

PETITORIO

Industria y Comercio
SUPERINTENDENCIA

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



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Act. 411 PRESENTACION Folios: 359

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22/09/2007

①

SOLICITUD DE:

☒ X

Patente de Invención

☐

Patente de Modelo de Utilidad

☒ X

Capítulo I

☐

Capítulo II

②

SOLICITANTE
(71)

Nombre: RANBAXY LABORATORIES LIMITED

Dirección: Plot No 90- Sector 32 Gurgaon, Haryana
122001, India

Nacionalidad o Domicilio: GURGAON, HARYANA, INDIA
Lugar de Constitución: GURGAON, HARYANA, INDIA

Teléfono: 3123600 Fax: 3122410

E-mail: general@cardenasycardenas.com

IDENTIFICACION

C.C.

☐

NIT

☐

C.E.

☐

Otro

☒ X

Cual

Número

③

REPRESENTANTE
O APODERADO

Nombre: DARIO CARDENAS NAVAS

Dirección: Carrera 7 No 71- 52 Torre B Piso 9

Teléfono: 3123600 Fax: 3122410

E-Mail: general@cardenasycardenas.com

IDENTIFICACION

C.C.

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☐

C.E.

☐

Otro

☐

Cual

Número 17.066.629 TP 1.250
C.S.J.

④

INVENTOR(ES)
(72)

Nombre:

1. Palle P. Venkata
2. Sattigeri Viswajanai Jitendra
3. Khera Manoj Kumar
4. Voleti Sreedhara Rao
5. Ray Abhijit
6. Dastidar G. Sunanda

Dirección:

1. Sylvan Heights Sanewadi Aundh, Pune, Maharashtra 411007, India
2. N-323, VijayrattanVihar Gurgaon, Haryana 122001, India
3. C-600/10, Krishna Colony Gurgaon, Haryana 122001, India
4. Apartment No 201 Mahalaksmi CGHS Plot-2, Sector-43 Gurgaon, Haryana 122001, India
5. Sector C-1, Flat No 1408 Vasant Kunj New Delhi, Dheli 110070, India
6. B-138, Sarita Vihar New Deli, Delhi 110044, India

Nacionalidad:

1. HINDÚ
2. HINDÚ
3. HINDÚ
4. HINDÚ
5. HINDÚ
6. HINDÚ

⑤

PCT (86)

Solicitud Internacional No. PCT/ IB2006/000349

Fecha Febrero 21, 2006

Publicación Internacional No. WO 2006/090235 A1

Fecha Agosto 31, 2006

⑥

Título(54):

DERIVADOS DEL ACIDO 5-FENIL-PENTANOICO COMO INHIBIDORES DE METALOPROTEINASA
DE LA MATRIZ PARA EL TRATAMIENTO DEL ASMA Y OTRAS ENFERMEDADES

⑦

Clasificación Internacional (51):

A61K 31/185 A61K 31/192

A61P 11/06 C07D 249/18

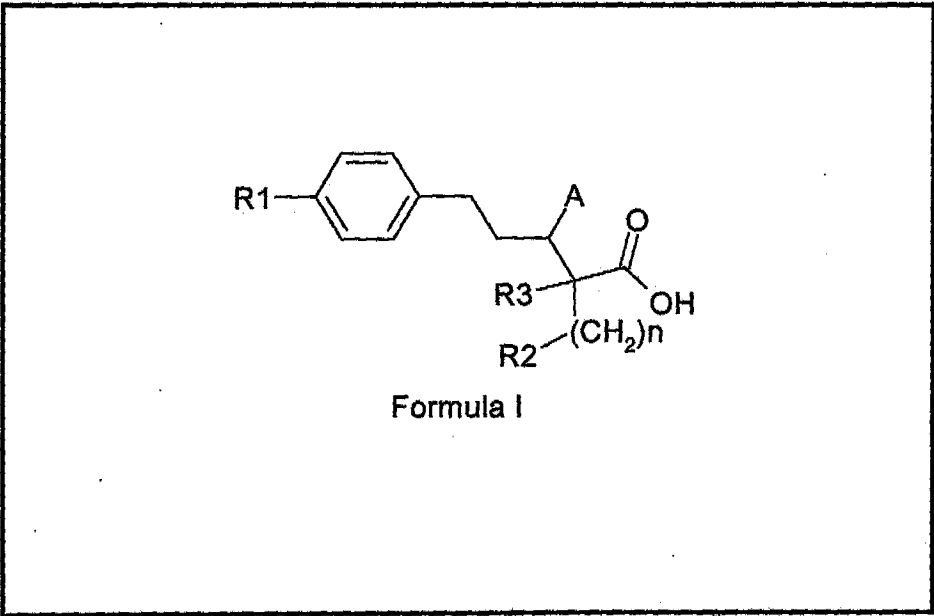
⑧ Prioridad SI ☒ NO ☐	(33)País de Origen INDIA	(32)Fecha Febrero 22, 2005	(31)N° de Solicitud 380/Del/2005

⑨ Comprobante de Pago No.:	07-76,104	Fecha	Sept 20, 2007
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⑩ ANEXOS

- ☒ Comprobante de pago de la tasa de presentación de la solicitud.
- ☐ Documento que acredita la existencia y representación legal cuando el solicitante sea persona jurídica.
- ☐ Poderes, si fuere el caso.
- ☒ Copia del documento de cesión del inventor al solicitante o a su causante.
- ☐ Declaraciones
- ☒ Copia de la solicitud internacional. (Resumen, descripción, reivindicaciones, dibujos)
- ☒ Traducción de la solicitud internacional al castellano. (Resumen, descripción, reivindicaciones, dibujos)
- ☐ Copia del examen preliminar internacional efectuado por la Autoridad Internacional de Examen Preliminar (IPEA).
- ☐ Traducción del examen preliminar internacional efectuado por la IPEA.
- ☐ De ser el caso, copia del contrato de acceso.
- ☐ De ser el caso, documento que acredite la licencia o autorización de uso de conocimientos tradicionales de las comunidades indígenas.
- ☐ De ser el caso, certificado de depósito del material biológico.
- ☐ Arte final 12x12.
- ☐ De ser el caso, información sobre otras solicitudes de patente o títulos obtenidos en el extranjero por el mismo titular o su causante, relacionadas parcial o totalmente con la invención de esta solicitud.
- ☒ De ser el caso, modificaciones efectuadas a la solicitud internacional.

11 FIGURA CARACTERISTICA



12 Solicito la Concesión de la patente.

NOMBRE: DARIO CARDENAS NAVAS

FIRMA:

C.C. 17.066.629 BTA TP 1,250 L
C.S.J.

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



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RECIBO OFICIAL DE CAJA : 07 - 76,104
FECHA : SEPTIEMBRE 20 DE 2007

***** CONSIGNACION *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
CARDENAS Y CARDENAS P.I. CONSIGNACION		BANCO POPULAR	050-00110-6	59812876	20/09/2007	6,302,000.00

***** CONCEPTO *****

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-01 SOLICITUDES	1 TRAMITES DE SOL. DE PATENTE DE IN	482,000.00
		TOTAL :	\$ 482,000.00

SON: CUATROCIENTOS OCHENTA Y DOS MIL PESOS

RESPONSABLE :

CARDENAS & CARDENAS

RECIBO DE CAJA APLICADO AL EXPEDIENTE No.

ABOGADO

ASSIGNMENT OF RIGHTS, TITLE AND INTEREST IN INVENTION

This is an Assignment of the following rights, title and interest (check all that apply):

- ☒ United States of America rights, title and interest in the invention
☒ Indian rights, title and interest in the invention
☒ Foreign (non-Indian, non-United States) rights, title and interest in the invention
____ United States Patent Application Serial No. _____
____ Date of Execution: _____ Date of Filing: _____
____ United States Provisional Patent Application Serial No. _____
____ United States Patent No(s). _____
☒ International (PCT) Patent Application Serial No. PCT/IB2006/000349
____ Other (specify) _____

Title of the Invention:

MATRIX METALLOPROTEINASE INHIBITORS

Inventors (assignors)

Name	Address
Venkata P. PALLE	Sylvan Heights Sanewadi, Aundh 411007 Pune, Maharashtra, INDIA
Viswajanani Jitendra SATTIGERI	N-323, Vijayrattan Vihar 122001 Gurgaon, Haryana, INDIA
Manoj Kumar KHERA	C-600/10, Krishna Colony 122001 Gurgaon, Haryana, INDIA
Sreedhara Rao VOLETI	Apartment No. 201, Mahalakshmi CGHS, Plot - 2, Sector - 43, 122001 Gurgaon, Haryana, INDIA
Abhijit RAY	Sector C-1, Flat No. 1408, Vasant Kunj 110070 New Delhi, Delhi, INDIA
Sunanda G. DASTIDAR	B-138, Sarita Vihar 110044 New Delhi, Delhi, INDIA

Assignee

Name	Address
Ranbaxy Laboratories Limited	Plot No. 90, Sector 32 Gurgaon 122001 Haryana, India

Whereas, we, the above-identified Inventors, have invented certain new and useful improvements in the Invention identified above and described in the above-identified patent application(s) and/or patent(s) (hereinafter referred to as "Invention");

And, whereas we desire to assign our above-identified rights, title and interest in the Invention to the above-identified Assignee;

Now, this indenture witnesseth, that for good and valuable consideration, the receipt of which is hereby acknowledged;

We hereby assign, sell and transfer our above-identified rights, title and interest in said Invention, said application(s) as identified above, including any divisions, continuations, and continuations-in-part thereof, and in and to any and all Letters Patent of the United States, and countries foreign thereto, which may be granted or have granted for said Invention, and in and to any and all reissues and reexaminations thereof, and in and to any and all priority rights, Convention rights, treaty rights, and other benefits accruing or to accrue to us with respect to the filing of applications for patents or securing of patents in the United States and countries foreign thereto, unto said Assignee;

We hereby covenant that the rights and property conveyed by this Assignment are free and clear of any encumbrance, and that we have full right to convey the rights and property as expressed herein;

And we hereby authorize and request the Commissioner of Patents and Trademarks to issue any United States Letters Patent which may issue for said Invention, and any other patent-issuing authority to issue any such Letters Patent which may issue for said Invention, directly to said Assignee, as assignee of the whole right, title and interest thereto;

Docket No. RLL-651

And we further agree to sign and execute all necessary and lawful future documents, including applications for foreign patents, for filing divisions, continuations and continuations-in-part of said application for patent, and/or, for obtaining any reissues or reexaminations of any Letters Patent which may be granted for the aforesaid Invention, as the Assignee or its Designee(s) may from time to time require and prepare at its own expense.

And we further agree, when requested, without further charge to Assignee but at its expense, to communicate to Assignee or its representatives all facts known to us regarding the aforesaid Invention and improvements, testify in any legal proceeding, sign all papers, make all rightful oaths or declarations, and generally perform all acts, which may be necessary, desirable or convenient, to aid Assignee in securing, maintaining and enforcing patents for the aforesaid inventions and improvements in the aforesaid countries, and for vesting title thereto in Assignee:

Inventors' Signatures

Name	Signature	Date
Venkata P. PALLE	P.V.P.P. Acharya	3/1/06
Viswajanani Jitendra SATTIGERI	Viswajanani J.S.	13/9/06
Manoj Kumar KHERA	Manoj K.	13/9/06
Sreedhara Rao VOLETI	Sreedhara R.	13/9/06
Abhijit RAY	Abhijit R.	13 Sep 06
Sunanda G. DASTIDAR	Sunanda G. Dastidar	13/9/06

<HOJA DE RUTA DE DOCUMENTOS

DEPARTAMENTO DE PROPIEDAD INTELECTUAL

CORRESPONSAL:			
CLIENTE (TITULAR)	CALSA DE COLOMBIA S.A.		
CONTACTO:	RUBIELA RAMIREZ		
REGISTRO SANITARIO:	Producto Graso Masaplus	CLASE	EXPED. / REG.
REGISTRO SANITARIO:			
CON CARGO A:	☐ Corresponsal ☒ Cliente (Titular)	☐ C&C P.I. ☐ C&C	☐ Personal
SOLICITADO POR:	ROLANDO ESCOBAR LOZANO		
DOCUMENTO:	(1) Documento (s) (CNRS) de No. Registro Sanitarios Fleischmann.		

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RECIBIDO: ____/____/____

TRAMITE:

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NOTARIADO Y REGISTRO			
MINRELACIONES VENEZUELA			
CONSULADO -GLORIA			
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MINRELACIONES			
FOTOCOPIAS			
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ENTREGADO AL ABOGADO RESPONSABLE			

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REGISTRO SANITARIO:	Producto Graso Masaplus	CLASE	EXPED. / REG.
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SOLICITADO POR:	ROLANDO ESCOBAR LOZANO		
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ENTREGADO A IVONNE y/o GLORIA EL: 19.09.2007

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C07D 211/88 (2006.01)

C-600/10, Krishna Colony, Gurgaon, Haryana 122001 (IN). **VOLETI, Sreedhara, Rao** [IN/IN]; Apartment No. 201, Mahalakshmi Cghs, Plot -2, Sector -43, Gurgaon, Haryana 122001 (IN). **RAY, Abhijit** [IN/IN]; Sector C-1, Flat No. 1408, Vasant Kunj, New Delhi, Delhi 110070 (IN). **DASTIDAR, Sunanda, G.** [IN/IN]; B-138, Sarita Vihar, New Delhi, Delhi 110044 (IN).

(74) Common Representative: **RANBAXY LABORATORIES LIMITED**; c/o DESHMUKH, Jay R., 600 College Road East, Suite 2100, Princeton, New Jersey 08540 (US).

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(71) Applicant (for all designated States except US): **RANBAXY LABORATORIES LIMITED** [IN/IN]; Plot No. 90, Sector 32, Gurgaon, Haryana 122001 (IN).

(72) Inventors; and

(75) Inventors/Applicants (for US only): **PALLE, Venkata, P.** [US/IN]; Sylvan Heights Sanewadi, Aundh, Pune, Maharashtra 411007 (IN). **SATTIGERI, Viswajanani, Jitendra** [IS/IN]; N-323, Vijayrattan Vihar, Gurgaon, Haryana 122001 (IN). **KHERA, Manoj, Kumar** [IN/IN];

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

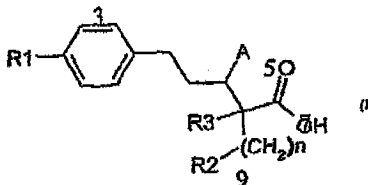
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[Continued on next page]

(54) Title: 5-PHENYL-PENTANOIC ACID DERIVATIVES AS MATRIX METALLOPROTEINASE INHIBITORS FOR THE TREATMENT OF ASTHMA AND OTHER DISEASES



(57) Abstract: The present invention relates to C ompounds having the structure of Formula I: wherein n is an integer from 1 to 5; R₁ is optionally substituted alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heterocyclyl, heteroaryl, aralkyl, alkoxy, aryloxy, alkenyloxy or alkynyloxy; R₂ is alkenyl, alleynyl, aryl, heterocyclyl, heteroaryl, cycloalkyl, NR₄R₅, -NHC(=Y)R₄, -NHC(=Y)NR₅R₆, -NHC(=O)OR₄, -NHSO₂R₄, C(=Y)NR₄R₅, C(=O)OR₄ [wherein Y is oxygen or sulphur], OR₅, -O(C=O)NR₄R₅, O-acyl, S(O)_mR₄, -SO₂N(R₄)₂, cyano, amidino or guanidino [wherein R₄ is alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heterocyclyl, heteroaryl, aralkyl, heteroarylalkyl, heterocyclylalkyl or cycloalkylalkyl and m is an integer 0-2; R₅ is hydrogen or R₄; R₆ is R₄ or -SO₂N(R₄)₂ and R₆ is hydrogen, alkyl, cycloalkyl, aralkyl, heteroarylalkyl, heterocyclylalkyl or cycloalkylalkyl]; R₃ is hydrogen, fluorine, alkyl, cycloalkylalkyl or aralkyl; A is OH, OR₄, -OC(=O)NR₄R₅, O-acyl, NH₂, NR₄R₅, -NHC(=Y)R₄, -NHC(=Y)NR₅R₆, -NHC(=O)OR₄, -NHSO₂R₄, and to processes for the 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 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.



— before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments

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

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 synthesis of the same. This invention also relates to pharmacological compositions
5 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 restenosis and ischemic heart failure, stroke, renal diseases, tumor metastasis, and other
10 inflammatory disorders characterized by over-expression and over-activation of an matrix metalloproteinase, using the compounds.

Background of the Invention

Matrix metalloproteinases (MMPs) are a naturally occurring superfamily of proteinases (enzymes) found in most mammals. The superfamily is composed of at least 26 members
15 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-12), the MT-MMPs (MMP-14, MMP-15) and sheddases such as TNF-converting enzymes
20 (TACE, ACE).

Matrix 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 MMPs is to catalyze the breakdown of connective tissues or extra-cellular matrix by their
25 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
30 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. 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.

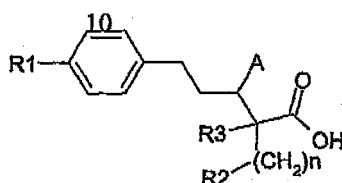
In another aspect, pharmaceutical compositions containing such compounds are provided together with acceptable carriers, excipients or diluents, which can be useful for the treatment of inflammatory and autoimmune diseases.

The racemates, enantiomers, diastereomers, rotational isomers, N-oxides, polymorphs, pharmaceutically acceptable salts and pharmaceutically acceptable solvates of these compounds, prodrugs and metabolites having the same type of activity are also

provided, as well as pharmaceutical compositions comprising the compounds, their metabolites, racemates, enantiomers, diastereomers, conformational isomers, N-oxides, polymorphs, solvates or pharmaceutically acceptable salts thereof, in combination with a pharmaceutically acceptable carrier and optionally included excipients.

5 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 1

wherein

n is an integer from 1 to 5;

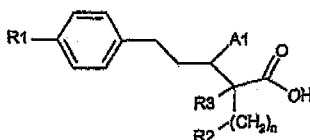
R_1 can be optionally substituted alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heterocyclyl, heteroaryl, aralkyl, alkoxy, aryloxy, alkenyloxy or alkynyloxy;

R_2 can be alkenyl, alkynyl, aryl, heterocyclyl, heteroaryl, cycloalkyl, NR_4R_5 , $-NHC(=Y)R_4$, $-NHC(=Y)NR_5R_x$, $-NHC(=O)OR_4$, $-NHOSO_2R_4$, $C(=Y)NR_4R_5$, $C(=O)OR_6$ [wherein Y can be oxygen or sulphur], OR_5 , $-OC(=O)NR_4R_5$, O-acyl, $S(O)_mR_4$, $-SO_2N(R_4)_2$, cyano, amidino or guanidino [wherein R_4 can be alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heterocyclyl, heteroaryl, aralkyl, heteroarylalkyl, heterocyclylalkyl or cycloalkylalkyl and m is an integer 0-2; R_5 can be hydrogen or R_4 ; R_x can be R_4 or $-SO_2N(R_4)_2$ and R_6 is hydrogen, alkyl, cycloalkyl, aralkyl, heteroarylalkyl, heterocyclylalkyl or cycloalkylalkyl];

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

30 A can be OH, OR₄, -OC(=O)NR₄R₅, O-acyl, NH₂, NR₄R₅, -NHC(=Y)R₄, -NHC(=Y)NR₅R₆, -NHC(=O)OR₄, -NHSO₂R₄.

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

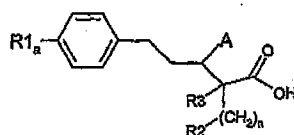


Formula Ia

wherein

- A1 can be OH, -OC(=O)NR₄R₅, NH₂, NR₄R₅, -NHC(=Y)R₄, -NHC(=Y)NR₅R_x,
 5 -NHC(=O)OR₄, -NHSO₂R₄;
 n, R₁, R₂, R₃ and R₄ can be as defined earlier.

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

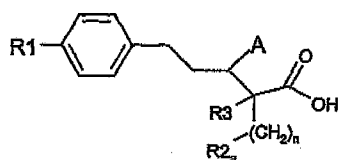


Formula Ib

wherein

- 10 R_{1a} can be aryl or heteroaryl;
 n, R₂, R₃ and A can be as defined earlier.

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



Formula Ic

wherein

- 15 R_{2a} can be NR₄R₅, -NHC(=Y)R₄, -NHC(=Y)NR₅R_x, -NHC(=O)OR₄, -NHSO₂R₄, 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 R_4 or $-SO_2N(R_4)_2$;

n , R_1 , R_3 and A can be as defined earlier.

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

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

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

10 5-(4'-Butylbiphenyl-4-yl)-2-[2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)ethyl]-3-hydroxypentanoic acid (Compound No. 3),

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

15 2-[2-(1,3-Dioxo-1,3-dihydro-2H-isoindol-2-yl)ethyl]-3-hydroxy-5-(4'-trifluoromethoxybiphenyl-4-yl)pentanoic acid (Compound No. 5),

2-[2-(1,3-Dioxo-1,3-dihydro-2H-isoindol-2-yl)ethyl]-5-(4'-ethoxybiphenyl-4-yl)-3-hydroxypentanoic acid (Compound No. 6),

2-[2-(1,3-Dioxo-1,3-dihydro-2H-isoindol-2-yl)ethyl]-5-(4'-formylbiphenyl-4-yl)-3-hydroxypentanoic acid (Compound No. 7),

20 2-[2-(1,3-Dioxo-1,3-dihydro-2H-isoindol-2-yl)ethyl]-3-hydroxy-5-(2',4',6'-trimethoxybiphenyl-4-yl)pentanoic acid (Compound No. 8),

2-[2-(1,3-Dioxo-1,3-dihydro-2H-isoindol-2-yl)ethyl]-3-hydroxy-5-(4'-propoxybiphenyl-4-yl)pentanoic acid (Compound No. 9),

25 5-(3',4'-Difluorobiphenyl-4-yl)-2-[2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)ethyl]-3-hydroxypentanoic acid (Compound No. 10),

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

5-Biphenyl-4-yl-2-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxypentanoic
acid (Compound No. 12),

5 (2*R*,3*S* + 2*S*,3*R*)-2-[2-(1,3-Dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-5-(4'-
formylbiphenyl-4-yl)-3-hydroxypentanoic acid (Compound No. 13),

(2*R*,3*R* + 2*S*,3*S*)-2-[2-(1,3-Dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-5-(4'-
formylbiphenyl-4-yl)-3-hydroxypentanoic acid (Compound No. 14),

(2*R*,3*R* + 2*S*,3*S*)-2-[2-(1,3-Dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxy-5-
10 (2',4',6'-trimethoxybiphenyl-4-yl)pentanoic acid (Compound No.15),

(2*R*,3*S* + 2*S*,3*R*)-2-[2-(1,3-Dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxy-5-
(2',4',6'-trimethoxybiphenyl-4-yl)pentanoic acid (Compound No. 16),

(2*R*,3*S* + 2*S*,3*R*)-5-(4'-Acetylbiphenyl-4-yl)-2-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-
yl)ethyl]-3-hydroxypentanoic acid (Compound No. 17),

15 (2*R*,3*R* + 2*S*,3*S*)-5-(4'-Acetylbiphenyl-4-yl)-2-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-
yl)ethyl]-3-hydroxypentanoic acid (Compound No. 18),

(2*R*,3*S* + 2*S*,3*R*)-2-[2-(1,3-Dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxy-5-(4'-
propoxybiphenyl-4-yl)pentanoic acid (Compound No. 19),

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

(2*R*,3*S* + 2*S*,3*R*)-5-(3',4'-Difluorobiphenyl-4-yl)-2-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-
2-yl)ethyl]-3-hydroxypentanoic acid (Compound No. 21),

(2*R*,3*R* + 2*S*,3*S*)-5-(3',4'-Difluorobiphenyl-4-yl)-2-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-
2-yl)ethyl]-3-hydroxypentanoic acid (Compound No. 22),

- 2-[2-(1,3-Dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxy-5-(4'-methoxybiphenyl-4-yl)pentanoic acid (Compound No. 23),
- 5-(2',3'-Dimethylbiphenyl-4-yl)-2-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxypentanoic acid (Compound No. 24),
- 5 2-[2-(1,3-Dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxy-5-[3'-(trifluoromethyl)biphenyl-4-yl]pentanoic acid (Compound No. 25),
- 2-[2-(1,3-Dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-5-(4'-ethylbiphenyl-4-yl)-3-hydroxypentanoic acid (Compound No. 26),
- 5-(3',5'-Dichlorobiphenyl-4-yl)-2-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxypentanoic acid (Compound No. 27),
- 10 5-[4'-Chloro-3'-(trifluoromethyl)biphenyl-4-yl]-2-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxypentanoic acid (Compound No. 28),
- 5-(2',5'-Difluorobiphenyl-4-yl)-2-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxypentanoic acid (Compound No. 29),
- 15 2-[2-(1,3-Dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxy-5-[2'-(trifluoromethoxy)biphenyl-4-yl]pentanoic acid (Compound No. 30),
- 2-[2-(1,3-Dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxy-5-[4'-(methylthio)biphenyl-4-yl]pentanoic acid (Compound No. 31),
- 2-[2-(1,3-Dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-5-(4'-fluoro-3'-methylbiphenyl-4-yl)-3-hydroxypentanoic acid (Compound No. 32),
- 20 2-[2-(1,3-Dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxy-5-(3'-isopropylbiphenyl-4-yl)pentanoic acid (Compound No. 33),
- 5-(3',4'-Dimethylbiphenyl-4-yl)-2-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxypentanoic acid (Compound No. 34),

- 5-(2',6'-Difluorobiphenyl-4-yl)-2-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxypentanoic acid (Compound No. 35),
- 2-[2-(1,3-Dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-5-(4'-fluorobiphenyl-4-yl)-3-hydroxypentanoic acid (Compound No. 36),
- 5 5-(3',5'-Difluorobiphenyl-4-yl)-2-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxypentanoic acid (Compound No. 37),
- 5-(3'-Chloro-4'-fluorobiphenyl-4-yl)-2-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxypentanoic acid (Compound No. 38),
- 5-(3',4'-Dimethoxybiphenyl-4-yl)-2-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxypentanoic acid (Compound No. 39),
- 10 5-(3'-Chlorobiphenyl-4-yl)-2-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxypentanoic acid (Compound No. 40),
- 2-[2-(1,3-Dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxy-5-(3'-methylbiphenyl-4-yl)pentanoic acid (Compound No. 41),
- 15 5-(2',3'-Difluorobiphenyl-4-yl)-2-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxypentanoic acid (Compound No. 42),
- 2-[2-(1,3-Dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-5-(2'-fluoro-3'-methoxybiphenyl-4-yl)-3-hydroxypentanoic acid (Compound No. 43),
- 2-[2-(1,3-Dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-5-(3'-fluoro-4'-methylbiphenyl-4-yl)-3-hydroxypentanoic acid (Compound No. 44),
- 20 5-Biphenyl-4-yl-3-hydroxy-2-{2-[(phenylacetyl)amino]ethyl}pentanoic acid (Compound No. 45),
- 2-(3-Biphenyl-4-yl-1-hydroxypropyl)-6-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)hexanoic acid (Compound No. 46),

- 5-Biphenyl-4-yl-3-hydroxy-2-[2-(1-oxophthalazin-2(1*H*)-yl)ethyl]pentanoic acid
(Compound No. 47),
- 5-Biphenyl-4-yl-2-[3-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)propyl]-3-hydroxypentanoic acid (Compound No. 48),
- 5 5-Biphenyl-4-yl-3-hydroxy-2-[2-(2'-oxospiro[cyclopropane-1,3'-indol]-1'(2'*H*)-yl)ethyl]pentanoic acid (Compound No. 49),
- 2-[2-(1,3-Dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxy-5-(4'-hydroxybiphenyl-4-yl)pentanoic acid (Compound No. 50),
- 3-Hydroxy-5-(4'-methoxybiphenyl-4-yl)-2-[2-(3-methyl-2,6-dioxo-3,6-dihydropyrimidin-1(2*H*)-yl)ethyl]pentanoic acid (Compound No. 51),
- 10 1-(2*H*)-yl)ethyl]pentanoic acid (Compound No. 51),
- 5-(4'-Chlorobiphenyl-4-yl)-3-hydroxy-2-[2-(3-methyl-2,6-dioxo-3,6-dihydropyrimidin-1(2*H*)-yl)ethyl]pentanoic acid (Compound No. 52),
- 5-(4'-Fluorobiphenyl-4-yl)-3-hydroxy-2-[2-(3-methyl-2,6-dioxo-3,6-dihydropyrimidin-1(2*H*)-yl)ethyl]pentanoic acid (Compound No. 53),
- 15 5-[4-(5-Chloro-2-thienyl)phenyl]-2-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxypentanoic acid (Compound No. 54),
- 4'-[4-Carboxy-6-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)-3-hydroxyhexyl]biphenyl-4-carboxylic acid (Compound No. 55),
- 2-[2-(1,3-Dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxy-5-[4'-(methoxycarbonyl)biphenyl-4-yl]pentanoic acid (Compound No. 56),
- 20 2-[2-(1,3-Dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxy-5-[4'-(trifluoromethyl)biphenyl-4-yl]pentanoic acid (Compound No. 57),
- 2-[2-(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. 58),

- 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);
- 5 2-[2-(1,3-Dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-5-(3'-fluorobiphenyl-4-yl)-3-hydroxypentanoic acid (Compound No. 61),
- 5-[4'-(Benzyloxy)-3'-fluorobiphenyl-4-yl]-2-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxypentanoic acid (Compound No. 62),
- 5-[4'-(Benzyloxy)biphenyl-4-yl]-2-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-
10 hydroxypentanoic acid (Compound No. 63),
- 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),
- 15 2-[2-(1,3-Dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxy-5-(4'-methylbiphenyl-4-yl)pentanoic acid (Compound No. 66),
- 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-
20 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),
- 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),
- 5 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),
- 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),
- 10 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),
- 15 (2*R*,3*S* + 2*S*,3*R*)-2-[2-(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. 78),
- (2*R*,3*R* + 2*S*,3*S*)-2-[2-(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. 79),
- (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-hydroxypentanoic acid (Compound No. 80),
- 20 (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 (Compound No. 81),
- (2*R*,3*S* + 2*S*,3*R*)-2-[2-(1,3-Dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-5-(4'-fluorobiphenyl-4-yl)-3-hydroxypentanoic acid (Compound No. 82),

- (2*R*,3*R* + 2*S*,3*S*)-2-[2-(1,3-Dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-5-(4'-fluorobiphenyl-4-yl)-3-hydroxypentanoic acid (Compound No. 83),
- 5-Biphenyl-4-yl-3-hydroxy-2-[2-(1-oxo-4-phenyl-4*a*,8*a*-dihydrophthalazin-2(1*H*)-yl)ethyl]pentanoic acid (Compound No. 84),
- 5 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-[(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-(4-fluorophenyl)sulfonyl]amino]ethyl)-3-hydroxypentanoic acid
10 (Compound No. 87),
- 5-Biphenyl-4-yl-2-(2-[[3-(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),
- 15 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-
20 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),
- 25 2-(3-Biphenyl-4-yl-1-hydroxypropyl)pent-4-ynoic acid (Compound No. 95),

- 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 5-{4-[6-(Dimethylamino)pyridin-3-yl]phenyl}-2-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxypentanoic acid (Compound No. 98),
- 2-[2-(1,3-Dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxy-5-[4'-(methylsulfonyl)biphenyl-4-yl]pentanoic acid (Compound No. 99),
- 5-[4'-(Aminocarbonyl)biphenyl-4-yl]-2-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxypentanoic acid (Compound No. 100),
- 10 5-[4-(1-Benzyl-1*H*-pyrazol-4-yl)phenyl]-2-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxypentanoic acid (Compound No. 101),
- 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),
- 15 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),
- 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]-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),

- (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),
- 5 2-[2-(1,3-Dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-5-(3'-fluoro-4'-methoxybiphenyl-4-yl)-3-hydroxypentanoic acid (Compound No. 110),
- (2*R*,3*S* + 2*S*,3*R*)-2-[2-(1,3-Dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxy-5-[4-(6-methylpyridin-3-yl)phenyl]pentanoic acid (Compound No. 111),
- (2*R*,3*R* + 2*S*,3*S*)-2-[2-(1,3-Dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxy-5-[4-(6-methylpyridin-3-yl)phenyl]pentanoic acid (Compound No. 112),
- 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),
- 2-[2-(1,3-Dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxy-5-(4-pyrimidin-5-ylphenyl)pentanoic acid (Compound No. 119),

- 5-Biphenyl-4-yl-3-hydroxy-2-[2-(7-methyl-4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)ethyl]pentanoic acid (Compound No. 120),
- 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 (2*R*,3*S*)-5-Biphenyl-4-yl-3-hydroxy-2-[2-(1*H*-indol-3-yl)ethyl]pentanoic acid (Compound No. 122),
- (2*R*,3*R*)-5-Biphenyl-4-yl-3-hydroxy-2-[2-(1*H*-indol-3-yl)ethyl]pentanoic acid (Compound No. 123),
- 5-Biphenyl-4-yl-3-hydroxy-2-[2-(1-oxo-1,3-dihydro-2*H*-isoindol-2-yl) butyl]pentanoic acid (Compound No. 124),
- 10 (2*R*,3*S*)-5-(4'-Chlorobiphenyl-4-yl)-2-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxypentanoic acid (Compound No.125),
- (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 (Compound No.126),
- 15 (2*R*,3*R*)-5-(4'-Chlorobiphenyl-4-yl)-2-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxypentanoic acid (Compound No.127),
- (2*S*,3*S*)-5-(4'-Chlorobiphenyl-4-yl)-2-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxypentanoic acid (Compound No.128),
- (2*R*,3*S*)-2-[2-(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. 129),
- 20 (2*S*,3*R*)-2-[2-(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. 130),
- (2*R*,3*R*)-2-[2-(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. 131),

(2S,3S)-2-[2-(1,3-Dioxo-1,3-dihydro-2H-isoindol-2-yl)ethyl]-3-hydroxy-5-[4-(6-methoxypyridin-3-yl)phenyl]pentanoic acid (Compound No. 132),

(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),

5 (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), and

10 (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).

In another embodiment, the invention encompasses separation of the individual 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
15 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.

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
20 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
25 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.

5 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.

- 10 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 , $\text{-NR}_f\text{R}_q$, $\text{-C(=O)NR}_f\text{R}_q$,
 15 $\text{-NHC(=O)NR}_f\text{R}_q$, -C(=O)heteroaryl , C(=O)heterocyclyl , $\text{-O-C(=O)NR}_f\text{R}_q$ {wherein R_f and R_q are independently selected from alkyl, alkenyl, cycloalkyl, cycloalkenyl, aryl, aralkyl, heterocyclyl, heteroaryl, heterocyclylalkyl, heteroarylalkyl}, nitro, or $\text{-SO}_2\text{R}_6$ (wherein R_6 is alkyl, alkenyl, alkynyl, cycloalkyl, aralkyl, aryl, heterocyclyl, heteroaryl, heteroarylalkyl or heterocyclylalkyl). Unless otherwise constrained by the definition,
 20 alkyl substituents may be further substituted by 1-3 substituents selected from alkyl, carboxy, $\text{-NR}_f\text{R}_q$, $\text{-C(=O)NR}_f\text{R}_q$, $\text{-OC(=O)NR}_f\text{R}_q$, $\text{-NHC(=O)NR}_f\text{R}_q$ (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 -NR_a - {wherein R_a is
 25 selected from hydrogen, alkyl, cycloalkyl, alkenyl, cycloalkenyl, alkynyl, aryl, acyl, aralkyl, -C(=O)OR_f (wherein R_f is the same as defined earlier), SO_2R_6 (where R_6 is as defined earlier), or $\text{-C(=O)NR}_f\text{R}_q$ (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, $\text{-NR}_f\text{R}_q$, $\text{-C(=O)NR}_f\text{R}_q$, $\text{-O-C(=O)NR}_f\text{R}_q$
 30 (wherein R_f and R_q are the same as defined earlier) hydroxy, alkoxy, halogen, CF_3 , cyano, and $\text{-SO}_2\text{R}_6$ (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 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, -NHC(=O)R_f, -NR_fR_q, -C(=O)NR_fR_q, -NHC(=O)NR_fR_q, -O-C(=O)NR_fR_q (wherein R_f and R_q are the same as defined earlier), 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 SO₂R₆ (wherein R₆ are is same as defined earlier). Unless otherwise constrained by the definition, alkenyl substituents optionally may be substituted further by 1-3 substituents selected from alkyl, carboxy, hydroxy, alkoxy, halogen, -CF₃, cyano, -NR_fR_q, -C(=O)NR_fR_q, -O-C(=O)NR_fR_q (wherein R_f and R_q are the same as defined earlier) and -SO₂R₆ (where R₆ 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 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, -NR_fR_q, -NHC(=O)NR_fR_q, -C(=O)NR_fR_q, -O-C(=O)NR_fR_q (wherein R_f and R_q are the same as defined earlier), or -SO₂R₆ (wherein R₆ 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, CF₃, -NR_fR_q, -C(=O)NR_fR_q, -NHC(=O)NR_fR_q, -C(=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).

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.

- 5 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, CF₃, cyano, nitro, COOR_e (wherein R_e is hydrogen, alkyl, alkenyl, cycloalkyl, aralkyl, heterocyclalkyl, heteroarylalkyl), NHC(=O)R_f,
 10 -NR_fR_q, -C(=O)NR_fR_q, -NHC(=O)NR_fR_q, -O-C(=O)NR_fR_q (wherein R_f and R_q are the same as defined earlier), -SO₂R_e (wherein R_e is same as defined earlier), carboxy, heterocyclyl, heteroaryl, heterocyclalkyl, 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.

- 15 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),
 20 hydroxy, alkyl, alkenyl, alkynyl, cycloalkyl, acyl, carboxy, aryl, alkoxy, aralkyl, cyano, nitro, heterocyclyl, heteroaryl, -NR_fR_q, CH=NOH, -(CH₂)_wC(=O)R_g {wherein w is an integer from 0-4 and R_g is hydrogen, hydroxy, OR_z, NR_fR_q, -NHOR_z or -NHOH},
 -C(=O)NR_fR_q and -NHC(=O)NR_fR_q, -SO₂R_e, -O-C(=O)NR_fR_q, -O-C(=O)R_e, -O-C(=O)OR_f (wherein R_e, R_f and R_q are as defined earlier, and R_z is alkyl, cycloalkyl, aryl,
 25 heteroaryl, heterocyclyl, heteroarylalkyl or heterocyclalkyl). Unless otherwise 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,
 30 furanyl, benzofuranyl, indolyl, benzothiazolyl, or benzoxazolyl, and the like.

- 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,
- 5 wherein the substituents are selected from halogen (*e.g.*, F, Cl, Br, I), hydroxy, alkyl, alkenyl, alkynyl, cycloalkyl, acyl, aryl, alkoxy, alkaryl, cyano, nitro, oxo, carboxy, heterocyclyl, heteroaryl, $-O-C(=O)R_5$, $-O-C(=O)OR_5$, $-C(=O)NR_5R_6$, SO_2R_6 , $-O-C(=O)NR_5R_6$, $-NHC(=O)NR_5R_6$, $-NR_5R_6$ (wherein R_5 , R_6 and R_7 are as defined earlier) or guanidine. Heterocyclyl can optionally include rings having one or more double bonds.
- 10 Unless otherwise constrained by the definition, the substituents are attached to the ring 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, dihydrobenzofuranyl, azabicyclohexyl, dihydroindolyl,
- 15 pyridinyl, isoindole 1,3-dione, piperidinyl or piperazinyl.

- 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,
- 20 including cyclopropyl, cyclobutyl, cyclooctyl, cyclopentenyl, and the like, or multiple ring 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,
- 25 acyl, acylamino, acyloxy, alkoxycarbonylamino, azido, cyano, halogen, hydroxy, oxo, thiocarbonyl, carboxy, carboxyalkyl, arylthio, thiol, alkylthio, aryl, aralkyl, aryloxy, aminosulfonyl, aminocarbonylamino, $-NR_5R_6$, $-NHC(=O)NR_5R_6$, $-NHC(=O)R_5$, $-C(=O)NR_5R_6$, $-O-C(=O)NR_5R_6$ (wherein R_5 and R_6 are the same as defined earlier), nitro, heterocyclyl, heteroaryl, heterocyclylalkyl, heteroarylalkyl, or SO_2-R_6 (wherein R_6 is same
- 30 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, CF_3 , $-NR_5R_6$, $-C(=O)NR_5R_6$, $-NHC(=O)NR_5R_6$, $-OC(=O)NR_5R_6$

(wherein R_f and R_g are the same as defined earlier), cyano or $-\text{SO}_2\text{R}_6$ (where R_6 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,
 5 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.

"Heterocyclalkyl" refers to alkyl-heterocycl group linked through alkyl
 10 portion, wherein the alkyl and heterocycl are as defined earlier.

"Amine," unless otherwise specified, refers to $-\text{NH}_2$. "Substituted amino" unless otherwise specified, refers to a group $-\text{N}(\text{R}_k)_2$ 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, heterocycl, heterocyclalkyl, heteroarylalkyl, acyl, $\text{S}(\text{O})_m\text{R}_6$ (wherein m and R_6 is the same as defined above), $-\text{C}(=\text{R}_v)\text{NR}_x\text{R}_y$ (wherein R_v is O or S & R_x and R_y are the same as defined earlier) or $\text{NHC}(=\text{R}_v)\text{NR}_x\text{R}_y$ (wherein R_v , R_x and R_y are the same as defined earlier).
 15 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, heterocycl, carboxy, $-\text{COOR}_7$ (wherein R_7 is the same as defined earlier), hydroxy, alkoxy, halogen, CF_3 , cyano, $-\text{C}(=\text{R}_v)\text{NR}_x\text{R}_y$ (wherein R_v is the same as defined earlier), $-\text{O}(\text{C}=\text{O})\text{NR}_x\text{R}_y$, $-\text{OC}(=\text{R}_v)\text{NR}_x\text{R}_y$ (wherein R_x , R_y and R_v are the same as defined earlier), $-\text{S}(\text{O})_m\text{R}_6$ (where R_6 and m is the same as defined above).
 20

"Acyl" refers to $-\text{C}(=\text{O})\text{R}''$ wherein R'' is selected from hydrogen, alkyl, cycloalkyl, aryl, aralkyl, heteroaryl, heterocycl, heteroarylalkyl or heterocyclalkyl.
 25

The term "thioacyl" refers to $-\text{C}(=\text{S})\text{R}_4$ wherein R_4 is the same as defined above. "Thiocarbonyl" refers to $-\text{C}(=\text{S})\text{H}$. "Substituted thiocarbonyl" refers to $-\text{C}(=\text{S})\text{R}''$, wherein R'' is selected from alkyl, cycloalkyl, aryl, aralkyl, heteroaryl, heterocycl, heteroarylalkyl or heterocyclalkyl, amine or substituted amine.

30 The term "halogen" refers to fluorine, chlorine, bromine or iodine;

34

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.

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, New York, N.Y., which is incorporated herein by reference. 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.

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

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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.

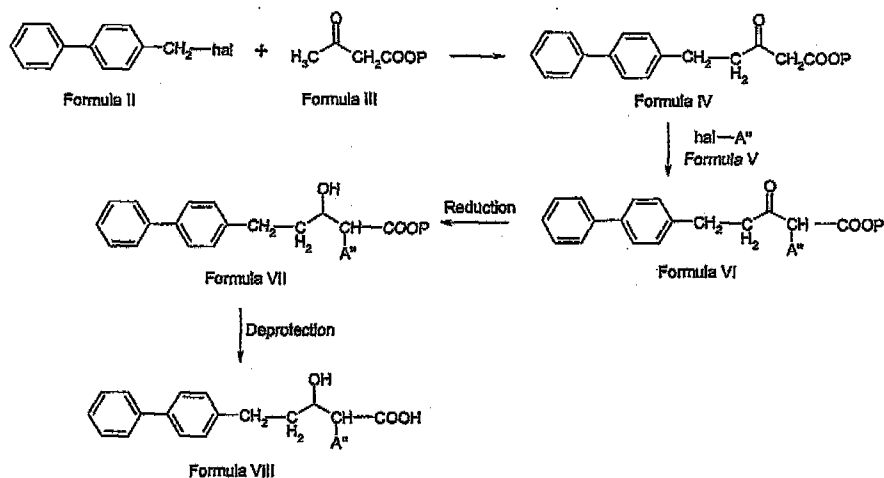
Detailed Description of the Invention

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.

Scheme I

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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 (for example, benzyl)] to give a compound

Formula IV, which on reaction with a compound of Formula V (wherein hal is the same as defined above and A" is aralkyl, heterocyclalkyl, 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.

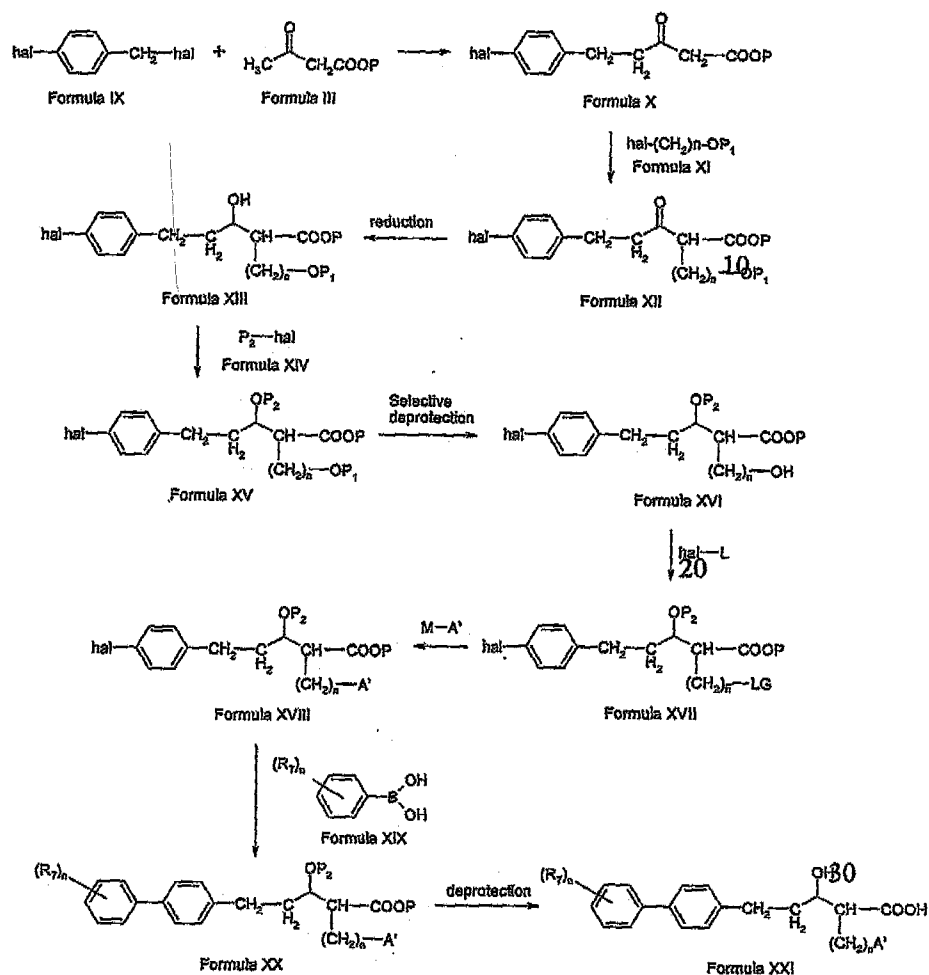
5 The reaction of a compound of Formula II with a compound of Formula III to give a compound of Formula IV can be carried out in the presence of a base or a combination thereof, for example, sodium hydride, butyl lithium or lithiumdiisopropylamide in an organic solvent, for example, tetrahydrofuran, dimethylformamide, dioxane or diethylether.

10 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
15 bromide, in an appropriate organic solvent for example, *t*-butanol, ethanol, tetrahydrofuran, dimethylformamide, diethylether or dioxane.

 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,
20 isopropylalcohol and/or tetrahydrofuran.

 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'



- 35 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
- 40 earlier and P_1 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 P_2 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, -NHSO₂R₄, (SO)_mR₄ (wherein R₄, R₅, R_x, Y and m are the same as defined earlier), aryl, heterocyclyl, heteroaryl, heterocyclylalkyl 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.

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

30 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-toulenesulphonate or trityl perchlorate, in an organic solvent, for example,

5 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, tetrahydrofuran, dimethylformamide, diethyl ether or dioxane.

10 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 diisopropylethylamine, in an organic solvent, for example, dichloromethane,

15 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, dimethylacetamide. Alternately, the reaction of a compound of Formula XVII with a

20 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.

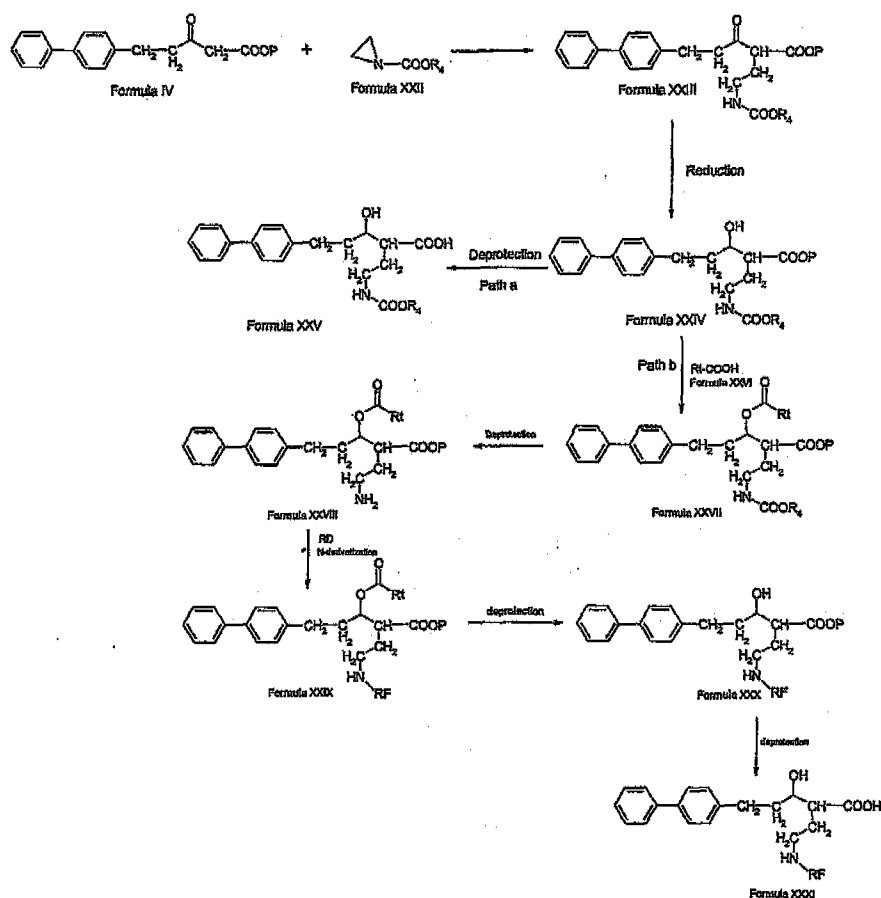
The reaction of a compound of Formula XVIII with a compound of Formula XIX

25 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,

30 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



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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

10 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 Rt is alkyl, aryl, cycloalkyl, aralkyl, heterocyclylalkyl or heteroarylalkyl) gives a compound of Formula 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 R_4COhal , $halCOOR_4$, R_4SO_2hal or $(R_4)N=C(=Y)$ wherein Y is O or S) to give a compound of Formula XXIX (wherein RF is R_4CO- , R_4SO_2- , R_4OCO- or $(R_4)NH-C(=Y)-$), which can undergo deprotection to give a compound of Formula XXX, which can undergo further 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, 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 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-methylmorpholine 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, 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.

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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 example, pyridine, N-methylmorpholine, N-ethyldiisopropylamine, triethylamine or

5 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-ethyldiisopropylamine, N-methylmorpholine or pyridine, in an organic solvent, for

10 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 example, triethylamine, N-ethyldiisopropylamine, N-methylmorpholine or pyridine, in an

15 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 presence of a base, for example, lithium hydroxide, sodium hydroxide, potassium

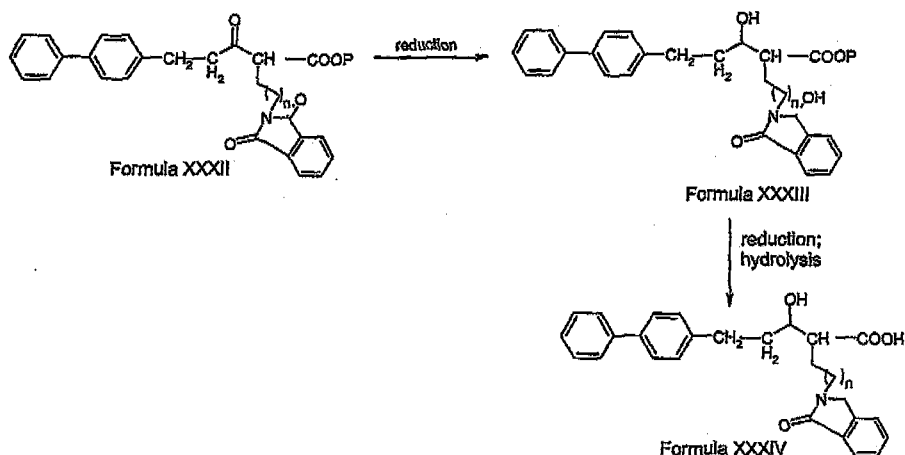
20 hydroxide, in an organic solvent, for example, methanol, tetrahydrofuran, water or mixtures thereof.

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,

25 dichloroethane, THF or dioxane in water.

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Scheme IV



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

5 undergo ionic hydrogenation wherein $\text{C}=\text{O}$ is reduced to CH_2 followed by hydrolysis to give a compound of Formula XXXIV.

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,

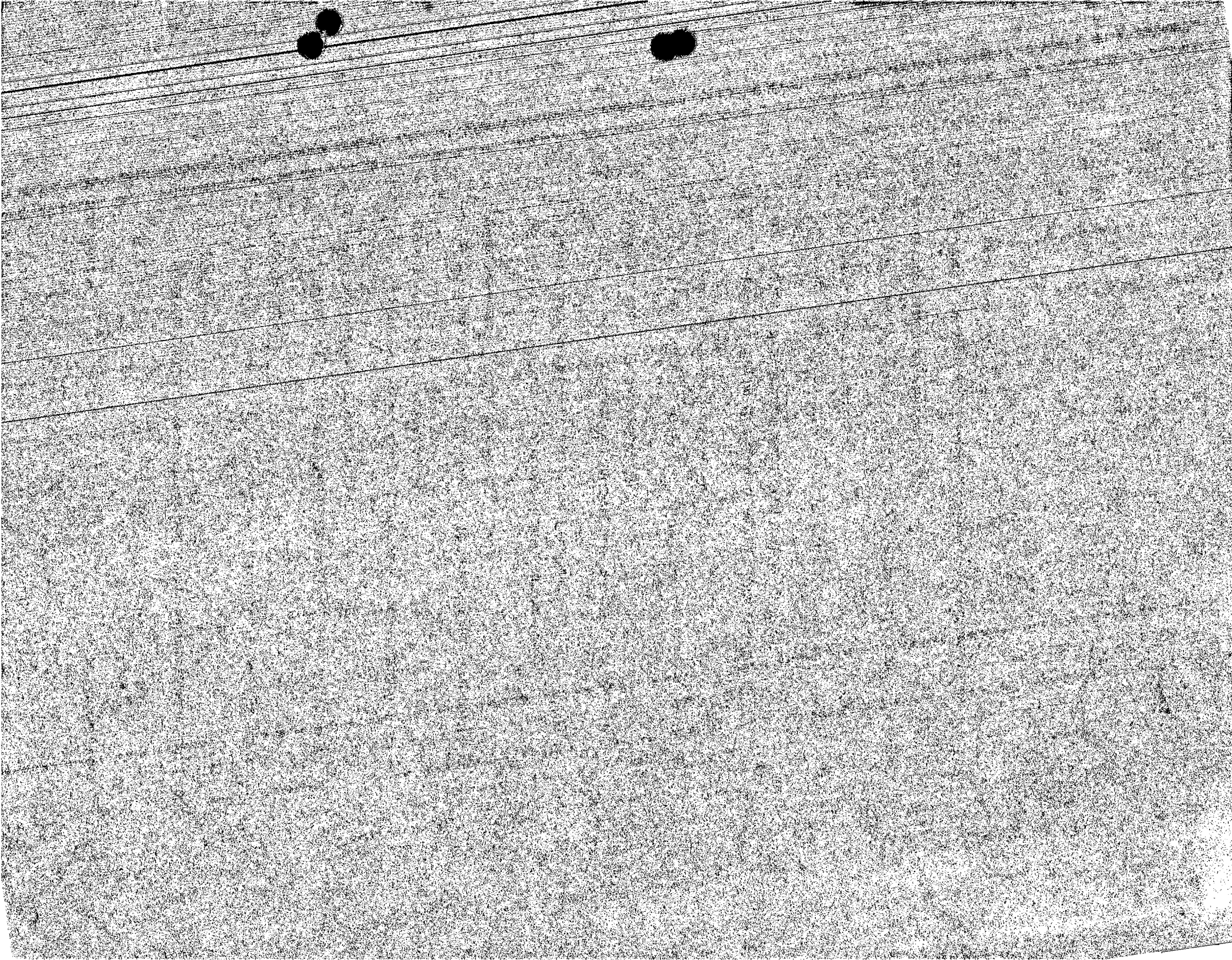
10 isopropylalcohol and/or tetrahydrofuran.

The conversion of a compound of Formula XXXIII to a compound of Formula XXXIV can be carried out under ionic hydrogenation conditions wherein the $\text{C}=\text{O}$ is reduced to CH_2 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

15 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),
- 5 5-(4'-*tert*-Butylbiphenyl-4-yl)-2-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxypentanoic acid (Compound No. 2),
- 5-(4'-Butylbiphenyl-4-yl)-2-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxypentanoic acid (Compound No. 3),
- 10 5-(4'-Chlorobiphenyl-4-yl)-2-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxypentanoic acid (Compound No. 4),
- 2-[2-(1,3-Dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxy-5-(4'-trifluoromethoxybiphenyl-4-yl)pentanoic acid (Compound No. 5),
- 2-[2-(1,3-Dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-5-(4'-ethoxybiphenyl-4-yl)-3-hydroxypentanoic acid (Compound No. 6),
- 15 2-[2-(1,3-Dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-5-(4'-formylbiphenyl-4-yl)-3-hydroxypentanoic acid (Compound No. 7),
- 2-[2-(1,3-Dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxy-5-(2',4',6'-trimethoxybiphenyl-4-yl)pentanoic acid (Compound No. 8),
- 2-[2-(1,3-Dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxy-5-(4'-propoxybiphenyl-4-yl)pentanoic acid (Compound No. 9),
- 20 5-(3',4'-Difluorobiphenyl-4-yl)-2-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxypentanoic acid (Compound No. 10),
- 2-(2-[(Benzyloxy)carbonyl]amino)ethyl)-5-biphenyl-4-yl-3-hydroxypentanoic acid (Compound No. 11),



- 5-Biphenyl-4-yl-2-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxypentanoic acid (Compound No. 12),
- 2-[2-(1,3-Dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxy-5-(4'-methoxybiphenyl-4-yl)pentanoic acid (Compound No. 23),
- 5 5-(2',3'-Dimethylbiphenyl-4-yl)-2-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxypentanoic acid (Compound No. 24),
- 2-[2-(1,3-Dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxy-5-[3'-(trifluoromethyl)biphenyl-4-yl]pentanoic acid (Compound No. 25),
- 2-[2-(1,3-Dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-5-(4'-ethylbiphenyl-4-yl)-3-
- 10 hydroxypentanoic acid (Compound No. 26),
- 5-(3',5'-Dichlorobiphenyl-4-yl)-2-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxypentanoic acid (Compound No. 27),
- 5-[4'-Chloro-3'-(trifluoromethyl)biphenyl-4-yl]-2-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxypentanoic acid (Compound No. 28),
- 15 5-(2',5'-Difluorobiphenyl-4-yl)-2-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxypentanoic acid (Compound No. 29),
- 2-[2-(1,3-Dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxy-5-[2'-(trifluoromethoxy)biphenyl-4-yl]pentanoic acid (Compound No. 30),
- 2-[2-(1,3-Dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxy-5-[4'-(methylthio)biphenyl-4-yl]pentanoic acid (Compound No. 31),
- 20 2-[2-(1,3-Dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-5-(4'-fluoro-3'-methylbiphenyl-4-yl)-3-hydroxypentanoic acid (Compound No. 32),
- 2-[2-(1,3-Dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxy-5-(3'-isopropylbiphenyl-4-yl)pentanoic acid (Compound No. 33),

- 5-(3',4'-Dimethylbiphenyl-4-yl)-2-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxypentanoic acid (Compound No. 34),
- 5-(2',6'-Difluorobiphenyl-4-yl)-2-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxypentanoic acid (Compound No. 35),
- 5 2-[2-(1,3-Dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-5-(4'-fluorobiphenyl-4-yl)-3-hydroxypentanoic acid (Compound No. 36),
- 5-(3',5'-Difluorobiphenyl-4-yl)-2-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxypentanoic acid (Compound No. 37),
- 5-(3'-Chloro-4'-fluorobiphenyl-4-yl)-2-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxypentanoic acid (Compound No. 38),
- 10 5-(3',4'-Dimethoxybiphenyl-4-yl)-2-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxypentanoic acid (Compound No. 39),
- 5-(3'-Chlorobiphenyl-4-yl)-2-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxypentanoic acid (Compound No. 40),
- 15 2-[2-(1,3-Dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxy-5-(3'-methylbiphenyl-4-yl)pentanoic acid (Compound No. 41),
- 5-(2',3'-Difluorobiphenyl-4-yl)-2-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxypentanoic acid (Compound No. 42),
- 2-[2-(1,3-Dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-5-(2'-fluoro-3'-methoxybiphenyl-4-yl)-3-hydroxypentanoic acid (Compound No. 43),
- 20 2-[2-(1,3-Dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-5-(3'-fluoro-4'-methylbiphenyl-4-yl)-3-hydroxypentanoic acid (Compound No. 44),
- 5-Biphenyl-4-yl-3-hydroxy-2-{2-[(phenylacetyl)amino]ethyl}pentanoic acid (Compound No. 45),

- 2-(3-Biphenyl-4-yl-1-hydroxypropyl)-6-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)hexanoic acid (Compound No. 46),
- 5-Biphenyl-4-yl-3-hydroxy-2-[2-(1-oxophthalazin-2(1*H*)-yl)ethyl]pentanoic acid (Compound No. 47),
- 5 5-Biphenyl-4-yl-2-[3-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)propyl]-3-hydroxypentanoic acid (Compound No. 48),
- 5-Biphenyl-4-yl-3-hydroxy-2-[2-(2'-oxospiro[cyclopropane-1,3'-indol]-1'(2'*H*)-yl)ethyl]pentanoic acid (Compound No. 49),
- 10 2-[2-(1,3-Dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxy-5-(4'-hydroxybiphenyl-4-yl)pentanoic acid (Compound No. 50),
- 3-Hydroxy-5-(4'-methoxybiphenyl-4-yl)-2-[2-(3-methyl-2,6-dioxo-3,6-dihydropyrimidin-1(2*H*)-yl)ethyl]pentanoic acid (Compound No. 51),
- 5-(4'-Chlorobiphenyl-4-yl)-3-hydroxy-2-[2-(3-methyl-2,6-dioxo-3,6-dihydropyrimidin-1(2*H*)-yl)ethyl]pentanoic acid (Compound No. 52),
- 15 5-(4'-Fluorobiphenyl-4-yl)-3-hydroxy-2-[2-(3-methyl-2,6-dioxo-3,6-dihydropyrimidin-1(2*H*)-yl)ethyl]pentanoic acid (Compound No. 53),
- 5-[4-(5-Chloro-2-thienyl)phenyl]-2-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxypentanoic acid (Compound No. 54),
- 20 4'-[4-Carboxy-6-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)-3-hydroxyhexyl]biphenyl-4-carboxylic acid (Compound No. 55),
- 2-[2-(1,3-Dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxy-5-[4'-(methoxycarbonyl)biphenyl-4-yl]pentanoic acid (Compound No. 56),
- 2-[2-(1,3-Dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxy-5-[4'-(trifluoromethyl)biphenyl-4-yl]pentanoic acid (Compound No. 57),

- 2-[2-(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. 58),
- 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),
- 2-[2-(1,3-Dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-5-(3'-fluorobiphenyl-4-yl)-3-hydroxypentanoic acid (Compound No. 61),
- 5-[4'-(Benzyloxy)-3'-fluorobiphenyl-4-yl]-2-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxypentanoic acid (Compound No. 62),
- 10 5-[4'-(Benzyloxy)biphenyl-4-yl]-2-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxypentanoic acid (Compound No. 63),
- 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),
- 15 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),
- 2-[2-(1,3-Dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxy-5-(4'-methylbiphenyl-4-yl)pentanoic acid (Compound No. 66),
- 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),
- 20 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),

- 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),
- 5 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),
- 10 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),
- 15 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),
- 20 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 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),
- 10 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),
- 15 2-(3-Biphenyl-4-yl-1-hydroxypropyl)pent-4-ynoic acid (Compound No. 95);
- 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),
- 20 5-{4-[6-(Dimethylamino)pyridin-3-yl]phenyl}-2-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxypentanoic acid (Compound No. 98),
- 2-[2-(1,3-Dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxy-5-[4'-(methylsulfonyl)biphenyl-4-yl]pentanoic acid (Compound No. 99),
- 5-[4'-(Aminocarbonyl)biphenyl-4-yl]-2-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxypentanoic acid (Compound No. 100),
- 25

- 5-[4-(1-Benzyl-1*H*-pyrazol-4-yl)phenyl]-2-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxypentanoic acid (Compound No. 101),
- 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),
- 10 2-[2-(1,3-Dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxy-5-(4-pyrimidin-5-ylphenyl)pentanoic acid (Compound No. 119),
- 5-Biphenyl-4-yl-3-hydroxy-2-[2-(7-methyl-4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)ethyl]pentanoic acid (Compound No. 120),
- 15 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
- 5-Biphenyl-4-yl-3-hydroxy-2-[2-(1-oxo-1,3-dihydro-2*H*-isoindol-2-yl) butyl]pentanoic acid (Compound No. 124).
- 20 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
- 25 of the reactions may be adjusted according to the requirements that arise during the process.

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.

- 5 The following illustrative compounds were separated into diastereomer pairs or single diastereomers:
- (2*R*,3*S* + 2*S*,3*R*)-2-[2-(1,3-Dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-5-(4'-formylbiphenyl-4-yl)-3-hydroxypentanoic acid (Compound No. 13),
- (2*R*,3*R* + 2*S*,3*S*)-2-[2-(1,3-Dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-5-(4'-formylbiphenyl-4-yl)-3-hydroxypentanoic acid (Compound No. 14),
- 10 (2*R*,3*R* + 2*S*,3*S*)-2-[2-(1,3-Dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxy-5-(2',4',6'-trimethoxybiphenyl-4-yl)pentanoic acid (Compound No.15),
- (2*R*,3*S* + 2*S*,3*R*)-2-[2-(1,3-Dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxy-5-(2',4',6'-trimethoxybiphenyl-4-yl)pentanoic acid (Compound No. 16),
- 15 (2*R*,3*S* + 2*S*,3*R*)-5-(4'-Acetylbiphenyl-4-yl)-2-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxypentanoic acid (Compound No. 17),
- (2*R*,3*R* + 2*S*,3*S*)-5-(4'-Acetylbiphenyl-4-yl)-2-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxypentanoic acid (Compound No. 18),
- (2*R*,3*S* + 2*S*,3*R*)-2-[2-(1,3-Dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxy-5-(4'-propoxybiphenyl-4-yl)pentanoic acid (Compound No. 19),
- 20 (2*R*,3*R* + 2*S*,3*S*)-2-[2-(1,3-Dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxy-5-(4'-propoxybiphenyl-4-yl)pentanoic acid (Compound No. 20),
- (2*R*,3*S* + 2*S*,3*R*)-5-(3',4'-Difluorobiphenyl-4-yl)-2-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxypentanoic acid (Compound No. 21),
- 25 (2*R*,3*R* + 2*S*,3*S*)-5-(3',4'-Difluorobiphenyl-4-yl)-2-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxypentanoic acid (Compound No. 22),

- (2*R*,3*S* + 2*S*,3*R*)-2-[2-(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. 78),
- (2*R*,3*R* + 2*S*,3*S*)-2-[2-(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. 79),
- 5 (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-hydroxypentanoic acid (Compound No. 80),
- (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 (Compound No. 81),
- 10 (2*R*,3*S* + 2*S*,3*R*)-2-[2-(1,3-Dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-5-(4'-fluorobiphenyl-4-yl)-3-hydroxypentanoic acid (Compound No. 82),
- (2*R*,3*R* + 2*S*,3*S*)-2-[2-(1,3-Dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-5-(4'-fluorobiphenyl-4-yl)-3-hydroxypentanoic acid (Compound No. 83),
- (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),
- 15 (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),
- (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),
- 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'-(trifluoromethyl)biphenyl-4-yl]pentanoic acid (Compound No. 109),
- 2-[2-(1,3-Dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-5-(3'-fluoro-4'-methoxybiphenyl-4-yl)-3-hydroxypentanoic acid (Compound No. 110),
- (2*R*,3*S* + 2*S*,3*R*)-2-[2-(1,3-Dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxy-5-[4-(6-methylpyridin-3-yl)phenyl]pentanoic acid (Compound No. 111),

- (2*R*,3*R* + 2*S*,3*S*)-2-[2-(1,3-Dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxy-5-[4-(6-methylpyridin-3-yl)phenyl]pentanoic acid (Compound No. 112),
- (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),
- 5 (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),
- 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]-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),
- (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),
- 15 (2*R*,3*S* + 2*S*,3*R*)-5-biphenyl-4-yl-3-hydroxy-2-[2-(1*H*-indol-3-yl)ethyl]pentanoic acid (Compound No. 122),
- (2*R*,3*R* + 2*S*,3*S*)-5-biphenyl-4-yl-3-hydroxy-2-[2-(1*H*-indol-3-yl)ethyl]pentanoic acid (Compound No. 123),
- (2*R*,3*S*)-5-(4'-Chlorobiphenyl-4-yl)-2-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-
- 20 3-hydroxypentanoic acid (Compound No. 125),
- (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 (Compound No. 126),
- (2*R*,3*R*)-5-(4'-Chlorobiphenyl-4-yl)-2-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxypentanoic acid (Compound No. 127),

- (2S,3S)-5-(4'-Chlorobiphenyl-4-yl)-2-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxypentanoic acid (Compound No.128),
- (2R,3S)-2-[2-(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. 129),
- 5 (2S,3R)-2-[2-(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. 130),
- (2R,3R)-2-[2-(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. 131),
- 10 (2S,3S)-2-[2-(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. 132),
- (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).

- Examples set forth demonstrates the general synthetic procedure for the
- 20 preparation of representative compounds. The examples are provided to illustrate particular aspect of the disclosure and do not limit the scope of the present invention

EXPERIMENTAL

GENERAL PROCEDURE

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

- 25 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 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 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 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(4*H*)-yl)ethyl]pentanoate

5 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 (104 mg) and stirred for 20 minutes. To the resulting reaction mixture was added 3-(2-bromoethyl)-1,2,3-benzotriazin-4(3*H*)-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
10 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 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
15 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-benzotriazin-3(4*H*)-yl)ethyl]pentanoate

To a solution of the compound (240 mg) obtained from step 2 above in methanol (4-5 ml) at -10 °C was added sodium borohydride (44 mg). The reaction
20 mixture was stirred for 2 hours at -10 °C to -2 °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
25 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(4*H*)-yl)ethyl]pentanoic acid

To a solution of the compound (100 mg) obtained from step 3 above in dichloromethane (2 ml) at 0 °C was added trifluoroacetic acid (8 ml) and stirred the
30 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 ($M^+ + 1$).

5 The following illustrative analogues were prepared analogously:

5-Biphenyl-4-yl-2-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxypentanoic acid (Compound No. 12),

2-(3-Biphenyl-4-yl-1-hydroxypropyl)-6-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)hexanoic acid (Compound No. 46),

10 5-Biphenyl-4-yl-3-hydroxy-2-[2-(1-oxophthalazin-2(1*H*)-yl)ethyl]pentanoic acid (Compound No. 47),

5-Biphenyl-4-yl-2-[3-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)propyl]-3-hydroxypentanoic acid (Compound No. 48),

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),

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),

20 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-3-hydroxy-2-[2-(5-methyl-1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]pentanoic acid (Compound No. 90),

25 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),
- 2-(3-Biphenyl-4-yl-1-hydroxypropyl)pent-4-ynoic acid (Compound No. 95);
- 5-Biphenyl-4-yl-3-hydroxy-2-[2-(2-oxo-1,3-benzoxazol-3(2*H*)-yl)ethyl]pentanoic acid
5 (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-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),
- 10 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-Biphenyl-4-yl-3-hydroxy-2-[2-(7-methyl-4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)ethyl]pentanoic acid (Compound No. 120), 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).
15

Scheme II, procedure:

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 (Compound No. 4)

20 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 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
25 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
5 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
10 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
15 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).

20 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
25 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)(dimethyl)silyl)oxy)ethyl)-5-(4-bromophenyl)-3-([4-(methyloxy)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-(methyloxy)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-(methyloxy)phenyl]methyl)oxy)-2-{2-[(methanesulfonyl)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-2H-isoindol-2-yl)ethyl]-5-(4-bromophenyl)-3-([4-(methyloxy)phenyl]methoxy)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 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 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-2H-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 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 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-2H-isoindol-2-yl)ethyl]-3-hydroxypentanoic acid

To a solution of the compound (120 mg) obtained from step 8 above in 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).

Mass (m/z): 478.0 ($M^+ + 1$).

The following illustrative compounds were prepared analogously:

- 5-(4'-*tert*-Butylbiphenyl-4-yl)-2-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxypentanoic acid (Compound No. 2),
- 5 5-(4'-Butylbiphenyl-4-yl)-2-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxypentanoic acid (Compound No. 3),
- 2-[2-(1,3-Dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxy-5-(4'-methoxybiphenyl-4-yl)pentanoic acid (Compound No. 5),
- 2-[2-(1,3-Dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-5-(4'-ethoxybiphenyl-4-yl)-3-hydroxypentanoic acid (Compound No. 6),
- 10 2-[2-(1,3-Dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-5-(4'-formylbiphenyl-4-yl)-3-hydroxypentanoic acid (Compound No. 7),
- 2-[2-(1,3-Dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxy-5-(2',4',6'-trimethoxybiphenyl-4-yl)pentanoic acid (Compound No. 8),
- 2-[2-(1,3-Dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxy-5-(4'-propoxybiphenyl-4-yl)pentanoic acid (Compound No. 9),
- 15 5-(3',4'-Difluorobiphenyl-4-yl)-2-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxypentanoic acid (Compound No. 10),
- 2-[2-(1,3-Dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxy-5-(4'-methoxybiphenyl-4-yl)pentanoic acid (Compound No. 23),
- 20 5-(2',3'-Dimethylbiphenyl-4-yl)-2-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxypentanoic acid (Compound No. 24),
- 2-[2-(1,3-Dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxy-5-[3'-(trifluoromethyl)biphenyl-4-yl]pentanoic acid (Compound No. 25),
- 2-[2-(1,3-Dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-5-(4'-ethylbiphenyl-4-yl)-3-hydroxypentanoic acid (Compound No. 26),
- 25

- 5-(3',5'-Dichlorobiphenyl-4-yl)-2-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxypentanoic acid (Compound No. 27),
- 5-[4'-Chloro-3'-(trifluoromethyl)biphenyl-4-yl]-2-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxypentanoic acid (Compound No. 28),
- 5 5-(2',5'-Difluorobiphenyl-4-yl)-2-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxypentanoic acid (Compound No. 29),
- 2-[2-(1,3-Dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxy-5-[2'-(trifluoromethoxy)biphenyl-4-yl]pentanoic acid (Compound No. 30),
- 2-[2-(1,3-Dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxy-5-[4'-(methylthio)biphenyl-4-yl]pentanoic acid (Compound No. 31),
- 10 2-[2-(1,3-Dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-5-(4'-fluoro-3'-methylbiphenyl-4-yl)-3-hydroxypentanoic acid (Compound No. 32),
- 2-[2-(1,3-Dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxy-5-(3'-isopropylbiphenyl-4-yl)pentanoic acid (Compound No. 33),
- 15 5-(3',4'-Dimethylbiphenyl-4-yl)-2-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxypentanoic acid (Compound No. 34),
- 5-(2',6'-Difluorobiphenyl-4-yl)-2-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxypentanoic acid (Compound No. 35),
- 2-[2-(1,3-Dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-5-(4'-fluorobiphenyl-4-yl)-3-
- 20 hydroxypentanoic acid (Compound No. 36),
- 5-(3',5'-Difluorobiphenyl-4-yl)-2-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxypentanoic acid (Compound No. 37),
- 5-(3'-Chloro-4'-fluorobiphenyl-4-yl)-2-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxypentanoic acid (Compound No. 38),

- 5-(3',4'-Dimethoxybiphenyl-4-yl)-2-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxypentanoic acid (Compound No. 39),
- 5-(3'-Chlorobiphenyl-4-yl)-2-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxypentanoic acid (Compound No. 40),
- 5 2-[2-(1,3-Dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxy-5-(3'-methylbiphenyl-4-yl)pentanoic acid (Compound No. 41),
- 5-(2',3'-Difluorobiphenyl-4-yl)-2-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxypentanoic acid (Compound No. 42),
- 10 2-[2-(1,3-Dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-5-(2'-fluoro-3'-methoxybiphenyl-4-yl)-3-hydroxypentanoic acid (Compound No. 43),
- 2-[2-(1,3-Dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-5-(3'-fluoro-4'-methylbiphenyl-4-yl)-3-hydroxypentanoic acid (Compound No. 44),
- 2-[2-(1,3-Dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxy-5-(4'-hydroxybiphenyl-4-yl)pentanoic acid (Compound No. 50),
- 15 3-Hydroxy-5-(4'-methoxybiphenyl-4-yl)-2-[2-(3-methyl-2,6-dioxo-3,6-dihydropyrimidin-1(2*H*)-yl)ethyl]pentanoic acid (Compound No. 51),
- 5-(4'-Chlorobiphenyl-4-yl)-3-hydroxy-2-[2-(3-methyl-2,6-dioxo-3,6-dihydropyrimidin-1(2*H*)-yl)ethyl]pentanoic acid (Compound No. 52),
- 5-(4'-Fluorobiphenyl-4-yl)-3-hydroxy-2-[2-(3-methyl-2,6-dioxo-3,6-dihydropyrimidin-1(2*H*)-yl)ethyl]pentanoic acid (Compound No. 53),
- 20 5-[4-(5-Chloro-2-thienyl)phenyl]-2-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxypentanoic acid (Compound No. 54),
- 4'-[4-Carboxy-6-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)-3-hydroxyhexyl]biphenyl-4-carboxylic acid (Compound No. 55),

- 2-[2-(1,3-Dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxy-5-[4'-(methoxycarbonyl)biphenyl-4-yl]pentanoic acid (Compound No. 56),
- 2-[2-(1,3-Dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxy-5-[4'-(trifluoromethyl)biphenyl-4-yl]pentanoic acid (Compound No. 57),
- 5 2-[2-(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. 58),
- 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),
- 10 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),
- 2-[2-(1,3-Dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-5-(3'-fluorobiphenyl-4-yl)-3-hydroxypentanoic acid (Compound No. 61),
- 5-[4'-(Benzyloxy)-3'-fluorobiphenyl-4-yl]-2-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxypentanoic acid (Compound No. 62),
- 15 5-[4'-(Benzyloxy)biphenyl-4-yl]-2-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxypentanoic acid (Compound No. 63),
- 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),
- 20 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),
- 2-[2-(1,3-Dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxy-5-(4'-methylbiphenyl-4-yl)pentanoic acid (Compound No. 66),
- 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 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-{4-[6-(Dimethylamino)pyridin-3-yl]phenyl}-2-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxypentanoic acid (Compound No. 98),

- 2-[2-(1,3-Dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxy-5-[4'-(methylsulfonyl)biphenyl-4-yl]pentanoic acid (Compound No. 99),
- 5-[4'-(Aminocarbonyl)biphenyl-4-yl]-2-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxypentanoic acid (Compound No. 100),
- 5 5-[4-(1-Benzyl-1*H*-pyrazol-4-yl)phenyl]-2-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxypentanoic acid (Compound No. 101),
- 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-[2-(1,3-Dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-5-(3'-fluoro-4'-methoxybiphenyl-4-yl)-3-hydroxypentanoic acid (Compound No. 110), and
- 10 2-[2-(1,3-Dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxy-5-(4-pyrimidin-5-ylphenyl)pentanoic acid (Compound No. 119).

Scheme III, path a procedure:

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

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
- 20 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
- 25 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

- 5 To a solution of the compound (100 mg) obtained from step 1 above in methanol (2 ml) at -10 °C to -2 °C was added sodium borohydride (9 mg) and stirred the mixture 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
10 water and brine, dried over anhydrous sodium sulphate and concentrated under reduced pressure. The residue thus obtained was purified by column chromatography using 5% 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

- 15 To a solution of the compound (40 mg) obtained from step 2 above in dry dichloromethane (10 ml) at 0 °C was added trifluoroacetic acid (0.5 ml) and anisole (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).
20 Mass (m/z): 448.1 ($M^+ + 1$).

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)

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

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 °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,
5 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 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).

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

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
20 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).

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

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
30 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).

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

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
10 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): 494.1 ($M^+ + 23$)

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

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),
20 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 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
25 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 purified by column chromatography using 10 % ethyl acetate in hexane as eluent to get the title compound (120 mg).

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

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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).

5
10 **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}aminoethyl}-3-hydroxypentanoic acid (Compound No. 92)

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

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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
5 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:
10 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
15 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
20

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.
25

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

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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 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-2H-isoindol-2-yl)ethyl]pentanoic acid

To a solution of the compound (160 mg) obtained from Step 2 above in 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-2H-isoindol-2-yl) butyl]pentanoic acid (Compound No. 124).

Example 8: Separation of (2R,3S) & (2S,3R)-5-(4'-chlorobiphenyl-4-yl)-2-[2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)ethyl]-3-hydroxypentanoic acid (Compound No. 80) and (2R,3R) & (2S,3S)-5-(4'-chlorobiphenyl-4-yl)-2-[2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)ethyl]-3-hydroxypentanoic acid (Compound No. 81)

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 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,

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- (2*R*,3*S* + 2*S*,3*R*)-2-[2-(1,3-Dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-5-(4'-formylbiphenyl-4-yl)-3-hydroxypentanoic acid (Compound No. 13),
- (2*R*,3*R* + 2*S*,3*S*)-2-[2-(1,3-Dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-5-(4'-formylbiphenyl-4-yl)-3-hydroxypentanoic acid (Compound No. 14),
- 5 (2*R*,3*R* + 2*S*,3*S*)-2-[2-(1,3-Dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxy-5-(2',4',6'-trimethoxybiphenyl-4-yl)pentanoic acid (Compound No.15),
- (2*R*,3*S* + 2*S*,3*R*)-2-[2-(1,3-Dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxy-5-(2',4',6'-trimethoxybiphenyl-4-yl)pentanoic acid (Compound No. 16),
- 10 (2*R*,3*S* + 2*S*,3*R*)-5-(4'-Acetylbiphenyl-4-yl)-2-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxypentanoic acid (Compound No. 17),
- (2*R*,3*R* + 2*S*,3*S*)-5-(4'-Acetylbiphenyl-4-yl)-2-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxypentanoic acid (Compound No. 18),
- (2*R*,3*S* + 2*S*,3*R*)-2-[2-(1,3-Dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxy-5-(4'-propoxybiphenyl-4-yl)pentanoic acid (Compound No. 19),
- 15 (2*R*,3*R* + 2*S*,3*S*)-2-[2-(1,3-Dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxy-5-(4'-propoxybiphenyl-4-yl)pentanoic acid (Compound No. 20),
- (2*R*,3*S* + 2*S*,3*R*)-5-(3',4'-Difluorobiphenyl-4-yl)-2-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxypentanoic acid (Compound No. 21),
- 20 (2*R*,3*R* + 2*S*,3*S*)-5-(3',4'-Difluorobiphenyl-4-yl)-2-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxypentanoic acid (Compound No. 22),
- (2*R*,3*S* + 2*S*,3*R*)-2-[2-(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. 78),
- (2*R*,3*R* + 2*S*,3*S*)-2-[2-(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. 79),

- (2*R*,3*S* + 2*S*,3*R*)-2-[2-(1,3-Dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-5-(4'-fluorobiphenyl-4-yl)-3-hydroxypentanoic acid (Compound No. 82),
- (2*R*,3*R* + 2*S*,3*S*)-2-[2-(1,3-Dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-5-(4'-fluorobiphenyl-4-yl)-3-hydroxypentanoic acid (Compound No. 83),
- 5 (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),
- (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),
- 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'-(trifluoromethyl)biphenyl-4-yl]pentanoic acid (Compound No. 109),
- 2-[2-(1,3-Dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-5-(3'-fluoro-4'-methoxybiphenyl-4-yl)-3-hydroxypentanoic acid (Compound No. 110),
- 15 (2*R*,3*S* + 2*S*,3*R*)-2-[2-(1,3-Dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxy-5-[4-(6-methylpyridin-3-yl)phenyl]pentanoic acid (Compound No. 111),
- (2*R*,3*R* + 2*S*,3*S*)-2-[2-(1,3-Dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxy-5-[4-(6-methylpyridin-3-yl)phenyl]pentanoic acid (Compound No. 112),
- (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),
- 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'-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),

- (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),
- 5 (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),
- (2*R*,3*R* + 2*S*,3*S*)-5-biphenyl-4-yl-3-hydroxy-2-[2-(1*H*-indol-3-yl)ethyl]pentanoic acid (Compound No. 122), and
- (2*R*,3*S*+2*S*,3*R*)-5-biphenyl-4-yl-3-hydroxy-2-[2-(1*H*-indol-3-yl)ethyl]pentanoic acid
- 10 (Compound No. 123).

- 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
- 15 time 60 minutes.

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

- (2*R*,3*S*)-5-(4'-Chlorobiphenyl-4-yl)-2-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxypentanoic acid (Compound No.125),
- 20 (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 (Compound No.126),
- (2*R*,3*R*)-5-(4'-Chlorobiphenyl-4-yl)-2-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxypentanoic acid (Compound No.127),
- (2*S*,3*S*)-5-(4'-Chlorobiphenyl-4-yl)-2-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-
- 25 3-hydroxypentanoic acid (Compound No.128),

- (2R,3S)-2-[2-(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. 129),
- (2S,3R)-2-[2-(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. 130),
- 5 (2R,3R)-2-[2-(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. 131),
- (2S,3S)-2-[2-(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. 132),
- (2R,3S)-3-Hydroxy-5-[4-(6-methoxypyridin-3-yl)phenyl]-2-[2-(4-oxo-1,2,3-benzotriazin-10 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
- 15 (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
- 20 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
- 25 &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

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substrate (ES001: Aliquots were freshly diluted in TCNB; stock: 2 mM) and increase in fluorescence was monitored at excitation wavelength 320 nm followed by emission at 405 nm for 25-30 cycles. Increase in fluorescence (RFU) was calculated for positive, negative and NCE/standard wells. The percent inhibition compared to controls was calculated and

5 IC₅₀ values determined using Graph-prism software.

Activities for MM9 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,

10 or from about 15 to about 2 nM, as compared to about 1.5 nM for marimasat.

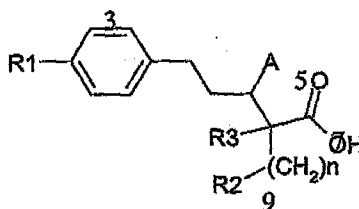
Activities for MM12 provided IC₅₀ values from about 10 micromolar to about 0.4 nM, or from about 1 micromolar to about 0.4 nM, or from about 300 nM to about 0.4 nM, or from about 100 nM to about 0.4 nM, or from about 50 nM to about 0.4 nM, or from about 30 nM to about 0.4 nM, or from about 20 nM to about 0.4 nM, or from about 15 to

15 about 0.4 nM, or from about 7 to about 0.4 nM as compared to about 0.9 nM for marimasat.

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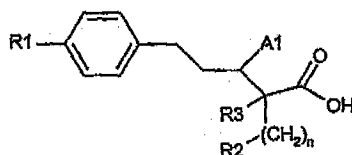
We claim:

1. 1. Compounds having the structure of Formula I:



Formula I

- wherein
- n is an integer from 1 to 5;
- R_1 is optionally substituted alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heterocyclyl, heteroaryl, aralkyl, alkoxy, aryloxy, alkenyloxy or alkynyloxy;
- R_2 is alkenyl, alkynyl, aryl, heterocyclyl, heteroaryl, cycloalkyl, NR_4R_5 , $-NHC(=Y)R_4$, $-NHC(=Y)NR_5R_x$, $-NHC(=O)OR_4$, $-NHSO_2R_4$, $C(=Y)NR_4R_5$, $C(=O)OR_6$ [wherein Y is oxygen or sulphur], OR_5 , $-OC(=O)NR_4R_5$, O -acyl, $S(O)_mR_4$, $-SO_2N(R_4)_2$, cyano, amidino or guanidino [wherein R_4 is alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heterocyclyl, heteroaryl, aralkyl, heteroarylalkyl, heterocyclylalkyl or cycloalkylalkyl and m is an integer 0-2; R_5 is hydrogen or R_4 ; R_x is R_4 or $-SO_2N(R_4)_2$ and R_6 is hydrogen, alkyl, cycloalkyl, aralkyl, heteroarylalkyl, heterocyclylalkyl or cycloalkylalkyl];
- R_3 is hydrogen, fluorine, alkyl, cycloalkylalkyl or aralkyl;
- A is OH , OR_4 , $-OC(=O)NR_4R_5$, O -acyl, NH_2 , NR_4R_5 , $-NHC(=Y)R_4$, $-NHC(=Y)NR_5R_x$, $-NHC(=O)OR_4$, $-NHSO_2R_4$.
2. A compound as claimed in claim 1 having the structure of Formula Ia:



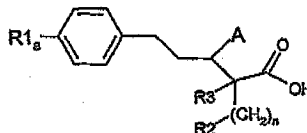
Formula Ia

- wherein

4 A1 is OH, -OC(=O)NR₄R₅, NH₂, NR₄R₅, -NHC(=Y)R₄, -NHC(=Y)NR₅R_x,
 5 -NHC(=O)OR₄, -NHSO₂R₄;

6 n, R₁, R₂, R₃ and R₄ are as define earlier.

1 3. A compound as claimed in claim 1 having the structure of Formula Ib:



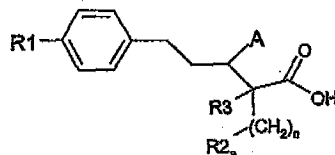
Formula Ib

2 wherein

4 R_{1a} is aryl or heteroaryl;

5 n, R₂, R₃ and A are as defined earlier.

1 4. A compound as claimed in claim 1 having the structure of Formula Ic:



Formula Ic

2 wherein

4 R_{2a} is NR₄R₅, -NHC(=Y)R₄, -NHC(=Y)NR₅R_x, -NHC(=O)OR₄, -NHSO₂R₄, amidino or
 5 guanidino [wherein Y is oxygen or sulphur and R₄ is alkyl, alkenyl, alkynyl, cycloalkyl,
 6 aryl, heterocyclyl, heteroaryl, aralkyl, heteroarylalkyl, heterocyclalkyl or cycloalkylalkyl
 7 and m is an integer 0-2; R₅ is hydrogen or R₄; R₄ and R₅ together may optionally form a
 8 heterocyclic ring containing one or more heteroatoms such as O, N or S and R_x is R₄ or -
 9 SO₂N(R₄)₂];

10 n, R₁, R₃ and A are as defined earlier.

1 5. A compound selected from the group consisting of

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

- 4 5-(4'-*tert*-Butylbiphenyl-4-yl)-2-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-
5 hydroxypentanoic acid (Compound No. 2),
- 6 5-(4'-Butylbiphenyl-4-yl)-2-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-
7 hydroxypentanoic acid (Compound No. 3),
- 8 5-(4'-Chlorobiphenyl-4-yl)-2-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-
9 hydroxypentanoic acid (Compound No. 4),
- 10 2-[2-(1,3-Dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxy-5-(4'-
11 trifluoromethoxybiphenyl-4-yl)pentanoic acid (Compound No. 5),
- 12 2-[2-(1,3-Dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-5-(4'-ethoxybiphenyl-4-yl)-3-
13 hydroxypentanoic acid (Compound No. 6),
- 14 2-[2-(1,3-Dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-5-(4'-formylbiphenyl-4-yl)-3-
15 hydroxypentanoic acid (Compound No. 7),
- 16 2-[2-(1,3-Dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxy-5-(2',4',6'-
17 trimethoxybiphenyl-4-yl)pentanoic acid (Compound No. 8),
- 18 2-[2-(1,3-Dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxy-5-(4'-propoxybiphenyl-4-
19 yl)pentanoic acid (Compound No. 9),
- 20 5-(3',4'-Difluorobiphenyl-4-yl)-2-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-
21 hydroxypentanoic acid (Compound No. 10),
- 22 2-(2-[[*(Benzyloxy)carbonyl*]amino]ethyl)-5-biphenyl-4-yl-3-hydroxypentanoic acid
23 (Compound No. 11),
- 24 5-Biphenyl-4-yl-2-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxypentanoic
25 acid (Compound No. 12),
- 26 (2*R*,3*S* + 2*S*,3*R*)-2-[2-(1,3-Dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-5-(4'-
27 formylbiphenyl-4-yl)-3-hydroxypentanoic acid (Compound No. 13),
- 28 (2*R*,3*R* + 2*S*,3*S*)-2-[2-(1,3-Dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-5-(4'-
29 formylbiphenyl-4-yl)-3-hydroxypentanoic acid (Compound No. 14),
- 30 (2*R*,3*R* + 2*S*,3*S*)-2-[2-(1,3-Dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxy-5-
31 (2',4',6'-trimethoxybiphenyl-4-yl)pentanoic acid (Compound No. 15),
- 32 (2*R*,3*S* + 2*S*,3*R*)-2-[2-(1,3-Dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxy-5-
33 (2',4',6'-trimethoxybiphenyl-4-yl)pentanoic acid (Compound No. 16),
- 34 (2*R*,3*S* + 2*S*,3*R*)-5-(4'-Acetylbiphenyl-4-yl)-2-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-
35 yl)ethyl]-3-hydroxypentanoic acid (Compound No. 17),
- 36 (2*R*,3*R* + 2*S*,3*S*)-5-(4'-Acetylbiphenyl-4-yl)-2-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-
37 yl)ethyl]-3-hydroxypentanoic acid (Compound No. 18),

- 38 (2*R*,3*S* + 2*S*,3*R*)-2-[2-(1,3-Dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxy-5-(4'-
39 propoxybiphenyl-4-yl)pentanoic acid (Compound No. 19),
- 40 (2*R*,3*R* + 2*S*,3*S*)-2-[2-(1,3-Dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxy-5-(4'-
41 propoxybiphenyl-4-yl)pentanoic acid (Compound No. 20),
- 42 (2*R*,3*S* + 2*S*,3*R*)-5-(3',4'-Difluorobiphenyl-4-yl)-2-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-
43 2-yl)ethyl]-3-hydroxypentanoic acid (Compound No. 21),
- 44 (2*R*,3*R* + 2*S*,3*S*)-5-(3',4'-Difluorobiphenyl-4-yl)-2-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-
45 2-yl)ethyl]-3-hydroxypentanoic acid (Compound No. 22),
- 46 2-[2-(1,3-Dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxy-5-(4'-methoxybiphenyl-4-
47 yl)pentanoic acid (Compound No. 23),
- 48 5-(2',3'-Dimethylbiphenyl-4-yl)-2-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-
49 hydroxypentanoic acid (Compound No. 24),
- 50 2-[2-(1,3-Dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxy-5-[3'-
51 (trifluoromethyl)biphenyl-4-yl]pentanoic acid (Compound No. 25),
- 52 2-[2-(1,3-Dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-5-(4'-ethylbiphenyl-4-yl)-3-
53 hydroxypentanoic acid (Compound No. 26),
- 54 5-(3',5'-Dichlorobiphenyl-4-yl)-2-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-
55 hydroxypentanoic acid (Compound No. 27),
- 56 5-[4'-Chloro-3'-(trifluoromethyl)biphenyl-4-yl]-2-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-
57 2-yl)ethyl]-3-hydroxypentanoic acid (Compound No. 28),
- 58 5-(2',5'-Difluorobiphenyl-4-yl)-2-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-
59 hydroxypentanoic acid (Compound No. 29),
- 60 2-[2-(1,3-Dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxy-5-[2'-
61 (trifluoromethoxy)biphenyl-4-yl]pentanoic acid (Compound No. 30),
- 62 2-[2-(1,3-Dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxy-5-[4'-
63 (methylthio)biphenyl-4-yl]pentanoic acid (Compound No. 31),
- 64 2-[2-(1,3-Dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-5-(4'-fluoro-3'-methylbiphenyl-4-yl)-
65 3-hydroxypentanoic acid (Compound No. 32),
- 66 2-[2-(1,3-Dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxy-5-(3'-isopropylbiphenyl-
67 4-yl)pentanoic acid (Compound No. 33),
- 68 5-(3',4'-Dimethylbiphenyl-4-yl)-2-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-
69 hydroxypentanoic acid (Compound No. 34),
- 70 5-(2',6'-Difluorobiphenyl-4-yl)-2-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-
71 hydroxypentanoic acid (Compound No. 35),

- 72 2-[2-(1,3-Dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-5-(4'-fluorobiphenyl-4-yl)-3-
73 hydroxypentanoic acid (Compound No. 36),
- 74 5-(3',5'-Difluorobiphenyl-4-yl)-2-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-
75 hydroxypentanoic acid (Compound No. 37),
- 76 5-(3'-Chloro-4'-fluorobiphenyl-4-yl)-2-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-
77 3-hydroxypentanoic acid (Compound No. 38),
- 78 5-(3',4'-Dimethoxybiphenyl-4-yl)-2-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-
79 hydroxypentanoic acid (Compound No. 39),
- 80 5-(3'-Chlorobiphenyl-4-yl)-2-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-
81 hydroxypentanoic acid (Compound No. 40),
- 82 2-[2-(1,3-Dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxy-5-(3'-methylbiphenyl-4-
83 yl)pentanoic acid (Compound No. 41),
- 84 5-(2',3'-Difluorobiphenyl-4-yl)-2-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-
85 hydroxypentanoic acid (Compound No. 42),
- 86 2-[2-(1,3-Dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-5-(2'-fluoro-3'-methoxybiphenyl-4-
87 yl)-3-hydroxypentanoic acid (Compound No. 43),
- 88 2-[2-(1,3-Dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-5-(3'-fluoro-4'-methylbiphenyl-4-yl)-
89 3-hydroxypentanoic acid (Compound No. 44),
- 90 5-Biphenyl-4-yl-3-hydroxy-2-[2-[(phenylacetyl)amino]ethyl]pentanoic acid (Compound
91 No. 45),
- 92 2-(3-Biphenyl-4-yl-1-hydroxypropyl)-6-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-
93 yl)hexanoic acid (Compound No. 46),
- 94 5-Biphenyl-4-yl-3-hydroxy-2-[2-(1-oxophthalazin-2(1*H*)-yl)ethyl]pentanoic acid
95 (Compound No. 47),
- 96 5-Biphenyl-4-yl-2-[3-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)propyl]-3-
97 hydroxypentanoic acid (Compound No. 48),
- 98 5-Biphenyl-4-yl-3-hydroxy-2-[2-(2'-oxospiro[cyclopropane-1,3'-indol]-1'(2'*H*)-
99 yl)ethyl]pentanoic acid (Compound No. 49),
- 100 2-[2-(1,3-Dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxy-5-(4'-hydroxybiphenyl-
101 4-yl)pentanoic acid (Compound No. 50),
- 102 3-Hydroxy-5-(4'-methoxybiphenyl-4-yl)-2-[2-(3-methyl-2,6-dioxo-3,6-dihydropyrimidin-
103 1(2*H*)-yl)ethyl]pentanoic acid (Compound No. 51),
- 104 5-(4'-Chlorobiphenyl-4-yl)-3-hydroxy-2-[2-(3-methyl-2,6-dioxo-3,6-dihydropyrimidin-
105 1(2*H*)-yl)ethyl]pentanoic acid (Compound No. 52),

- 106 5-(4'-Fluorobiphenyl-4-yl)-3-hydroxy-2-[2-(3-methyl-2,6-dioxo-3,6-dihydropyrimidin-
107 1(2*H*)-yl)ethyl]pentanoic acid (Compound No. 53),
- 108 5-[4-(5-Chloro-2-thienyl)phenyl]-2-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-
109 hydroxypentanoic acid (Compound No. 54),
- 110 4'-[4-Carboxy-6-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)-3-hydroxyhexyl]biphenyl-4-
111 carboxylic acid (Compound No. 55),
- 112 2-[2-(1,3-Dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxy-5-[4'-
113 (methoxycarbonyl)biphenyl-4-yl]pentanoic acid (Compound No. 56),
- 114 2-[2-(1,3-Dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxy-5-[4'-
115 (trifluoromethyl)biphenyl-4-yl]pentanoic acid (Compound No. 57),
- 116 2-[2-(1,3-Dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxy-5-[4-(6-methoxypyridin-
117 3-yl)phenyl]pentanoic acid (Compound No. 58),
- 118 3-Hydroxy-2-[2-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)ethyl]-5-[4'-
119 (trifluoromethyl)biphenyl-4-yl]pentanoic acid (Compound No. 59),
- 120 5-(3',4'-Difluorobiphenyl-4-yl)-3-hydroxy-2-[2-(4-oxo-1,2,3-benzotriazin-3(4*H*)-
121 yl)ethyl]pentanoic acid (Compound No. 60),
- 122 2-[2-(1,3-Dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-5-(3'-fluorobiphenyl-4-yl)-3-
123 hydroxypentanoic acid (Compound No. 61),
- 124 5-[4'-(Benzyloxy)-3'-fluorobiphenyl-4-yl]-2-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-
125 yl)ethyl]-3-hydroxypentanoic acid (Compound No. 62),
- 126 5-[4'-(Benzyloxy)biphenyl-4-yl]-2-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-
127 hydroxypentanoic acid (Compound No. 63),
- 128 3-Hydroxy-5-(4'-methoxybiphenyl-4-yl)-2-[2-(4-oxo-1,2,3-benzotriazin-3(4*H*)-
129 yl)ethyl]pentanoic acid (Compound No. 64),
- 130 5-(4'-Chlorobiphenyl-4-yl)-3-hydroxy-2-[2-(4-oxo-1,2,3-benzotriazin-3(4*H*)-
131 yl)ethyl]pentanoic acid (Compound No. 65),
- 132 2-[2-(1,3-Dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxy-5-(4'-methylbiphenyl-4-
133 yl)pentanoic acid (Compound No. 66),
- 134 3-Hydroxy-5-[4-(6-methoxypyridin-3-yl)phenyl]-2-[2-(4-oxo-1,2,3-benzotriazin-3(4*H*)-
135 yl)ethyl]pentanoic acid (Compound No. 67),
- 136 3-Hydroxy-5-(4'-methylbiphenyl-4-yl)-2-[2-(5-methyl-1,3-dioxo-1,3-dihydro-2*H*-isoindol-
137 2-yl)ethyl]pentanoic acid (Compound No. 68),
- 138 5-(4'-Chlorobiphenyl-4-yl)-3-hydroxy-2-[2-(5-methyl-1,3-dioxo-1,3-dihydro-2*H*-isoindol-
139 2-yl)ethyl]pentanoic acid (Compound No. 69),

- 140 3-Hydroxy-2-[2-(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)ethyl]-5-[4'-
141 (trifluoromethoxy)biphenyl-4-yl]pentanoic acid (Compound No. 70),
- 142 5-(4'-Fluorobiphenyl-4-yl)-3-hydroxy-2-[2-(4-oxo-1,2,3-benzotriazin-3(4*H*)-
143 yl)ethyl]pentanoic acid (Compound No. 71),
- 144 3-hydroxy-5-(4'-methylbiphenyl-4-yl)-2-[2-(4-oxo-1,2,3-benzotriazin-3(4*H*)-
145 yl)ethyl]pentanoic acid (Compound No. 72),
- 146 5-(4'-Cyanobiphenyl-4-yl)-3-hydroxy-2-[2-(4-oxo-1,2,3-benzotriazin-3(4*H*)-
147 yl)ethyl]pentanoic acid (Compound No. 73),
- 148 5-(4'-Fluorobiphenyl-4-yl)-3-hydroxy-2-[2-(5-methyl-1,3-dioxo-1,3-dihydro-2*H*-isoindol-
149 2-yl)ethyl]pentanoic acid (Compound No. 74),
- 150 3-Hydroxy-5-[4-(6-methoxypyridin-3-yl)phenyl]-2-[2-(5-methyl-1,3-dioxo-1,3-dihydro-
151 2*H*-isoindol-2-yl)ethyl]pentanoic acid (Compound No. 75),
- 152 5-(4'-Ethylbiphenyl-4-yl)-3-hydroxy-2-[2-(4-oxo-1,2,3-benzotriazin-3(4*H*)-
153 yl)ethyl]pentanoic acid (Compound No. 76),
- 154 3-Hydroxy-2-[2-(5-methyl-1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-5-[4'-
155 (trifluoromethyl)biphenyl-4-yl]pentanoic acid (Compound No. 77),
- 156 (2*R*,3*S* + 2*S*,3*R*)-2-[2-(1,3-Dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxy-5-[4-(6-
157 methoxypyridin-3-yl)phenyl]pentanoic acid (Compound No. 78),
- 158 (2*R*,3*R* + 2*S*,3*S*)-2-[2-(1,3-Dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxy-5-[4-(6-
159 methoxypyridin-3-yl)phenyl]pentanoic acid (Compound No. 79),
- 160 (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-
161 yl)ethyl]-3-hydroxypentanoic acid (Compound No. 80),
- 162 (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-
163 yl)ethyl]-3-hydroxypentanoic acid (Compound No. 81),
- 164 (2*R*,3*S* + 2*S*,3*R*)-2-[2-(1,3-Dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-5-(4'-
165 fluorobiphenyl-4-yl)-3-hydroxypentanoic acid (Compound No. 82),
- 166 (2*R*,3*R* + 2*S*,3*S*)-2-[2-(1,3-Dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-5-(4'-
167 fluorobiphenyl-4-yl)-3-hydroxypentanoic acid (Compound No. 83),
- 168 5-Biphenyl-4-yl-3-hydroxy-2-[2-(1-oxo-4-phenyl-4a,8a-dihydrophthalazin-2(1*H*)-
169 yl)ethyl]pentanoic acid (Compound No. 84),
- 170 5-Biphenyl-4-yl-3-hydroxy-2-[2-(3-oxo-2,3-dihydro-4*H*-1,4-benzoxazin-4-
171 yl)ethyl]pentanoic acid (Compound No. 85),
- 172 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-
173 yl]ethyl}-3-hydroxypentanoic acid (Compound No. 86),

- 174 5-Biphenyl-4-yl-2-(2-{{(4-fluorophenyl)sulfonyl}amino}ethyl)-3-hydroxypentanoic acid
175 (Compound No. 87),
- 176 5-Biphenyl-4-yl-2-(2-{{(3-fluorophenyl)acetyl}amino}ethyl)-3-hydroxypentanoic acid
177 (Compound No. 88),
- 178 5-Biphenyl-4-yl-2-{2-[(4-fluorobenzoyl)amino]ethyl}-3-hydroxypentanoic acid
179 (Compound No. 89),
- 180 5-Biphenyl-4-yl-3-hydroxy-2-[2-(5-methyl-1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-
181 yl)ethyl]pentanoic acid (Compound No. 90),
- 182 5-Biphenyl-4-yl-3-hydroxy-2-[2-(1-oxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]pentanoic
183 acid (Compound No. 91).
- 184 5-Biphenyl-4-yl-2-[2-{{[(4-fluorophenyl)amino]carbonyl}amino}ethyl]-3-
185 hydroxypentanoic acid (Compound No. 92),
- 186 5-Biphenyl-4-yl-2-[2-(4,4-dimethyl-2,6-dioxopiperidin-1-yl)ethyl]-3-hydroxypentanoic
187 acid (Compound No. 93),
- 188 5-Biphenyl-4-yl-2-[2-(7,9-dioxo-8-azaspiro[4.5]dec-8-yl)ethyl]-3-hydroxypentanoic acid
189 (Compound No. 94),
- 190 2-(3-Biphenyl-4-yl-1-hydroxypropyl)pent-4-ynoic acid (Compound No. 95);
- 191 5-Biphenyl-4-yl-3-hydroxy-2-[2-(2-oxo-1,3-benzoxazol-3(2*H*)-yl)ethyl]pentanoic acid
192 (Compound No. 96)
- 193 2-[2-(5-*tert*-Butyl-1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxy-5-[4-(6-
194 methoxypyridin-3-yl)phenyl]pentanoic acid (Compound No. 97),
- 195 5-{4-[6-(Dimethylamino)pyridin-3-yl]phenyl}-2-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-
196 2-yl)ethyl]-3-hydroxypentanoic acid (Compound No. 98),
- 197 2-[2-(1,3-Dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxy-5-[4'-
198 (methylsulfonyl)biphenyl-4-yl]pentanoic acid (Compound No. 99),
- 199 5-[4'-(Aminocarbonyl)biphenyl-4-yl]-2-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-
200 yl)ethyl]-3-hydroxypentanoic acid (Compound No. 100),
- 201 5-[4-(1-Benzyl-1*H*-pyrazol-4-yl)phenyl]-2-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-
202 yl)ethyl]-3-hydroxypentanoic acid (Compound No. 101),
- 203 5-Biphenyl-4-yl-2-[2-(5,6-dichloro-1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-
204 hydroxypentanoic acid (Compound No. 102),
- 205 5-Biphenyl-4-yl-2-[2-(2,4-dioxo-1,4-dihydroquinazolin-3(2*H*)-yl)ethyl]-3-
206 hydroxypentanoic acid (Compound No. 103),

- 207 5-Biphenyl-4-yl-2-[2-(1,3-dioxo-1,3-dihydro-2*H*-pyrrolo[3,4-*c*]pyridin-2-yl)ethyl]-3-
208 hydroxypentanoic acid (Compound No. 104),
- 209 2-[2-(5-*tert*-Butyl-1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-5-(3',4'-
210 difluorobiphenyl-4-yl)-3-hydroxypentanoic acid (Compound No. 105),
- 211 (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'-
212 fluorobiphenyl-4-yl)-3-hydroxypentanoic acid (Compound No. 106),
- 213 (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-
214 hydroxy-5-[4'-(trifluoromethyl)biphenyl-4-yl]pentanoic acid (Compound No. 107),
- 215 (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'-
216 fluorobiphenyl-4-yl)-3-hydroxypentanoic acid (Compound No. 108),
- 217 (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-
218 hydroxy-5-[4'-(trifluoromethyl)biphenyl-4-yl]pentanoic acid (Compound No. 109),
- 219 2-[2-(1,3-Dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-5-(3'-fluoro-4'-methoxybiphenyl-4-
220 yl)-3-hydroxypentanoic acid (Compound No. 110),
- 221 (2*R*,3*S* + 2*S*,3*R*)-2-[2-(1,3-Dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxy-5-[4-(6-
222 methylpyridin-3-yl)phenyl]pentanoic acid (Compound No. 111),
- 223 (2*R*,3*R* + 2*S*,3*S*)-2-[2-(1,3-Dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxy-5-[4-(6-
224 methylpyridin-3-yl)phenyl]pentanoic acid (Compound No. 112),
- 225 (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-
226 hydroxy-5-(4'-methylbiphenyl-4-yl)pentanoic acid (Compound No. 113),
- 227 (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-
228 hydroxy-5-(4'-methylbiphenyl-4-yl)pentanoic acid (Compound No. 114),
- 229 (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-
230 hydroxy-5-(4'-methoxybiphenyl-4-yl)pentanoic acid (Compound No. 115),
- 231 (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'-
232 chlorobiphenyl-4-yl)-3-hydroxypentanoic acid (Compound No. 116),
- 233 (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'-
234 chlorobiphenyl-4-yl)-3-hydroxypentanoic acid (Compound No. 117),
- 235 (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-
236 hydroxy-5-(4'-methoxybiphenyl-4-yl)pentanoic acid (Compound No. 118),
- 237 2-[2-(1,3-Dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxy-5-(4-pyrimidin-5-
238 ylphenyl)pentanoic acid (Compound No. 119),
- 239 5-Biphenyl-4-yl-3-hydroxy-2-[2-(7-methyl-4-oxo-1,2,3-benzotriazin-3(4*H*)-
240 yl)ethyl]pentanoic acid (Compound No. 120),

- 241 5-Biphenyl-4-yl-2-[2-(5-*tert*-butyl-1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-
242 hydroxypentanoic acid (Compound No. 121),
- 243 (2*R*,3*S*)-5-Biphenyl-4-yl-3-hydroxy-2-[2-(1*H*-indol-3-yl)ethyl]pentanoic acid (Compound
244 No. 122),
- 245 (2*R*,3*R*)-5-Biphenyl-4-yl-3-hydroxy-2-[2-(1*H*-indol-3-yl)ethyl]pentanoic acid (Compound
246 No. 123),
- 247 5-Biphenyl-4-yl-3-hydroxy-2-[2-(1-oxo-1,3-dihydro-2*H*-isoindol-2-yl) butyl]pentanoic
248 acid (Compound No. 124),
- 249 (2*R*,3*S*)-5-(4'-Chlorobiphenyl-4-yl)-2-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-
250 3-hydroxypentanoic acid (Compound No.125),
- 251 (2*S*,3*R*)-5-(4'-Chlorobiphenyl-4-yl)-2-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-
252 3-hydroxypentanoic acid (Compound No.126),
- 253 (2*R*,3*R*)-5-(4'-Chlorobiphenyl-4-yl)-2-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-
254 3-hydroxypentanoic acid (Compound No.127),
- 255 (2*S*,3*S*)-5-(4'-Chlorobiphenyl-4-yl)-2-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-
256 3-hydroxypentanoic acid (Compound No.128),
- 257 (2*R*,3*S*)-2-[2-(1,3-Dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxy-5-[4-(6-
258 methoxypyridin-3-yl)phenyl]pentanoic acid (Compound No. 129),
- 259 (2*S*,3*R*)-2-[2-(1,3-Dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxy-5-[4-(6-
260 methoxypyridin-3-yl)phenyl]pentanoic acid (Compound No. 130),
- 261 (2*R*,3*R*)-2-[2-(1,3-Dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxy-5-[4-(6-
262 methoxypyridin-3-yl)phenyl]pentanoic acid (Compound No. 131),
- 263 (2*S*,3*S*)-2-[2-(1,3-Dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxy-5-[4-(6-
264 methoxypyridin-3-yl)phenyl]pentanoic acid (Compound No. 132),
- 265 (2*R*,3*S*)-3-Hydroxy-5-[4-(6-methoxypyridin-3-yl)phenyl]-2-[2-(4-oxo-1,2,3-benzotriazin-
266 3(4*H*)-yl)ethyl]pentanoic acid (Compound No.133),
- 267 (2*S*,3*R*)-3-Hydroxy-5-[4-(6-methoxypyridin-3-yl)phenyl]-2-[2-(4-oxo-1,2,3-benzotriazin-
268 3(4*H*)-yl)ethyl]pentanoic acid (Compound No.134),
- 269 (2*R*,3*R*)-3-Hydroxy-5-[4-(6-methoxypyridin-3-yl)phenyl]-2-[2-(4-oxo-1,2,3-benzotriazin-
270 3(4*H*)-yl)ethyl]pentanoic acid (Compound No.135), and
- 271 (2*S*,3*S*)-3-Hydroxy-5-[4-(6-methoxypyridin-3-yl)phenyl]-2-[2-(4-oxo-1,2,3-benzotriazin-
272 3(4*H*)-yl)ethyl]pentanoic acid (Compound No.136).

1 6. A pharmaceutical composition comprising therapeutically effective amount of a
2 compound as defined in claim 1 together with pharmaceutically acceptable carrier,
3 excipients or diluents.

1 7. A pharmaceutical composition of claim 6 further comprising one or more
2 additional active ingredients selected from:

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

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

13 c) immunosuppressive agents including cyclosporine, azathioprine and
14 methotrexate, anti-inflammatory corticosteroids.

1 8. A method for treatment or prophylaxis of an animal or a human suffering from a
2 inflammatory diseases and associated pathologies which comprises administering to said
3 mammal an effective amount of a compound according to claim 1.

1 9. A method for treatment or prophylaxis of an animal or a human suffering from a
2 inflammatory diseases and associated pathologies which comprises administering to said
3 mammal an effective amount of pharmaceutical composition according to claim 6.

1 10. A method for treatment or prophylaxis of an animal or a human suffering from a
2 inflammatory diseases and associated pathologies which comprises administering to said
3 mammal an effective amount of pharmaceutical composition according to claim 7.

1 11. A method according to claim 8, wherein inflammatory diseases and associated
2 pathologies include asthma, rheumatoid arthritis, COPD, rhinitis, osteoarthritis, psoriatic
3 arthritis, psoriasis, pulmonary fibrosis, pulmonary inflammation, acute respiratory distress
4 syndrome, periodontitis, multiple sclerosis, gingivitis, atherosclerosis, neointimal

5 proliferation, which leads to restenosis and ischemic heart failure, stroke, renal diseases
6 and tumor metastasis.

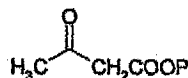
1 12. A process for preparing a compound of Formula VIII comprising :

2 a. reacting a compound of Formula II



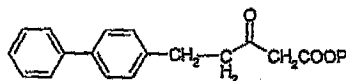
Formula II

4 with a compound of Formula III



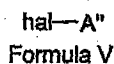
Formula III

6 to give a compound Formula IV;

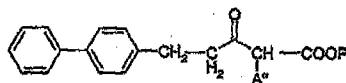


Formula IV

8 b. reacting a compound Formula IV with a compound of Formula V

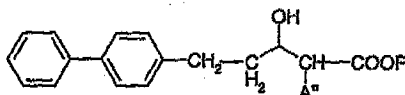


10 to give a compound of Formula VI;



Formula VI

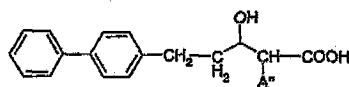
12 c. reducing a compound of Formula VI to give a compound of Formula VII;
13 and



Formula VII

15 d. deprotecting a compound of Formula VII to give a compound of Formula
16 VIII

82



Formula VIII

wherein

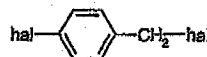
hal is Cl, Br or I;

P is alkyl (for example, tert-butyl, ethyl or methyl) or aralkyl (for example, benzyl);

A'' is aralkyl, heterocyclalkyl, heteroarylalkyl or cycloalkylalkyl.

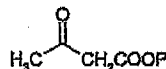
13. A process for preparing a compound of Formula XXI comprising:

a. reacting a compound of Formula IX



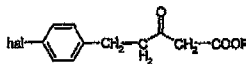
Formula IX

with a compound of Formula III



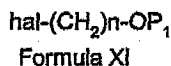
Formula III

to give a compound of Formula X;



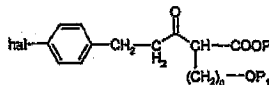
Formula X

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



Formula XI

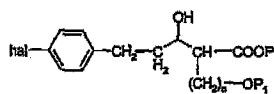
to give a compound of Formula XII;



Formula XII

c. reducing a compound of Formula XII to give a compound of Formula XIII;

83



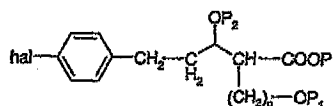
Formula XIII

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



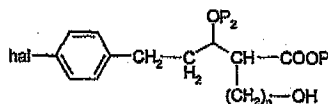
Formula XIV

to give a compound of Formula XV;



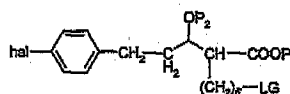
Formula XV

e. deprotecting a compound of Formula XV to give a compound of Formula XVI;



Formula XVI

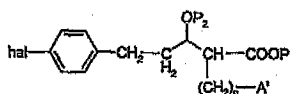
f. converting a compound of Formula XVI to a compound of Formula XVII



Formula XVII

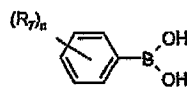
by reaction with a compound of Formula L-hal;

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



Formula XVIII

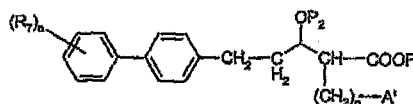
h. reacting a compound of Formula XVIII with a compound of Formula XIX



Formula XIX

84

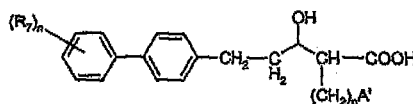
29 to form a compound of Formula XX; and



Formula XX

30

31 i. deprotecting a compound of Formula XX to give a compound of Formula
32 XXI



Formula XXI

33

34 wherein

35 P is alkyl (for example, tert-butyl, ethyl or methyl) or aralkyl (for example, benzyl);

36 P₁ is silyl protecting group for example, tert-butyldimethylsilane, tert-
37 butyldiphenylsilane or triisopropylsilane;

38 P₂ is aralkyl (for example, benzyl, 4-methoxybenzyl or 2,4,6-trimethoxybenzyl) or
39 heterocyclyl (for example, tetrahydropyranyl);

40 hal is Cl, Br or I;

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

42 A' is aryl, heteroaryl, heterocyclyl or cycloalkyl and M is metal for example,
43 potassium, lithium or sodium;

44 A'' is aralkyl, heterocyclylalkyl, heteroarylalkyl or cycloalkylalkyl;

45 n is an integer from 1 to 5

46 R₇ is hydrogen, halogen (F, Cl, Br, I), hydroxy, -COOR₄, alkyl, alkenyl, alkynyl,
47 cycloalkyl, alkoxy, alkenyloxy, alkynyloxy, aryloxy, heterocyclyloxy,
48 heteroaryloxy, cycloalkyloxy, acyl, thioacyl, cyano, nitro, amino, -CHO, -OCF₃, -
49 CF₃, -SCF₃, -NR₄R₅, -C(=Y)NR₄R₅, -NHC(=Y)R₄, -NHC(=Y)NR₅R₆, -
50 NHC(=O)OR₄, -NHSO₂R₄, (SO)_mR₄, aryl, heterocyclyl, heteroaryl,
51 heterocyclylalkyl or heteroarylalkyl which may optionally be substituted further;

52 R_4 is alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heterocyclyl, heteroaryl, aralkyl,
 53 heteroarylalkyl, heterocyclylalkyl or cycloalkylalkyl;

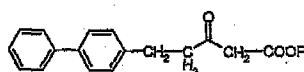
54 m is an integer 0-2;

55 R_5 is hydrogen or R_4 ; and

56 R_x is R_4 or $-\text{SO}_2\text{N}(R_4)_2$.

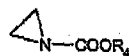
1 14. A process for preparing a compound of Formula XXV comprising:

2 a. reacting a compound of Formula IV



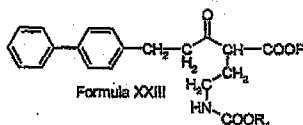
Formula IV

4 with a compound of Formula XXII



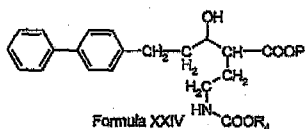
Formula XXII

6 to give a compound of Formula XXIII;



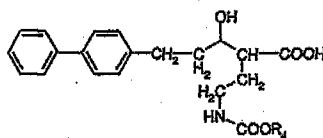
Formula XXIII

8 b. reducing a compound of Formula XXIII to give a compound of Formula
 9 XXIV; and



Formula XXIV

11 c. deprotecting a compound of Formula XXIV to give a compound of
 12 Formula XXV



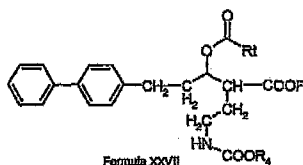
Formula XXV

- 14 wherein
- 15 P is alkyl (for example, tert-butyl, ethyl or methyl) or aralkyl (for example, benzyl);
- 16 R₄ is alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heterocyclyl, heteroaryl, aralkyl,
- 17 heteroarylalkyl, heterocyclalkyl or cycloalkylalkyl.

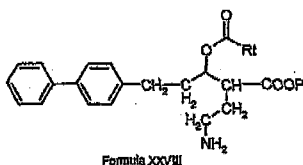
- 1 15. A process for preparing a compound of Formula XXXI comprising:
- 2 a. reacting a compound of Formula XXIV with a compound of Formula
- 3 XXVI

R₁-COOH
Formula XXVI

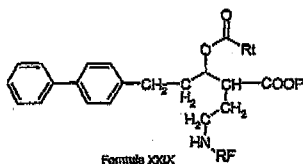
- 5 to give a compound of Formula XXVII;



- 6
- 7 b. deprotecting a compound of Formula XXVII to give a compound of
- 8 Formula XXVIII;

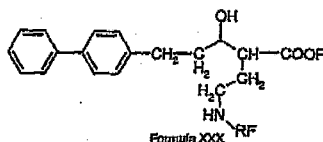


- 9
- 10 c. derivatizing a compound of Formula XXVIII with a compound of Formula
- 11 RD to give a compound of Formula XXIX;



- 12
- 13 d. deprotecting a compound of Formula XXIX to give a compound of
- 14 Formula XXX; and

87

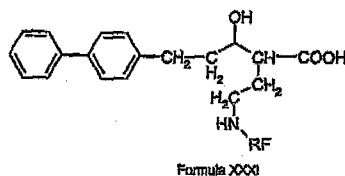


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17

e. deprotecting a compound of Formula XXXI to give a compound of Formula XXXI



18

19

wherein

20

RD is $R_4\text{COhal}$, halCOOR_4 , $R_4\text{SO}_2\text{hal}$ or $(R_4)\text{N}=\text{C}(=\text{Y})$;

21

RF is $R_4\text{CO}-$, $R_4\text{OCO}-$, $R_4\text{SO}_2-$ or $(R_4)\text{NH}-\text{C}(=\text{Y})-$;

22

R_4 is alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heterocyclyl, heteroaryl, aralkyl, heteroarylalkyl, heterocyclalkyl or cycloalkylalkyl;

23

24

Y is oxygen or sulphur;

25

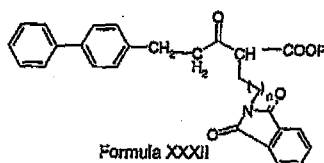
Rt is alkyl, aryl, cycloalkyl, aralkyl, heterocyclalkyl or heteroarylalkyl;

26

hal is Cl, Br or I.

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

a. reducing a compound of Formula XXXII

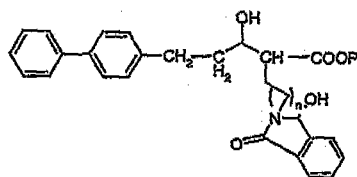


3

4

to give a compound of Formula XXXIII; and

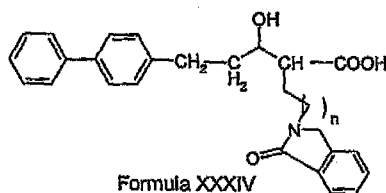
88



Formula XXXIII

5

- 6 b. hydrolyzing a compound of Formula XXXIII to give a compound of
7 Formula XXXIV



Formula XXXIV

8

- 1 17. A process for separation a compound of Formula VIII, Formula XXI, Formula
2 XXV, Formula XXXI or Formula XXXIV into diastereomer pairs or single diastereomers
3 by preparative thin layer chromatography and/or by HPLC, using an achiral or chiral
4 column.

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2006/000349

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D249/18 C07D209/48 C07D237/32 C07D209/12 C07D239/54
C07D213/64 C07D265/28 C07D211/88 C07D207/40 C07D263/58
C07D239/96 C07D471/04 C07D401/10 C07D403/10 A61P11/06

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D A61P

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

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

EPO-Internal, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2004/110974 A (GLAXO GROUP LIMITED) 23 December 2004 (2004-12-23) cited in the application examples 8-12	1-17
P, X	WO 2005/026120 A (GLAXO GROUP LIMITED) 24 March 2005 (2005-03-24) examples 1-12	1-17

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

☒ See patent family annex.

* Special categories of cited documents:

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

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

Date of the actual completion of the international search

30 June 2006

Date of mailing of the international search report

13/07/2006

Name and mailing address of the ISA/

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel: (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Cortés, J

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2006/000349

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB2006/000349

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

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

1. ☒ Claims Nos.: —
because they relate to subject matter not required to be searched by this Authority, namely:
Although claims 8-11 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

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

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

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

Remark on Protest

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

INTERNATIONAL SEARCH REPORT

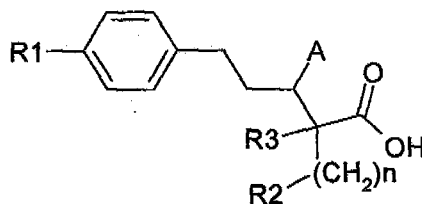
Information on patent family members

national application No
PCT/IB2006/000349

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2004110974 A	23-12-2004	EP 1654213 A1	10-05-2006
WO 2005026120 A	24-03-2005	AU 2004272280 A1	24-03-2005
		CA 2538315 A1	24-03-2005
		EP 1663970 A1	07-06-2006

Amendment to claims

1. (Amended) ~~A~~ Compounds of having ~~the structure~~ of Formula I:



Formula I

wherein:

n is an integer from 1 to 5;

R_1 is optionally substituted alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heterocyclyl, heteroaryl, aralkyl, alkoxy, aryloxy, alkenyloxy or alkynyloxy;

R_2 is alkenyl, alkynyl, aryl, heterocyclyl, heteroaryl, cycloalkyl, NR_4R_5 , $-NHC(=Y)R_4$, $-NHC(=Y)NR_5R_x$, $-NHC(=O)OR_4$, $-NHSO_2R_4$, $C(=Y)NR_4R_5$, $C(=O)OR_6$ [wherein Y is oxygen or sulphur], OR_5 , $-OC(=O)NR_4R_5$, O-acyl, $S(O)_mR_4$, $-SO_2N(R_4)_2$, cyano, amidino or guanidine [wherein R_4 is alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heterocyclyl, heteroaryl, aralkyl, heteroarylalkyl, heterocyclylalkyl or cycloalkylalkyl and m is an integer 0-2; R_5 is hydrogen or R_4 ; R_x is R_4 or $-SO_2N(R_4)_2$ and R_6 is hydrogen, alkyl, cycloalkyl, aralkyl, heteroarylalkyl, heterocyclylalkyl or cycloalkylalkyl];

wherein:

Y is oxygen or sulphur,

R_4 is alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heterocyclyl, heteroaryl, aralkyl, heteroarylalkyl, heterocyclylalkyl or cycloalkylalkyl;

m is an integer 0-2;

R_5 is hydrogen or R_4 ;

R_x is R_4 or $-SO_2N(R_4)_2$ and

R_6 is hydrogen, alkyl, cycloalkyl, aralkyl, heteroarylalkyl, heterocyclylalkyl or cycloalkylalkyl;

R_3 is hydrogen, fluorine, alkyl, cycloalkylalkyl or aralkyl;

A is OH, OR_4 , $-OC(=O)NR_4R_5$, O-acyl, NH_2 , NR_4R_5 , $-NHC(=Y)R_4$, $-NHC(=Y)NR_5R_x$, $-NHC(=O)OR_4$, $-NHSO_2R_4$.

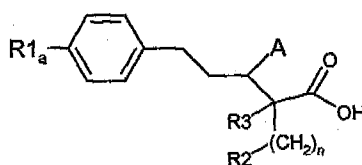
2. (Amended) A compound according to as-claimed in claim 1 having the a structure of Formula Ia:

wherein:

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

n, Y, R_x, R₁, R₂, R₃, and R₄ and R₅ are as defined in claim 1 earlier.

3. (Amended) A compound according to as-claimed in claim 1 having the a structure of Formula Ib:



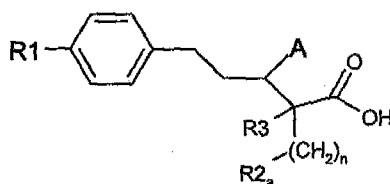
Formula Ib

wherein:

R_{1a} is aryl or heteroaryl;

n, R₂, R₃ and A are as defined in claim 1 earlier.

4. (Amended) A compound as claimed in claim 1 having the structure of Formula Ic:



Formula Ic

wherein:

R_{2a} is NR₄R₅, -NHC(=Y)R₄, -NHC(=Y)NR₅R_x, -NHC(=O)OR₄, -NHSO₂R₄, amidino or guanidino [~~wherein Y is oxygen or sulphur and R₄ is alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heterocyclyl, heteroaryl, aralkyl, heteroarylalkyl, heterocyclylalkyl 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];~~

wherein:

Y is oxygen or sulphur;

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

m is an integer 0-2;

R₅ is hydrogen or R₄; or R₄ and R₅ together may optionally form a heterocyclic ring containing one or more heteroatoms such as O, N or S;

R_x is R₄ or -SO₂N(R₄)₂; and

n, R₁, R₃ and A are as defined in claim 1 earlier.

5. (Amended) A compound which is selected from the group consisting of :

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

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

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

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

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

2-[2-(1,3-Dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-5-(4'-ethoxybiphenyl-4-yl)-3-hydroxypentanoic acid (Compound No. 6),

2-[2-(1,3-Dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-5-(4'-formylbiphenyl-4-yl)-3-hydroxypentanoic acid (Compound No. 7),

2-[2-(1,3-Dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxy-5-(2',4',6'-trimethoxybiphenyl-4-yl)pentanoic acid (Compound No. 8),

2-[2-(1,3-Dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxy-5-(4'-propoxybiphenyl-4-yl)pentanoic acid (Compound No. 9),

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

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

5-Biphenyl-4-yl-2-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxypentanoic acid (Compound No. 12),

(2*R*,3*S* + 2*S*,3*R*)-2-[2-(1,3-Dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-5-(4'-formylbiphenyl-4-yl)-3-hydroxypentanoic acid (Compound No. 13),

(2*R*,3*R* + 2*S*,3*S*)-2-[2-(1,3-Dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-5-(4'-formylbiphenyl-4-yl)-3-hydroxypentanoic acid (Compound No. 14),

(2*R*,3*R* + 2*S*,3*S*)-2-[2-(1,3-Dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxy-5-(2',4',6'-trimethoxybiphenyl-4-yl)pentanoic acid (Compound No. 15),

(2*R*,3*S* + 2*S*,3*R*)-2-[2-(1,3-Dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxy-5-(2',4',6'-trimethoxybiphenyl-4-yl)pentanoic acid (Compound No. 16),

(2*R*,3*S* + 2*S*,3*R*)-5-(4'-Acetylbiphenyl-4-yl)-2-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxypentanoic acid (Compound No. 17),

(2*R*,3*R* + 2*S*,3*S*)-5-(4'-Acetylbiphenyl-4-yl)-2-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxypentanoic acid (Compound No. 18),

(2*R*,3*S* + 2*S*,3*R*)-2-[2-(1,3-Dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxy-5-(4'-propoxybiphenyl-4-yl)pentanoic acid (Compound No. 19),

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

(2*R*,3*S* + 2*S*,3*R*)-5-(3',4'-Difluorobiphenyl-4-yl)-2-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxypentanoic acid (Compound No. 21),

(2*R*,3*R* + 2*S*,3*S*)-5-(3',4'-Difluorobiphenyl-4-yl)-2-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxypentanoic acid (Compound No. 22),

2-[2-(1,3-Dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxy-5-(4'-methoxybiphenyl-4-yl)pentanoic acid (Compound No. 23),

5-(2',3'-Dimethylbiphenyl-4-yl)-2-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxypentanoic acid (Compound No. 24),

2-[2-(1,3-Dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxy-5-[3'-(trifluoromethyl)biphenyl-4-yl]pentanoic acid (Compound No. 25),

2-[2-(1,3-Dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-5-(4'-ethylbiphenyl-4-yl)-3-hydroxypentanoic acid (Compound No. 26),

5-(3',5'-Dichlorobiphenyl-4-yl)-2-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxypentanoic acid (Compound No. 27),

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5-[4'-Chloro-3'-(trifluoromethyl)biphenyl-4-yl]-2-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxypentanoic acid (Compound No. 28),

5-(2',5'-Difluorobiphenyl-4-yl)-2-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxypentanoic acid (Compound No. 29),

2-[2-(1,3-Dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxy-5-[2'-(trifluoromethoxy)biphenyl-4-yl]pentanoic acid (Compound No. 30),

~~2-[2-(1,3-Dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxy-5-[4'-(methylthio)biphenyl-4-yl]pentanoic acid (Compound No. 31),~~

2-[2-(1,3-Dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-5-(4'-fluoro-3'-methylbiphenyl-4-yl)-3-hydroxypentanoic acid (Compound No. 32),

2-[2-(1,3-Dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxy-5-(3'-isopropylbiphenyl-4-yl)pentanoic acid (Compound No. 33),

5-(3',4'-Dimethylbiphenyl-4-yl)-2-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxypentanoic acid (Compound No. 34),

5-(2',6'-Difluorobiphenyl-4-yl)-2-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxypentanoic acid (Compound No. 35),

2-[2-(1,3-Dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-5-(4'-fluorobiphenyl-4-yl)-3-hydroxypentanoic acid (Compound No. 36),

5-(3',5'-Difluorobiphenyl-4-yl)-2-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxypentanoic acid (Compound No. 37),

5-(3'-Chloro-4'-fluorobiphenyl-4-yl)-2-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxypentanoic acid (Compound No. 38),

5-(3',4'-Dimethoxybiphenyl-4-yl)-2-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxypentanoic acid (Compound No. 39),

5-(3'-Chlorobiphenyl-4-yl)-2-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxypentanoic acid (Compound No. 40),

2-[2-(1,3-Dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxy-5-(3'-methylbiphenyl-4-yl)pentanoic acid (Compound No. 41),

5-(2',3'-Difluorobiphenyl-4-yl)-2-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxypentanoic acid (Compound No. 42),

2-[2-(1,3-Dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-5-(2'-fluoro-3'-methoxybiphenyl-4-yl)-3-hydroxypentanoic acid (Compound No. 43),

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- 2-[2-(1,3-Dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-5-(3'-fluoro-4'-methylbiphenyl-4-yl)-3-hydroxypentanoic acid (Compound No. 44),
- 5-Biphenyl-4-yl-3-hydroxy-2-{2-[(phenylacetyl)amino]ethyl}pentanoic acid (Compound No. 45),
- 2-(3-Biphenyl-4-yl-1-hydroxypropyl)-6-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)hexanoic acid (Compound No. 46),
- 5-Biphenyl-4-yl-3-hydroxy-2-[2-(1-oxophthalazin-2(1*H*)-yl)ethyl]pentanoic acid (Compound No. 47),
- 5-Biphenyl-4-yl-2-[3-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)propyl]-3-hydroxypentanoic acid (Compound No. 48),
- 5-Biphenyl-4-yl-3-hydroxy-2-[2-(2'-oxospiro[cyclopropane-1,3'-indol]-1'(2'*H*)-yl)ethyl]pentanoic acid (Compound No. 49),
- 2-[2-(1,3-Dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxy-5-(4'-hydroxybiphenyl-4-yl)pentanoic acid (Compound No. 50),
- 3-Hydroxy-5-(4'-methoxybiphenyl-4-yl)-2-[2-(3-methyl-2,6-dioxo-3,6-dihydropyrimidin-1(2*H*)-yl)ethyl]pentanoic acid (Compound No. 51),
- 5-(4'-Chlorobiphenyl-4-yl)-3-hydroxy-2-[2-(3-methyl-2,6-dioxo-3,6-dihydropyrimidin-1(2*H*)-yl)ethyl]pentanoic acid (Compound No. 52),
- 5-(4'-Fluorobiphenyl-4-yl)-3-hydroxy-2-[2-(3-methyl-2,6-dioxo-3,6-dihydropyrimidin-1(2*H*)-yl)ethyl]pentanoic acid (Compound No. 53),
- 5-[4-(5-Chloro-2-thienyl)phenyl]-2-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxypentanoic acid (Compound No. 54),
- 4'-[4-Carboxy-6-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)-3-hydroxyhexyl]biphenyl-4-carboxylic acid (Compound No. 55),
- 2-[2-(1,3-Dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxy-5-[4'-(methoxycarbonyl)biphenyl-4-yl]pentanoic acid (Compound No. 56),
- 2-[2-(1,3-Dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxy-5-[4'-(trifluoromethyl)biphenyl-4-yl]pentanoic acid (Compound No. 57),
- 2-[2-(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. 58),
- 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(4H)-yl)ethyl]pentanoic acid (Compound No. 60),
- 2-[2-(1,3-Dioxo-1,3-dihydro-2H-isoindol-2-yl)ethyl]-5-(3'-fluorobiphenyl-4-yl)-3-hydroxypentanoic acid (Compound No. 61),
- 5-[4'-(Benzyloxy)-3'-fluorobiphenyl-4-yl]-2-[2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)ethyl]-3-hydroxypentanoic acid (Compound No. 62),
- 5-[4'-(Benzyloxy)biphenyl-4-yl]-2-[2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)ethyl]-3-hydroxypentanoic acid (Compound No. 63),
- 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),
- 2-[2-(1,3-Dioxo-1,3-dihydro-2H-isoindol-2-yl)ethyl]-3-hydroxy-5-(4'-methylbiphenyl-4-yl)pentanoic acid (Compound No. 66),
- 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),

(2R,3S + 2S,3R)-2-[2-(1,3-Dioxo-1,3-dihydro-2H-isoindol-2-yl)ethyl]-3-hydroxy-5-[4-(6-methoxypyridin-3-yl)phenyl]pentanoic acid (Compound No. 78),

(2R,3R + 2S,3S)-2-[2-(1,3-Dioxo-1,3-dihydro-2H-isoindol-2-yl)ethyl]-3-hydroxy-5-[4-(6-methoxypyridin-3-yl)phenyl]pentanoic acid (Compound No. 79),

(2R,3R + 2S,3S)-5-(4'-Chlorobiphenyl-4-yl)-2-[2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)ethyl]-3-hydroxypentanoic acid (Compound No. 80),

(2R,3S + 2S,3R)-5-(4'-Chlorobiphenyl-4-yl)-2-[2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)ethyl]-3-hydroxypentanoic acid (Compound No. 81),

(2R,3S + 2S,3R)-2-[2-(1,3-Dioxo-1,3-dihydro-2H-isoindol-2-yl)ethyl]-5-(4'-fluorobiphenyl-4-yl)-3-hydroxypentanoic acid (Compound No. 82),

(2R,3R + 2S,3S)-2-[2-(1,3-Dioxo-1,3-dihydro-2H-isoindol-2-yl)ethyl]-5-(4'-fluorobiphenyl-4-yl)-3-hydroxypentanoic acid (Compound No. 83),

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),
- 2-(3-Biphenyl-4-yl-1-hydroxypropyl)pent-4-ynoic acid (Compound No. 95);
- 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-{4-[6-(Dimethylamino)pyridin-3-yl]phenyl}-2-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxypentanoic acid (Compound No. 98),
- 2-[2-(1,3-Dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxy-5-[4'-(methylsulfonyl)biphenyl-4-yl]pentanoic acid (Compound No. 99),
- 5-[4'-(Aminocarbonyl)biphenyl-4-yl]-2-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxypentanoic acid (Compound No. 100),
- 5-[4-(1-Benzyl-1*H*-pyrazol-4-yl)phenyl]-2-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxypentanoic acid (Compound No. 101),
- 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),
- 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),
- (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-[2-(1,3-Dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-5-(3'-fluoro-4'-methoxybiphenyl-4-yl)-3-hydroxypentanoic acid (Compound No. 110),

(2*R*,3*S* + 2*S*,3*R*)-2-[2-(1,3-Dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxy-5-[4-(6-methylpyridin-3-yl)phenyl]pentanoic acid (Compound No. 111),

(2*R*,3*R* + 2*S*,3*S*)-2-[2-(1,3-Dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxy-5-[4-(6-methylpyridin-3-yl)phenyl]pentanoic acid (Compound No. 112),

(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),

(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),

(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),

~~2-[2-(1,3-Dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxy-5-(4-pyrimidin-5-yl)phenyl]pentanoic acid (Compound No. 119),~~

5-Biphenyl-4-yl-3-hydroxy-2-[2-(7-methyl-4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)ethyl]pentanoic acid (Compound No. 120),

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),

(2*R*,3*S*)-5-Biphenyl-4-yl-3-hydroxy-2-[2-(1*H*-indol-3-yl)ethyl]pentanoic acid (Compound No. 122),

(2*R*,3*R*)-5-Biphenyl-4-yl-3-hydroxy-2-[2-(1*H*-indol-3-yl)ethyl]pentanoic acid (Compound No. 123),

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

(2R,3S)-5-(4'-Chlorobiphenyl-4-yl)-2-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxypentanoic acid (Compound No.125),

(2S,3R)-5-(4'-Chlorobiphenyl-4-yl)-2-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxypentanoic acid (Compound No.126),

(2R,3R)-5-(4'-Chlorobiphenyl-4-yl)-2-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxypentanoic acid (Compound No.127),

(2S,3S)-5-(4'-Chlorobiphenyl-4-yl)-2-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxypentanoic acid (Compound No.128),

(2R,3S)-2-[2-(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. 129),

(2S,3R)-2-[2-(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. 130),

(2R,3R)-2-[2-(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. 131),

(2S,3S)-2-[2-(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. 132),

(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~~ or

(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).

6. (Amended) A pharmaceutical composition comprising therapeutically effective amount of a compound as defined in claim 1 ~~together with~~ and pharmaceutically acceptable carrier, excipients or diluents.

7. (Amended) A pharmaceutical composition of claim 6 further comprising one or more additional active ingredients selected from:

- a) Anti-inflammatory agents, experimental or commercial including (i) 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, or (v) interleukin-I inhibitors;

b) antihypertensive agents, including (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 or (iv) calcium channel blockers; and

c) immunosuppressive agents including cyclosporine, azathioprine and methotrexate, anti-inflammatory corticosteroids.

8. (Amended) A method for treatment or prophylaxis of an animal or a human suffering from a-inflammatory diseases and associated pathologies which comprises administering to the animal or human ~~said mammal~~ an effective amount of a compound according to claim 1.

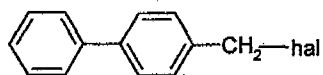
9. (Amended) A method for treatment or prophylaxis of an animal or a human suffering from a inflammatory diseases and associated pathologies which comprises administering to the animal or human ~~said mammal~~ an effective amount of pharmaceutical composition according to claim 6.

10. (Amended) A method for treatment or prophylaxis of an animal or a human suffering from a inflammatory diseases and associated pathologies which comprises administering to the animal or human ~~said mammal~~ an effective amount of pharmaceutical composition according to claim 7.

11. (Amended) A method according to claim 8, wherein the inflammatory diseases and associated pathologies include asthma, rheumatoid arthritis, COPD, rhinitis, osteoarthritis, psoriatic arthritis, psoriasis, pulmonary fibrosis, pulmonary inflammation, acute respiratory distress syndrome, perodontitis, multiple sclerosis, gingivitis, atherosclerosis, neointimal proliferation, which leads to restenosis and ischemic heart failure, stroke, renal diseases or and tumor metastasis.

12. (Amended) A process for preparing a compound of Formula VIII comprising :

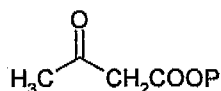
a. reacting a compound of Formula II



Formula II

; wherein hal is hal is Cl, Br or I;

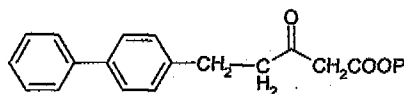
with a compound of Formula III



Formula III

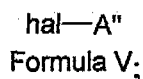
; wherein P is alkyl or aralkyl selected from tert-butyl, ethyl, methyl or benzyl);

to give a compound Formula IV;



Formula IV

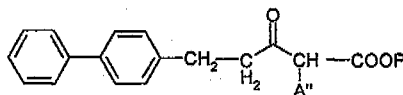
b. reacting a compound Formula IV with a compound of Formula V



Formula V;

wherein:A'' is selected from aralkyl, heterocyclalkyl, heteroarylalkyl or cycloalkylalkyl; andHal or halogen is selected from Cl, Br or I;

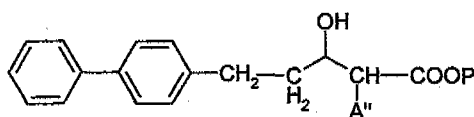
to give a compound of Formula VI;



Formula VI

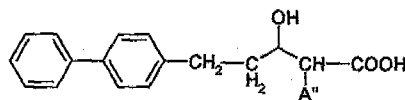
c. reducing a compound of Formula VI to give a compound of Formula VII;

and



Formula VII

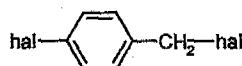
d. deprotecting a compound of Formula VII to give a compound of Formula VIII



Formula VIII

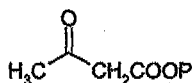
13. (Amended) A process for preparing a compound of Formula XXI comprising:

a. reacting a compound of Formula IX



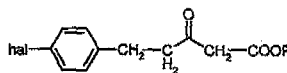
Formula IX

with a compound of Formula III



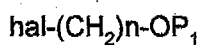
Formula III

to give a compound of Formula X;



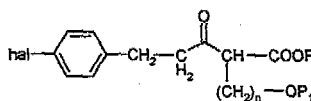
Formula X

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



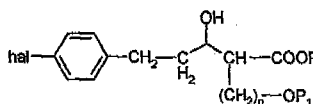
Formula XI

to give a compound of Formula XII;



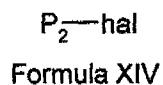
Formula XII

c. reducing a compound of Formula XII to give a compound of Formula XIII;

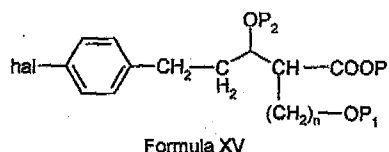


Formula XIII

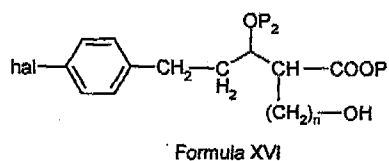
d. reacting a compound of Formula XIII with a compound of Formula XIV



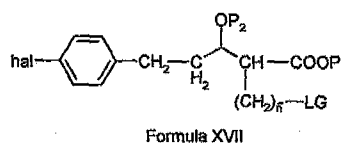
to give a compound of Formula XV;



e. deprotecting a compound of Formula XV to give a compound of Formula XVI;

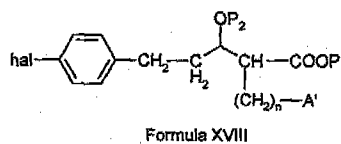


f. converting a compound of Formula XVI to a compound of Formula XVII

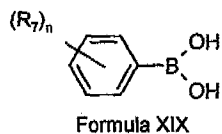


by reaction with a compound of Formula L-hal;

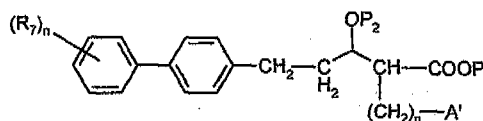
g. reacting a compound of Formula XVII with a compound of Formula M-A' or A' to give a compound of Formula XVIII;



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

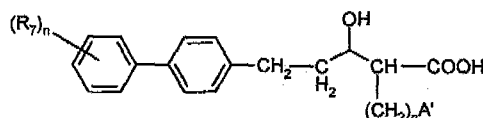


to form a compound of Formula XX; and



Formula XX

- i. deprotecting a compound of Formula XX to give a compound of Formula XXI



Formula XXI

wherein:

P is alkyl (for example, tert-butyl, ethyl or methyl) or aralkyl selected from tert-butyl, ethyl or methyl) (or example, benzyl);

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

P₂ is aralkyl (for example, benzyl, 4-methoxybenzyl or 2,4,6-trimethoxybenzyl) or heterocyclyl selected from benzyl, 4-methoxybenzyl or 2,4,6-trimethoxybenzyl) (for example, 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 aryl, heteroaryl, heterocyclyl or cycloalkyl and M is metal for example, selected from potassium, lithium or sodium;

A'' is aralkyl, heterocyclylalkyl, heteroarylalkyl or cycloalkylalkyl;

n is an integer from 1 to 5

R₇ is hydrogen, halogen (F, Cl, Br, I), hydroxy, -COOR₄, alkyl, alkenyl, alkynyl, cycloalkyl, alkoxy, alkenyloxy, alkynyloxy, aryloxy, heterocycliloxy, 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, -NHSO₂R₄, (SO)_mR₄, aryl, heterocyclyl, heteroaryl, heterocyclylalkyl or heteroarylalkyl which may optionally be substituted further;

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

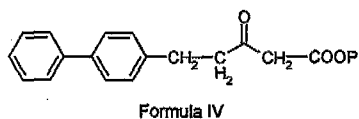
m is an integer 0-2;

R₅ is hydrogen or R₄; and

R_x is R₄ or -SO₂N(R₄)₂.

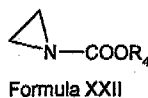
14. (Amended) A process for preparing a compound of Formula XXV comprising:

a. reacting a compound of Formula IV



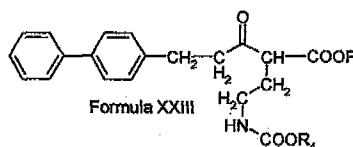
wherein P is selected from alkyl or aralkyl selected from tert-butyl, ethyl, methyl or benzyl;

with a compound of Formula XXII

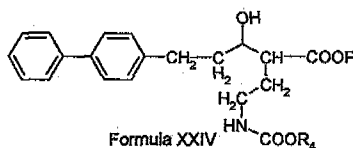


R₄ is alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heterocyclyl, heteroaryl, aralkyl, heteroarylalkyl, heterocyclylalkyl or cycloalkylalkyl;

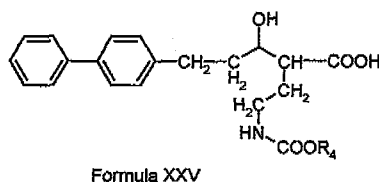
to give a compound of Formula XXIII;



b. reducing a compound of Formula XXIII to give a compound of Formula XXIV; and



c. deprotecting a compound of Formula XXIV to give a compound of Formula XXV



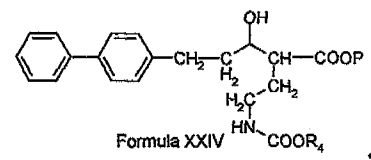
wherein:

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

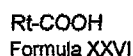
R_4 is ~~alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heterocyclyl, heteroaryl, aralkyl, heteroarylalkyl, heterocyclalkyl or cycloalkylalkyl.~~

15. (Amended) A process for preparing a compound of Formula XXXI comprising:

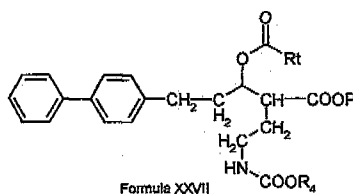
a. reacting a compound of Formula XXIV



with a compound of Formula XXVI:



to give a compound of Formula XXVII:



wherein:

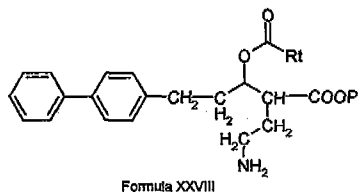
P is ... [Need to define P, protecting group],

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

and

R_4 is ~~alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heterocyclyl, heteroaryl, aralkyl, heteroarylalkyl, heterocyclalkyl or cycloalkylalkyl;~~

b. deprotecting a compound of Formula XXVII to give a compound of Formula XXVIII:



, wherein P and Rt are as defined above;

to give a compound of Formula XXIX;:



Y is oxygen or sulphur;

Formula XXX 'RF'

e. deprotecting a compound of Formula XXX to give a compound of Formula XXXI:



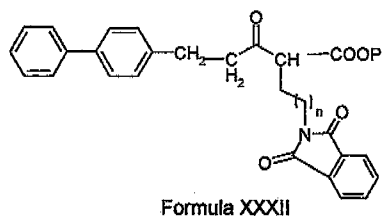
~~Y is oxygen or sulphur:~~

~~Rt is alkyl, aryl, cycloalkyl, aralkyl, heterocyclalalkyl or heteroarylalkyl;~~

~~hal is Cl, Br or I.~~

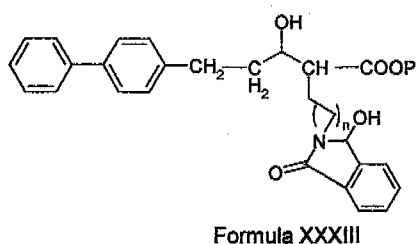
16. (Amended) A process for preparing a compound of Formula XXXIV comprising:

a. reducing a compound of Formula XXXII

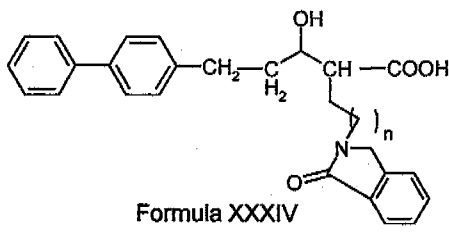


wherein P is a protecting group;

to give a compound of Formula XXXIII; and



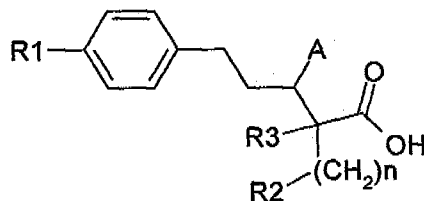
b. hydrolyzing a compound of Formula XXXIII to give a compound of Formula XXXIV



17. (Amended) 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 ~~and/or~~ by HPLC (High Pressure Liquid Chromatography, using an achiral or chiral separation column.

Amendment to claims – CORRECTED 21 August 2007

1. (Amended) A ~~C~~compounds of having the structure of Formula I:



Formula I

wherein:

n is an integer from 1 to 5;

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

R₂ is 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 is oxygen or sulphur], OR₅, -OC(=O)NR₄R₅, O-acyl, S(O)_mR₄, -SO₂N(R₄)₂, cyano, amidino or guanidine [wherein R₄ is alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heterocyclyl, heteroaryl, aralkyl, heteroarylalkyl, heterocyclylalkyl or cycloalkylalkyl and m is an integer 0-2; R₅ is hydrogen or R₄; R_x is R₄ or -SO₂N(R₄)₂ and R₆ is hydrogen, alkyl, cycloalkyl, aralkyl, heteroarylalkyl, heterocyclylalkyl or cycloalkylalkyl];

wherein:

Y is oxygen or sulphur.

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

m is an integer 0-2;

R₅ is hydrogen or R₄;

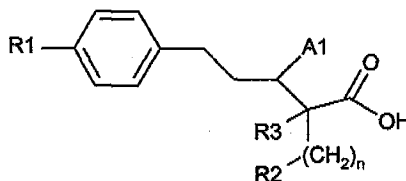
R_x is R₄ or -SO₂N(R₄)₂ and

R₆ is hydrogen, alkyl, cycloalkyl, aralkyl, heteroarylalkyl, heterocyclylalkyl or cycloalkylalkyl;

R_3 is hydrogen, fluorine, alkyl, cycloalkylalkyl or aralkyl;

A is OH, OR_4 , $-OC(=O)NR_4R_5$, O-acyl, NH_2 , NR_4R_5 , $-NHC(=Y)R_4$, $-NHC(=Y)NR_5R_x$, $-NHC(=O)OR_4$, $-NHSO_2R_4$.

2. (Amended) A compound according to as claimed in claim 1 having ~~the~~ a structure of Formula Ia:



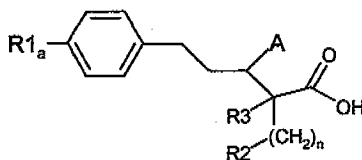
Formula Ia

wherein:

A1 is OH, $-OC(=O)NR_4R_5$, NH_2 , NR_4R_5 , $-NHC(=Y)R_4$, $-NHC(=Y)NR_5R_x$, $-NHC(=O)OR_4$, $-NHSO_2R_4$; and

n, Y, R_x , R_1 , R_2 , R_3 , and R_4 and R_5 are as defined in claim 1 ~~earlier~~.

3. (Amended) A compound according to as claimed in claim 1 having ~~the~~ a structure of Formula Ib:



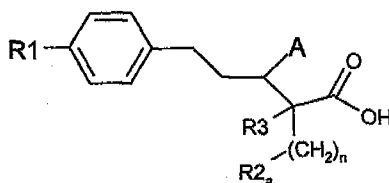
Formula Ib

wherein:

R_{1a} is aryl or heteroaryl;

n, R_2 , R_3 and A are as defined in claim 1 ~~earlier~~.

4. (Amended) A compound as claimed in claim 1 having the structure of Formula Ic:



Formula Ic

wherein:

R_{2a} is NR_4R_5 , $-NHC(=Y)R_4$, $-NHC(=Y)NR_5R_x$, $-NHC(=O)OR_4$, $-NHSO_2R_4$, amidino or guanidino [wherein Y is oxygen or sulphur and R_4 is alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heterocyclyl, heteroaryl, aralkyl, heteroarylalkyl, heterocyclalkyl or cycloalkylalkyl and m is an integer 0-2; R_5 is hydrogen or R_4 ; R_4 and R_5 together may optionally form a heterocyclic ring containing one or more heteroatoms such as O, N or S and R_x is R_4 or $-SO_2N(R_4)_2$];

wherein:

Y is oxygen or sulphur;

R_4 is alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heterocyclyl, heteroaryl, aralkyl, heteroarylalkyl, heterocyclalkyl or cycloalkylalkyl;

m is an integer 0-2;

R_5 is hydrogen or R_4 ; or R_4 and R_5 together may optionally form a heterocyclic ring containing one or more heteroatoms such as O, N or S;

R_x is R_4 or $-SO_2N(R_4)_2$; and

n, R_1 , R_3 and A are as defined in claim 1 earlier.

5. (Amended) A compound which is selected from the group consisting of:

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

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

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

- 5-(4'-Chlorobiphenyl-4-yl)-2-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxypentanoic acid (Compound No. 4),
- ~~2-[2-(1,3-Dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxy-5-(4'-trifluoromethoxybiphenyl-4-yl)pentanoic acid (Compound No. 5),~~
- 2-[2-(1,3-Dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-5-(4'-ethoxybiphenyl-4-yl)-3-hydroxypentanoic acid (Compound No. 6),
- 2-[2-(1,3-Dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-5-(4'-formylbiphenyl-4-yl)-3-hydroxypentanoic acid (Compound No. 7),
- 2-[2-(1,3-Dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxy-5-(2',4',6'-trimethoxybiphenyl-4-yl)pentanoic acid (Compound No. 8),
- 2-[2-(1,3-Dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxy-5-(4'-propoxybiphenyl-4-yl)pentanoic acid (Compound No. 9),
- 5-(3',4'-Difluorobiphenyl-4-yl)-2-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxypentanoic acid (Compound No. 10),
- 2-(2-{[(Benzyloxy)carbonyl]amino}ethyl)-5-biphenyl-4-yl-3-hydroxypentanoic acid (Compound No. 11),
- ~~5-Biphenyl-4-yl-2-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxypentanoic acid (Compound No. 12),~~
- (2*R*,3*S* + 2*S*,3*R*)-2-[2-(1,3-Dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-5-(4'-formylbiphenyl-4-yl)-3-hydroxypentanoic acid (Compound No. 13),
- (2*R*,3*R* + 2*S*,3*S*)-2-[2-(1,3-Dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-5-(4'-formylbiphenyl-4-yl)-3-hydroxypentanoic acid (Compound No. 14),
- (2*R*,3*R* + 2*S*,3*S*)-2-[2-(1,3-Dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxy-5-(2',4',6'-trimethoxybiphenyl-4-yl)pentanoic acid (Compound No. 15),
- (2*R*,3*S* + 2*S*,3*R*)-2-[2-(1,3-Dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxy-5-(2',4',6'-trimethoxybiphenyl-4-yl)pentanoic acid (Compound No. 16),
- (2*R*,3*S* + 2*S*,3*R*)-5-(4'-Acetylbiphenyl-4-yl)-2-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxypentanoic acid (Compound No. 17),
- (2*R*,3*R* + 2*S*,3*S*)-5-(4'-Acetylbiphenyl-4-yl)-2-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxypentanoic acid (Compound No. 18),
- (2*R*,3*S* + 2*S*,3*R*)-2-[2-(1,3-Dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxy-5-(4'-propoxybiphenyl-4-yl)pentanoic acid (Compound No. 19),

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

(2*R*,3*S* + 2*S*,3*R*)-5-(3',4'-Difluorobiphenyl-4-yl)-2-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxypentanoic acid (Compound No. 21),

(2*R*,3*R* + 2*S*,3*S*)-5-(3',4'-Difluorobiphenyl-4-yl)-2-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxypentanoic acid (Compound No. 22),

2-[2-(1,3-Dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxy-5-(4'-methoxybiphenyl-4-yl)pentanoic acid (Compound No. 23),

5-(2',3'-Dimethylbiphenyl-4-yl)-2-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxypentanoic acid (Compound No. 24),

2-[2-(1,3-Dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxy-5-[3'-(trifluoromethyl)biphenyl-4-yl]pentanoic acid (Compound No. 25),

2-[2-(1,3-Dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-5-(4'-ethylbiphenyl-4-yl)-3-hydroxypentanoic acid (Compound No. 26),

5-(3',5'-Dichlorobiphenyl-4-yl)-2-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxypentanoic acid (Compound No. 27),

5-[4'-Chloro-3'-(trifluoromethyl)biphenyl-4-yl]-2-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxypentanoic acid (Compound No. 28),

5-(2',5'-Difluorobiphenyl-4-yl)-2-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxypentanoic acid (Compound No. 29),

2-[2-(1,3-Dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxy-5-[2'-(trifluoromethoxy)biphenyl-4-yl]pentanoic acid (Compound No. 30),

~~2-[2-(1,3-Dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxy-5-[4'-(methylthio)biphenyl-4-yl]pentanoic acid (Compound No. 31),~~

2-[2-(1,3-Dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-5-(4'-fluoro-3'-methylbiphenyl-4-yl)-3-hydroxypentanoic acid (Compound No. 32),

2-[2-(1,3-Dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxy-5-(3'-isopropylbiphenyl-4-yl)pentanoic acid (Compound No. 33),

5-(3',4'-Dimethylbiphenyl-4-yl)-2-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxypentanoic acid (Compound No. 34),

5-(2',6'-Difluorobiphenyl-4-yl)-2-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxypentanoic acid (Compound No. 35),

- 2-[2-(1,3-Dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-5-(4'-fluorobiphenyl-4-yl)-3-hydroxypentanoic acid (Compound No. 36),
- 5-(3',5'-Difluorobiphenyl-4-yl)-2-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxypentanoic acid (Compound No. 37),
- 5-(3'-Chloro-4'-fluorobiphenyl-4-yl)-2-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxypentanoic acid (Compound No. 38),
- 5-(3',4'-Dimethoxybiphenyl-4-yl)-2-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxypentanoic acid (Compound No. 39),
- 5-(3'-Chlorobiphenyl-4-yl)-2-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxypentanoic acid (Compound No. 40),
- 2-[2-(1,3-Dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxy-5-(3'-methylbiphenyl-4-yl)pentanoic acid (Compound No. 41),
- 5-(2',3'-Difluorobiphenyl-4-yl)-2-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxypentanoic acid (Compound No. 42),
- 2-[2-(1,3-Dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-5-(2'-fluoro-3'-methoxybiphenyl-4-yl)-3-hydroxypentanoic acid (Compound No. 43),
- 2-[2-(1,3-Dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-5-(3'-fluoro-4'-methylbiphenyl-4-yl)-3-hydroxypentanoic acid (Compound No. 44),
- 5-Biphenyl-4-yl-3-hydroxy-2-{2-[(phenylacetyl)amino]ethyl}pentanoic acid (Compound No. 45),
- 2-(3-Biphenyl-4-yl-1-hydroxypropyl)-6-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)hexanoic acid (Compound No. 46),
- 5-Biphenyl-4-yl-3-hydroxy-2-[2-(1-oxophthalazin-2(1*H*)-yl)ethyl]pentanoic acid (Compound No. 47),
- 5-Biphenyl-4-yl-2-[3-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)propyl]-3-hydroxypentanoic acid (Compound No. 48),
- 5-Biphenyl-4-yl-3-hydroxy-2-[2-(2'-oxospiro[cyclopropane-1,3'-indol]-1'(2'*H*)-yl)ethyl]pentanoic acid (Compound No. 49),
- 2-[2-(1,3-Dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxy-5-(4'-hydroxybiphenyl-4-yl)pentanoic acid (Compound No. 50),
- 3-Hydroxy-5-(4'-methoxybiphenyl-4-yl)-2-[2-(3-methyl-2,6-dioxo-3,6-dihydropyrimidin-1(2*H*)-yl)ethyl]pentanoic acid (Compound No. 51),

- 5-(4'-Chlorobiphenyl-4-yl)-3-hydroxy-2-[2-(3-methyl-2,6-dioxo-3,6-dihydropyrimidin-1(2*H*)-yl)ethyl]pentanoic acid (Compound No. 52),
- 5-(4'-Fluorobiphenyl-4-yl)-3-hydroxy-2-[2-(3-methyl-2,6-dioxo-3,6-dihydropyrimidin-1(2*H*)-yl)ethyl]pentanoic acid (Compound No. 53),
- 5-[4-(5-Chloro-2-thienyl)phenyl]-2-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxypentanoic acid (Compound No. 54),
- 4'-[4-Carboxy-6-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)-3-hydroxyhexyl]biphenyl-4-carboxylic acid (Compound No. 55),
- 2-[2-(1,3-Dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxy-5-[4'-(methoxycarbonyl)biphenyl-4-yl]pentanoic acid (Compound No. 56),
- 2-[2-(1,3-Dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxy-5-[4'-(trifluoromethyl)biphenyl-4-yl]pentanoic acid (Compound No. 57),
- 2-[2-(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. 58),
- 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),
- 2-[2-(1,3-Dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-5-(3'-fluorobiphenyl-4-yl)-3-hydroxypentanoic acid (Compound No. 61),
- 5-[4'-(Benzyloxy)-3'-fluorobiphenyl-4-yl]-2-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxypentanoic acid (Compound No. 62),
- 5-[4'-(Benzyloxy)biphenyl-4-yl]-2-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxypentanoic acid (Compound No. 63),
- 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),
- 2-[2-(1,3-Dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxy-5-(4'-methylbiphenyl-4-yl)pentanoic acid (Compound No. 66),
- 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),
- 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),
- 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),
- 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),
- (2*R*,3*S* + 2*S*,3*R*)-2-[2-(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. 78),
- (2*R*,3*R* + 2*S*,3*S*)-2-[2-(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. 79),
- (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-hydroxypentanoic acid (Compound No. 80),
- (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 (Compound No. 81),
- (2*R*,3*S* + 2*S*,3*R*)-2-[2-(1,3-Dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-5-(4'-fluorobiphenyl-4-yl)-3-hydroxypentanoic acid (Compound No. 82),
- (2*R*,3*R* + 2*S*,3*S*)-2-[2-(1,3-Dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-5-(4'-fluorobiphenyl-4-yl)-3-hydroxypentanoic acid (Compound No. 83),

- 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-[(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-(4-fluorophenyl)sulfonyl]amino]ethyl)-3-hydroxypentanoic acid (Compound No. 87),
- 5-Biphenyl-4-yl-2-(2-[[3-(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),
- 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),
- 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),
- 2-(3-Biphenyl-4-yl-1-hydroxypropyl)pent-4-ynoic acid (Compound No. 95);
- 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-{4-[6-(Dimethylamino)pyridin-3-yl]phenyl}-2-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxypentanoic acid (Compound No. 98),
- 2-[2-(1,3-Dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxy-5-[4'-(methylsulfonyl)biphenyl-4-yl]pentanoic acid (Compound No. 99),
- 5-[4'-(Aminocarbonyl)biphenyl-4-yl]-2-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxypentanoic acid (Compound No. 100),

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5-[4-(1-Benzyl-1*H*-pyrazol-4-yl)phenyl]-2-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxypentanoic acid (Compound No. 101),

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),

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),

(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-[2-(1,3-Dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-5-(3'-fluoro-4'-methoxybiphenyl-4-yl)-3-hydroxypentanoic acid (Compound No. 110),

(2*R*,3*S* + 2*S*,3*R*)-2-[2-(1,3-Dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxy-5-[4-(6-methylpyridin-3-yl)phenyl]pentanoic acid (Compound No. 111),

(2*R*,3*R* + 2*S*,3*S*)-2-[2-(1,3-Dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxy-5-[4-(6-methylpyridin-3-yl)phenyl]pentanoic acid (Compound No. 112),

(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),

(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),

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(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),

(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),

~~2-[2-(1,3-Dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxy-5-(4-pyrimidin-5-ylphenyl)pentanoic acid (Compound No. 119),~~

5-Biphenyl-4-yl-3-hydroxy-2-[2-(7-methyl-4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)ethyl]pentanoic acid (Compound No. 120),

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),

(2*R*,3*S*)-5-Biphenyl-4-yl-3-hydroxy-2-[2-(1*H*-indol-3-yl)ethyl]pentanoic acid (Compound No. 122),

(2*R*,3*R*)-5-Biphenyl-4-yl-3-hydroxy-2-[2-(1*H*-indol-3-yl)ethyl]pentanoic acid (Compound No. 123),

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

(2*R*,3*S*)-5-(4'-Chlorobiphenyl-4-yl)-2-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxypentanoic acid (Compound No.125),

(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 (Compound No.126),

(2*R*,3*R*)-5-(4'-Chlorobiphenyl-4-yl)-2-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxypentanoic acid (Compound No.127),

(2*S*,3*S*)-5-(4'-Chlorobiphenyl-4-yl)-2-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxypentanoic acid (Compound No.128),

(2*R*,3*S*) -2-[2-(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. 129),

(2*S*,3*R*)- 2-[2-(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. 130),

(2*R*,3*R*)- 2-[2-(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. 131),

(2*S*,3*S*)- 2-[2-(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. 132),

(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), ~~and~~ 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. (Amended) A pharmaceutical composition comprising therapeutically effective amount of a compound as defined in claim 1 ~~together with~~ and pharmaceutically acceptable carrier, excipients or diluents.

7. (Amended) A pharmaceutical composition of claim 6 further comprising one or more additional active ingredients selected from:

a) Anti-inflammatory agents, experimental or commercial including (i) 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, or (v) interleukin-I inhibitors;

b) antihypertensive agents, including (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~~ or (iv) calcium channel blockers; and

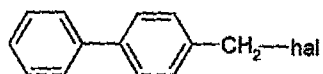
c) immunosuppressive agents including cyclosporine, azathioprine and methotrexate, anti-inflammatory corticosteroids.

8. (Amended) A method for treatment or prophylaxis of an animal or a human suffering from ~~a~~-inflammatory diseases and associated pathologies which comprises administering to the animal or human ~~said mammal~~ an effective amount of a compound according to claim 1.

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9. (Amended) A method for treatment or prophylaxis of an animal or a human suffering from a inflammatory diseases and associated pathologies which comprises administering to the animal or human ~~said mammal~~ an effective amount of pharmaceutical composition according to claim 6.
10. (Amended) A method for treatment or prophylaxis of an animal or a human suffering from a inflammatory diseases and associated pathologies which comprises administering to the animal or human ~~said mammal~~ an effective amount of pharmaceutical composition according to claim 7.
11. (Amended) A method according to claim 8, wherein the inflammatory diseases and associated pathologies include asthma, rheumatoid arthritis, COPD, rhinitis, osteoarthritis, psoriatic arthritis, psoriasis, pulmonary fibrosis, pulmonary inflammation, acute respiratory distress syndrome, perodontitis, multiple sclerosis, gingivitis, atherosclerosis, neointimal proliferation, which leads to restenosis and ischemic heart faliure, stroke, renal diseases or ~~and~~ tumor metastasis.
12. (Amended) A process for preparing a compound of Formula VIII comprising :

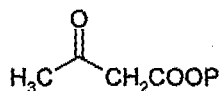
- a) reacting a compound of Formula II



Formula II ;

wherein hal is hal is Cl, Br or I:

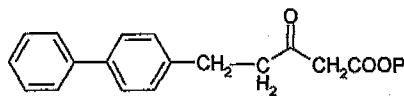
with a compound of Formula III



Formula III ;

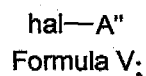
wherein P is alkyl or aralkyl selected from tert-butyl, ethyl, methyl or benzyl:

to give a compound Formula IV;



Formula IV

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

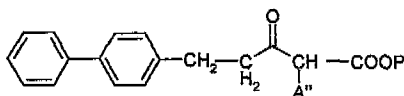


wherein:

A'' is selected from aralkyl, heterocyclalkyl, heteroarylalkyl or cycloalkylalkyl; and

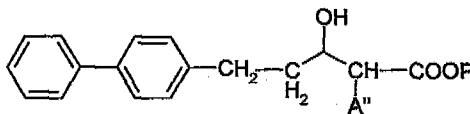
Hal or halogen is selected from Cl, Br or I;

to give a compound of Formula VI;



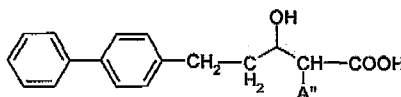
Formula VI

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



Formula VII

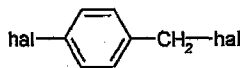
- d) deprotecting a compound of Formula VII to give a compound of Formula VIII



Formula VIII

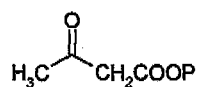
13. (Amended) A process for preparing a compound of Formula XXI comprising:

- a) reacting a compound of Formula IX



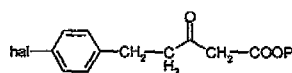
Formula IX

with a compound of Formula III



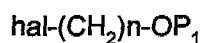
Formula III

to give a compound of Formula X;



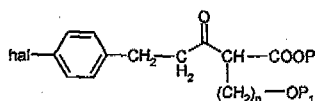
Formula X

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



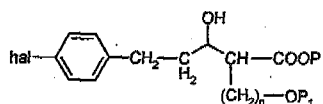
Formula XI

to give a compound of Formula XII;



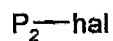
Formula XII

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



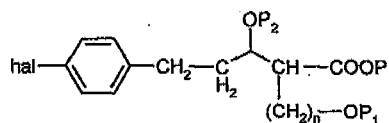
Formula XIII

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



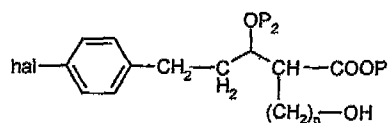
Formula XIV

to give a compound of Formula XV;



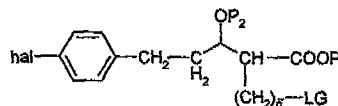
Formula XV

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



Formula XVI

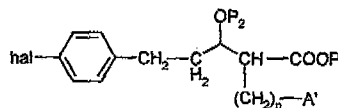
- f) converting a compound of Formula XVI to a compound of Formula XVII



Formula XVII

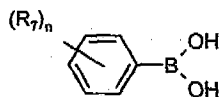
by reaction with a compound of Formula L-hal;

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



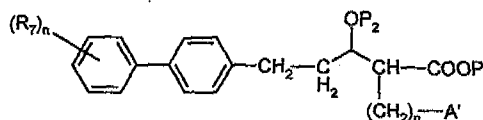
Formula XVIII

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



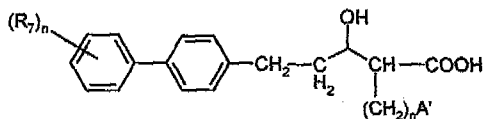
Formula XIX

to form a compound of Formula XX; and



Formula XX

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



Formula XXI

wherein:

P is alkyl (~~for example, tert-butyl, ethyl or methyl~~) or aralkyl selected from tert-butyl, ethyl or methyl) (~~or example, benzyl~~);

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

P₂ is aralkyl (~~for example, benzyl, 4-methoxybenzyl or 2,4,6-trimethoxybenzyl~~) or heterocyclyl selected from benzyl, 4-methoxybenzyl or 2,4,6-trimethoxybenzyl) (~~for example, 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 aryl, heteroaryl, heterocyclyl or cycloalkyl and M is metal ~~for example,~~ selected from potassium, lithium or sodium;

A'' is aralkyl, heterocyclylalkyl, heteroarylalkyl or cycloalkylalkyl;

n is an integer from 1 to 5

R₇ is hydrogen, halogen (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, -NHSO₂R₄, (SO)_mR₄, aryl, heterocyclyl, heteroaryl, heterocyclylalkyl or heteroarylalkyl which may optionally be substituted further;

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

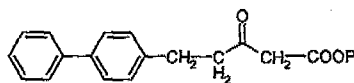
m is an integer 0-2;

R₅ is hydrogen or R₄; and

R_x is R₄ or -SO₂N(R₄)₂.

14. (Amended) A process for preparing a compound of Formula XXV comprising:

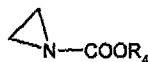
a) reacting a compound of Formula IV



Formula IV

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

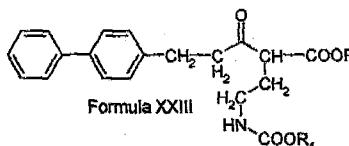
with a compound of Formula XXII



Formula XXII

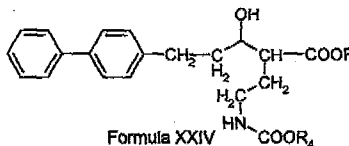
R_4 is alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heterocyclyl, heteroaryl, aralkyl, heteroarylalkyl, heterocyclylalkyl or cycloalkylalkyl;

to give a compound of Formula XXIII;



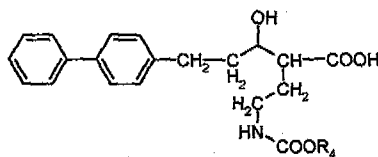
Formula XXIII

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



Formula XXIV

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



Formula XXV

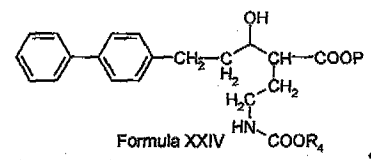
wherein:

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

R_4 is alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heterocyclyl, heteroaryl, aralkyl, heteroarylalkyl, heterocyclylalkyl or cycloalkylalkyl.

15. (Amended) A process for preparing a compound of Formula XXXI comprising:

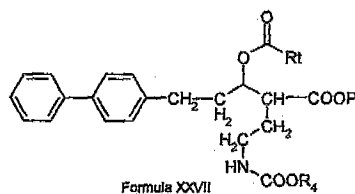
a) reacting a compound of Formula XXIV



with a compound of Formula XXVI:



to give a compound of Formula XXVII:



wherein:

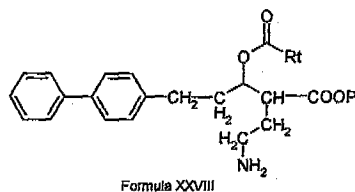
P is is alkyl or aralkyl selected from tert-butyl, ethyl, methyl or benzyl,

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

and

R_4 is alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heterocyclyl, heteroaryl, aralkyl, heteroarylalkyl, heterocyclylalkyl or cycloalkylalkyl;

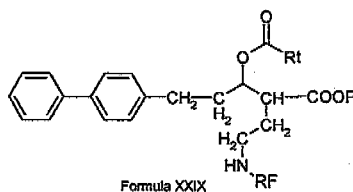
b) deprotecting a compound of Formula XXVII to give a compound of Formula XXVIII:



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;

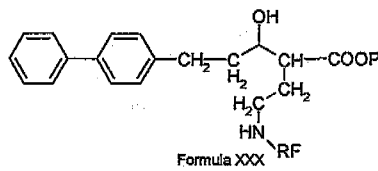
to give a compound of Formula XXIX;



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

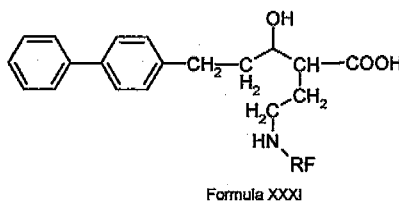
Y is oxygen or sulphur;

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



wherein Rf and P are as defined above;

e) deprotecting a compound of Formula XXX to give a compound of Formula XXXI;



wherein

RD is R_4COhal , $halCOOR_4$, R_4SO_2hal or $(R_4)N=C(=Y)$;

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

R_4 is alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heterocyclyl, heteroaryl, aralkyl, heteroarylalkyl, heterocyclylalkyl or cycloalkylalkyl;

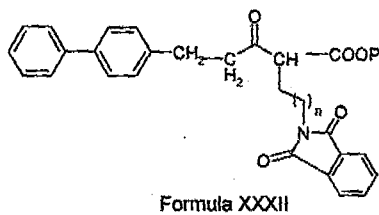
~~Y is oxygen or sulphur;~~

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

~~hal is Cl, Br or I.~~

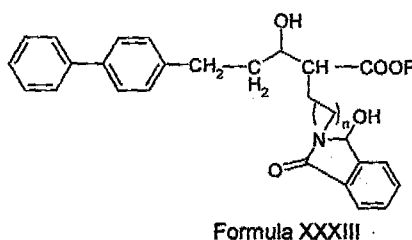
16. (Amended) A process for preparing a compound of Formula XXXIV comprising:

a) reducing a compound of Formula XXXII

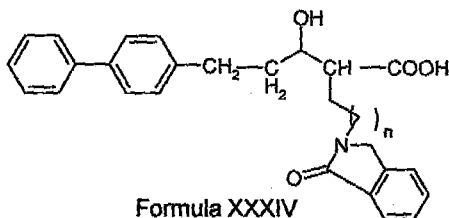


wherein P is a protecting group;

to give a compound of Formula XXXIII; and

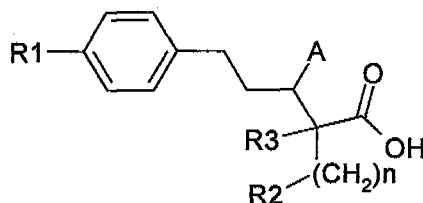


b) hydrolyzing a compound of Formula XXXIII to give a compound of Formula XXXIV



17. (Amended) 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 and/or by HPLC (High Pressure Liquid Chromatography, using an achiral or chiral separation column.

1. A compound of Formula I:



Formula I

wherein:

n is an integer from 1 to 5;

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

R₂ is alkenyl, alkynyl, aryl, heterocyclyl, heteroaryl, cycloalkyl, NR_4R_5 , -NHC(=Y)R_4 , $\text{-NHC(=Y)NR}_5\text{R}_x$, -NHC(=O)OR_4 , $\text{-NH}\text{SO}_2\text{R}_4$, $\text{C(=Y)NR}_4\text{R}_5$, C(=O)OR_6 , OR_5 , $\text{-OC(=O)NR}_4\text{R}_5$, O-acyl, $\text{S(O)}_m\text{R}_4$, $\text{-SO}_2\text{N(R}_4)_2$, cyano, amidino or guanidine;

wherein:

Y is oxygen or sulphur,

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

m is an integer 0-2;

R₅ is hydrogen or **R₄**;

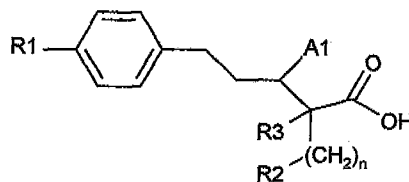
R_x is **R₄** or $\text{-SO}_2\text{N(R}_4)_2$ and

R₆ is hydrogen, alkyl, cycloalkyl, aralkyl, heteroarylalkyl, heterocyclylalkyl or cycloalkylalkyl;

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

A is OH, OR_4 , $\text{-OC(=O)NR}_4\text{R}_5$, O-acyl, NH_2 , NR_4R_5 , -NHC(=Y)R_4 , $\text{-NHC(=Y)NR}_5\text{R}_x$, -NHC(=O)OR_4 , $\text{-NH}\text{SO}_2\text{R}_4$.

2. A compound according to claim 1 having a structure of Formula Ia:



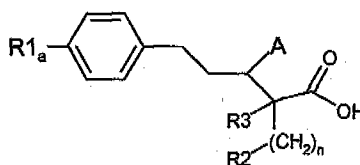
Formula Ia

wherein:

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

n, Y, R_x, R₁, R₂, R₃, R₄ and R₅ are as defined in claim 1.

3. A compound according to claim 1 having a structure of Formula Ib:



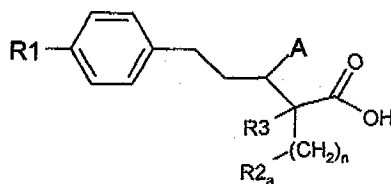
Formula Ib

wherein:

R_{1a} is aryl or heteroaryl;

n, R₂, R₃ and A are as defined in claim 1.

4. A compound as claimed in claim 1 having the structure of Formula Ic:



Formula Ic

wherein:

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

wherein:

Y is oxygen or sulphur;

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

m is an integer 0-2;

R₅ is hydrogen or R₄; or R₄ and R₅ together may optionally form a heterocyclic ring containing one or more heteroatoms such as O, N or S;

R_x is R₄ or -SO₂N(R₄)₂; and

n, R₁, R₃ and A are as defined in claim 1.

5. A compound 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),

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

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

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

2-[2-(1,3-Dioxo-1,3-dihydro-2H-isoindol-2-yl)ethyl]-5-(4'-ethoxybiphenyl-4-yl)-3-hydroxypentanoic acid (Compound No. 6),

2-[2-(1,3-Dioxo-1,3-dihydro-2H-isoindol-2-yl)ethyl]-5-(4'-formylbiphenyl-4-yl)-3-hydroxypentanoic acid (Compound No. 7),

2-[2-(1,3-Dioxo-1,3-dihydro-2H-isoindol-2-yl)ethyl]-3-hydroxy-5-(2',4',6'-trimethoxybiphenyl-4-yl)pentanoic acid (Compound No. 8),

2-[2-(1,3-Dioxo-1,3-dihydro-2H-isoindol-2-yl)ethyl]-3-hydroxy-5-(4'-propoxybiphenyl-4-yl)pentanoic acid (Compound No. 9),

5-(3',4'-Difluorobiphenyl-4-yl)-2-[2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)ethyl]-3-hydroxypentanoic acid (Compound No. 10),

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

(2*R*,3*S* + 2*S*,3*R*)-2-[2-(1,3-Dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-5-(4'-formylbiphenyl-4-yl)-3-hydroxypentanoic acid (Compound No. 13),

(2*R*,3*R* + 2*S*,3*S*)-2-[2-(1,3-Dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-5-(4'-formylbiphenyl-4-yl)-3-hydroxypentanoic acid (Compound No. 14),

(2*R*,3*R* + 2*S*,3*S*)-2-[2-(1,3-Dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxy-5-(2',4',6'-trimethoxybiphenyl-4-yl)pentanoic acid (Compound No. 15),

(2*R*,3*S* + 2*S*,3*R*)-2-[2-(1,3-Dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxy-5-(2',4',6'-trimethoxybiphenyl-4-yl)pentanoic acid (Compound No. 16),

(2*R*,3*S* + 2*S*,3*R*)-5-(4'-Acetylbiphenyl-4-yl)-2-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxypentanoic acid (Compound No. 17),

(2*R*,3*R* + 2*S*,3*S*)-5-(4'-Acetylbiphenyl-4-yl)-2-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxypentanoic acid (Compound No. 18),

(2*R*,3*S* + 2*S*,3*R*)-2-[2-(1,3-Dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxy-5-(4'-propoxybiphenyl-4-yl)pentanoic acid (Compound No. 19),

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

(2*R*,3*S* + 2*S*,3*R*)-5-(3',4'-Difluorobiphenyl-4-yl)-2-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxypentanoic acid (Compound No. 21),

(2*R*,3*R* + 2*S*,3*S*)-5-(3',4'-Difluorobiphenyl-4-yl)-2-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxypentanoic acid (Compound No. 22),

2-[2-(1,3-Dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxy-5-(4'-methoxybiphenyl-4-yl)pentanoic acid (Compound No. 23),

5-(2',3'-Dimethylbiphenyl-4-yl)-2-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxypentanoic acid (Compound No. 24),

2-[2-(1,3-Dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxy-5-[3'-(trifluoromethyl)biphenyl-4-yl]pentanoic acid (Compound No. 25),

2-[2-(1,3-Dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-5-(4'-ethylbiphenyl-4-yl)-3-hydroxypentanoic acid (Compound No. 26),

5-(3',5'-Dichlorobiphenyl-4-yl)-2-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxypentanoic acid (Compound No. 27),

5-[4'-Chloro-3'-(trifluoromethyl)biphenyl-4-yl]-2-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxypentanoic acid (Compound No. 28),

- 5-(2',5'-Difluorobiphenyl-4-yl)-2-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxypentanoic acid (Compound No. 29),
- 2-[2-(1,3-Dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxy-5-[2'-(trifluoromethoxy)biphenyl-4-yl]pentanoic acid (Compound No. 30),
- 2-[2-(1,3-Dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-5-(4'-fluoro-3'-methylbiphenyl-4-yl)-3-hydroxypentanoic acid (Compound No. 32),
- 2-[2-(1,3-Dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxy-5-(3'-isopropylbiphenyl-4-yl)pentanoic acid (Compound No. 33),
- 5-(3',4'-Dimethylbiphenyl-4-yl)-2-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxypentanoic acid (Compound No. 34),
- 5-(2',6'-Difluorobiphenyl-4-yl)-2-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxypentanoic acid (Compound No. 35),
- 2-[2-(1,3-Dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-5-(4'-fluorobiphenyl-4-yl)-3-hydroxypentanoic acid (Compound No. 36),
- 5-(3',5'-Difluorobiphenyl-4-yl)-2-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxypentanoic acid (Compound No. 37),
- 5-(3'-Chloro-4'-fluorobiphenyl-4-yl)-2-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxypentanoic acid (Compound No. 38),
- 5-(3',4'-Dimethoxybiphenyl-4-yl)-2-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxypentanoic acid (Compound No. 39),
- 5-(3'-Chlorobiphenyl-4-yl)-2-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxypentanoic acid (Compound No. 40),
- 2-[2-(1,3-Dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxy-5-(3'-methylbiphenyl-4-yl)pentanoic acid (Compound No. 41),
- 5-(2',3'-Difluorobiphenyl-4-yl)-2-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxypentanoic acid (Compound No. 42),
- 2-[2-(1,3-Dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-5-(2'-fluoro-3'-methoxybiphenyl-4-yl)-3-hydroxypentanoic acid (Compound No. 43),
- 2-[2-(1,3-Dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-5-(3'-fluoro-4'-methylbiphenyl-4-yl)-3-hydroxypentanoic acid (Compound No. 44),
- 5-Biphenyl-4-yl-3-hydroxy-2-{2-[(phenylacetyl)amino]ethyl}pentanoic acid (Compound No. 45),

- 2-(3-Biphenyl-4-yl-1-hydroxypropyl)-6-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)hexanoic acid (Compound No. 46),
- 5-Biphenyl-4-yl-3-hydroxy-2-[2-(1-oxophthalazin-2(1*H*)-yl)ethyl]pentanoic acid (Compound No. 47),
- 5-Biphenyl-4-yl-2-[3-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)propyl]-3-hydroxypentanoic acid (Compound No. 48),
- 5-Biphenyl-4-yl-3-hydroxy-2-[2-(2'-oxospiro[cyclopropane-1,3'-indol]-1'(2'*H*)-yl)ethyl]pentanoic acid (Compound No. 49),
- 2-[2-(1,3-Dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxy-5-(4'-hydroxybiphenyl-4-yl)pentanoic acid (Compound No. 50),
- 3-Hydroxy-5-(4'-methoxybiphenyl-4-yl)-2-[2-(3-methyl-2,6-dioxo-3,6-dihydropyrimidin-1(2*H*)-yl)ethyl]pentanoic acid (Compound No. 51),
- 5-(4'-Chlorobiphenyl-4-yl)-3-hydroxy-2-[2-(3-methyl-2,6-dioxo-3,6-dihydropyrimidin-1(2*H*)-yl)ethyl]pentanoic acid (Compound No. 52),
- 5-(4'-Fluorobiphenyl-4-yl)-3-hydroxy-2-[2-(3-methyl-2,6-dioxo-3,6-dihydropyrimidin-1(2*H*)-yl)ethyl]pentanoic acid (Compound No. 53),
- 5-[4-(5-Chloro-2-thienyl)phenyl]-2-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxypentanoic acid (Compound No. 54),
- 4'-[4-Carboxy-6-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)-3-hydroxyhexyl]biphenyl-4-carboxylic acid (Compound No. 55),
- 2-[2-(1,3-Dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxy-5-[4'-(methoxycarbonyl)biphenyl-4-yl]pentanoic acid (Compound No. 56),
- 2-[2-(1,3-Dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxy-5-[4'-(trifluoromethyl)biphenyl-4-yl]pentanoic acid (Compound No. 57),
- 2-[2-(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. 58),
- 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),
- 2-[2-(1,3-Dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-5-(3'-fluorobiphenyl-4-yl)-3-hydroxypentanoic acid (Compound No. 61),

5-[4'-(Benzyloxy)-3'-fluorobiphenyl-4-yl]-2-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxypentanoic acid (Compound No. 62),

5-[4'-(Benzyloxy)biphenyl-4-yl]-2-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxypentanoic acid (Compound No. 63),

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),

2-[2-(1,3-Dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxy-5-(4'-methylbiphenyl-4-yl)pentanoic acid (Compound No. 66),

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),

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),

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),

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),

(2*R*,3*S* + 2*S*,3*R*)-2-[2-(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. 78),

(2*R*,3*R* + 2*S*,3*S*)-2-[2-(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. 79),

(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-hydroxypentanoic acid (Compound No. 80),

(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 (Compound No. 81),

(2*R*,3*S* + 2*S*,3*R*)-2-[2-(1,3-Dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-5-(4'-fluorobiphenyl-4-yl)-3-hydroxypentanoic acid (Compound No. 82),

(2*R*,3*R* + 2*S*,3*S*)-2-[2-(1,3-Dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-5-(4'-fluorobiphenyl-4-yl)-3-hydroxypentanoic acid (Compound No. 83),

5-Biphenyl-4-yl-3-hydroxy-2-[2-(1-oxo-4-phenyl-4*a*,8*a*-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-[(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),

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),

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),

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),

2-(3-Biphenyl-4-yl-1-hydroxypropyl)pent-4-ynoic acid (Compound No. 95);

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-{4-[6-(Dimethylamino)pyridin-3-yl]phenyl}-2-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxypentanoic acid (Compound No. 98),

2-[2-(1,3-Dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxy-5-[4'-(methylsulfonyl)biphenyl-4-yl]pentanoic acid (Compound No. 99),

5-[4'-(Aminocarbonyl)biphenyl-4-yl]-2-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxypentanoic acid (Compound No. 100),

5-[4-(1-Benzyl-1*H*-pyrazol-4-yl)phenyl]-2-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxypentanoic acid (Compound No. 101),

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),

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),

(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-[2-(1,3-Dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-5-(3'-fluoro-4'-methoxybiphenyl-4-yl)-3-hydroxypentanoic acid (Compound No. 110),

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(2*R*,3*S* + 2*S*,3*R*)-2-[2-(1,3-Dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxy-5-[4-(6-methylpyridin-3-yl)phenyl]pentanoic acid (Compound No. 111),

(2*R*,3*R* + 2*S*,3*S*)-2-[2-(1,3-Dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxy-5-[4-(6-methylpyridin-3-yl)phenyl]pentanoic acid (Compound No. 112),

(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),

(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),

(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),

5-Biphenyl-4-yl-3-hydroxy-2-[2-(7-methyl-4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)ethyl]pentanoic acid (Compound No. 120),

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),

(2*R*,3*S*)-5-Biphenyl-4-yl-3-hydroxy-2-[2-(1*H*-indol-3-yl)ethyl]pentanoic acid (Compound No. 122),

(2*R*,3*R*)-5-Biphenyl-4-yl-3-hydroxy-2-[2-(1*H*-indol-3-yl)ethyl]pentanoic acid (Compound No. 123),

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

(2*R*,3*S*)-5-(4'-Chlorobiphenyl-4-yl)-2-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxypentanoic acid (Compound No. 125),

(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 (Compound No. 126),

(2*R*,3*R*)-5-(4'-Chlorobiphenyl-4-yl)-2-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxypentanoic acid (Compound No. 127),

(2S,3S)-5-(4'-Chlorobiphenyl-4-yl)-2-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-3-hydroxypentanoic acid (Compound No.128),

(2R,3S) -2-[2-(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. 129),

(2S,3R)- 2-[2-(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. 130),

(2R,3R)- 2-[2-(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. 131),

(2S,3S)- 2-[2-(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. 132),

(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), or

(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).

6. A pharmaceutical composition comprising therapeutically effective amount of a compound as defined in claim 1 and pharmaceutically acceptable carrier, excipients or diluents.

7. A pharmaceutical composition of claim 6 further comprising one or more additional active ingredients selected from:

- a) Anti-inflammatory agents, experimental or commercial including (i) 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, or (v) interleukin-I inhibitors;
- b) antihypertensive agents, including (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, or (iv) calcium channel blockers; and

c) immunosuppressive agents including cyclosporine, azathioprine and methotrexate, anti-inflammatory corticosteroids.

8. A method for treatment or prophylaxis of an animal or a human suffering from inflammatory diseases and associated pathologies which comprises administering to the animal or human an effective amount of a compound according to claim 1.

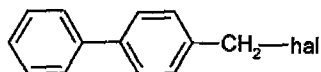
9. A method for treatment or prophylaxis of an animal or a human suffering from inflammatory diseases and associated pathologies which comprises administering to the animal or human an effective amount of pharmaceutical composition according to claim 6.

10. A method for treatment or prophylaxis of an animal or a human suffering from inflammatory diseases and associated pathologies which comprises administering to the animal or human an effective amount of pharmaceutical composition according to claim 7.

11. A method according to claim 8, wherein the inflammatory diseases and associated pathologies include 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 restenosis and ischemic heart failure, stroke, renal diseases or tumor metastasis.

12. A process for preparing a compound of Formula VIII comprising:

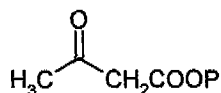
a) reacting a compound of Formula II



Formula II ;

wherein hal is Cl, Br or I;

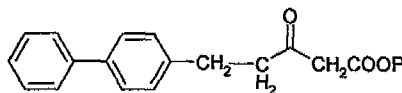
with a compound of Formula III



Formula III

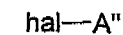
;

wherein P is alkyl or aralkyl selected from tert-butyl, ethyl, methyl or benzyl;
to give a compound Formula IV;



Formula IV

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



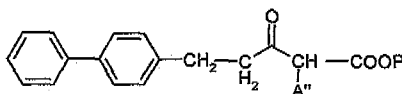
Formula V;

wherein:

A'' is selected from aralkyl, heterocyclalkyl, heteroarylalkyl or cycloalkylalkyl; and

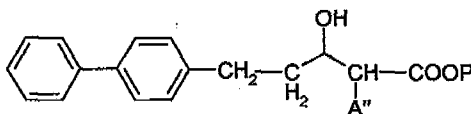
Hal or halogen is selected from Cl, Br or I;

to give a compound of Formula VI;



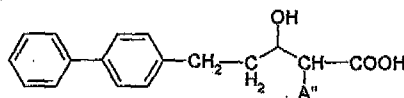
Formula VI

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



Formula VII

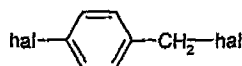
d) deprotecting a compound of Formula VII to give a compound of Formula VIII



Formula VIII

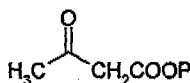
13. A process for preparing a compound of Formula XXI comprising:

a) reacting a compound of Formula IX



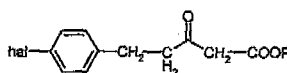
Formula IX

with a compound of Formula III



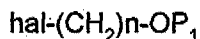
Formula III

to give a compound of Formula X;



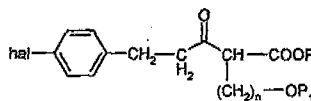
Formula X

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



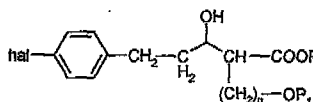
Formula XI

to give a compound of Formula XII;



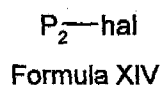
Formula XII

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

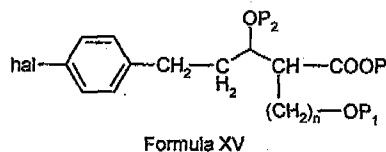


Formula XIII

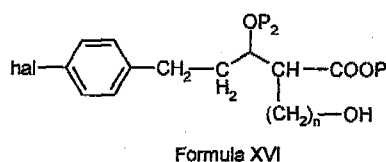
d) reacting a compound of Formula XIII with a compound of Formula XIV



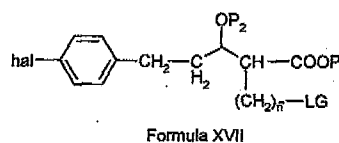
to give a compound of Formula XV;



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

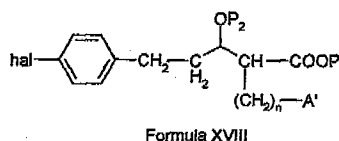


f) converting a compound of Formula XVI to a compound of Formula XVII

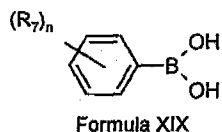


by reaction with a compound of Formula L-hal;

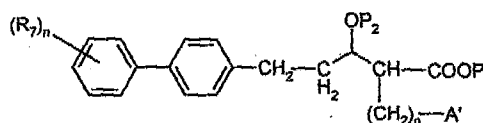
g) reacting a compound of Formula XVII with a compound of Formula M-A' or A' to give a compound of Formula XVIII;



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

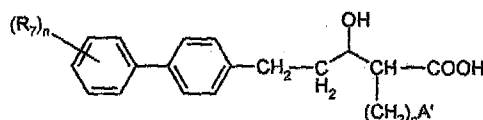


to form a compound of Formula XX; and



Formula XX

i) deprotecting a compound of Formula XX to give 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 aryl, heteroaryl, heterocyclyl or cycloalkyl and M is metal selected from potassium, lithium or sodium;

A'' is aralkyl, heterocyclylalkyl, heteroarylalkyl or cycloalkylalkyl;

n is an integer from 1 to 5

R₇ is hydrogen, halogen (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, -NHSO₂R₄, (SO)_mR₄, aryl, heterocyclyl, heteroaryl, heterocyclylalkyl or heteroarylalkyl which may optionally be substituted further;

R_4 is alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heterocyclyl, heteroaryl, aralkyl, heteroarylalkyl, heterocyclalkyl or cycloalkylalkyl;

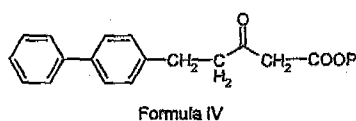
m is an integer 0-2;

R_5 is hydrogen or R_4 ; and

R_x is R_4 or $-\text{SO}_2\text{N}(R_4)_2$.

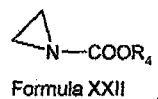
14. A process for preparing a compound of Formula XXV comprising:

a) reacting a compound of Formula IV



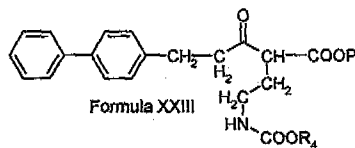
wherein P is alkyl or aralkyl selected from tert-butyl, ethyl, methyl or benzyl;

with a compound of Formula XXII

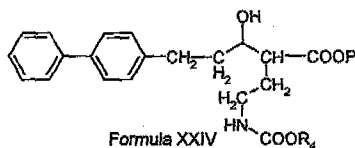


R_4 is alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heterocyclyl, heteroaryl, aralkyl, heteroarylalkyl, heterocyclalkyl or cycloalkylalkyl;

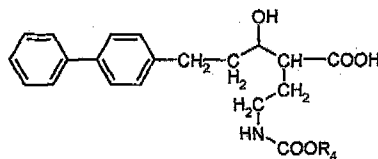
to give a compound of Formula XXIII;



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



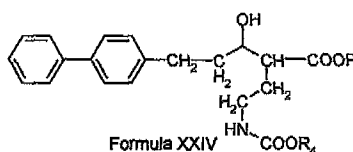
- c) deprotecting a compound of Formula XXIV to give a compound of Formula XXV



Formula XXV

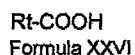
15. A process for preparing a compound of Formula XXXI comprising:

- a) reacting a compound of Formula XXIV

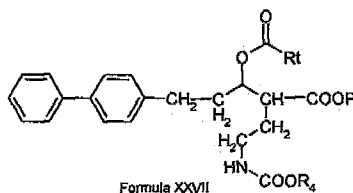


Formula XXIV

with a compound of Formula XXVI:



to give a compound of Formula XXVII:



Formula XXVII

wherein:

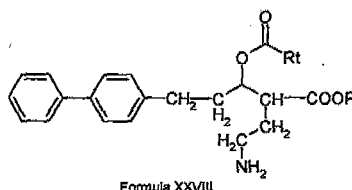
P is is alkyl or aralkyl selected from tert-butyl, ethyl, methyl or benzyl,

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

and

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

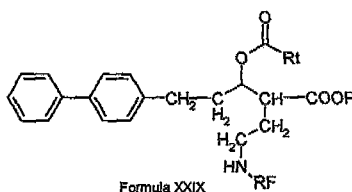
- b) deprotecting a compound of Formula XXVII to give a compound of Formula XXVIII:



wherein P and Rt are as defined above;

c) derivatizing a compound of Formula XXVIII with a compound of Formula RD, wherein: RD is $R_4\text{COhal}$, halCOOR_4 , $R_4\text{SO}_2\text{hal}$ or $(R_4)\text{N}=\text{C}(=\text{Y})$, and hal is Cl, Br or I; and Y is oxygen or sulphur;

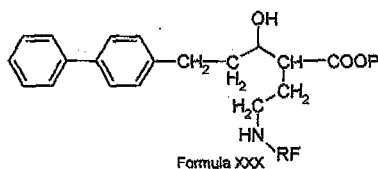
to give a compound of Formula XXIX:



wherein: RF is $R_4\text{CO}-$, $R_4\text{OCO}-$, $R_4\text{SO}_2-$ or $(R_4)\text{NH}-\text{C}(=\text{Y})-$;

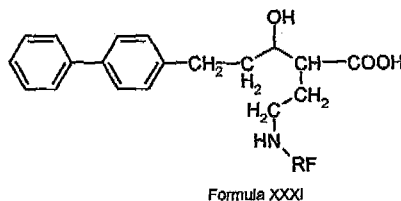
Y is oxygen or sulphur;

d) deprotecting a compound of Formula XXIX to give a compound of Formula XXX:



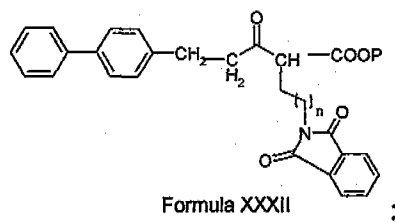
wherein Rf and P are as defined above;

e) deprotecting a compound of Formula XXX to give a compound of Formula XXXI:



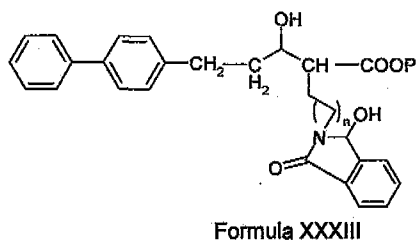
16. A process for preparing a compound of Formula XXXIV comprising:

- a) reducing a compound of Formula XXXII

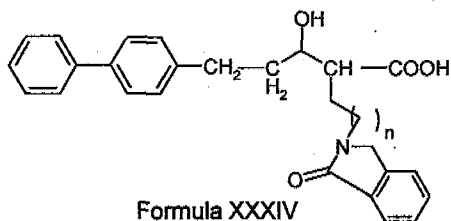


wherein P is a protecting group;

to give a compound of Formula XXXIII; and



- b) hydrolyzing a compound of Formula XXXIII to give a compound of Formula XXXIV



17. 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 (High Pressure Liquid Chromatography, using an achiral or chiral separation column.

HOJA DE INFORMACIÓN DEL SOLICITANTE Y DEL INVENTOR**Solicitud Internacional No. PCT/IB2006/000349****Fecha de radicación Internacional: 21 Febrero 2006****Basada en la solicitud India No. 380/Del/2005 radicada 22 Febrero 2005****Título: DERIVADOS DEL ÁCIDO 5-FENIL-PENTANÓICO COMO INHIBIDORES DE METALOPROTEINASA DE LA MATRIZ PARA EL TRATAMIENTO DEL ASMA Y OTRAS ENFERMEDADES.**

<u>Solicitante</u>		RAMBAXY LABORATORIES LIMITED Plot No.90-Sector 32 Gurgaon, Haryana 122001 India (Una corporación India)
<u>Inventores</u>	1.	Venkata P. PALLE Sylvan Heights Sanewadi Aundh, Pune, Maharashtra 411007 India
	2.	Viswajanani, Jitendra SATTIGERI N-323, VijayrattanVihar Gurgaon, Haryana 122001 India
	3.	Manoj, Kumar KHERA C-600/10, Krishna Colony Gurgaon, Haryana 122001 India
	4.	Sreedhara, Rao VOLETI Apartment No.201 Mahalakshmi CGHS Plot-2, Sector-43 Gurgaon, Haryana 122001 India
	5.	Abhijit RAY Sector C-1, Flat No. 1408 Vasant Kunj New Delhi, Delhi 110070 India.
		Sunanda, G. DASTIDAR B-138, Sarita Vihar New Deli, Delhi 110044 India

Información adicional

- Todos los inventores anteriores son ciudadanos de la India
La solicitud India de prioridad se radicó a nombre de Ranbaxy Laboratories Limited.
- Se ejecutó una transferencia entre Ranbaxy Laboratories limited y los inventores en septiembre 13, 2006 y mayo 31, 2007.

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HOJA DE INFORMACIÓN DEL SOLICITANTE Y DEL INVENTOR**Solicitud Internacional No. PCT/IB2006/000349****Fecha de radicación Internacional: 21 Febrero 2006****Basada en la solicitud India No. 380/Del/2005 radicada 22 Febrero 2005****Título: DERIVADOS DEL ÁCIDO 5-FENIL-PENTANÓICO COMO INHIBIDORES DE METALOPROTEINASA DE LA MATRIZ PARA EL TRATAMIENTO DEL ASMA Y OTRAS ENFERMEDADES.**

<u>Solicitante</u>		RAMBAXY LABORATORIES LIMITED Plot No.90-Sector 32 Gurgaon, Haryana 122001 India (Una corporación India)
<u>Inventores</u>	1.	Venkata P. PALLE Sylvan Heights Sanewadi Aundh, Pune, Maharashtra 411007 India
	2.	Viswajanani, Jitendra SATTIGERI N-323, VijayrattanVihar Gurgaon, Haryana 122001 India
	3.	Manoj, Kumar KHERA C-600/10, Krishna Colony Gurgaon, Haryana 122001 India
	4.	Sreedhara, Rao VOLETI Apartment No.201 Mahalakshmi CGHS Plot-2, Sector-43 Gurgaon, Haryana 122001 India
	5.	Abhijit RAY Sector C-1, Flat No. 1408 Vasant Kunj New Delhi, Delhi 110070 India.
		Sunanda, G. DASTIDAR B-138, Sarita Vihar New Deli, Delhi 110044 India

Información adicional

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La solicitud India de prioridad se radicó a nombre de Ranbaxy Laboratories Limited.

- Se ejecutó una transferencia entre Ranbaxy Laboratories limited y los inventores en septiembre 13, 2006 y mayo 31, 2007.

“Amina”, a menos que se especifique otra cosa, se refiere a -NH_2 . “Amino sustituido”, a menos que se especifique otra cosa, se refiere a un grupo $\text{-N(R}_k)_2$ en donde cada R_k se selecciona independientemente del grupo hidrógeno con la condición que ambos grupos R_k no sean hidrógenos (definidos como “amino”), alquilo, alquenilo, alquinilo, cicloalquilo, arilo, heteroarilo, heterociclilo, heterociclilalquilo, heteroarilalquilo, acilo, $\text{S(O}_m\text{)R}_6$ (en donde m y R_6 son los mismos definidos antes), $\text{-C(=R}_v\text{)NR}_x\text{R}_y$ (en donde R_v es O o S & R_x y R_y son los mismos definidos antes) o $\text{-NHC(=R}_v\text{)NR}_x\text{R}_y$ (en donde R_v , R_y y R_x son los mismos definidos antes). A menos que por definición se obligue otra cosa, todos los sustituyentes amino además pueden estar opcionalmente sustituidos por 1-3 sustituyentes escogidos de alquilo, aralquilo, cicloalquilo, arilo, heteroarilo, heterociclilo, carboxi, -COOR (en donde R_7 es el mismo que se definió antes), hidroxil, alcoxi, halógeno, CF_3 , ciano, $\text{-C(=R}_v\text{)NR}_x\text{R}_y$ (en donde R_v es el mismo que se definió antes), $\text{-OC(C=O)NR}_x\text{R}_y$, $\text{-OC(=R}_v\text{)NR}_x\text{R}_y$ (en donde R_x , R_y y R_v son los mismos definidos antes), $\text{-S(O}_m\text{)R}_6$ (en donde R_6 (en donde R_6 m son los mismos definidos antes).

“Acilo” se refiere a -C(=O)R en donde R se selecciona de hidrógeno, alquilo, cicloalquilo, arilo, aralquilo, heteroarilo, heterociclilo, heteroarilalquilo o heterociclilalquilo.

El término “tioacilo” se refiere a -C(=S)R_4 en donde R_4 es el mismo que se definió antes.

“Tiocarbonilo” se refiere a -C(=S)H . “Tiocarbonilo sustituido” se refiere a -C(=S)R , en donde R se selecciona de alquilo, cicloalquilo, arilo, aralquilo, heteroarilo, heterociclilo, heteroarilalquilo o heterociclilalquilo, amina o amina sustituida.

El término “halógeno” se refiere a flúor, cloro, bromo o yodo.

TRAPASO DE DERECHOS, TÍTULO E INTERÉS EN LA INVENCION

Este es un traspaso de los siguientes derechos, título e interés (marque todos los que aplican)

- ☒ Derechos en los Estados Unidos de América, título e interés en la invención
☒ Derechos en la India, título e interés en la invención
☒ Derechos extranjeros (fuera de la India, fuera de Estados Unidos), título e interés en la invención
 Solicitud de Patente de los Estados Unidos Serial No _____
 Fecha de Ejecución _____ Fecha de Radicación _____
 Solicitud e Patente Provisional en Estados Unidos Serial No. _____
 Patente en Estados Unidos No(s): _____
☒ Solicitud de Patente Internacional PCT Serial No. PCT/IB2006/00034393
 Otros (especifique)

Título de la Invención.

INHIBIDORES DE METALOPROTEINASA DE LA MATRIZ

I(cedentes) inventores

Nombre	Dirección
Venkata P. PALLE	Sylvan Heights Sanewadi411007 Aundh, Pune, Maharashtra India
Viswajanani, Jitendra SATTIGERI	N-323, VijayrattanVihar 122001 Gurgaon, Haryana India
Manoj, Kumar KHERA	C-600/10, Krishna Colony122001 Gurgaon, Haryana India
Sreedhara, Rao VOLETI	Apartment No.201 Mahalakshmi CGHS Plot-2, Sector-43 12200 Gurgaon, Haryana India
Abhijit RAY	Sector C-1, Flat No. 1408 Vasant Kunj 110070 New Delhi, Delhi India
Sunanda, G. DASTIDAR	B-138, Sarita Vihar110044 New Deli, Delhi India

Apoderado

Nombre	Dirección
RAMBAXY LABORATORIES LIMITED	Plot No.90-Sector 32 Gurgaon122001, Haryana India

Puesto que nosotros, los inventores anteriormente identificados, hemos inventado ciertas mejoras nuevas y útiles en la invención identificada

anteriormente y descrita en la solicitud(es) de patente(s) identificada (s) y/o patente(s) (aquí anteriormente referidas como "Invención").

Y, puesto que nosotros deseamos transferir nuestros derechos anteriormente identificados, título e interés en la invención al apoderado identificado anteriormente.

Ahora, este documento confirma, que para una consideración buena y valiosa, la recepción se reconoce por este medio;

Nosotros por este medio traspasamos, vendemos y transferimos nuestros derechos anteriormente identificados, título e interés en dicha invención, de dichas solicitudes como se identificó anteriormente, incluyendo cualquier división, continuaciones y continuaciones en parte de ellas, y en y para cualquiera y todas las cartas de patente de los Estados Unidos, y demás países extranjeros los cuales pueden otorgar y tener otorgamiento para dicha invención, y en y para cualquiera y todas las nuevas ediciones y revisiones de ellas, y en y para cualquiera y todos los derechos de prioridad, derechos del acuerdo, derechos del pacto y otros beneficios acumulados o que se acumulen para nosotros con respecto a la radicación de solicitudes para patentes o para asegurar las patentes en los Estados Unidos y demás países extranjeros, hacia dicho apoderado;

Nosotros por este medio declaramos que los derechos y la propiedad cedida por este traspaso están libres y claros de cualquier impedimento, y que nosotros tenemos completamente los derechos para ceder los derechos como aquí se expresó;

Y nosotros por este medio autorizamos y solicitamos al Comisionado de Patentes y marcas registradas para publicar cualquier carta de Patentes de los

Estados Unidos que puedan publicarse para dicha invención, y cualquier otra autoridad de publicación de patentes, para publicar cualquiera de tales cartas de patente que se pueden publicar para dicha invención, directamente para dicho apoderado, como apoderado de los derechos totales, título e interés de ésta;

Y nosotros además estamos de acuerdo con firmar y ejecutar todo lo necesario y documentos futuros de acuerdo con la ley, incluyendo solicitudes para patentes en el extranjero, para radicar divisiones, continuaciones y continuaciones en parte de dicha solicitud para patente, y/o, para obtener cualquier re-edición o revisión de cualquier carta de Patente que puedan ser otorgadas por la antedicha invención, como el Apoderado o su Designado(s) puedan de vez en cuando requerir y preparar a su propia cuenta.

Y nosotros además estamos de acuerdo, cuando se requiera, sin cargos adicionales al apoderado pero a su cuenta, para comunicar al Apoderado o sus representantes todos los hechos conocidos por nosotros en consideración con la invención antedicha y las mejoras, testificar en cualquier procedimiento legal, firmar todos los documentos, hacer todos los juramentos legales o declaraciones y en general ejecutar todos los actos, que puedan ser necesarios, deseables o convenientes para ayudar al apoderado en asegurar, mantener y reforzar las patentes para las invenciones antedichas y mejoras en los antedichos países y para conferir título en ello al apoderado.

Firmas de los Inventores

Nombre	Firma	Fecha
Venkata P. PALLE	Aparece la firma	31/5/07
Viswajanani, Jitendra SATTIGERI	Aparece la firma	13/0/06

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Manoj, Kumar KHERA	Aparece la firma	13/0/06
Sreedhara, Rao VOLETI	Aparece la firma	13/0/06
Abhijit RAY	Aparece la firma	13/0/06
Sunanda, G. DASTIDAR	Aparece la firma	13/0/06

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(12) SOLICITUD INTERNACIONAL PUBLICADA BAJO EL TRATADO DE COOPERACIÓN DE PATENTES (PCT)

(19) Organización de propiedad
Intellectual Mundial
Oficina Internacional

(43) Fecha de publicación internacional

31 Agosto 2006 (31.08.2006)

PCT

(10) Número de Publicación Internacional

WO 2006/ 090235 A1

(51) Clasificación de la patente internacional⁷

C07D 249/18 (2006.01) C07D 207/40 (2006.01)
C07D 209/48 (2006.01) C07D 263/58 (2006.01)
C07D 237/32 (2006.01) C07D 239/796 (2006.01)
C07D 209/12 (2006.01) C07D 471/04 (2006.01)
C07D 239/54 (2006.01) C07D 401/10 (2006.01)
C07D 213/64 (2006.01) C07D 403/10 (2006.01)
C07D 265/28 (2006.01) A61P 11/06 (2006.01)
C07D 211/88 (2006.01)

(21) Numero de solicitud internacional: PCT/IB2006/000349

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(25) Idioma de radicación: Ingles

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(30) Fecha prioritaria: 380/Del/2005 22 Febrero 2006 (22.02.2005) IN

(71) Solicitante (para todos los estados designados excepto US):
RANBAXY LABORATORIES LIMITED [IN/IN]; Plot No.90, Sector 32, Gurgaon,
Haryana 122001 (IN)

(72) Inventores; y

(75) Inventores / solicitantes (para US solamente): 'PALLE, Venkata, P. [US/IN];
Sylvan Heights Sanewadi, Aundh, Pune, Maharashtra 411007
(IN). SATTIGERI, Viswajanani, Jitendra [IS/IN]; N-323, VijayrattanVihar,
Gurgaon, Haryana 122001 (IN), KHERA, Manoj, Kumar [IN/IN]; C-600/10,
Krishna Colony, Gurgaon, Haryana 122001 (IN). VOLETI Sreedhara, Rao
[IN/IN]; Apartment No.201 Mahalakshmi Cghs, Plot-2, Sector-43 Gurgaon,
Haryana 122001 (IN). RAY, Abhijit [IN/IN]; Sector C-1, Flat No. 1408, Vasant
Kunj, New Delhi, Delhi 110070 (IN). DASTIDAR, Sunanda, G. [IN/IN]; B-138,
Sarita Vihar, New Delhi, Delhi 110044 (IN)

(74) Representante Común: RAMBAXY
LABORATORIES LIMITED; C/O
DESHMUKH, Jay, R., 600 College Road
East, Suite 2100, Princeton, New Jersey
08549 (US)

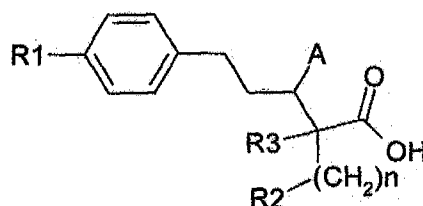
(81) Estados designados (a menos que se indique
de otra manera, para cada clase de
protección nacional disponible): AE, AG, AL,
AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY,
BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK,
DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE,
GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG,
KM, KN, KP, KR, KZ, LC, LK, LR, LS,
LT, LU, LV, LY, MA, MD, MG, MK, MN, MW,
MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH,
PL, PT, RO, RU, SC, SD, SE, SG, SK, SL,
SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG,
US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Estados designados (a menos que se indique
de otra manera, para cada clase de
protección regional disponible): ARIPO (BW,
GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ,
TZ, UG, ZM, ZW), Eurasia (AM, AZ, BY, KG,
KZ, MD, RU, TJ, TM), Europa (AT, BE, BG,
CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB,
GR, HU, IE, IT, LT, LU, LV, MC, NL, PL, PT,
RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG,
CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN,
TD, TG).

Publicado:
- Con informe de búsqueda Internacional

Continúa en la próxima pagina

(54): TITULO: DERIVADOS DEL ÁCIDO 5-FENIL-PENTANÓICO COMO INHIBIDORES DE LA METALOPROTEINASA DE LA
MATRIZ PARA EL TRATAMIENTO DE ASMA Y OTRAS ENFERMEDADES



Formula I

(57) Resumen: La presente invención se refiere a compuestos que tienen la estructura de la Fórmula I: en donde n es un entero del 5; R₁ es opcionalmente puede ser alquilo opcionalmente alquilo sustituido, alquenoilo, alquinoilo, cicloalquilo, arilo, heterociclilo, heteroarilo, aralquilo, alcoxi, ariloxi, alquenoilo o alquinoilo; R₂ puede ser alquenoilo, alquinoilo, arilo, heterociclilo, heteroarilo, cicloalquilo, NR₄R₅, -NHC(=Y)R₄, -NHC(=Y)NR₅R₆, -NHC(=O)OR₄, -NHSO₂R₄, C(=Y)NR₄R₅, C(=O)OR₆ [en donde Y es oxígeno o azufre], -OR₅, -OC(=O)NR₄R₅, O-acilo, S(O)_mR₄, -SO₂N(R₄)₂, ciano, amidino o guanidino [en donde R₄ es alquilo, alquenoilo, alquinoilo, cicloalquilo, arilo, heterociclilo, heteroarilo, aralquilo, heteroarilalquilo, heterociclilalquilo o cicloalquilalquilo y m es un entero 0-2; R₅ es hidrógeno o R₄; R₆ es hidrógenoalquilo, cicloalquilo, aralquilo, heteroarilalquilo, heterociclilalquilo o cicloalquilalquilo]; R₃ es hidrógeno, flúor, alquilo, cicloalquilalquilo o arilalquilo, A es OH OH, OR₄, -OC(=O)NR₄R₅, O-acilo, NH₂, NR₄R₅, -NHC(=Y)R₄, -NHC(=Y)NR₅R₆, -NHC(=O)OR₄, -NHSO₂R₄ y a los procesos para la síntesis de los mismos. Esta invención también se refiere a composiciones farmacéuticas que contienen los compuestos de la presente invención, y a los métodos para tratamiento de asma, artritis reumatoide, COPD, rinitis, osteoartritis psoriática, psoriasis, fibrosis pulmonar, inflamación pulmonar, síndrome de diéstris respiratorio agudo, periodontitis, esclerosis múltiple, gingivitis, aterosclerosis, proliferación neo-intima, los cuales conducen a restenosis y a falla isquémica del corazón, ataques, enfermedades renales, metástasis tumoral y otros desordenes inflamatorios caracterizados por la sobre-expresión y la sobre-activación de una metaloproteinasas de la matriz, utilizando los compuestos

WO 2004/110983 A3

- antes de la expiración del tiempo límite para enmendar las reivindicaciones y ser republicado en el evento de recibo de las enmiendas

Para los códigos de dos letras y otras abreviaturas referirse a la "Notas Guía sobre Códigos y Abreviaturas" que aparece al comienzo de cada publicación regular de la Gaceta PCT

INFORME DE BUSQUEDA INTERNACIONAL

Solicitud internacional No.
PCT/EP2006/000349

A. CLASIFICACION DE LA MATERIA OBJETO					
INV.	C07D249/18	C07D209/48	C07D237/32	C07D209/12	C07239/54
	C07D213/64	C07D265/28	C07D211/88	C07D207/40	C07263/58
	C07D239/96	C07D741/04	C07D401/10	C07D403/10	A61P11/06
De acuerdo con la clasificación internacional de patentes (IPC) o ambas la clasificación nacional y IPC					
B. CAMPOS BUSCADOS					
Documentación mínima buscada (sistema de clasificación seguida de símbolos de clasificación)					
C07D	A61P				
Otra documentación buscada además de la documentación mínima a la extensión que tales documentos están incluidos en los campos buscados					
Base de datos electrónica consultada durante la búsqueda internacional (nombre de la base de datos y, donde sea practicado, términos de búsqueda usados)					
EPO-Internal, WPI Data					
C. DOCUMENTOS QUE SE CONSIDERAN RELEVANTES					
Categoría *	Cita del documento, con indicación donde sea apropiado de los pasajes relevantes				Relevante para la reivindicación No.
X	WO 2004/110974 A (GRUPO GLAXO LIMITADA) 23 Diciembre 2004 (2004-12-23) El documento en su totalidad				1-17
P, X	WO 2005/026120 A(GRUPO GLAXO LIMITADA) 24 Marzo 2005 (2005-03-24) Ejemplos 1-12				1-17

☒	Otros documentos están listados en la continuación del recuadro C.	☒	Ver anexo de familia de patentes
* Categorías especiales de los documentos citados: "A" Documentos que definen el estado general del arte que no se considere que sea de relevancia particular. "E" Ultimo documento pero publicado en o después de la fecha de radicación internacional. "L" Documento que puede causar dudas sobre la(s) reivindicación(es) o el que se cita para establecer la fecha de publicación de otra cita u otra razón especial (como se especifica). "O" Documentos que se refieren a una divulgación oral, uso, exhibición u otros medios. "P" Documento publicado antes de la fecha de radicación internacional pero mas tarde de la fecha de prioridad reivindicada.		"T" Ultimo documento publicado después de la fecha de radicación internacional o de la fecha prioritaria y que no este en conflicto con la solicitud pero se cita para entender el principio o teoría que subraya la invención "X" Documento de relevancia particular; la invención reivindicada no puede considerarse novedosa o no puede ser considerada que involucre un nivel inventivo cuando el documento se toma solo "Y" Documento de relevancia particular; la invención reivindicada no se puede considerar que involucre un nivel inventivo cuando el documento esté combinado con uno o más de otros documentos, tal combinación es obvia para una persona versada en el arte. "&" Miembro de documento de la misma familia de patentes	
Fecha al completar realmente la búsqueda internacional 30 Junio 2006		Fecha del correo del informe internacional de búsqueda 13/07/2006	
Nombre y Dirección de Correo de la ISA Oficina Europea de Patentes, P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk Tel. (+ 31- 70) 340-2040 Tx: 31 651 epo nl, Fax : (+ 31- 70) 340-3016		Oficial autorizado Cortés, J	

INFORME DE BUSQUEDA INTERNACIONAL

Solicitud internacional No.
PCT/ IB2006/000349

Recuadro II Observaciones en donde ciertas reivindicaciones se encontraron no buscadas (continuación del ítem 2 de la primera hoja)

No ha sido establecido Informe de Búsqueda Internacional respecto de ciertas reivindicaciones bajo el Artículo 17 (2) (a) por las siguientes razones:

- ☒ Reivindicaciones Nos.
Porque ellas se relacionan con la materia objeto no requieren ser buscadas por esta autoridad, a saber:
Aunque las reivindicaciones 8 - 11-38 se dirigen a un método de tratamiento del cuerpo humano/animal, la búsqueda se llevo a cabo y se baso en los efectos pretendidos del compuesto / composición.
- ☐ Reivindicaciones Nos.:
Porque ellas se relacionan con partes de la Solicitud Internacional que no cumplen con los requerimientos prescritos tal que no se puede llevar una búsqueda internacional extensa significativa, especialmente:
- ☐ Reivindicaciones Nos.
Porque ellas son reivindicaciones dependientes y no están delineadas de acuerdo con la segunda y tercera frases de la Regla 6.4 (a).

Recuadro III Observaciones en donde esta carente la unidad de invención (Continuación del ítem 3 de la primera hoja)

Esta Autoridad de Búsqueda Internacional encontró múltiples invenciones en esta Solicitud Internacional, como sigue:

- ☐ Como todos los costos de búsqueda adicional requeridos fueron pagados a tiempo por el solicitante, este Informe de Búsqueda Internacional cubre todas las reivindicaciones que se pueden buscar.
- ☐ Como todas las reivindicaciones que se pueden buscar podrían ser buscadas sin producción justificando un costo adicional, esta Autoridad no solicita el pago de cualquier costo adicional.
- ☐ Como solamente algunos de los costos de búsqueda adicional requeridos fueron pagados a tiempo por el solicitante, este Informe de Búsqueda Internacional cubre solamente las reivindicaciones para las cuales se pagaron los costos, específicamente las reivindicaciones Nos.:
- ☐ Los costos de búsqueda adicional requeridos no fueron pagados a tiempo por el solicitante. En consecuencia este Informe de Búsqueda Internacional esta restringido a la primera invención mencionada en las reivindicaciones; es decir cubierta por las reivindicaciones Nos.:

Observaciones sobre objeciones

- ☐ Los costos de búsqueda adicional fueron anexados con las objeciones del solicitante
- ☐ Las objeciones no están acompañadas del pago de los costos de búsqueda adicional

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**DERIVADOS DEL ÁCIDO 5-FENIL-PENTANÓICO COMO INHIBIDORES DE LA
METALOPROTEINASA DE LA MATRIZ PARA EL TRATAMIENTO DE ASMA Y
OTRAS ENFERMEDADES**

Campo de la Invención

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La presente invención se refiere a ciertos β -hidroxi-ácidos y a los procesos para la síntesis de los mismos. Esta invención también se refiere a composiciones farmacológicas que contienen los compuestos de la presente invención, y a métodos para el tratamiento del asma, artritis reumatoide, COPD, rinitis, osteoartritis, artritis psoriásica, psoriasis, fibrosis pulmonar, inflamación pulmonar, síndrome de diestres respiratorio agudo, periodontitis, esclerosis múltiple, gingivitis, aterosclerosis, proliferación neo-intimal, los cuales conducen a restenosis y a falla isquémica del corazón, ataques, enfermedades renales, metástasis tumoral y otros desórdenes inflamatorios caracterizados por la sobre-
expresión y la sobre-activación de una metaloproteinasa de la matriz, utilizando los compuestos.

Antecedentes de la Invención

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Las metaloproteinasas (MMPs) son una superfamilia de proteinasas (enzimas) de ocurrencia natural que se encuentra en la mayoría de los mamíferos. La superfamilia esta compuesta de por lo menos 26 miembros de enzimas que contienen cinc, producidas por cualquier tipo de células y que comparten características estructurales y funcionales. Con base en la estructura y las consideraciones funcionales, las proteinasas se han clasificado en diferentes familias y sub-familias (Hopper, NM, 1994, FEBS) tales como colagenasas (MMP-1, MMP13), gelatinasas (MMP-2, MMP-9), metaloelastasas (MMP-12), las MT-

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MMPs (MMP-14, MMP-15) y las sheddases tales como las enzimas que convierten TNF (TACE, ACE).

Se cree que las metaloproteinasas son importantes en una plétora de procesos de enfermedades fisiológicas que involucran remodelaciones tales como el desarrollo embrionario, formación de huesos y remodelación uterina durante la menstruación. La función biológica principal de las MMPs es catalizar la desintegración de los tejidos conectivos o matriz extra-celular, por su capacidad para hidrolizar varios componentes del tejido o matriz. Aparte de la función en la degradación de del tejido conectivo, Las MMPs siempre están involucradas en la activación de zimógenos (pro) formas de otras MMPs por lo que inducen la activación MMP. También están involucradas en la biosíntesis de alfa-TNF el cual está implicado en muchas condiciones patológicas.

La MMP-12 también conocida como macrófago-elastasa o metaloelastasa, se expresa en macrófagos activados y se ha demostrado que se secreta de los macrófagos alveolares de los fumadores, así como también de las células de la espuma en lesiones ateroscleróticas. La MMP-12 en estudios de noqueo con ratones ha mostrado el desarrollo de enfisema significativo, apoyando así su función en el COPD. La MMP-9 (gelatinasa B, 92 KDa colagenasa tipo IV) es un miembro de la familia MMP que se libera como pro-enzima y subsiguientemente se activa vía la cascada proteasa *in vivo*. La concentración de MMP-9 se incrementa en enfermedades como el asma, la fibrosis pulmonar intersticial (IPF), el síndrome de diéstrres respiratorio en adultos (ARDS), y enfermedad pulmonar obstructiva crónica (COPD). A causa de su capacidad proteolítica, la MMP-9 esta implicada en la remodelación de tejidos de las vías aéreas y los pulmones en las enfermedades inflamatorias crónicas tales como asma severa y COPD. La MMP-9

también es probablemente importante fisiológicamente por su capacidad para regular la digestión de componentes de la matriz extra-celular así como también la actividad de otras proteasas y citokinas. La MMP-9 es secretada en los neutrófilos, macrófagos, osteoclastos los cuales se inducen fácilmente por citokinas y factores de crecimiento, y juegan un papel en varios procesos fisiológicos y patológicos.

La sobre-expresión o sobre-activación de una MMP o un imbalance entre una MMP y un inhibidor natural de tejido (i.e., endógeno) de una metaloproteinasa de la matriz (TIMP) ha sido ligada a la patogénesis de enfermedades caracterizadas por la desintegración del tejido conectivo o matriz extra-celular.

Ejemplos de condiciones inflamatorias y desórdenes auto-inmunes en los que los compuestos de la invención tienen efectos potencialmente benéficos incluyen enfermedades del tracto respiratorio tales como asma (incluyendo reacciones asmáticas inducidas por alergenitos) fibrosis quística, bronquitis, enfermedad pulmonar obstructiva crónica (COPD), síndrome de diéstrés respiratorio en adultos (ARDS), inflamación pulmonar crónica, rinitis y desórdenes inflamatorios del tracto respiratorio superior (URID), lesión del pulmón inducida por el ventilador, silicosis, sarcoidosis pulmonar, fibrosis idiopática pulmonar, displasia bronco-pulmonar, artritis e.g., artritis reumatoide, osteoartritis, artritis infecciosa, artritis psoriásica, artritis traumática, artritis del sarampión, síndrome de Reiter, artritis por gota, sinovitis aguda de la gota por falla de la unión prostética, espondilitis y condiciones inflamatorias no articulares, e.g., síndrome del disco intervertebral herniado/ roto/ prolapsado, bursitis, tendinitis, síndrome fibromiálgico tenosinovítico y otras condiciones inflamatorias asociadas con esguince de ligamentos y tensiones de la región músculo-esquelética, desórdenes inflamatorios del tracto gastrointestinal, e.g., colitis ulcerosa, diverticulitis,

enfermedad de Crohn, enfermedades inflamatorias del intestino, síndrome de intestino irritable y gastritis, esclerosis múltiple, escleroderma sistémico de lupus eritematoso, exocrinopatía auto-inmune, encefalomiелitis auto-inmune, diabetes, angiogenesis de tumor y metástasis, cáncer incluyendo carcinoma de seno, colon, recto, pulmón, riñón, ovario, estómago, útero, páncreas, hígado, oral, laringe y próstata, melanoma, leucemia aguda y crónica, enfermedad periodontal, enfermedad neurodegenerativa, enfermedad de Alzheimer, enfermedad de Parkinson, epilepsia, degeneración muscular, hernia inguinal, degeneración retinal, retinopatía diabética, degeneración macular, inflamación ocular, enfermedad de desorción del hueso, osteoporosis, osteopetrosis, rechazo de aloinjerto reacción injerto vs., anfitrión, sepsis, endotoxemia, síndrome de choque tóxico, tuberculosis, neumonía de organización intersticial criptogénica, meningitis bacteriana, caquexia sistémica, caquexia secundaria a la infección o malignidad, caquexia secundaria al síndrome de inmunodeficiencia adquirido (AIDS), malaria, lepra, leishmaniasis, enfermedad de Lyme, glomerulonefritis, glomeruloesclerosis, fibrosis renal, fibrosis hepática, pancreatitis, hepatitis, endometriosis, dolor, e.g., que está asociado con inflamación y/o trauma, enfermedades inflamatorias de la piel, e.g., dermatitis, úlceras de la piel, psoriasis, eczema, demencia por valvulitis vascular sistémica, trombosis, aterosclerosis, restenosis, lesión de repercusión, placas de calcificación, miocarditis, aneurisma, ataque, hipertensión pulmonar, remodelación ventricular izquierda y falla cardíaca. Las enfermedades de principal interés incluyen COPD y enfermedades inflamatorias del tracto respiratorio y enfermedades de articulaciones y vasculares. Se apreciará por aquellos versados en el arte que las referencias hechas aquí para tratamiento se extienden a la profilaxis así como también al tratamiento de condiciones establecidas.

La inhibición de la actividad de una o más de las MMP puede ser beneficiosa en estas enfermedades o condiciones. Por ejemplo, varias

enfermedades inflamatorias y alérgicas tales como inflamación de las articulaciones, inflamación del tracto GI, inflamación de la piel, remodelación del colágeno, etc.

5 La investigación se llevó a cabo para identificar inhibidores que sean selectivos e.g., para unos pocos de los sub-tipos de MMP. Un inhibidor MMP de selectividad mejorada evitaría los efectos colaterales potenciales con la inhibición de MMPs que no están involucradas en la patogénesis de la enfermedad que se esta tratando. Además el uso de inhibidores MMP más selectivos requeriría la
10 administración de cantidades más bajas del inhibidor para el tratamiento de enfermedad que serian requeridos de otra manera y, después de la administración, repartidos *in vivo* entre múltiples MMPs. Más aún, la administración de una cantidad baja del compuesto mejoraría el margen de seguridad entre la dosis requerida del inhibidor para actividad terapéutica y la
15 dosis del inhibidor a la cual se observa toxicidad.

El diseño y la aplicación terapéutica de los inhibidores MMP han revelado que el requerimiento de una molécula para que sea un inhibidor efectivo de enzimas de la clase MMP es un grupo funcional (e.g., ácido carboxílico, ácido
20 hidroxámico o sulfhidrilo) capaz de secuestrar a los iones Zn^{2+} del sitio activo (Whittaker, et al., *Chem. Rev.*, 1999, 99, 2735-76).

WO 04/110974 divulga compuestos y sus funciones fisiológicas derivadas como inhibidores de las enzimas metaloproteinasas de la matriz. WO 04/113279
25 divulga inhibidores de las metaloproteinasas de la matriz. La patente U.S. No. 6, 350, 885, divulga compuestos heteroaromáticos tricíclicos y sus derivados como inhibidores de las metaloproteinasas de la matriz. WO 98/09940 divulga ácidos

bifenilbutíricos y sus derivados como inhibidores de las metaloproteinasas de la matriz. *J. Med. Chem.*, 1968, vol. 11(6), 1139-1144 divulga la síntesis y la actividad anti-inflamatoria del ácido 4-(-bifenil)-3-hidroxibutírico o ácidos 5-biarilpentanóicos y derivados como inhibidores de las metaloproteinasas de la

5 matriz.

Resumen de la Invención

La presente invención divulga una clase novedosa de compuestos que son

10 inhibidores duales de las MMP 9/12 y tienen perfiles de actividad deseable. Los compuestos de esta invención tienen potencia benéfica, selectividad y/o propiedades fármaco-cinéticas.

En un aspecto, se proporcionan inhibidores de las metaloproteinasas de la

15 matriz, los cuales pueden ser útiles como agentes terapéuticos o profilácticos seguros para el tratamiento de varias enfermedades inflamatorias y alérgicas. También proporciona los procesos para la síntesis de tales compuestos.

En otro aspecto, se proporcionan composiciones farmacéuticas que

20 contienen tales compuestos junto con vehículos aceptables, excipientes o diluyentes que pueden ser útiles para el tratamiento de enfermedades inflamatorias y enfermedades auto-inmunes.

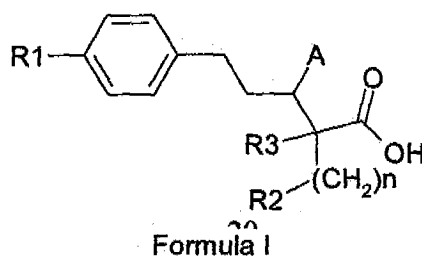
También se proporcionan los racematos, enantiómeros, diasterómeros,

25 isómeros rotacionales, N-óxidos, polimorfos, sales aceptables farmacéuticamente solvatos aceptables farmacéuticamente de éstos compuestos, pro-drogas y

metabolitos que tienen el mismo tipo de actividad, así como también composiciones farmacéuticas que comprenden los compuestos, sus metabolitos, racematos, enantiómeros, diasterómeros, isómeros conformacionales, N-óxidos, polimorfos, solvatos o sales aceptables farmacéuticamente de éstos, en
 5 combinación con un vehículo aceptable farmacéuticamente y opcionalmente se incluyen excipientes.

En la descripción que sigue a continuación se exponen otros aspectos, y en parte serán claros a partir de la descripción o se pueden aprender de la práctica de la invención.
 10 de la invención.

De acuerdo con un aspecto, se proporcionan compuestos que tienen la estructura de la Fórmula I:



En donde

n es un entero de 1 a 5;

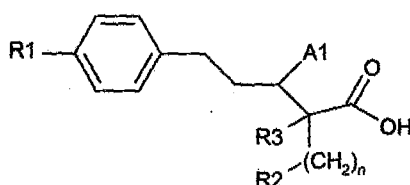
R_1 puede ser alquilo opcionalmente sustituido, alquenilo, alquinilo, cicloalquilo, arilo, heterociclilo, heteroarilo, aralquilo, alcoxi, ariloxi, alqueniloxi o alquiniloxi;

25 R_2 puede ser alquenilo, alquinilo, arilo, heterociclilo, heteroarilo, cicloalquilo, NR_4R_5 , $-NHC(=Y)R_4$, $-NHC(=Y)NR_5R_x$, $-NHC(=O)OR_4$, $-NH SO_2R_4$, $C(=Y)NR_4R_5$, $C(=O)OR_6$ [en donde Y puede ser oxígeno o azufre], $-OR_5$, $-OC(=O)NR_4R_5$, O-acilo, $S(O)_mR_4$, $-SO_2N(R_4)_2$, ciano, amidino o guanidino [en donde R_4 es alquilo, alquenilo, alquinilo, cicloalquilo, arilo, heterociclilo, heteroarilo, aralquilo, heteroarilalquilo, heterociclilalquilo o cicloalquilalquilo];
 30

R_3 puede ser hidrógeno, flúor, alquilo, cicloalquilalquilo o aralquilo;

A puede ser OH , OR_4 , $-OC(=O)NR_4R_5$, O -acilo, NH_2 , NR_4R_5 , $-NHC(=Y)R_4$, $-NHC(=Y)NR_5R_x$, $-NHC(=O)OR_4$, $-NHSO_2R_4$.

- 5 En una incorporación, la invención se refiere a compuestos de Fórmula general Ia,



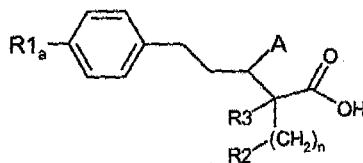
Fórmula Ia

En donde

- $A1$ puede ser OH , $-OC(=O)NR_4R_5$, NH_2 , NR_4R_5 , $-NHC(=Y)R_4$, $-NHC(=Y)NR_5R_x$, $-NHC(=O)OR_4$, $-NHSO_2R_4$;

n , R_1 , R_2 , R_3 , y R_4 pueden ser como se definió antes.

En otra incorporación, la invención se refiere a compuestos de Fórmula general Ib,



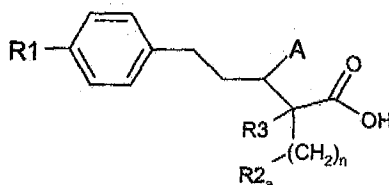
Fórmula Ib

En donde:

R_{1a} puede ser arilo o heteroarilo;

n , R_2 , R_3 y A pueden ser como se definió antes.

En otra incorporación, la invención se refiere a compuestos de Fórmula general Ic,



Formula Ic

5 En donde:

R_{2a} puede ser NR_4R_5 , $-NHC(=Y)R_4$, $-NHC(=Y)NR_5R_x$, $-NHC(=O)OR_4$, $-NH\text{SO}_2R_4$, amidino o guanidino [en donde Y puede ser oxígeno o azufre, R_4 puede ser alquilo, alquenilo, alquinilo, cicloalquilo, arilo, heterociclilo, heteroarilo, aralquilo, heteroarilalquilo, heterociclilaquilo o cicloalquilalquilo y m es un entero 0-2; R_5 es

10 hidrógeno o R_4 ; o R_4 y R_5 juntos opcionalmente pueden formar un anillo heterocíclico que contiene uno o más heteroátomos tales como O, N o S y R_x es R_4 o $-\text{SO}_2\text{N}(R_4)_2$; y n, R_1 , R_3 y A pueden ser como se definió antes.

En aún otra incorporación, la invención abarca compuestos que incluyen,

15 por ejemplo:

Ácido 5-Bifenil-4-il-3-hidroxi-2-[2-(4-oxo-1,2,3-benzotriazin-3(4H)-il)etil]pentanóico (Compuesto No. 1),

Ácido 5-(4'-ter-Butilbifenil-4-il)-2-[2-(1,3-dioxo-1,3-dihidro-2H-isoindol-2-il)etil]-3-hidroxi-2-pentanóico (Compuesto No. 2),

20 Ácido 5-(4'-Butilbifenil-4-il)-2-[2-(1,3-dioxo-1,3-dihidro-2H-isoindol-2-il)etil]-3-hidroxi-2-pentanóico (Compuesto No. 3),

Ácido 5-(4'-Clorobifenil-4-il)-2-[2-(1,3-dioxo-1,3-dihidro-2H-isoindol-2-il)etil]-3-hidroxi-2-pentanóico (Compuesto No. 4),

Ácido 2-[2-(1,3-Dioxo-1,3-dihidro-2*H*-isoindol-2-il)etil]-3hidroxi-5-(4'-trifluorometoxibefinil-4-il)pentanóico (Compuesto No.5),

Ácido 2-[2-(1,3-Dioxo-1,3-dihidro-2*H*-isoindol-2-il)etil]-5-(4'-etoxibifenil-4-il)-3-hidroxipentanóico (Compuesto No. 6),

5 Ácido 2-[2-(1,3-Dioxo-1,3-dihidro-2*H*-isoindol-2-il)etil]-5-(4'-formilbifenil-4-il)-3-hidroxipentanóico (Compuesto No. 7),

Ácido 2-[2-(1,3-Dioxo-1,3-dihidro-2*H*-isoindol-2-il)etil]-3-hidroxi-5-(2',4',6'-trimetoxibifenil-4-il)pentanóico (Compuesto No. 8),

10 Ácido 2-[2-(1,3-Dioxo-1,3-dihidro-2*H*-isoindol-2-il)etil]-3-hidroxi-5-(4'-propoxibifenil-4-il)pentanóico (Compuesto No. 9),

Ácido 5-(3',4'-Difluorobifenil-4-il)-2-[2-(1,3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)etil]-3-hidroxipentanóico (Compuesto No. 10),

Ácido 2-(2-[[Benciloxi]carbonil]amino)etil)-5-bifenil-4-il-3-hidroxipentanóico (Compuesto No. 11).

15 Ácido 5-Bifenil-4-il-2-[2-(1,3-dihidro-2*H*-isoindol-2-il)etil]-3-hidroxipentanóico (Compuesto No. 12)

Ácido (2*R*,3*S* + 2*S*,3*R*)-2-[2-(1,3-Dioxo-1,3-dihidro-2*H*-isoindol-2-il)etil]-5-(4'-formilbifenil-4-il)-3-hidroxipentanóico (Compuesto No. 13),

20 Ácido (2*R*,3*R* + 2*S*,3*S*)-2-[2-(1,3-Dioxo-1,3-dihidro-2*H*-isoindol-2-il)etil]-5-(4'-formilbifenil-4-il)-3-hidroxipentanóico (Compuesto No. 14),

Ácido (2*R*,3*R* + 2*S*,3*S*)-2-[2-(1,3-Dioxo-1,3-dihidro-2*H*-isoindol-2-il)etil]-3-hidroxi-5-(2',4',6'-trimetoxibifenil-4-il)pentanóico (Compuesto No.15),

Ácido (2*R*,3*S* + 2*S*,3*R*)-2-[2-(1,3-Dioxo-1,3-dihidro-2*H*-isoindol-2-il)etil]-3-hidroxi-5-(2',4',6'-trimetoxibifenil-4-il)pentanóico (Compuesto No. 16),

Ácido (2*R*,3*S* + 2*S*,3*R*)-5-(4'-Acetilbifenil-4-il)-2-[2-(1,3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)etil]-3-hidroxipentanóico (Compuesto No. 17),

Ácido (2*R*,3*R* + 2*S*,3*S*)-5-(4'-Acetilbifenil-4-il)-2-[2-(1,3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)etil]-3-hidroxipentanóico (Compuesto No. 18),

- 5 Ácido (2*R*,3*S* + 2*S*,3*R*)-2-[2-(1,3-Dioxo-1,3-dihidro-2*H*-isoindol-2-il)etil]-3-hidroxi-5-(4'-propoxibifenil-4-il)pentanóico (Compuesto No. 19),

Ácido (2*R*,3*R* + 2*S*,3*S*)-2-[2-(1,3-Dioxo-1,3-dihidro-2*H*-isoindol-2-il)etil]-3-hidroxi-5-(4'-propoxibifenil-4-il)pentanóico (Compuesto No. 20),

- 10 Ácido (2*R*,3*S* + 2*S*,3*R*)-5-(3',4'-Difluorobifenil-4-il)-2-[2-(1,3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)etil]-3-hidroxipentanóico (Compuesto No. 21),

Ácido (2*R*,3*R* + 2*S*,3*S*)-5-(3',4'-Difluorobifenil-4-il)-2-[2-(1,3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)etil]-3-hidroxipentanóico (Compuesto No. 22),

Ácido 2-[2-(1,3-Dioxo-1,3-dihidro-2*H*-isoindol-2-il)etil]-3-hidroxi-5-(4'-metoxibifenil-4-il)pentanóico (Compuesto. 23),

- 15 Ácido 5-(2',3'-Dimetilbifenil-4-il)-2-[2-(1,3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)etil]-3-hidroxipentanóico (Compuesto No. 24),

Ácido 2-[2-(1,3-Dioxo-1,3-dihidro-2*H*-isoindol-2-il)etil]-3-hidroxi-5-[3'-(trifluorometil)bifenil-4-il]pentanóico (Compuesto No. 25),

- 20 Ácido 2-[2-(1,3-Dioxo-1,3-dihidro-2*H*-isoindol-2-il)etil]-5-(4'-etilbifenil-4-il)-3-hidroxipentanóico (Compuesto No. 26),

Ácido 5-(3',5'-Diclorobifenil-4-il)-2-[2-(1,3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)etil]-3-hidroxipentanóico (Compuesto No. 27),

Ácido 5-[4'-Cloro-3'-(trifluorometil)bifenil-4-il]-2-[2-(1,3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)etil]-3-hidroxipentanóico (Compuesto No. 28),

Ácido 5-(2',5'-Difluorobifenil-4-il)-2-[2-(1,3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)etil]-3-hidroxicpentanóico (Compuesto No. 29),

Ácido 2-[2-(1,3-Dioxo-1,3-dihidro-2*H*-isoindol-2-il)etil]-3-hidroxi-5-[2'-(trifluorometoxi)bifenil-4-il]pentanóico (Compuesto No. 30),

5 Ácido 2-[2-(1,3-Dioxo-1,3-dihidro-2*H*-isoindol-2-il)etil]-3-hidroxi-5-[4'-(metiltio)bifenil-4-il]pentanóico (Compuesto No. 31),

Ácido 2-[2-(1,3-Dioxo-1,3-dihidro-2*H*-isoindol-2-il)etil]-5-(4'-fluoro-3'-metilbifenil-4-il)-3-hidroxicpentanóico (Compuesto No. 32),

10 Ácido 2-[2-(1,3-Dioxo-1,3-dihidro-2*H*-isoindol-2-il)etil]-3-hidroxi-5-(3'-isopropilbifenil-4-il)pentanóico (Compuesto No. 33),

Ácido 5-(3',4'-Dimetilbifenil-4-il)-2-[2-(1,3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)etil]-3-hidroxicpentanóico (Compuesto No. 34),

Ácido 5-(2',6'-Difluorobifenil-4-il)-2-[2-(1,3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)etil]-3-hidroxicpentanóico (Compuesto No. 35),

15 Ácido 2-[2-(1,3-Dioxo-1,3-dihidro-2*H*-isoindol-2-il)etil]-5-(4'-fluorobifenil-4-il)-3-hidroxicpentanóico (Compuesto No. 36),

Ácido 5-(3',5'-Difluorobifenil-4-il)-2-[2-(1,3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)etil]-3-hidroxicpentanóico (Compuesto No. 37),

20 Ácido 5-(3'-Cloro-4'-fluorobifenil-4-il)-2-[2-(1,3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)etil]-3-hidroxicpentanóico (Compuesto No. 38),

Ácido 5-(3',4'-Dimetoxibifenil-4-il)-2-[2-(1,3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)etil]-3-hidroxicpentanóico (Compuesto No. 39),

Ácido 5-(3'-Clorobifenil-4-il)-2-[2-(1,3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)etil]-3-hidroxicpentanóico (Compuesto No. 40),

Ácido 2-[2-(1,3-Dioxo-1,3-dihidro-2*H*-isoindol-2-il)etil]-3-hidroxi-5-(3'-metilbifenil-4-il)pentanóico (Compuesto No. 41),

Ácido 5-(2',3'-Difluorobifenil-4-il)-2-[2-(1,3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)etil]-3-hidroxi-5-(3'-metilbifenil-4-il)pentanóico (Compuesto No. 42),

5 Ácido 2-[2-(1,3-Dioxo-1,3-dihidro-2*H*-isoindol-2-il)etil]-5-(2'-fluoro-3'-metoxibifenil-4-il)-3-hidroxi-5-(3'-metilbifenil-4-il)pentanóico (Compuesto No. 43),

Ácido 2-[2-(1,3-Dioxo-1,3-dihidro-2*H*-isoindol-2-il)etil]-5-(3'-fluoro-4'-metilbifenil-4-il)-3-hidroxi-5-(3'-metilbifenil-4-il)pentanóico (Compuesto No. 44),

10 Ácido 5-Bifenil-4-il-3-hidroxi-2-{2-[(fenilacetil)amino]etil}pentanóico (Compuesto No. 45),

Ácido 2-(3-Bifenil-4-il-1-hidroxi-2-propil)-6-(1,3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)hexanóico (Compuesto No. 46),

Ácido 5-Bifenil-4-il-3-hidroxi-2-[2-(1-oxoftalazin-2(1*H*)-il)etil]pentanóico (Compuesto No. 47),

15 Ácido 5-Bifenil-4-il-2-[3-(1,3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)propil]-3-hidroxi-5-(3'-metilbifenil-4-il)pentanóico (Compuesto No. 48),

Ácido 5-Bifenil-4-il-3-hidroxi-2-[2-(2'-oxospiro[ciclopropan-1,3'-indol]-1'(2*H*)-il)etil]pentanóico (Compuesto No. 49),

20 Ácido 2-[2-(1,3-Dioxo-1,3-dihidro-2*H*-isoindol-2-il)etil]-3-hidroxi-5-(4'-hidroxibifenil-4-il)pentanóico (Compuesto No. 50),

Ácido 3-Hidroxi-5-(4'-metoxibifenil-4-il)-2-[2-(3-metil-2,6-dioxo-3,6-dihidropirimidin-1(2*H*)-il)etil]pentanóico (Compuesto No. 51),

Ácido 5-(4'-Clorobifenil-4-il)-3-hidroxi-2-[2-(3-metil-2,6-dioxo-3,6-dihidropirimidin-1(2*H*)-il)etil]pentanóico (Compuesto No. 52),

Ácido 5-(4'-Fluorobifenil-4-il)-3-hidroxi-2-[2-(3-metil-2,6-dioxo-3,6-dihidropirimidin-1(2H)-il)etil]pentanóico (Compuesto No. 53),

Ácido 5-[4-(5-Cloro-2-tienil)fenil]-2-[2-(1,3-dioxo-1,3-dihidro-2H-isoindol-2-il)etil]-3-hidroxipentanóico (Compuesto No. 54),

- 5 Ácido 4'-[4-Carboxi-6-(1,3-dioxo-1,3-dihidro-2H-isoindol-2-il)-3-hidroxi]hexil]bifenil-4-carboxílico (Compuesto No. 55),

Ácido 2-[2-(1,3-Dioxo-1,3-dihidro-2H-isoindol-2-il)etil]-3-hidroxi-5-[4'-(metoxycarbonil)bifenil-4-il]pentanóico (Compuesto No. 56),

- 10 Ácido 2-[2-(1,3-Dioxo-1,3-dihidro-2H-isoindol-2-il)etil]-3-hidroxi-5-[4'-(trifluorometil)bifenil-4-il]pentanóico (Compuesto No. 57),

Ácido 2-[2-(1,3-Dioxo-1,3-dihidro-2H-isoindol-2-il)etil]-3-hidroxi-5-[4-(6-metoxipiridin-3-il)fenil]pentanóico (Compuesto No. 58),

Ácido 3-Hidroxi-2-[2-(4-oxo-1,2,3-benzotriazin-3(4H)-il)etil]-5-[4'-(trifluorometil)bifenil-4-il]pentanóico (Compuesto No. 59),

- 15 Ácido 5-(3',4'-Difluorobifenil-4-il)-3-hidroxi-2-[2-(4-oxo-1,2,3-benzotriazin-3(4H)-il)etil]pentanóico (Compuesto No. 60),

Ácido 2-[2-(1,3-Dioxo-1,3-dihidro-2H-isoindol-2-il)etil]-5-(3'-fluorobifenil-4-il)-3-hidroxipentanóico (Compuesto No. 61),

- 20 Ácido 5-[4'-(Benciloxi)-3'-fluorobifenil-4-il]-2-[2-(1,3-dioxo-1,3-dihidro-2H-isoindol-2-il)etil]-3-hidroxipentanóico (Compuesto No. 62),

Ácido 5-[4'-(Benciloxi)bifenil-4-il]-2-[2-(1,3-dioxo-1,3-dihidro-2H-isoindol-2-il)etil]-3-hidroxipentanóico (Compuesto No. 63),

Ácido 3-Hidroxi-5-(4'-metoxibifenil-4-il)-2-[2-(4-oxo-1,2,3-benzotriazin-3(4H)-il)etil]pentanóico (Compuesto No. 64),

Ácido 5-(4'-Clorobifenil-4-il)-3-hidroxi-2-[2-(4-oxo-1,2,3-benzotriazin-3(4H)-il)etil]pentanóico (Compuesto No. 65),

Ácido 2-[2-(1,3-Dioxo-1,3-dihidro-2H-isoindol-2-il)etil]-3-hidroxi-5-(4'-metilbifenil-4-il)pentanóico (Compuesto No. 66),

5 Ácido 3-Hidroxi-5-[4-(6-metoxipiridin-3-il)fenil]-2-[2-(4-oxo-1,2,3-benzotriazin-3(4H)-il)etil]pentanóico (Compuesto No. 67),

Ácido 3-Hidroxi-5-(4'-metilbifenil-4-il)-2-[2-(5-metil-1,3-dioxo-1,3-dihidro-2H-isoindol-2-il)etil]pentanóico (Compuesto No. 68),

10 Ácido 5-(4'-Clorobifenil-4-il)-3-hidroxi-2-[2-(5-metil-1,3-dioxo-1,3-dihidro-2H-isoindol-2-il)etil]pentanóico (Compuesto No. 69),

Ácido 3-Hidroxi-2-[2-(4-oxo-1,2,3-benzotriazin-3(4H)-il)etil]-5-[4'-(trifluorometoxi)bifenil-4-il]pentanóico (Compuesto No. 70),

Ácido 5-(4'-Fluorobifenil-4-il)-3-hidroxi-2-[2-(4-oxo-1,2,3-benzotriazin-3(4H)-il)etil]pentanóico (Compuesto No. 71),

15 Ácido 3-hidroxi-5-(4'-metilbifenil-4-il)-2-[2-(4-oxo-1,2,3-benzotriazin-3(4H)-il)etil]pentanóico (Compuesto No. 72),

Ácido 5-(4'-Cianobifenil-4-il)-3-hidroxi-2-[2-(4-oxo-1,2,3-benzotriazin-3(4H)-il)etil]pentanóico (Compuesto No. 73),

20 Ácido 5-(4'-Fluorobifenil-4-il)-3-hidroxi-2-[2-(5-metil-1,3-dioxo-1,3-dihidro-2H-isoindol-2-il)etil]pentanóico (Compuesto No. 74),

Ácido 3-Hidroxi-5-[4-(6-metoxipiridin-3-il)fenil]-2-[2-(5-metil-1,3-dioxo-1,3-dihidro-2H-isoindol-2-il)etil]pentanóico (Compuesto No. 75),

Ácido 5-(4'-Etilbifenil-4-il)-3-hidroxi-2-[2-(4-oxo-1,2,3-benzotriazin-3(4H)-il)etil]pentanóico (Compuesto No. 76),

Ácido 3-Hidroxi-2-[2-(5-metil-1,3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)etil]-5-[4'-(trifluorometil)bifenil-4-il]pentanóico (Compuesto No. 77),

Ácido (2*R*,3*S* + 2*S*,3*R*)-2-[2-(1,3-Dioxo-1,3-dihidro-2*H*-isoindol-2-il)etil]-3-hidroxi-5-[4-(6-metoxipiridin-3-il)fenil]pentanóico (Compuesto No. 78),

5 Ácido (2*R*,3*R* + 2*S*,3*S*)-2-[2-(1,3-Dioxo-1,3-dihidro-2*H*-isoindol-2-il)etil]-3-hidroxi-5-[4-(6-metoxipiridin-3-il)fenil]pentanóico (Compuesto No. 79),

Ácido (2*R*,3*R* + 2*S*,3*S*)-5-(4'-Clorobifenil-4-il)-2-[2-(1,3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)etil]-3-hidroxipentanóico (Compuesto No. 80),

10 Ácido (2*R*,3*S* + 2*S*,3*R*)-5-(4'-Clorobifenil-4-il)-2-[2-(1,3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)etil]-3-hidroxipentanóico (Compuesto No. 81),

Ácido (2*R*,3*S* + 2*S*,3*R*)-2-[2-(1,3-Dioxo-1,3-dihidro-2*H*-isoindol-2-il)etil]-5-(4'-fluorobifenil-4-il)-3-hidroxipentanóico (Compuesto No. 82),

Ácido (2*R*,3*R* + 2*S*,3*S*)-2-[2-(1,3-Dioxo-1,3-dihidro-2*H*-isoindol-2-il)etil]-5-(4'-fluorobifenil-4-il)-3-hidroxipentanóico (Compuesto No. 83),

15 Ácido 5-Bifenil-4-il-3-hidroxi-2-[2-(1-oxo-4-fenil-4*a*,8*a*-dihidroftalazin-2(1*H*)-il)etil]pentanóico (Compuesto No. 84),

Ácido 5-Bifenil-4-il-3-hidroxi-2-[2-(3-oxo-2,3-dihidro-4*H*-1,4-benzoxazin-4-il)etil]pentanóico (Compuesto No. 85),

20 Ácido 5-Bifenil-4-il-2-[2-[(3*aR*,7*aS*)-1,3-dioxo-1,3,3*a*,4,7,7*a*-hexahidro-2*H*-isoindol-2-il)etil]-3-hidroxipentanóico (Compuesto No. 86),

Ácido 5-Bifenil-4-il-2-(2-[[4-fluorofenil)sulfonyl]amino]etil)-3-hidroxipentanóico (Compuesto No. 87),

Ácido 5-Bifenil-4-il-2-(2-[[3-fluorofenil]cetil]amino)etil)-3-hidroxipentanóico (Compuesto No. 88),

Ácido 5-Bifenil-4-il-2-[2-[(4-fluorobenzoil)amino]etil]-3-hidroxipentanóico
(Compuesto No. 89),

Ácido 5-Bifenil-4-il-3-hidroxi-2-[2-(5-metil-1,3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)etil]pentanóico (Compuesto No. 90),

5 Ácido 5-Bifenil-4-il-3-hidroxi-2-[2-(1-oxo-1,3-dihidro-2*H*-isoindol-2-il)etil]pentanóico
(Compuesto No. 91).

Ácido 5-Bifenil-4-il-2-[2-({[(4-fluorofenil)amino]carbonil}amino)etil]-3-hidroxipentanóico (Compuesto No. 92),

10 Ácido 5-Bifenil-4-il-2-[2-(4,4-dimetil-2,6-dioxopiperidin-1-il)etil]-3-hidroxipentanóico
(Compuesto No. 93),

Ácido 5-Bifenil-4-il-2-[2-(7,9-dioxo-8-azaspiro[4.5]dec-8-il)etil]-3-hidroxipentanóico
(Compuesto No. 94),

Ácido 2-(3-Bifenil-4-il-1-hidroxipropil)pent-4-inoico (Compuesto No. 95);

15 Ácido 5-Bifenil-4-il-3-hidroxi-2-[2-(2-oxo-1,3-benzoxazol-3(2*H*)-il)etil]pentanóico
(Compuesto No. 96)

Ácido 2-[2-(5-*ter*-Butil-1,3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)etil]-3-hidroxi-5-[4-(6-metoxipiridin-3-il)fenil]pentanóico (Compuesto No. 97),

Ácido 5-{4-[6-(Dimetilamino)piridin-3-il]fenil}-2-[2-(1,3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)etil]-3-hidroxipentanóico (Compuesto No. 98),

20 Ácido 2-[2-(1,3-Dioxo-1,3-dihidro-2*H*-isoindol-2-il)etil]-3-hidroxi-5-[4'-(metilsulfonil)bifenil-4-il]pentanóico (Compuesto No. 99),

Ácido 5-[4'-(Aminocarbonil)bifenil-4-il]-2-[2-(1,3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)etil]-3-hidroxipentanóico (Compuesto No. 100),

Ácido 5-[4-(1-Bencil-1*H*-pirazol-4-il)fenil]-2-[2-(1,3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)etil]-3-hidroxipentanóico (Compuesto No. 101),

Ácido 5-Bifenil-4-il-2-[2-(5,6-dicloro-1,3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)etil]-3-hidroxipentanóico (Compuesto No. 102),

5 Ácido 5-Bifenil-4-il-2-[2-(2,4-dioxo-1,4-dihidroquinazolin-3(2*H*)-il)etil]-3-hidroxipentanóico (Compuesto No. 103),

Ácido 5-Bifenil-4-il-2-[2-(1,3-dioxo-1,3-dihidro-2*H*-pirrol[3,4-*c*]piridin-2-il)etil]-3-hidroxipentanóico (Compuesto No. 104),

10 Ácido 2-[2-(5-*ter*-Butil-1,3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)etil]-5-(3',4'-difluorobifenil-4-il)-3-hidroxipentanóico (Compuesto No. 105),

Ácido (2*R*,3*S* + 2*S*,3*R*)-2-[2-(5-*ter*-Butil-1,3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)etil]-5-(4'-fluorobifenil-4-il)-3-hidroxipentanóico (Compuesto No. 106),

Ácido (2*R*,3*S* + 2*S*,3*R*)-2-[2-(5-*ter*-Butil-1,3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)etil]-3-hidroxi-5-[4'-(trifluorometil)bifenil-4-il]pentanóico (Compuesto No. 107),

15 Ácido (2*R*,3*R* + 2*S*,3*S*)-2-[2-(5-*ter*-Butil-1,3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)etil]-5-(4'-fluorobifenil-4-il)-3-hidroxipentanóico (Compuesto No. 108),

Ácido (2*R*,3*R* + 2*S*,3*S*)-2-[2-(5-*ter*-Butil-1,3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)etil]-3-hidroxi-5-[4'-(trifluorometil)bifenil-4-il]pentanóico (Compuesto No. 109),

20 Ácido 2-[2-(1,3-Dioxo-1,3-dihidro-2*H*-isoindol-2-il)etil]-5-(3'-fluoro-4'-metoxibifenil-4-il)-3-hidroxipentanóico (Compuesto No. 110),

Ácido (2*R*,3*S* + 2*S*,3*R*)-2-[2-(1,3-Dioxo-1,3-dihidro-2*H*-isoindol-2-il)etil]-3-hidroxi-5-[4-(6-metilpiridin-3-il)fenil]pentanóico (Compuesto No. 111),

Ácido (2*R*,3*R* + 2*S*,3*S*)-2-[2-(1,3-Dioxo-1,3-dihidro-2*H*-isoindol-2-il)etil]-3-hidroxi-5-[4-(6-metilpiridin-3-il)fenil]pentanóico (Compuesto No. 112),

Ácido (2*R*,3*R* + 2*S*,3*S*)-2-[2-(5-*ter*-Butil-1,3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)etil]-3-hidroxi-5-(4'-metilbifenil-4-il)pentanóico (Compuesto No. 113),

Ácido (2*R*,3*S* + 2*S*,3*R*)-2-[2-(5-*ter*-Butil-1,3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)etil]-3-hidroxi-5-(4'-metilbifenil-4-il)pentanóico (Compuesto No. 114),

- 5 Ácido (2*R*,3*R* + 2*S*,3*S*)-2-[2-(5-*ter*-Butil-1,3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)etil]-3-hidroxi-5-(4'-metoxibifenil-4-il)pentanóico (Compuesto No. 115),

Ácido (2*R*,3*R* + 2*S*,3*S*)-2-[2-(5-*ter*-Butil-1,3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)etil]-5-(4'-clorobifenil-4-il)-3-hidroxipentanóico (Compuesto No.116),

- 10 Ácido (2*R*,3*S* + 2*S*,3*R*)-2-[2-(5-*ter*-Butil-1,3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)etil]-5-(4'-clorobifenil-4-il)-3-hidroxipentanóico (Compuesto No. 117),

Ácido (2*R*,3*S* + 2*S*,3*R*)-2-[2-(5-*ter*-Butil-1,3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)etil]-3-hidroxi-5-(4'-metoxibifenil-4-il)pentanóico (Compuesto No. 118),

Ácido 2-[2-(1,3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)etil]-3-hidroxi-5-(4-pirimidin-5-ilfenil)pentanóico (Compuesto No 119),

- 15 Ácido 5-Bifenil-4-il-3-hidroxi-2-[2-(7-metil-4-oxo-1,2,3-benzotriazin-3(4*H*)-il)etil]pentanóico (Compuesto No. 120),

Ácido 5-Bifenil-4-il-2-[2-(5-*ter*-Butil-1,3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)etil]-3-hidroxipentanóico (Compuesto No. 121),

- 20 Ácido (2*R*,3*S*)-5-Bifenil-4-il-3-hidroxi-2-[2-(1*H*-indol-3-il)etil]pentanóico (Compuesto No. 122),

Ácido (2*R*,3*R*)-5-Bifenil-4-il-3-hidroxi-2-[2-(1*H*-indol-3-il)etil]pentanóico (Compuesto No. 123),

Ácido 5-Bifenil-4-il-3-hidroxi-2-[2-(1-oxo-1,3-dihidro-2*H*-isoindol-2-il)butil]pentanóico (Compuesto No. 124),

Ácido (2R,3S)-5-(4'-Clorobifenil-4-il)-2-[2-(1,3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)etil]-3-hidroxipentanóico (Compuesto No.125),

Ácido (2S,3R)-5-(4'-Clorobifenil-4-il)-2-[2-(1,3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)etil]-3-hidroxipentanóico (Compuesto No.126),

5 Ácido (2R,3R)-5-(4'-Clorobifenil-4-il)-2-[2-(1,3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)etil]-3-hidroxipentanóico (Compuesto No.127),

Ácido (2S,3S)-5-(4'-Clorobifenil-4-il)-2-[2-(1,3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)etil]-3-hidroxipentanóico (Compuesto No.128),

10 Ácido (2R,3S) -2-[2-(1,3-Dioxo-1,3-dihidro-2*H*-isoindol-2-il)etil]-3-hidroxi-5-[4-(6-metoxipiridin-3-il)fenil]pentanóico (Compuesto No. 129),

Ácido (2S,3R)- 2-[2-(1,3-Dioxo-1,3-dihidro-2*H*-isoindol-2-il)etil]-3-hidroxi-5-[4-(6-metoxipiridin-3-il)fenil]pentanóico (Compuesto No. 130),

Ácido (2R,3R)- 2-[2-(1,3-Dioxo-1,3-dihidro-2*H*-isoindol-2-il)etil]-3-hidroxi-5-[4-(6-metoxipiridin-3-il)fenil]pentanóico (Compuesto No. 131),

15 Ácido (2S,3S)- 2-[2-(1,3-Dioxo-1,3-dihidro-2*H*-isoindol-2-il)etil]-3-hidroxi-5-[4-(6-metoxipiridin-3-il)fenil]pentanóico (Compuesto No. 132),

Ácido (2R,3S)- 3-Hidroxi-5-[4-(6-metoxipiridin-3-il)fenil]-2-[2-(4-oxo-1,2,3-benzotriazin-3(4*H*)-il)etil]pentanóico (Compuesto No.133),

20 Ácido (2S,3R)- 3-Hidroxi-5-[4-(6-metoxipiridin-3-il)fenil]-2-[2-(4-oxo-1,2,3-benzotriazin-3(4*H*)-il)etil]pentanóico (Compuesto No.134),

Ácido (2R,3R)- 3-Hidroxi-5-[4-(6-metoxipiridin-3-il)fenil]-2-[2-(4-oxo-1,2,3-benzotriazin-3(4*H*)-il)etil]pentanóico (Compuesto No.135), y

Ácido (2S,3S)- 3-Hidroxi-5-[4-(6-metoxipiridin-3-il)fenil]-2-[2-(4-oxo-1,2,3-benzotriazin-3(4*H*)-il)etil]pentanóico (Compuesto No.136).

En otra incorporación, la invención abarca la separación de los enantiómeros individuales o pares de diasterómeros o diasterómeros únicos. Una persona ordinariamente versada en el arte de esta invención, opcionalmente puede escoger uno o más vías para obtener los compuestos puros quiralmente. La presente invención incluye la separación de representativa de un conjunto de compuestos ya sea como pares de diasterómeros o de diasterómeros únicos por cromatografía preparativa en capa delgada y/o HPLC, utilizando una columna aquiral o quiral según se requiera.

En aún otra incorporación, la presente invención se refiere a dosis efectivas terapéuticamente de un compuesto de Fórmula I en combinación con uno o más de otros agentes terapéuticos utilizados para el tratamiento de varias enfermedades inflamatorias y alérgicas. Ejemplos de tales compuestos terapéuticos incluyen pero no se limitan a,

1) agentes anti-inflamatorios, experimentales o comerciales tales como (i) agentes anti-inflamatorios no esteroideos piroxicam, diclofenac, ácidos propiónicos, fenamatos, pirazolonas, salicilatos, inhibidores de la PDE-4/p38 MAP Kinasa/Catepsina (ii) inhibidores leucotrienos LTC₄/LTD₄/LTE₄/LTB₄, inhibidores de la 5-lipoxigenasa y antagonistas del receptor PAF, (iii) inhibidores de Cox-2 (iv) inhibidores de MMP, e (v) inhibidores de interleukina-I;

2) Agentes anti-hipertensivos, (i) inhibidores ACE, e.g., enalapril, lisinopril, valsartan, telmisartan y quinapril, (ii) antagonistas y agonistas del receptor de angiotensina II, e.g., losartan, candesartan, irbesartan, valsartan, y eprosartan, (iii) β -bloqueadores, y (iv) bloqueadores de los canales de calcio;

o bloq. β -adrenérgicos

antih/pase.

3) Agentes inmuno-supresores tales como ciclosporina, azatioprina y metotrexato, y corticosteroides anti-inflamatorios.

Las siguientes definiciones aplican a los términos aquí utilizados

El término "alquilo" a menos que se especifique otra cosa, se refiere a mono-radicales ramificado o no ramificado de cadenas hidrocarbonadas que tienen de 1 a 20 átomos de carbono. Este término se puede ejemplificar por grupos tales como metilo, etilo, n-propilo, iso-propilo, iso-butilo, sec-butilo, t-butilo, iso-pentilo, neopentilo, n-hexilo, n-decilo, tetradecilo, y similares. Los grupos alquilo, además pueden estar sustituidos con uno o más sustituyente seleccionados de alquenilo, alquinilo, alcoxi, cicloalquilo, cicloalquenilo, acilo, acilamino, aciloxi, alcoxicarbonilamino, azido, ciano, halógeno, hidroxilo, oxo, tiocarbonilo, carboxi, carboxialquilo, arilo, heterociclilo, ariltio, tiol, alquiltio, ariloxi, nitro, aminosulfonilo, COOH , aminocarbonilamino, $-\text{NHC}(=\text{O})\text{R}_f$, $-\text{NR}_f\text{R}_q$, $-\text{C}(=\text{O})\text{NR}_f\text{R}_q$, $-\text{NHC}(=\text{O})\text{NR}_f\text{R}_q$, $-\text{C}(=\text{O})\text{heteroarilo}$, $-\text{C}(=\text{O})\text{heterociclilo}$, $-\text{O}-\text{C}(=\text{O})\text{NR}_f\text{R}_q$ { en donde R_f y R_q se seleccionan independientemente de alquilo, alquenilo, cicloalquilo, arilo, aralquilo, heterociclilo, heteroarilo, heterociclilalquilo, heteroarilalquilo,}, nitro, o $-\text{SO}_2\text{R}_6$ (en donde R_6 es alquilo, alquenilo, alquinilo, cicloalquilo, aralquilo, arilo, heterociclilo, heteroarilo, heteroarilalquilo o heterociclilalquilo). A menos que sea obligado por definición, los sustituyentes alquilo además pueden estar sustituidos por 1-3 sustituyentes seleccionados de alquilo, carboxi, $-\text{NR}_f\text{R}_q$, $-\text{C}(=\text{O})\text{NR}_f\text{R}_q$, $-\text{O}-\text{C}(=\text{O})\text{NR}_f\text{R}_q$, $-\text{NHC}(=\text{O})\text{NR}_f\text{R}_q$, (en donde R_f y R_q son los mismos definidos anteriormente), hidroxilo, alcoxi, halógeno, CF_3 , ciano, y $-\text{SO}_2\text{R}_6$ (en donde R_6 es el mismo definido anteriormente); o un grupo alquilo también puede estar interrumpido por 1-5 átomos de grupos seleccionados independientemente de oxígeno, azufre o $-\text{NR}_a-$ {en donde R_a se selecciona de hidrógeno, alquilo, cicloalquilo, alquenilo, cicloalquenilo, alquinilo, arilo, acilo, aralquilo, $-\text{C}(=\text{O})\text{OR}_f$ (en donde R_f es el mismo que se definió antes), SO_2R_6 (en donde R_6 es el mismo que se definió antes), o $-\text{C}(=\text{O})\text{OR}_f$ (en donde R_f y R_q son como se definió antes)}. A menos que por definición se obligue otra cosa,

todos los sustituyentes pueden además estar sustituidos por 1-3 sustituyentes seleccionados de alquilo, carboxi, $-NR_fR_q$, $-C(=O)NR_fR_q$, $-O-C(=O)NR_fR_q$ (en donde R_f y R_q son los mismos que se definieron antes); hidroxi, alcoxi, halógeno, CF_3 , ciano, y $-SO_2R_6$ (en donde R_6 es el mismo definido anteriormente); o un

5 grupo alquilo según se definió antes que tiene ambos sustituyentes como se definió antes y también está interrumpido por grupos de 1-5 átomos como se definió antes.

El término "alquenilo", a menos que se especifique otra cosa, se refiere a

10 mono-radicales de un grupo hidrocarburo insaturado ramificado o no ramificado que tiene de 2 a 20 átomos de carbono con geometría cis, trans o geminal. En el evento que el alquenilo esté unido a un heteroátomo, el doble enlace no puede estar en alfa respecto del heteroátomo. Los grupos alquenilos además pueden estar sustituidos con uno o más sustituyentes seleccionados de, alquilo, alquino,

15 alcoxi, cicloalquilo, cicloalquenilo, acilo, acilamino, aciloxi, $-NHC(=O)R_f$, $-NR_fR_q$, $-C(=O)NR_fR_q$, $-NHC(=O)NR_fR_q$, $-O-C(=O)-NR_fR_q$, (en donde R_f y R_q son los mismos definidos anteriormente), alcoxicarbonilamino, azido, ciano, halógeno, hidroxi, oxo, tiocarbonilo, carboxi, ariltio, tiol, alquiltio, arilo, aralquilo, ariloxi, heterociclilo, heteroarilo, heterociclicualquilo, heteroarilalquilo, aminosulfonilo,

20 aminocarbonilamino, alcoxi-amino, nitro o SO_2R_6 (en donde R_6 es el mismo que se definió antes). A menos que por definición se obligue otra cosa, los sustituyentes alquenilo opcionalmente pueden estar sustituidos por 1-3 sustituyentes seleccionados de alquilo, carboxi, hidroxi, alcoxi, halógeno, CF_3 , ciano, $-NR_fR_q$, $-C(=O)NR_fR_q$, $-O-C(=O)NR_fR_q$ (en donde R_f y R_q son los mismos que se definieron

25 antes) y $-SO_2R_6$ (en donde R_6 es el mismo definido antes).

El término "alquinilo", a menos que se especifique otra cosa, se refiere a un mono-radical de un grupo hidrocarburo insaturado que tiene de 2 a 20 átomos de carbono. En el evento que el alquinilo esté unido a un heteroátomo, el triple enlace no puede estar en alfa respecto del heteroátomo. Los grupos alquínulos además

5 pueden estar sustituidos con uno o más sustituyentes seleccionados de, alquilo, alquenilo, alcoxi, cicloalquilo, cicloalquenilo, acilo, acilamino, aciloxi, alcóxicarbonilamino, azido, ciano, halógeno, hidroxilo, oxo, tiocarbonilo, carboxi, ariltio, tiol, alquiltio, arilo, aralquilo, ariloxi, aminosulfonilo, aminocarbonilamino, nitro, heterociclilo, heteroarilo, heterociclilalquilo, heteroarilalquilo, $-NHC(=O)R_f$, $-NR_fR_q$, $-NHC(=O)NR_fR_q$, $-C(=O)NR_fR_q$, $-O-C(=O)NR_fR_q$, (en donde R_f y R_q son

10 los mismos definidos anteriormente), o SO_2R_6 (en donde R_6 es el mismo que se definió antes). A menos que por definición se obligue otra cosa, los sustituyentes alquinilo opcionalmente pueden estar además sustituidos por 1-3 sustituyentes seleccionados de alquilo, carboxi, carboxialquilo, hidroxilo, alcoxi, halógeno, CF_3 ,

15 ciano, $-NR_fR_q$, $-C(=O)NR_fR_q$, $-NHC(=O)R_fR_q$, $-C(=O)NR_fR_q$ (en donde R_f y R_q son los mismos que se definieron antes) ciano o $-SO_2R_6$ (en donde R_6 es el mismo definido antes).

El término "aralquilo" a menos que se especifique otra cosa, se refiere a alquil-arilo unido a través de una porción alquilo (donde alquilo es como se definió antes) y la

20 porción alquilo contiene 1-6 átomos de carbono y el arilo es como se define más adelante. Ejemplos de grupos aralquilo incluyen bencilo, etilfenilo y similares

El término "arilo", a menos que se especifique otra cosa, se refiere a grupos carboxílicos aromáticos, por ejemplo, anillos fenil, bifenil, naftil y similares, opcionalmente sustituidos con 1-3 sustituyentes seleccionados de halógeno (e.g.,

25 F, Cl, Br, I), hidroxilo, alquilo, alquenilo, alquinilo, cicloalquilo, alcoxi, acilo, ariloxi, CF_3 , ciano, nitro $COOR_6$ (en donde R_6 es hidrógeno, alquilo, alquenilo, cicloalquilo, aralquilo, heterociclilalquilo, heteroarilalquilo), $-NHC(=O)R_f$, $-NR_fR_q$, $-C(=O)NR_fR_q$, $-NHC(=O)NR_fR_q$, $-O-C(=O)NR_fR_q$ (en donde R_f y R_q son los mismos

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que se definieron antes), carboxi, heterociclilo, heteroarilo, heterociclicualquilo, heteroarilalquilo o aminocarbonilamino. El grupo arilo opcionalmente puede estar unido a un grupo carboxilo, en donde el grupo cicloalquilo opcionalmente puede contener heteroátomos seleccionados de O, N o S.

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El término "ariloxi" denota el grupo O-arilo, en donde el arilo es como se definió antes.

El término "heteroarilo", a menos que se especifique otra cosa, se refiere a una estructura de anillo aromático que contiene 5 o 6 átomos en el anillo, o un grupo aromático bicíclico que tiene de 8 a 10 átomos en el anillo, con uno o más heteroátomos seleccionados independientemente de N, O o S opcionalmente sustituido con 1 a 4 sustituyentes seleccionados de halógenos (e.g., F, Cl, Br, I), hidroxilo, alquilo, alqueno, alquino, cicloalquilo, acilo, carboxi, arilo, alcoxi, aralquilo, ciano, nitro, heterociclilo, heteroarilo, $-NR_fR_q$, $CH=NOH$, $-(CH_2)_wC(=O)R_g$ { en donde w es un entero de 0 a 4 y R_g es hidrógeno, hidroxilo, OR_f , $-NR_fR_q$, $-NHOR_z$ o $-NHOH$ }, $-C(=O)NR_fR_q$ y $-NHC(=O)NR_fR_q$, $-SO_2R_6$, $-O-C(=O)NR_fR_q$, $-O-C(=O)R_f$, $-O-C(=O)OR_f$ (en donde R_6 , R_f y R_q son como se definió antes, y R_z es alquilo, cicloalquilo, arilo, heteroarilo, heterociclilo, heteroarilalquilo o heterociclicualquilo). A menos que por definición se obligue otra cosa, los sustituyentes están unidos a un átomo del anillo, i.e., un carbono o un heteroátomo en el anillo. Ejemplos de grupos heteroarilo incluyen oxazolilo, imidazolilo, pirrolilo, 1,2,3-triazolilo, 1,2,4-triazolilo, tetrazolilo, tiazolilo, oxadiazolilo, benzoimidazolilo, tiadiazolilo, piridinilo, piridazinilo, pirimidinilo, pirazinilo, tienilo, isoxazolilo, triazinilo, furanilo, benzofuranilo, indolilo, benzotiazolilo o benzoxazolilo y similares.

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El término "heterociclilo", a menos que se especifique otra cosa se refiere a grupos mono-cíclicos no aromáticos o cicloalquilos bicíclicos que tienen 5 a 10 átomos en donde 1 a 4 átomos de carbono en el anillo están reemplazados por heteroátomos seleccionados de O, S o N, y opcionalmente son heteroarilos benzofusionados o fusionados que tienen 5 a 6 miembros en el anillo y/o opcionalmente están sustituidos, en donde los sustituyentes se seleccionan de halógenos (e.g., F, Cl, Br, I) hidroxí, alquilo, alquenilo, alquinilo, cicloalquilo, acilo, arilo, alcoxi, alcarilo, ciano, nitro, oxo, carboxi, heterociclilo, heteroarilo, -O-C(=O)R_f, -O-C(=O)OR_f, -C(=O)NR_fR_q, -SO₂R₆, -O-C(=O)NR_fR_q, -NHC(=O)NR_fR_q, -NR_fR_q, (en donde R₆, R_f y R_q son como se definió antes) o guanidino. El heterociclilo opcionalmente puede incluir anillos que tienen uno o más dobles enlaces. A menos que por definición se obligue otra cosa, los sustituyentes están unidos a un átomo del anillo, i.e., un carbono o heteroátomo en el anillo. También, a menos que por definición se obligue otra cosa, el anillo heterociclilo opcionalmente puede contener uno o más enlaces olefinicos. Ejemplos de grupos heterociclicos incluyen oxazolidinilo, tetrahidrofuranilo, dihidrofuranilo, dihidropiridinilo, dihidroisoxazolilo, dihidrobenzofurilo, azabicilohexilo, dihidroindolilo, piridinilo, isoindol 1,3-diona, piperidinilo o piperazinilo.

El término "cicloalquilo", a menos que se especifique otra cosa, se refiere a grupos alquilo cíclicos de 3 a 20 átomos de carbono que tienen un único anillo o múltiples anillos condensados, los cuales opcionalmente pueden contener uno o más enlaces olefinicos, a menos que por definición se obligue otra cosa. Tales grupos cicloalquilo pueden incluir, por ejemplo, estructuras anillo único, incluyendo ciclopropilo, ciclobutilo, ciclooctilo, ciclopentenilo, y similares, o estructuras de múltiples anillos, incluyendo adamantilo y biciclo [2.2.1] heptano, o grupos alquilo cíclicos a los cuales se ha fusionado un grupo arilo, por ejemplo, indano, y similares. También se pueden incluir estructuras espiro y anillos fusionados.

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Además los grupos cicloalquilo pueden estar sustituidos con uno o más sustituyentes seleccionados de alquilo, alquenilo, alquinilo, alcoxi, cicloalquilo, cicloalquenilo, acilo, acilamino, aciloxi, alcoxicarbonilamino, azido, ciano, halógeno, hidroxilo, oxo, tiocarbonilo, carboxi, carboxialquilo, ariltio, tiol, alquiltio, arilo, aralquilo, ariloxi, aminosulfonilo, aminocarbonilamino, $-NR_fR_q$, $-NHC(=O)NR_fR_q$, $-NHC(=O)R_f$, $-C(=O)NR_fR_q$, $-O-C(=O)NR_fR_q$ (en donde R_f y R_q son los mismos que se definieron antes), nitro, heterociclilo, heteroarilo, heterociclilalquilo, heteroarilalquilo, o $-SO_2R_6$ (en donde R_6 es el mismo que se definió antes). A menos que por definición se obligue otra cosa, los sustituyentes cicloalquilo además pueden estar opcionalmente sustituidos por 1-3 sustituyentes seleccionados de alquilo, carboxi, hidroxilo, alcoxi, halógeno, CF_3 , $-NR_fR_q$, $-C(=O)NR_fR_q$, $-NHC(=O)NR_fR_q$, $-O-C(=O)NR_fR_q$ (en donde R_f y R_q son los mismos que se definieron antes), ciano o $-SO_2R_6$ (donde R_6 el mismo que se definió antes). "Cicloalquilalquilo" se refiere a un grupo alquilo-cicloalquilo unido a través de la porción alquilo, en donde el alquilo y el cicloalquilo son los mismos que se definieron antes.

El término "cicloalquilalquilo" se refiere un grupo cicloalquilo unido a través de la porción alquilo, en donde el alquilo tiene de 1 a 6 átomos de carbono y los cicloalquilos son los mismos que se definieron antes.

"Heteroarilalquilo" se refiere a un grupo alquil-heteroarilo unido a través de la porción alquilo, en donde el alquilo y el heteroarilo son como se definió antes.

"Heterociclilalquilo" se refiere a un grupo alquil-heterociclilo unido a través de la porción alquilo, en donde el alquilo y el heterociclilo son como se definió antes.

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“Amina”, a menos que se especifique otra cosa, se refiere a $-NH_2$. “Amino sustituido”, a menos que se especifique otra cosa, se refiere a un grupo $-N(R_k)_2$ en donde cada R_k se selecciona independientemente del grupo hidrógeno con la condición que ambos grupos R_k no sean hidrógenos (definidos como “amino”), alquilo, alquenilo, alquinilo, cicloalquilo, arilo, heteroarilo, heterociclilo, heterociclilalquilo, heteroarilalquilo, acilo, $S(O_m)R_6$ (en donde m y R_6 son los mismos definidos antes), $-C(=R_v)NR_xR_y$ (en donde R_v es O o S & R_x y R_y son los mismos definidos antes) o $-NHC(=R_v)NR_xR_y$ (en donde R_v , R_y y R_x son los mismos definidos antes). A menos que por definición se obligue otra cosa, todos los sustituyentes amino además pueden estar opcionalmente sustituidos por 1-3 sustituyentes escogidos de alquilo, aralquilo, cicloalquilo, arilo, heteroarilo, heterociclilo, carboxi, $-COOR$ (en donde R_7 es el mismo que se definió antes), hidroxilo, alcoxi, halógeno, CF_3 , ciano, $-C(=R_v)NR_xR_y$ (en donde R_v es el mismo que se definió antes), $-OC(C=O)NR_xR_y$, $-OC(=R_v)NR_xR_y$ (en donde R_x , R_y y R_v son los mismos definidos antes), $-S(O_m)R_6$ (en donde R_6 (en donde R_6 m son los mismos definidos antes).

“Acilo” se refiere a $-C(=O)R$ en donde R se selecciona de hidrógeno, alquilo, cicloalquilo, arilo, aralquilo, heteroarilo, heterociclilo, heteroarilalquilo o heterociclilalquilo.

El término “tioacilo” se refiere a $-C(=S)R_4$ en donde R_4 es el mismo que se definió antes.

“Tiocarbonilo” se refiere a $-C(=S)H$. “Tiocarbonilo sustituido” se refiere a $-C(=S)R$, en donde R se selecciona de alquilo, cicloalquilo, arilo, aralquilo, heteroarilo, heterociclilo, heteroarilalquilo o heterociclilalquilo, amina o amina sustituida.

El término “halógeno” se refiere a flúor, cloro, bromo o yodo.

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El término "Grupo saliente" se refiere a grupos que exhiben o exhiben potencialmente las propiedades de ser lábiles bajo las condiciones de síntesis y también, que se separan fácilmente de los productos sintéticos bajo condiciones
5 definidas. Ejemplos de grupos salientes incluyen, pero no se limitan a, halógeno (e.g., F, Cl, Br, I), triflatos, tosilatos, mesilatos alcoxi, tioalcoxi o radicales hidroxí y similares.

El término "Grupos protectores" se refiere a grupos que evitan la reacción química en un sitio de la molécula con el propósito que no sea afectado durante la
10 modificación química de tal molécula. A menos que se especifique otra cosa, los grupos protectores se pueden utilizar sobre grupos tales como, hidroxí, amino o carboxí. Ejemplos de grupos protectores se encuentran en T.W. Greene and P.G.M. Wuts, "Protective Groups in Organic Synthesis", 2ª Ed., John Wiley and Sons, New York, N.Y., el cual se incorpora aquí por referencia. Las especies de
15 los grupos carboxílico protectores, amino protectores o hidroxí protectores empleados no son críticas, mientras que las mitades/mitad derivadas sean estables a las condiciones de las reacciones subsiguientes y puedan ser removidas sin romper el resto de la molécula.

20 Los compuestos de esta invención pueden contener uno o más átomos de carbono asimétricos y por lo tanto se pueden presentar como mezclas racémicas, enantiómeros y diastereómeros. Estos compuestos también pueden existir como conformeros/rotámeros. Todas las formas isoméricas de éstos compuestos se incluyen en la presente invención. Cada carbono estereogénico puede estar en la
25 configuración *R* o *S*. Aunque los compuestos específicos ejemplificados en esta solicitud puedan estar representados en una configuración estereoquímica particular, los compuestos que tienen ya sea la estereoquímica opuesta en

cualquier centro quiral o mezclas de ellos estan previstos como parte de la invención.

El término "*sales aceptables farmacéuticamente*" que forma parte de esta invención incluye las sales de mitades ácido carboxílico, las cuales se pueden preparar por reacción del compuesto con bases apropiadas para proporcionar las sales por adición de base correspondientes. Ejemplos de tales bases son los hidróxidos de metales alcalinos, hidróxido de sodio e hidróxido de litio; hidroxidos de metales alcalino-térreos tales como hidróxido de magnesio e hidróxido de calcio. Además las sales de bases orgánicas tales como lisina, arginina, guanidina, etanolamina, collina y similares; también se incluyen bases inorgánicas e.g., sales de amonio o amonio sustituido. Donde quiera que sea apropiado, los compuestos de la presente invención también pueden formar sales por adición de ácido, por tratamiento de dichos compuestos con ácidos orgánicos e inorgánicos aceptables farmacéuticamente, e.g., haluros de hidrógeno tales como clorhídrico, bromhídrico, yodhídrico; otros ácidos minerales y sus correspondientes sales tales como sulfato, nitrato, fosfato, etc.; y alquil y mono-arilsulfonatos, tales como etano sulfonato, tolueno sulfonato y benceno sulfonato; y otros ácidos orgánicos y sus correspondientes sales tales como acetato, tartrato, maleato, succinato, citrato etc.

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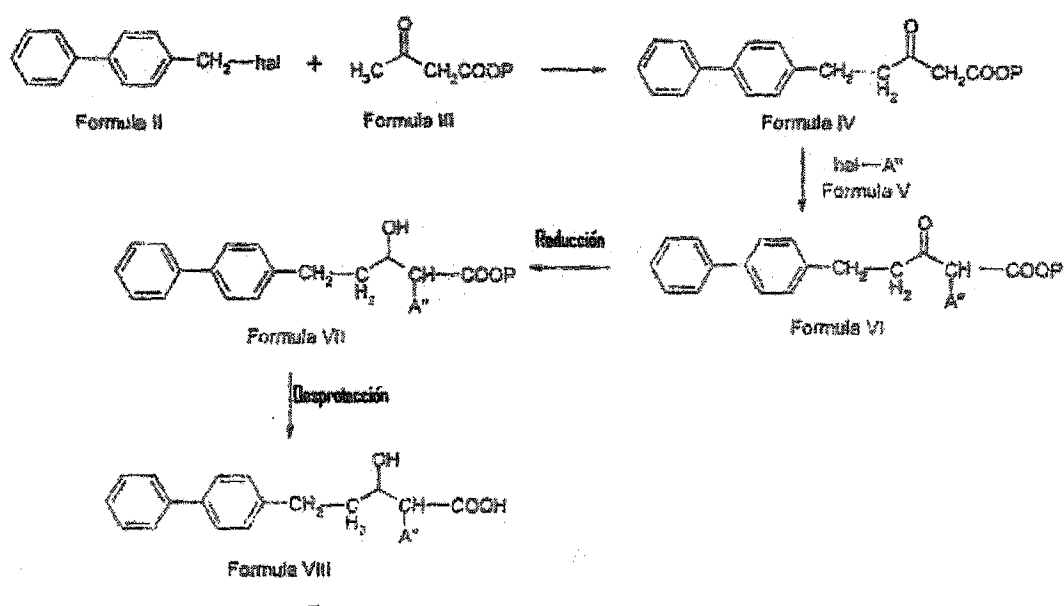
Descripción detallada de la invención

Los compuestos de la presente invención se pueden preparar por técnicas bien conocidas de la síntesis orgánica y son familiares para una persona versada en el arte de esta invención. Además, por el proceso descrito aquí se pueden preparar los compuestos de la presente invención, sin embargo no pueden ser, únicamente los medios por los cuales se puedan sintetizar los compuestos

descritos por otra parte las varias etapas sintéticas descritas aquí se pueden realizar en una secuencia alterna con el propósito de producir los compuestos deseados.

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Esquema I



Los compuestos de la Fórmula VIII se pueden preparar por ejemplo, siguiendo la ruta sintética como se describió en el esquema I. Así, un compuesto de fórmula II (donde hal es Cl, Br o I) puede reaccionar con un compuesto de Fórmula III [donde P es alquil (por ejemplo, terbutil, etil o metil) o araquil (o ejemplo, bencil)] para dar un compuesto de Fórmula IV, el cual por reacción con un compuesto de Fórmula V (donde hal es lo mismo definido anteriormente y "A" es araquil, heterocicloaquil, heteroaquil o cicloalquilalquil) puede formar un compuesto de Fórmula VI. Un compuesto de Fórmula VI por reducción puede formar un compuesto de Fórmula VII, el cual por desprotección puede producir un compuesto de Fórmula VIII.

La reacción de un compuesto de Fórmula II con un compuesto de Fórmula III para dar un compuesto de Fórmula IV se puede realizar en presencia de una

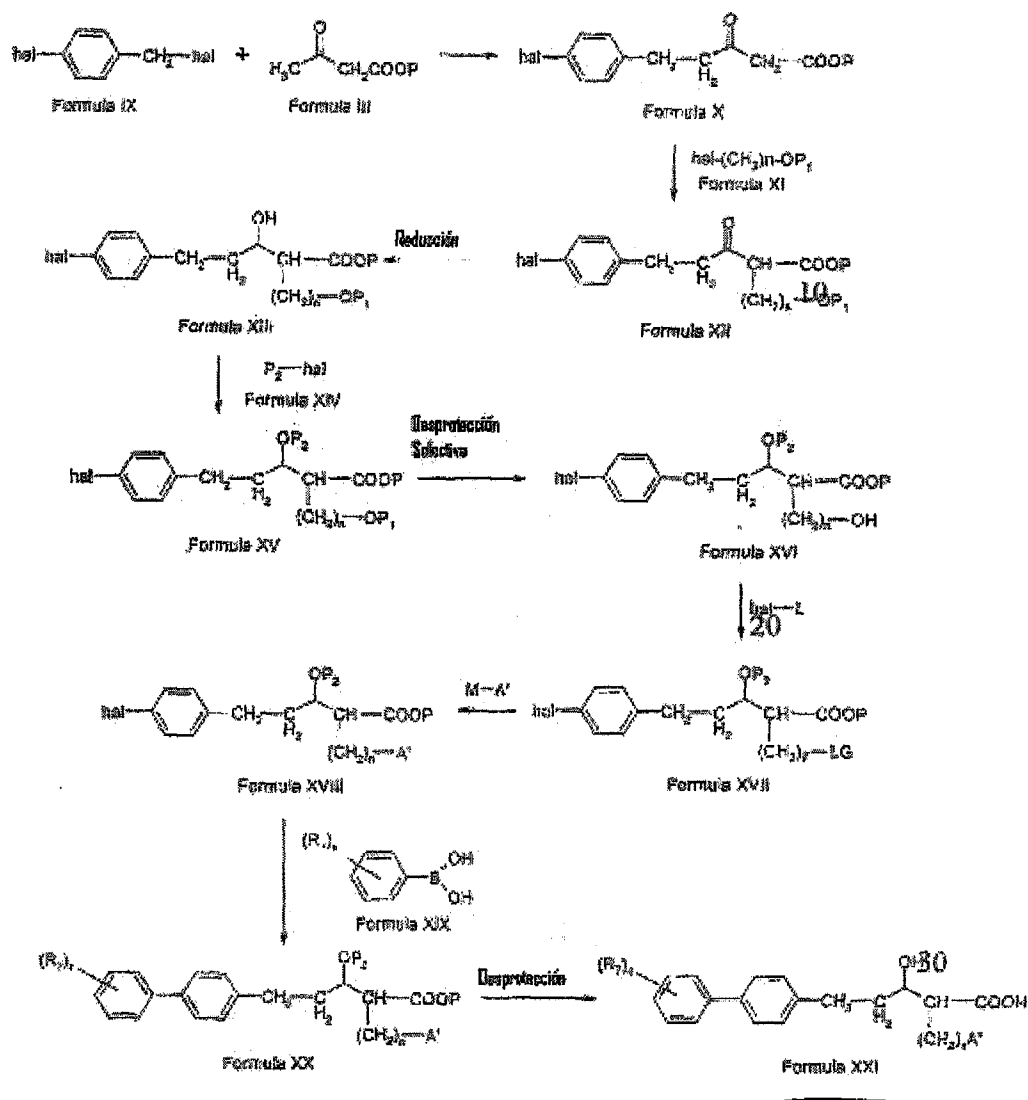
base o una combinación de ellas, por ejemplo, hidruro de sodio, butil litio o diisopropilamida de litio en un solvente orgánico, por ejemplo, tetrahidrofurano, dimetilformamida, dioxano o dietiléter.

- 5 La reacción de un compuesto de Fórmula IV con un compuesto de Fórmula V para dar un compuesto de Fórmula VI se puede realizar en la presencia de una base, por ejemplo, ter-butóxido de potasio, (m) etóxido de sodio, hidruro de sodio, diisopropilamida de litio, butil litio o hexametildisilazida de litio, sodio o potasio, opcionalmente en presencia de
- 10 un catalizador, por ejemplo, yoduro de tetrabutilamonio o bromuro de tetrabutilamonio, en un solvente t-butanol, etanol, tetrahidrofurano, dimetilformamida, dietiléter o dioxano.

- El compuesto de Fórmula VI por reducción para dar un compuesto de
- 15 Fórmula VII en presencia de un agente reductor, por ejemplo borohidruro de sodio o borohidruro de litio en un solvente orgánico, por ejemplo, metanol, etanol, propanol, isopropil alcohol y/o tetrahidrofurano.

- La hidrólisis de un compuesto de Fórmula VII para dar un compuesto de
- 20 Fórmula VIII, donde P es t-butil se puede realizar con ácidos, por ejemplo, ácido trifluoroacético o ácido clorhídrico, en un solvente orgánico o en un sistema solvente que incluya, por ejemplo, diclorometano, dicloroetano, THF o dioxano en agua.

Esquema II'



Un compuesto de Fórmula XXI se puede preparar, por ejemplo, siguiendo la ruta sintética como se describió, por ejemplo, en el esquema II. Así un compuesto de Fórmula IX (donde hal es el mismo definido antes) por reacción de un

5 compuesto de Fórmula III (donde P es el mismo definido antes) para dar un compuesto de Fórmula X que se puede hacer reaccionar con un compuesto de Fórmula XI (en donde hal y n son los mismos definidos antes y P_1 es grupo protector silil) por ejemplo, ter-butildimetil-silano, terbutildifenilsilano o triisopropilsilano para dar el compuesto de Fórmula XII, el cual puede por

10 reducción dar un compuesto de Fórmula XIII. El compuesto de Fórmula XIII por reacción con un compuesto de Fórmula XIV [donde P_2 es aralquil (por ejemplo, bencil, 4-metoxibencil o 2, 4, 6 - trimetoxibencil) o heterociclicil (por ejemplo, tetrahidropiramil)] puede formar un compuesto de Fórmula XV, el cual por

desprotección selectiva forma un compuesto de Fórmula XVI, que se pueda luego convertir a un compuesto de Fórmula XVII (donde LG es un grupo saliente tal como mesil, tosil o trifil o un haluro (hal) como se definió antes) por reacción o con un compuesto de Fórmula L-hal (donde L es metanosulfonil, p-toluensulfonil y hal, es lo mismo definido anteriormente), por reacción con anhídrido triflico o por reacción con trifenilfosfina y una fuente de haluro tal como tetrabromuro de carbono o yodo. Un compuesto de Fórmula XVII puede reaccionar con un compuesto de Fórmula M-A' (donde A' es aril, heteroaril, heterociclil o cicloalquil y M es un metal por ejemplo, potasio, litio o sodio) o por reacción de A' en presencia de una base para producir un compuesto de Fórmula XVIII. El compuesto de Fórmula XVIII puede reaccionar con un compuesto de Fórmula XIX (donde n es un entero desde 1 a 5 y R₇ es hidrógeno, halógeno (F, Cl, Br, I), hidroxil, -COOH, -COOR₄ (donde R₄ es el mismo definido antes), alquil, alquenil, alquinil, cicloalquil, alcoxi, alqueniloxi, alquiniloxi, ariloxi, heterocicliloxi, heteroariloxi, cicloalquiloxi, acil, tioacil, ciano, nitro, amino, -CHO, -OCF₃, -CF₃, -SCF₃, NR₄R₅, -C(=Y)NR₄R₅, -NHC(=Y)R₄, -NHC(=Y)NR₅R_x, -NHC(=O)OR₄, -NHSO₂R₄(SO)_mR₄ (donde R₄, R₅, R_x, Y y m son los mismos definidos antes) aril, heterociclil, heteroaril, heterociclilalquil, o heteroarilalquil los cuales pueden ser sustituidos opcionalmente además) para formar un compuesto de fórmula XX, el cual puede estar desprotegido para formar un compuesto de Fórmula XXI.

La reacción de un compuesto de Fórmula IX con un compuesto de Fórmula III para dar un compuesto de Fórmula X se puede realizar de manera similar a la reacción de un compuesto de Fórmula II y un compuesto de Fórmula III para producir un compuesto de Fórmula IV.

La reacción de un compuesto de Fórmula X con un compuesto de Fórmula XI para dar un compuesto de Fórmula XII se puede realizar de manera similar, a la reacción de un compuesto de Fórmula IV con un compuesto de Fórmula V para dar un compuesto de Fórmula VI.

La reducción de un compuesto de Fórmula XII para dar un compuesto de Fórmula XIII se puede realizar de manera similar a la reducción de un compuesto de Fórmula VI para dar un compuesto de Fórmula VII.

La reacción de un compuesto de Fórmula XIII con un compuesto de Fórmula XIV para dar un compuesto de Fórmula XV se puede realizar en presencia de un ácido de Lewis, por ejemplo trifluoruro de boro, ácido triflico, ácido alcanforsulfónico, piridinium p-toluensulfonato o trilit perclorato, en un solvente orgánico, por ejemplo tetrahidrofurano, dimetilformamida, dietiléter o dioxano.

La desprotección selectiva de un compuesto de Fórmula XV para dar un compuesto de Fórmula XVI se puede realizar con agentes desprotectores, por ejemplo, fluoruro de tetrabutilamonio o fluoruro de potasio, en un solvente orgánico, por ejemplo, tetrahidrofurano, dimetilformamida, dietiléter o dioxano.

Un compuesto de Fórmula XVI se puede hacer reaccionar con un compuesto de Fórmula L-hal, anhídrido triflico o por reacción con trifenilfosfina y una fuente de haluro tal como tetrabromuro de carbono, o yodo para dar un compuesto de Fórmula XVII, opcionalmente en presencia de una base, por ejemplo, trietilamina, piridina, N-metilmorfolina o diisopropiletilamina, en un solvente orgánico, por ejemplo diclorometano, dicloroetano, o tetrahidrofurano.

La reacción de un compuesto de Fórmula XVII con un compuesto de Fórmula M-A' para producir un compuesto de Fórmula XVIII se puede realizar en un solvente orgánico, por ejemplo, tetrahidrofurano, dimetilsulfóxido, dimetilformamida, acetonitrilo, dioxano, dimetilacetamida. Alternativamente, la

5 reacción de un compuesto de Fórmula XVII con un compuesto de Fórmula A' para producir un compuesto de Fórmula XVIII se puede realizar en presencia de una base, por ejemplo, hidruro de sodio, terbutóxido de potasio, (m) etóxido de sodio, en un solvente orgánico, por ejemplo, tetrahidrofurano, dimetilsulfóxido, dimetilformamida, acetonitrilo, dioxano, dimetilacetamida.

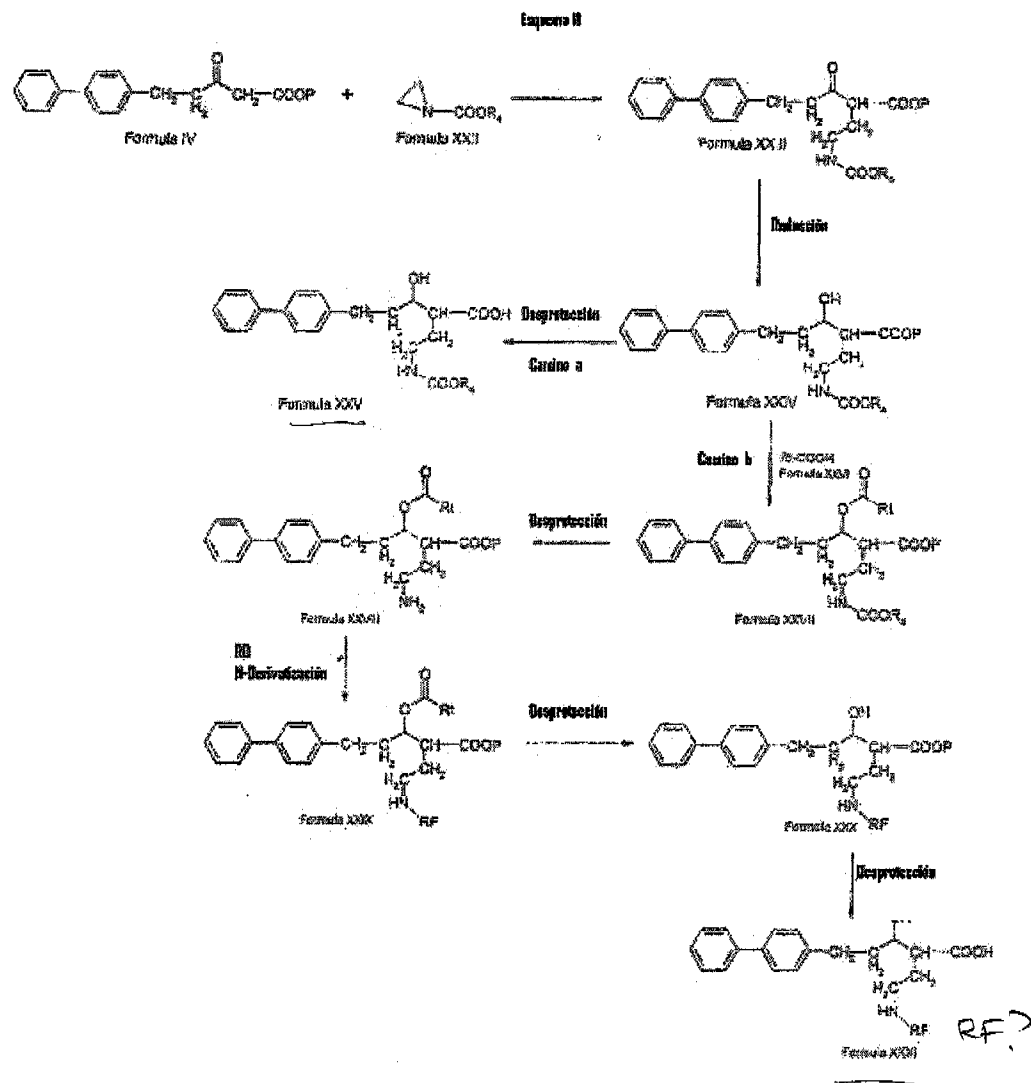
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La reacción de un compuesto de Fórmula XVIII con un compuesto de Fórmula XIX se puede realizar en presencia de un catalizador metálico, tal como tetrakis (trifenilfosfina) Paladio(0), tetrakis (triciclohexilfosfina) Paladio (0), tetrakis (tr – ter–butilfosfina) Paladio (0) o acetato de paladio y trifenilfosfina, en presencia

15 de una base, tal como carbonato de potasio o carbonato de cesio, en un solvente orgánico, tal como tolueno, dimetilsulfóxido, dimetilformamida, tetrahidrofurano, dioxano o dietiléter.

La desprotección de un compuesto de Fórmula XX para dar un compuesto

20 de Fórmula XXI se puede realizar de manera similar a la del compuesto de Fórmula VII para dar un compuesto de Fórmula VIII.



5

Un compuesto de Fórmula XXV y XXXI se puede preparar, por ejemplo, siguiendo la ruta sintética como se mostró, por ejemplo, en el esquema III. Entonces un compuesto de Fórmula IV (donde P es como se definió antes) puede reaccionar con un compuesto de Fórmula XXII (donde R₄ es el definido anteriormente) para dar un compuesto de Fórmula XXIII.

Ruta a: La cual por reducción puede dar un compuesto de Fórmula XXVI, el cual puede ser desprotegido posteriormente para producir un compuesto de Formula XXV, o

Ruta b: La cual por reacción con un compuesto de Fórmula XXVI (donde R_t es alquil, aril, cicloalquil, aralquil, heterocicloalquil o heteroarilalquil) da un

compuesto de Fórmula XXVII el cual con desprotección de un compuesto de Fórmula XXVIII, el cual por N-derivatización con un compuesto de Fórmula RD (donde RD es R_4COhal , $halCOOR_4$, R_4SO_2hal , o $(R_4)N=C(=Y)$ donde Y es O ó S) para dar un compuesto de Fórmula XXIX (donde RF es R_4CO- , R_4SO_2- , R_4OCO- ó $(R_4)NH-C(=y)$) el cual por desprotección puede dar un compuesto de Fórmula XXX, que puede mediante posterior desprotección dar un compuesto de Fórmula XXXI.

La reacción de un compuesto de Fórmula IV con un compuesto de Fórmula XXII para dar un compuesto de Fórmula XXIII se puede realizar en presencia de una base, por ejemplo, terbutóxido de potasio, hidruro de sodio, (m) etóxido de sodio, diisopropilamida de litio, y/o butillitio, en un solvente orgánico, por ejemplo, tetrahidrofurano, dimetilformamida, dietiléter o dioxano.

La reducción de un compuesto de Fórmula XXIII para dar un compuesto de Fórmula XXIV se puede realizar de manera similar a la reducción de un compuesto de Fórmula VI para dar un compuesto de Fórmula VII.

La desprotección de un compuesto de Fórmula XXIV (ruta a) para dar un compuesto de Fórmula XXV se puede realizar de manera similar como la del compuesto de Fórmula VII para dar un compuesto de Fórmula VIII.

La reacción de un compuesto de Fórmula XXIV (ruta b) con un compuesto de Fórmula XXVI para dar un compuesto de Fórmula XXVII se puede realizar usando agentes de copulación, tales como EDCI o DCC, en presencia de una base, tal como dimetilaminopiridina, N-metilmorfolina, o diisopropiletilamina, en una solvente orgánico, tal como diclorometano, dicloroetano, cloroformo y tetracloruro de carbono.

La desprotección de un compuesto de Fórmula XXVII para dar un compuesto de Fórmula XXVIII se puede realizar en presencia de un agente desprotector, por ejemplo, paladio o carbón en presencia de hidrógeno gaseoso, o
5 paladio sobre carbón con una fuente de hidrógeno gaseoso, por ejemplo, formiato de amonio, ciclohexeno o ácido fórmico.

La N-derivatización de un compuesto de Fórmula XXVIII con un compuesto de Fórmula RD (donde RD es R_4COhal o $halCOOR_4$) para dar un compuesto de
10 Fórmula XXIX (donde RF es R_4CO- , R_4OCO-) se puede realizar en presencia de una base, por ejemplo, piridina, N-metil-morfolina, N-etildiisopropilamina, trietilamina, o carbonato de potasio.

La N-derivatización de un compuesto de Fórmula XXVIII con un compuesto
15 de Fórmula RD (donde RD es R_4SO_2hal) para dar un compuesto de Fórmula XXIX (donde RF es R_4SO_2) se puede realizar en presencia de una base, por ejemplo, trietilamina, N-etildiisopropilamina, N-metilmorfolina o piridina, en un solvente orgánico, por ejemplo diclorometano, dicloroetano, tetracloruro de carbono o cloroformo.

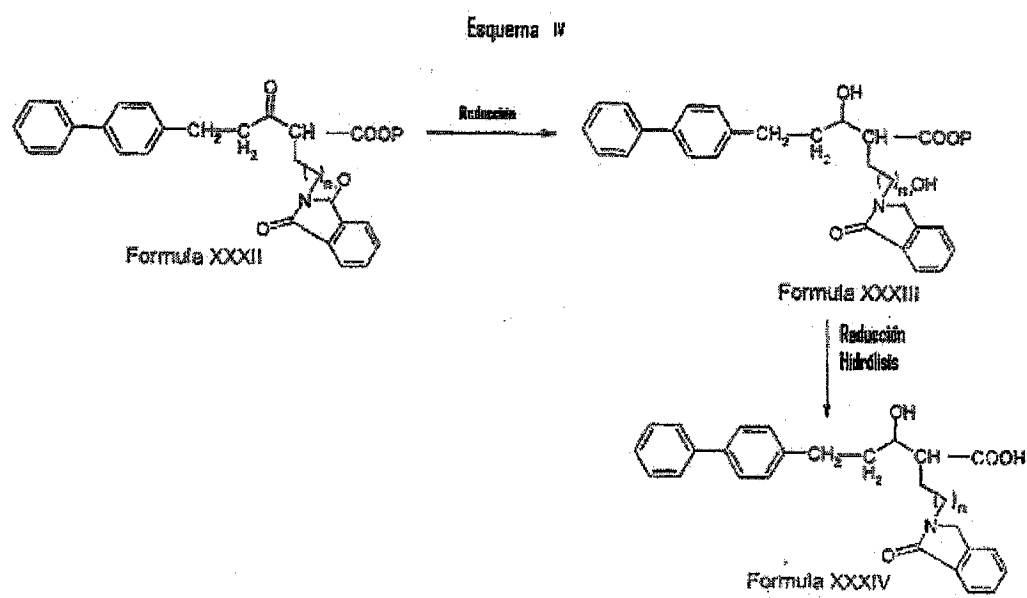
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La N-derivatización de un compuesto de Fórmula XXVIII con un compuesto de Fórmula RD (donde RD es $(R_4)N=C(=Y)$) para dar un compuesto de Fórmula
XXIX (donde RF es $(R_4)NH-C(=Y)$) se puede realizar opcionalmente en presencia de una base, por ejemplo trietilamina, N-etildiisopropilamina, N-dimetilmorfolina o
25 piridina, en un solvente orgánico por ejemplo, diclorometano, dicloroetano, tetracloruro de carbono o cloroformo.

La desprotección del grupo protector del del hidroxilo secundario tal como el grupo acilo, de un compuesto de Fórmula XXIX para dar un compuesto de Fórmula XXX se puede realizar en presencia de una base, por ejemplo, hidróxido de litio, hidróxido de potasio, en un solvente orgánico, por ejemplo, metanol, tetrahidrofurano, agua o mezclas de ellos.

La desprotección de un compuesto de Fórmula XXX para dar un compuesto de Fórmula XXXI se puede realizar con ácidos, por ejemplo, ácido trifluoroacético o ácido clorhídrico en un solvente orgánico o un sistema de solventes, por ejemplo, diclorometano, cloroformo, dicloroetano, THF o dioxano en agua.

Esquema IV



Los compuestos de Fórmula XXXIV se pueden preparar por ejemplo, siguiendo la ruta sintética como se describió en el esquema IV. Por el tanto un compuesto de Fórmula XXXII por reducción pueden dar un compuesto de Fórmula XXXIII, el cual puede por hidrogenación iónica donde $C=O$ se reduce a CH_2 seguida por hidrólisis para dar un compuesto de Fórmula XXXIV.

El compuesto de Fórmula XXXII puede bajo reducción dar un compuesto de fórmula XXXIII en presencia de un agente reductor, por ejemplo, borohidruro de sodio o borohidruro de litio en un solvente orgánico, por ejemplo, metanol, etanol, propanol, isopropilalcohol y/o tetrahidrofurano.

5

La conversión de un compuesto de Fórmula XXXIII a un compuesto de Fórmula XXXIV se puede realizar por condiciones de hidrogenación iónica donde $C=O$ se reduce a CH_2 , seguida por una hidrólisis in situ de éster (donde P es t-butil). Las condiciones de hidrogenación iónica que se puedan realizar incluyen la

10 reacción de un compuesto de Fórmula XXXIII con borohidruro o trietilsilano con ácidos, por ejemplo, ácido trifluoroacético en un solvente orgánico, por ejemplo, diclorometano, dicloroetano o THF, y in situ el grupo t-butil sensible al ácido se puede remover para proveer un compuesto de Fórmula XXXIV

15 Los siguientes compuestos ilustrativos se prepararon siguiendo los esquemas I, II, III o IV como se describió anteriormente:

Ácido 5-Bifenil-4-il-3-hidroxi-2-[2-(4-oxo-1,2,3-benzotriazin-3(4H)-il)etil]pentanóico (Compuesto No. 1),

Ácido 5-(4'-ter-Butilbifenil-4-il)-2-[2-(1,3-dioxo-1,3-dihidro-2H-isoindol-2-il)etil]-3-
20 hidroxipentanóico (Compuesto No. 2),

Ácido 5-(4'-Butilbifenil-4-il)-2-[2-(1,3-dioxo-1,3-dihidro-2H-isoindol-2-il)etil]-3-
hidroxipentanóico (Compuesto No. 3),

Ácido 5-(4'-Clorobifenil-4-il)-2-[2-(1,3-dioxo-1,3-dihidro-2H-isoindol-2-il)etil]-3-
hidroxipentanóico (Compuesto No. 4),

25 Ácido 2-[2-(1,3-Dioxo-1,3-dihidro-2H-isoindol-2-il)etil]-3hidroxi-5-(4'-trifluorometoxibefinil-4-il)pentanóico (Compuesto No.5),

Ácido 2-[2-(1,3-Dioxo-1,3-dihidro-2*H*-isoindol-2-il)etil]-5-(4'-etoxibifenil-4-il)-3-hidroxicipentanóico (Compuesto No. 6),

Ácido 2-[2-(1,3-Dioxo-1,3-dihidro-2*H*-isoindol-2-il)etil]-5-(4'-formilbifenil-4-il)-3-hidroxicipentanóico (Compuesto No. 7),

5 Ácido 2-[2-(1,3-Dioxo-1,3-dihidro-2*H*-isoindol-2-il)etil]-3-hidroxi-5-(2',4',6'-trimetoxibifenil-4-il)pentanóico (Compuesto No. 8),

Ácido 2-[2-(1,3-Dioxo-1,3-dihidro-2*H*-isoindol-2-il)etil]-3-hidroxi-5-(4'-propoxibifenil-4-il)pentanóico (Compuesto No. 9),

10 Ácido 5-(3',4'-Difluorobifenil-4-il)-2-[2-(1,3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)etil]-3-hidroxicipentanóico (Compuesto No. 10),

Ácido 2-(2-[[Benciloxi]carbonil]amino)etil)-5-bifenil-4-il-3-hidroxicipentanóico (Compuesto No. 11).

Ácido 5-Bifenil-4-il-2-[2-(1,3-dihidro-2*H*-isoindol-2-il)etil]-3-hidroxicipentanóico (Compuesto No. 12)

15 Ácido 2-[2-(1,3-Dioxo-1,3-dihidro-2*H*-isoindol-2-il)etil]-3-hidroxi-5-(4'-metoxibifenil-4-il)pentanóico (Compuesto. 23),

Ácido 5-(2',3'-Dimetilbifenil-4-il)-2-[2-(1,3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)etil]-3-hidroxicipentanóico (Compuesto No. 24),

20 Ácido 2-[2-(1,3-Dioxo-1,3-dihidro-2*H*-isoindol-2-il)etil]-3-hidroxi-5-[3'-(trifluorometil)bifenil-4-il]pentanóico (Compuesto No. 25),

Ácido 2-[2-(1,3-Dioxo-1,3-dihidro-2*H*-isoindol-2-il)etil]-5-(4'-etilbifenil-4-il)-3-hidroxicipentanóico (Compuesto No. 26),

Ácido 5-(3',5'-Diclorobifenil-4-il)-2-[2-(1,3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)etil]-3-hidroxicipentanóico (Compuesto No. 27),

Ácido 5-[4'-Cloro-3'-(trifluorometil)bifenil-4-il]-2-[2-(1,3-dioxo-1,3-dihidro-2H-isoindol-2-il)etil]-3-hidroxipentanóico (Compuesto No. 28),

Ácido 5-(2',5'-Difluorobifenil-4-il)-2-[2-(1,3-dioxo-1,3-dihidro-2H-isoindol-2-il)etil]-3-hidroxipentanóico (Compuesto No. 29),

5 Ácido 2-[2-(1,3-Dioxo-1,3-dihidro-2H-isoindol-2-il)etil]-3-hidroxi-5-[2'-(trifluorometoxi)bifenil-4-il]pentanóico (Compuesto No. 30),

Ácido 2-[2-(1,3-Dioxo-1,3-dihidro-2H-isoindol-2-il)etil]-3-hidroxi-5-[4'-(metiltio)bifenil-4-il]pentanóico (Compuesto No. 31),

10 Ácido 2-[2-(1,3-Dioxo-1,3-dihidro-2H-isoindol-2-il)etil]-5-(4'-fluoro-3'-metilbifenil-4-il)-3-hidroxipentanóico (Compuesto No. 32),

Ácido 2-[2-(1,3-Dioxo-1,3-dihidro-2H-isoindol-2-il)etil]-3-hidroxi-5-(3'-isopropilbifenil-4-il)pentanóico (Compuesto No. 33),

Ácido 5-(3',4'-Dimetilbifenil-4-il)-2-[2-(1,3-dioxo-1,3-dihidro-2H-isoindol-2-il)etil]-3-hidroxipentanóico (Compuesto No. 34),

15 Ácido 5-(2',6'-Difluorobifenil-4-il)-2-[2-(1,3-dioxo-1,3-dihidro-2H-isoindol-2-il)etil]-3-hidroxipentanóico (Compuesto No. 35),

Ácido 2-[2-(1,3-Dioxo-1,3-dihidro-2H-isoindol-2-il)etil]-5-(4'-fluorobifenil-4-il)-3-hidroxipentanóico (Compuesto No. 36),

20 Ácido 5-(3',5'-Difluorobifenil-4-il)-2-[2-(1,3-dioxo-1,3-dihidro-2H-isoindol-2-il)etil]-3-hidroxipentanóico (Compuesto No. 37),

Ácido 5-(3'-Cloro-4'-fluorobifenil-4-il)-2-[2-(1,3-dioxo-1,3-dihidro-2H-isoindol-2-il)etil]-3-hidroxipentanóico (Compuesto No. 38),

Ácido 5-(3',4'-Dimetoxibifenil-4-il)-2-[2-(1,3-dioxo-1,3-dihidro-2H-isoindol-2-il)etil]-3-hidroxipentanóico (Compuesto No. 39),

Ácido 5-(3'-Clorobifenil-4-il)-2-[2-(1,3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)etil]-3-hidroxipentanóico (Compuesto No. 40),

Ácido 2-[2-(1,3-Dioxo-1,3-dihidro-2*H*-isoindol-2-il)etil]-3-hidroxi-5-(3'-metilbifenil-4-il)pentanóico (Compuesto No. 41),

5 Ácido 5-(2',3'-Difluorobifenil-4-il)-2-[2-(1,3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)etil]-3-hidroxipentanóico (Compuesto No. 42),

Ácido 2-[2-(1,3-Dioxo-1,3-dihidro-2*H*-isoindol-2-il)etil]-5-(2'-fluoro-3'-metoxibifenil-4-il)-3-hidroxipentanóico (Compuesto No. 43),

10 Ácido 2-[2-(1,3-Dioxo-1,3-dihidro-2*H*-isoindol-2-il)etil]-5-(3'-fluoro-4'-metilbifenil-4-il)-3-hidroxipentanóico (Compuesto No. 44),

Ácido 5-Bifenil-4-il-3-hidroxi-2-{2-[(fenilacetil)amino]etil}pentanóico (Compuesto No. 45),

Ácido 2-(3-Bifenil-4-il-1-hidroxipropil)-6-(1,3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)hexanóico (Compuesto No. 46),

15 Ácido 5-Bifenil-4-il-3-hidroxi-2-[2-(1-oxoftalazin-2(1*H*)-il)etil]pentanóico (Compuesto No. 47),

Ácido 5-Bifenil-4-il-2-[3-(1,3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)propil]-3-hidroxipentanóico (Compuesto No. 48),

20 Ácido 5-Bifenil-4-il-3-hidroxi-2-[2-(2'-oxospiro[ciclopropan-1,3'-indol]-1'(2'*H*)-il)etil]pentanóico (Compuesto No. 49),

Ácido 2-[2-(1,3-Dioxo-1,3-dihidro-2*H*-isoindol-2-il)etil]-3-hidroxi-5-(4'-hidroxibifenil-4-il)pentanóico (Compuesto No. 50),

Ácido 3-Hidroxi-5-(4'-metoxibifenil-4-il)-2-[2-(3-metil-2,6-dioxo-3,6-dihidropirimidin-1(2*H*)-il)etil]pentanóico (Compuesto No. 51),

Ácido 5-(4'-Clorobifenil-4-il)-3-hidroxi-2-[2-(3-metil-2,6-dioxo-3,6-dihidropirimidin-1(2H)-il)etil]pentanóico (Compuesto No. 52),

Ácido 5-(4'-Fluorobifenil-4-il)-3-hidroxi-2-[2-(3-metil-2,6-dioxo-3,6-dihidropirimidin-1(2H)-il)etil]pentanóico (Compuesto No. 53),

5 Ácido 5-[4-(5-Cloro-2-tienil)fenil]-2-[2-(1,3-dioxo-1,3-dihidro-2H-isoindol-2-il)etil]-3-hidroxipentanóico (Compuesto No. 54),

Ácido 4'-[4-Carboxi-6-(1,3-dioxo-1,3-dihidro-2H-isoindol-2-il)-3-hidroxi]hexil]bifenil-4-carboxílico (Compuesto No. 55),

10 Ácido 2-[2-(1,3-Dioxo-1,3-dihidro-2H-isoindol-2-il)etil]-3-hidroxi-5-[4'-(metoxycarbonil)bifenil-4-il]pentanóico (Compuesto No. 56),

Ácido 2-[2-(1,3-Dioxo-1,3-dihidro-2H-isoindol-2-il)etil]-3-hidroxi-5-[4'-(trifluorometil)bifenil-4-il]pentanóico (Compuesto No. 57),

Ácido 2-[2-(1,3-Dioxo-1,3-dihidro-2H-isoindol-2-il)etil]-3-hidroxi-5-[4-(6-metoxipiridin-3-il)fenil]pentanóico (Compuesto No. 58),

15 Ácido 3-Hidroxi-2-[2-(4-oxo-1,2,3-benzotriazin-3(4H)-il)etil]-5-[4'-(trifluorometil)bifenil-4-il]pentanóico (Compuesto No. 59),

Ácido 5-(3',4'-Difluorobifenil-4-il)-3-hidroxi-2-[2-(4-oxo-1,2,3-benzotriazin-3(4H)-il)etil]pentanóico (Compuesto No. 60),

20 Ácido 2-[2-(1,3-Dioxo-1,3-dihidro-2H-isoindol-2-il)etil]-5-(3'-fluorobifenil-4-il)-3-hidroxipentanóico (Compuesto No. 61),

Ácido 5-[4'-(Benciloxi)-3'-fluorobifenil-4-il]-2-[2-(1,3-dioxo-1,3-dihidro-2H-isoindol-2-il)etil]-3-hidroxipentanóico (Compuesto No. 62),

Ácido 5-[4'-(Benciloxi)bifenil-4-il]-2-[2-(1,3-dioxo-1,3-dihidro-2H-isoindol-2-il)etil]-3-hidroxipentanóico (Compuesto No. 63),

Ácido 3-Hidroxi-5-(4'-metoxibifenil-4-il)-2-[2-(4-oxo-1,2,3-benzotriazin-3(4H)-il)etil]pentanóico (Compuesto No. 64),

Ácido 5-(4'-Clorobifenil-4-il)-3-hidroxi-2-[2-(4-oxo-1,2,3-benzotriazin-3(4H)-il)etil]pentanóico (Compuesto No. 65),

5 Ácido 2-[2-(1,3-Dioxo-1,3-dihidro-2H-isoindol-2-il)etil]-3-hidroxi-5-(4'-metilbifenil-4-il)pentanóico (Compuesto No. 66),

Ácido 3-Hidroxi-5-[4-(6-metoxipiridin-3-il)fenil]-2-[2-(4-oxo-1,2,3-benzotriazin-3(4H)-il)etil]pentanóico (Compuesto No. 67),

10 Ácido 3-Hidroxi-5-(4'-metilbifenil-4-il)-2-[2-(5-metil-1,3-dioxo-1,3-dihidro-2H-isoindol-2-il)etil]pentanóico (Compuesto No. 68),

Ácido 5-(4'-Clorobifenil-4-il)-3-hidroxi-2-[2-(5-metil-1,3-dioxo-1,3-dihidro-2H-isoindol-2-il)etil]pentanóico (Compuesto No. 69),

Ácido 3-Hidroxi-2-[2-(4-oxo-1,2,3-benzotriazin-3(4H)-il)etil]-5-[4'-(trifluorometoxi)bifenil-4-il]pentanóico (Compuesto No. 70),

15 Ácido 5-(4'-Fluorobifenil-4-il)-3-hidroxi-2-[2-(4-oxo-1,2,3-benzotriazin-3(4H)-il)etil]pentanóico (Compuesto No. 71),

Ácido 3-hidroxi-5-(4'-metilbifenil-4-il)-2-[2-(4-oxo-1,2,3-benzotriazin-3(4H)-il)etil]pentanóico (Compuesto No. 72),

20 Ácido 5-(4'-Cianobifenil-4-il)-3-hidroxi-2-[2-(4-oxo-1,2,3-benzotriazin-3(4H)-il)etil]pentanóico (Compuesto No. 73),

Ácido 5-(4'-Fluorobifenil-4-il)-3-hidroxi-2-[2-(5-metil-1,3-dioxo-1,3-dihidro-2H-isoindol-2-il)etil]pentanóico (Compuesto No. 74),

Ácido 3-Hidroxi-5-[4-(6-metoxipiridin-3-il)fenil]-2-[2-(5-metil-1,3-dioxo-1,3-dihidro-2H-isoindol-2-il)etil]pentanóico (Compuesto No. 75),

DIVISIÓN DE NUEVAS CREACIONES

RADICACIÓN EXPEDIENTE No. 07-98104

EL EXTRACTO DE LA PRESENTE SOLICITUD DE **PATENTE DE INVENCION**

FUE PUBLICADO EN LA GACETA DE PROPIEDAD INDUSTRIAL No **591** DE

FECHA **30 DE ABRIL DE 2008** EL TÉRMINO HÁBIL SEÑALADO POR LA LEY

EXPIRA EL **30 DE JULIO DE 2008**

NOTA: Dentro del plazo de los seis (6) meses siguientes a partir de la fecha de publicación en la gaceta de Propiedad Industrial, deberá solicitar y cancelar el examen de patentabilidad so pena de que la solicitud caiga en abandono, de acuerdo con lo establecido en el Artículo 44 de la Decisión 486/2000.

SE PRESENTARON OPOSICIONES POR PARTE DE TERCEROS.

SI _____

NO X

Ácido 5-(4'-Etilbifenil-4-il)-3-hidroxi-2-[2-(4-oxo-1,2,3-benzotriazin-3(4H)-il)etil]pentanóico (Compuesto No. 76),

Ácido 3-Hidroxi-2-[2-(5-metil-1,3-dioxo-1,3-dihidro-2H-isoindol-2-il)etil]-5-[4'-(trifluorometil)bifenil-4-il]pentanóico (Compuesto No. 77),

5 Ácido 5-Bifenil-4-il-3-hidroxi-2-[2-(1-oxo-4-fenil-4a,8a-dihidroftalazin-2(1H)-il)etil]pentanóico (Compuesto No. 84),

Ácido 5-Bifenil-4-il-3-hidroxi-2-[2-(3-oxo-2,3-dihidro-4H-1,4-benzoxazin-4-il)etil]pentanóico (Compuesto No. 85),

10 Ácido 5-Bifenil-4-il-2-{2-[(3aR,7aS)-1,3-dioxo-1,3,3a,4,7,7a-hexahidro-2H-isoindol-2-il]etil}-3-hidroxipentanóico (Compuesto No. 86),

Ácido 5-Bifenil-4-il-2-(2-[[4-fluorofenil)sulfonyl]amino]etil)-3-hidroxipentanóico (Compuesto No. 87),

Ácido 5-Bifenil-4-il-2-(2-[[3-fluorofenil]cetil]amino)etil)-3-hidroxipentanóico (Compuesto No. 88),

15 Ácido 5-Bifenil-4-il-2-{2-[(4-fluorobenzoyl)amino]etil}-3-hidroxipentanóico (Compuesto No. 89),

Ácido 5-Bifenil-4-il-3-hidroxi-2-[2-(5-metil-1,3-dioxo-1,3-dihidro-2H-isoindol-2-il)etil]pentanóico (Compuesto No. 90),

20 Ácido 5-Bifenil-4-il-3-hidroxi-2-[2-(1-oxo-1,3-dihidro-2H-isoindol-2-il)etil]pentanóico (Compuesto No. 91).

Ácido 5-Bifenil-4-il-2-[2-([4-fluorofenil]amino)carbonil]amino)etil]-3-hidroxipentanóico (Compuesto No. 92),

Ácido 5-Bifenil-4-il-2-[2-(4,4-dimetil-2,6-dioxopiperidin-1-il)etil]-3-hidroxipentanóico (Compuesto No. 93),

Ácido 5-Bifenil-4-il-2-[2-(7,9-dioxo-8-azaspiro[4.5]dec-8-il)etil]-3-hidroxipentanóico
(Compuesto No. 94),

Ácido 2-(3-Bifenil-4-il-1-hidroxipropil)pent-4-inoico (Compuesto No. 95);

Ácido 5-Bifenil-4-il-3-hidroxi-2-[2-(2-oxo-1,3-benzoxazol-3(2H)-il)etil]pentanóico
(Compuesto No. 96)

Ácido 2-[2-(5-*ter*-Butil-1,3-dioxo-1,3-dihidro-2H-isoindol-2-il)etil]-3-hidroxi-5-[4-(6-
metoxipiridin-3-il)fenil]pentanóico (Compuesto No. 97),

Ácido 5-{4-[6-(Dimetilamino)piridin-3-il]fenil}-2-[2-(1,3-dioxo-1,3-dihidro-2H-
isoindol-2-il)etil]-3-hidroxipentanóico (Compuesto No. 98),

Ácido 2-[2-(1,3-Dioxo-1,3-dihidro-2H-isoindol-2-il)etil]-3-hidroxi-5-[4'-
(metilsulfonil)bifenil-4-il]pentanóico (Compuesto No. 99),

Ácido 5-[4'-(Aminocarbonil)bifenil-4-il]-2-[2-(1,3-dioxo-1,3-dihidro-2H-isoindol-2-
il)etil]-3-hidroxipentanóico (Compuesto No. 100),

Ácido 5-[4-(1-Bencil-1H-pirazol-4-il)fenil]-2-[2-(1,3-dioxo-1,3-dihidro-2H-isoindol-2-
il)etil]-3-hidroxipentanóico (Compuesto No. 101),

Ácido 5-Bifenil-4-il-2-[2-(5,6-dicloro-1,3-dioxo-1,3-dihidro-2H-isoindol-2-il)etil]-3-
hidroxipentanóico (Compuesto No. 102),

Ácido 5-Bifenil-4-il-2-[2-(2,4-dioxo-1,4-dihidroquinazolin-3(2H)-il)etil]-3-
hidroxipentanóico (Compuesto No. 103),

Ácido 5-Bifenil-4-il-2-[2-(1,3-dioxo-1,3-dihidro-2H-pirrol[3,4-c]piridin-2-il)etil]-3-
hidroxipentanóico (Compuesto No. 104),

Ácido 2-[2-(5-*ter*-Butil-1,3-dioxo-1,3-dihidro-2H-isoindol-2-il)etil]-5-(3',4'-
difluorobifenil-4-il)-3-hidroxipentanóico (Compuesto No. 105),

Ácido 2-[2-(1,3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)etil]-3-hidroxi-5-(4-pirimidin-5-ilfenil)pentanóico (Compuesto No 119),

Ácido 5-Bifenil-4-il-3-hidroxi-2-[2-(7-metil-4-oxo-1,2,3-benzotriazin-3(4*H*)-il)etil]pentanóico (Compuesto No. 120),

5 Ácido 5-Bifenil-4-il-2-[2-(5-*ter*-Butil-1,3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)etil]-3-hidroxipentanóico (Compuesto No. 121),

Ácido 5-Bifenil-4-il-3-hidroxi-2-[2-(1-oxo-1,3-dihidro-2*H*-isoindol-2-il)butil]pentanóico (Compuesto No. 124),

10 En los esquemas anteriores cuando se mencionan bases, ácidos, solventes, agentes de condensación, agentes reductores, agentes desprotectores, agentes hidrolizantes, catalizadores metálicos, etc., se debe entender que también se pueden utilizar otros ácidos, bases, solventes, agentes de condensación, agentes reductores, agentes desprotectores, agentes hidrolizantes, catalizadores
15 metálicos, etc., conocidos por aquellos versados en el arte. Similarmente, la temperatura de reacción y la duración de las reacciones se pueden ajustar de acuerdo con los requerimientos que se presenten durante el proceso.

Los compuestos preparados mediante los esquemas anteriores I a IV
20 pueden contener uno o más átomos de carbono asimétricos y se separan en los pares de diasterómeros o en diaterómeros únicos por cromatografía preparativa en capa delgada y /o HPLC, utilizando una columna aquiral o quiral según se requiera.

Los siguientes compuestos ilustrativos se separan en pares de diaterómeros o en diastéromeros únicos:

Ácido (2*R*,3*S* + 2*S*,3*R*)-2-[2-(1,3-Dioxo-1,3-dihidro-2*H*-isoindol-2-il)etil]-5-(4'-formilbifenil-4-il)-3-hidroxipentanóico (Compuesto No. 13),

- 5 Ácido (2*R*,3*R* + 2*S*,3*S*)-2-[2-(1,3-Dioxo-1,3-dihidro-2*H*-isoindol-2-il)etil]-5-(4'-formilbifenil-4-il)-3-hidroxipentanóico (Compuesto No. 14),

Ácido (2*R*,3*R* + 2*S*,3*S*)-2-[2-(1,3-Dioxo-1,3-dihidro-2*H*-isoindol-2-il)etil]-3-hidroxi-5-(2',4',6'-trimetoxibifenil-4-il)pentanóico (Compuesto No.15),

- 10 Ácido (2*R*,3*S* + 2*S*,3*R*)-2-[2-(1,3-Dioxo-1,3-dihidro-2*H*-isoindol-2-il)etil]-3-hidroxi-5-(2',4',6'-trimetoxibifenil-4-il)pentanóico (Compuesto No. 16),

Ácido (2*R*,3*S* + 2*S*,3*R*)-5-(4'-Acetilbifenil-4-il)-2-[2-(1,3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)etil]-3-hidroxipentanóico (Compuesto No. 17),

Ácido (2*R*,3*R* + 2*S*,3*S*)-5-(4'-Acetilbifenil-4-il)-2-[2-(1,3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)etil]-3-hidroxipentanóico (Compuesto No. 18),

- 15 Ácido (2*R*,3*S* + 2*S*,3*R*)-2-[2-(1,3-Dioxo-1,3-dihidro-2*H*-isoindol-2-il)etil]-3-hidroxi-5-(4'-propoxibifenil-4-il)pentanóico (Compuesto No. 19),

Ácido (2*R*,3*R* + 2*S*,3*S*)-2-[2-(1,3-Dioxo-1,3-dihidro-2*H*-isoindol-2-il)etil]-3-hidroxi-5-(4'-propoxibifenil-4-il)pentanóico (Compuesto No. 20),

- 20 Ácido (2*R*,3*S* + 2*S*,3*R*)-5-(3',4'-Difluorobifenil-4-il)-2-[2-(1,3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)etil]-3-hidroxipentanóico (Compuesto No. 21),

Ácido (2*R*,3*R* + 2*S*,3*S*)-5-(3',4'-Difluorobifenil-4-il)-2-[2-(1,3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)etil]-3-hidroxipentanóico (Compuesto No. 22),

Ácido (2*R*,3*S* + 2*S*,3*R*)-2-[2-(1,3-Dioxo-1,3-dihidro-2*H*-isoindol-2-il)etil]-3-hidroxi-5-[4-(6-metoxipiridin-3-il)fenil]pentanóico (Compuesto No. 78),

Ácido (2*R*,3*R* + 2*S*,3*S*)-2-[2-(1,3-Dioxo-1,3-dihidro-2*H*-isoindol-2-il)etil]-3-hidroxi-5-[4-(6-metoxipiridin-3-il)fenil]pentanóico (Compuesto No. 79),

Ácido 5-Bifenil-4-il-3-hidroxi-2-[2-(1-oxo-1,3-dihidro-2*H*-isoindol-2-il)butil]pentanóico (Compuesto No. 124),

5 Ácido (2*R*,3*S* + 2*S*,3*R*)-5-(4'-Clorobifenil-4-il)-2-[2-(1,3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)etil]-3-hidroxipentanóico (Compuesto No. 81),

Ácido (2*R*,3*S* + 2*S*,3*R*)-2-[2-(1,3-Dioxo-1,3-dihidro-2*H*-isoindol-2-il)etil]-5-(4'-fluorobifenil-4-il)-3-hidroxipentanóico (Compuesto No. 82),

10 Ácido (2*R*,3*R* + 2*S*,3*S*)-2-[2-(1,3-Dioxo-1,3-dihidro-2*H*-isoindol-2-il)etil]-5-(4'-fluorobifenil-4-il)-3-hidroxipentanóico (Compuesto No. 83),

Ácido (2*R*,3*S* + 2*S*,3*R*)-2-[2-(5-*ter*-Butil-1,3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)etil]-5-(4'-fluorobifenil-4-il)-3-hidroxipentanóico (Compuesto No. 106),

Ácido (2*R*,3*S* + 2*S*,3*R*)-2-[2-(5-*ter*-Butil-1,3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)etil]-3-hidroxi-5-[4'-(trifluorometil)bifenil-4-il]pentanóico (Compuesto No. 107),

15 Ácido (2*R*,3*R* + 2*S*,3*S*)-2-[2-(5-*ter*-Butil-1,3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)etil]-5-(4'-fluorobifenil-4-il)-3-hidroxipentanóico (Compuesto No. 108),

Ácido (2*R*,3*R* + 2*S*,3*S*)-2-[2-(5-*ter*-Butil-1,3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)etil]-3-hidroxi-5-[4'-(trifluorometil)bifenil-4-il]pentanóico (Compuesto No. 109),

20 Ácido 2-[2-(1,3-Dioxo-1,3-dihidro-2*H*-isoindol-2-il)etil]-5-(3'-fluoro-4'-metoxibifenil-4-il)-3-hidroxipentanóico (Compuesto No. 110),

Ácido (2*R*,3*S* + 2*S*,3*R*)-2-[2-(1,3-Dioxo-1,3-dihidro-2*H*-isoindol-2-il)etil]-3-hidroxi-5-[4-(6-metilpiridin-3-il)fenil]pentanóico (Compuesto No. 111),

Ácido (2*R*,3*R* + 2*S*,3*S*)-2-[2-(1,3-Dioxo-1,3-dihidro-2*H*-isoindol-2-il)etil]-3-hidroxi-5-[4-(6-metilpiridin-3-il)fenil]pentanóico (Compuesto No. 112),

Ácido (2*R*,3*R* + 2*S*,3*S*)-2-[2-(5-*ter*-Butil-1,3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)etil]-3-hidroxi-5-(4'-metilbifenil-4-il)pentanóico (Compuesto No. 113),

Ácido (2*R*,3*S* + 2*S*,3*R*)-2-[2-(5-*ter*-Butil-1,3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)etil]-3-hidroxi-5-(4'-metilbifenil-4-il)pentanóico (Compuesto No. 114),

- 5 Ácido (2*R*,3*R* + 2*S*,3*S*)-2-[2-(5-*ter*-Butil-1,3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)etil]-3-hidroxi-5-(4'-metoxibifenil-4-il)pentanóico (Compuesto No. 115),

Ácido (2*R*,3*R* + 2*S*,3*S*)-2-[2-(5-*ter*-Butil-1,3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)etil]-5-(4'-clorobifenil-4-il)-3-hidroxipentanóico (Compuesto No.116),

- 10 Ácido (2*R*,3*S* + 2*S*,3*R*)-2-[2-(5-*ter*-Butil-1,3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)etil]-5-(4'-clorobifenil-4-il)-3-hidroxipentanóico (Compuesto No. 117),

Ácido (2*R*,3*S* + 2*S*,3*R*)-2-[2-(5-*ter*-Butil-1,3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)etil]-3-hidroxi-5-(4'-metoxibifenil-4-il)pentanóico (Compuesto No. 118),

Ácido (2*R*,3*S*)-5-Bifenil-4-il-3-hidroxi-2-[2-(1*H*-indol-3-il)etil]pentanóico (Compuesto No. 122),

- 15 Ácido (2*R*,3*R*)-5-Bifenil-4-il-3-hidroxi-2-[2-(1*H*-indol-3-il)etil]pentanóico (Compuesto No. 123),

Ácido (2*R*,3*S*)-5-(4'-Clorobifenil-4-il)-2-[2-(1,3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)etil]-3-hidroxipentanóico (Compuesto No.125),

- 20 Ácido (2*S*,3*R*)-5-(4'-Clorobifenil-4-il)-2-[2-(1,3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)etil]-3-hidroxipentanóico (Compuesto No.126),

Ácido (2*R*,3*R*)-5-(4'-Clorobifenil-4-il)-2-[2-(1,3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)etil]-3-hidroxipentanóico (Compuesto No.127),

Ácido (2*S*,3*S*)-5-(4'-Clorobifenil-4-il)-2-[2-(1,3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)etil]-3-hidroxipentanóico (Compuesto No.128),

Ácido (2R,3S) -2-[2-(1,3-Dioxo-1,3-dihidro-2*H*-isoindol-2-il)etil]-3-hidroxi-5-[4-(6-metoxipiridin-3-il)fenil]pentanóico (Compuesto No. 129),

Ácido (2S,3R)- 2-[2-(1,3-Dioxo-1,3-dihidro-2*H*-isoindol-2-il)etil]-3-hidroxi-5-[4-(6-metoxipiridin-3-il)fenil]pentanóico (Compuesto No. 130),

- 5 Ácido (2R,3R)- 2-[2-(1,3-Dioxo-1,3-dihidro-2*H*-isoindol-2-il)etil]-3-hidroxi-5-[4-(6-metoxipiridin-3-il)fenil]pentanóico (Compuesto No. 131),

Ácido (2S,3S)- 2-[2-(1,3-Dioxo-1,3-dihidro-2*H*-isoindol-2-il)etil]-3-hidroxi-5-[4-(6-metoxipiridin-3-il)fenil]pentanóico (Compuesto No. 132),

- 10 Ácido (2R,3S)- 3-Hidroxi-5-[4-(6-metoxipiridin-3-il)fenil]-2-[2-(4-oxo-1,2,3-benzotriazin-3(4*H*)-il)etil]pentanóico (Compuesto No.133),

Ácido (2S,3R)- 3-Hidroxi-5-[4-(6-metoxipiridin-3-il)fenil]-2-[2-(4-oxo-1,2,3-benzotriazin-3(4*H*)-il)etil]pentanóico (Compuesto No.134),

Ácido (2R,3R)- 3-Hidroxi-5-[4-(6-metoxipiridin-3-il)fenil]-2-[2-(4-oxo-1,2,3-benzotriazin-3(4*H*)-il)etil]pentanóico (Compuesto No.135), y

- 15 Ácido (2S,3S)- 3-Hidroxi-5-[4-(6-metoxipiridin-3-il)fenil]-2-[2-(4-oxo-1,2,3-benzotriazin-3(4*H*)-il)etil]pentanóico (Compuesto No.136).

Los ejemplos establecidos demuestran el procedimiento general de síntesis para la preparación de los compuestos representativos. Los ejemplos se proporcionan para ilustrar aspectos particulares de la divulgación y no limitan el
20 alcance de la invención.

PARTE EXPERIMENTAL

PROCEDIMIENTO GENERAL

230

Síntesis de 3-(2-bromoetil)-1,2,3-bencenotriazin-4(3H)-ona

A una solución del compuesto 1,2,3-tribenzotriazin-4(3H)-ona (500 mg) (disponible comercialmente) en dimetilformamida (13 mL) se adicionó carbonato de potasio anhidro (2.8 g) y se agitó por 20 minutos. A éste se agregó
5 dibromometano (2 g) y se agitó la mezcla de reacción primero a temperatura ambiente por unos pocos minutos y luego a 60 °C por dos horas. El sólido así obtenido se filtró y el filtrado se concentró a presión reducida. El residuo así
10 obtenido se diluyó con agua y se extrajo con acetato de etilo. Se separó la capa orgánica, se lavó con agua y solución salina y se secó sobre sulfato de sodio anhidro. El solvente se evaporó a presión reducida y el residuo así obtenido se purificó por cromatografía de columna utilizando acetato de etilo al 20% en hexano como eluyente para dar el compuesto título (590 mg).

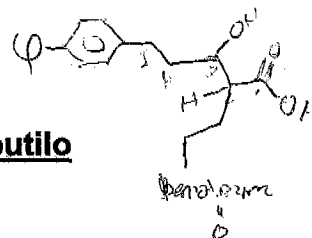
Síntesis de 4-(bromometil)bifenil

Se agregó tetrabromuro de carbono (8.99 g) y trifenilfosfina (7.11 g) a una
15 solución en agitación de bifenil-4-il-metanol (5.00 g) en diclorometano (100 mL) a temperatura ambiente y se agitó la mezcla de reacción por aproximadamente 2 horas a la misma temperatura. El solvente se evaporó a presión reducida y el residuo así obtenido se purificó por cromatografía de columna utilizando dietil éter al 5% en hexano como eluyente para dar el compuesto título (6.37 g).

20

Esquema I. Procedimiento:

Ejemplo 1: Síntesis del Ácido 5-Bifenil-4-il-3-hidroxi-2-[2-(4-oxo-1,2,3-benzotriazin-3(4H)-il)etil]pentanoico (Compuesto No. 1)

Etapas 1: Síntesis de 5-bifenil-4-il-3-oxopentanoato de *ter*-butilo

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Una solución de acetoacetato de ter-butilo (7.2 g) en tetrahidrofurano (80 mL) se agregó a una solución en agitación de hidruro de sodio (1.33 g) en tetrahidrofurano (60 mL) a 0 °C bajo atmósfera de nitrógeno. La mezcla de reacción se agitó por 10 minutos y luego se agregó gota a gota butil litio (23 mL, 2.5 M en hexano) durante 10 minutos. La mezcla de reacción resultante se agitó por 10 minutos. Se agregó en 10 minutos una solución de 4-(bromoetil) bifenilo (12.5 g) en tetrahidrofurano (60 mL) y la solución resultante se agitó a 0°C por aproximadamente 2 horas. A la mezcla resultante se le adicionó ácido clorhídrico (6M, 15 mL) y luego se extrajo la mezcla con dietil éter. Se combinaron las capas orgánicas, se lavó con agua y solución salina y se secó sobre sulfato de sodio anhidro. El solvente se evaporó a presión reducida y el residuo así obtenido se purificó por cromatografía de columna en sílica gel utilizando acetato de etilo al 8% en hexano como eluyente para dar el compuesto título (7.5 g).

Etapas 2: Síntesis de 5-Bifenil-4-il-3-oxo-2-[2-(4-oxo-1,2,3-benzotriazin-3(4H)-il)etil]pentanoato de ter-butilo

A una solución del compuesto (300 mg) obtenido en la etapa 1 anterior en tetrahidrofuran seco (a mL) y ter-butanol (4 mL) a 0°C se agregó terbotóxido de potasio (104 mg) y se agitó por 20 minutos. A la mezcla de reacción resultante se agregó 3-(2-bromoetil)-1,2,3-benzotriazin-4(3H)-ona (235 mg) y yoduro de tetrabutilamonio (348 mg) y la mezcla se agitó por 30 minutos a 0°C, seguido por agitación a temperatura ambiente por 30 minutos y finalmente a 80°C por cerca de 5-6 horas. El solvente se evaporó a presión reducida y el residuo así obtenido se diluyó con agua y se extrajo con acetato de etilo. La capa orgánica se lavó con agua y solución salina, se secó sobre sulfato de sodio anhidro y se filtró. El solvente se evaporó a presión reducida y el residuo así obtenido se purificó por cromatografía de columna utilizando acetato de etilo al 20% en hexano como eluyente para dar el compuesto título (240 mg).

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Etapa 3: Síntesis de 5-Bifenil-4-il-3-hidroxi-2-[2-(4-oxo-1,2,3-benzotriazin-3(4H)-il)etil]pentanoato de *ter*-butilo.

A la solución del compuesto (240 mg) obtenido en la etapa 2 anterior en metanol (4.5 mL) a 10°C se agregó borohidruro de sodio (44 mg). La mezcla de
5 reacción se agitó por 2 horas a -10°C a -2°C. El solvente se evaporó a presión reducida y el residuo así obtenido se recibió en cloruro de amonio saturada y se extrajo con acetato de etilo. La capa orgánica se lavó con agua y solución salina y se secó sobre sulfato de sodio anhidro y se se concentró a presión reducida. El residuo así obtenido se purificó por cromatografía de columna utilizando acetato
10 de etilo al 30% en hexano como eluyente para dar el compuesto título (100 mg).

Etapa 4: Síntesis del Ácido 5-Bifenil-4-il-3-hidroxi-2-[2-(4-oxo-1,2,3-benzotriazin-3(4H)-il)etil]pentanóico.

A la solución del compuesto (100 mg) obtenido en la etapa 3 anterior en diclorometano (2 mL) a 0°C se adicionó ácido trifluoroacético (8 mL) y la mezcla de
15 reacción se agitó por cerca de 2-3 horas y luego se agitó por 3 horas a temperatura ambiente. El solvente y los reactivos en exceso se evaporaron a presión reducida y el residuo así obtenido se purificó por cromatografía preparativa en capa delgada (eluyente- acetato de etilo) para dar el compuesto título (40 mg).

Masa (m/z): 444.1 (M⁺+1)

20 Los siguientes análogos ilustrativos se prepararon de manera similar:

Ácido 5-Bifenil-4-il-2-[2-(1,3-dihidro-2*H*-isoindol-2-il)etil]-3-hidroxi-pentanóico
(Compuesto No. 12)

Ácido 2-(3-Bifenil-4-il-1-hidroxi-propil)-6-(1,3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)-hexanóico (Compuesto No. 46),

Ácido 5-Bifenil-4-il-3-hidroxi-2-[2-(1-oxoftalazin-2(1*H*)-il)etil]pentanóico
(Compuesto No. 47),

Ácido 5-Bifenil-4-il-2-[3-(1,3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)propil]-3-
hidroxipentanóico (Compuesto No. 48),

5 Ácido 5-Bifenil-4-il-3-hidroxi-2-[2-(2'-oxospiro[ciclopropan-1,3'-indol]-1'(2'*H*)-
il)etil]pentanóico (Compuesto No. 49),

Ácido 5-Bifenil-4-il-3-hidroxi-2-[2-(1-oxo-4-fenil-4a,8a-dihidroftalazin-2(1*H*)-
il)etil]pentanóico (Compuesto No. 84),

10 Ácido 5-Bifenil-4-il-3-hidroxi-2-[2-(3-oxo-2,3-dihidro-4*H*-1,4-benzoxazin-4-
il)etil]pentanóico (Compuesto No. 85),

Ácido 5-Bifenil-4-il-2-[2-[(3a*R*,7a*S*)-1,3-dioxo-1,3,3a,4,7,7a-hexahidro-2*H*-isoindol-
2-il]etil]-3-hidroxipentanóico (Compuesto No. 86),

Ácido 5-Bifenil-4-il-3-hidroxi-2-[2-(5-metil-1,3-dioxo-1,3-dihidro-2*H*-isoindol-2-
il)etil]pentanóico (Compuesto No. 90),

15 Ácido 5-Bifenil-4-il-2-[2-(4,4-dimetil-2,6-dioxopiperidin-1-il)etil]-3-hidroxipentanóico
(Compuesto No. 93),

Ácido 5-Bifenil-4-il-2-[2-(7,9-dioxo-8-azaspiro[4.5]dec-8-il)etil]-3-hidroxipentanóico
(Compuesto No. 94),

Ácido 2-(3-Bifenil-4-il-1-hidroxipropil)pent-4-inoico (Compuesto No. 95);

20 Ácido 5-Bifenil-4-il-3-hidroxi-2-[2-(2-oxo-1,3-benzoxazol-3(2*H*)-il)etil]pentanóico
(Compuesto No. 96)

Ácido 5-Bifenil-4-il-2-[2-(5,6-dicloro-1,3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)etil]-3-
hidroxipentanóico (Compuesto No. 102),

Ácido 5-Bifenil-4-il-2-[2-(2,4-dioxo-1,4-dihidroquinazolin-3(2H)-il)etil]-3-hidroxpentanóico (Compuesto No. 103),

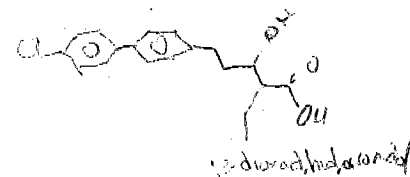
Ácido 5-Bifenil-4-il-2-[2-(1,3-dioxo-1,3-dihidro-2H-pirrol[3,4-c]piridin-2-il)etil]-3-hidroxpentanóico (Compuesto No. 104),

5 Ácido 5-Bifenil-4-il-3-hidroxi-2-[2-(7-metil-4-oxo-1,2,3-benzotriazin-3(4H)-il)etil]pentanóico (Compuesto No. 120),

Ácido 5-Bifenil-4-il-2-[2-(5-ter-Butil-1,3-dioxo-1,3-dihidro-2H-isoindol-2-il)etil]-3-hidroxpentanóico (Compuesto No. 121),

10 Esquema II, Procedimiento

Ejemplo 2: Síntesis del Ácido 5-(4'-Clorobifenil-4-il)-2-[2-(1,3-dioxo-1,3-dihidro-2H-isoindol-2-il)etil]-3-hidroxpentanóico (Compuesto No. 4).



15 **Etapas 1: Síntesis del éster terbutílico del ácido 5-(4-bromo-fenil) 3-oxo-pentanóico.**

Acetoacetato de terbutilo (23.8 ml) Se adicionó gota a gota durante 15 minutos a una suspensión agitada de hidruro de sodio (8.9 mg) en tetrahidrofurano a 0°C en atmósfera de nitrógeno. Después de agitar durante 20 minutos se adiciono n-butil litio en hexano y se continuó la agitación por 10 minutos más. La solución resultante se trató goteando con una solución de bromuro de 4-bromobencilo (14.19 mg) en tetrahidrofurano (100 ml) y luego se calentó a temperatura ambiente. La reacción se agitó durante 40 minutos a temperatura ambiente y se detuvo con HCl (6M, 5ml). La mezcla resultante se extrajo con dietil éter. Las fases orgánicas se combinaron, lavaron con solución salina y se secaron sobre sulfato de sodio anhidro. El solvente se evaporó bajo presión reducida. El residuo

obtenido se purificó por cromatografía flash utilizando 5% de acetato de etilo en hexano como eluyente para producir el compuesto título (37g).

5 **Etap 2: Síntesis de 2-(2-[[[1,1-dimetiletil)dimetil)silil]oxi}etil)-5-(4-bromofenil)-3-oxopentanoato de 1,1-dimetiletilo.**

Una solución del compuesto (9,7g) obtenido en la etapa 1 anteriormente, en dimetil formamida (25ml) se adicionó gota a gota durante 20 minutos a una suspensión de hidruro de sodio (1,42g) en agitación en dimetilformamida (25 ml) a 10 0°C bajo atmósfera de nitrógeno, se agitó la mezcla reaccionante durante 20 minutos. A esta mezcla se le adicionó (2-bromoetoxi)-t-butil dimetilsilano (8,50g) por goteo durante 20 minutos a 0°C, luego la mezcla reaccionante se calentó a 70°C por cerca de 3-4 horas. Al enfriar a temperatura ambiente la reacción se detuvo con agua. Al residuo se le hizo reparto entre solución de cloruro de amonio 15 saturada y diclorometano. Se continuaron las fases organicas, se lavó con agua y con solución salina, y se secó sobre sulfato de sodio anhidro y se concentró bajo presión reducida. El residuo entonces obtenido se purificó por cromatografía en columna usando acetato de etilo al 8% en hexano como eluyente para producir el compuesto título (9.5g)

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Etap 3: Síntesis de 2-(2-[[[1,1-dimetiletil)(dimetil)silil]oxi}etil)-3-hidroxi-5-bromofenilpentanoato de 1,1-dimetiletilo

Se adicionaron (0,46g) de borohidruro de sodio a una solución en agitación 25 del compuesto (4.2g) obtenido de la etapa 2 anteriormente, en metanol (50 ml) a 0°C bajo atmósfera de nitrógeno y se agitó la mezcla reaccionante por aproximadamente 2 horas. La mezcla reaccionante se detuvo con solución saturada acuosa de cloruro de amonio (100ml) y se extrajo con dietiléter. Las capas

orgánicas se combinaron, se lavó con agua y solución salina y se secó con sulfato de sodio anhidro y se concentró bajo presión reducida. El residuo así obtenido se purifican por cromatografía en columna usando acetato de etilo al 25% en hexano como eluyente para producir el compuesto título (3.7g)

5

Etapas 4: Síntesis de 2-(2-(((1,1-dimetiletil)(dimetil)silil)oxi)etil)-5-(4-bromofenil)-3-([4-(metiloxi)fenil]metil)oxi)pentanoato de 1,1-dimetiletilo.

Se adiciona eterato trifluoruro de boro (5.0ml) a una solución en agitación del compuesto (4.0) obtenido en la etapa 3 anteriormente y (3.26g) de 4-metoxibencil 2, 2, 2-tricloroetanimidoato en tetrahidrofurano (40ml) a 0°C en atmosfera de nitrógeno. A la reacción se le permitió calentarse hasta temperatura ambiente, temperatura a la cual se continuó agitando durante 2 horas. El solvente se evaporó a presión reducida y el residuo así obtenido se purifico por cromatografía en columna usando acetato de etilo al 20% en hexano como eluyente para producir el compuesto título (3.8g)

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Etapas 5: Síntesis de 2-(2-hidroxietil)-5-(4-bromofenil)-3-([4-(metiloxi)fenil]metil)oxi)pentanoato de 1,1 -dimetiletilo.

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Una solución de fluoruro de tetra-n-butilamonio (0.45ml) se adicionó gota a gota durante 15 minutos a una solución del compuesto (200mg) obtenido en la etapa 4, anteriormente, en tetrahidrofurano (5ml) a 0°C en atmosfera de nitrógeno. La mezcla reaccionante se calentó a temperatura ambiente a la cual la agitación se continuó durante 2 horas. Los volátiles se evaporaron a presión reducida y al residuo así obtenido se le hizo reparto entre acetato de etilo y agua. Las fases se separaron y la capa acuosa se lavó con acetato de etilo. Las capas orgánicas se combinaron, se lavó con agua y solución salina, se secó en sulfato de sodio

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orgánicas se combinaron, se lavó con agua y solución salina y se secó con sulfato de sodio anhidro y se concentró bajo presión reducida. El residuo así obtenido se purifican por cromatografía en columna usando acetato de etilo al 25% en hexano como eluyente para producir el compuesto título (3.7g)

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Etapa 4: Síntesis de 2-(2-(((1,1-dimetiletil)(dimetil)silil)oxi)etil)-5-(4-bromofenil)-3-([4-(metiloxi)fenil]metil)oxi)pentanoato de 1,1-dimetiletilo.

Se adiciona eterato trifluoruro de boro (5.0ml) a una solución en agitación del compuesto (4.0) obtenido en la etapa 3 anteriormente y (3.26g) de 4-metoxibencil 2, 2, 2-tricloroetanimidoato en tetrahidrofurano (40ml) a 0°C en atmosfera de nitrógeno. A la reacción se le permitió calentarse hasta temperatura ambiente, temperatura a la cual se continuó agitando durante 2 horas. El solvente se evaporó a presión reducida y el residuo así obtenido se purifico por cromatografía en columna usando acetato de etilo al 20% en hexano como eluyente para producir el compuesto título (3.8g)

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Etapa 5: Síntesis de 2-(2-hidroxiethyl)-5-4(4-bromofenil)-3-([4-(metiloxi)fenil]metil)oxi)pentanoato de 1,1 -dimetiletilo.

25

Una solución de fluoruro de tetra-n-butilamonio (0.45ml) se adicionó gota a gota durante 15 minutos a una solución del compuesto (200mg) obtenido en la etapa 4, anteriormente, en tetrahidrofurano (5ml) a 0°C en atmosfera de nitrógeno. La mezcla reaccionante se calentó a temperatura ambiente a la cual la agitación se continuó durante 2 horas. Los volátiles se evaporaron a presión reducida y al residuo así obtenido se le hizo reparto entre acetato de etilo y agua. Las fases se separaron y la capa acuosa se lavó con acetato de etilo. Las capas orgánicas se combinaron, se lavó con agua y solución salina, se secó en sulfato de sodio

anhidro y se concentró a presión reducida para producir el compuesto título (120mg)

**Etapa 6: Síntesis de 5-(4-bromofenil)-3-([4-(metiloxi)fenil]metil)oxi)-2-{2-
5 [(metilsulfonil)oxi]etil}pentanoato de 1,1-dimetilo.**

Se adiciona cloruro de metanosulfonil (0,63g) en una porción a una solución en agitación del compuesto (2.99g) obtenida de la etapa 5 anteriormente, y trietilamina (2,6ml) en diclorometano (50ml) a temperatura ambiente en atmósfera
10 de nitrógeno y se agito a temperatura ambiente durante 1 hora. A la mezcla cruda se le hizo reparto entre solución acuosa saturada de ácido cítrico y diclorometano. Las fases se separaron y la capa orgánica se concentró a presión reducida para producir el compuesto título (3.2g)

15 Etapa 7: Síntesis de 2-[2-(1,3-dioxo -1,3-dihidro-2H-isoindol-2-il) etil]-5-(4-bromofenil)-3-([4-(metiloxi)fenil]metil)oxi)pentanoato de 1,1-dimetiletilo.

Se adicionó (1,25g) ftalimida de potasio en una porción a una solución en agitación del compuesto (3.5g) obtenido en la etapa 6 anteriormente, en
20 dimetilformamida (25ml) a temperatura ambiente en atmósfera de nitrógeno. La solución resultante se calentó a 80°C por cerca de 2 horas y luego se enfrió a temperatura ambiente. Los volátiles se evaporaron a presión reducida y al residuo entonces obtenido se le hizo reparto entre diclorometano y agua. Las capas se separaron y la fase orgánica se evaporó a sequedad a presión reducida. El
25 residuo entonces obtenido se purificó por cromatografía en columna utilizando acetato de etilo al 20% en hexano como eluyente para producir el compuesto título (2.45g)

Etapa 8: Síntesis de *ter*-butil 5-(4'-clorobifenil-4-il)-2-[2-(1,3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)etil]-3-[(4-metoxibencil)oxi]pentanoato de *ter*butilo.

A la solución del compuesto (200mg) obtenido en la etapa 7 anteriormente,
5 ácido (4-clorofenil) borónico (90mg) y carbonato de potasio (133mg) en
dimetilformamida (3ml) se adicionó a tetrakis (trifenilfosfina) paladio (o) (18,5mg) y
la mezcla reaccionante se agitó por 6 horas a cerca de 100°C. la mezcla
reaccionante resultante se diluyó con agua y se extrajo con acetato de etilo. Se
reparó, la capa orgánica, se lavó con agua y solución salina, se secó sobre sulfato
10 de sodio anhidro y se concentró a presión reducida. El residuo así obtenido se
purificó por cromatografía en columna usando acetato de etilo al 20% en hexano
como eluyente para producir el compuesto título (116mg)

**Etapa 9: Síntesis de ácido 5-(4'-clorodifenil-4-il)-2-[2-(1,3-dioxo-1,3-dihidro-
15 2*H*-isoindol-2-il)etil] 3-hidroxipentanóico.**

A una solución del compuesto (120mg) obtenido anteriormente de la etapa
8, en diclorometano (5ml) se le adicionó ácido trifluoroacético (2ml), y se agitó la
mezcla de reacción durante 2 horas a temperatura ambiente.

20

El solvente se evaporó a presión reducida y el residuo así obtenido se purificó por
cromatografía preparativa de capa delgada (eluyente: acetato de etilo al 60% en
hexano) para producir el compuesto título (68mg)

25 Masa (m/z): 478.6 ($M^+ + 1$)

Los siguientes compuestos ilustrativos se prepararon de manera similar:

24

Ácido 5-(4'-*ter*-Butilbifenil-4-il)-2-[2-(1,3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)etil]-3-hidroxicpentanóico (Compuesto No. 2),

Ácido 5-(4'-Butilbifenil-4-il)-2-[2-(1,3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)etil]-3-hidroxicpentanóico (Compuesto No. 3),

5 Ácido 2-[2-(1,3-Dioxo-1,3-dihidro-2*H*-isoindol-2-il)etil]-3hidroxi-5-(4'-trifluorometoxibefinil-4-il)pentanóico (Compuesto No.5),

Ácido 2-[2-(1,3-Dioxo-1,3-dihidro-2*H*-isoindol-2-il)etil]-5-(4'-etoxibifenil-4-il)-3-hidroxicpentanóico (Compuesto No. 6),

Ácido 2-[2-(1,3-Dioxo-1,3-dihidro-2*H*-isoindol-2-il)etil]-5-(4'-formilbifenil-4-il)-3-
10 hidroxicpentanóico (Compuesto No. 7),

Ácido 2-[2-(1,3-Dioxo-1,3-dihidro-2*H*-isoindol-2-il)etil]-3-hidroxi-5-(2',4',6'-trimetoxibifenil-4-il)pentanóico (Compuesto No. 8),

Ácido 2-[2-(1,3-Dioxo-1,3-dihidro-2*H*-isoindol-2-il)etil]-3-hidroxi-5-(4'-propoxibifenil-4-il)pentanóico (Compuesto No. 9),

15 Ácido 5-(3',4'-Difluorobifenil-4-il)-2-[2-(1,3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)etil]-3-hidroxicpentanóico (Compuesto No. 10),

Ácido 2-[2-(1,3-Dioxo-1,3-dihidro-2*H*-isoindol-2-il)etil]-3-hidroxi-5-(4'-metoxibifenil-4-il)pentanóico (Compuesto. 23),

Ácido 5-(2',3'-Dimetilbifenil-4-il)-2-[2-(1,3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)etil]-3-
20 hidroxicpentanóico (Compuesto No. 24),

Ácido 2-[2-(1,3-Dioxo-1,3-dihidro-2*H*-isoindol-2-il)etil]-3-hidroxi-5-[3'-(trifluorometil)bifenil-4-il]pentanóico (Compuesto No. 25),

Ácido 2-[2-(1,3-Dioxo-1,3-dihidro-2*H*-isoindol-2-il)etil]-5-(4'-etilbifenil-4-il)-3-hidroxicpentanóico (Compuesto No. 26),

240

Ácido 5-(3',5'-Diclorobifenil-4-il)-2-[2-(1,3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)etil]-3-hidroxicipentanóico (Compuesto No. 27),

Ácido 5-[4'-Cloro-3'-(trifluorometil)bifenil-4-il]-2-[2-(1,3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)etil]-3-hidroxicipentanóico (Compuesto No. 28),

5 Ácido 5-(2',5'-Difluorobifenil-4-il)-2-[2-(1,3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)etil]-3-hidroxicipentanóico (Compuesto No. 29),

Ácido 2-[2-(1,3-Dioxo-1,3-dihidro-2*H*-isoindol-2-il)etil]-3-hidroxi-5-[2'-(trifluorometoxi)bifenil-4-il]pentanóico (Compuesto No. 30),

10 Ácido 2-[2-(1,3-Dioxo-1,3-dihidro-2*H*-isoindol-2-il)etil]-3-hidroxi-5-[4'-(metiltio)bifenil-4-il]pentanóico (Compuesto No. 31),

Ácido 2-[2-(1,3-Dioxo-1,3-dihidro-2*H*-isoindol-2-il)etil]-5-(4'-fluoro-3'-metilbifenil-4-il)-3-hidroxicipentanóico (Compuesto No. 32),

Ácido 2-[2-(1,3-Dioxo-1,3-dihidro-2*H*-isoindol-2-il)etil]-3-hidroxi-5-(3'-isopropilbifenil-4-il)pentanóico (Compuesto No. 33),

15 Ácido 5-(3',4'-Dimetilbifenil-4-il)-2-[2-(1,3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)etil]-3-hidroxicipentanóico (Compuesto No. 34),

Ácido 5-(2',6'-Difluorobifenil-4-il)-2-[2-(1,3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)etil]-3-hidroxicipentanóico (Compuesto No. 35),

20 Ácido 2-[2-(1,3-Dioxo-1,3-dihidro-2*H*-isoindol-2-il)etil]-5-(4'-fluorobifenil-4-il)-3-hidroxicipentanóico (Compuesto No. 36),

Ácido 5-(3',5'-Difluorobifenil-4-il)-2-[2-(1,3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)etil]-3-hidroxicipentanóico (Compuesto No. 37),

Ácido 5-(3'-Cloro-4'-fluorobifenil-4-il)-2-[2-(1,3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)etil]-3-hidroxicipentanóico (Compuesto No. 38),

Ácido 5-(3',4'-Dimetoxibifenil-4-il)-2-[2-(1,3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)etil]-3-hidroxicpentanóico (Compuesto No. 39),

Ácido 5-(3'-Clorobifenil-4-il)-2-[2-(1,3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)etil]-3-hidroxicpentanóico (Compuesto No. 40),

- 5 Ácido 2-[2-(1,3-Dioxo-1,3-dihidro-2*H*-isoindol-2-il)etil]-3-hidroxi-5-(3'-metilbifenil-4-il)pentanóico (Compuesto No. 41),

Ácido 5-(2',3'-Difluorobifenil-4-il)-2-[2-(1,3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)etil]-3-hidroxicpentanóico (Compuesto No. 42),

- 10 Ácido 2-[2-(1,3-Dioxo-1,3-dihidro-2*H*-isoindol-2-il)etil]-5-(2'-fluoro-3'-metoxibifenil-4-il)-3-hidroxicpentanóico (Compuesto No. 43),

Ácido 2-[2-(1,3-Dioxo-1,3-dihidro-2*H*-isoindol-2-il)etil]-5-(3'-fluoro-4'-metilbifenil-4-il)-3-hidroxicpentanóico (Compuesto No. 44),

Ácido 2-[2-(1,3-Dioxo-1,3-dihidro-2*H*-isoindol-2-il)etil]-3-hidroxi-5-(4'-hidroxibifenil-4-il)pentanóico (Compuesto No. 50),

- 15 Ácido 3-Hidroxi-5-(4'-metoxibifenil-4-il)-2-[2-(3-metil-2,6-dioxo-3,6-dihidropirimidin-1(2*H*)-il)etil]pentanóico (Compuesto No. 51),

Ácido 5-(4'-Clorobifenil-4-il)-3-hidroxi-2-[2-(3-metil-2,6-dioxo-3,6-dihidropirimidin-1(2*H*)-il)etil]pentanóico (Compuesto No. 52),

- 20 Ácido 5-(4'-Fluorobifenil-4-il)-3-hidroxi-2-[2-(3-metil-2,6-dioxo-3,6-dihidropirimidin-1(2*H*)-il)etil]pentanóico (Compuesto No. 53),

Ácido 5-[4-(5-Cloro-2-tienil)fenil]-2-[2-(1,3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)etil]-3-hidroxicpentanóico (Compuesto No. 54),

Ácido 4'-[4-Carboxi-6-(1,3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)-3-hidroxi]hexil]bifenil-4-carboxílico (Compuesto No. 55),

Ácido 2-[2-(1,3-Dioxo-1,3-dihidro-2*H*-isoindol-2-il)etil]-3-hidroxi-5-[4'-(metoxycarbonil)bifenil-4-il]pentanóico (Compuesto No. 56),

Ácido 2-[2-(1,3-Dioxo-1,3-dihidro-2*H*-isoindol-2-il)etil]-3-hidroxi-5-[4'-(trifluorometil)bifenil-4-il]pentanóico (Compuesto No. 57),

5 Ácido 2-[2-(1,3-Dioxo-1,3-dihidro-2*H*-isoindol-2-il)etil]-3-hidroxi-5-[4-(6-metoxipiridin-3-il)fenil]pentanóico (Compuesto No. 58),

Ácido 3-Hidroxi-2-[2-(4-oxo-1,2,3-benzotriazin-3(4*H*)-il)etil]-5-[4'-(trifluorometil)bifenil-4-il]pentanóico (Compuesto No. 59),

10 Ácido 5-(3',4'-Difluorobifenil-4-il)-3-hidroxi-2-[2-(4-oxo-1,2,3-benzotriazin-3(4*H*)-il)etil]pentanóico (Compuesto No. 60),

Ácido 2-[2-(1,3-Dioxo-1,3-dihidro-2*H*-isoindol-2-il)etil]-5-(3'-fluorobifenil-4-il)-3-hidroxipentanóico (Compuesto No. 61),

Ácido 5-[4'-(Benciloxi)-3'-fluorobifenil-4-il]-2-[2-(1,3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)etil]-3-hidroxipentanóico (Compuesto No. 62),

15 Ácido 5-[4'-(Benciloxi)bifenil-4-il]-2-[2-(1,3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)etil]-3-hidroxipentanóico (Compuesto No. 63),

Ácido 3-Hidroxi-5-(4'-metoxibifenil-4-il)-2-[2-(4-oxo-1,2,3-benzotriazin-3(4*H*)-il)etil]pentanóico (Compuesto No. 64),

20 Ácido 5-(4'-Clorobifenil-4-il)-3-hidroxi-2-[2-(4-oxo-1,2,3-benzotriazin-3(4*H*)-il)etil]pentanóico (Compuesto No. 65),

Ácido 2-[2-(1,3-Dioxo-1,3-dihidro-2*H*-isoindol-2-il)etil]-3-hidroxi-5-(4'-metilbifenil-4-il)pentanóico (Compuesto No. 66),

Ácido 3-Hidroxi-5-[4-(6-metoxipiridin-3-il)fenil]-2-[2-(4-oxo-1,2,3-benzotriazin-3(4*H*)-il)etil]pentanóico (Compuesto No. 67),

Ácido 3-Hidroxi-5-(4'-metilbifenil-4-il)-2-[2-(5-metil-1,3-dioxo-1,3-dihidro-2H-isoindol-2-il)etil]pentanóico (Compuesto No. 68),

Ácido 5-(4'-Clorobifenil-4-il)-3-hidroxi-2-[2-(5-metil-1,3-dioxo-1,3-dihidro-2H-isoindol-2-il)etil]pentanóico (Compuesto No. 69),

5 Ácido 3-Hidroxi-2-[2-(4-oxo-1,2,3-benzotriazin-3(4H)-il)etil]-5-[4'-(trifluorometoxi)bifenil-4-il]pentanóico (Compuesto No. 70),

Ácido 5-(4'-Fluorobifenil-4-il)-3-hidroxi-2-[2-(4-oxo-1,2,3-benzotriazin-3(4H)-il)etil]pentanóico (Compuesto No. 71),

10 Ácido 3-hidroxi-5-(4'-metilbifenil-4-il)-2-[2-(4-oxo-1,2,3-benzotriazin-3(4H)-il)etil]pentanóico (Compuesto No. 72),

Ácido 5-(4'-Cianobifenil-4-il)-3-hidroxi-2-[2-(4-oxo-1,2,3-benzotriazin-3(4H)-il)etil]pentanóico (Compuesto No. 73),

Ácido 5-(4'-Fluorobifenil-4-il)-3-hidroxi-2-[2-(5-metil-1,3-dioxo-1,3-dihidro-2H-isoindol-2-il)etil]pentanóico (Compuesto No. 74),

15 Ácido 3-Hidroxi-5-[4-(6-metoxipiridin-3-il)fenil]-2-[2-(5-metil-1,3-dioxo-1,3-dihidro-2H-isoindol-2-il)etil]pentanóico (Compuesto No. 75),

Ácido 5-(4'-Etilbifenil-4-il)-3-hidroxi-2-[2-(4-oxo-1,2,3-benzotriazin-3(4H)-il)etil]pentanóico (Compuesto No. 76),

20 Ácido 3-Hidroxi-2-[2-(5-metil-1,3-dioxo-1,3-dihidro-2H-isoindol-2-il)etil]-5-[4'-(trifluorometil)bifenil-4-il]pentanóico (Compuesto No. 77),

Ácido 2-[2-(5-ter-Butil-1,3-dioxo-1,3-dihidro-2H-isoindol-2-il)etil]-3-hidroxi-5-[4-(6-metoxipiridin-3-il)fenil]pentanóico (Compuesto No. 97),

Ácido 5-{4-[6-(Dimetilamino)piridin-3-il]fenil}-2-[2-(1,3-dioxo-1,3-dihidro-2H-isoindol-2-il)etil]-3-hidroxipentanóico (Compuesto No. 98),

Ácido 2-[2-(1,3-Dioxo-1,3-dihidro-2*H*-isoindol-2-il)etil]-3-hidroxi-5-[4'-(metilsulfonil)bifenil-4-il]pentanóico (Compuesto No. 99),

Ácido 5-[4'-(Aminocarbonil)bifenil-4-il]-2-[2-(1,3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)etil]-3-hidroxipentanóico (Compuesto No. 100),

5 Ácido 5-[4-(1-Bencil-1*H*-pirazol-4-il)fenil]-2-[2-(1,3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)etil]-3-hidroxipentanóico (Compuesto No. 101),

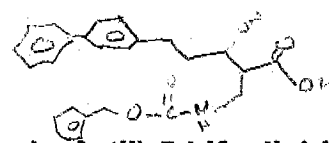
Ácido 2-[2-(5-*ter*-Butil-1,3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)etil]-5-(3',4'-difluorobifenil-4-il)-3-hidroxipentanóico (Compuesto No. 105),

10 Ácido 2-[2-(1,3-Dioxo-1,3-dihidro-2*H*-isoindol-2-il)etil]-5-(3'-fluoro-4'-metoxibifenil-4-il)-3-hidroxipentanóico (Compuesto No. 110), y

Ácido 2-[2-(1,3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)etil]-3-hidroxi-5-(4-pirimidin-5-ilfenil)pentanóico (Compuesto No 119).

Esquema III, Ruta de un procedimiento

15 Ejemplo 3: Síntesis de Ácido 2-(2-[(Benciloxi)carbonil]amino)etil)-5-bifenil-4-il-3-hidroxipentanóico (Compuesto No. 11).



Etap a 1: Síntesis de 2-(2-[(Benciloxi)carbonil]amino)etil)-5-bifenil-4-il-3-hidroxipentanoato de *ter*-butilo

20 A una solución de 5-bifenil-4-il-3-oxopentanoato de *ter*-butilo (237 mg) en tetraahidrofurano (4 mL) y alcohol terbitílico (4 mL) a 0°C bajo atmósfera inertese agregó *ter*-butóxido de potasio (98 mg) y se agitó por 20 minutos. Luego a ésta a 0°C se agregó yoduro de *n*-terbutilamonio (27 mg) y aziridina-1-carboxilato de bencilo (130 mg) y se agitó la mezcla de reacción por 5 minutos. La mezcla de reacción resultante se calentó a temperatura ambiente y luego además se calentó

a 70°C por 2 horas. El solvente se evaporó a presión reducida y el residuo así obtenido se recibió sobre agua y se extrajo con acetato d etilo. Las capas orgánicas combinadas se lavaron con agua y solución salina, se secó sobre sulfato de sodio anhidro y se concentró a presión reducida El residuo obtenido se
5 purificó por cromatografía en columna utilizando como eluyente acetato de etilo al 20% en hexano, para producir el compuesto título (60mg)

Etapa 2: Síntesis de 2-(2-[[benciloxi]carbonil]amino}etil)-5-bifenil-4-il-3 hidroxipentanoato de ter-butilo

10

Se adicionó borohidruro de sodio (9 mg) a una solución, en metanol (2 ml), a -10° a -2°C del compuesto (100mg) obtenido anteriormente en la etapa 1, se agitó la mezcla durante 40 minutos a la misma temperatura. El solvente se evaporó a presión reducida y el residuo así obtenido se estabilizó con una solución
15 saturada de cloruro de amonio y se extrajo con acetato de etilo. Las capas orgánicas combinadas se lavaron con agua y solución salina, se secaron sobre sulfato de sodio anhidro y se concentraron a presión reducida. El residuo así obtenido se purificó por cromatografía en columna utilizando metanol al 5% en diclorometano, como eluyente para producir el compuesto título (80mg)

20

Etapa 3: Síntesis del ácido 2-(2-[[benciloxi] carbonil]amino}etil) -5- bifenil-4-il-3-hidroxipentanoico

A una solución del compuesto (40mg) obtenido de la etapa 2, anterior en
25 dicloro metano (10mg) seco a 0°C se adicionó ácido trifluoroacético (0,5ml) y anisol (0,05ml) y se agitó durante 4 horas. El solvente y el exceso de reactivos se evaporaron a presión reducida y el residuo así obtenido se purificó por

cromatografía en columna utilizando acetato de etilo al 60% en hexano para producir el compuesto título (25mg)

Masa (m/z): 448.1 ($M^+ + 1$)

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Esquema III Procedimiento ruta B.

Ejemplo 4: Síntesis del Ácido 5-Bifenil-4-il-2-(2-[(4-fluorofenil)sulfonil]amino)etil)-3-hidroxipentanóico (Compuesto No. 87)



Etapas 1: Síntesis de Benzoato de 4-[(benciloxi)carbonil]amino)-1-(2-bifenil-4-ilet)-2-ter-butoxicarbonil)butilo.

10

Se adicionó ácido benzoico (48,5mg), 4-dimetilamino piridina (24,3mg) y trietilamina (0,08ml) a una solución de 2-(2-[(benciloxi)carbonil]amino)etil)-5-bifenil-4-il-3-hidroxipentanoato de ter-butilo (200mg) en diclorometano (5ml) a 0°C y a la mezcla de reacción se agitó durante 15 minutos. 1-etil-3-(3'-dimetilaminopropil)-carboimida (152mg) se añadieron a la mezcla de reacción y se agitó durante toda la noche. La mezcla reaccionante se puso en agua destilada y se extrajo con diclorometano (20ml). La capa orgánica se lavó con solución de bicarbonato de sodio diluida, solución salina, y se evaporó al vacío. El residuo así obtenido, se purificó por cromatografía en columna usando acetato de etilo al 10% en hexano como eluyente para producir el compuesto título (180mg)

15

20

Etapas 2: Síntesis de Benzoato de 4-amino-1-(2-bifenil-4-ilet)-2-(ter-butoxicarbonil)butilo.

25

Se adicionó paladio al 10% sobre carbón (100mg) a la solución del compuesto (170 mg), obtenido de la etapa 1 anterior, en acetato de etilo (10ml); la

mezcla reacción se agitó en atmósfera de hidrógeno (40psi) durante 4 horas seguido por filtración a través de celita. El filtrado se concentró a presión reducida para obtener el compuesto título (100mg)

5 **Etapla 3: Síntesis de Benzoato de 1-(2-bifenil-4-iletil)-2-(ter-butoxicarbonil)-4-
{(4-fluorofenil)sulfonil]amino}butilo.**

Se adicionaron 4-fluorobenceno sulfonil cloruro (62mg) y trietilamina a 0°C a la solución del compuesto (150mg), obtenido de la etapa 2 anterior, en diclorometano (5ml) y la mezcla de reacción se agitó durante 4 horas. La mezcla
10 de reacción se diluyó con agua destilada y se extrajo con diclorometano (15ml). La capa orgánica se lavó con agua, ácido clorhídrico diluido frio y solución salina, se secó sobre sulfato de sodio anhidro y se evaporó a presión reducida. El residuo así obtenido se purificó por cromatografía en columna usando acetato de etilo al 10% en hexano, como eluyente para producir el compuesto título (100mg)

15

**Etapla 4: Síntesis de 5-bifenil-4-il-2-(2-{(4-fluorofenil)sulfonil]amino}etil)-3-
hidroxipropanoato de ter-butilo.**

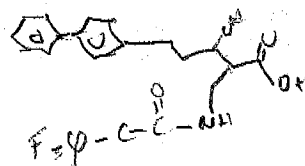
A una solución del compuesto (100mg) obtenido en la etapa 3 anterior, en tetrahidrofurano: metanol: agua (3:1:1,5mL) se le adicionó una solución acuosa de
20 hidróxido de litio (18 mg en 1 mL de agua). La mezcla de reacción resultante se agitó durante toda la noche. La mezcla de reacción se concentró y el residuo así obtenido se diluyó con agua acidificada con solución diluida de ácido clorhídrico y se extrajo con acetato de etilo. La capa orgánica se lavó con agua destilada y solución salina, se secó sobre sulfato de sodio anhidro y se concentró a presión
25 reducida para producir el compuesto título (94mg).

**Etapla 5: Síntesis de Ácido 5-bifenil-4-il-2-(2-{(4-
fluorofenil)sulfonil]amino}etil)-3-hidroxipentanóico.**

A la solución del compuesto (100mg) obtenido en la etapa 4 anterior, en diclorometano (5ml) se adicionó ácido trifluoroacético (0,5ml) y la mezcla de reacción se agitó durante 2 horas. La mezcla de reacción se concentró. Al residuo se le pasó nitrógeno y se secó en alto vacío y se purificó por cromatografía preparativa de capa delgada usando metanol al 12% en diclorometano para producir el compuesto título (30mg)

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

Ejemplo 5: Síntesis de Ácido 5-Bifenil-4-il-2-(2-[(3-fluorofenil)acetil]amino)etil)-3-hidroxipentanóico (Compuesto No. 88).



Etapla 1: Síntesis de benzoato de 1-(2-bifenil-4-iletíl)-2-(ter-butoxicarbonil)-4-[(4-fluorobenzoil)amino]butilo.

A una solución de benzoato de 4-amino-1-(2-bifenil-4-iletíl)-2-(ter-butoxicarbonil)butil (150mg) obtenido del ejemplo 3, etapa 2 en dimetilformamida (2ml) anhidra a 0°C, 1-etil-3-(3'-dimetilaminapropil)-carbodi-imida (92mg) y ácido 4-fluorobenzoico (45mg) y N-metilmorfolina (0,05ml) y la mezcla de reacción se agitó durante toda la noche. La mezcla de reacción se puso en agua destilada y se extrajo con acetato de etilo. La capa orgánica se lavó con agua destilada y solución salina y se secó sobre sulfato de sodio anhidro evaporando luego a presión reducida. El residuo así obtenido se purificó por cromatografía en columna acetato de etilo al 10% en hexano como eluyente para lograr el compuesto título (120mg)

Etapla 2: Síntesis de 5-bifenil-4-il-2-{2[(4-fluorobenzoil)amino]etil}-3-hidroxipropanato de ter-butilo.

A la solución del compuesto (120mg) obtenido de la etapa 1 anterior, en tetrahidrofurano: metanol: agua (3:1:1,5ml) se adicionó solución acuosa de hidróxido de litio (22mg) y la mezcla de reacción se agitó durante la noche. La mezcla reaccionante se concentró y el residuo así obtenido se puso en agua destilada, se acidificó con solución de ácido clorhídrico diluido y se extrajo con acetato de etilo. La capa orgánica se lavó con agua destilada y la solución salina y se secó sobre sulfato de sodio anhidro. El solvente se evaporó a presión reducida para producir el compuesto título (100mg)

10

Etapla 3: Síntesis de Ácido 5-bifenil-4-il-2-{2[(4-fluorobenzoil)amino]etil}-3-hidroxipentanoato de *ter*-butilo.

Se adicionó ácido trifluoroacético a una solución del compuesto obtenido en la etapa 2 anterior (100mg), en diclorometano (5ml) y la mezcla de reacción se agitó durante 2 horas. La mezcla de reacción, se concentró. Al residuo se le paso nitrógeno gaseoso, se secó a alto vacío, y se purificó por cromatografía de capa fina preparativa usando metanol al 12% en diclorometano para producir el compuesto título (30mg)

15

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

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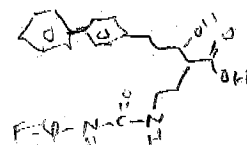
Los siguientes análogos ilustrativos se prepararon de manera similar,

Ácido 5-Bifenil-4-il-3-hidroxi-2-{2-[(fenilacetil)amino]etil}pentanóico (Compuesto No. 45, y

Ácido 5-Bifenil-4-il-2-{2-[(4-fluorobenzoil)amino]etil}-3-hidroxipentanóico (Compuesto No. 89),

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Ejemplo 6: Síntesis de Ácido 5-Bifenil-4-il-2-[2-(((4-fluorofenil) amino]carbonil}amino)etil]-3-hidroxipentanóico (Compuesto No. 92).



Etapa 1: Síntesis de Benzoato de 1-(2-bifenil-4-iletil)-2-(ter- butoxicarbonil)-4-(((4-fluorofenil) amino]carbonil}amino)butilo.

A una solución benzoato de 4-amino-1-(2-bifenil-4-iletil)-2-(ter- butoxicarbonil) butil (100mg) obtenido del ejemplo 3, etapa 2 en diclorometano a 0°C se adicionó 4-fluoro-fenil isocianato (29mg) bajo atmósfera de argón y la mezcla de reacción se agitó por 1 hora. La mezcla de reacción se secó en alto vacío para producir el compuesto título (130mg)

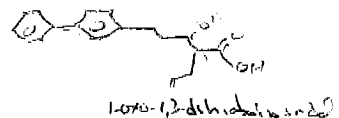
Etapa 2: Síntesis de ácido 5-bifenil-4-il-2[2-(((4-fluorofenil) amino]carbonil}amino)etil]-3-hidroxipentanóico.

Se adicionó solución acuosa de hidróxido de litio (22mg en 1 ml) a una solución del compuesto (130mg) obtenido de la etapa 1 anterior, en tetrahidrofurano: metanol: agua (3:1: 1,5ml) y la mezcla de reacción se agitó a 40°C durante la noche. La mezcla de reacción se concentró y el residuo así obtenido se puso en agua destilada, se acidificó con solución diluída de ácido clorhídrico y se extrajo con acetato de etilo. La capa orgánica se lavó con agua destilada y solución salina y se secó sobre sulfato de sodio anhidro. El solvente se evaporó a presión reducida para producir el compuesto título (40mg)

Masa (m/z): 473 ($M^+ + 23$); 451.1 ($M + 1$)

Esquemas IV, Procedimiento

Ejemplo 7: Síntesis de Ácido 5-Bifenil-4-il-3-hidroxi-2-[2-(1-oxo-1,3-dihidro-2H-isoindol-2-il)etil]pentanóico (Compuesto No. 91).



Etapa 1: Síntesis de 5-bifenil-4-il-2-[2-(1,3-dioxo-1,3-dihidro-2H-isoindol-2-il)etil]-3-oxopentanoato de *ter*-butilo.

El compuesto título se preparó siguiendo el procedimiento como se describió en el ejemplo 1, etapa 2, usando 2-(2-bromoetil)-1H-isoindol-1,3(2H)-diona en lugar de 3-(2-bromoetil)-1,2,3-benzotriazin -4 (3H)-ona

Etapa 2: Síntesis de 5-bifenil-4-il-3-hidroxi-2-[2-(1-hidroxi-3-oxo-1,3-dihidro-2H-isoindol-2-il)etil]pentanoato de *ter*-butilo.

10 A la solución del compuesto (165mg) preparado en al etapa 1 anterior, en metanol anhidro y THF (1:1,8ml) a -20°C se le adicionó borohidruro de sodio (38mg) y la mezcla de reacción de agitó a rt por 3 horas y luego a 45°C durante 1 hora.

La mezcla de reacción se enfrió a 0°C y se esatbilizó con solución saturada de cloruro de amonio. Los solventes se evaporaron al vacío y el residuo se puso en 15 agua y se extrajo con acetato de etilo. Los extractos orgánicos combinado se lavaron con agua y solución salina y se secaron con sulfato de sodio anhidro. El solvente se evaporó a presión reducida para obtener el compuesto título crudo (165mg)

Etapa 3: Síntesis de Ácido 5-bifenil-4-il-3-hidroxi-2-[2-(1-oxo-1,3-dihidro-2H-isoindol-2-il)etil]pentanoico.

A la solución del compuesto (160mg) obtenido de la etapa 2 anterior, en ácido trifluoroacético (2ml) a temperatura ambiente se le adicionó borohidruro de sodio (36mg) y se agitó durante 1 hora. Los volátiles se evaporaron a presión reducida y 25 el residuo se purificó por TLC preparativa usando metanol al 10% - DCM como fase móvil (100mg)

Masa (m/z): 430.0 (M+1)

El siguiente análogo ilustrativo se preparó de manera similar.

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Ácido 5-bifenil-4-il-3-hidroxi-2-[2-(1-oxo-1,3-dihidro-2*H*-isoindol-2-il)butil]pentanóico (Compuesto No. 124),

Ejemplo 8: Separación de Ácido (2*R*,3*R* + 2*S*,3*S*)-5-(4'-Clorobifenil-4-il)-2-[2-(1,3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)etil]-3-hidroxipentanóico (Compuesto No. 80) y

5 Ácido (2*R*,3*S* + 2*S*,3*R*)-5-(4'-Clorobifenil-4-il)-2-[2-(1,3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)etil]-3-hidroxipentanóico (Compuesto No. 81),

El compuesto No. 4 (30mg) se cargó a cromatografía de capa preparativa y la placa de TLC se corrió usando acetona al 30% en diclorometano como fase
10 móvil. Las bandas diastereoméricas deseadas se separaron por corte. El gel de silicogel de las bandas individuales que contienen los pares de compuestos individuales se cargó en una columna corta y se hizo purificación cromatográfica por elución con metanol al 5% en DCM produciendo en compuestos títulos correspondientes. Compuesto No. 80: 6mg. Compuesto No. 81: 16mg

15 Los siguientes pares de diastereómeros ilustrativo se separaron de manera similar.

Ácido (2*R*,3*S* + 2*S*,3*R*)-2-[2-(1,3-Dioxo-1,3-dihidro-2*H*-isoindol-2-il)etil]-5-(4'-formilbifenil-4-il)-3-hidroxipentanóico (Compuesto No. 13),

Ácido (2*R*,3*R* + 2*S*,3*S*)-2-[2-(1,3-Dioxo-1,3-dihidro-2*H*-isoindol-2-il)etil]-5-(4'-formilbifenil-4-il)-3-hidroxipentanóico (Compuesto No. 14),

20 Ácido (2*R*,3*R* + 2*S*,3*S*)-2-[2-(1,3-Dioxo-1,3-dihidro-2*H*-isoindol-2-il)etil]-3-hidroxi-5-(2',4',6'-trimetoxibifenil-4-il)pentanóico (Compuesto No.15),

Ácido (2*R*,3*S* + 2*S*,3*R*)-2-[2-(1,3-Dioxo-1,3-dihidro-2*H*-isoindol-2-il)etil]-3-hidroxi-5-(2',4',6'-trimetoxibifenil-4-il)pentanóico (Compuesto No. 16),

25 Ácido (2*R*,3*S* + 2*S*,3*R*)-5-(4'-Acetilbifenil-4-il)-2-[2-(1,3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)etil]-3-hidroxipentanóico (Compuesto No. 17),

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Ácido (2*R*,3*R* + 2*S*,3*S*)-5-(4'-Acetilbifenil-4-il)-2-[2-(1,3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)etil]-3-hidroxipentanóico (Compuesto No. 18),

Ácido (2*R*,3*S* + 2*S*,3*R*)-2-[2-(1,3-Dioxo-1,3-dihidro-2*H*-isoindol-2-il)etil]-3-hidroxi-5-(4'-propoxibifenil-4-il)pentanóico (Compuesto No. 19),

5. Ácido (2*R*,3*R* + 2*S*,3*S*)-2-[2-(1,3-Dioxo-1,3-dihidro-2*H*-isoindol-2-il)etil]-3-hidroxi-5-(4'-propoxibifenil-4-il)pentanóico (Compuesto No. 20),

Ácido (2*R*,3*S* + 2*S*,3*R*)-5-(3',4'-Difluorobifenil-4-il)-2-[2-(1,3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)etil]-3-hidroxipentanóico (Compuesto No. 21),

10. Ácido (2*R*,3*R* + 2*S*,3*S*)-5-(3',4'-Difluorobifenil-4-il)-2-[2-(1,3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)etil]-3-hidroxipentanóico (Compuesto No. 22),

Ácido (2*R*,3*S* + 2*S*,3*R*)-2-[2-(1,3-Dioxo-1,3-dihidro-2*H*-isoindol-2-il)etil]-3-hidroxi-5-[4-(6-metoxipiridin-3-il)fenil]pentanóico (Compuesto No. 78),

Ácido (2*R*,3*R* + 2*S*,3*S*)-2-[2-(1,3-Dioxo-1,3-dihidro-2*H*-isoindol-2-il)etil]-3-hidroxi-5-[4-(6-metoxipiridin-3-il)fenil]pentanóico (Compuesto No. 79),

15. Ácido (2*R*,3*S* + 2*S*,3*R*)-2-[2-(1,3-Dioxo-1,3-dihidro-2*H*-isoindol-2-il)etil]-5-(4'-fluorobifenil-4-il)-3-hidroxipentanóico (Compuesto No. 82),

Ácido (2*R*,3*R* + 2*S*,3*S*)-2-[2-(1,3-Dioxo-1,3-dihidro-2*H*-isoindol-2-il)etil]-5-(4'-fluorobifenil-4-il)-3-hidroxipentanóico (Compuesto No. 83),

20. Ácido (2*R*,3*S* + 2*S*,3*R*)-2-[2-(5-*ter*-Butil-1,3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)etil]-5-(4'-fluorobifenil-4-il)-3-hidroxipentanóico (Compuesto No. 106),

Ácido (2*R*,3*S* + 2*S*,3*R*)-2-[2-(5-*ter*-Butil-1,3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)etil]-3-hidroxi-5-[4'-(trifluorometil)bifenil-4-il]pentanóico (Compuesto No. 107),

Ácido (2*R*,3*R* + 2*S*,3*S*)-2-[2-(5-*ter*-Butil-1,3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)etil]-5-(4'-fluorobifenil-4-il)-3-hidroxipentanóico (Compuesto No. 108),

Ácido (2*R*,3*R* + 2*S*,3*S*)-2-[2-(5-*ter*-Butil-1,3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)etil]-3-hidroxi-5-[4'-(trifluorometil)bifenil-4-il]pentanóico (Compuesto No. 109),

Ácido 2-[2-(1,3-Dioxo-1,3-dihidro-2*H*-isoindol-2-il)etil]-5-(3'-fluoro-4'-metoxibifenil-4-il)-3-hidroxipentanóico (Compuesto No. 110),

- 5 Ácido (2*R*,3*S* + 2*S*,3*R*)-2-[2-(1,3-Dioxo-1,3-dihidro-2*H*-isoindol-2-il)etil]-3-hidroxi-5-[4-(6-metilpiridin-3-il)fenil]pentanóico (Compuesto No. 111),

Ácido (2*R*,3*R* + 2*S*,3*S*)-2-[2-(1,3-Dioxo-1,3-dihidro-2*H*-isoindol-2-il)etil]-3-hidroxi-5-[4-(6-metilpiridin-3-il)fenil]pentanóico (Compuesto No. 112),

- 10 Ácido (2*R*,3*R* + 2*S*,3*S*)-2-[2-(5-*ter*-Butil-1,3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)etil]-3-hidroxi-5-(4'-metilbifenil-4-il)pentanóico (Compuesto No. 113),

Ácido (2*R*,3*S* + 2*S*,3*R*)-2-[2-(5-*ter*-Butil-1,3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)etil]-3-hidroxi-5-(4'-metilbifenil-4-il)pentanóico (Compuesto No. 114),

Ácido (2*R*,3*R* + 2*S*,3*S*)-2-[2-(5-*ter*-Butil-1,3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)etil]-3-hidroxi-5-(4'-metoxibifenil-4-il)pentanóico (Compuesto No. 115),

- 15 Ácido (2*R*,3*R* + 2*S*,3*S*)-2-[2-(5-*ter*-Butil-1,3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)etil]-5-(4'-clorobifenil-4-il)-3-hidroxipentanóico (Compuesto No. 116),

Ácido (2*R*,3*S* + 2*S*,3*R*)-2-[2-(5-*ter*-Butil-1,3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)etil]-5-(4'-clorobifenil-4-il)-3-hidroxipentanóico (Compuesto No. 117),

- 20 Ácido (2*R*,3*S* + 2*S*,3*R*)-2-[2-(5-*ter*-Butil-1,3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)etil]-3-hidroxi-5-(4'-metoxibifenil-4-il)pentanóico (Compuesto No. 118),

Ácido (2*R*,3*S*)-5-Bifenil-4-il-3-hidroxi-2-[2-(1*H*-indol-3-il)etil]pentanóico (Compuesto No. 122),

Ácido (2*R*,3*R*)-5-Bifenil-4-il-3-hidroxi-2-[2-(1*H*-indol-3-il)etil]pentanóico (Compuesto No. 123).

Se llevó a cabo análisis/separación por HPLC quiral, por ejemplo, utilizando el sistema Waters HPLC LC Module I Plus con detector UV 486 utilizando una columna Chiracel OJ-H(250* 4.6), fase móvil 60:40 de TFA al 0.1% en
5 hexano:etanol; tasa de flujo 0.7 mL/min, tiempo de corrida 60 minutos.

Los siguientes diasterómeros únicos ilustrativos se separaron utilizando condiciones HPLC quiral,

Ácido (2R,3S)-5-(4'-Clorobifenil-4-il)-2-[2-(1,3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)etil]-3-hidroxipentanóico (Compuesto No.125),

10 Ácido (2S,3R)-5-(4'-Clorobifenil-4-il)-2-[2-(1,3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)etil]-3-hidroxipentanóico (Compuesto No.126),

Ácido (2R,3R)-5-(4'-Clorobifenil-4-il)-2-[2-(1,3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)etil]-3-hidroxipentanóico (Compuesto No.127),

15 Ácido (2S,3S)-5-(4'-Clorobifenil-4-il)-2-[2-(1,3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)etil]-3-hidroxipentanóico (Compuesto No.128),

Ácido (2R,3S) -2-[2-(1,3-Dioxo-1,3-dihidro-2*H*-isoindol-2-il)etil]-3-hidroxi-5-[4-(6-metoxipiridin-3-il)fenil]pentanóico (Compuesto No. 129),

Ácido (2S,3R)- 2-[2-(1,3-Dioxo-1,3-dihidro-2*H*-isoindol-2-il)etil]-3-hidroxi-5-[4-(6-metoxipiridin-3-il)fenil]pentanóico (Compuesto No. 130),

20 Ácido (2R,3R)- 2-[2-(1,3-Dioxo-1,3-dihidro-2*H*-isoindol-2-il)etil]-3-hidroxi-5-[4-(6-metoxipiridin-3-il)fenil]pentanóico (Compuesto No. 131),

Ácido (2S,3S)- 2-[2-(1,3-Dioxo-1,3-dihidro-2*H*-isoindol-2-il)etil]-3-hidroxi-5-[4-(6-metoxipiridin-3-il)fenil]pentanóico (Compuesto No. 132),

Ácido (2R,3S)- 3-Hidroxi-5-[4-(6-metoxipiridin-3-il)fenil]-2-[2-(4-oxo-1,2,3-benzotriazin-3(4H)-il)etil]pentanóico (Compuesto No.133),

Ácido (2S,3R)- 3-Hidroxi-5-[4-(6-metoxipiridin-3-il)fenil]-2-[2-(4-oxo-1,2,3-benzotriazin-3(4H)-il)etil]pentanóico (Compuesto No.134),

5 Ácido (2R,3R)- 3-Hidroxi-5-[4-(6-metoxipiridin-3-il)fenil]-2-[2-(4-oxo-1,2,3-benzotriazin-3(4H)-il)etil]pentanóico (Compuesto No.135), y

Ácido (2S,3S)- 3-Hidroxi-5-[4-(6-metoxipiridin-3-il)fenil]-2-[2-(4-oxo-1,2,3-benzotriazin-3(4H)-il)etil]pentanóico (Compuesto No.136).

Análisis para Metaloproteinasas de la Matriz (MMPs)

10 Se prepararon estándares NCEs (stock 10 mM) en DMSO al 100 % y se hicieron diluciones subsiguientes en 50% DMSO - 50 %-TCNB (Tris 50mM, CaCl₂ 10mM, 150 mM de NaCl, 0.05% Brij-35, pH 7.5). A pozos de 96 placas de pozo se agregaron 1 µL del compuesto y 88 µL de TCNB para alcanzar la concentración final deseada de NCE (la concentración final de DMSO no debe exceder el 0.5%).

15 A cada pozo se agregó 1 µL de MMPs recombinantes activadas (20-100 ng/100 µL de mezcla de reacción) excepto al "pozo negativo" (las enzimas MMP-1, 9 & 14 requieren activación previa. Para éstas, las enzimas suministradas se incubaron bien sea con APMA, concentración final 1mM, por un período de 1 hora a 37 °C). Se incubó a temperatura ambiente por 4-5 minutos. La reacción se inició con 10

20 µL de sustrato 100 µM (ES001: las alícuotas eran recientemente diluidas en TCNB; stock 2mM) y se monitoreó el aumento en la fluorescencia a la longitud de onda de excitación 320 nm seguido de la emisión a 405 nm por 25-30 ciclos. Se calculó el aumento en fluorescencia (RFU) para los pozos estándar positivos, negativos y NCE. Se calculó el porcentaje de inhibición por comparación con los

25 controles y se determinó el valor IC₅₀ utilizando el software Graph-prism.

Los activados para MM9 dieron valores IC_{50} de cerca de 10 micromolar a cerca de 2 nM, o de cerca de 1 micromolar a cerca de 2 nM, o de cerca de 650 nM a cerca de 2 nM, o de cerca de 300 nM a cerca de 2 nM, o de cerca de 100 nM a cerca de 2 nM, o de cerca de 50 nM a cerca de 2 nM, o de cerca de 30 nM a cerca de 2 nM, o de cerca de 20 nM a cerca de 2 nM, o de cerca de 15 nM a cerca de 2 nM, comparados con cerca de 1.5 nM para marimasat.

Los activados para MM12 dieron valores IC_{50} de cerca de 10 micromolar a cerca de 0.4 nM, o de cerca de 1 micromolar a cerca de 0.4 nM, o de cerca de 300 nM a cerca de 0.4 nM, o de cerca de 100 nM a 0.4 nM, o de cerca de 50 nM a cerca de 0.4 nM, o de cerca de 30 nM a cerca de 0.4 nM, o de cerca de 20 nM a cerca de 0.4 nM, o de cerca de 15 nM a cerca de 0.4 nM, o de cerca de 7 nM a cerca de 0.4 nM comparados con cerca de 0.9 nM para marimasat.