

5-PHENYL-PENTANOIC ACID DERIVATIVES AS MATRIX METALLOPROTEINASE INHIBITORS
FOR THE TREATMENT OF ASTHMA AND OTHER DISEASES

Field of the Invention

The present invention relates to certain beta hydroxy acids and to processes for the
5 synthesis of the same. This invention also relates to pharmacological compositions
containing the compounds of the present invention, and methods of treating asthma,
rheumatoid arthritis, COPD, rhinitis, osteoarthritis, psoriatic arthritis, psoriasis, pulmonary
fibrosis, pulmonary inflammation, acute respiratory distress syndrome, periodontitis,
multiple sclerosis, gingivitis, atherosclerosis, neointimal proliferation, which leads to
10 restenosis and ischemic heart failure, stroke, renal diseases, tumor metastasis, and other
inflammatory disorders characterized by over-expression and over-activation of an matrix
metalloproteinase, using the compounds.

Background of the Invention

Metalloproteinases (MMPs) are a naturally occurring superfamily of proteinases
15 (enzymes) found in most mammals. The superfamily is composed of at least 26 members
of zinc-containing enzymes produced by many cell types and sharing structural and
functional features. Based on structural and functional considerations proteinases have
been classified into different families and subfamilies (Hopper, NM, 1994, FEBS) such as
collagenases (MMP-1, MMP-13), gelatinases (MMP-2, MMP-9), metalloelastases (MMP-
20 12), the MT-MMPs (MMP-14, MMP-15) and sheddases such as TNF-converting enzymes
(TACE, ACE).

Metalloproteinases are believed to be important in a plethora of physiological
disease processes that involve remodeling such as embryonic development, bone
formation and uterine remodeling during menstruation. One major biological function of
25 MMPs is to catalyze the breakdown of connective tissues or extra-cellular matrix by their
ability to hydrolyze various components of tissue or matrix. Apart from their role in
degrading connective tissue, MMPs are always involved in the activation of zymogen
(pro) forms of other MMPs thereby inducing MMP activation. They are also involved in
biosynthesis of TNF-alpha which is implicated in many pathological conditions.

MMP-12 also known as macrophage elastase or metalloelastase is expressed in activated macrophages and has been shown to be secreted from alveolar macrophages from smokers as well as in foam cells in atherosclerotic lesions. MMP-12 knockout mouse studies have shown the development of significant emphysema, thus supporting its role in COPD. MMP-9 (gelatinase B, 92 kDa type IV collagenase) is one member of the MMP family that is released as a proenzyme and subsequently activated via a protease cascade *in vivo*. The concentration of MMP-9 is increased in diseases like asthma, interstitial pulmonary fibrosis (IPF), adult respiratory distress syndrome (ARDS), and in chronic obstructive pulmonary disease (COPD). Because of its proteolytic ability, MMP-9 has been implicated in tissue remodelling of the airways and lungs in chronic inflammatory diseases such as severe asthma and COPD. MMP-9 is also likely to be physiologically important because of its ability to regulate the digestion of components of the extracellular matrix as well as the activity of other proteases and cytokines. MMP-9 is secreted in neutrophils, macrophages, osteoclasts, which are easily induced by cytokines and growth factors, and plays a role in various physiological and pathological processes.

Over-expression or over-activation of an MMP or an imbalance between an MMP and a natural (i.e., endogenous) tissue inhibitor of a matrix metalloproteinase (TIMP) has been linked to a pathogenesis of diseases characterized by the breakdown of connective tissue or extracellular matrix.

Examples of inflammatory conditions and autoimmune disorders in which the compounds of the invention have potentially beneficial effects include diseases of the respiratory tract such as asthma (including allergen-induced asthmatic reactions), cystic fibrosis, bronchitis (including chronic bronchitis), chronic obstructive pulmonary disease (COPD), adult respiratory distress syndrome (ARDS), chronic pulmonary inflammation, rhinitis and upper respiratory tract inflammatory disorders (URID), ventilator induced lung injury, silicosis, pulmonary sarcoidosis, idiopathic pulmonary fibrosis, bronchopulmonary dysplasia, arthritis e.g., rheumatoid arthritis, osteoarthritis, infectious arthritis, psoriasis arthritis, traumatic arthritis, rubella arthritis, Reiter's syndrome, gouty arthritis and prosthetic joint failure gout acute synovitis, spondylitis and non-articular inflammatory conditions, e.g., herniated/ruptured/prolapsed intervertebral disk syndrome, bursitis, tendonitis, tenosynovitic fibromyalgic syndrome and other inflammatory conditions

associated with ligamentous sprain and regional musculoskeletal strain, inflammatory disorders of the gastrointestinal tract, e.g., ulcerative colitis, diverticulitis, Crohn's disease, inflammatory bowel diseases, irritable bowel syndrome and gastritis, multiple sclerosis, systemic lupus erythematosus scleroderma, autoimmune exocrinopathy, autoimmune encephalomyelitis, diabetes, tumor angiogenesis and metastasis, cancer including carcinoma of the breast, colon, rectum, lung, kidney, ovary, stomach, uterus, pancreas, liver, oral, laryngeal and prostate, melanoma, acute and chronic leukemia, periodontal disease, neurodegenerative disease Alzheimer's disease, Parkinson's disease, epilepsy, muscle degeneration, inguinal hernia retinal degeneration, diabetic retinopathy, macular degeneration, ocular inflammation, bone desorption diseases, osteoporosis, osteopetrosis, graft vs. host reaction allograft rejections, sepsis, endotoxemia, toxic shock syndrome, tuberculosis, usual interstitial and cryptogenic organizing pneumonia, bacterial meningitis, systemic cachexia, cachexia secondary to infection or malignancy, cachexia secondary to acquired immune deficiency syndrome (AIDS), malaria, leprosy, leishmaniasis, Lyme disease, glomerulonephritis, glomerulosclerosis, renal fibrosis, liver fibrosis, pancreatitis, hepatitis, endometriosis, pain, e.g., that associated with inflammation and/or trauma, inflammatory diseases of the skin, e.g., dermatitis, dermatitis, skin ulcers, psoriasis, eczema, systemic valvulitis vascular dementia, thrombosis, atherosclerosis, restenosis, reperfusion injury, plaque calcification, myocarditis, aneurysm, stroke, pulmonary hypertension, left ventricular remodeling and heart failure. Diseases of principal interest include COPD and inflammatory diseases of the respiratory tract and joints and vascular diseases. It will be appreciated by those skilled in the art that reference herein to treatment extends to prophylaxis as well as the treatment of established conditions.

Inhibition of the activity of one or more MMPs may be of benefit in these diseases or conditions, for example, various inflammatory and allergic diseases such as, inflammation of the joint, inflammation of the GI tract, inflammation of the skin, collagen remodeling, etc.

Research has been carried out into the identification of inhibitors that are selective e.g., for a few of the MMP subtypes. An MMP inhibitor of improved selectivity would avoid potential side effects associated with inhibition of MMPs that are not involved in the pathogenesis of the disease being treated. Further, use of more selective MMP inhibitors

would require administration of a lower amount of the inhibitor for treatment of disease than would otherwise be required and, after administration, partitioned *in vivo* among multiple MMPs. Still further, the administration of a lower amount of compound would improve the margin of safety between the dose of the inhibitor required for therapeutic activity and the dose of the inhibitor at which toxicity is observed.

The design and therapeutic application of MMP inhibitors has revealed that the requirement of a molecule to be an effective inhibitor of MMP class of enzymes is a functional group (e.g., carboxylic acid, hydroxamic acid or sulphydryl) capable of chelating to the active site Zn^{2+} ion (Whittaker, et al., *Chem. Rev.*, 1999, 99, 2735-76).

WO 04/110974 discloses compounds and their physiologically functional derivatives as inhibitors of matrix metalloproteinase enzymes. WO 04/113279 discloses inhibitors of matrix metalloproteinase. WO05/026120 discloses particular matrix metalloproteinase inhibitors which may find use in treating disease wherein inappropriate metalloprotease activity results in degradation of connective tissue and inflammation. U.S. Patent No. 6,350,885 discloses tricyclic heteroaromatic compounds and their derivatives as inhibitors of matrix metalloproteinases. WO 98/09940 discloses biphenyl butyric acids and their derivatives as inhibitors of matrix metalloproteinases. *J. Med. Chem.*, 1968, vol. 11(6), 1139-1144 discloses synthesis and anti-inflammatory activity of 4-(p-biphenyl)-3-hydroxybutyric acid and related compounds. WO 96/15096 discloses substituted 4-biarylbutyric or 5-biarylpentanoic acids and derivatives as matrix metalloproteinase inhibitors.

Summary of the Invention

The present invention discloses a novel class of compounds that are dual MMP-9/12 inhibitors and have desirable activity profiles. The compounds of this invention have beneficial potency, selectivity and/or pharmacokinetic properties.

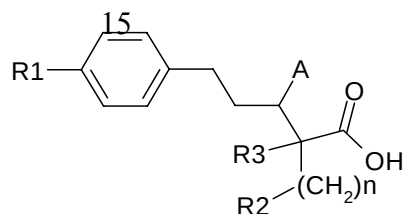
In one aspect, there are provided matrix metalloprotease inhibitors, which can be useful as safe and effective therapeutic or prophylactic agents for the treatment of various inflammatory and allergic diseases. Also provided are processes for synthesizing such compounds.

In another aspect, pharmaceutical compositions containing such compounds are provided together with acceptable carriers, excipients or diluents, which can be useful for the treatment of inflammatory and autoimmune diseases.

The racemates, enantiomers, diastereomers, rotational isomers, , polymorphs, pharmaceutically acceptable salts and pharmaceutically acceptable solvates of these compounds, , as well as pharmaceutical compositions comprising the compounds, their, racemates, enantiomers, diastereomers, conformational isomers, , polymorphs, solvates or pharmaceutically acceptable salts thereof, in combination with a pharmaceutically acceptable carrier and optionally included excipients.

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

In accordance with one aspect, there are provided compounds having the structure of Formula I:



Formula I

wherein

n is an integer from 1 to 5;

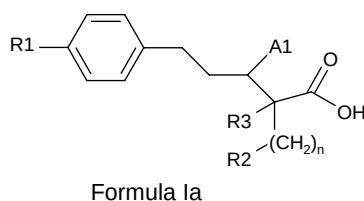
R₁ can be optionally substituted alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heterocyclyl, heteroaryl, aralkyl, alkoxy, aryloxy, alkenyloxy or alkynyloxy;

R₂ can be alkenyl, alkynyl, aryl, heterocyclyl, heteroaryl, cycloalkyl, NR₄R₅, -NHC(=Y)R₄, -NHC(=Y)NR₅R_x, -NHC(=O)OR₄, -NHSO₂R₄, C(=Y)NR₄R₅, C(=O)OR₆ [wherein **Y** can be oxygen or sulphur], OR₅, -OC(=O)NR₄R₅, O-acyl, S(O)_mR₄, -SO₂N(R₄)₂, cyano, amidino or guanidino [wherein R₄ can be alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heterocyclyl, heteroaryl, aralkyl, heteroarylalkyl, heterocyclalkyl or cycloalkylalkyl and m is an integer 0-2; R₅ can be hydrogen or R₄; R_x can be R₄ or -SO₂N(R₄)₂ and R₆ is hydrogen, alkyl, cycloalkyl, aralkyl, heteroarylalkyl, heterocyclalkyl or cycloalkylalkyl];

R₃ can be hydrogen, fluorine, alkyl, cycloalkylalkyl or aralkyl;

A can be OH, OR₄, -OC(=O)NR₄R₅, O-acyl, NH₂, NR₄R₅, -NHC(=Y)R₄,
-NHC(=Y)NR₅R_x, -NHC(=O)OR₄, -NHSO₂R₄.

5 In one embodiment, the invention relates to compounds of general Formula Ia,

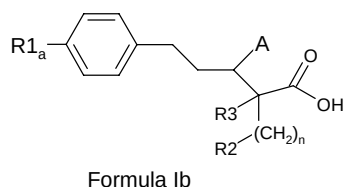


wherein

A1 can be OH, -OC(=O)NR₄R₅, NH₂, NR₄R₅, -NHC(=Y)R₄, -NHC(=Y)NR₅R_x,
-NHC(=O)OR₄, -NHSO₂R₄;

10 n, R₁, R₂, R₃ and R₄ can be as defined earlier.

In another embodiment, the invention relates to compounds of general Formula Ib,

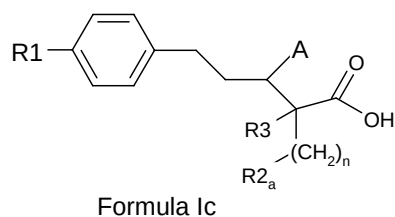


wherein

R_{1a} can be aryl or heteroaryl;

15 **n, R₂, R₃ and A** can be as defined earlier.

In another embodiment, the invention relates to compounds of general Formula Ic,



wherein

R_{2a} can be NR₄R₅, -NHC(=Y)R₄, -NHC(=Y)NR₅R_x, -NHC(=O)OR₄, -NH₂SO₂R₄, amidino or guanidino [wherein **Y** can be oxygen or sulphur and R₄ can be alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heterocyclyl, heteroaryl, aralkyl, heteroarylalkyl, heterocyclalkyl or cycloalkylalkyl and m is an integer 0-2; R₅ is hydrogen or R₄; R₄ and R₅ together may optionally form a heterocyclic ring containing one or more heteroatoms such as O, N or S and R_x is R₄ or -SO₂N(R₄)₂];

n, **R₁**, **R₃** and **A** can be as defined earlier.

In yet another embodiment, the invention encompasses compounds that include, for example

10 5-Biphenyl-4-yl-3-hydroxy-2-[2-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)ethyl]pentanoic acid (Compound No. 1),

2-(2-{[(Benzyloxy)carbonyl]amino}ethyl)-5-biphenyl-4-yl-3-hydroxypentanoic acid (Compound No. 11).

15 5-Biphenyl-4-yl-3-hydroxy-2-{2-[(phenylacetyl)amino]ethyl}pentanoic acid (Compound No. 45),

5-Biphenyl-4-yl-3-hydroxy-2-[2-(1-oxophthalazin-2(1*H*)-yl)ethyl]pentanoic acid (Compound No. 47),

5-Biphenyl-4-yl-3-hydroxy-2-[2-(2'-oxospiro[cyclopropane-1,3'-indol]-1'(2'*H*)-yl)ethyl]pentanoic acid (Compound No. 49),

20 3-Hydroxy-2-[2-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)ethyl]-5-[4'-(trifluoromethyl)biphenyl-4-yl]pentanoic acid (Compound No. 59),

5-(3',4'-Difluorobiphenyl-4-yl)-3-hydroxy-2-[2-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)ethyl]pentanoic acid (Compound No. 60),

25 3-Hydroxy-5-(4'-methoxybiphenyl-4-yl)-2-[2-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)ethyl]pentanoic acid (Compound No. 64),

5-(4'-Chlorobiphenyl-4-yl)-3-hydroxy-2-[2-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)ethyl]pentanoic acid (Compound No. 65),

3-Hydroxy-5-[4-(6-methoxypyridin-3-yl)phenyl]-2-[2-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)ethyl]pentanoic acid (Compound No.67),

5 3-Hydroxy-5-(4'-methylbiphenyl-4-yl)-2-[2-(5-methyl-1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]pentanoic acid (Compound No. 68),

5-(4'-Chlorobiphenyl-4-yl)-3-hydroxy-2-[2-(5-methyl-1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]pentanoic acid (Compound No. 69),

10 3-Hydroxy-2-[2-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)ethyl]-5-[4'-(trifluoromethoxy)biphenyl-4-yl]pentanoic acid (Compound No. 70),

5-(4'-Fluorobiphenyl-4-yl)-3-hydroxy-2-[2-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)ethyl]pentanoic acid (Compound No. 71),

3-Hydroxy-5-(4'-methylbiphenyl-4-yl)-2-[2-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)ethyl]pentanoic acid (Compound No. 72),

15 5-(4'-Cyanobiphenyl-4-yl)-3-hydroxy-2-[2-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)ethyl]pentanoic acid (Compound No. 73),

5-(4'-Fluorobiphenyl-4-yl)-3-hydroxy-2-[2-(5-methyl-1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]pentanoic acid (Compound No. 74),

20 3-Hydroxy-5-[4-(6-methoxypyridin-3-yl)phenyl]-2-[2-(5-methyl-1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]pentanoic acid (Compound No. 75),

5-(4'-Ethylbiphenyl-4-yl)-3-hydroxy-2-[2-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)ethyl]pentanoic acid (Compound No. 76),

3-Hydroxy-2-[2-(5-methyl-1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-5-[4'-(trifluoromethyl)biphenyl-4-yl]pentanoic acid (Compound No. 77),

5-Biphenyl-4-yl-3-hydroxy-2-[2-(1-oxo-4-phenyl-4a,8a-dihydrophthalazin-2(1*H*)-yl)ethyl]pentanoic acid (Compound No. 84),

5-Biphenyl-4-yl-3-hydroxy-2-[2-(3-oxo-2,3-dihydro-4*H*-1,4-benzoxazin-4-yl)ethyl]pentanoic acid (Compound No. 85),

5 5-Biphenyl-4-yl-2-{2-[(3*aR*,7*aS*)-1,3-dioxo-1,3,3*a*,4,7,7*a*-hexahydro-2*H*-isoindol-2-yl]ethyl}-3-hydroxypentanoic acid (Compound No. 86),

5-Biphenyl-4-yl-2-(2-{[(4-fluorophenyl)sulfonyl]amino}ethyl)-3-hydroxypentanoic acid (Compound No. 87),

10 5-Biphenyl-4-yl-2-(2-{[(3-fluorophenyl)acetyl]amino}ethyl)-3-hydroxypentanoic acid (Compound No. 88),

5-Biphenyl-4-yl-2-{2-[(4-fluorobenzoyl)amino]ethyl}-3-hydroxypentanoic acid (Compound No. 89),

5-Biphenyl-4-yl-3-hydroxy-2-[2-(5-methyl-1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]pentanoic acid (Compound No. 90),

15 5-Biphenyl-4-yl-3-hydroxy-2-[2-(1-oxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]pentanoic acid (Compound No. 91).

5-Biphenyl-4-yl-2-[2-({[(4-fluorophenyl)amino]carbonyl}amino)ethyl]-3-hydroxypentanoic acid (Compound No. 92),

20 5-Biphenyl-4-yl-2-[2-(4,4-dimethyl-2,6-dioxopiperidin-1-yl)ethyl]-3-hydroxypentanoic acid (Compound No. 93),

5-Biphenyl-4-yl-2-[2-(7,9-dioxo-8-azaspiro[4.5]dec-8-yl)ethyl]-3-hydroxypentanoic acid (Compound No. 94),

5-Biphenyl-4-yl-3-hydroxy-2-[2-(2-oxo-1,3-benzoxazol-3(2*H*)-yl)ethyl]pentanoic acid (Compound No. 96),

2-[2-(5-*tert*-Butyl-1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxy-5-[4-(6-methoxypyridin-3-yl)phenyl]pentanoic acid (Compound No. 97),

5-Biphenyl-4-yl-2-[2-(5,6-dichloro-1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxypentanoic acid (Compound No. 102),

5 5-Biphenyl-4-yl-2-[2-(2,4-dioxo-1,4-dihydroquinazolin-3(2*H*)-yl)ethyl]-3-hydroxypentanoic acid (Compound No. 103),

5-Biphenyl-4-yl-2-[2-(1,3-dioxo-1,3-dihydro-2*H*-pyrrolo[3,4-*c*]pyridin-2-yl)ethyl]-3-hydroxypentanoic acid (Compound No. 104),

2-[2-(5-*tert*-Butyl-1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-5-(3',4'-difluorobiphenyl-4-yl)-3-hydroxypentanoic acid (Compound No. 105),

(2*R*,3*S* + 2*S*,3*R*)-2-[2-(5-*tert*-Butyl-1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-5-(4'-fluorobiphenyl-4-yl)-3-hydroxypentanoic acid (Compound No. 106),

(2*R*,3*S* + 2*S*,3*R*)-2-[2-(5-*tert*-Butyl-1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxy-5-[4'-(trifluoromethyl)biphenyl-4-yl]pentanoic acid (Compound No. 107),

15 (2*R*,3*R* + 2*S*,3*S*)-2-[2-(5-*tert*-Butyl-1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-5-(4'-fluorobiphenyl-4-yl)-3-hydroxypentanoic acid (Compound No. 108),

(2*R*,3*R* + 2*S*,3*S*)-2-[2-(5-*tert*-Butyl-1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxy-5-[4'-(trifluoromethyl)biphenyl-4-yl]pentanoic acid (Compound No. 109),

20 (2*R*,3*R* + 2*S*,3*S*)-2-[2-(5-*tert*-Butyl-1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxy-5-(4'-methylbiphenyl-4-yl)pentanoic acid (Compound No. 113),

(2*R*,3*S* + 2*S*,3*R*)-2-[2-(5-*tert*-Butyl-1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxy-5-(4'-methylbiphenyl-4-yl)pentanoic acid (Compound No. 114),

(2*R*,3*R* + 2*S*,3*S*)-2-[2-(5-*tert*-Butyl-1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxy-5-(4'-methoxybiphenyl-4-yl)pentanoic acid (Compound No. 115),

(2R,3R + 2S,3S)-2-[2-(5-*tert*-Butyl-1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-5-(4'-chlorobiphenyl-4-yl)-3-hydroxypentanoic acid (Compound No.116),

(2R,3S + 2S,3R)-2-[2-(5-*tert*-Butyl-1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-5-(4'-chlorobiphenyl-4-yl)-3-hydroxypentanoic acid(Compound No. 117),

5 (2R,3S + 2S,3R)-2-[2-(5-*tert*-Butyl-1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxy-5-(4'-methoxybiphenyl-4-yl)pentanoic acid (Compound No. 118),

5-Biphenyl-4-yl-2-[2-(5-*tert*-butyl-1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxypentanoic acid (Compound No. 121),

5-Biphenyl-4-yl-3-hydroxy-2-[2-(1-oxo-1,3-dihydro-2*H*-isoindol-2-yl) butyl]pentanoic
10 acid (Compound No. 124),

(2R,3S)-3-Hydroxy-5-[4-(6-methoxypyridin-3-yl)phenyl]-2-[2-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)ethyl]pentanoic acid (Compound No.133),

(2S,3R)-3-Hydroxy-5-[4-(6-methoxypyridin-3-yl)phenyl]-2-[2-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)ethyl]pentanoic acid (Compound No.134),

15 (2R,3R)-3-Hydroxy-5-[4-(6-methoxypyridin-3-yl)phenyl]-2-[2-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)ethyl]pentanoic acid (Compound No.135), and

(2S,3S)-3-Hydroxy-5-[4-(6-methoxypyridin-3-yl)phenyl]-2-[2-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)ethyl]pentanoic acid (Compound No.136).

In another embodiment, the invention encompasses separation of the individual
20 enantiomers or diastereomer pairs or single diastereomers. A person ordinarily skilled in the art of this invention may optionally choose one or more ways to obtain chirally pure compounds. The present invention includes separation of a representative set of compounds either as diastereomeric pairs or single diastereomers by preparative thin layer chromatography and/or by HPLC, using an achiral or chiral column as required.

25 In yet another embodiment, the present invention relates to the therapeutically effective dose of a compound of Formula I in combination with one or more of other

therapeutic agents used for treating various inflammatory and allergic diseases. Examples of such therapeutic agents include, but are not limited to,

1) anti-inflammatory agents, experimental or commercial (i) such as nonsteroidal anti-inflammatory agents piroxicam, diclofenac, propionic acids, fenamates, pyrazolones, salicylates, PDE-4/p38 MAP Kinase/Cathepsin inhibitors, (ii) leukotrienes LTC₄/LTD₄/LTE₄/LTB₄- Inhibitors, 5-lipoxygenase inhibitors and PAF- receptor antagonists, (iii) Cox-2 inhibitors, (iv) MMP inhibitors, and (v) interleukin-I inhibitors;

2) antihypertensive agents, (i) ACE inhibitors, e.g., enalapril, lisinopril, valsartan, telmisartan and quinapril, (ii) angiotensin II receptor antagonists and agonists, e.g., losartan, candesartan, irbesartan, valsartan, and eprosartan, (iii) β -blockers, and (iv) calcium channel blockers;

3) immunosuppressive agents such as cyclosporine, azathioprine and methotrexate, and anti-inflammatory corticosteroids.

The following definitions apply to terms as used herein.

The term "alkyl," unless otherwise specified, refers to a monoradical branched or unbranched saturated hydrocarbon chain having from 1 to 20 carbon atoms. This term can be exemplified by groups such as methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, sec-butyl, t-butyl, n-pentyl, isopentyl, neopentyl, n-hexyl, n-decyl, tetradecyl, and the like. Alkyl groups may be substituted further with one or more substituents selected from alkenyl, alkynyl, alkoxy, cycloalkyl, cycloalkenyl, acyl, acylamino, acyloxy, alkoxycarbonylamino, azido, cyano, halogen, hydroxy, oxo, thiocarbonyl, carboxy, carboxyalkyl, aryl, heterocyclyl, heteroaryl, arylthio, thiol, alkylthio, aryloxy, nitro, aminosulfonyl, COOH, aminocarbonylamino, -NHC(=O)R_f, -NR_fR_q, -C(=O)NR_fR_q, -NHC(=O)NR_fR_q, -C(=O)heteroaryl, C(=O)heterocyclyl, -O-C(=O)NR_fR_q {wherein R_f and R_q are independently selected from alkyl, alkenyl, cycloalkyl, cycloalkenyl, aryl, aralkyl, heterocyclyl, heteroaryl, heterocyclylalkyl, heteroarylalkyl}, nitro, or -SO₂R₆ (wherein R₆ is alkyl, alkenyl, alkynyl, cycloalkyl, aralkyl, aryl, heterocyclyl, heteroaryl, heteroarylalkyl or heterocyclylalkyl). Unless otherwise constrained by the definition, alkyl substituents may be further substituted by 1-3 substituents selected from alkyl, carboxy, -NR_fR_q, -C(=O)NR_fR_q, -OC(=O)NR_fR_q, -NHC(=O)NR_fR_q (wherein R_f and R_q

are the same as defined earlier), hydroxy, alkoxy, halogen, CF_3 , cyano, and $-\text{SO}_2\text{R}_6$,
 (wherein R_6 are the same as defined earlier); or an alkyl group also may be interrupted by
 1-5 atoms of groups independently selected from oxygen, sulfur or $-\text{NR}_a$ - {wherein R_a is
 selected from hydrogen, alkyl, cycloalkyl, alkenyl, cycloalkenyl, alkynyl, aryl, acyl,
 5 aralkyl, $-\text{C}(=\text{O})\text{OR}_f$ (wherein R_f is the same as defined earlier), SO_2R_6 (where R_6 is as
 defined earlier), or $-\text{C}(=\text{O})\text{NR}_f\text{R}_q$ (wherein R_f and R_q are as defined earlier)}. Unless
 otherwise constrained by the definition, all substituents may be substituted further by 1-3
 substituents selected from alkyl, carboxy, $-\text{NR}_f\text{R}_q$, $-\text{C}(=\text{O})\text{NR}_f\text{R}_q$, $-\text{O}-\text{C}(=\text{O})\text{NR}_f\text{R}_q$
 (wherein R_f and R_q are the same as defined earlier) hydroxy, alkoxy, halogen, CF_3 , cyano,
 10 and $-\text{SO}_2\text{R}_6$ (where R_6 is same as defined earlier); or an alkyl group as defined above that
 has both substituents as defined above and is also interrupted by 1-5 atoms or groups as
 defined above.

The term “alkenyl,” unless otherwise specified, refers to a monoradical of a
 branched or unbranched unsaturated hydrocarbon group having from 2 to 20 carbon atoms
 15 with cis, trans, or geminal geometry. In the event that alkenyl is attached to a heteroatom,
 the double bond cannot be alpha to the heteroatom. Alkenyl groups may be substituted
 further with one or more substituents selected from alkyl, alkynyl, alkoxy, cycloalkyl,
 cycloalkenyl, acyl, acylamino, acyloxy, $-\text{NHC}(=\text{O})\text{R}_f$, $-\text{NR}_f\text{R}_q$, $-\text{C}(=\text{O})\text{NR}_f\text{R}_q$,
 $-\text{NHC}(=\text{O})\text{NR}_f\text{R}_q$, $-\text{O}-\text{C}(=\text{O})\text{NR}_f\text{R}_q$ (wherein R_f and R_q are the same as defined earlier),
 20 alkoxycarbonylamino, azido, cyano, halogen, hydroxy, oxo, thiocarbonyl, carboxy,
 arylthio, thiol, alkylthio, aryl, aralkyl, aryloxy, heterocyclyl, heteroaryl, heterocyclyl alkyl,
 heteroaryl alkyl, aminosulfonyl, aminocarbonylamino, alkoxyamino, nitro, or SO_2R_6
 (wherein R_6 are is same as defined earlier). Unless otherwise constrained by the
 definition, alkenyl substituents optionally may be substituted further by 1-3 substituents
 25 selected from alkyl, carboxy, hydroxy, alkoxy, halogen, $-\text{CF}_3$, cyano, $-\text{NR}_f\text{R}_q$,
 $-\text{C}(=\text{O})\text{NR}_f\text{R}_q$, $-\text{O}-\text{C}(=\text{O})\text{NR}_f\text{R}_q$ (wherein R_f and R_q are the same as defined earlier) and
 $-\text{SO}_2\text{R}_6$ (where R_6 is same as defined earlier).

The term “alkynyl,” unless otherwise specified, refers to a monoradical of an
 unsaturated hydrocarbon, having from 2 to 20 carbon atoms. In the event that alkynyl is
 30 attached to a heteroatom, the triple bond cannot be alpha to the heteroatom. Alkynyl
 groups may be substituted further with one or more substituents selected from alkyl,

alkenyl, alkoxy, cycloalkyl, cycloalkenyl, acyl, acylamino, acyloxy, alkoxycarbonylamino, azido, cyano, halogen, hydroxy, oxo, thiocarbonyl, carboxy, arylthio, thiol, alkylthio, aryl, aralkyl, aryloxy, aminosulfonyl, aminocarbonylamino, nitro, heterocyclyl, heteroaryl, heterocyclylalkyl, heteroarylalkyl, -NHC(=O)R_f , $\text{-NR}_f\text{R}_q$, $\text{-NHC(=O)NR}_f\text{R}_q$,
 5 $\text{-C(=O)NR}_f\text{R}_q$, $\text{-O-C(=O)NR}_f\text{R}_q$ (wherein R_f and R_q are the same as defined earlier), or $\text{-SO}_2\text{R}_6$ (wherein R_6 is as defined earlier). Unless otherwise constrained by the definition, alkynyl substituents optionally may be substituted further by 1-3 substituents selected from alkyl, carboxy, carboxyalkyl, hydroxy, alkoxy, halogen, CF_3 , $\text{-NR}_f\text{R}_q$, $\text{-C(=O)NR}_f\text{R}_q$, $\text{-NHC(=O)NR}_f\text{R}_q$, $\text{-C(=O)NR}_f\text{R}_q$ (wherein R_f and R_q are the same as defined earlier),
 10 cyano, or $\text{-SO}_2\text{R}_6$ (where R_6 is same as defined earlier).

The term “aralkyl,” unless otherwise specified, refers to alkyl-aryl linked through an alkyl portion (wherein alkyl is as defined above) and the alkyl portion contains 1-6 carbon atoms and aryl is as defined below. Examples of aralkyl groups include benzyl, ethylphenyl and the like.

15 The term “aryl,” unless otherwise specified, refers to carbocyclic aromatic groups, for example, phenyl, biphenyl or naphthyl ring and the like, optionally substituted with 1 to 3 substituents selected from halogen (*e.g.*, F, Cl, Br, I), hydroxy, alkyl, alkenyl, alkynyl, cycloalkyl, alkoxy, acyl, aryloxy, CF_3 , cyano, nitro, COOR_e (wherein R_e is hydrogen, alkyl, alkenyl, cycloalkyl, aralkyl, heterocyclylalkyl, heteroarylalkyl), NHC(=O)R_f ,
 20 $\text{-NR}_f\text{R}_q$, $\text{-C(=O)NR}_f\text{R}_q$, $\text{-NHC(=O)NR}_f\text{R}_q$, $\text{-O-C(=O)NR}_f\text{R}_q$ (wherein R_f and R_q are the same as defined earlier), $\text{-SO}_2\text{R}_6$ (wherein R_6 is same as defined earlier), carboxy, heterocyclyl, heteroaryl, heterocyclylalkyl, heteroarylalkyl or amino carbonyl amino. The aryl group optionally may be fused with a cycloalkyl group, wherein the cycloalkyl group may optionally contain heteroatoms selected from O, N or S.

25 The term “aryloxy” denotes the group O-aryl, wherein aryl is as defined above.

The term “heteroaryl,” unless otherwise specified, refers to an aromatic ring structure containing 5 or 6 ring atoms, or a bicyclic aromatic group having from 8 to 10 ring atoms, with one or more heteroatom(s) independently selected from N, O or S optionally substituted with 1 to 4 substituent(s) selected from halogen (*e.g.*, F, Cl, Br, I),
 30 hydroxy, alkyl, alkenyl, alkynyl, cycloalkyl, acyl, carboxy, aryl, alkoxy, aralkyl, cyano, nitro, heterocyclyl, heteroaryl, $\text{-NR}_f\text{R}_q$, CH=NOH , $\text{-(CH}_2\text{)}_w\text{C(=O)R}_g$ {wherein w is an

integer from 0-4 and R_g is hydrogen, hydroxy, OR_f , NR_fR_q , $-NHOR_z$ or $-NHOH$, $-C(=O)NR_fR_q$ and $-NHC(=O)NR_fR_q$, $-SO_2R_6$, $-O-C(=O)NR_fR_q$, $-O-C(=O)R_f$, $-O-C(=O)OR_f$ (wherein R_6 , R_f and R_q are as defined earlier, and R_z is alkyl, cycloalkyl, aryl, heteroaryl, heterocyclyl, heteroarylalkyl or heterocyclalkyl). Unless otherwise
 5 constrained by the definition, the substituents are attached to a ring atom, *i.e.*, carbon or heteroatom in the ring. Examples of heteroaryl groups include oxazolyl, imidazolyl, pyrrolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, tetrazolyl, thiazolyl, oxadiazolyl, benzoimidazolyl, thiadiazolyl, pyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl, thienyl, isoxazolyl, triazinyl, furanyl, benzofuranyl, indolyl, benzothiazolyl, or benzoxazolyl, and the like.

10 The term ‘heterocyclyl,’ unless otherwise specified, refers to a non-aromatic monocyclic or bicyclic cycloalkyl group having 5 to 10 atoms wherein 1 to 4 carbon atoms in a ring are replaced by heteroatoms selected from O, S or N, and optionally are benzofused or fused heteroaryl having 5-6 ring members and/or optionally are substituted, wherein the substituents are selected from halogen (*e.g.*, F, Cl, Br, I), hydroxy, alkyl,
 15 alkenyl, alkynyl, cycloalkyl, acyl, aryl, alkoxy, alkaryl, cyano, nitro, oxo, carboxy, heterocyclyl, heteroaryl, $-O-C(=O)R_f$, $-O-C(=O)OR_f$, $-C(=O)NR_fR_q$, SO_2R_6 , $-O-C(=O)NR_fR_q$, $-NHC(=O)NR_fR_q$, $-NR_fR_q$ (wherein R_6 , R_f and R_q are as defined earlier) or guanidine. Heterocyclyl can optionally include rings having one or more double bonds. Unless otherwise constrained by the definition, the substituents are attached to the ring
 20 atom, *i.e.*, carbon or heteroatom in the ring. Also, unless otherwise constrained by the definition, the heterocyclyl ring optionally may contain one or more olefinic bond(s). Examples of heterocyclyl groups include oxazolidinyl, tetrahydrofuranyl, dihydrofuranyl, dihydropyridinyl, dihydroisoxazolyl, dihydrobenzofuryl, azabicyclohexyl, dihydroindolyl, pyridinyl, isoindole 1,3-dione, piperidinyl or piperazinyl.

25 The term ‘cycloalkyl,’ unless otherwise specified, refers to cyclic alkyl groups of from 3 to 20 carbon atoms having a single cyclic ring or multiple condensed rings, which may optionally contain one or more olefinic bonds, unless otherwise constrained by the definition. Such cycloalkyl groups can include, for example, single ring structures, including cyclopropyl, cyclobutyl, cyclooctyl, cyclopentenyl, and the like, or multiple ring
 30 structures, including adamantanyl, and bicyclo [2.2.1] heptane, or cyclic alkyl groups to which is fused an aryl group, for example, indane, and the like. Spiro and fused ring

structures can also be included. Cycloalkyl groups may be substituted further with one or more substituents selected from alkyl, alkenyl, alkynyl, alkoxy, cycloalkyl, cycloalkenyl, acyl, acylamino, acyloxy, alkoxycarbonylamino, azido, cyano, halogen, hydroxy, oxo, thiocarbonyl, carboxy, carboxyalkyl, arylthio, thiol, alkylthio, aryl, aralkyl, aryloxy, aminosulfonyl, aminocarbonylamino, -NR_fR_q, -NHC(=O)NR_fR_q, -NHC(=O)R_f, -C(=O)NR_fR_q, -O-C(=O)NR_fR_q (wherein R_f and R_q are the same as defined earlier), nitro, heterocyclyl, heteroaryl, heterocyclylalkyl, heteroarylalkyl, or SO₂-R₆ (wherein R₆ is same as defined earlier). Unless otherwise constrained by the definition, cycloalkyl substituents optionally may be substituted further by 1-3 substituents selected from alkyl, carboxy, hydroxy, alkoxy, halogen, CF₃, -NR_fR_q, -C(=O)NR_fR_q, -NHC(=O)NR_fR_q, -OC(=O)NR_fR_q (wherein R_f and R_q are the same as defined earlier), cyano or -SO₂R₆ (where R₆ is same as defined earlier). “Cycloalkylalkyl” refers to alkyl-cycloalkyl group linked through alkyl portion, wherein the alkyl and cycloalkyl are the same as defined earlier.

The term “cycloalkylalkyl” refers to cycloalkyl group linked through alkyl portion, wherein the alkyl having 1 to 6 carbon atoms and cycloalkyl are the same as defined earlier.

“Heteroarylalkyl” refers to alkyl-heteroaryl group linked through alkyl portion, wherein the alkyl and heteroaryl are as defined earlier.

“Heterocyclylalkyl” refers to alkyl-heterocyclyl group linked through alkyl portion, wherein the alkyl and heterocyclyl are as defined earlier.

“Amine,” unless otherwise specified, refers to -NH₂. “Substituted amino” unless otherwise specified, refers to a group -N(R_k)₂ wherein each R_k is independently selected from the group hydrogen provided that both R_k groups are not hydrogen (defined as “amino”), alkyl, alkenyl, alkynyl, aralkyl, cycloalkyl, aryl, heteroaryl, heterocyclyl, heterocyclylalkyl, heteroarylalkyl, acyl, S(O)_mR₆ (wherein m and R₆ is the same as defined above), -C(=R_v)NR_xR_y (wherein R_v is O or S & R_x and R_y are the same as defined earlier) or NHC(=R_v)NR_yR_x (wherein R_v, R_y and R_x are the same as defined earlier). Unless otherwise constrained by the definition, all amino substituents may optionally be further substituted by 1-3 substituents chosen from alkyl, aralkyl, cycloalkyl, aryl, heteroaryl, heterocyclyl, carboxy, -COOR₇ (wherein R₇ is the same as defined earlier), hydroxy, alkoxy, halogen, CF₃, cyano, -C(=R_v)NR_xR_y (wherein R_v is the same as defined

earlier), $-O(C=O)NR_xR_y$, $-OC(=R_v)NR_xR_y$ (wherein R_x , R_y and R_v are the same as defined earlier), $-S(O)_mR_6$ (where R_6 and m is the same as defined above).

“Acyl” refers to $-C(=O)R''$ wherein R'' is selected from hydrogen, alkyl, cycloalkyl, aryl, aralkyl, heteroaryl, heterocyclyl, heteroarylalkyl or heterocyclalkyl.

- 5 The term “thioacyl” refers to $-C(=S)R_4$ wherein R_4 is the same as defined above. “Thiocarbonyl” refers to $-C(=S)H$. “Substituted thiocarbonyl” refers to $-C(=S)R''$, wherein R'' is selected from alkyl, cycloalkyl, aryl, aralkyl, heteroaryl, heterocyclyl, heteroarylalkyl or heterocyclalkyl, amine or substituted amine.

The term “halogen” refers to fluorine, chlorine, bromine or iodine;

- 10 The term “leaving group” refers to groups that exhibit or potentially exhibit the properties of being labile under the synthetic conditions and also, of being readily separated from synthetic products under defined conditions. Examples of leaving groups include, but are not limited to, halogen (*e.g.*, F, Cl, Br, I), triflates, tosylate, mesylates, alkoxy, thioalkoxy, or hydroxy radicals and the like.

- 15 The term “protecting groups” refers to moieties that prevent chemical reaction at a location of a molecule intended to be left unaffected during chemical modification of such molecule. Unless otherwise specified, protecting groups may be used on groups, such as hydroxy, amino, or carboxy. Examples of protecting groups are found in T.W. Greene and P.G.M. Wuts, “Protective Groups in Organic Synthesis”, 2nd Ed., John Wiley and Sons,
20 New York, N.Y.,. The species of the carboxylic protecting groups, amino protecting groups or hydroxy protecting groups employed are not critical, as long as the derivatised moieties/moiety is/are stable to conditions of subsequent reactions and can be removed without disrupting the remainder of the molecule.

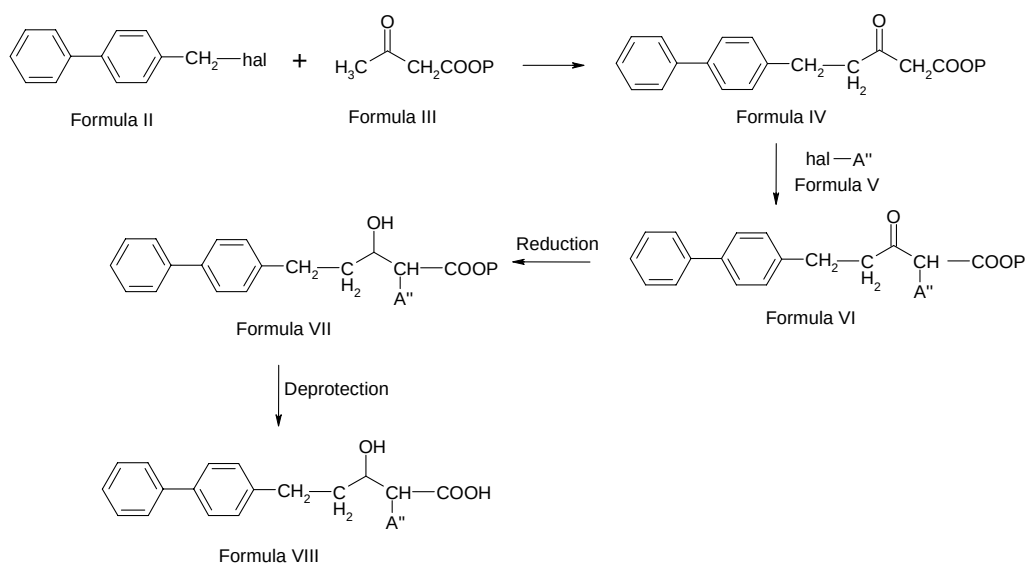
- 25 The compounds of this invention can contain one or more asymmetric carbon atoms and thus may occur as racemic mixtures, enantiomers and diastereomers. These compounds can also exist as conformers/rotamers. All such isomeric forms of these compounds are included in the present invention. Each stereogenic carbon may be of the *R* or *S* configuration. Although the specific compounds exemplified in this application may be depicted in a particular stereochemical configuration, compounds having either the

opposite stereochemistry at any given chiral center or mixtures thereof are envisioned as part of the invention.

The term “*pharmaceutically acceptable salts*” forming part of this invention includes the salts of carboxylic acid moiety, which may be prepared by reacting the compound with appropriate base to provide corresponding base addition salts. Examples of such bases are alkali metal hydroxide including potassium hydroxide, sodium hydroxide and lithium hydroxide; alkaline earth metal hydroxides such as magnesium hydroxide and calcium hydroxide. Further the salts of organic bases such as lysine, arginine, guanidine, ethanolamine, choline and the like; inorganic bases e.g., ammonium or substituted ammonium salts are also included. Wherever appropriate, compounds of the present invention may also form the acid addition salts by treating the said compounds with pharmaceutically acceptable organic and inorganic acids, e.g., hydrohalides such as hydrochloride, hydrobromide, hydroiodide; other mineral acids and their corresponding salts such as sulphate, nitrate, phosphate etc.; and alkyl and mono-arylsulphonates such as ethane sulphonate, toluene sulphonate and benzene sulphonate; and other organic acids and their corresponding salts such as acetate, tartarate, maleate, succinate, citrate etc.

Detailed Description of the Invention

Compounds of the present invention may be prepared by techniques well known in the organic synthesis and familiar to a practitioner ordinarily skilled in art of this invention. In addition, the process described herein may prepare the compounds of the present invention, however that may not be the only means by which the compounds described may be synthesised. Further, the various synthetic steps described herein may be performed in an alternate sequence in order to give the desired compounds.



5

10 Compounds of Formula VIII can be prepared by, for example, following the synthetic route as depicted in Scheme I. Thus a compound of Formula II (wherein hal is Cl, Br or I) can be reacted with a compound of Formula III [wherein P is alkyl (for example, tert-butyl, ethyl or methyl) or aralkyl (or example, benzyl)] to give a compound

15 Formula IV, which on reaction with a compound of Formula V (wherein hal is the same as defined above and A" is aralkyl, heterocyclylalkyl, heteroarylalkyl or cycloalkylalkyl) can form a compound of Formula VI. A compound of Formula VI on reduction can form a compound of Formula VII, which on deprotection can yield a compound of Formula VIII.

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 the presence of a base or a combination thereof, for example, sodium hydride, butyl lithium or lithiumdiisopropylamide in an organic solvent, for example, tetrahydrofuran, dimethylformamide, dioxane or diethylether.

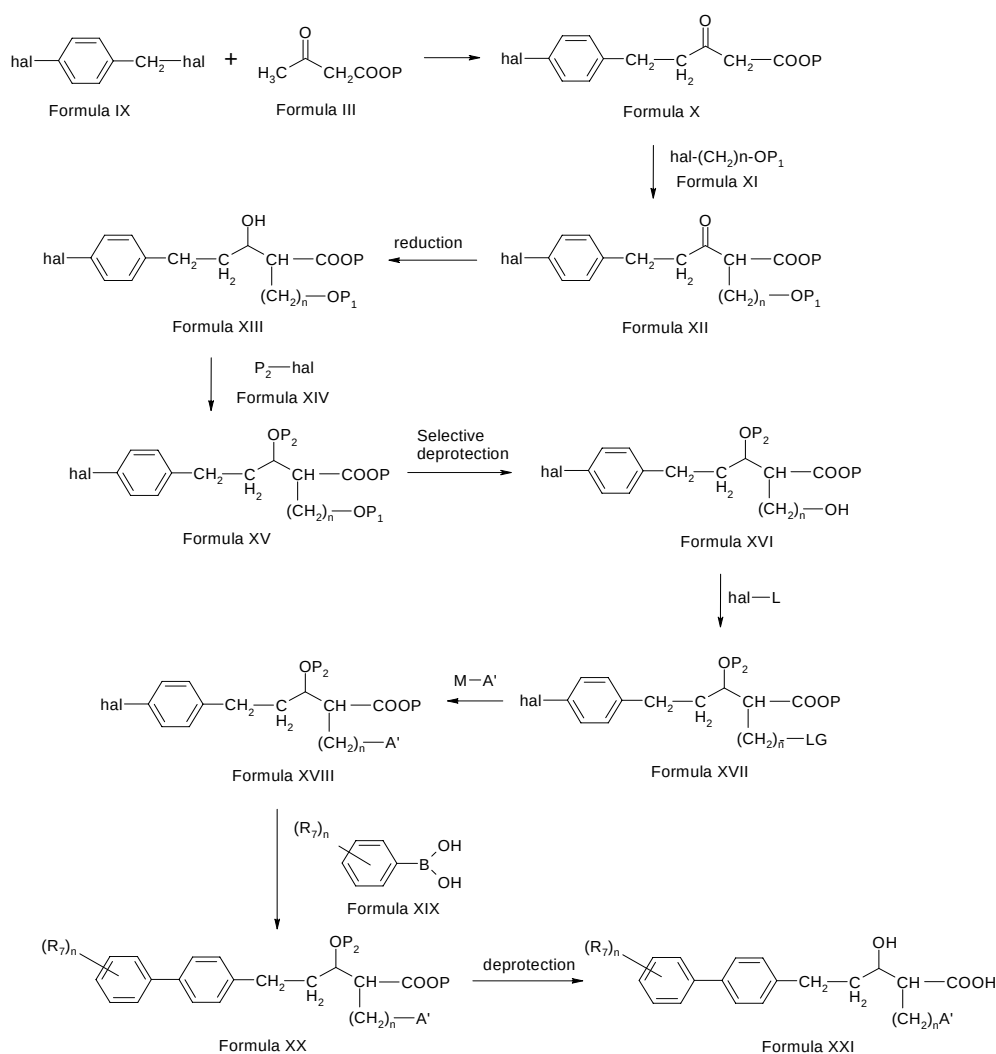
The reaction of a compound of Formula IV with a compound of Formula V to give a compound of Formula VI can be carried out in the presence of a base for example, potassium tert-butoxide, sodium (m)ethoxide, sodium hydride, lithium diisopropylamide, butyl lithium or lithium/sodium/potassium hexamethyldisilazide, optionally in the presence of a catalyst, for example, tetrabutylammonium iodide or tetrabutylammonium bromide, in an appropriate organic solvent for example, *t*-butanol, ethanol, tetrahydrofuran, dimethylformamide, diethylether or dioxane.

25

The compound of Formula VI undergoes reduction to give a compound of Formula VII in the presence of reducing agent, for example, sodium borohydride or lithium borohydride in organic solvent, for example, methanol, ethanol, propanol, isopropylalcohol and/or tetrahydrofuran.

- 5 The hydrolysis of a compound of Formula VII to give a compound of Formula VIII, when P is *t*-butyl can be carried out with acids, for example, trifluoroacetic acid or hydrochloric acid, in an organic solvent or a solvent system including, for example, dichloromethane, dichloroethane, THF or dioxane in water.

Scheme II



A compound of Formula XXI can be prepared, for example, by following the synthetic route as depicted, for example, in Scheme II. Thus a compound of Formula IX (wherein hal is the same as defined earlier) on reaction with a compound of Formula III (wherein P is the same as defined earlier) can give a compound of Formula X, which can be reacted with a compound of Formula XI (wherein hal and n are the same as defined earlier and P₁ is silyl protecting group for example, tert-butyldimethylsilane, tert-butyldiphenylsilane or triisopropylsilane to give a compound of Formula XII, which can undergo reduction to give a compound of Formula XIII. The compound of Formula XIII on reaction with a compound of Formula XIV [wherein P₂ is aralkyl (for example, benzyl, 4-methoxybenzyl or 2,4,6-trimethoxybenzyl) or heterocyclyl (for example, tetrahydropyranyl)] can form a compound of Formula XV, which can undergo selective deprotection to form a compound of Formula XVI, which can then be converted to a compound of Formula XVII (wherein LG is a leaving group such as mesyl, tosyl or triflyl or a halide (hal) as defined earlier) by reaction either with a compound of Formula L-hal (wherein L is methanesulphonyl, p-toluenesulphonyl and hal is the same as defined earlier), by reaction with triflic anhydride or by reaction with triphenylphosphine and a halide source such as carbon tetrabromide or iodine. A compound of Formula XVII can be reacted with a compound of Formula M-A' (wherein A' is aryl, heteroaryl, heterocyclyl or cycloalkyl and M is metal for example, potassium, lithium or sodium) or by reaction of A' in the presence of a base to yield a compound of Formula XVIII. The compound of Formula XVIII can be reacted with a compound of Formula XIX (wherein n is an integer from 1 to 5 and R₇ is hydrogen, halogen (F, Cl, Br, I), hydroxy, -COOH, -COOR₄ (wherein R₄ is the same as defined earlier), alkyl, alkenyl, alkynyl, cycloalkyl, alkoxy, alkenyloxy, alkynyloxy, aryloxy, heterocyclyloxy, heteroaryloxy, cycloalkyloxy, acyl, thioacyl, cyano, nitro, amino, -CHO, -OCF₃, -CF₃, -SCF₃, -NR₄R₅, -C(=Y)NR₄R₅, -NHC(=Y)R₄, -NHC(=Y)NR₅R_x, -NHC(=O)OR₄, -NH₂SO₂R₄, (SO)_mR₄ (wherein R₄, R₅, R_x, Y and m are the same as defined earlier), aryl, heterocyclyl, heteroaryl, heterocyclalkyl or heteroarylalkyl which may optionally be substituted further) to form a compound of Formula XX, which can be deprotected to form a compound of Formula XXI.

The reaction of a compound of Formula IX with a compound of Formula III to give a compound of Formula X can be carried out similarly to the reaction of a compound of Formula II and a compound of Formula III to yield a compound of Formula IV.

The reaction of a compound of Formula X with a compound of Formula XI to give a compound of Formula XII can be carried out similarly to the reaction of a compound of Formula IV with a compound of Formula V to give a compound of Formula VI.

The reduction of a compound of Formula XII to give a compound of Formula XIII
5 can be carried out similarly to the reduction of a compound of Formula VI to give a compound of Formula VII.

The reaction of a compound of Formula XIII with a compound of Formula XIV to give a compound of Formula XV can be carried out in the presence of Lewis acid, for example, boron trifluoride, triflic acid, camphor sulphonic acid, pyridinium p-
10 toluenesulphonate or trityl perchlorate, in an organic solvent, for example, tetrahydrofuran, dimethylformamide, diethyl ether or dioxane.

The selective deprotection of a compound of Formula XV to give a compound of Formula XVI can be carried out with deprotecting agents, for example, tetrabutylammonium fluoride or potassium fluoride, in an organic solvent, for example,
15 tetrahydrofuran, dimethylformamide, diethyl ether or dioxane.

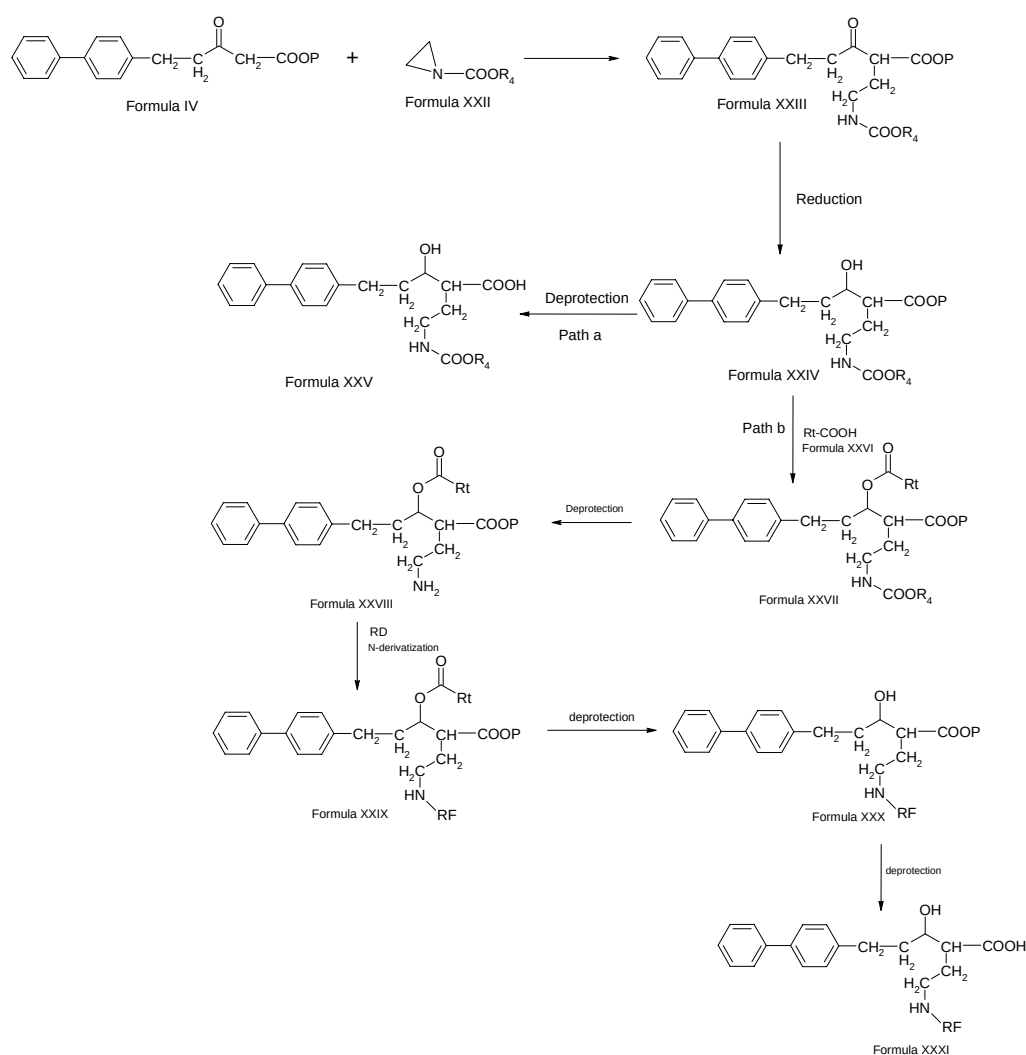
A compound of Formula XVI can be reacted with a compound of Formula L-hal, triflic anhydride or by reaction with triphenylphosphine and a halide source such as carbon tetrabromide or iodine to give a compound of Formula XVII, optionally in the presence of a base, for example, triethylamine, pyridine, N-methylmorpholine or
20 diisopropylethylamine, in an organic solvent, for example, dichloromethane, dichloroethane, or tetrahydrofuran.

The reaction of a compound of Formula XVII with a compound of Formula M-A' to yield a compound of Formula XVIII can be carried out in an organic solvent, for example, tetrahydrofuran, dimethyl sulphoxide, dimethylformamide, acetonitrile, dioxane,
25 dimethylacetamide. Alternately, the reaction of a compound of Formula XVII with a compound of Formula A' to yield a compound of Formula XVIII can be carried out in the presence of a base, for example, sodium hydride, potassium tert-butoxide, sodium (m)ethoxide, in an organic solvent, for example, tetrahydrofuran, dimethyl sulphoxide, dimethylformamide, acetonitrile, dioxane, dimethylacetamide.

The reaction of a compound of Formula XVIII with a compound of Formula XIX can be carried out in the presence of a metal catalyst such as tetrakis(triphenylphosphine) palladium (0), tetrakis(tricyclohexylphosphine) palladium (0), tetrakis(tri-tert-butylphosphine) palladium (0) or palladium acetate and triphenylphosphine, in the presence of a base, such as potassium carbonate or cesium carbonate, in an organic solvent, such as toluene, dimethyl sulphoxide, dimethylformamide, tetrahydrofuran, dioxane or diethyl ether.

The deprotection of a compound of Formula XX to give a compound of Formula XXI can be carried out similarly as that of a compound of Formula VII to give a compound of Formula VIII.

Scheme III



A compound of Formulae XXV and XXXI can be prepared, for example, by following the synthetic route as depicted., for example, in Scheme III. Thus a compound of Formula IV (wherein P is the same as defined earlier) can be reacted with a compound of Formula XXII (wherein R₄ is the same as defined earlier) to give a compound of

5 Formula XXIII,

Path a: which on reduction can give a compound of Formula XXIV, which can be further deprotected to yield a compound of Formula XXV, or

Path b: which on reaction with a compound of Formula XXVI (wherein R_t is alkyl, aryl, cycloalkyl, aralkyl, heterocyclalkyl or heteroarylalkyl) gives a compound of Formula
10 XXVII, which can undergo deprotection to give a compound of Formula XXVIII, which can undergo N-derivatization with a compound of Formula RD (wherein RD is R₄COhal, halCOOR₄, R₄SO₂hal or (R₄)N=C(=Y) wherein Y is O or S) to give a compound of Formula XXIX (wherein RF is R₄CO-, R₄SO₂-, R₄OCO- or (R₄)NH-C(=Y)-), which can undergo deprotection to give a compound of Formula XXX, which can undergo further
15 deprotection to give a compound of Formula XXXI.

The reaction of a compound of Formula IV with a compound of Formula XXII to give a compound of Formula XXIII can be carried out in the presence of a base, for example, potassium tert-butoxide, sodium hydride, sodium (m)ethoxide, lithium diisopropylamide, and/or butyl lithium, in an organic solvent, for example,
20 tetrahydrofuran, dimethylformamide, diethyl ether or dioxane.

The reduction of a compound of Formula XXIII to give a compound of Formula XXIV can be carried out similarly to the reduction of a compound of Formula VI to give a compound of Formula VII.

The deprotection of a compound of Formula XXIV (path *a*) to give a compound of
25 Formula XXV can be carried out similarly as that of a compound of Formula VII to give a compound of Formula VIII.

The reaction of a compound of Formula XXIV (path *b*) with a compound of Formula XXVI to give a compound of Formula XXVII can be carried out using coupling agents, such as EDCI or DCC, in the presence of base, such as dimethylaminopyridine, N-

methyldimorpholine or diisopropylethylamine, in an organic solvent, such as dichloromethane, dichloroethane, chloroform and carbon tetrachloride.

The deprotection of a compound of Formula XXVII to give a compound of Formula XXVIII can be carried out in the presence of a deprotecting agent, for example,
 5 palladium on carbon in presence of hydrogen gas, or palladium on carbon with a source of hydrogen gas, for example, ammonium formate, cyclohexene or formic acid.

The N-derivatization of a compound of Formula XXVIII with a compound of Formula RD (wherein RD is R_4COhal or $halCOOR_4$) to give a compound of Formula XXIX (wherein RF is R_4CO- , R_4OCO-) can be carried out in the presence of a base, for
 10 example, pyridine, N-methyldimorpholine, N-ethyldiisopropylamine, triethylamine or potassium carbonate.

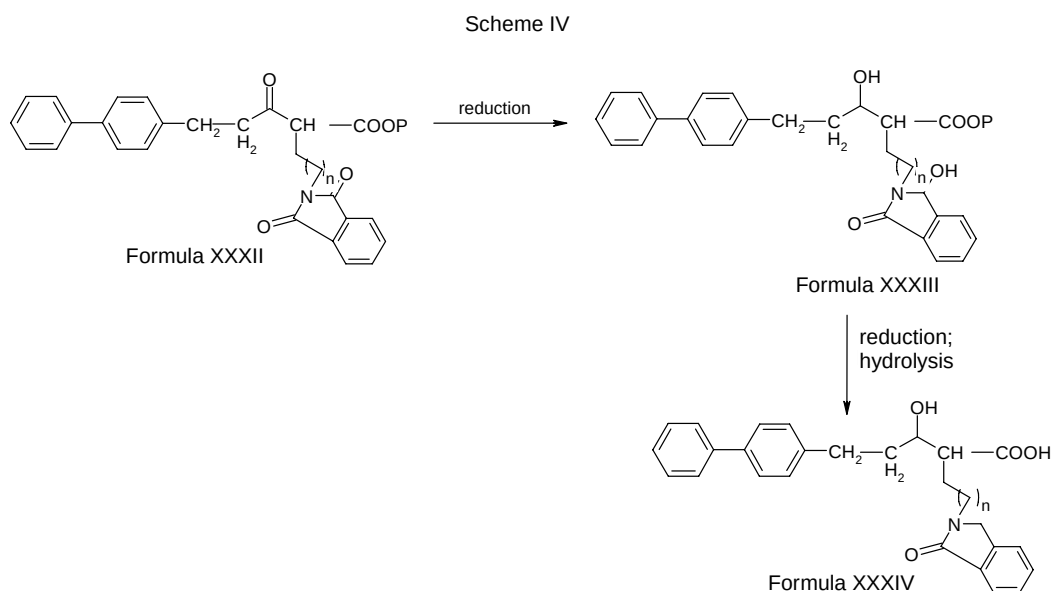
The N-derivatization of a compound of Formula XXVIII with a compound of Formula RD (wherein RD is R_4SO_2hal) to give a compound of Formula XXIX (wherein RF is R_4SO_2-) can be carried out in the presence of a base, for example, triethylamine, N-
 15 ethyldiisopropylamine, N-methyldimorpholine or pyridine, in an organic solvent, for example, dichloromethane, dichloroethane, carbon tetrachloride or chloroform.

The N-derivatization of a compound of Formula XXVIII with a compound of Formula RD (wherein RD is $(R_4)N=C(=Y)$) to give a compound of Formula XXIX (wherein RF is $(R_4)NH-C(=Y)-$) can be carried out optionally in the presence of a base, for
 20 example, triethylamine, N-ethyldiisopropylamine, N-methyldimorpholine or pyridine, in an organic solvent for example, dichloromethane, dichloroethane, carbon tetrachloride or chloroform.

The deprotection of the secondary hydroxyl protecting group such as acyl group, of a compound of Formula XXIX to give a compound of Formula XXX can be carried out in
 25 presence of a base, for example, lithium hydroxide, sodium hydroxide, potassium hydroxide, in an organic solvent, for example, methanol, tetrahydrofuran, water or mixtures thereof.

The deprotection of a compound of Formula XXX to give a compound of Formula XXXI can be carried out with acids, for example, trifluoroacetic acid or hydrochloric acid,

in an organic solvent or a solvent system, for example, dichloromethane, chloroform, dichloroethane, THF or dioxane in water.



5 Compounds of Formula XXXIV can be prepared, for example, by following the synthetic route as depicted, for example, in Scheme IV. Thus a compound of Formula XXXII can undergo reduction to give a compound of Formula XXXIII, which can undergo ionic hydrogenation wherein C=O is reduced to CH₂ followed by hydrolysis to give a compound of Formula XXXIV.

10 The compound of Formula XXXII can undergo reduction to give a compound of Formula XXXIII in the presence of reducing agent, for example, sodium borohydride or lithium borohydride in organic solvent, for example, methanol, ethanol, propanol, isopropylalcohol and/or tetrahydrofuran.

15 The conversion of a compound of Formula XXXIII to a compound of Formula XXXIV can be carried out under ionic hydrogenation conditions wherein the C=O is reduced to CH₂ followed by in-situ hydrolysis of the ester (when P is t-butyl). Ionic hydrogenation conditions that may be carried out include reaction of a compound of Formula XXXIII with sodium borohydride or triethylsilane with acids, for example, trifluoroacetic acid in an organic solvent, for example, dichloromethane, dichloroethane

or THF, and in-situ the acid-sensitive *t*-butyl group can be removed to provide a compound of Formula XXXIV.

The following illustrative compounds were prepared following Schemes I, II, III or IV described above:

5-Biphenyl-4-yl-3-hydroxy-2-[2-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)ethyl]pentanoic acid (Compound No. 1),

2-(2-{[(Benzyloxy)carbonyl]amino}ethyl)-5-biphenyl-4-yl-3-hydroxypentanoic acid (Compound No. 11),

10 5-Biphenyl-4-yl-3-hydroxy-2-{2-[(phenylacetyl)amino]ethyl}pentanoic acid (Compound No. 45),

5-Biphenyl-4-yl-3-hydroxy-2-[2-(1-oxophthalazin-2(1*H*)-yl)ethyl]pentanoic acid (Compound No. 47),

15 5-Biphenyl-4-yl-3-hydroxy-2-[2-(2'-oxospiro[cyclopropane-1,3'-indol]-1'(2'*H*)-yl)ethyl]pentanoic acid (Compound No. 49),

3-Hydroxy-2-[2-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)ethyl]-5-[4'-(trifluoromethyl)biphenyl-4-yl]pentanoic acid (Compound No. 59),

5-(3',4'-Difluorobiphenyl-4-yl)-3-hydroxy-2-[2-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)ethyl]pentanoic acid (Compound No. 60),

20 3-Hydroxy-5-(4'-methoxybiphenyl-4-yl)-2-[2-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)ethyl]pentanoic acid (Compound No. 64),

5-(4'-Chlorobiphenyl-4-yl)-3-hydroxy-2-[2-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)ethyl]pentanoic acid (Compound No. 65),

25 3-Hydroxy-5-[4-(6-methoxypyridin-3-yl)phenyl]-2-[2-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)ethyl]pentanoic acid (Compound No. 67),

3-Hydroxy-5-(4'-methylbiphenyl-4-yl)-2-[2-(5-methyl-1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]pentanoic acid (Compound No. 68),

5-(4'-Chlorobiphenyl-4-yl)-3-hydroxy-2-[2-(5-methyl-1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]pentanoic acid (Compound No. 69),

5 3-Hydroxy-2-[2-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)ethyl]-5-[4'-(trifluoromethoxy)biphenyl-4-yl]pentanoic acid (Compound No. 70),

5-(4'-Fluorobiphenyl-4-yl)-3-hydroxy-2-[2-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)ethyl]pentanoic acid (Compound No. 71),

3-hydroxy-5-(4'-methylbiphenyl-4-yl)-2-[2-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)ethyl]pentanoic acid (Compound No. 72),
10

5-(4'-Cyanobiphenyl-4-yl)-3-hydroxy-2-[2-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)ethyl]pentanoic acid (Compound No. 73),

5-(4'-Fluorobiphenyl-4-yl)-3-hydroxy-2-[2-(5-methyl-1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]pentanoic acid (Compound No. 74),

15 3-Hydroxy-5-[4-(6-methoxypyridin-3-yl)phenyl]-2-[2-(5-methyl-1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]pentanoic acid (Compound No. 75),

5-(4'-Ethylbiphenyl-4-yl)-3-hydroxy-2-[2-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)ethyl]pentanoic acid (Compound No. 76),

3-Hydroxy-2-[2-(5-methyl-1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-5-[4'-(trifluoromethyl)biphenyl-4-yl]pentanoic acid (Compound No. 77),
20

5-Biphenyl-4-yl-3-hydroxy-2-[2-(1-oxo-4-phenyl-4a,8a-dihydrophthalazin-2(1*H*)-yl)ethyl]pentanoic acid (Compound No. 84).

5-Biphenyl-4-yl-3-hydroxy-2-[2-(3-oxo-2,3-dihydro-4*H*-1,4-benzoxazin-4-yl)ethyl]pentanoic acid (Compound No. 85),

5-Biphenyl-4-yl-2-{2-[(3a*R*,7a*S*)-1,3-dioxo-1,3,3a,4,7,7a-hexahydro-2*H*-isoindol-2-yl]ethyl}-3-hydroxypentanoic acid (Compound No. 86),

5-Biphenyl-4-yl-2-(2-{[(4-fluorophenyl)sulfonyl]amino}ethyl)-3-hydroxypentanoic acid (Compound No. 87),

5 5-Biphenyl-4-yl-2-(2-{[(3-fluorophenyl)acetyl]amino}ethyl)-3-hydroxypentanoic acid (Compound No. 88),

5-Biphenyl-4-yl-2-{2-[(4-fluorobenzoyl)amino]ethyl}-3-hydroxypentanoic acid (Compound No. 89),

10 5-Biphenyl-4-yl-3-hydroxy-2-[2-(5-methyl-1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]pentanoic acid (Compound No. 90),

5-Biphenyl-4-yl-3-hydroxy-2-[2-(1-oxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]pentanoic acid (Compound No. 91).

5-Biphenyl-4-yl-2-[2-({[(4-fluorophenyl)amino]carbonyl}amino)ethyl]-3-hydroxypentanoic acid (Compound No. 92),

15 5-Biphenyl-4-yl-2-[2-(4,4-dimethyl-2,6-dioxopiperidin-1-yl)ethyl]-3-hydroxypentanoic acid (Compound No. 93),

5-Biphenyl-4-yl-2-[2-(7,9-dioxo-8-azaspiro[4.5]dec-8-yl)ethyl]-3-hydroxypentanoic acid (Compound No. 94),

20 5-Biphenyl-4-yl-3-hydroxy-2-[2-(2-oxo-1,3-benzoxazol-3(2*H*)-yl)ethyl]pentanoic acid (Compound No. 96),

2-[2-(5-*tert*-Butyl-1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxy-5-[4-(6-methoxypyridin-3-yl)phenyl]pentanoic acid (Compound No. 97),

5-Biphenyl-4-yl-2-[2-(5,6-dichloro-1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxypentanoic acid (Compound No. 102),

5-Biphenyl-4-yl-2-[2-(2,4-dioxo-1,4-dihydroquinazolin-3(2*H*)-yl)ethyl]-3-hydroxypentanoic acid (Compound No. 103),

5-Biphenyl-4-yl-2-[2-(1,3-dioxo-1,3-dihydro-2*H*-pyrrolo[3,4-*c*]pyridin-2-yl)ethyl]-3-hydroxypentanoic acid (Compound No. 104),

5 2-[2-(5-*tert*-Butyl-1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-5-(3',4'-difluorobiphenyl-4-yl)-3-hydroxypentanoic acid (Compound No. 105),

5-Biphenyl-4-yl-2-[2-(5-*tert*-butyl-1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxypentanoic acid (Compound No. 121), and

10 5-Biphenyl-4-yl-3-hydroxy-2-[2-(1-oxo-1,3-dihydro-2*H*-isoindol-2-yl) butyl]pentanoic acid (Compound No. 124).

In the above schemes, where specific bases, acids, solvents, condensing agents, reducing agent, deprotecting agent, hydrolyzing agents, metal catalysts etc., are mentioned, it is to be understood that other acids, bases, solvents, condensing agents, reducing agent, deprotecting agent, hydrolyzing agents, metal catalysts etc., known to those skilled in the art may also be used. Similarly, the reaction temperature and duration of the reactions may be adjusted according to the requirements that arise during the process.

20 The compounds prepared by above Schemes I to IV may contain one or more asymmetric carbon atoms and were separated into diastereomer pairs or single diastereomers by preparative thin layer chromatography and/or by HPLC, using an achiral or chiral column as required.

The following illustrative compounds were separated into diastereomer pairs or single diastereomers:

25 (2*R*,3*S* + 2*S*,3*R*)-2-[2-(5-*tert*-Butyl-1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-5-(4'-fluorobiphenyl-4-yl)-3-hydroxypentanoic acid (Compound No. 106),

(2R,3S + 2S,3R)-2-[2-(5-*tert*-Butyl-1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxy-5-[4'-(trifluoromethyl)biphenyl-4-yl]pentanoic acid (Compound No. 107),

(2R,3R + 2S,3S)-2-[2-(5-*tert*-Butyl-1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-5-(4'-fluorobiphenyl-4-yl)-3-hydroxypentanoic acid (Compound No. 108),

5 (2R,3R + 2S,3S)-2-[2-(5-*tert*-Butyl-1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxy-5-[4'-(trifluoromethyl)biphenyl-4-yl]pentanoic acid (Compound No. 109),

(2R,3R + 2S,3S)-2-[2-(5-*tert*-Butyl-1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxy-5-(4'-methylbiphenyl-4-yl)pentanoic acid (Compound No. 113),

10 (2R,3S + 2S,3R)-2-[2-(5-*tert*-Butyl-1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxy-5-(4'-methylbiphenyl-4-yl)pentanoic acid (Compound No. 114),

(2R,3R + 2S,3S)-2-[2-(5-*tert*-Butyl-1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxy-5-(4'-methoxybiphenyl-4-yl)pentanoic acid (Compound No. 115),

(2R,3R + 2S,3S)-2-[2-(5-*tert*-Butyl-1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-5-(4'-chlorobiphenyl-4-yl)-3-hydroxypentanoic acid (Compound No. 116),

15 (2R,3S + 2S,3R)-2-[2-(5-*tert*-Butyl-1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-5-(4'-chlorobiphenyl-4-yl)-3-hydroxypentanoic acid (Compound No. 117),

(2R,3S + 2S,3R)-2-[2-(5-*tert*-Butyl-1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxy-5-(4'-methoxybiphenyl-4-yl)pentanoic acid (Compound No. 118),

20 (2R,3S)-3-Hydroxy-5-[4-(6-methoxypyridin-3-yl)phenyl]-2-[2-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)ethyl]pentanoic acid (Compound No. 133),

(2S,3R)-3-Hydroxy-5-[4-(6-methoxypyridin-3-yl)phenyl]-2-[2-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)ethyl]pentanoic acid (Compound No. 134),

(2R,3R)-3-Hydroxy-5-[4-(6-methoxypyridin-3-yl)phenyl]-2-[2-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)ethyl]pentanoic acid (Compound No. 135), and

(2S,3S)-3-Hydroxy-5-[4-(6-methoxypyridin-3-yl)phenyl]-2-[2-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)ethyl]pentanoic acid (Compound No.136).

Examples set forth demonstrate the general synthetic procedure for the preparation of representative compounds. The examples are provided to illustrate particular aspects of the disclosure

EXPERIMENTAL

GENERAL PROCEDURE

Synthesis of 3-(2-bromoethyl)-1,2,3-benzotriazin-4(3*H*)-one

To a solution of the compound 1,2,3-benzotriazin-4(3*H*)-one (500 mg) (commercially available) in dimethylformamide (13 ml) was added anhydrous potassium carbonate (2.8 g) and stirred for 20 minutes. To it was added dibromoethane (2 g) and stirred the reaction mixture first at room temperature for few minutes and then at 60 °C for 2 hours. The solid thus obtained was filtered and the filtrate was concentrated under reduced pressure. The residue thus obtained was diluted with water and extracted with ethylacetate. The organic layer was separated, washed with water and brine and dried over anhydrous sodium sulphate. The solvent was evaporated under reduced pressure and the residue thus obtained was purified by column chromatography using 20% ethyl acetate in hexane as eluant to furnish the title compound (590 mg).

Synthesis of 4-(bromomethyl)biphenyl

Carbon tetrabromide (8.99 g) and triphenylphosphine (7.11 g) were added to a stirred solution of biphenyl-4-yl-methanol (5.00 g) in dichloromethane (100 ml) at room temperature and stirred the reaction mixture for approximately 2 hours at the same temperature. The solvent was evaporated under reduced pressure and the residue thus obtained was purified by column chromatography using 5% diethylether in hexane as eluant to furnish the title compound (6.37 g).

Scheme I, procedure:

Example 1: Synthesis of 5-biphenyl-4-yl-3-hydroxy-2-[2-(4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]-pentanoic acid (Compound No. 1)

Step 1: Synthesis of *tert*-butyl 5-biphenyl-4-yl-3-oxopentanoate

A solution of *tert*-butyl acetoacetate (7.2 g) in tetrahydrofuran (80 ml) was added
 5 to a stirred solution of sodium hydride (1.33 g) in tetrahydrofuran (60 ml) at 0 °C under
 nitrogen atmosphere. The reaction mixture was stirred for 10 minutes followed by the
 addition of *n*-butyl lithium (23 ml, 2.5 M solution in hexane) dropwise over 10 minutes.
 The resulting reaction mixture was stirred for 10 minutes. A solution of 4-(bromomethyl)
 biphenyl (12.5 g) in tetrahydrofuran (60 ml) was added over 10 minutes and the resulting
 10 solution was stirred at 0 °C for approximately 2 hours. To resulting mixture was added
 hydrochloric acid (6 M, 15 ml) followed by extracting the mixture with diethyl ether. The
 organic layers were combined, washed with water and brine and dried over anhydrous
 sodium sulphate. The solvent was evaporated under reduced pressure and the residue thus
 obtained was purified by silica gel column chromatography using 8% ethyl acetate-hexane
 15 as eluant to furnish the title compound (7.5 g).

Step 2: Synthesis of *tert*-butyl 5-biphenyl-4-yl-3-oxo-2-[2-(4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]pentanoate

To a solution of the compound (300 mg) obtained from step 1 above in dry
 tetrahydrofuran (4 ml) and *tert*-butanol (4 ml) at 0 °C was added potassium *tert*-butoxide
 20 (104 mg) and stirred for 20 minutes. To the resulting reaction mixture was added 3-(2-
 bromoethyl)-1,2,3-benzotriazin-4(3H)-one (235 mg) and tetrabutylammonium iodide (349
 mg) and the mixture was further stirred for 30 minutes at 0 °C, followed by stirring at room
 temperature for 30 minutes and finally at 80 °C for about 5-6 hours. The solvent was
 evaporated under reduced pressure and the residue thus obtained was diluted with water
 25 and extracted with ethyl acetate. The organic layer was washed with water and brine,
 dried over anhydrous sodium sulphate and filtered. The solvent was evaporated under
 reduced pressure and the residue thus obtained was purified by column chromatography
 using 20% ethyl acetate in hexane as eluant to furnish the title compound (240 mg).

**Step 3: Synthesis of *tert*-butyl 5-biphenyl-4-yl-3-hydroxy-2-[2-(4-oxo-1,2,3-
 30 benzotriazin-3(4H)-yl)ethyl]pentanoate**

To a solution of the compound (240 mg) obtained from step 2 above in methanol (4-5 ml) at $-10\text{ }^{\circ}\text{C}$ was added sodium borohydride (44 mg). The reaction mixture was stirred for 2 hours at $-10\text{ }^{\circ}\text{C}$ to $-2\text{ }^{\circ}\text{C}$. The solvent was evaporated under reduced pressure and the residue thus obtained was taken in saturated ammonium chloride and extracted with ethyl acetate. The organic layer was washed with water and brine and dried over anhydrous sodium sulphate and concentrated under reduced pressure. The residue thus obtained was purified by column chromatography using 30% ethyl acetate in hexane as eluant to furnish the title compound (100 mg).

Step 4: Synthesis of 5-biphenyl-4-yl-3-hydroxy-2-[2-(4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]pentanoic acid

To a solution of the compound (100 mg) obtained from step 3 above in dichloromethane (2 ml) at $0\text{ }^{\circ}\text{C}$ was added trifluoroacetic acid (8 ml) and stirred the reaction mixture for about 2-3 hours and then at room temperature for 3 hours. The solvent and excess reagents were evaporated under reduced pressure and the residue thus obtained was purified by preparative thin layer chromatography (eluant -ethyl acetate) to furnish the title compound (40 mg).

Mass (m/z): 444.1 ($M^{+} + 1$).

The following illustrative analogues were prepared analogously:

5-Biphenyl-4-yl-3-hydroxy-2-[2-(1-oxophthalazin-2(1H)-yl)ethyl]pentanoic acid
(Compound No. 47),

5-Biphenyl-4-yl-3-hydroxy-2-[2-(2'-oxospiro[cyclopropane-1,3'-indol]-1'(2H)-yl)ethyl]pentanoic acid (Compound No. 49),

5-Biphenyl-4-yl-3-hydroxy-2-[2-(1-oxo-4-phenyl-4a,8a-dihydrophthalazin-2(1H)-yl)ethyl]pentanoic acid (Compound No. 84).

5-Biphenyl-4-yl-3-hydroxy-2-[2-(3-oxo-2,3-dihydro-4H-1,4-benzoxazin-4-yl)ethyl]pentanoic acid (Compound No. 85),

5-Biphenyl-4-yl-2-{2-[(3aR,7aS)-1,3-dioxo-1,3,3a,4,7,7a-hexahydro-2H-isoindol-2-yl]ethyl}-3-hydroxypentanoic acid (Compound No. 86),

5-Biphenyl-4-yl-3-hydroxy-2-[2-(5-methyl-1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]pentanoic acid (Compound No. 90),

5-Biphenyl-4-yl-2-[2-(4,4-dimethyl-2,6-dioxopiperidin-1-yl)ethyl]-3-hydroxypentanoic acid (Compound No. 93),

5 5-Biphenyl-4-yl-2-[2-(7,9-dioxo-8-azaspiro[4.5]dec-8-yl)ethyl]-3-hydroxypentanoic acid (Compound No. 94),

5-Biphenyl-4-yl-3-hydroxy-2-[2-(2-oxo-1,3-benzoxazol-3(2*H*)-yl)ethyl]pentanoic acid (Compound No. 96)

5-Biphenyl-4-yl-2-[2-(5,6-dichloro-1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-
10 hydroxypentanoic acid (Compound No. 102),

5-Biphenyl-4-yl-2-[2-(2,4-dioxo-1,4-dihydroquinazolin-3(2*H*)-yl)ethyl]-3-hydroxypentanoic acid (Compound No. 103),

5-Biphenyl-4-yl-2-[2-(1,3-dioxo-1,3-dihydro-2*H*-pyrrolo[3,4-*c*]pyridin-2-yl)ethyl]-3-hydroxypentanoic acid (Compound No. 104),

15 and

5-Biphenyl-4-yl-2-[2-(5-*tert*-butyl-1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxypentanoic acid (Compound No. 121).

Scheme II, procedure:

20 Example 2: Synthesis of 5-(4'-chlorobiphenyl-4-yl)-2-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxypentanoic acid

Step 1: Synthesis of 5-(4-bromo-phenyl)-3-oxo-pentanoic acid *tert*-butyl ester

tert-Butyl acetoacetate (23.8 ml) was added dropwise over 15 minutes to a stirred suspension of sodium hydride (8.9 mg) in tetrahydrofuran at 0 °C under nitrogen
25 atmosphere. After stirring for 20 minutes *n*-butyl lithium in hexane (111 ml) was added then stirring continued for a further ten minutes. The resulting solution was treated

dropwise with a solution of 4-bromobenzyl bromide (14.19 g) in tetrahydrofuran (100 ml) and then warmed to room temperature. The reaction was stirred for 40 minutes at room temperature and then quenched with HCl (6M, 5 ml). The resulting mixture was extracted with diethyl ether. The organic phases were combined, washed with brine and dried over anhydrous sodium sulphate. The solvent was evaporated under reduced pressure. The residue was thus obtained was purified via flash chromatography using 5% ethyl acetate in hexane as eluant to furnish the title compound (37 g).

Step 2: Synthesis of 1,1-dimethylethyl 2-(2-((1,1-dimethylethyl) (dimethyl) silyl)oxy)ethyl)-5-(4-bromophenyl)-3-oxopentanoate

A solution of the compound (9.7 g) obtained from step 1 above in dimethylformamide (25 ml) was added dropwise over 20 minutes to a stirred suspension of sodium hydride (1.42 g) in dimethylformamide (25 ml) at 0 °C under nitrogen atmosphere and stirred the reaction mixture for 20 minutes. To it was added (2-bromoethoxy)-t-butyldimethylsilane (8.50 g) dropwise over 20 minutes at 0 °C then the reaction mixture was heated to 70 °C for about 3-4 hour. On cooling to room temperature the reaction was quenched with water. The residue was partitioned between saturated aqueous ammonium chloride solution and dichloromethane. The organic phases were combined, washed with water and brine, dried over anhydrous sodium sulphate and concentrated under reduced pressure. The residue thus obtained was purified by column chromatography using 8% ethyl acetate in hexane as eluant to furnish the title compound (9.5 g).

Step 3: Synthesis of 1,1-dimethylethyl 2-(2-((1,1-dimethylethyl) (dimethyl)silyl)oxy)ethyl)-3-hydroxy-5-(bromophenyl)pentanoate

Sodium borohydride (0.46 g) was added portion wise to a stirred solution of the compound (4.2 g) obtained from step 2 above in methanol (50 ml) at 0 °C under nitrogen atmosphere and stirred the reaction mixture for approximately 2 hours. The mixture was quenched with saturated aqueous ammonium chloride solution (100 ml) and extracted with diethyl ether. The organic layers were combined, washed with water and brine, dried over anhydrous sodium sulphate and concentrated under reduced pressure. The residue thus obtained was purified by column chromatography using 25% ethyl acetate in hexane as eluant to furnish the title compound (3.7 g).

Step 4: Synthesis of 1,1-dimethylethyl 2-(2-((1,1-dimethylethyl)(dimethylsilyl)oxy)ethyl)-5-(4-bromophenyl)-3-([4-(methoxy) phenyl]methyl)oxy)pentanoate

Boron trifluoride etherate (5.0 ml) was added to a stirred solution of the compound (4.0 g) obtained from step 3 above and 4-methoxybenzyl 2,2,2-trichloroethanimidoate (3.26 g) in tetrahydrofuran (40 ml) at 0 °C under nitrogen atmosphere. The reaction was allowed to warm to room temperature at which stirring was continued for 2 hour. The solvent was evaporated under reduced pressure and the residue thus obtained was purified by column chromatography using 20% ethyl acetate in hexane as eluant to furnish the title compound (3.8 g).

Step 5: Synthesis of 1,1-dimethylethyl 2-(2-hydroxyethyl)-5-(4-bromophenyl)-3-([4-(methoxy)phenyl]methyl)oxy)pentanoate

A solution of tetra-n-butylammonium fluoride (0.45 ml) was added dropwise over 15 minutes to a stirred solution of the compound (200 mg) obtained from step 4 above in tetrahydrofuran (5 ml) at 0 °C under nitrogen atmosphere. The reaction mixture was allowed to warm to room temperature at which stirring was continued for 2 hour. The volatiles were evaporated under reduced pressure and the residue thus obtained was partitioned between ethyl acetate and water. The phases were separated and the aqueous layer was washed with ethyl acetate. The organic layers were combined, washed with water and brine, dried over anhydrous sodium sulphate and concentrated under reduced pressure to furnish the title compound (120 mg).

Step 6: Synthesis of 1,1-Dimethylethyl 5-(4-bromophenyl)-3-([4-(methoxy)phenyl]methyl)oxy)-2-{2-[(methylsulfonyl)oxy]ethyl}pentanoate

Methanesulfonyl chloride (0.63 ml) was added in one portion to a stirred solution of the compound (2.99 g) obtained from step 5 above and triethylamine (2.6 ml) in dichloromethane (50 ml) at room temperature under nitrogen atmosphere and stirred at room temperature for 1 hour. The crude mixture was partitioned between saturated aqueous citric acid solution and dichloromethane. The phases were separated and the organic layer was concentrated under reduced pressure to furnish the title compound (3.2g).

Step 7: Synthesis of 1,1-Dimethylethyl 2-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-5-(4-bromophenyl)-3-([4-(methoxy)phenyl]methyl)oxy]pentanoate

Potassium phthalimide (1.25 g) was added in one portion to a stirred solution of the compound (3.5 g) obtained from step 6 above in dimethylformamide (25 ml) at room
 5 temperature under nitrogen atmosphere. The resulting solution was heated at 80 °C for about 2 hours and then cooled to room temperature. The volatiles were evaporated under reduced pressure and the residue thus obtained was partitioned between dichloromethane and water. The layers were separated and the organic phase evaporated to dryness under reduced pressure. The residue thus obtained was purified by column chromatography
 10 using 20% ethyl acetate in hexane as eluant to furnish the title compound (2.45 g).

Step 8: Synthesis of *tert*-butyl 5-(4'-chlorobiphenyl-4-yl)-2-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-[(4-methoxybenzyl)oxy]pentanoate

To a solution of the compound (200 mg) obtained from step 7 above, (4-chlorophenyl)boronic acid (90 mg) and potassium carbonate (133 mg) in
 15 dimethylformamide (3 ml) was added tetrakis(triphenylphosphine)palladium (0) (18.5 mg) and stirred the reaction mixture for 6 hours at about 100 °C. The resulting reaction mixture was diluted with water and extracted with ethyl acetate. The organic layer was separated, washed with water and brine, dried over anhydrous sodium sulphate and concentrated under reduced pressure. The residue thus obtained was purified by column
 20 chromatography using 20% ethyl acetate in hexane as eluant to furnish the title compound (116 mg).

Step 9: Synthesis of 5-(4'-chlorobiphenyl-4-yl)-2-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxypentanoic acid

To a solution of the compound (120 mg) obtained from step 8 above in
 25 dichloromethane (5 ml) was added trifluoroacetic acid (2 ml) and stirred the reaction mixture for 2 hours at room temperature. The solvent was evaporated under reduced pressure and the residue thus obtained was purified by preparative thin layer chromatography (eluant: 60% ethyl acetate in hexane) to furnish the title compound (68 mg).

30 **Mass (m/z):** 478.0 ($M^{+}+1$).

The following illustrative compounds were prepared analogously:

3-Hydroxy-2-[2-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)ethyl]-5-[4'-(trifluoromethyl)biphenyl-4-yl]pentanoic acid (Compound No. 59),

5 5-(3',4'-Difluorobiphenyl-4-yl)-3-hydroxy-2-[2-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)ethyl]pentanoic acid (Compound No. 60),

3-Hydroxy-5-(4'-methoxybiphenyl-4-yl)-2-[2-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)ethyl]pentanoic acid (Compound No. 64),

5-(4'-Chlorobiphenyl-4-yl)-3-hydroxy-2-[2-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)ethyl]pentanoic acid (Compound No. 65),

10 3-Hydroxy-5-[4-(6-methoxypyridin-3-yl)phenyl]-2-[2-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)ethyl]pentanoic acid (Compound No. 67),

3-Hydroxy-5-(4'-methylbiphenyl-4-yl)-2-[2-(5-methyl-1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]pentanoic acid (Compound No. 68),

15 5-(4'-Chlorobiphenyl-4-yl)-3-hydroxy-2-[2-(5-methyl-1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]pentanoic acid (Compound No. 69),

3-Hydroxy-2-[2-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)ethyl]-5-[4'-(trifluoromethoxy)biphenyl-4-yl]pentanoic acid (Compound No. 70),

5-(4'-Fluorobiphenyl-4-yl)-3-hydroxy-2-[2-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)ethyl]pentanoic acid (Compound No. 71),

20 3-Hydroxy-5-(4'-methylbiphenyl-4-yl)-2-[2-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)ethyl]pentanoic acid (Compound No. 72),

5-(4'-Cyanobiphenyl-4-yl)-3-hydroxy-2-[2-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)ethyl]pentanoic acid (Compound No. 73),

25 5-(4'-Fluorobiphenyl-4-yl)-3-hydroxy-2-[2-(5-methyl-1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]pentanoic acid (Compound No. 74),

3-Hydroxy-5-[4-(6-methoxypyridin-3-yl)phenyl]-2-[2-(5-methyl-1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]pentanoic acid (Compound No. 75),

5-(4'-Ethylbiphenyl-4-yl)-3-hydroxy-2-[2-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)ethyl]pentanoic acid (Compound No. 76),

5 3-Hydroxy-2-[2-(5-methyl-1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-5-[4'-(trifluoromethyl)biphenyl-4-yl]pentanoic acid (Compound No. 77),

2-[2-(5-*tert*-Butyl-1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxy-5-[4-(6-methoxypyridin-3-yl)phenyl]pentanoic acid (Compound No. 97),

2-[2-(5-*tert*-Butyl-1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-5-(3',4'-difluorobiphenyl-4-yl)-3-hydroxypentanoic acid (Compound No. 105),

Scheme III, path a procedure:

Example 3: Synthesis of 2-(2-{[(benzyloxy)carbonyl]amino}ethyl)-5-biphenyl-4-yl-3-hydroxypentanoic acid (Compound No. 11)

15 **Step 1: Synthesis of *tert*-butyl 2-(2-{[(benzyloxy)carbonyl]amino}ethyl)-5-biphenyl-4-yl-3-oxopentanoate**

To a solution of the compound *tert*-butyl 5-biphenyl-4-yl-3-oxopentanoate (237 mg,) in tetrahydrofuran (4 ml) and *tert*-butyl alcohol (4 ml) at 0°C under inert atmosphere was added potassium *tert*-butoxide (98 mg) and stirred for 20 minutes. To this at 0 °C was then added *n*-tetrabutylammonium iodide (27 mg) and benzyl aziridine-1-carboxylate (130 mg) and stirred the reaction mixture for 5 minutes. The resulting reaction mixture was warmed to room temperature and then further heated at 70 °C for 2 hours. The solvent was evaporated under reduced pressure and the residue thus obtained was taken in water and extracted with ethyl acetate. The combined organic layers were washed with water and brine, dried over anhydrous sodium sulphate and concentrated under reduced pressure. The residue thus obtained was purified by column chromatography using 20% ethyl acetate in hexane as eluant to furnish the title compound (60 mg).

Step 2: Synthesis of *tert*-butyl 2-(2-{{(benzyloxy)carbonyl}amino}ethyl)-5-biphenyl-4-yl-3-hydroxypentanoate

To a solution of the compound (100 mg) obtained from step 1 above in methanol (2 ml) at $-10\text{ }^{\circ}\text{C}$ to $-2\text{ }^{\circ}\text{C}$ was added sodium borohydride (9 mg) and stirred the mixture
 5 for 40 minutes at the same temperature. The solvent was evaporated under reduced pressure and the residue thus obtained was quenched with saturated solution of ammonium chloride and extracted with ethyl acetate. The combined organic layers were washed with water and brine, dried over anhydrous sodium sulphate and concentrated under reduced pressure. The residue thus obtained was purified by column chromatography using 5%
 10 methanol in dichloromethane as eluant to furnish the title compound (80 mg).

Step 3: Synthesis of 2-(2-{{(benzyloxy)carbonyl}amino}ethyl)-5-biphenyl-4-yl-3-hydroxypentanoic acid

To a solution of the compound (40 mg) obtained from step 2 above in dry dichloromethane (10 ml) at $0\text{ }^{\circ}\text{C}$ was added trifluoroacetic acid (0.5 ml) and anisole
 15 (0.05 ml) and stirred for 4 hours. The solvent and excess reagents were evaporated under reduced pressure and the residue thus obtained was purified by column chromatography using 60% ethyl acetate in hexane as eluant to furnish the title compound (25 mg).

Mass (m/z): 448.1 ($M^{+}+1$).

20 **Scheme III, path b procedure:**

Example 4: Synthesis of 5-biphenyl-4-yl-2-(2-{{(4-fluorophenyl)sulfonyl}amino}ethyl)-3-hydroxypentanoic acid (Compound No. 87)

Step 1: Synthesis of 4-{{(benzyloxy)carbonyl}amino}-1-(2-biphenyl-4-ylethyl)-2-(*tert*-butoxycarbonyl)butyl benzoate

25 Benzoic acid (48.5 mg), 4-dimethylaminopyridine (24.3 mg) and triethylamine (0.08 ml) were added to a solution of *tert*-butyl 2-(2-{{(benzyloxy)carbonyl}amino}ethyl)-5-biphenyl-4-yl-3-hydroxypentanoate (200 mg) in dichloromethane (5 ml) at $0\text{ }^{\circ}\text{C}$ and the reaction mixture was stirred for 15 minutes. 1-Ethyl-3-(3'-dimethylaminopropyl)-carbodiimide (152 mg) was added and the reaction mixture was stirred overnight. The

reaction mixture was taken in distill water and extracted with dichloromethane (20 ml). The organic layer was washed with dilute sodium bicarbonate solution, brine solution, dried over anhydrous sodium sulphate and evaporated under vacuum. The residue thus obtained was purified by column chromatography using 10% ethyl acetate in hexane as eluent to furnish the title compound (180 mg).

Step 2: Synthesis of 4-amino-1-(2-biphenyl-4-ylethyl)-2-(tert-butoxycarbonyl)butyl benzoate

10% Palladium on charcoal (100 mg) was added to the solution of the compound (170 mg) obtained from the step 1 above in ethyl acetate (10 ml) and the reaction mixture was shaken under hydrogen atmosphere (40 psi) for 4 hours followed by filtration through celite. The filtrate was then concentrated under reduced pressure to furnish the title compound (100 mg).

Step 3: Synthesis of 1-(2-biphenyl-4-ylethyl)-2-(tert-butoxycarbonyl)-4-[(4-fluorophenyl)sulfonyl]amino}butyl benzoate

15 4-Fluorobenzene sulphonylchloride (62 mg) and triethyl amine were added at 0 °C to the solution of the compound (150 mg) obtained from the step 2 above in dichloromethane (5 ml) and the reaction mixture was stirred for 3 hours. The reaction mixture was diluted with distilled water and extracted with dichloromethane (15 ml). The organic layer was washed with water, cold dilute hydrochloric acid and brine solution, dried over anhydrous sodium sulphate and evaporated under reduced pressure. The residue thus obtained was purified by column chromatography using 10% ethylacetate in hexane as eluent to furnish the title compound (100 mg).

Step 4: Synthesis of tert-butyl 5-biphenyl-4-yl-2-(2-[(4-fluorophenyl)sulfonyl]amino}ethyl)-3-hydroxypentanoate

25 Aqueous solution of lithium hydroxide (18 mg in 1 ml of water) was added to a solution of the compound (100 mg) obtained from Step 3 above in tetrahydrofuran: methanol: water (3: 1: 1, 5 ml). The resulting reaction mixture was stirred overnight. The reaction mixture was concentrated and the residue thus obtained was diluted with water, acidified with dilute hydrochloric acid solution and extracted with ethyl acetate. The organic layer was washed with distilled water and brine solution, dried over anhydrous

sodium sulphate and concentrated under reduced pressure to furnish the title compound (94 mg).

Step 5: Synthesis of 5-biphenyl-4-yl-2-(2-[(4-fluorophenyl)sulfonyl]amino)ethyl)-3-hydroxypentanoic acid

5 Trifluoroacetic acid (0.5 ml) was added to the solution of the compound (100 mg) obtained from the step 4 above in dichloromethane (5 ml) and the reaction mixture was stirred for 2 hours. The reaction mixture was then concentrated. The residue was flushed with nitrogen gas and dried on high vacuum and purified by preparative thin layer chromatography using 12 % methanol in dichloromethane to furnish the title compound
10 (30 mg).

Mass (m/z): 494.1 ($M^+ + 23$)

Example 5: Synthesis of 5-biphenyl-4-yl-2-(2-[(3-fluorophenyl)acetyl]amino)ethyl)-3-hydroxypentanoic acid (Compound No. 88)

15 **Step 1: Synthesis of 1-(2-biphenyl-4-ylethyl)-2-(tert-butoxycarbonyl)-4-[(4-fluorobenzoyl)amino]butyl benzoate**

4-Fluorobenzoic acid (45 mg), N-methylmorpholine (0.05 ml), hydroxybenzotriazole (51.5 mg) were added to the solution of 4-amino-1-(2-biphenyl-4-ylethyl)-2-(tert-butoxycarbonyl)butyl benzoate (150 mg) obtained from Example 3, step 2
20 in dry dimethylformamide (2 ml) at 0 °C, 1-ethyl-3-(3'-dimethylaminopropyl)-carbodiimide (92 mg) was added and the reaction mixture was stirred overnight. The reaction mixture was taken in distilled water and extracted with ethylacetate. The organic layer was washed with distilled water and brine solution and dried over anhydrous sodium sulphate followed by evaporation under reduced pressure. The residue thus obtained was
25 purified by column chromatography using 10 % ethyl acetate in hexane as eluent to get the title compound (120 mg).

Step 2: Synthesis of tert-butyl 5-biphenyl-4-yl-2-{2-[(4-fluorobenzoyl)amino]ethyl}-3-hydroxypentanoate

Aqueous solution of lithium hydroxide (22 mg) was added to a solution of the compound (120 mg) obtained from Step 1 above, in tetrahydrofuran: methanol: water (3: 1: 1, 5 ml) and the reaction mixture was stirred overnight. The reaction mixture was concentrated and the residue thus obtained was taken in distilled water, acidified with dilute hydrochloric acid solution and extracted with ethyl acetate. The organic layer was washed with distilled water and brine solution and dried over anhydrous sodium sulphate. The solvent was evaporated under reduced pressure to furnish the title compound (100 mg).

Step 3: Synthesis of 5-biphenyl-4-yl-2-{2-[(4-fluorobenzoyl)amino]ethyl}-3-hydroxypentanoic acid

Trifluoroacetic acid (0.5 ml) was added to a solution of the compound obtained from the step 2 above (100 mg) in dichloromethane (5 ml) and the reaction mixture was stirred for 2 hours. The reaction mixture was then concentrated. The residue was flushed with nitrogen gas and dried on high vacuum and purified by preparative thin layer chromatography using 12 % methanol in dichloromethane to furnish the title compound (30 mg).

Mass (m/z): 458.1 ($M^+ + 23$).

The following illustrative analogues were prepared analogously,

5-Biphenyl-4-yl-3-hydroxy-2-{2-[(phenylacetyl)amino]ethyl}pentanoic acid (Compound No. 45), and

5-Biphenyl-4-yl-2-{2-[(4-fluorobenzoyl)amino]ethyl}-3-hydroxypentanoic acid (Compound No. 89)

Example 6: Synthesis of 5-biphenyl-4-yl-2-[2-({[(4-fluorophenyl)amino]carbonyl}amino)ethyl]-3-hydroxypentanoic acid (Compound No. 92)

Step 1: Synthesis of 1-(2-biphenyl-4-ylethyl)-2-(tert-butoxycarbonyl)-4-({[(4-fluorophenyl)amino]carbonyl}amino)butyl benzoate

4-Fluorophenyl isocyanate (29 mg) was added to the solution of 4-amino-1-(2-biphenyl-4-ylethyl)-2-(*tert*-butoxycarbonyl)butyl benzoate (100 mg) obtained from Example 3, step 2 in dry dichloromethane at 0 °C under argon atmosphere and the reaction mixture stirred for 1 hour. The reaction mixture was dried over high vacuum to furnish the title compound (130 mg).

Step 2: Synthesis of 5-biphenyl-4-yl-2-[2-({[(4-fluorophenyl)amino]carbonyl}amino)ethyl]-3-hydroxypentanoic acid

Aqueous solution of lithium hydroxide (22 mg in 1 ml) was added to the solution of the compound (130 mg) obtained from Step 1 above, in tetrahydrofuran: methanol: water (3: 1: 1, 5 ml) and the reaction mixture was stirred at 40 °C overnight. The reaction mixture was concentrated and the residue thus obtained was taken in distilled water, acidified with dilute hydrochloric acid solution and extracted with ethyl acetate. The organic layer was washed with distilled water and brine solution and dried over anhydrous sodium sulphate. The solvent was evaporated under reduced pressure to furnish the title compound (40 mg)

Mass (m/z): 473 ($M^{+} + 23$); 451.1 ($M+1$)

Scheme IV, Procedure

Example 7: Synthesis of 5-biphenyl-4-yl-3-hydroxy-2-[2-(1-oxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]pentanoic acid Compound No. 91

Step 1: Synthesis of *tert*-butyl 5-biphenyl-4-yl-2-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-oxopentanoate

The title compound was prepared following the procedure as depicted in Example 1, step 2, by using 2-(2-bromoethyl)-1*H*-isoindole-1,3(2*H*)-dione in place of 3-(2-bromoethyl)-1,2,3-benzotriazin-4(3*H*)-one.

Step 2: Synthesis of *tert*-butyl 5-biphenyl-4-yl-3-hydroxy-2-[2-(1-hydroxy-3-oxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]pentanoate

To a solution of the compound (165 mg) prepared from Step 1 above, in dry methanol and THF (1:1, 8 ml) at -20 °C was added sodium borohydride (38 mg) and the

reaction mixture was stirred at rt for 3 h and then at 45 °C for 1 hour. The reaction mixture was cooled to 0 °C and quenched with saturated ammonium chloride solution. The solvents were evaporated in vacuo and the residue taken into water and extracted with ethyl acetate. The combined organic extracts were washed with water and brine and dried
 5 over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure to obtain the crude title compound (165 mg).

Step 3: Synthesis of 5-biphenyl-4-yl-3-hydroxy-2-[2-(1-oxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]pentanoic acid

To a solution of the compound (160 mg) obtained from Step 2 above in
 10 trifluoroacetic acid (2 ml) at room temperature was added sodium borohydride (36 mg) and stirred for 1 h. The volatiles were evaporated under reduced pressure and the residue purified by preparative TLC using 10% methanol-DCM as the mobile phase (100 mg).
 Mass (m/z): 430.0 (M+1).

The following illustrative analogue was prepared analogously,

15 5-Biphenyl-4-yl-3-hydroxy-2-[2-(1-oxo-1,3-dihydro-2*H*-isoindol-2-yl) butyl]pentanoic acid (Compound No. 124).

Example 8: Separation of (2*R*,3*S*) & (2*S*,3*R*)-5-(4'-chlorobiphenyl-4-yl)-2-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxypentanoic acid and (2*R*,3*R*) & (2*S*,3*S*)-5-(4'-chlorobiphenyl-4-yl)-2-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-
 20 hydroxypentanoic acid

Compound No. 4 (30 mg) was loaded on preparative thin layer chromatography and the TLC plate was run using 30% acetone in dichloromethane as the mobile phase. The desired diastereomeric bands were cut separately. The silica gel of the individual
 25 bands containing the individual compound pairs was loaded on a short column and chromatographic purification by elution with 5% methanol in DCM yielded the corresponding title compounds. Compound No. 80: 6 mg. Compound No. 81: 16 mg.

The following pairs of illustrative diastereomers were separated analogously,

(2*R*,3*S* + 2*S*,3*R*)-2-[2-(5-*tert*-Butyl-1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-5-(4'-fluorobiphenyl-4-yl)-3-hydroxypentanoic acid (Compound No. 106),

(2*R*,3*S* + 2*S*,3*R*)-2-[2-(5-*tert*-Butyl-1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxy-5-[4'-(trifluoromethyl)biphenyl-4-yl]pentanoic acid (Compound No. 107),

- 5 (2*R*,3*R* + 2*S*,3*S*)-2-[2-(5-*tert*-Butyl-1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-5-(4'-fluorobiphenyl-4-yl)-3-hydroxypentanoic acid (Compound No. 108),

(2*R*,3*R* + 2*S*,3*S*)-2-[2-(5-*tert*-Butyl-1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxy-5-[4'-(trifluoromethyl)biphenyl-4-yl]pentanoic acid (Compound No. 109),

2

- 10 (2*R*,3*R* + 2*S*,3*S*)-2-[2-(5-*tert*-Butyl-1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxy-5-(4'-methylbiphenyl-4-yl)pentanoic acid (Compound No. 113),

(2*R*,3*S* + 2*S*,3*R*)-2-[2-(5-*tert*-Butyl-1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxy-5-(4'-methylbiphenyl-4-yl)pentanoic acid (Compound No. 114),

- 15 (2*R*,3*R* + 2*S*,3*S*)-2-[2-(5-*tert*-Butyl-1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxy-5-(4'-methoxybiphenyl-4-yl)pentanoic acid (Compound No. 115),

(2*R*,3*R* + 2*S*,3*S*)-2-[2-(5-*tert*-Butyl-1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-5-(4'-chlorobiphenyl-4-yl)-3-hydroxypentanoic acid (Compound No. 116),

(2*R*,3*S* + 2*S*,3*R*)-2-[2-(5-*tert*-Butyl-1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-5-(4'-chlorobiphenyl-4-yl)-3-hydroxypentanoic acid (Compound No. 117),

- 20 (2*R*,3*S* + 2*S*,3*R*)-2-[2-(5-*tert*-Butyl-1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxy-5-(4'-methoxybiphenyl-4-yl)pentanoic acid (Compound No. 118),

Chiral HPLC analysis/separation was carried out for example, using Waters HPLC LC Module I Plus system with UV 486 detector using a Chiralcel OJ-H (250* 4.6) column; mobile phase: 60 : 40 of 0.1% TFA in hexane: ethanol; flow rate 0.7 mL/min, run time 60 minutes.

- 25

The following illustrative single diastereomers were separated using chiral HPLC conditions,

(2R,3S)- 3-Hydroxy-5-[4-(6-methoxypyridin-3-yl)phenyl]-2-[2-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)ethyl]pentanoic acid (Compound No.133),

5 (2S,3R)- 3-Hydroxy-5-[4-(6-methoxypyridin-3-yl)phenyl]-2-[2-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)ethyl]pentanoic acid (Compound No.134),

(2R,3R)- 3-Hydroxy-5-[4-(6-methoxypyridin-3-yl)phenyl]-2-[2-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)ethyl]pentanoic acid (Compound No.135), and

10 (2S,3S)-3-Hydroxy-5-[4-(6-methoxypyridin-3-yl)phenyl]-2-[2-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)ethyl]pentanoic acid (Compound No.136).

Assay for Matrix Metallo Proteinases (MMPs)

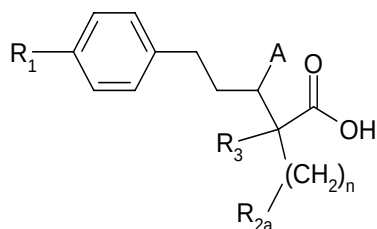
NCEs/standards were prepared (stock 10 mM) in 100% DMSO and subsequent dilutions were made in 50% DMSO-50% TCNB (50 mM Tris, 10 mM CaCl₂, 150 mM NaCl, 0.05% Brij-35, pH 7.5). 1 µl of the compound and 88 µl of TCNB was added to wells of 96 well plate to achieve the desired final concentration of NCE (final DMSO concentration should not exceed 0.5%). 1 µl of activated, recombinant MMPs was added to each well (20-100 ng/100 µl reaction mixture) except the “negative well”. (MMP-1, 9 & 14 enzymes require prior activation. For this, supplied enzyme was incubated with either APMA, final concentration 1 mM, for a time period of 1 hr at 37°C). Incubation was done at room temperature for 4-5 min. Reaction was initiated with 10 µl of 100 µM substrate (ES001: Aliquots were freshly diluted in TCNB; stock: 2 mM) and increase in florescence was monitored at excitation wavelength 320 nm followed by emission at 405 nm for 25-30 cycles. Increase in florescence (RFU) was calculated for positive, negative and NCE/standard wells. The percent inhibition compared to controls was calculated and IC₅₀ values determined using Graph-prism software.

Activities for MMP9 provided IC₅₀ values from about 10 micromolar to about 2 nM, or from about 1 micromolar to about 2 nM, or from about 650 nM to about 2 nM, or

from about 300 nM to about 2 nM, or from about 100 nM to about 2 nM, or from about 50 nM to about 2 nM, or from about 30 nM to about 2 nM, or from about 20 nM to about 2 nM, or from about 15 to about 2 nM, as compared to about 1.5 nM for marimasat.

Activities for MMP12 provided IC₅₀ values from about 10 micromolar to about 0.4 nM, or from about 1 micromolar to about 0.4 nM, or from about 300 nM to about 0.4 nM, or from about 100 nM to about 0.4 nM, or from about 50 nM to about 0.4 nM, or from about 30 nM to about 0.4 nM, or from about 20 nM to about 0.4 nM, or from about 15 to about 0.4 nM, or from about 7 to about 0.4 nM as compared to about 0.9 nM for marimasat.

1. A compound of Formula Ic



Ic

or racemates, enantiomers, diastereomers, and pharmaceutically acceptable salts thereof, wherein:

n is an integer from 1 to 5;

R₁ is alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heterocyclyl, heteroaryl, aralkyl, alkoxy, aryloxy, alkenyloxy or alkynyloxy, each of which is optionally substituted;

R_{2a} is NR₄R₅, NHC(=Y)R₄, NHC(=Y)NR₅R_x, NHC(=O)OR₄, NHSO₂R₄, amidino or guanidino;

wherein Y is oxygen or sulfur;

R₄ is alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heterocyclyl, heteroaryl, aralkyl, heteroarylalkyl, heterocyclalkyl or cycloalkylalkyl;

R₅ is hydrogen or R₄;

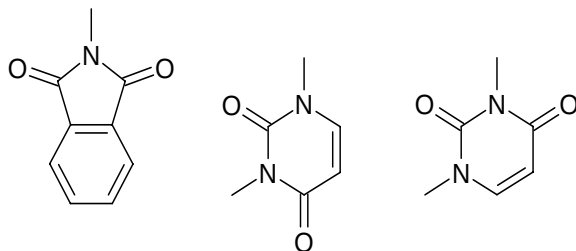
R₄ and R₅ together optionally forms a heterocyclic ring containing one or more heteroatoms selected from O, N or S; and

R_x is R₄ or SO₂N(R₄)₂;

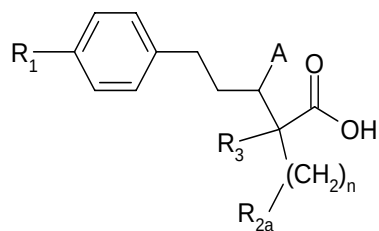
R₃ is hydrogen, fluorine, alkyl, cycloalkyl or aralkyl;

A is OH, OR₄, -OC(=O)NR₄R₅, O-acyl, NH₂, NR₄R₅, -NHC(=Y)R₄, -NHC(=Y)NR₅R_x, NHC(=O)OR₄, NHSO₂R₄;

provided that R_{2a} is not selected from:



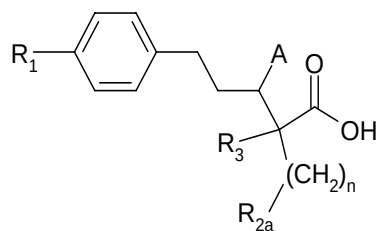
2. A compound according to claim 1 having the structure of Formula Ic:



Ic

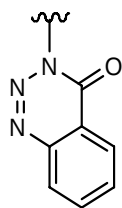
wherein **R₁** is aryl or heteroaryl.

3. A compound according to claim 1 having the structure of Formula Ic:

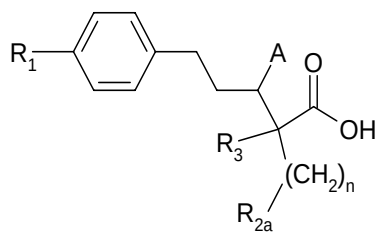


Ic

wherein **R_{2a}** is a group of formula:



4. A compound according to claim 1 having the structure of Formula Ic:



wherein **R₁** is heteroaryl.

5. A compound according to claim 1 which is:

5-Biphenyl-4-yl-3-hydroxy-2-[2-(4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]pentanoic acid (Compound No. 1),

2-(2-{[(Benzyloxy)carbonyl]amino}ethyl)-5-biphenyl-4-yl-3-hydroxypentanoic acid (Compound No. 11),

5-Biphenyl-4-yl-3-hydroxy-2-{2-[(phenylacetyl)amino]ethyl}pentanoic acid (Compound No. 45),

5-Biphenyl-4-yl-3-hydroxy-2-[2-(1-oxophthalazin-2(1H)-yl)ethyl]pentanoic acid (Compound No. 47),

5-Biphenyl-4-yl-3-hydroxy-2-[2-(2'-oxospiro[cyclopropane-1,3'-indol]-1'(2'H)-yl)ethyl]pentanoic acid (Compound No. 49),

3-Hydroxy-2-[2-(4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]-5-[4'-(trifluoromethyl)biphenyl-4-yl]pentanoic acid (Compound No. 59),

5-(3',4'-Difluorobiphenyl-4-yl)-3-hydroxy-2-[2-(4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]pentanoic acid (Compound No. 60),

3-Hydroxy-5-(4'-methoxybiphenyl-4-yl)-2-[2-(4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]pentanoic acid (Compound No. 64),

5-(4'-Chlorobiphenyl-4-yl)-3-hydroxy-2-[2-(4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]pentanoic acid (Compound No. 65),

3-Hydroxy-5-[4-(6-methoxypyridin-3-yl)phenyl]-2-[2-(4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]pentanoic acid (Compound No. 67),

3-Hydroxy-5-(4'-methylbiphenyl-4-yl)-2-[2-(5-methyl-1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)ethyl]pentanoic acid (Compound No. 68),

5-(4'-Chlorobiphenyl-4-yl)-3-hydroxy-2-[2-(5-methyl-1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)ethyl]pentanoic acid (Compound No. 69),

3-Hydroxy-2-[2-(4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]-5-[4'-(trifluoromethoxy)biphenyl-4-yl]pentanoic acid (Compound No. 70),

5-(4'-Fluorobiphenyl-4-yl)-3-hydroxy-2-[2-(4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]pentanoic acid (Compound No. 71),

3-hydroxy-5-(4'-methylbiphenyl-4-yl)-2-[2-(4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]pentanoic acid (Compound No. 72),

5-(4'-Cyanobiphenyl-4-yl)-3-hydroxy-2-[2-(4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]pentanoic acid (Compound No. 73),

5-(4'-Fluorobiphenyl-4-yl)-3-hydroxy-2-[2-(5-methyl-1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)ethyl]pentanoic acid (Compound No. 74),

3-Hydroxy-5-[4-(6-methoxypyridin-3-yl)phenyl]-2-[2-(5-methyl-1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)ethyl]pentanoic acid (Compound No. 75),

5-(4'-Ethylbiphenyl-4-yl)-3-hydroxy-2-[2-(4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]pentanoic acid (Compound No. 76),

3-Hydroxy-2-[2-(5-methyl-1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)ethyl]-5-[4'-(trifluoromethyl)biphenyl-4-yl]pentanoic acid (Compound No. 77),

5-Biphenyl-4-yl-3-hydroxy-2-[2-(1-oxo-4-phenyl-4a,8a-dihydrophthalazin-2(1H)-yl)ethyl]pentanoic acid (Compound No. 84),

5-Biphenyl-4-yl-3-hydroxy-2-[2-(3-oxo-2,3-dihydro-4H-1,4-benzoxazin-4-yl)ethyl]pentanoic acid (Compound No. 85),

5-Biphenyl-4-yl-2-{2-[(3aR,7aS)-1,3-dioxo-1,3,3a,4,7,7a-hexahydro-2H-isoindol-2-yl]ethyl}-3-hydroxypentanoic acid (Compound No. 86),

5-Biphenyl-4-yl-2-(2-{[(4-fluorophenyl)sulfonyl]amino}ethyl)-3-hydroxypentanoic acid (Compound No. 87),

5-Biphenyl-4-yl-2-(2-{[(3-fluorophenyl)acetyl]amino}ethyl)-3-hydroxypentanoic acid (Compound No. 88),

5-Biphenyl-4-yl-2-{2-[(4-fluorobenzoyl)amino]ethyl}-3-hydroxypentanoic acid (Compound No. 89),

5-Biphenyl-4-yl-3-hydroxy-2-[2-(5-methyl-1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)ethyl]pentanoic acid (Compound No. 90),

5-Biphenyl-4-yl-3-hydroxy-2-[2-(1-oxo-1,3-dihydro-2H-isoindol-2-yl)ethyl]pentanoic acid (Compound No. 91),

5-Biphenyl-4-yl-2-[2-({[(4-fluorophenyl)amino]carbonyl}amino)ethyl]-3-hydroxypentanoic acid (Compound No. 92),

5-Biphenyl-4-yl-2-[2-(4,4-dimethyl-2,6-dioxopiperidin-1-yl)ethyl]-3-hydroxypentanoic acid (Compound No. 93),

5-Biphenyl-4-yl-2-[2-(7,9-dioxo-8-azaspiro[4.5]dec-8-yl)ethyl]-3-hydroxypentanoic acid (Compound No. 94),

5-Biphenyl-4-yl-3-hydroxy-2-[2-(2-oxo-1,3-benzoxazol-3(2H)-yl)ethyl]pentanoic acid (Compound No. 96),

2-[2-(5-tert-Butyl-1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)ethyl]-3-hydroxy-5-[4-(6-methoxypyridin-3-yl)phenyl]pentanoic acid (Compound No. 97),

5-Biphenyl-4-yl-2-[2-(5,6-dichloro-1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)ethyl]-3-hydroxypentanoic acid (Compound No. 102),

5-Biphenyl-4-yl-2-[2-(2,4-dioxo-1,4-dihydroquinazolin-3(2H)-yl)ethyl]-3-hydroxypentanoic acid (Compound No. 103),

5-Biphenyl-4-yl-2-[2-(1,3-dioxo-1,3-dihydro-2H-pyrrolo[3,4-c]pyridin-2-yl)ethyl]-3-hydroxypentanoic acid (Compound No. 104),

2-[2-(5-tert-Butyl-1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)ethyl]-5-(3',4'-difluorobiphenyl-4-yl)-3-hydroxypentanoic acid (Compound No. 105),

(2R,3S + 2S,3R)-2-[2-(5-tert-Butyl-1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)ethyl]-5-(4'-fluorobiphenyl-4-yl)-3-hydroxypentanoic acid (Compound No. 106),

(2R,3S + 2S,3R)-2-[2-(5-tert-Butyl-1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)ethyl]-3-hydroxy-5-[4'-(trifluoromethyl)biphenyl-4-yl]pentanoic acid (Compound No. 107),

(2R,3R + 2S,3S)-2-[2-(5-tert-Butyl-1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)ethyl]-5-(4'-fluorobiphenyl-4-yl)-3-hydroxypentanoic acid (Compound No. 108),

(2R,3R + 2S,3S)-2-[2-(5-tert-Butyl-1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)ethyl]-3-hydroxy-5-[4'-(trifluoromethyl)biphenyl-4-yl]pentanoic acid (Compound No. 109),

(2R,3R + 2S,3S)-2-[2-(5-tert-Butyl-1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)ethyl]-3-hydroxy-5-(4'-methylbiphenyl-4-yl)pentanoic acid (Compound No. 113),

(2R,3S + 2S,3R)-2-[2-(5-tert-Butyl-1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)ethyl]-3-hydroxy-5-(4'-methylbiphenyl-4-yl)pentanoic acid (Compound No. 114),

(2R,3R + 2S,3S)-2-[2-(5-tert-Butyl-1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)ethyl]-3-hydroxy-5-(4'-methoxybiphenyl-4-yl)pentanoic acid (Compound No. 115),

(2R,3R + 2S,3S)-2-[2-(5-tert-Butyl-1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)ethyl]-5-(4'-chlorobiphenyl-4-yl)-3-hydroxypentanoic acid (Compound No. 116),

(2R,3S + 2S,3R)-2-[2-(5-tert-Butyl-1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)ethyl]-5-(4'-chlorobiphenyl-4-yl)-3-hydroxypentanoic acid (Compound No. 117),

(2R,3S + 2S,3R)-2-[2-(5-tert-Butyl-1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)ethyl]-3-hydroxy-5-(4'-methoxybiphenyl-4-yl)pentanoic acid (Compound No. 118),

5-Biphenyl-4-yl-2-[2-(5-tert-butyl-1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)ethyl]-3-hydroxypentanoic acid (Compound No. 121),

5-Biphenyl-4-yl-3-hydroxy-2-[2-(1-oxo-1,3-dihydro-2H-isoindol-2-yl)butyl]pentanoic acid (Compound No. 124),

(2R,3S)- 3-Hydroxy-5-[4-(6-methoxypyridin-3-yl)phenyl]-2-[2-(4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]pentanoic acid (Compound No. 133),

(2S,3R)- 3-Hydroxy-5-[4-(6-methoxypyridin-3-yl)phenyl]-2-[2-(4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]pentanoic acid (Compound No. 134),

(2R,3R)- 3-Hydroxy-5-[4-(6-methoxypyridin-3-yl)phenyl]-2-[2-(4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]pentanoic acid (Compound No. 135), or

(2S,3S)- 3-Hydroxy-5-[4-(6-methoxypyridin-3-yl)phenyl]-2-[2-(4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]pentanoic acid (Compound No. 136).

6. A compound according to claim 5 which is:

5-Biphenyl-4-yl-3-hydroxy-2-[2-(4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]pentanoic acid (Compound No. 1), or

2-(2-{[(Benzyloxy)carbonyl]amino}ethyl)-5-biphenyl-4-yl-3-hydroxypentanoic acid (Compound No. 11).

7. A compound according to claim 5 which is:

3-Hydroxy-2-[2-(4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]-5-[4'-(trifluoromethyl)biphenyl-4-yl]pentanoic acid (Compound No. 59),

5-(3',4'-Difluorobiphenyl-4-yl)-3-hydroxy-2-[2-(4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]pentanoic acid (Compound No. 60),

3-Hydroxy-5-(4'-methoxybiphenyl-4-yl)-2-[2-(4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]pentanoic acid (Compound No. 64),

5-(4'-Chlorobiphenyl-4-yl)-3-hydroxy-2-[2-(4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]pentanoic acid (Compound No. 65),

3-Hydroxy-5-[4-(6-methoxypyridin-3-yl)phenyl]-2-[2-(4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]pentanoic acid (Compound No. 67),

5-(4'-Chlorobiphenyl-4-yl)-3-hydroxy-2-[2-(5-methyl-1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)ethyl]pentanoic acid (Compound No. 69),

3-Hydroxy-2-[2-(4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]-5-[4'-(trifluoromethoxy)biphenyl-4-yl]pentanoic acid (Compound No. 70),

3-hydroxy-5-(4'-methylbiphenyl-4-yl)-2-[2-(4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]pentanoic acid (Compound No. 72),

3-Hydroxy-5-[4-(6-methoxypyridin-3-yl)phenyl]-2-[2-(5-methyl-1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)ethyl]pentanoic acid (Compound No. 75),

5-(4'-Ethylbiphenyl-4-yl)-3-hydroxy-2-[2-(4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]pentanoic acid (Compound No. 76),

3-Hydroxy-2-[2-(5-methyl-1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)ethyl]-5-[4'-(trifluoromethyl)biphenyl-4-yl]pentanoic acid (Compound No. 77),

5-Biphenyl-4-yl-3-hydroxy-2-[2-(5-methyl-1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)ethyl]pentanoic acid (Compound No. 90),

2-[2-(5-tert-Butyl-1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)ethyl]-3-hydroxy-5-[4-(6-methoxypyridin-3-yl)phenyl]pentanoic acid (Compound No. 97),

5-Biphenyl-4-yl-2-[2-(5,6-dichloro-1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)ethyl]-3-hydroxypentanoic acid (Compound No. 102),

(2R,3S + 2S,3R)-2-[2-(5-tert-Butyl-1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)ethyl]-3-hydroxy-5-[4'-(trifluoromethyl)biphenyl-4-yl]pentanoic acid (Compound No. 107),

(2R,3R + 2S,3S)-2-[2-(5-tert-Butyl-1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)ethyl]-3-hydroxy-5-[4'-(trifluoromethyl)biphenyl-4-yl]pentanoic acid (Compound No. 109),

(2R,3R + 2S,3S)-2-[2-(5-tert-Butyl-1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)ethyl]-3-hydroxy-5-(4'-methoxybiphenyl-4-yl)pentanoic acid (Compound No. 115),

(2R,3R + 2S,3S)-2-[2-(5-tert-Butyl-1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)ethyl]-5-(4'-chlorobiphenyl-4-yl)-3-hydroxypentanoic acid (Compound No. 116),

(2R,3S + 2S,3R)-2-[2-(5-tert-Butyl-1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)ethyl]-5-(4'-chlorobiphenyl-4-yl)-3-hydroxypentanoic acid (Compound No. 117),

(2R,3S + 2S,3R)-2-[2-(5-tert-Butyl-1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)ethyl]-3-hydroxy-5-(4'-methoxybiphenyl-4-yl)pentanoic acid (Compound No. 118),

(2R,3S)-3-Hydroxy-5-[4-(6-methoxypyridin-3-yl)phenyl]-2-[2-(4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]pentanoic acid (Compound No. 133),

(2S,3R)-3-Hydroxy-5-[4-(6-methoxypyridin-3-yl)phenyl]-2-[2-(4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]pentanoic acid (Compound No. 134), or

(2S,3S)-3-Hydroxy-5-[4-(6-methoxypyridin-3-yl)phenyl]-2-[2-(4-oxo-1,2,3-benzotriazin-3(4H)-yl)ethyl]pentanoic acid (Compound No. 136).

8. A pharmaceutical composition comprising a therapeutically effective amount of a compound according to any one of claims 1 to 7 together with a pharmaceutically acceptable carrier, excipient or diluent.

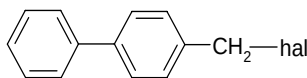
9. A pharmaceutical composition according to claim 8 further comprising one or more additional active ingredients selected from:

a. Anti-inflammatory agents selected from:

- (i) nonsteroidal anti-inflammatory agents selected from piroxicam, diclofenac, propionic acids, fenamates, pyrazolones, salicylates, PDE-4/pd38 MAP Kinase/Cathepsin inhibitors;
- (ii) leukotrienes, LTC₄/LTD₄/LTE₄/LTB₄- Inhibitors, 5-lipoxygenase inhibitors and PAF receptor antagonists;
- (iii) Cox-2 inhibitors;

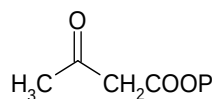
- (iv) MMP inhibitors; or
- (v) interleukin-I inhibitors;
- b. antihypertensive agents selected from:
 - (i) ACE inhibitors selected from enalapril, lisinopril, valsartan, telmisartan or quinapril;
 - (ii) angiotensin II receptor antagonists and agonists selected from, losartan, candesartan, irbesartan, valsartan or eprosartan,
 - (iii) β -blockers; or (iv) calcium channel blockers; or
- c. immunosuppressive agents selected from cyclosporine, azathioprine or methotrexate; or anti-inflammatory corticosteroids.

10. A compound according to any one of claims 1 to 7 for use in medicine.
11. A compound according to any one of claims 1 to 7 for use in the treatment or prophylaxis of an animal or a human suffering from an inflammatory diseases or an associated pathology.
12. The use of a compound according to any one of claims 1 to 7 in the preparation of an agent for the treatment or prophylaxis of inflammatory diseases or associated pathologies.
13. A compound according to claim 11 or a use according to claim 12, wherein the inflammatory disease or associated pathology is asthma, rheumatoid arthritis, COPD, rhinitis, osteoarthritis, psoriatic arthritis, psoriasis, pulmonary fibrosis, pulmonary inflammation, acute respiratory distress syndrome, perodontitis, multiple sclerosis, gingivitis, atherosclerosis, neointimal proliferation associated with restenosis and ischemic heart failure, stroke, renal disease or tumour metastasis.
14. A process for preparing a compound of Formula VIII comprising :
 - a) reacting a compound of Formula II



Formula II

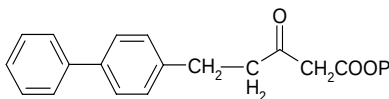
wherein hal is Cl, Br or I;
with a compound of Formula III



Formula III

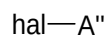
wherein P is alkyl or aralkyl selected from tert-butyl, ethyl, methyl or benzyl;

to form a compound Formula IV;



Formula IV

b) reacting a compound Formula IV with a compound of Formula V



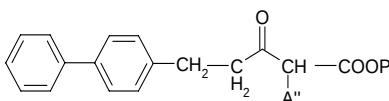
Formula V

wherein:

A'' is selected from $(\text{CH}_2)_n\text{-NR}_4\text{R}_5$, $(\text{CH}_2)_n\text{-NHC(=Y)R}_4$, $(\text{CH}_2)_n\text{-NHC(=Y)NR}_5\text{R}_x$, $(\text{CH}_2)_n\text{-NHC(=O)OR}_4$, $(\text{CH}_2)_n\text{-NHSO}_2\text{R}_4$, $(\text{CH}_2)_n\text{-amidino}$ or $(\text{CH}_2)_n\text{-guanidino}$ (wherein n is an integer from 1 to 5); and

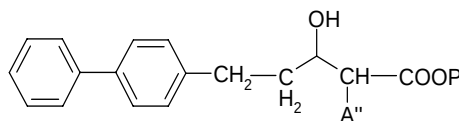
Hal is a halogen is selected from Cl, Br or I;

to form a compound of Formula VI;



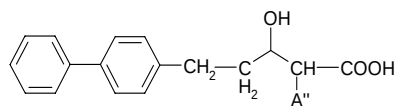
Formula VI

c) reducing a compound of Formula VI to form a compound of Formula VII;
and



Formula VII

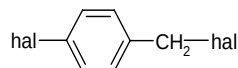
d) deprotecting a compound of Formula VII to form a compound of Formula VIII



Formula VIII

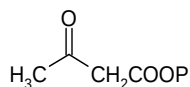
15. A process for preparing a compound of Formula XXI comprising:

a) reacting a compound of Formula IX



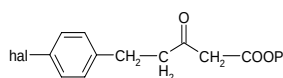
Formula IX

with a compound of Formula III



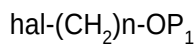
Formula III

to form a compound of Formula X;



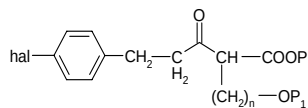
Formula X

b) reacting a compound of Formula X with a compound of Formula XI



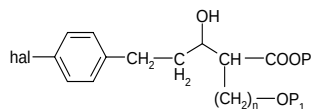
Formula XI

to form a compound of Formula XII;



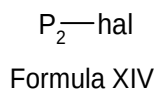
Formula XII

c) reducing a compound of Formula XII to form a compound of Formula XIII;

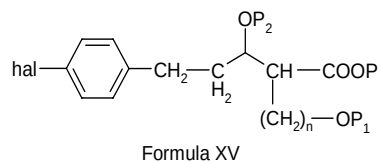


Formula XIII

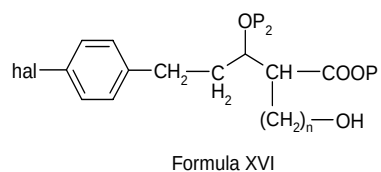
d) reacting a compound of Formula XIII with a compound of Formula XIV



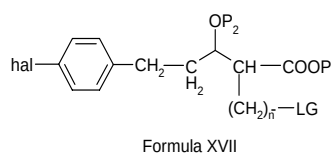
to form a compound of Formula XV;



e) deprotecting a compound of Formula XV to form a compound of Formula XVI;

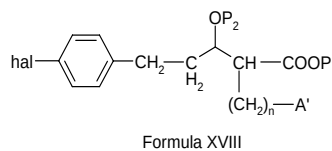


f) converting a compound of Formula XVI to form a compound of Formula XVII

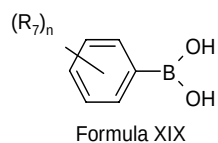


by reaction with a compound of Formula L-hal (wherein L is methanesulphonyl, p-toluenesulphonyl, and hal is halogen);

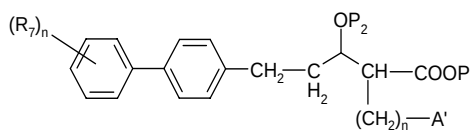
g) reacting a compound of Formula XVII with a compound of Formula M-A' or A' to form a compound of Formula XVIII;



h) reacting a compound of Formula XVIII with a compound of Formula XIX

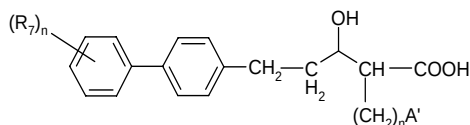


to form a compound of Formula XX; and



Formula XX

- i) deprotecting a compound of Formula XX to form a compound of Formula XXI



Formula XXI

wherein:

P is alkyl or aralkyl selected from tert-butyl, ethyl or methyl or benzyl;

P₁ is silyl protecting group selected from tert-butyldimethylsilane, tert-butyldiphenylsilane or triisopropylsilane;

P₂ is aralkyl or heterocyclyl selected from benzyl, 4-methoxybenzyl or 2,4,6-trimethoxybenzyl or tetrahydropyranyl;

hal or halogen is Cl, Br or I;

LG is a leaving group such as mesyl, tosyl or triflyl or a halide (hal);

A' is NR₄R₅, NHC(=Y)R₄, NHC(=Y)NR₅R_x, NHC(=O)OR₄, NH₂SO₂R₄, amidino or guanidino, and M is metal selected from potassium, lithium or sodium;

R₇ is hydrogen, halogen (wherein the halogen attached to R₇ is F, Cl, Br, I), hydroxy, -COOR₄, alkyl, alkenyl, alkynyl, cycloalkyl, alkoxy, alkenyloxy, alkynyloxy, aryloxy, heterocyclyloxy, heteroaryloxy, cycloalkyloxy, acyl, thioacyl, cyano, nitro, amino, -CHO, -OCF₃, -CF₃, -SCF₃, -NR₄R₅, -C(=Y)NR₄R₅, -NHC(=Y)R₄, -NHC(=Y)NR₅R_x, -NHC(=O)OR₄, -NH₂SO₂R₄, (SO)_mR₄, aryl, heterocyclyl, heteroaryl, heterocyclylalkyl or heteroarylalkyl which is optionally substituted further;

R₄ is alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heterocyclyl, heteroaryl, aralkyl, heteroarylalkyl, heterocyclylalkyl or cycloalkylalkyl;

m is an integer 0-2;

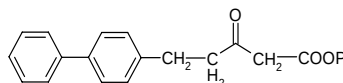
n is an integer from 1 to 5;

R₅ is hydrogen or R₄; and

R_x is R₄ or -SO₂N(R₄)₂.

16. A process for preparing a compound of Formula XXV comprising:

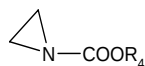
a) reacting a compound of Formula IV



Formula IV

wherein P is alkyl or aralkyl selected from tert-butyl, ethyl or methyl or benzyl;

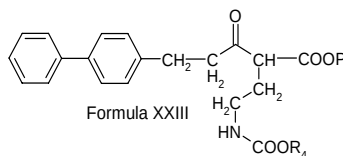
with a compound of Formula XXII



Formula XXII

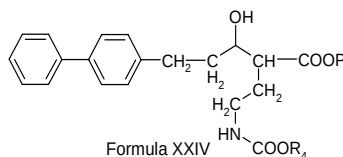
R₄ is alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heterocyclyl, heteroaryl, aralkyl, heteroarylalkyl, heterocyclalkyl or cycloalkylalkyl each of which is optionally substituted further,

to form a compound of Formula XXIII;



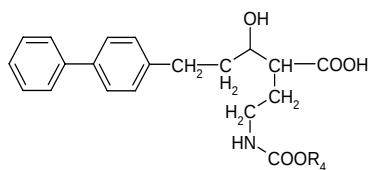
Formula XXIII

b) reducing a compound of Formula XXIII to form a compound of Formula XXIV; and



Formula XXIV

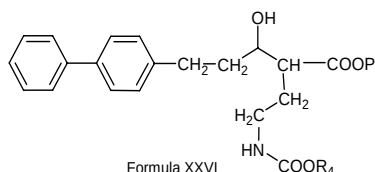
c) deprotecting a compound of Formula XXIV to form a compound of Formula XXV



Formula XXV

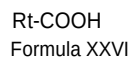
17. A process for preparing a compound of Formula XXXI comprising:

a) reacting a compound of Formula XXIV



Formula XXVI

with a compound of Formula XXVII:



to form a compound of Formula XXVII:

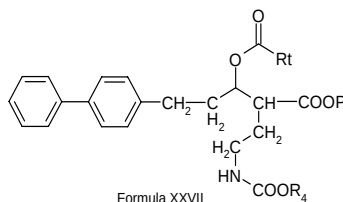
wherein:

P is alkyl or aralkyl selected from tert-butyl, ethyl, methyl or benzyl;

Rt is alkyl, aryl, cycloalkyl, aralkyl, heterocyclylalkyl or heteroarylalkyl;

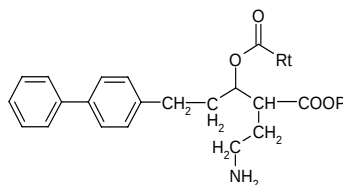
and

R4 is alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heterocyclyl, heteroaryl, aralkyl, heteroarylalkyl, heterocyclylalkyl or cycloalkylalkyl;



Formula XXVII

b) deprotecting a compound of Formula XXVII to form a compound of Formula XXVIII:

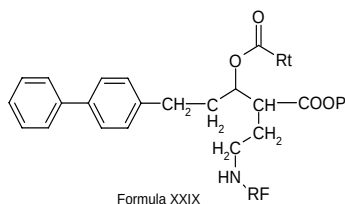


Formula XXVIII

wherein P and Rt are as defined above;

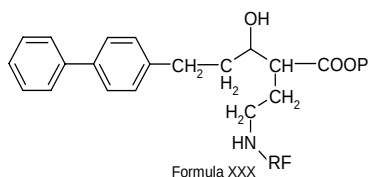
- c) derivatizing a compound of Formula XXVIII with a compound of Formula RD, wherein: RD is R_4COhal , $halCOOR_4$, R_4SO_2hal or $(R_4)N=C(=Y)$, and hal is Cl, Br or I; and Y is oxygen or sulphur;

to form a compound of Formula XXIX:

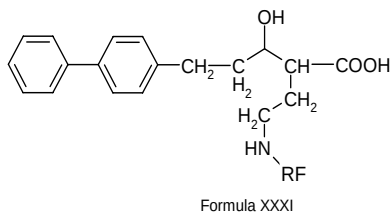


wherein RF is R_4CO- , R_4SO_2- , R_4OCO- or $(R_4)NH-C(=Y)-$;

- d) deprotecting a compound of Formula XXIX to form a compound of Formula XXX; and



- e) deprotecting a compound of Formula XXX to form a compound of Formula XXXI;



18. A process for separation of a compound of Formula VIII, Formula XXI, Formula XXV, Formula XXXI or Formula XXXIV into diastereomer pairs or single diastereomers by preparative thin layer chromatography or by HPLC using an achiral or chiral column.