3,5-dihydroxy-heptanoic acid
Yield : 5g (84.6%)

Step II: Preparation of disodium salt of compound of Formula XVa

A compound of XVa (1 equiv.), tetrahydrofuran:methanol (1:1) and sodium hydroxide (1N, 2 equiv.) solution were stirred at ambient temperature for about 2 hours. Disodium salt of compound of Formula XVa was isolated by evaporating solvent under reduced pressure. The residue was washed with diethylether, dried *in vacuo* to afford the pure compound in a yield of 4.5g (84.9%). The following compound was prepared by following above procedures.

Disodium salt of (3R,5R)-7-[2-(4-fluorophenyl)-5- isopropyl-3-phenyl-4-[4-carboxyphenyl)amino) carbonyl]-pyrrol-1-yl]-3,5-dihydroxy-heptanoic acid
^{1}H NMR (DMSO, 300 MHz):δ 1.135-1.179 (m, 2H), 1.365 (d, J=6.3Hz, 6H), 1.752 (brs, 4H), 1.752-1.779 (m, 1H), 1.950-1.998 (m, 1H), 2.733 (s, 1H), 2.89 (s, 1H), 3.607-3.75 (m, 3H), 3.924-4.004 (m, 2H), 6.99-7.07 (m, 5H), 7.155-7.247 (m, 4H), 7.4 (d, J=6Hz, 2H), 7.70 (d, J=9Hz, 2H), 9.827 (s, 1H); MS (positive ion mode): m/z 603.13 ($Acid^+$ +1) ; Yield : 4.5g (84.9%).

SCHEME II

Preparation of Compound of Formula XIX

To a solution of a compound of Formula XVIII (4.5 mmoles; prepared according to procedure as described in *Tet. Let.*, 43:1161 (2002) and *J. Org. Chem.*, 50:438 (1985), in toluene (15 ml) was added a compound of Formula V (4.9 mmoles), piperidine (0.02 ml) and acetic acid (0.054 ml). The mixture was heated at reflux with azeotropic removal of water for about 4 to 6 hours. The reaction mixture was concentrated and the residue was extracted in dichloromethane. The organic layer was washed with 1N hydrochloric acid solution, sodium bicarbonate solution, brine, dried over anhydrous sodium sulphate, and concentrated. The crude product was purified on a chromatographic column (silica gel, 100-200 mesh, 2% EtOAc-hexane).

Preparation of compound of Formula XX

A compound of Formula XIX (6.49 mmoles), a compound of Formula VII (7.14 mmoles), 3-ethyl-5- (2-hydroxyethyl)-4-methyl thiazolium bromide (1.298 mmoles), triethylamine (6.49 mmoles), and ethanol (0.6 ml) were placed in a 30 ml vial, flushed with argon and the vial sealed properly. The reaction mixture was stirred at 70°C for about 12 to 15 hours. To the reaction mixture was added ethyl acetate, the mixture was washed with water, 6N hydrochloric acid, again with water and brine, dried over anhydrous sodium sulphate, and concentrated to give crude product. The crude product was purified on a chromatographic column (silica gel 100-200 mesh) using 7% ethyl acetate in hexane.

Preparation of compound of Formula XXI

To a solution of Formula XX (4.62 mmoles) in heptane: toluene: tetrahydrofuran (4:1:1) was added a compound of Formula IX (6.99 mmoles) and pivalic acid (4.768 mmoles). The mixture was refluxed with azeotropic removal of water for about 22 to 25 hours. The reaction mixture was concentrated, ethyl acetate was added, the reaction mixture was washed with sodium bicarbonate solution and brine, dried over anhydrous sodium sulphate and concentrated to give the crude product. The crude product was purified on column (silica gel, 100-200 mesh) using 7% ethyl acetate in hexane.

Preparation of compound of Formula XXII

To a solution of a compound of Formula XXI (0.8g) in methanol: dioxan (2:8) mixture was added 10% palladium carbon (50% wet, 60% w/w). The resulting reaction mixture was hydrogenated at 40 psi for about 2.5 hours. After the reaction was over, the reaction mixture was passed through celite and the resulting solution was concentrated under vacuum to give the required product, which was further used as such for next step.

Preparation of compound of Formula X : path a

To a solution of a compound of Formula XXII (1 equiv) in benzene at 0°C under argon, oxalyl chloride (2.0 equiv) was added dropwise. After the evolution of gas had ceased, the reaction mixture was heated on oil bath at 70°C for 2 hours. The reaction mixture was evaporated to dryness. The residue was dissolved in benzene (dry) and added at ambient temperature to a solution of amine of formula III (1.1 equiv.) in benzene. The reaction mixture was then heated to 70°C until completion of reaction. Volatiles were removed in vacuo and the residue was purified on a chromatographic column (silica gel, 100-200 mesh). The following compound was prepared following above general procedure

(6-{2-[3-(2-Acetylphenylcarbamoyl)-5-(4-fluorophenyl)-2-isopropyl-4-phenyl-pyrrol-1-yl]-ethyl}-2,2-dimethyl-[1,3]dioxan-4-yl)-acetic acid tert-butyl ester

^{1}H NMR($CDCl_3$, 300MHz):δ 1.0-1.15 (m, 1H), 1.30 (s, 1H), 1.33 (s, 3H), 1.44 (s, 9H), 1.48 (d, J=6.0Hz, 6H), 2.23 (dd, J=15.0 & 6.0Hz, 1H), 2.35-2.5 (m, 4H), 3.35 (sept. J=6.0Hz, 1H), 3.64-3.89 (m, 2H), 4.0-4.25 (m, 2H), 6.93-7.08 (m, 8H), 7.18-7.22 (m, 2H), 7.50 (d, J=9.0Hz, 1H), 7.69 (d, J=6.0Hz, 1H), 8.82 (d, J=9.0Hz, 1H), 11.02 (brs, 1H); MS (positive ion): m/z 697.500 $[M+1]^+$; Yield= 59%

Preparation of compound of Formula X : path b

To a solution of a compound of Formula XXII (1.2 mmole) in dimethylformamide (2.5 ml) was added diisopropylethylamine (2.4 mmole) and O-benzotriazol-1-yl-N,N,N′,N′-tetramethyl uronium hexafluorophosphate (HBTU) (1.2 mmoles). To the resulting clear solution was then added cyclohexylamine (1.2 mmoles) in dimethylformamide (0.5 ml). The reaction mixture was stirred at 50°C to 60°C overnight. To the reaction mixture was added water and the mixture was extracted with dichloromethane, the organic layer was washed with water, brine, dried over anhydrous sodium sulphate and concentrated to get the crude product. The crude product was purified

by column chromatography (silica gel, 100-200 mesh) using 10 % ethyl acetate in hexane. The following compound was prepared as per this protocol.

(6-{2-[3-Cyclohexylcarbamoyl)-5-(4-fluorophenyl)-2-isopropyl-4-phenyl-pyrrol-1-yl]-ethyl}-2,2-dimethyl-[1,3]dioxan-4-yl)-acetic acid tert-butyl ester

^{1}H NMR($CDCl_3$, 300 MHz):δ 0.7-0.88 (m, 2H), 0.97-1.05 (m, 2H), 1.20-1.30 (m, 4H), 1.30-1.34 (s, 3H), 1.43 (s, 9H), 1.47 (d, J=6.9Hz, 6H), 1.43-1.48 (m, 2H), 1.63 (brs, 3H), 2.25 (dd, J=15 & 6Hz, 1H), 2.35 (dd, J=15 & 6.9Hz, 1H), 3.35 (sept, J=6.9Hz, 1H), 3.69-3.81 (m, 3H), 3.85-4.15 (m, 1H), 4.15-4.25 (m, 1H), 6.91-6.99 (m, 3H), 7.07-7.15 (m, 6H); MS (positive ion mode): m/z 661 (M^++1)

Preparation of hemi calcium salt of Formula XI

(a) To a solution of a compound of Formula X in methanol and tetrahydrofuran (1:1) was added 1N hydrochloric acid (3 equiv) and the mixture stirred at ambient temperature. After the complete hydrolysis of ketal, the reaction mixture was cooled to 0°C and sodium hydroxide pellets (6 equiv) were added. The reaction was then stirred at ambient temperature. At the end of ester hydrolysis, solvents were removed and the residue was dissolved in water, the aqueous layer was washed with ether, and neutralized with 1N hydrochloric acid. The organic phase was extracted into ethyl acetate, and concentrated. The residue was then purified on a chromatographic column (silica gel 100-200 mesh).

(b) To an aqueous solution of the sodium salt of the acid (prepared by adding 1 equivalent 1N sodium hydroxide solution) was added dropwise an aqueous solution (1M) of calcium acetate (0.55 equiv). White precipitate was obtained, which was filtered, washed with copious amount of water, and dried in vacuo.

The following compounds were prepared following above general procedure

Hemi calcium salt of (3R,5R)-7-[2-(4-fluorophenyl)-5- isopropyl-3-phenyl-4-[(cyclohexylamino) carbonyl)]-pyrrol-1-yl]-3,5-dihydroxy-heptanoic acid

^{1}H NMR(DMSO-d_6, D_2O exchanged, 300MHz):δ 0.99 (brs, 2H), 1.2-1.35 (m, 5H), 1.35-1.50 (m, 7H), 1.55 (m, 4H), 1.90-2.1 (m, 1H), 2.10-2.20 (m, 1H), 3.17-3.20 (m, 1H), 3.51 (brs, 1H), 3.73 (brs, 1H), 7.02-7.36 (m, 9H); MS (positive ion mode): m/z 565 (acid+1).

Hemi calcium salt of (3R,5R)-7-[2-(4-fluorophenyl)-5-isopropyl-3-phenyl-4-[(2-acetylphenylamino) carbonyl]-pyrrol-1-yl]-3,5-dihydroxy-heptanoic acid

^{1}H NMR(DMSO-d_6, 300MHz):δ 1.10-1.25 (m, 2H), 1.39 (d, J=6.0Hz, 6H), 1.5-1.7 (m, 2H), 1.77 (dd, J=150 & 6.0Hz, 1H), 1.97 (dd, J=15.0 & 3.0Hz, 1H), 2.38 (s, 3H), 6.94-7.01 (m, 5H), 7.08-7.20 (m, 3H), 7.29-7.34 (m, 2H), 7.56 (t, J=9.0Hz, 1H), 7.87 (d, J=6.0Hz, 1H), 8.58 (d, 9.0Hz, 1H), 10.98 (s, 1H); MS (positive ion): m/z 601.300 [Acid+1]$^+$; Yield= 28%; m. pt: 202.6-208.7°C.

Scheme IIIa

Preparation of Compound of Formula XIX

To a solution of a compound of Formula XVIII (4.5 mmoles; prepared according to procedure as described in *Tet. Let.*, 43:1161 (2002) and *J. Org. Chem.*, 50:438 (1985)) in toluene (15 ml) was added a compound of Formula V (4.9 mmoles), piperidine (0.02 ml) and acetic acid (0.054 ml). The mixture was heated at reflux with azeotropic removal of water for about 4 to 6 hours. The reaction mixture was concentrated and the residue was extracted in dichloromethane. The organic layer was washed with 1N hydrochloric acid solution, sodium bicarbonate solution, brine, dried over anhydrous sodium sulphate, and was concentrated. The crude product was purified on a chromatographic column (silica gel, 100-200 mesh, 2% EtOAc-hexane).

^{1}H NMR($CDCl_3$, 300MHz):δ 1.02 (d, J=6.9Hz, 6H), 2.65 (sept, J=7.2Hz, 1H), 5.26 (s, 2H), 7.25 (s, 2H), 7.25 (brs, 10H), 7.81 (s, 1H).). isomer 2 : ^{1}H NMR($CDCl_3$, 300MHz): δ 1.02 (d, J = 6.9 Hz, 6H), 2.65 (sept, J = 6.9 Hz, 1H), 5.27 (s, 2H), 7.36 (brs, 10H), 7.82 (s, 1H).MS (+ ve ion mode): m/z 309 (M^++1); Yield: 70%

Preparation of compound of Formula XX

A compound of Formula XIX (6.49 mmoles), a compound of Formula VII (7.14 mmoles), 3-ethyl-5- (2-hydroxyethyl)-4-methyl thiazolium bromide (1.298 mmoles), triethylamine (6.49 mmoles), and ethanol (0.6 ml) were placed in a 30 ml vial, the reaction was flushed with argon and the vial was sealed properly. The reaction mixture was stirred at 70°C for about 12 to 15 hours. To the reaction mixture was added ethyl acetate, the mixture was washed with water, 6N hydrochloric acid, again with water and brine, was dried over anhydrous sodium sulphate, and was concentrated to give crude product. The crude product was purified on a chromatographic column (silica gel 100-200 mesh) using 7% ethyl acetate in hexane.

^{1}H NMR($CDCl_3$, 300MHz): (1:1 mixture of diastereomers)δ 0.48 (d, J=6.9Hz, 3H), 0.91 (d, J=6.6Hz, 3H), 1.07 (d, J=6.6Hz, 3H), 1.21 (d,J=6.9Hz, 3H), 2.30 (sept, J=6.6Hz, 1H), 2.82 (sept, 6.6Hz, 1H), 4.76 (d, J=14Hz, 1H), 4.77 (d, J=12.3Hz, 1H), 5.33 (d, J=11.1Hz, 1H), 5.35 (d, J=11.1Hz, 1H), 7.02 (t, J=8.4Hz, 6H), 7.22-7.29 (m, 8H), 7.75-7.99 (m, 4H); MS (+ ve ion mode): m/z 433 (M^++1). Yield: 72%

Preparation of compound of Formula XXI

To a solution of Formula XX (4.62 mmoles) in heptane:toluene:tetrahydrofuran (4:1:1) was added a compound of Formula IX (6.99 mmoles) and pivalic acid (4.768 mmoles). The mixture was refluxed with azeotropic removal of water for about 22 to 25 hours. The reaction mixture was concentrated, ethyl acetate was added, and the reaction mixture was washed with sodium bicarbonate solution and brine, was dried over anhydrous sodium sulphate and was concentrated to give the crude product. The crude product was purified on column (silica gel, 100-200 mesh) using 7% ethyl acetate in hexane.

^{1}H NMR($CDCl_3$, 300MHz):δ 0.99-1.08 (m, 2H), 1.25 (s, 3H), 1.34 (s), 1.43 (s, 9H), 1.96 (d, J=6Hz, 6H), 1.58-1.63 (m, 2H), 2.21 (dd, J=158.6Hz, 1H), 2.37 (dd, J=15 & 9Hz, 1H), 3.51 (sept, J=6Hz), 3.65 (brs, 1H), 3.75-3.85 (m, 1H), 4.00-4.25 (m, 2H), 5.03 (s, 2H), 6.83-7.25 (m, 14H). MS (+ ve ion mode): m/z 670 (M^++1). yield 74%

Preparation of compound of Formula XXII

To a solution of a compound of Formula XXI (0.8g) in methanol:dioxan (2:8) mixture was added 10% palladium carbon (50% wet, 60% w/w). The resulting reaction mixture was hydrogenated at 40 psi for about 2.5 hours. After the reaction was over, the reaction mixture was passed through celite and the resulting solution was concentrated under vacuum to give the required product, which was further used as such for next step.

^{1}H NMR($CDCl_3$, 300MHz):δ 0.95-1.05 (m, 1H), 1.21-1.28 (m, 1H), 1.28 (s, 3H), 1.34 (s, 3H), 1.43 (s, 9H), 1.47 (d, J=7.1Hz), 1.59-1.65 (m, 2H), 2.22 (dd, J=15.2 & 6.1Hz, 1H), 2.35 (dd, J=15.2 & 6.1Hz, 1H), 3.61-3.66 (m, 2H), 3.67-3.86 (m, 1H), 4.00-4.15 (m, 2H), 6.95 (t, J=9Hz, 2H), 7.06-7.15 (m, 7H) MS (+ ve ion mode): m/z 586 (M^++1) Yield 76%

Preparation of compound of Formula Xa: path a

To a solution of a compound of Formula XXII (1 equiv) in benzene at 0°C under argon, oxalyl chloride (2.0 equiv) is added dropwise. After the evolution of gas ceases,

the reaction mixture is heated on oil bath at 70°C for 2 hours. The reaction mixture is evaporated to dryness. The residue is dissolved in benzene (dry) and is added at ambient temperature to a solution of amine of Formula IIIa (1.1 equiv.) in presence of triethylamine, in benzene. The reaction mixture is then heated to 70°C until completion of reaction. Volatiles are removed *in vacuo* and the residue is purified on a chromatographic column (silica gel, 100-200 mesh).

Preparation of compound of Formula Xa: path b

To a solution of a compound of Formula XXII (1.2 mmole) in dimethylformamide (2.5 ml) is added diisopropylethylamine (2.4 mmole) and O-benzotriazol-1-yl-N,N,N',N'-tetramethyl uronium hexafluorophosphate (HBTU) (1.2 mmoles). To the resulting clear solution is then added cyclohexylamine (1.2 mmoles) in dimethylformamide (0.5 ml). The reaction mixture is stirred at 50°C to 60°C overnight. To the reaction mixture is added water and the mixture is extracted with dichloromethane, the organic layer is washed with water, brine, is dried over anhydrous sodium sulphate and is concentrated to get the crude product. The crude product is purified by column chromatography (silica gel, 100-200 mesh) using 10 % ethyl acetate in hexane.

Preparation of hemi calcium salt of Formula XIa

(a) To a solution of a compound of Formula Xa in methanol and tetrahydrofuran (1:1) is added 1N hydrochloric acid (3 equiv) and the mixture is stirred at ambient temperature. After the complete hydrolysis of ketal, the reaction mixture is cooled to 0°C and sodium hydroxide pellets (6 equiv) are added. The reaction is then stirred at ambient temperature. At the end of ester hydrolysis, solvents are removed and the residue is dissolved in water; the aqueous layer is washed with ether, and is neutralized with 1N hydrochloric acid. The organics phase is extracted into ethyl acetate, and concentrated. The residue is then purified on a chromatographic column (silica gel 100-200 mesh).

(b) To an aqueous solution of the sodium salt of the acid (is prepared by adding 1 equivalent 1N sodium hydroxide solution) is added dropwise an aqueous solution (1M) of calcium acetate (0.55 equiv). White precipitate is obtained, which is filtered, is washed with copious amount of water, and is dried in vacuo. The following compounds can be prepared following scheme Ib or IIIa or both.

(3R,5R)-7-[2-(4-fluorophenyl)-5- isopropyl-3-phenyl-4-[4-acetoxymethylphenyl)amino) carbonyl]-pyrrol-1-yl]-3,5-dihydroxy-heptanoic acid (Compound No. 2a) and its hemicalcium salt,

(3R,5R)-7-[2-(4-fluorophenyl)-5-isopropyl-3-phenyl-4-[4-phenylthiocarbamoyloxymethylphenyl)amino)carbonyl]-pyrrol-1-yl]-3,5-dihydroxy-heptanoic acid (Compound No. 3a) and its hemicalcium salt,

(3R,5R)-7-[2-(4-fluorophenyl)-5- isopropyl-3-phenyl-4-[4-propionyloxymethylphenyl)amino) carbonyl]-pyrrol-1-yl]-3,5-dihydroxy-heptanoic acid (Compound No. 4a) and its hemicalcium salt,

(3R,5R)-7-[2-(4-fluorophenyl)-5- isopropyl-3-phenyl-4-[4-octylcarbamoyloxymethyl phenyl)amino) carbonyl]-pyrrol-1-yl]-3,5-dihydroxy-heptanoic acid (Compound No. 5a) and its hemicalcium salt,

(3R, 5R)-7-[2-(4-fluorophenyl)-5- isopropyl-3-phenyl-4-[4-phenylacetoxymethyl phenyl)amino) carbonyl]-pyrrol-1-yl]-3,5-dihydroxy-heptanoic acid (Compound No. 6a) and its hemicalcium salt,

(3R, 5R)-7-[2-(4-fluorophenyl)-5- isopropyl-3-phenyl-4-[4-phenylcarbamoyloxymethyl phenyl)amino) carbonyl]-pyrrol-1-yl]-3,5-dihydroxy-heptanoic acid (Compound No. 7a) and its hemicalcium salt,

(3R, 5R)-7-[2-(4-fluorophenyl)-5- isopropyl-3-phenyl-4-[4-benzoyloxymethyl phenyl)amino) carbonyl]-pyrrol-1-yl]-3,5-dihydroxy-heptanoic acid (Compound No. 8a) and its hemicalcium salt,

(3R, 5R)-7-[2-(4-fluorophenyl)-5- isopropyl-3-phenyl-4-[4-isonicotinoyloxymethyl phenyl)amino) carbonyl]-pyrrol-1-yl]-3,5-dihydroxy-heptanoic acid (Compound No. 9a) and its hemicalcium salt,

(3R, 5R)-7-[2-(4-fluorophenyl)-5-isopropyl-3-phenyl-4- [4-pyridin-4-ylcarbamoyloxymethyl phenyl) amino) carbonyl]-pyrrol-1-yl]-3,5-dihydroxy-heptanoic acid (Compound No. 10a) and its hemicalcium salt,

(3R, 5R)-7-[2-(4-fluorophenyl)-5- isopropyl-3-phenyl-4-[4-phenylcarbamoyl phenyl)amino) carbonyl]-pyrrol-1-yl]-3,5-dihydroxy-heptanoic acid (Compound No. 11a) and its hemicalcium salt,

(3R, 5R)-7-[2-(4-fluorophenyl)-5- isopropyl-3-phenyl-4-[4-cyclohexylcarbamoyl-phenyl) amino) carbonyl]-pyrrol-1-yl]-3,5-dihydroxy-heptanoic acid (Compound No. 12a) and its hemicalcium salt,

(3R, 5R)-7-[2-(4-fluorophenyl)-5- isopropyl-3-phenyl-4-[4-methylcarbamoyl)-phenyl)amino) carbonyl]-pyrrol-1-yl]-3,5-dihydroxy-heptanoic acid (Compound No. 13a) and its hemicalcium salt,

(3R, 5R)-7-[2-(4-fluorophenyl)-5- isopropyl-3-phenyl-4-[4-benzylcarbamoyl)-phenyl)amino) carbonyl]-pyrrol-1-yl]-3,5-dihydroxy-heptanoic acid (Compound No. 14a) and its hemicalcium salt,

(3R, 5R)-7-[2-(4-fluorophenyl)-5- isopropyl-3-phenyl-4-[4-(morpholine-4-carbonyl)-phenyl)amino) carbonyl]-pyrrol-1-yl]-3,5-dihydroxy-heptanoic acid (Compound No. 15) and its hemicalcium salt,

(3R, 5R)-7-[2-(4-fluorophenyl)-5- isopropyl-3-phenyl-4-[4-(piperidine-1-carbonyl)-phenyl)amino) carbonyl]-pyrrol-1-yl]-3,5-dihydroxy-heptanoic acid (Compound No. 16) and its hemicalcium salt,

(3R, 5R)-7-[2-(4-fluorophenyl)-5- isopropyl-3-phenyl-4-[4-benzylamino phenyl)amino) carbonyl]-pyrrol-1-yl]-3,5-dihydroxy-heptanoic acid (Compound No. 17) and its hemicalcium salt,

(3R,5R)-7-[2-(4-fluorophenyl)-5- isopropyl-3-phenyl-4-[4-(1-hydroxyethyl)phenylamino) carbonyl]-pyrrol-1-yl]-3,5-dihydroxy-heptanoic acid (Compound No. 18) and its hemicalcium salt,

(3R,5R)-7-[2-(4-fluorophenyl)-5- isopropyl-3-phenyl-4-[4-(2-hydroxyethyl) phenylamino) carbonyl]-pyrrol-1-yl]-3,5-dihydroxy-heptanoic acid (Compound No. 19) and its hemicalcium salt,

(3R,5R)-7-[2-(4-fluorophenyl)-5- isopropyl-3-phenyl-4-[4-(3-hydroxypropyl phenylamino) carbonyl]-pyrrol-1-yl]-3,5-dihydroxy-heptanoic acid (Compound No. 20) and its hemicalcium salt,

(3R,5R)-7-[2-(4-fluorophenyl)-5- isopropyl-3-phenyl-4-[(4-methoxymethyl phenylamino) carbonyl]-pyrrol-1-yl]-3,5-dihydroxy-heptanoic acid (Compound No. 21) and its hemicalcium salt,

(3R,5R)-7-[2-(4-fluorophenyl)-5- isopropyl-3-phenyl-4-[(4-ethoxymethyl phenylamino) carbonyl]-pyrrol-1-yl]-3,5-dihydroxy-heptanoic acid (Compound No. 22) and its hemicalcium salt,

(3R,5R)-7-[2-(4-fluorophenyl)-5- isopropyl-3-phenyl-4-[(4-isopropoxymethyl phenylamino) carbonyl]-pyrrol-1-yl]-3,5-dihydroxy-heptanoic acid (Compound No. 23) and its hemicalcium salt,

(3R,5R)-7-[2-(4-fluorophenyl)-5- isopropyl-3-phenyl-4-[(4-propoxymethyl phenylamino) carbonyl]-pyrrol-1-yl]-3,5-dihydroxy-heptanoic acid (Compound No. 24) and its hemicalcium salt,

(3R,5R)-7-[2-(4-fluorophenyl)-5- isopropyl-3-phenyl-4-[(4-methoxymethoxymethylphenylamino) carbonyl]-pyrrol-1-yl]-3,5-dihydroxy-heptanoic acid (Compound No. 25) and its hemicalcium salt,

(3R,5R)-7-[2-(4-fluorophenyl)-5- isopropyl-3-phenyl-4-[(4-cyclohexyloxymethyl phenylamino) carbonyl]-pyrrol-1-yl]-3,5-dihydroxy-heptanoic acid (Compound No. 26) and its hemicalcium salt,

(3R,5R)-7-[2-(4-fluorophenyl)-5- isopropyl-3-phenyl-4-[(4-cyclopentyloxymethyl phenylamino) carbonyl]-pyrrol-1-yl]-3,5-dihydroxy-heptanoic acid (Compound No. 27) and its hemicalcium salt,

(3R,5R)-7-[2-(4-fluorophenyl)-5- isopropyl-3-phenyl-4-[(4-benzyloxymethyl phenylamino) carbonyl]-pyrrol-1-yl]-3,5-dihydroxy-heptanoic acid (Compound No. 28) and its hemicalcium salt,

(3R,5R)-7-[2-(4-fluorophenyl)-5- isopropyl-3-phenyl-4-[(4-chlorobenzyloxymethyl phenylamino) carbonyl]-pyrrol-1-yl]-3,5-dihydroxy-heptanoic acid (Compound No. 29) and its hemicalcium salt,

(3R,5R)-7-[2-(4-fluorophenyl)-5- isopropyl-3-phenyl-4-[(4-methoxybenzyloxymethyl phenylamino) carbonyl]-pyrrol-1-yl]-3,5-dihydroxy-heptanoic acid (Compound No. 30) and its hemicalcium salt,

(3R,5R)-7-[2-(4-fluorophenyl)-5- isopropyl-3-phenyl-4-[(4-phenoxymethylphenylamino) carbonyl]-pyrrol-1-yl]-3,5-dihydroxy-heptanoic acid (Compound No. 31) and its hemicalcium salt,

(3R,5R)-7-[2-(4-fluorophenyl)-5- isopropyl-3-phenyl-4-[(4-chlorophenoxymethyl phenylamino) carbonyl]-pyrrol-1-yl]-3,5-dihydroxy-heptanoic acid (Compound No. 32) and its hemicalcium salt,

(3R,5R)-7-[2-(4-fluorophenyl)-5- isopropyl-3-phenyl-4-[(4-acetylaminophenylamino) carbonyl]-pyrrol-1-yl]-3,5-dihydroxy-heptanoic acid (Compound No. 33) and its hemicalcium salt,

(3R,5R)-7-[2-(4-fluorophenyl)-5- isopropyl-3-phenyl-4-[(4-benzoylamino phenylamino) carbonyl]-pyrrol-1-yl]-3,5-dihydroxy-heptanoic acid (Compound No. 34) and its hemicalcium salt,

(3R,5R)-7-[2-(4-fluorophenyl)-5- isopropyl-3-phenyl-4-[(4-benzenesulfonylamino phenylamino) carbonyl]-pyrrol-1-yl]-3,5-dihydroxy-heptanoic acid (Compound No. 36) and its hemicalcium salt,

(3R,5R)-7-[2-(4-fluorophenyl)-5- isopropyl-3-phenyl-4-[4-(3-phenyl-ureido)-phenylamino) carbonyl]-pyrrol-1-yl]-3,5-dihydroxy-heptanoic acid (Compound No. 37) and its hemicalcium salt,

(3R,5R)-7-[2-(4-fluorophenyl)-5- isopropyl-3-phenyl-4-[4-(3-methyl-ureido)-phenylamino) carbonyl]-pyrrol-1-yl]-3,5-dihydroxy-heptanoic acid (Compound No. 38) and its hemicalcium salt,

(3R,5R)-7-[2-(4-fluorophenyl)-5- isopropyl-3-phenyl-4-[4-(3-benzyll-ureido)-phenylamino) carbonyl]-pyrrol-1-yl]-3,5-dihydroxy-heptanoic acid (Compound No. 39) and its hemicalcium salt,

(3R,5R)-7-[2-(4-fluorophenyl)-5- isopropyl-3-phenyl-4-[4-(3-benzyl-thioureido)-phenylamino) carbonyl]-pyrrol-1-yl]-3,5-dihydroxy-heptanoic acid (Compound No. 40) and its hemicalcium salt,

(3R,5R)-7-[2-(4-fluorophenyl)-5- isopropyl-3-phenyl-4-[4-(3-phenyl-thioureido)-phenylamino) carbonyl]-pyrrol-1-yl]-3,5-dihydroxy-heptanoic acid (Compound No. 41) and its hemicalcium salt,

(3R,5R)-7-[2-(4-fluorophenyl)-5- isopropyl-3-phenyl-4-[4-(3-methyl-thioureido)-phenylamino) carbonyl]-pyrrol-1-yl]-3,5-dihydroxy-heptanoic acid (Compound No. 42) and its hemicalcium salt.

Pharmacological activity

The compounds disclosed herein have activity as inhibitors of 3-hydroxy-3-methyl-glutanyl coenzyme A (HMG-CoA) reductase, and thus are useful in inhibiting cholesterol biosynthesis and/or in lowering triglycerides.

The compounds described herein are screened in an *in-vitro* HMG-CoA reductase enzyme assay as described by Kubo et al., *Endocrinology* 120:214 (1987) and Hellar et al., *Biochem and Biophys. Res. Comm.* 50:859 (1973).

HMG-CoA reductase is a rate-limiting enzyme in the cholesterol biosynthesis, catalyzing the following reaction.

$[^{14}C]$ HMG-CoA + 2NADPH $+2H^+ \longrightarrow [^{14}C]$ mevanolate + CoA $+2NADP^+$

microsomes, utilizing 2.5 μM $[^{14}C]$ HMG-CoA as a substrate. The reaction is carried out in presence of 100 mM KH_2PO_4, 20 mM G-6-P, 2.5 mM NADP, 10 mM EDTA, 5 mM DTT and 1.4 G-6-P dehydrogenase, at 37° C for 15 minutes and quantitating $[^{14}C]$ mevalonate as an end product. For IC_{50} determination, the compounds dissolved in 1% dimethylsulfoxide are preincubated with liver microsomes at 37°C for 30 minutes.

The IC_{50} for HMG-CoA reductase inhibition in rat liver microsome ranged from 0.1 to 0.96 nM. The compounds disclosed herein ranged from being equipotent to 4 fold more potent than atorvastatin. Some of the compounds disclosed herein were more potent than atorvastatin in inhibiting cholesterol synthesis *in vivo* rat model. Some of the compounds disclosed herein have intrinsic clearance in human liver microsome significantly less than atorvastatin and are not major substrate for CYP3A4 (cytochrome p450 3A4). Some of the compounds exhibit potency and selectivity greater than atorvastatin in inhibition of cholesterol synthesis in rat primary hepatocytes over inhibition of cholesterol synthesis in extra hepatic cells/cell lines [e.g. NRK-49F (Fibroblast) and L6 (Myoblast)].

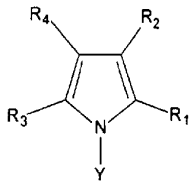
While the present invention has been described in terms of its specific embodiments, certain modifications and equivalents will be apparent to those skilled in the art and are intended to be included within the scope of the present invention.

Throughout this specification and the claims which follow, unless the context requires otherwise, the word "comprise", and variations such as "comprises" and "comprising", will be understood to imply the inclusion of a stated integer or step or group of integers or steps but not the exclusion of any other integer or step or group of integers or steps.

The reference to any prior art in this specification is not, and should not be taken as, an acknowledgment or any form or suggestion that the prior art forms part of the common general knowledge in Australia.

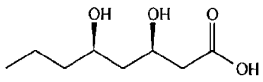
The claims defining the invention are as follows:

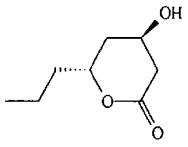
1. A compound of the structure of Formula I,



Formula I

or a pharmaceutically acceptable salt thereof, pharmaceutically acceptable tautomer, racemate, pure enantiomer, diastereoisomer or a lactone form or N-oxide thereof, wherein

Y = 

or 

R_1 is C_1-C_6 alkyl, C_3-C_6 cycloalkyl, or optionally substituted phenyl (wherein up to three substituents are independently selected from halogens, C_1-C_6 alkyl, cyano, and C_1-C_3 perfluoroalkyl);

R_2 is optionally substituted phenyl (wherein up to three substituents are independently selected from cyano, acetyl, and optionally substituted amino, wherein up to two amino substituents are independently selected from C_1-C_6 alkyl, C_3-C_6 cycloalkyl, acetyl, and sulfonamide);

R_3 is optionally substituted C_1-C_6 alkyl or C_3-C_6 cycloalkyl (wherein substituents are independently selected from halogens, hydroxyl, C_1-C_3 alkoxy and protected hydroxyl); or

R_3 is $-NR_8R_9$, wherein R_8 and R_9 are optionally substituted C_1-C_6 alkyl (wherein the optional substituent(s) is/are selected from halogens, hydroxy, C_1-C_3 alkoxy and protected hydroxyl);

R_4 is

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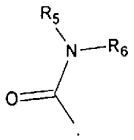

wherein **R_5** is hydrogen and **R_6** is aryl substituted with C_1-C_6 alkyl substituted with one or two substituents independently selected from hydroxyl and protected hydroxyl

with the provisio that R_2 is phenyl only when:

R_6 is phenyl substituted with hydroxyalkyl.

2. A compound according to claim 1 wherein R_2 is phenyl, R_5 and R_6 are respectively, hydrogen and phenyl substituted with one or more alkyl of from one to six carbon atoms, substituted with hydroxyl.

3. A compound according to claim 1 or 2 wherein R_6 is phenyl substituted with C_1-C_6 alkyl substituted with one or two substituents independently selected from hydroxyl and protected hydroxyl.

4. A compound according to claim 1 wherein R_2 is phenyl, R_5 is hydrogen and R_6 is phenyl substituted with hydroxylated alkyl of from one to six carbon atoms.

5. A compound according to claim 1 wherein R_6 is 4-hydroxymethyl phenyl.

6. A compound according to claim 1 wherein R_3 is alkyl of from one to six carbon atoms or cycloalkyl of from three to six carbon atoms.

7. A compound according to claim 1 wherein R_3 is isopropyl.

8. A compound of the chemical formula:

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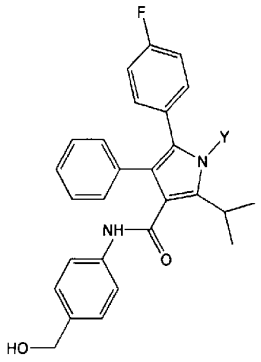
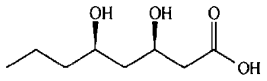
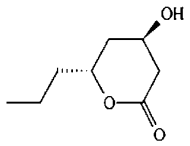


wherein

Y = 

or 

or a pharmaceutically acceptable salt thereof.

9. A compound, which is (3R,5R)-7-[2-(4-fluorophenyl)-5- isopropyl-3-phenyl-4-[(4-hydroxymethylphenylamino)carbonyl]-pyrrol-1-yl]-3,5-dihydroxy-heptanoic acid or a pharmaceutically acceptable salt thereof.

10. A pharmaceutically acceptable salt of a compound of claim 1, wherein the salt is selected from the group consisting of lithium, sodium, potassium, calcium, magnesium, zinc, aluminium, amino acid, ammonium, mono-alkyl ammonium, dialkyl ammonium, trialkyl ammonium and N-methyl glucamine.

11. The pharmaceutically acceptable salt of claim 10, wherein the salt is sodium salt.

12. The pharmaceutically acceptable salt of claim 10, wherein the salt is potassium salt.

13. The pharmaceutically acceptable salt of claim 10, wherein the salt is hemicalcium salt.

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14. The pharmaceutically acceptable salt of claim 10, wherein the salt is hemimagnesium salt.

15. The pharmaceutically acceptable salt of claim 10, wherein the salt is hemizinc salt.

16. The pharmaceutically acceptable salt of claim 10, wherein the salt is N-methyl glucamine salt.

17. A pharmaceutical composition comprising a therapeutically effective amount of a compound of claim 1 together with a pharmaceutically acceptable carrier, excipient or diluent.

18. The pharmaceutical composition of Claim 17, wherein the composition is formulated as an oral tablet.

19. A method of treating diabetes or a disease selected from the group consisting of arteriosclerosis, atherosclerosis, hyperlipidemia, hyperlipoproteinemia, hypercholesterolemia, hypertriglyceridemia, hypertension, stroke, ischemia, peripheral vascular disease, peripheral arterial disease, coronary heart disease, myocardial infarction, cerebral infarction, myocardial microvascular disease, dementia, Alzheimer's disease, angina and restenosis in a mammal in need of such treatment comprising administering a therapeutically-effective amount of a compound of any one of claims 1 to 16 to the mammal.

20. The method according to claim 19 wherein the disease is hyperlipidemia.

21. The method according to claim 19 wherein the disease is hypercholesterolemia.

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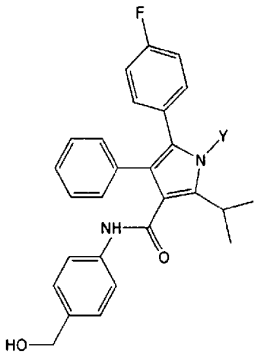
22. The method according to claim 19 wherein the disease is hyperlipoproteinemia.

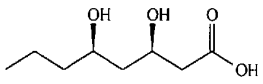
23. The method according to claim 19 wherein the disease is hypertriglyceridemia.

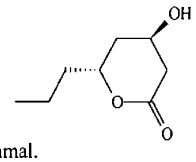
24. The method according to claim 19 wherein the disease is hypertension.

25. A method of treating hyperlipidemia, in a mammal in need of such treatment comprising administering a therapeutically-effective amount of compound of the chemical formula:



wherein

Y = 

or 

or a pharmaceutically acceptable salt thereof, to the mammal.

26. A method of treating hypertriglyceridemia, in a mammal in need of such treatment comprising administering a therapeutically-effective amount of compound of the chemical formula:

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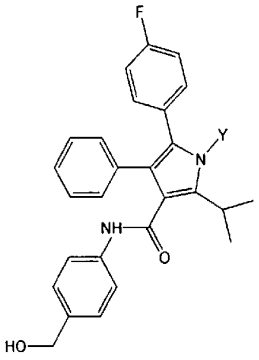
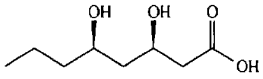
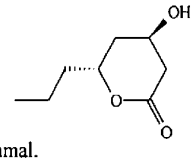


wherein

Y = 

or 

or a pharmaceutically acceptable salt thereof, to the mammal.

27. Use of a compound according to any one of claims 1 to 16 or a pharmaceutical composition of claim 17 or 18 in the treatment of diabetes or a disease selected from the group consisting of arteriosclerosis, atherosclerosis, hyperlipidemia, hyperlipoproteinemia, hypercholesterolemia, hypertriglyceridemia, hypertension, stroke, ischemia, peripheral vascular disease, peripheral arterial disease, coronary heart disease, myocardial infarction, cerebral infarction, myocardial microvascular disease, dementia, Alzheimer's disease, angina and restenosis.

28. A compound according to claim 1 substantially as herein before described with reference to the Examples.

29. Use of the compound of any one of claims 1 to 16 in the manufacture of a medicament of the treatment of diabetes or a disease selected from the group consisting of arteriosclerosis, atherosclerosis, hyperlipidemia, hyperlipoproteinemia, hypercholesterolemia, hypertriglyceridemia, hypertension, stroke, ischemia, peripheral vascular disease, peripheral arterial disease, coronary heart disease, myocardial infarction, cerebral infarction, myocardial microvascular disease, dementia, Alzheimer's disease, angina and restenosis.